Volk *BMC Veterinary Research* (2015) 11:174
DOI 10.1186/s12917-015-0460-3

BMC Veterinary Research

EDITORIAL Open Access

International Veterinary Epilepsy Task Force consensus reports on epilepsy definition, classification and terminology, affected dog breeds, diagnosis, treatment, outcome measures of therapeutic trials, neuroimaging and neuropathology in companion animals

Holger A. Volk

Keywords: Epilepsy, Seizures, Dog, Classification, Semiology

Editorial

Epilepsy is one of the most common chronic neurological diseases in companion animals. Its prevalence has been estimated to be 0.6-0.75 % in the general dog population [1, 2], which means that nearly every 130th dog presenting in a veterinary practice will have epilepsy. Dogs and cats with epilepsy experience debilitating epileptic seizures, but epilepsy causes more than recurrent epileptic seizures alone. Patients with epilepsy can suffer from transient postictal behavioural changes and/or clinical deficits. Furthermore, affected dogs have a shortened life expectancy, and are at an increased risk of developing comorbidities affecting the interictal period, such as neurobehavioural changes, and a reduced quality of life [3–6]. The impact of the disease does not only affect the patient, but also affects the quality of life of the pet's owner [5–7]. Based on the importance of epilepsy for clinical and especially neurological practice a flourish of studies have been performed and published over the last 30 years.

Despite this plethora of new information, the classifications, definitions, terminology, therapeutic outcome measures, neuroimaging and neuropathological standards have differed between many of these studies, making it difficult to draw comparisons. This could potentially limit their scientific impact. Furthermore, this has prevented the implementation of a common understanding of epilepsy and standardized professional guidelines, which could support clinicians when diagnosing companion animals with epilepsy and advising their owners. Many of the classifications, definitions and terminology used have reflected the most recent proposals of that time of an international human epilepsy organisation, the International League Against Epilepsy (ILAE). Since the 1960s the ILAE have worked on defining, classifying and agreeing on the terminology used in human epilepsy [8–14]. The ILAE sees itself as "*the world's preeminent association of physicians and other health professionals working towards a world where no persons' life is limited by epilepsy*" and has the mission "*to ensure that health professionals, patients and their care providers, governments, and the public world-wide have the educational and research resources that are essential in understanding, diagnosing and treating persons with epilepsy*" (ILAE homepage www.ilae.org). The ILAE builds taskforces to fulfil its mission, resulting in the publication of consensus statements to provide the scientific and clinical framework for the epilepsy community. These consensus statements are regularly reviewed every 5-10 years, reflecting the constant improvements in our understanding of the disease, its treatment, comorbidities and complications.

In 2014, a group of Veterinary Neurology Specialists and Non-specialists founded the International Veterinary

Correspondence: hvolk@rvc.ac.uk
Department of Clinical Science and Services, Royal Veterinary College, Hatfield, AL9 7TA Hertfordshire, UK

Epilepsy Task Force (IVETF). The IVETF is deliberately independent to any other veterinary or human organisation and its main aim is to provide the veterinary community, breeders and dog (and in part cat) owners with consensus statements on the key areas in the field of epilepsy. There is a 'chain of care' from the animal's breeder and owner through the first opinion practitioner to the neurology specialist and neuroscientist. Each consensus statement aims to be a 'user friendly', pragmatic, reliable and valid tool for the benefit of all of these stakeholder groups. Furthermore, IVETF has worked towards building a scientific and clinical framework to manage and research epilepsy appropriately, and to provide a platform to enable communication with other stakeholders using the same, agreed "common language". Each consensus statement is based upon the current published understanding of epilepsy and represents in parts the authors' interpretation of the published evidence. IVETF reflected new thoughts from the human ILAE, but also considered well accepted veterinary terminology and practice. To ensure we had a broad range of stakeholders involved, the consensus-working group was composed of and/or consulted veterinary and human neurologists and neuroscientists, practitioners, neuropharmacologists and neuropathologists. It is the first time that so many clinicians and scientists have united and formally agreed on the key aspects of companion animal epilepsy. This culminated in twenty-six co-authors being involved in the process of developing seven consensus statements. These consensus statements should be seen as the beginning rather than the end of this process, with the IVETF planning to broaden its remit and membership in the future.

The IVETF has agreed on the following consensus statements. The IVETF hopes that each statement will help advance the field of canine and feline epilepsy and ultimately lead to better care for our patients:

1. International Veterinary Epilepsy Task Force consensus report on epilepsy definition, classification and terminology in companion animals
2. International Veterinary Epilepsy Task Force Consensus Proposal: Diagnostic approach to epilepsy in dogs
3. International Veterinary Epilepsy Task Force current understanding of idiopathic epilepsy of genetic or suspected genetic origin in purebred dogs
4. International Veterinary Epilepsy Task Force consensus proposal: Medical treatment of canine epilepsy in Europe
5. International Veterinary Epilepsy Task Force Consensus Proposal: Outcome of therapeutic interventions in canine and feline epilepsy
6. International Veterinary Epilepsy Task Force recommendations for a veterinary epilepsy-specific MRI protocol
7. International Veterinary Epilepsy Task Force recommendations for systematic sampling and processing of brains from epileptic dogs and cats

Abbreviations

IVETF: International Veterinary Epilepsy Task Force; ILAE: International League Against Epilepsy.

Competing interests

Following reimbursements, fees and funding have been received by the author in the last three years and have been declared in the competing interest section. HAV has received fees for acting as a consultantfor Boehringer Ingelheim (consultancy pre and post launch of imepitoin). HAV has been responsible principalinvestigator of several research studies concerning imepitoin financed by Boehringer Ingelheim and hasreceived speaking fees from Boehringer Ingelheim. HAV received funding for a collaborative project fromDesitin and Nestlé Purina Research.

Received: 3 June 2015 Accepted: 29 June 2015
Published online: 28 August 2015

References

1. Kearsley-Fleet L, O'Neill DG, Volk HA, Church DB, Brodbelt DC. Prevalence and risk factors for canine epilepsy of unknown origin in the UK. Vet Rec. 2013;172(13):338.
2. Heske L, Nodtvedt A, Jaderlund KH, Berendt M, Egenvall A. A cohort study of epilepsy among 665,000 insured dogs: incidence, mortality and survival after diagnosis. Veterinary journal. 2014;202(3):471–6.
3. Shihab N, Bowen J, Volk HA. Behavioral changes in dogs associated with the development of idiopathic epilepsy. Epilepsy Behav. 2011;21(2):160–7.
4. Berendt M, Gredal H, Ersbøll AK, Alving J. Premature death, risk factors, and life patterns in dogs with epilepsy. J Vet Intern Med. 2007;21(4):754–9.
5. Chang Y, Mellor DJ, Anderson TJ. Idiopathic epilepsy in dogs: owners' perspectives on management with phenobarbitone and/or potassium bromide. J Small Anim Pract. 2006;47(10):574–81.
6. Wessmann A, Volk HA, Parkin T, Ortega M, Anderson TJ. Living with canine idiopathic epilepsy: a questionnaire-based evaluation of quality of life. J Int Med. 2012;26:1.
7. Lord LK, Podell M. Owner perception of the care of long-term phenobarbital-treated epileptic dogs. J Small Anim Pract. 1999;40(1):11–5.
8. Berg AT, Berkovic SF, Brodie MJ, Buchhalter J, Cross JH, Van Emde BW, et al. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005-2009. Epilepsia. 2010;51(4):676–85.
9. Berg AT, Scheffer IE. New concepts in classification of the epilepsies: entering the 21st century. Epilepsia. 2011;52(6):1058–62.
10. Shorvon SD. The etiologic classification of epilepsy. Epilepsia. 2011;52(6):1052–7.
11. Fisher RS, Van Emde BW, Blume W, Elger C, Genton P, Lee P, et al. Epileptic seizures and epilepsy: definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). Epilepsia. 2005;46(4):470–2.
12. From the Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised clinical and electroencephalographic classification of epileptic seizures. Epilepsia. 1981;22(4):489–501.
13. Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised classification of epilepsies and epileptic syndromes. Epilepsia. 1989;30(4):389–99.
14. Commission on Epidemiology and Prognosis, International League Against Epilepsy. Guidelines for epidemiologic studies on epilepsy. Epilepsia. 1993;34(4):592–6.

Berendt et al. BMC Veterinary Research (2015) 11:182
DOI 10.1186/s12917-015-0461-2

BMC Veterinary Research

CORRESPONDENCE Open Access

International veterinary epilepsy task force consensus report on epilepsy definition, classification and terminology in companion animals

Mette Berendt[1*], Robyn G. Farquhar[2], Paul J. J. Mandigers[3], Akos Pakozdy[4], Sofie F. M. Bhatti[5], Luisa De Risio[6], Andrea Fischer[7], Sam Long[8], Kaspar Matiasek[9], Karen Muñana[10], Edward E. Patterson[11], Jacques Penderis[12], Simon Platt[13], Michael Podell[14], Heidrun Potschka[15], Martí Batlle Pumarola[16], Clare Rusbridge[17,18], Veronika M. Stein[19], Andrea Tipold[19] and Holger A. Volk[20]

Abstract

Dogs with epilepsy are among the commonest neurological patients in veterinary practice and therefore have historically attracted much attention with regard to definitions, clinical approach and management. A number of classification proposals for canine epilepsy have been published during the years reflecting always in parts the current proposals coming from the human epilepsy organisation the International League Against Epilepsy (ILAE). It has however not been possible to gain agreed consensus, "a common language", for the classification and terminology used between veterinary and human neurologists and neuroscientists, practitioners, neuropharmacologists and neuropathologists. This has led to an unfortunate situation where different veterinary publications and textbook chapters on epilepsy merely reflect individual author preferences with respect to terminology, which can be confusing to the readers and influence the definition and diagnosis of epilepsy in first line practice and research studies.
In this document the International Veterinary Epilepsy Task Force (IVETF) discusses current understanding of canine epilepsy and presents our 2015 proposal for terminology and classification of epilepsy and epileptic seizures. We propose a classification system which reflects new thoughts from the human ILAE but also roots in former well accepted terminology. We think that this classification system can be used by all stakeholders.

Keywords: Epilepsy, Seizures, Dog, Classification, Semiology

Background

Epilepsy is a complex brain disease where sudden and abnormal activity in neuronal networks causes the prominent clinical sign of seizures characterised by motor, autonomic and/or behavioural features. Epileptic seizures are episodic and brief (in most cases less than 2–3 min). Epilepsy can rise from a plethora of causes. A few rare cases are purely genetic (e.g. channelopathies), some are developmental and have complex genetic and epigenetic influences (e.g. neuronal migration disorders) and some are caused by injury to the brain (e.g. trauma, infectious, inflammatory, vascular or neoplastic disease). In a significant number of cases, the cause is not clear. Although the mechanisms behind companion animal epilepsy are largely uncovered, it is clear that epilepsy in some purebred dogs is a direct result of a genetic defect, where seizures are the core clinical sign of disease. This has been described for the Lagotto Romagnolo, Belgian shepherd and Boerboels [1–4]. A high epilepsy prevalence in a specific breed or the accumulation of epileptic individuals within specific dog families are strong indicators of inherited epilepsy, but often it is unknown if genetic defects are the sole cause of the epilepsy or if the epilepsy might arise from multifactorial causal influences including environmental, developmental, provoking and genetic factors, and similar issues apply to human cases [5].

The true prevalence of epilepsy in dogs is unknown and has been estimated to be 0.6–0.75 % in the general

* Correspondence: mbe@sund.ku.dk
[1]Department of Veterinary Clinical and Animal Sciences, Faculty of Health and Medical Sciences, University of Copenhagen, Frederiksberg C, Denmark
Full list of author information is available at the end of the article

dog population [6, 7]. Epidemiological population prevalence studies in specific breeds with idiopathic epilepsy has been conducted in the Labrador retriever (3.1 %), Belgian shepherd (9.4 %) and petit Basset Griffon vendeen (8.9 %), and pedigree studies in the Boxer, Irish wolfhound, English Springer spaniel, Vizsla, Bernese mountain dog, Standard poodle, Belgian shepherd, Border collie, Australian shepherd and Border terrier among others, and these have provided evidence for inherited epilepsy [8–25] (for further information on epilepsy related to specific breeds see Hülsmeyer et al. [26]). Given the heterogeneity of epilepsy where causes and signs of disease are greatly variable, a standardised terminology and classification system for epilepsy is crucial in order to provide accurate descriptive information for diagnostic and communicative processes.

Since 1964 epilepsy and epileptic seizures have in human medicine been organized and categorized in a classification and terminology system, published by the International League Against Epilepsy—ILAE [27–33]. The ILAE sees itself as *"the world's preeminent association of physicians and other health professionals working towards a world where no persons' life is limited by epilepsy"* and the noble mission of this organization is *"to ensure that health professionals, patients and their care providers, governments, and the public world-wide have the educational and research resources that are essential in understanding, diagnosing and treating persons with epilepsy"* (ILAE homepage www.ilae.org).

The 1985 classification of seizure types and the 1989 classification of the epilepsies continues to be used worldwide in human epilepsy [32, 34]. However, in recent years, the ILAE classification task force has taken to continually updating and revising on the subject of epilepsy producing new consensus documents approximately every 5 years with the most recent being published in 2010 and a further version is currently under much debate [27]. The terminology and classification framework they provide is seen as an ever evolving process, reflecting the constant gain in our understanding of the disease and the complications inherent in ambiguous, misinterpreted and potentially stigmatising vocabulary. This has generated considerable discussion amongst their members reflecting the complexity of the task.

In veterinary medicine, a number of classification proposals for canine epilepsy have been published over the years always reflecting in part the current ILAE proposals (e.g. [35–38]). There remains, however, a lack of a consensus, a common 'language', for the classification and terminology used between veterinary and human neurologists and neuroscientists, practitioners, neuropharmacologists and neuropathologists. Companion animal epilepsy papers reflect a variety of modifications of the definitions of epilepsy and epileptic seizures derived from the core classification documents of the ILAE (e.g. [1, 7, 9–15, 17, 23–25, 27, 28, 30–36, 38–46]. This has led to an unfortunate situation where different veterinary publications and textbook chapters on epilepsy merely reflect individual author preferences with respect to terminology, which can be confusing for the reader. Put in a scientific and educational perspective, the existing lack of uniformity with respect to definitions and terminology furthermore represents a major problem, as comparisons between research studies are compromised. Even more important, it prevents the implementation of a common understanding of epilepsy and standardized professional guidelines which can help clinicians when diagnosing animals with epilepsy and advising the owners.

Terminology and classification of epilepsy should be a 'user friendly', reliable and valid tool for the benefit of different users and the patient [47]. There is a 'chain of care' from the pet's owner through the primary clinician to neurology specialists and researchers. The language should be concise to reduce errors and to simplify conversation. The first opinion veterinarian and specialists alike should be able to use the classification framework to manage the disease appropriately and to communicate with others using the same language. In the age of the internet, the pet owner also needs to be able to, at least in part, comprehend the terminology used. The scientist should find in the classification a pragmatic and reliable instrument to investigate the disease's aetiology, pathophysiology, treatment, and outcome. Finally terminology should reflect current knowledge and not be changed for the sake of change, which has recently also been emphasized by Shorvon (2014) [5] and others with respect to the ILAE discussions on classification. Otherwise important historical data might be lost and in some cases it might be wise to stay with terms which are in widespread use and have stood a test of time instead of a rapid change of terminology emanating from academic discussions [5]. Considering these issues, terminology and classification needs to fulfil dissimilar and sometimes antagonistic needs and at the same time be adaptable to change.

In adopting the terms associated with human epilepsy we should acknowledge some of the very significant differences when applying it to small animal patients. We cannot interview our patients as in human medicine and the clinician's interpretation of the patient's seizure signs are invariably restricted to the owner's description and often a poor quality video(s). Typically electroencephalography (EEG) is an impractical tool in animals and so cannot contribute to a general classification scheme—in contrast to the situation in human medicine. Furthermore some owners will decline diagnostic investigation due to financial concerns or because some procedures

require general anaesthesia, and therefore the owners' report of seizure history and phenomenology, supported by digital (video) recordings, remain the most central diagnostic epilepsy marker in companion animals (in fact as it does in humans).

Another discrepancy between people and animals which must be addressed is the assessment of possible impairment of consciousness during seizures. The determination of consciousness impairment is challenging and often very important to people because of personal and public safety. The ILAE classification cites consciousness as an important factor for diagnosis. Veterinary medicine is better aligned with the challenges facing paediatric medicine in this regard.

This consensus statement group aims to provide the veterinary community with a proposal focused on the classification of epilepsy and epileptic seizures. To ensure we have all stakeholders involved, the consensus-working group is composed of veterinary and human neurologists and neuroscientists, practitioners, neuropharmacologists and neuropathologists.

Proposal

In recent years the ILAE has been able to advance human epilepsy classification to a sophisticated level as a consequence of advanced diagnostics and the uncovering of an increasing number of mechanisms (including genetic) that lead to epilepsy. The definition of epilepsy accepted by the ILAE in 2005 reflected the immense progress with respect to the identification of aetiologies and the understanding of seizure generation. Here an epileptic seizure was defined as: *"A transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain"*, and epilepsy was defined as: *"A disorder of the brain characterized by an enduring predisposition to generate epileptic seizures and by the neurobiologic, cognitive, psychological, and social consequences of this condition. The definition of epilepsy requires the occurrence of at least one epileptic seizure"* [30]. In 2010 the ILAE refined the definitions even further [27]; to demonstrate the on-going discussions in the ILAE, it has recently been proposed that epilepsy should be considered a true disease of the brain [48]. This contradicts the previous understanding of epilepsy as a condition of the brain—or a collection of signs from the brain. Berg and Scheffer stated back in 2011 [28]: "These proposals are not meant to be permanent, but form part of a transition to a system that will ultimately allow for meaningful translation of scientific understanding to the classification of the epilepsies for clinical and other purposes". Although we need to move veterinary epilepsy classification forward we also must, as in human medicine, consider carefully whether any change of terminology is meaningful [5]; we must accept that currently we have not advanced the scientific understanding of the mechanisms leading to epilepsy in companion animals to the level applicable to the ILAE.

In the following sections the IVETF discusses the current understanding of companion animal epilepsy and presents our 2015 proposal for terminology and classification of epilepsy and epileptic seizures. We propose a classification system which reflects new thoughts from the human ILAE but also has its roots in former well accepted terminology. We think that this classification system can be used by all stakeholders. The classification has two elements: (a) an aetiological element and (b) a seizure type classification.

Definitions

In human medicine, epilepsy can often be confirmed by electroencephalography (EEG) although epileptic people may have a normal EEG and an abnormal EEG can also exist in people without epilepsy. The use of EEG in veterinary medicine is currently of questionable routine clinical value and therefore our definitions should be seen as clinically operational and reflecting expert knowledge in the field with respect to the typical appearance of epileptic seizures and their symptomatology. This is not a major drawback, and for definition purposes, it is reasonable (in human and animal epilepsy) to define seizures and epilepsy by the clinical appearance of seizures. Please also refer to the glossary for further definitions not listed in the main text.

Seizure

The term can be used for any sudden, short lasting and transient event. It does not imply that the event is epileptic.

Epileptic seizure

Manifestation(s) of excessive synchronous, usually self-limiting epileptic activity of neurons in the brain. This results in a transient occurrence of signs which may be characterized by short episodes with convulsions or focal motor, autonomic or behavioural features and due to abnormal excessive and/or synchronous epileptic neuronal activity in the brain.

Reactive seizure

A reactive seizure is a seizure occurring as a natural response from the normal brain to a transient disturbance in function (metabolic or toxic in nature)—which is reversible when the cause or disturbance is rectified. A provoked seizure can be considered as being synonymous with a reactive seizure.

Epilepsy

Epilepsy is defined as a disease of the brain characterized by an enduring predisposition to generate epileptic seizures. This definition is usually practically applied as having at least two unprovoked epileptic seizures >24 h apart [48].

Classification

Historically veterinary medicine has operated with various terminology/synonyms for epilepsy types defined by aetiology and phenotypic manifestations which are themselves defined by the distribution of abnormal electrical activity in the brain. The development of ILAE classifications and changes in veterinary epilepsy terminology throughout time are detailed in Table 1 and 2.

Epilepsy types defined by aetiology

Idiopathic epilepsy

Idiopathic epilepsy (idiopathic defined as a disease in its own right, per se) should be seen as the overarching and bridging term, which can be sub-classified into three sub-groups reflecting the advancements in the field:

1. Idiopathic epilepsy (genetic epilepsy)—a causative gene for epilepsy has been identified/confirmed genetic background
2. Idiopathic epilepsy (suspected genetic epilepsy)—a genetic influence supported by a high breed prevalence (>2 %), genealogical analysis and/or familial accumulation of epileptic individuals[*,**].
   [*]*Shorvon stated in 2014* [5]*: "It seems very likely that the genetic influences in idiopathic epilepsies probably are complex involving multiple genes and interactions between genes (epistatic) and between genes and the environment (epigenetic)".*
   [**]*A list of breeds with a high epilepsy incidence or prevalence compared to the general background population can be found in Hülsmeyer et al.* [26]*. Please note that the epilepsy status within breeds may fluctuate over time and furthermore be influenced by differences between countries (e.g. due to preferences with respect to currently popular breeding lines).*
3. Idiopathic epilepsy (epilepsy of unknown cause)—epilepsy in which the nature of the underlying cause is as yet unknown and with no indication of structural epilepsy.

Please see consensus on Diagnostic approach to epilepsy in dogs [49] for further information on diagnostic work-up.

Structural epilepsy

Structural epilepsy is characterized by epileptic seizures which are provoked by intracranial/cerebral pathology including vascular, inflammatory/infectious, traumatic, anomalous/developmental, neoplastic and degenerative diseases confirmed by diagnostic imaging, cerebrospinal fluid examination, DNA testing or post mortem findings (see consensus on Diagnostic approach to epilepsy in dogs [49]). Lafora disease progressive myoclonic epilepsy would be classified under structural epilepsy as the gene defect results in a storage disease which alters the brain structurally and where the epileptic seizures associated with the structural changes in the brain are one of the multiple clinical and neurological signs associated with the primary storage disease [50].

Classification by seizure semiology (seizure type classification)

Focal epileptic seizures

Focal epileptic seizures are characterized by lateralized and/or regional signs (motor, autonomic or behavioural signs, alone or in combination). The ictal onset is consistent from one epileptic seizure to another. They may be discretely localised or more widely distributed. Focal epileptic seizures may originate in subcortical structures, with preferential propagation patterns that can involve the contralateral hemisphere. With focal epileptic seizures, the abnormal electrical activity arises in a localized group of neurons or network within one hemisphere. The clinical signs reflect the functions of the area or areas involved.

Focal epileptic seizures can present as:

- Motor (episodic focal motor phenomena e.g. facial twitches, repeated jerking head movements, rhythmic blinking, twitching of facial musculature or repeated rhythmic jerks of one extremity)
- Autonomic (with parasympathetic and epigastric components e.g. dilated pupils, hypersalivation or vomiting)
- Behavioural (focal epileptic seizure activity which in humans can represent psychic and/or sensory seizure phenomena may in animals result in a short lasting episodic change in behaviour such as e.g. anxiousness, restlessnesss, unexplainable fear reactions or abnormal attention seeking/'clinging' to the owner.

Generalized epileptic seizures

Generalized epileptic seizures are characteried by bilateral involvement (both sides of body and therefore both cerebral hemispheres involved). Generalized epileptic seizures may occur alone or evolve from a focal epileptic seizure start. In dogs and cats generalized epileptic seizures predominantly present as tonic, clonic or tonic-clonic epileptic seizures. As a rule the animal will lose consciousness during convulsive epileptic seizures (myoclonic seizures excluded). Salivation, urination and/or defecation furthermore often also occur (myoclonic seizures excluded).

Table 1 Veterinary terminology and its most common amendments over time

	Early terminology	Terminology currently in use	Suggested veterinary terminology 2015
EPILEPTIC SEIZURES			
An epileptic seizure with clinical signs indicating activity which starts in a localised area in the brain -Will present with focal motor, autonomic or behavioural signs alone or in combination	Petit Mal Aura	Partial/focal seizure - Simple partial/focal seizure (consciousness unimpaired[a]) - Complex partial/focal seizure (consciousness impaired[a])	Focal epileptic seizure[a]
An epileptic seizure with clinical signs indicating activity involving both cerebral hemispheres from the start. -In dogs and cats the seizure presents predominantly as immediate 'convulsions' and loss of consciousness. Salivation, urination and/or defecation often also occur during convulsions. May also (but rare) present as atonic or myoclonic seizures	Grand Mal (always implicating convulsions)	Primary generalized seizure	Generalized epileptic seizure
An epileptic seizure which starts in a localized area in the brain and spreads subsequently to involve both hemispheres. -In dogs and cats the seizure starts with localized motor, autonomic and/or behavioural signs rapidly followed by convulsions. Salivation, urination and/or defecation often also occur during convulsions.	Partial seizure with secondary generalization (secondary generalized seizure)	Focal seizure with secondary generalization	Focal epileptic seizure evolving to become generalized
EPILEPSY			
Epilepsy classified by aetiology	Primary Epilepsy - Epilepsy where no structural cerebral pathology is suspected	Idiopathic Epilepsy - Epilepsy where no structural cerebral pathology is suspected. A genetic component may be involved	Idiopathic Epilepsy 1. Proven genetic background 2. Suspected genetic background 3. Unknown cause and no indication of structural epilepsy
Epilepsy classified by aetiology	Secondary or Acquired epilepsy - Epilepsy caused by identified cerebral pathology	Symptomatic Epilepsy - Epilepsy caused by identified cerebral pathology	Structural epilepsy - Epilepsy caused by identified cerebral pathology
Epilepsy classified by aetiology	Cryptogenic - Meaning hidden	Probably or possibly symptomatic epilepsy - A suspected symptomatic cause, which however remains obscure	Unknown cause

[a]Regarding our ability to evaluate if consciousness is unimpaired or impaired during focal seizures (former termed simple and complex focal seizures). We recommend that it is not attempted to interpret signs occurring during focal seizures where dogs may appear e.g. confused, unable to recognize the owner or not responding to commands as impaired consciousness, as this cannot objectively be investigated in animals

Table 2 Development of ILAE classifications

ILAE 1981 and 1989	ILAE 2010	Berg and Scheffer 2011 [28]
Generalized seizures are those in which the first clinical and electroencephalographic changes indicate initial involvement of both cerebral hemispheres.	Generalized seizures are conceptualized as originating at some point within and rapidly engaging bilaterally distributed networks. Such bilateral networks can include cortical and subcortical structures, but do not necessarily include the entire cortex. Generalized seizures can be asymmetric.	
Focal seizures (previously defined as partial) are those in which the first clinical and electroencephalographic changes indicate initial activation of a system of neurons limited to a part of one cerebral hemisphere.	Focal seizures are conceptualized as originating at some point within networks limited to one hemisphere. They may be discretely localized or more widely distributed. Focal seizures may originate in subcortical structures. For each seizure type, ictal onset is consistent from one seizure to another, with preferential propagation patterns that can involve the contralateral hemisphere. The Glossary of Ictal Semiology [51] Provides an initial vocabulary which, while in need of revision and expansion, is an example of the type of "dictionary" needed for discussing seizure semiology. This not only allows but requires greater precision in seizure description. Terms such as hypermotor, akinetic, versive, hemiconvulsion, and retained responsiveness or awareness communicate much more information about a patient's seizure manifestations than do the terms complex and simple partial.	
Idiopathic epilepsy: there is no underlying cause other than a possible hereditary predisposition.	Genetic epilepsy: the epilepsy is, as best as understood, the direct result of a known or presumed genetic defect(s) in which seizures are the core symptom of the disorder. This attribution must be supported by specific forms of evidence (e.g. specific molecular genetic studies or family studies).	Genetic: The epilepsy is a direct result of a genetic cause. Ideally, a gene and the mechanisms should be identified; however, this term would also apply to electroclinical syndromes for which twin or family segregation studies reproducibly show clinical evidence of a genetic basis (e.g., in the case of the genetic generalized epilepsies). At this time, channelopathies are the best example of genetic epilepsies. Ultimately, we expect causes of epilepsies to be identified by the mechanisms involved (i.e., channelopathies, mitochondrial respiratory chaindefects, etc.).
Symptomatic epilepsy: this type of epilepsy is the consequence of a known or suspected disorder of the central nervous system.	Structural and metabolic epilepsy: this type of epilepsy is the secondary result of a distinct structural or metabolic condition. These structural or metabolic disorders may be of acquired or genetic origin (as is the case for malformations of cortical development and certain metabolic disorders).	Structural-Metabolic: The epilepsy is the secondary result of a separate structural or metabolic condition. Structural and metabolic were combined to separate the concept from genetic and also because the two are often inseparable. Note that structural brain lesions, including many malformations of cortical development, often have genetic causes and most metabolic disorders are also of genetic origin. The distinction between "genetic epilepsy" and epilepsy due to a structural/metabolic cause is far from perfect, but we anticipate more specific characterizations of cause in the upcoming years.
Cryptogenic (probable symptomatic) epilepsy: this refers to a disorder whose cause is hidden or occult. Cryptogenic epilepsies are presumed to be symptomatic.	Unknown epilepsy: the nature of the underlying cause is as yet unknown; it may have a fundamental genetic basis (e.g., a previously unrecognized channelopathy) or it may be the consequence of an unrecognized structural or metabolic disorder not yet identified.	Unknown: Plain and direct, this label simply and accurately indicates ignorance and that further investigation is needed to identify the cause of the epilepsy. Unlike cryptogenic (presumed symptomatic), it makes no presumptions and requires no explanation or reinterpretation.

Generalized convulsive epileptic seizures involving bilateral motor activity

- Tonic-clonic
- Tonic
- Clonic
- Myoclonic (Jerking movements usually affecting both sides of the body)

Non-convulsive generalized epileptic seizures

- Atonic (also called 'drop attacks'—sudden and general loss of muscle tone which usually cause the animal to collapse)

Focal epileptic seizures evolving into generalized epileptic seizures

Focal epileptic seizures can spread from initial regional cerebral involvement to bilateral cerebral involvement. The seizure will start with regional motor, autonomic and/or behavioural signs and then rapidly be followed by a convulsive stage with bilateral tonic, clonic or tonic-clonic activity and loss of consciousness. This is the most common seizure type observed in the dog. The onset of the focal epileptic seizure is often very short (seconds to minutes) after which follows the secondary generalisation with convulsions. The focal epileptic seizure onset may be difficult to detect due to its brief nature. When taking the seizure history, clients should be interviewed thoroughly about what (or if something) happens before convulsions (please see De Risio et al. [49] for further information on diagnostic work-up).

The semiological description of an epileptic seizure

If classification is to be carried out according to seizure type, it makes sense to have a systematic way of describing seizures. The evolution of the seizure over time is what is important.

Phases associated with epileptic seizures

The epileptic seizure is classified as the ictus (seizure activity)—followed by a postictal phase (where the normal brain function is restored). The ictus may consist of a generalized epileptic seizure alone, a focal epileptic seizure alone, or a focal epileptic seizure which evolves into a generalized seizure. In the postictal phase, the brain restores its normal function. The postictal phase may be very short or last for several hours to days. Typically, the animal is disoriented, may have behavioural abnormalities such as repetitive vocalisation, compulsive locomotion failing to avoid obstacles, be tired, ataxic, hungry or thirsty, express a need to urinate, defecate or appear exhausted and sleep for a longer period of time. Postictal blindness or aggression may also be present.

Prodrome

In some animals (but not so common), ictus may be preceded by a so-called prodrome, a long-term (hours to days) change in disposition and indicator of forthcoming seizures. Humans may experience days of, for example, irritability, withdrawal or other emotional aberrations. In dogs the most common prodromal signs described are hours or days of restlessness, anxiousness, appear as being irritated (e.g. with uncharacteristic aggression towards other pets), or attention-seeking behaviour which is known to the owner as a long-term marker of a forthcoming seizure episode. Prodromes (if present) can represent a potential important therapeutic window for pulse therapy. Prodromal signs must be discriminated from focal seizure signs. Prodromal signs are defined by their long lasting nature whereas focal seizures which may display similar signs when they occur alone or before generalized convulsive seizures are very short (seconds to minutes).

Consciousness in focal epileptic seizures

Variable to no impairment of consciousness may appear during focal seizures. However, we propose that no attempt should be made to evaluate if consciousness is unimpaired or impaired (previously described as simple or complex focal (or partial) seizures respectively). Although animals may appear as if consciousness is impaired during focal epileptic seizures (awake but being confused, not recognizing the owner, not responding to commands) we cannot assess this objectively. It will always be a subjective interpretation in animals that cannot report what they are experiencing. Therefore it is not meaningful to subclassify focal epileptic seizures using consciousness.

Agreed modified glossary of descriptive terminology for ictal semiology in accordance with the ILAE guidelines (based on Blume et al. [51])

The glossary of descriptive terminology was discussed within the IVETF in 2014. The terms that the majority of the group (>50 % of 95%CI from 14 raters) felt could be also used to describe ictal semiology are listed below:

I. General terms

1.0 Semiology That branch of linguistics concerned with clinical signs.

2.0 Epileptic seizure Manifestation(s) of excessive synchronous, usually self-limiting epileptic activity of neurons in the brain. This results in a transient occurrence of signs which may be characterized by short episodes with convulsions or focal motor, autonomic or behavioural features and due to abnormal excessive or synchronous epileptic neuronal activity in the brain.

3.0 ICTUS A sudden neurological occurrence such as a stroke or an epileptic seizure.

4.0 Epilepsy Epilepsy is defined as a disease of the brain characterized by an enduring predisposition to generate epileptic seizures. This definition is usually practically applied as having at least two unprovoked epileptic seizures >24 h apart [48].

5.0 Focal epileptic seizures are conceptualized as originating within networks limited to one hemisphere. They may be discretely localized or more widely distributed. Focal epileptic seizures may originate in subcortical structures. For each epileptic seizure type, ictal onset is consistent from one seizure to another, with preferential propagation patterns that can involve the contralateral hemisphere [27].

6.0 Generalised epileptic seizure An epileptic seizure whose initial semiology indicates, or is consistent with, more than minimal involvement of both cerebral hemispheres. Generalized epileptic seizures are conceptualized as originating at some point within, and rapidly engaging, bilaterally distributed networks [27].

7.0 Convulsion Primarily a lay term. Episodes of excessive, abnormal muscle contractions, usually bilateral, which may be sustained or interrupted.

II. Terms describing epileptic seizure semiology

These are descriptors of seizures unless specified otherwise.

1.0 Motor Involves skeletal musculature resulting in any phenotypic manifestation. The motor event could consist of an increase (positive) or decrease (negative) in muscle contraction to produce a movement. Unless noted, the following terms are adjectives modifying "motor seizure" or "seizure" e.g. "tonic motor seizure or dystonic seizure", and whose definitions can usually be understood as prefaced by: "refers to …".

1.1.1 Tonic A sustained increase in muscle contraction lasting a few seconds to minutes.

1.1.1.2.1 Versive A sustained, forced conjugate ocular, cephalic and/or truncal rotation or lateral deviation from the midline.

1.1.1.2.2 Dystonic Sustained contractions of both agonist and antagonist muscles producing athetoid or twisting movements which when prolonged may produce abnormal postures.

1.1.2 Myoclonic (adjective); Myoclonus (noun) Sudden, brief (<100 msec) involuntary single or multiple contraction(s) of muscles(s) or muscle groups of variable topography (axial, proximal limb, distal).

1.1.2.1 Clonic Myoclonus which is regularly repetitive, involves the same muscle groups, at a frequency of about 2–3 seconds, and is prolonged. Synonym: rhythmic myoclonus.

1.1.3 Tonic-clonic A sequence consisting of a tonic followed by a clonic phase. Variants such as clonic-tonic-clonic may be seen.

1.1.3.1 Generalised tonic-clonic epileptic seizure (Formerly "Grand Mal" Seizure) Noun: Bilateral symmetrical tonic contraction then bilateral clonic contractions of somatic muscles usually associated with autonomic phenomena.

1.1.4 Atonic Sudden loss or diminution of muscle tone without an apparent preceding myoclonic or tonic event lasting one to two seconds or more, involving head, trunk, jaw or limb musculature.

1.1.5 Synchronous (Asynchronous) Motor events occurring (not) at the same time or at the same rate in sets of body parts.

1.2 Automatism Noun: A more or less coordinated, repetitive, motor activity usually occurring when cognition is impaired and for which the subject is usually amnesic afterwards. This often resembles a voluntary movement, and may consist of inappropriate continuation of ongoing preictal motor activity.

The following adjectives are usually employed to modify "automatism".

1.2.1 Oroalimentary Lip smacking, lip pursing, chewing, licking, teeth grinding or swallowing.

1.2.2 Pedal Indicates principally distal component involvement, bilateral or unilateral. Usually running movement.

2.0 Non-motor

2.1 Aura* Noun: A 'subjective' ictal phenomenon that, in a given patient, may precede an observable seizure; if alone, constitutes a sensory seizure. This can result in behavioral changes such as fear, aggression, searching behaviour, attention, body sensation.

*What is an aura? Commonly owners report that they can foresee a motor seizure when specific, and to the owner, well known signs repeatedly appear within seconds or minutes prior to convulsions. The term aura has in the past been used to describe such a forewarning of convulsions. This term originated from human epileptology where aura in early ILAE classifications was used "to denote symptomatology that encompasses subjective sensory phenomena as well as vegetative signs (for example, the epigastric sensations accompanying mesial temporal epilepsy)" and thus did not include motor phenomena. The

group recommends that the term aura is not used in veterinary medicine. The signs occurring as the first indication of seizure activity (marking the beginning of ictus) and interpreted by the dog owner as a warning sign is indeed a focal seizure onset and should be referred to as such.

2.2 Autonomic A sensation consistent with involvement of the autonomic nervous system, including cardiovascular, gastrointestinal, sudomotor, vasomotor and thermoregulatory functions. In companion animals, salivation, mydriasis, urination and/or defecation may commonly be observed.

3.0 Somatotopic modifiers

3.1 Laterality

3.1.1 Unilateral Exclusive or virtually exclusive involvement of one side as a motor, sensory or autonomic phenomenon.

3.1.1.1 HEMI- A prefix to other descriptors e.g. hemiclonic.

3.1.2 Generalised (syn. "bilateral") More than minimal involvement of each side as a motor or autonomic phenomenon.

Motor component: further modified as:

3.1.2.1 Asymmetrical Clear distinction in quantity and/or distribution of activity on the two sides.

3.1.2.2 Symmetrical Virtual bilateral equality in these respects.

3.2 Body part Refers to area involved i.e. limb, face, trunk and other.

3.2.1 Axial Involves trunk, including neck.

3.2.2 Proximal limb Signifies involvement from shoulders to metacarpus, hip to metatarsus.

3.2.3 Distal limb Indicates involvement of paws.

4.0 Modifiers and descriptors of epileptic seizure timing The following terms are listed in the form (adjective, noun, verb) according to principal usage; as adjective unless specified.

4.1 Incidence Noun: Refers to the number of epileptic seizures within a time period or the number of seizure days per unit of time.

4.1.1 Regular, irregular Consistent (inconsistent) or predictable (unpredictable, chaotic) intervals between such events.

4.1.2 Cluster Incidence of epileptic seizures within a given period (usually one or a few days) which exceeds the average of incidence over a longer period for the patient. Cluster seizures can be defined clinically as two or more seizures within a 24-h period.

4.1.3 Provocative factor Noun: Transient and sporadic endogenous or exogenous element capable of augmenting seizure incidence in the patient with chronic epilepsy and evoking seizures in susceptible non-epileptic individuals.

4.1.3.1 Reactive A reactive seizure is a seizure occurring as a natural response from the normal brain to a transient disturbance in function (metabolic or toxic in nature)—which is reversible when the cause or disturbance is rectified. A provoked seizure can be considered as being synonymous with a reactive seizure.

4.1.3.2 Reflex Objectively and consistently demonstrated to be evoked by a specific afferent stimulus or by activity of the patient. Afferent stimuli can be: elementary, i.e. unstructured (light flashes, startle, a monotone sound) or elaborate i.e. structured, (a symphony). Activity may be elementary, e.g. motor (a movement).

5.0 Duration Time between the beginning of initial epileptic seizure manifestations, such as the e.g., focal epileptic seizure signs or full body convulsions to the cessation of experienced or observed epileptic seizure activity. Does not include non-specific seizure premonitions or postictal states.

5.1 Status epilepticus An epileptic seizure which shows no clinical signs of arresting after a duration encompassing the great majority of seizures of that type in most patients or recurrent epileptic seizures without resumption of baseline central nervous system function interictally. Status epilepticus can be defined clinically as (a) greater than 5 min of continuous epileptic seizures or (b) two or more discrete epileptic seizures between which there is incomplete recovery of consciousness (for generalized convulsive seizures).

6.0 Severity A multicomponent assessment of an epileptic seizure by observers and the patient.

Components primarily of observer assessment include: duration, extent of motor involvement, impairment of interaction with environment intra-ictally, maximum number of seizures per unit of time.

7.0 Prodrome A pre-ictal phenomenon. A subjective or objective clinical alteration that heralds the onset of an epileptic seizure but does not form part of it. Prodrome is a long lasting event (hours to days) and should not be confused with focal onset seizure signs which are very brief events (seconds to minutes).

8.0 Postictal phenomenon A transient clinical abnormality of central nervous system function that appears or becomes accentuated when clinical signs of the ictus have ended.

8.1 Lateralising (TODD'S (or bravais')) phenomenon Any unilateral postictal dysfunction relating to motor, somatosensory and/or integrative functions including visual, auditory or somatosensory.

8.1 Non-lateralising phenomenon Behavioural changes such as fear, aggression, increased appetite.

Abbreviations

IVETF: International Veterinary Epilepsy Task Force; ILAE: International League Against Epilepsy.

Competing interests

Following reimbursements, fees and funding have been received by the authors in the last three years and have been declared in the competing interest section. CR, RGF, HAV, KM and JP have received fees for acting as a consultant for Boehringer Ingelheim (KM, MP: consultancy during development and approval of imepitoin; CR: pain consultancy; RGF, JP, HAV: consultancy pre and post launch of imepitoin). AT has been an advisor for Boehringer Ingelheim. SFMB, HAV and AT have been responsible principal investigator of several research studies concerning imepitoin financed by Boehringer Ingelheim. SFMB, HAV, JP, HP, MB, CR and AF received speaking fees from Boehringer Ingelheim. HP received consulting and speaking fees and funding for a collaborative project from Eisai Co. LTD. HAV received funding for a collaborative project from Desitin and Nestlé Purina Research. AF and LDR received reimbursements from Boehringer Ingelheim. LDR has received consulting and speaking fees from Vetoquinol. MP has received consultant fees for Aratana. The other authors declared that they have no competing interests.

Authors' contributions

MB chaired the classification, definition and terminology working group (MB, RGF, PJJM, AP) and wrote the first draft of the consensus paper with the help of RGF, PJJM, AP and HAV. HAV designed and analysed the questionnaire to facilitate the discussion about the definitions listed in the glossary. All authors read, critiqued, commented and approved the final manuscript.

Authors' information

Chair of IVETF: Holger A Volk, Department of Clinical Science and Services, Royal Veterinary College, Hatfield, Hertfordshire, UK; hvolk@rvc.ac.uk.
All other co-authors are members of IVETF, are listed alphabetically and have approved the consensus statements.

Acknowledgements

The authors are grateful to all owners of epileptic pets and veterinary colleagues who have inspired the group to create consensus statements. We thank all the breeders and breed clubs for their support. We would especially like to thank Professor Simon Shorvon for the critical review of the consensus statements. His great insight has been immensely helpful. The authors also would like to thank the research office for assessing the manuscript according to the Royal Veterinary College's code of good research practice (Authorisation Number – CCS_ 01023). This study was not financially supported by any organization or grant.
Other members of the classification, definition and terminology working group (alphabetically listed).

Author details

[1]Department of Veterinary Clinical and Animal Sciences, Faculty of Health and Medical Sciences, University of Copenhagen, Frederiksberg C, Denmark. [2]Fernside Veterinary Centre, 205 Shenley Road, Borehamwood, SG9 0TH Hertfordshire, UK. [3]Department of Clinical Sciences of Companion Animals, Utrecht University, Yalelaan 108, 3583 CM Utrecht, The Netherlands. [4]Clinical Unit of Internal Medicine Small Animals, University of Veterinary Medicine, Veterinärplatz 1, 1210 Vienna, Austria. [5]Department of Small Animal Medicine and Clinical Biology, Faculty of Veterinary Medicine, Ghent University, Salisburylaan 133, Merelbeke 9820, Belgium. [6]Animal Health Trust, Lanwades Park, Kentford, Newmarket, CB8 7UU Suffolk, UK. [7]Centre for Clinical Veterinary Medicine, Ludwig-Maximilians-University, Veterinärstr. 13, 80539 Munich, Germany. [8]University of Melbourne, 250 Princes Highway, Weibee, 3015 Victoria, Australia. [9]Section of Clinical & Comparative Neuropathology, Centre for Clinical Veterinary Medicine, Ludwig-Maximilians-University, Veterinärstr. 13, 80539 Munich, Germany. [10]Department of Clinical Sciences, College of Veterinary Medicine, North Carolina State University, 1052 William Moore Drive, Raleigh, NC 27607, USA. [11]University of Minnesota College of Veterinary Medicine, D426 Veterinary Medical Center, 1352 Boyd Avenue, St. Paul, MN 55108, USA. [12]Vet Extra Neurology, Broadleys Veterinary Hospital, Craig Leith Road, Stirling, FK7 7LE Stirlingshire, UK. [13]College of Veterinary Medicine, University of Georgia, 501 DW Brooks Drive, Athens, GA 30602, USA. [14]Chicago Veterinary Neurology and Neurosurgery, 3123 N. Clybourn Avenue, Chicago, IL 60618, USA. [15]Department of Pharmacology, Toxicology and Pharmacy, Ludwig-Maximillians-University, Königinstr. 16, 80539 Munich, Germany. [16]Department of Animal Medicine and Surgery, Veterinary Faculty, Universitat Autònoma de Barcelona, Campus UAB, Bellaterra, 08193 Barcelona, Spain. [17]Fitzpatrick Referrals, Halfway Lane, Eashing, Godalming, GU7 2QQ Surrey, UK. [18]School of Veterinary Medicine, Faculty of Health & Medical Sciences, University of Surrey, Guildford, GU2 7TE Surrey, UK. [19]Department of Small Animal Medicine and Surgery, University of Veterinary Medicine Hannover, Bünteweg 9, 30559 Hannover, Germany. [20]Department of Clinical Science and Services, Royal Veterinary College, Hatfield, AL9 7TA Hertfordshire, UK.

Received: 3 June 2015 Accepted: 29 June 2015
Published online: 28 August 2015

References

1. Jokinen TS, Metsähonkala L, Bergamasco L, Viitmaa R, Syrjä P, Lohi H, et al. Benign familial juvenile epilepsy in Lagotto Romagnolo dogs. J Vet Intern Med. 2007;21(3):464–71.
2. Seppala EH, Jokinen TS, Fukata M, Fukata Y, Webster MT, Karlsson EK, et al. LGI2 truncation causes a remitting focal epilepsy in dogs. PLoS Genet. 2011;7(7):e1002194.
3. Seppala EH, Koskinen LLE, Gulløv CH, Jokinen P, Karlskov-Mortensen P, Bergamasco L, et al. Identification of a novel idiopathic epilepsy locus in Belgian Shepherd dogs. PLoS One. 2012;7(3):e33549.
4. Stassen W, van Steenbeek F, van Rhijn N, Tenwolde R, Leegwater P. Identification of a novel epilepsy gene in Boerboel dogs. J Vet Intern Med. 2013;27:30.
5. Shorvon S. The concept of symptomatic epilepsy and the complexities of assigning cause in epilepsy. Epilepsy Behav. 2014;32C:1–8.
6. Kearsley-Fleet L, O'Neill DG, Volk HA, Church DB, Brodbelt DC. Prevalence and risk factors for canine epilepsy of unknown origin in the UK. Vet Rec. 2013;172(13):338.
7. Heske L, Nodtvedt A, Jaderlund KH, Berendt M, Egenvall A. A cohort study of epilepsy among 665,000 insured dogs: incidence, mortality and survival after diagnosis. Vet J. 2014;202(3):471–6.
8. Famula TR, Oberbauer AM, Brown KN. Heritability of epileptic seizures in the Belgian tervueren. J Small Anim Pract. 1997;38(8):349–52.
9. Jaggy A, Faissler D, Gaillard C, Srenk P, Graber H. Genetic aspects of idiopathic epilepsy in Labrador retrievers. J Small Anim Pract. 1998;39(6):275–80.
10. Kathmann I, Jaggy A, Busato A, Bartschi M, Gaillard C. Clinical and genetic investigations of idiopathic epilepsy in the Bernese mountain dog. J Small Anim Pract. 1999;40(7):319–25.
11. Nielen AL, Knol BW, van Hagen MA, van der Gaag I. Genetic and epidemiological investigation of a birth cohort of boxers. Tijdschr Diergeneeskd. 2003;128(19):586–90.
12. Berendt M, Gredal H, Pedersen LG, Alban L, Alving J. A cross-sectional study of epilepsy in Danish Labrador Retrievers: prevalence and selected risk factors. J Vet Intern Med. 2002;16(3):262–8.
13. Patterson EE, Mickelson JR, Da Y, Roberts MC, McVey AS, O'Brien DP, et al. Clinical characteristics and inheritance of idiopathic epilepsy in Vizslas. J Vet Intern Med. 2004;17(3):319–25.
14. Patterson EE, Armstrong PJ, O'Brien DP, Roberts MC, Johnson GS, Mickelson JR. Clinical description and mode of inheritance of idiopathic epilepsy in English springer spaniels. J Am Vet Med Assoc. 2005;226(1):54–8.
15. Casal ML, Munuve RM, Janis MA, Werner P, Henthorn PS. Epilepsy in Irish Wolfhounds. J Vet Intern Med. 2006;20(1):131–5.
16. Berendt M, Gulløv CH, Christensen SLK, Gudmundsdottir H, Gredal H, Fredholm M, et al. Prevalence and characteristics of epilepsy in the Belgian shepherd variants Groenendael and Tervueren born in Denmark 1995–2004. Acta Vet Scand. 2008;50:51.

17. Kloene J, Sewell A, Hamann H, Distl O, Tipold A. Klinische Untersuchungen zu Krampfanfällen bei Border Terriern. Kleintierpraxis. 2008;8(1):5–12.
18. Berendt M, Gulløv CH, Fredholm M. Focal epilepsy in the Belgian shepherd: evidence for simple Mendelian inheritance. J Small Anim Pract. 2009;50(12):655–61.
19. Gulløv CH, Toft N, Baadsager MMN, Berendt M. Epilepsy in the Petit Basset Griffon Vendeen: Prevalence, Semiology, and Clinical Phenotype. J Vet Intern Med. 2011;25(6):1372–8.
20. Oberbauer A, Grossman D, Irion D, Schaffer A, Eggleston M, Famula T. The genetics of epilepsy in the Belgian tervuren and sheepdog. J Heredity Vol. 2003;94:57–63.
21. Oberbauer AM, Belanger JM, Grossman DI, Regan KR, Famula TR. Genome-wide linkage scan for loci associated with epilepsy in Belgian shepherd dogs. BMC Genet. 2010;11:35.
22. Ekenstedt KJ, Oberbauer AM. Inherited Epilepsy in Dogs. Top Companion Anim Med. 2013;28(2):51–8.
23. Hülsmeyer V, Zimmermann R, Brauer C, Sauter-Louis C, Fischer A. Epilepsy in Border Collies: clinical manifestation, outcome, and mode of inheritance. J Vet Intern Med. 2010;24(1):171–8.
24. Weissl J, Hulsmeyer V, Brauer C, Tipold A, Koskinen LL, Kyöstilä K, Lohi H, Sauter-Louis C, Wolf M, Fischer A. Disease Progression and Treatment Response of Idiopathic Epilepsy in Australian Shepherd Dogs. J Vet Int Med 2012;26:116-125.
25. Licht BG, Lin S, Luo Y, Hyson LL, Licht MH, Harper KM, et al. Clinical characteristics and mode of inheritance of familial focal seizures in Standard Poodles. J Am Vet Med Assoc. 2007;231(10):1520–8.
26. Hülsmeyer VI, Fischer A, Mandigers P, DeRisio L, Berendt M, Rusbridge C, et al. Current evidence for idiopathic epilepsy in purebred dogs. BMC veterinary research 2015. (In press).
27. Berg AT, Berkovic SF, Brodie MJ, Buchhalter J, Cross JH, Van Emde BW, et al. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005–2009. Epilepsia. 2010;51(4):676–85.
28. Berg AT, Scheffer IE. New concepts in classification of the epilepsies: Entering the 21st century. Epilepsia. 2011;52(6):1058–62.
29. Shorvon SD. The etiologic classification of epilepsy. Epilepsia. 2011;52(6):1052–7.
30. Fisher RS, Van Emde BW, Blume W, Elger C, Genton P, Lee P, et al. Epileptic seizures and epilepsy: definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). Epilepsia. 2005;46(4):470–2.
31. Proposal for revised clinical and electroencephalographic classification of epileptic seizures. From the Commission on Classification and Terminology of the International League Against Epilepsy. Epilepsia 1981. 22(4):489–501.
32. Proposal for revised classification of epilepsies and epileptic syndromes. Commission on Classification and Terminology of the International League Against Epilepsy. Epilepsia 1989. 30(4):389–399.
33. Guidelines for epidemiologic studies on epilepsy. Commission on Epidemiology and Prognosis, International League Against Epilepsy. Epilepsia 1993. 34(4):592–596.
34. Proposal for classification of epilepsies and epileptic syndromes. Commission on Classification and Terminology of the International League Against Epilepsy. Epilepsia 1985. 26(3):268–278.
35. Berendt M, Gram L. Epilepsy and seizure classification in 63 dogs: a reappraisal of veterinary epilepsy terminology. J Vet Intern Med. 1999;13(1):14–20.
36. Podell M: Seizures. In: BSAVA Manual of Canine and Feline Neurology. edn. Edited by Platt S, Olby N. BSAVA; 2013. 117–135.
37. Mariani CL. Terminology and Classification of Seizures and Epilepsy in Veterinary Patients. Top Companion Anim Med. 2013;28(2):34–41.
38. Licht BG, Licht MH, Harper KM, Lin S, Curtin JJ, Hyson LL, et al. Clinical presentations of naturally occurring canine seizures: similarities to human seizures. Epilepsy Behav. 2002;3(5):460–70.
39. Srenk P, Jaggy A. Interictal electroencephalographic findings in a family of golden retrievers with idiopathic epilepsy. J Small Anim Pract. 1996;37(7):317–21.
40. Podell M, Fenner WR, Powers JD. Seizure classification in dogs from a nonreferral-based population. J Am Vet Med Assoc. 1995;206(11):1721–8.
41. Heynold Y, Faissler D, Steffen F, Jaggy A. Clinical, epidemiological and treatment results of idiopathic epilepsy in 54 labrador retrievers: a long-term study. J Small Anim Pract. 1997;38(1):7–14.
42. Jaggy A, Bernardini M. Idiopathic epilepsy in 125 dogs: a long-term study. Clinical and electroencephalographic findings. J Small Anim Pract. 1998;39(1):23–9.
43. Morita T, Shimada A, Takeuchi T, Hikasa Y, Sawada M, Ohiwa S, et al. Cliniconeuropathologic findings of familial frontal lobe epilepsy in Shetland sheepdogs. Can J Vet Res. 2002;66(1):35–41.
44. Chang Y, Mellor DJ, Anderson TJ. Idiopathic epilepsy in dogs: owners' perspectives on management with phenobarbitone and/or potassium bromide. J Small Anim Pract. 2006;47(10):574–81.
45. Volk HA, Matiasek LA, Luján Feliu-Pascual A, Platt SR, Chandler KE. The efficacy and tolerability of levetiracetam in pharmacoresistant epileptic dogs. Vet J. 2008;176(3):310–9.
46. Pákozdy A, Leschnik M, Tichy AG, Thalhammer JG. Retrospective clinical comparison of idiopathic versus symptomatic epilepsy in 240 dogs with seizures. Acta Vet Hung. 2008;56(4):471–83.
47. Beghi E. New classification proposals for epilepsy: a real advancement in the nosography of the disease? Epilepsia. 2011;52(6):1197–8. discussion 1205–1199.
48. Fisher RS, Acevedo C, Arzimanoglou A, Bogacz A, Cross JH, Elger CE, et al. ILAE Official Report: A practical clinical definition of epilepsy. Epilepsia. 2014;55(4):475–82.
49. De Risio L, Bhatti S, Muñana KR, Penderis J, Stein VM, Tipold A, et al. International Veterinary Epilepsy Task Force Consensus Proposal: Diagnostic approach to epilepsy in dogs. BMC veterinary research 2015.
50. Lohi H, Young EJ, Fitzmaurice SN, Rusbridge C, Chan EM, Vervoort M, et al. Expanded repeat in canine epilepsy. Science. 2005;307(5706):81.
51. Blume WT, Lüders HO, Mizrahi E, Tassinari C, van Emde BW, Engel J. Glossary of descriptive terminology for ictal semiology: report of the ILAE task force on classification and terminology. Epilepsia. 2001;42(9):1212–8.

De Risio et al. BMC Veterinary Research (2015) 11:148
DOI 10.1186/s12917-015-0462-1

BMC Veterinary Research

CORRESPONDENCE Open Access

International veterinary epilepsy task force consensus proposal: diagnostic approach to epilepsy in dogs

Luisa De Risio[1*], Sofie Bhatti[2], Karen Muñana[3], Jacques Penderis[4], Veronika Stein[5], Andrea Tipold[5], Mette Berendt[6], Robyn Farqhuar[7], Andrea Fischer[8], Sam Long[9], Paul JJ. Mandigers[10], Kaspar Matiasek[11], Rowena MA Packer[12], Akos Pakozdy[13], Ned Patterson[14], Simon Platt[15], Michael Podell[16], Heidrun Potschka[17], Martí Pumarola Batlle[18], Clare Rusbridge[19,20] and Holger A. Volk[12]

Abstract

This article outlines the consensus proposal on diagnosis of epilepsy in dogs by the International Veterinary Epilepsy Task Force. The aim of this consensus proposal is to improve consistency in the diagnosis of epilepsy in the clinical and research settings. The diagnostic approach to the patient presenting with a history of suspected epileptic seizures incorporates two fundamental steps: to establish if the events the animal is demonstrating truly represent epileptic seizures and if so, to identify their underlying cause. Differentiation of epileptic seizures from other non-epileptic episodic paroxysmal events can be challenging. Criteria that can be used to make this differentiation are presented in detail and discussed. Criteria for the diagnosis of idiopathic epilepsy (IE) are described in a three-tier system. Tier I confidence level for the diagnosis of IE is based on a history of two or more unprovoked epileptic seizures occurring at least 24 h apart, age at epileptic seizure onset of between six months and six years, unremarkable inter-ictal physical and neurological examination, and no significant abnormalities on minimum data base blood tests and urinalysis. Tier II confidence level for the diagnosis of IE is based on the factors listed in tier I and unremarkable fasting and post-prandial bile acids, magnetic resonance imaging (MRI) of the brain (based on an epilepsy-specific brain MRI protocol) and cerebrospinal fluid (CSF) analysis. Tier III confidence level for the diagnosis of IE is based on the factors listed in tier I and II and identification of electroencephalographic abnormalities characteristic for seizure disorders. The authors recommend performing MRI of the brain and routine CSF analysis, after exclusion of reactive seizures, in dogs with age at epileptic seizure onset <6 months or >6 years, inter-ictal neurological abnormalities consistent with intracranial neurolocalisation, status epilepticus or cluster seizure at epileptic seizure onset, or a previous presumptive diagnosis of IE and drug-resistance with a single antiepileptic drug titrated to the highest tolerable dose.
This consensus article represents the basis for a more standardised diagnostic approach to the seizure patient. These recommendations will evolve over time with advances in neuroimaging, electroencephalography, and molecular genetics of canine epilepsy.

Keywords: Dog, Seizure, Epilepsy, Idiopathic epilepsy, Diagnosis

* Correspondence: luisa.derisio@aht.org.uk
[1]Animal Health Trust, Lanwades Park, Kentford, Newmarket, CB8 7UU Suffolk, UK
Full list of author information is available at the end of the article

Background

An epileptic seizure is "a transient occurrence of signs due to abnormal excessive or synchronous neuronal activity in the brain" [1] which may manifest in different ways and may be caused by a variety of underlying aetiologies. Epilepsy is defined as a disease of the brain characterized by an enduring predisposition to generate epileptic seizures. This definition is usually practically applied as the occurrence of two or more unprovoked epileptic seizures at least 24 h apart [2].

The term idiopathic epilepsy (IE) has been used in a variety of settings in the veterinary literature and by veterinarians in clinical practice. Analogous with a recently debated proposal for a revised classification by the International League against Epilepsy (ILAE) [3], it has also been proposed that the term idiopathic should be replaced in the veterinary literature [4]. The term genetic epilepsy was therefore introduced to refer to epilepsy occurring as a direct result of a known or strongly suspected genetic defect (or defects) and in which epileptic seizures are the primary clinical sign of the disorder. In general, genetic epilepsies usually have no identifiable structural brain lesions or other neurologic deficits, and have an age-dependent onset. The term unknown epilepsy has been proposed to refer to epilepsy where the underlying cause is unknown [3, 4]. However, a more recent review article discussed how the substitution of the term 'idiopathic' with 'genetic' may be misleading and idiopathic epilepsy was defined as an epilepsy of predominantly genetic or presumed genetic origin in which there were no gross neuroanatomic or neuropathologic abnormalities nor other relevant underlying diseases [5]. In our consensus proposal on classification and terminology (see consensus on epilepsy definition, classification and terminology in companion animals) we have explained why we recommend retaining the term IE, and have defined IE as a disease in its own right, *per se*. A genetic origin of IE is supported by genetic testing (when available) and a genetic influence is supported by a high breed prevalence (>2 %), genealogical analysis and/or familial accumulation of epileptic individuals. However in the clinical setting IE remains most commonly a diagnosis of exclusion following diagnostic investigations for causes of reactive seizures and structural epilepsy.

To date different criteria have been used in the veterinary literature to diagnose IE. The majority of veterinary studies have used a history of recurrent epileptic seizures, an unremarkable inter-ictal clinical and neurological examination and an unremarkable complete blood cell count and serum biochemistry profile as the minimum criteria for its diagnosis. However, the exact parameters included in the biochemistry profile vary among studies and institutions. Age at seizure onset has not been consistently used as a diagnostic criteria, and when used the age range has varied, most commonly being 1 to 5 years, 6 months to 5 years or 6 months to 6 years. An unremarkable magnetic resonance imaging (MRI) study of the brain and cerebrospinal fluid (CSF) analysis have been used inconsistently as diagnostic criteria and there has been wide variability in MRI protocols. To further support the diagnosis of IE, particularly when brain MRI was not performed, a minimum follow-up period ranging from 1 to 3 years without the development of inter-ictal neurological deficits has also been suggested [6–8].

To improve consistency in the diagnosis of IE amongst institutions and clinical studies we have produced the following consensus proposal.

Criteria for the diagnosis of epileptic seizures

The diagnostic approach to the patient presenting with a history of suspected epileptic seizures incorporates two fundamental steps:

1. Establish if the events the animal is demonstrating truly represent epileptic seizures or are consistent with a different episodic paroxysmal disorder.
2. Identify the underlying cause of the epileptic seizure.

1. Is the animal having epileptic seizures?

First of all the clinician needs to determine whether the dog is indeed having epileptic seizures. A detailed and accurate history is the foundation for investigation of the seizure patient [9]. The owner of the epileptic dog should complete a standardised epilepsy questionnaire (Additional file 1) and obtain video-footage whenever possible. This information can help the clinician to clarify the nature of the event (*e.g.,* epileptic seizure versus other episodic paroxysmal event) and its phenotype. Numerous disorders can result in episodic paroxysmal events that may mimic epileptic seizures. A detailed review of paroxysmal movement disorders as well as other events which may mimic epileptic seizures is beyond the scope of this consensus article and can be found elsewhere [10, 11]. The main focus of this section of our consensus article is the criteria allowing differentiation of epileptic seizures from other non-epileptic episodic paroxysmal events (Table 1).

A complete clinical and neurological examination may help identify abnormalities suggestive of underlying disease processes, including cardiovascular system abnormalities in dogs with syncope and clinical signs of neuromuscular disease, vestibular dysfunction or forebrain disease.

Paroxysmal movement disorders or paroxysmal dyskinesias refer to abnormal, sudden, involuntary contraction of a group of skeletal muscles which recur episodically [10]. These paroxysms can be challenging to differentiate from

Table 1 Clinical characteristics of episodic disorders

Discriminator	Syncope	Narcolepsy/ Cataplexy	Neuromuscular weakness	Paroxysmal behaviour changes (compulsive disorder)	Vestibular attack	Paroxysmal Dyskinesia	Idiopathic head tremor	Seizure
Clinical status between episodes	Normal or arrhythmia, pulse deficits, heart murmur, cyanosis, abnormal lung auscultation	Altered sleep/wake cycle, normal clinical examination	Normal or generalised weakness, muscle atrophy, pain, decreased reflexes	Normal	Normal	Normal	Normal	Normal or forebrain signs
Precipitating event or trigger	Exercise, excitement	Excitement, eating	Activity, exercise	Behavioural triggers (*e.g.,* fear)	None	None or activity, exercise, excitement, stress	None or stress, fatigue, overstimulation	None or flashing lights, anxiety, stress
Pre-event changes	None	None	None	None	None	None	None	Pre-ictal signs may be observed including: anxiety, restlessness, increased affection, contact-seeking, withdrawal, hiding, aggressiveness, and vocalization
Event description	Brief, sudden collapse and rapid recovery	Sudden collapse	Stiff, stilted gait prior to collapse	Pacing, barking, licking, chasing imaginary objects or tail, chewing objects	Head tilt, nystagmus, vestibular ataxia, collapse towards side of head tilt	Dystonia, chorea, ballismus, athetosis, tremors, impaired posture, inability to stand or walk	Vertical or horizontal rhythmic head movement	Depending on seizure focus, focal or generalized, tonic-clonic movements most common
Level of consciousness	Reduced to absent	Normal if only cataplexy. Absent (asleep) in narcolepsy	Normal	Normal	Normal or disorientated	Normal	Normal	Often impaired
Autonomic signs	Possible abnormalities of heart rate and rhythm	None	None	None	None	None	None	Possible: hypersalivation, defaecation, urination
Muscle tone	Flaccid (all body)	Flaccid (all body)	Often flaccid (can appear spastic with certain myopathies)	Normal	Unilateral decrease in extensor muscle tone	Hypertonicity (focal or generalised)	Normal	Typically increased: tonic (hypertonicity) or alternating tonic-clonic movements
Lateralising signs	No	No	No	No	Yes	Possible	No	Possible
Duration	Seconds	Seconds to minutes	Minutes to hours	Minutes to hours	Seconds to hours	Seconds to hours	Seconds to hours	Seconds to minutes or > 5 min in case of status epilepticus

Table 1 Clinical characteristics of episodic disorders *(Continued)*

Post-episodic changes	None	None	None	None	None	None or tiredness	None, tiredness, or restlessness	Post-ictal signs frequently occur including: disorientation, aggressive behaviour, restlessness, pacing, lethargy, deep sleep, hunger, thirst, ataxia, proprioceptive deficits, and blindness
Further comments	May be accompanied by cough, increased respiratory noise	Often occurs in young purebred dogs.	May be accompanied by dysphagia, dysphonia, regurgitation, dyspnoea	History of anxiety disorder	Subtle signs of vestibular disease might persist	Interaction with the owner can alleviate or interrupt the episode. Consider breed specific disorders and age at onset.	Episodes can be interrupted by the owner	Facial muscles often involved during the ictus

epileptic seizures, particularly from focal motor epileptic seizures. Animals affected by movement disorders are often normal between episodes. The absence of other clinical signs during the episodes, including autonomic signs, changes in consciousness and electroencephalographic abnormalities, have been suggested to support the diagnosis of paroxysmal movement disorders [10]. However, focal epileptic seizures can occur with no concurrent alteration in consciousness or autonomic signs and electroencephalography (EEG) is often challenging to perform in the clinical setting. In a recent study evaluating the diagnostic utility of inter-ictal short time EEG recordings in epileptic dogs under general anaesthesia with propofol and the muscle relaxant rocuronium bromide, interictal paroxysmal epileptiform activity was detected in only 25 % of IE dogs [12]. The signalment and age at onset of the paroxysmal event can assist in establishing the nature of these events. Certain movement disorders are breed-specific, generally occur in young dogs and their phenotype may be well characterised [10]. To date the associated genetic defect (*e.g.,* deletion in the gene *BCAN*) has been identified only in Cavalier King Charles spaniels with paroxysmal exercise-induced dyskinesia (also known as episodic falling) [13, 14]. Genetic investigations in other breeds are ongoing. Identification of causative genetic mutations of breed specific movement disorders will significantly improve our ability to diagnose these conditions. Interestingly, specific mutations in human patients with dyskinesias may also be associated with epileptic seizures or a high occurrence of seizure disorders in their relatives [15].

A genetic predisposition to IE has been suggested in numerous canine breeds [16] and a familial history of recurrent epileptic seizures or IE should raise the suspicion of IE, although diagnostic procedures need to be performed to exclude other aetiologies. Generalised epileptic seizures typically occur at rest or during sleep, last less than 5 min and are usually followed by abnormal clinical manifestations (post-ictal signs) including disorientation, restlessness, pacing, lethargy, deep sleep, hunger, thirst, ataxia, proprioceptive deficits, and less commonly, aggressive behaviour and blindness. The presence of impaired consciousness (*e.g.,* altered awareness and responsiveness to the environment and stimuli), oro-facial muscle involvement, autonomic signs and convulsions during the ictus all support the classification of the episodes as epileptic seizures. During the ictus (particularly during the generalized epileptic seizure phase) the animal cannot be distracted and the owner cannot alter the course of the event by manipulating the dog. Conversely, dogs with paroxysmal movement disorders tend to continue to attempt to perform the activity they were previously doing (*e.g.,* playing) during the paroxysmal event and owner intervention may alter the course of the episode. For example, in the majority of Dobermanns with idiopathic head tremor, the owners reported that they could consistently interrupt each head tremor episode. In some cases, stroking the dogs, talking to them, or asking them to get up was sufficient to interrupt the episode. In other cases, stronger stimuli (favourite toys or snacks, encouraging them, taking them for a walk) were needed to interrupt the head tremor episode [17]. Similarly in a study in English bulldogs with idiopathic head tremors, several owners reported that distraction or treats were generally sufficient to alter or stop the episodes [18].

A recent study highlighted the challenge in differentiating epileptic and non-epileptic paroxysmal events. This study investigated the level of agreement between veterinarians (both neurology specialists and non-specialists) in the description and classification of videos depicting canine and feline paroxysmal events, where the observers were blinded to the history, results of diagnostic investigations and treatment response [19]. The level of agreement on whether a paroxysmal event was an epileptic seizure or other paroxysm was fair. Overall agreement on epileptic seizure type was moderate. Generalised epileptic seizures had the highest level of agreement and focal epileptic seizures had the lowest. Agreement was fair for level of consciousness and the presence of autonomic signs, but poor for neurobehavioral signs. Agreement for motor signs ranged from poor to moderate. There were significant differences in epileptic seizure semiology and classification between specialists and non-specialists.

Absolute confirmation of the epileptic nature of an event can only be obtained by observing simultaneously the characteristic EEG changes and physical manifestation of the seizures, however this is rarely practical in veterinary medicine and currently there is no reliable, standard protocol for acquiring EEG recordings in dogs. Physiological artifacts (*e.g.,* muscle contractions, electrocardiogram, electrooculogram) and physical factors (*e.g.,* EEG instrumentation, electrode type and montage, methods of patient restraint) affect acquisition and interpretation of EEG tracings [20]. Variability in the physical factors mentioned above has contributed to discrepancies in the results of numerous veterinary studies evaluating EEG. Efforts are currently in progress to further develop EEG recording in veterinary clinical practice. Although it is unlikely that EEG will become a routine diagnostic procedure for all epileptic dogs in the near future, EEG may become more widely used by veterinary neurology specialists for the investigation of selected cases (*e.g.,* dogs in which a diagnosis of epilepsy versus other episodic paroxysmal disorder is particularly challenging). As an example, a veterinary video-EEG study diagnosed a juvenile Chihuahua with subtle myoclonic

absence events with perioral myoclonia and head twitching [21]. The author identified bilateral generalised synchronous 4Hz spike-and-wave complexes on ictal EEG time locked with the "absence-like" event, along with rhythmically correlated head and nose twitching. In this case video-EEG was essential to confirm the epileptic nature of the episodes. Currently the paucity of veterinary literature does not allow a clear consensus recommendation for EEG recording in veterinary patients to be proposed.

2. What is the cause of the epileptic seizure?

After having established that the episodic paroxysmal events do indeed represent epileptic seizures, the next step is to determine the underlying cause as this will have major implications on treatment selection and prognosis. Both intra and extra cranial disorders can cause seizure activity.

Reactive seizures Reactive seizures can result from systemic metabolic disorders (*e.g.,* hypoglycaemia, electrolyte disorders, portosystemic shunt resulting in hepatic encephalopathy) or from intoxications (*e.g.,* carbamates, organophosphates, lead poisoning, ethylene glycol toxicity, metaldehyde, strychnine). The history and clinical presentation may help the clinician to suspect a particular aetiology, although diagnosing certain intoxications can be quite challenging. In a recent study the most frequent cause of reactive seizures were intoxications (39 %, 37/96 of dogs) and hypoglycaemia (32 %, 31/96 of dogs) [22]. In this study, 41 % (39/96) of dogs were presented in status epilepticus [22]. Another study showed that dogs with reactive seizures caused by exogenous toxicity have a significantly higher risk of developing status epilepticus, particularly as first manifestation of a seizure disorder, than dogs with other seizure aetiologies [23]. Dogs with poisoning had a 2.7 times higher risk of presenting in status epilepticus at seizure onset than dogs with IE or structural epilepsy [23]. The clinical presentation in dogs with metabolic and toxic disorders is variable and depends on the underlying aetiology. Toxic disorders often have an acute (< 24 h) onset and neurological signs may be preceded or accompanied by gastrointestinal, cardiovascular or respiratory signs. Dependent on the specific toxin, muscle tremors and fasciculations are frequently the initial clinical signs. Metabolic disorders can present with an acute, subacute, or chronic onset and may be progressive or relapsing and remitting. For example, chronic lead intoxication may result in recurrent seizures. Systemic clinical abnormalities can often be detected on general physical examination. Generally neurological examination reveals deficits consistent with diffuse, bilateral and often symmetrical forebrain involvement.

Structural epilepsy Structural forebrain disorders resulting in epileptic seizures include a large array of conditions including vascular, inflammatory/ infectious, traumatic, anomalous/ developmental, neoplastic and degenerative diseases. Neurological examination is often abnormal and may reveal asymmetric neurological deficits in dogs with lateralised brain pathology. In a recent study, 47 % of dogs with lateralised structural cerebral lesions had asymmetrical neurological deficits and 55 % of dogs with symmetrical structural brain lesions had symmetrical neurological deficits identified on neurological examination [24]. Dogs with inter-ictal neurological abnormalities were 16.5 times more likely to have an asymmetrical structural cerebral lesion and 12.5 times more likely to have a symmetrical structural cerebral lesion than IE [24]. A normal inter-ictal neurological examination, however, does not completely rule out structural epilepsy as focal lesions in particular areas of the forebrain, such as the olfactory bulb, frontal and pyriform lobes ("clinically silent regions") can result in epileptic seizures without any other neurological signs. Indeed, in the study mentioned above, 23 % (34/146) of dogs with structural epilepsy had a normal neurological examination in the inter-ictal period. In a study on risk factors for development of epileptic seizures in dogs with intracranial neoplasia, an epileptic seizure was the first sign of intracranial disease noted by the owners in 76 % of dogs and dogs with frontal lobe neoplasia were more likely to develop epileptic seizures than dogs with neoplasia in other intracranial locations [25].

The inter-ictal neurological status has been combined with the dog's age at epileptic seizure onset in an attempt to predict the probability of identifying structural cerebral disorders in dogs presenting with recurrent epileptic seizures (see section below on recommendation on when to perform MRI of the brain).

Epileptic seizure type (*e.g.,* focal versus generalised) should not be used as an isolated variable to predict the presence of structural cerebral disease. Indeed focal epileptic seizures have been reported in dogs with IE [26–29] and in a recent study the prevalence of generalised epileptic seizures was similar between dogs with IE (77 %) and dogs with asymmetrical structural cerebral lesion (79 %) [24]. Furthermore, in a study in dogs with epileptic seizures associated with intracranial neoplasia, 93 % of dogs had generalised epileptic seizures and 7 % had focal epileptic seizures [25]. A detailed description of diagnosis of exogenous toxic, metabolic and structural forebrain disorders is beyond the scope of this consensus article and can be found elsewhere [30–32].

Idiopathic epilepsy The diagnosis of IE is one of exclusion and is made based on the age at epileptic seizure onset, unremarkable inter-ictal physical and neurological examinations, and exclusion of metabolic, toxic and

structural cerebral disorders by means of diagnostic investigations. A history of IE in genetically related dogs further supports the diagnosis.

The dog's age range at seizure onset has been evaluated in various studies in order to predict the likelihood of diagnosing IE (see *recommendation on when to perform MRI of the brain*).

Criteria for the diagnosis of Idiopathic epilepsy

Tier I confidence level for the diagnosis of IE

A history of two or more unprovoked epileptic seizures occurring at least 24 h apart, age at epileptic seizure onset of between 6 months and 6 years, unremarkable inter-ictal physical and neurological examination (except for antiepileptic drug (AED) induced neurologic abnormalities and post-ictal neurologic deficits), and no clinically significant abnormalities on minimum data base (MDB) blood tests and urinalysis. MDB blood tests include: complete blood cell count (CBC), serum biochemistry profile (sodium, potassium, chloride, calcium, phosphate, alanine aminotransferase (ALT), alkaline phosphatise (ALP), total bilirubin, urea, creatinine, total protein, albumin, glucose, cholesterol, triglycerides, and fasting bile acids and/or ammonia). Urinalysis includes specific gravity, protein, glucose, pH, and sediment cytology. A family history of IE further supports the diagnosis.

Dogs with suspected AED-induced neurologic abnormalities and/ or postictal neurologic deficits should be re-examined when steady state serum concentrations of AED is achieved or resolution of post-ictal changes is expected (within less than 1 week), respectively.

Neurobehavioural comorbidities can occur in dogs with IE [33], similarly to human patients [34], and their presence should therefore not imply a diagnosis of structural epilepsy. However MRI studies of the brain (see consensus statement on epilepsy-specific brain MRI protocol) and CSF analysis are recommended in these dogs.

Additional discretionary laboratory parameters depending on the index of disease suspicion include: fasting and post-prandial bile acids, fasted ammonia and abdominal ultrasound when hepatic encephalopathy is suspected; total T4 (TT4), free T4 (fT4), and thyroid stimulating hormone (TSH) when thyroid disorders are suspected (thyroid testing should be performed prior to long term treatment with AEDs due to possible interactions between AED and the thyroid hormones); fructosamine, glucose curve and/ or glucose:insulin ratio when insulinoma is suspected; serum creatine kinase (CK) activity and lactate levels whenever muscle disease is suspected (results should be interpreted in relation to time of sampling since the last epileptic seizure event and severity and duration of the epileptic seizure event, as excessive muscle activity during epileptic seizures activity can transiently increase CK activity and lactate levels); serology/ polymerase chain reaction (PCR)/ antigen testing for regional infectious disorders (these should be performed whenever infectious disorders are suspected); vitamin B12 when cobalamin malabsorption is considered; ionized calcium when hypocalcemia is suspected; testing for specific toxins or toxicological screening by mass spectroscopy when toxin exposure is suspected; quantification of amino acids and organic acids and determination of glycosaminoglycans, oligosaccharides, purines, and pyrimidines in serum, CSF or urine when inborn errors of metabolism are suspected; genetic testing when a disorder with known genetic mutation is suspected (*e.g.,* benign familial juvenile epilepsy in the Lagotto Romagnolo, progressive myoclonic epilepsy in miniature wire haired Dachshunds, L-2-hydroxyglutaric aciduria in Staffordshire bull terriers). In addition, imaging of the thorax and abdomen should be performed when metastatic neoplastic disease is a possibility. Ocular fundic examination and non-invasive blood pressure measurement should also be performed when hypertension is suspected. Further details on diagnostic investigations to identify underlying aetiologies of seizures can be found elsewhere [30].

Tier II confidence level for the diagnosis of IE

Unremarkable fasting and post-prandial bile acids, MRI of the brain (see consensus statement on epilepsy-specific brain MRI protocol) and CSF analysis in addition to factors listed in tier I.

If abnormalities compatible with seizure-associated changes are identified on MRI, the MRI protocol should be repeated after a 16 week seizure free interval (whenever possible) (see below: *Epileptic seizure-associated CSF and brain MRI changes*).

If the results of routine CSF analysis are abnormal then additional testing on CSF and serum for regional infectious disorders should be performed. CSF abnormalities (generally mild) may occur as a result of epileptic seizure activity [35] (see below: *Epileptic seizure-associated CSF and brain MRI changes*). Time to resolution of epileptic seizure-associated CSF abnormalities is unknown. If CSF abnormalities are present but the results of investigations for infectious disorders on CSF and serum are negative and brain MRI is unremarkable or shows post-ictal changes, then the CSF analysis should be repeated following a seizure free interval of at least 6 weeks.

Tier III confidence level for the diagnosis of IE

Identification of ictal or inter-ictal EEG abnormalities characteristic for seizure disorders according to criteria validated in human medicine, in addition to factors listed in tier I and II. However, further research is

needed to characterise the optimal protocol for EEG use in clinical veterinary practice.

Epileptic seizure-associated CSF and brain MRI changes Epileptic seizure activity has been reported to cause CSF abnormalities [35] and intraparenchymal cerebral signal changes on MRI performed within 14 days of the last epileptic seizure [36]. The MRI signal changes are located unilaterally or bilaterally, predominantly in the piriform and temporal lobes, and sometimes also in the olfactory bulb and frontal lobe. The signal changes are characterised by varying degrees of hyperintensity on T2 weighted, FLAIR and diffusion-weighted imaging, hypointensity on T1 weighted images, and occasionally heterogenous contrast enhancement following gadolinium administration [36, 37]. Following antiepileptic treatment only, these signal changes partly or completely resolved on repeated MRI 10 to 16 weeks later, indicating that these changes most likely represent cytotoxic and vasogenic oedema induced by the epileptic seizures. Histologic examination of the affected temporal cortex, hippocampus and piriform lobe revealed oedema, neovascularization, reactive astrocytosis, and acute neuronal necrosis [36]. Repeated MRI of the brain after a period of seizure control, along with clinical and CSF analysis findings, may help to differentiate epileptic seizure-induced changes from inflammatory or neoplastic epileptogenic structural lesions [36].

Mild postictal CSF pleocytosis and sometimes also increased protein concentration have been reported as a transient CSF abnormality in people, generally following repetitive generalized tonic-clonic seizures [38]. Mild CSF pleocytosis (up to 12 WBC/μl, reference range 0–5 WBC/μl) has also been identified following single focal or generalized tonic-clonic seizures in a small number of patients, particularly when CSF sampling occurred within 12 h of the last seizure [39]. A study in idiopathic epileptic dogs identified an association between CSF white blood cell (WBC) count and time interval between the last seizure and the collection of the CSF. The longer the time interval, the lower the CSF WBC count. However, the CSF WBC count was within the reference range (≤5 WBC/μl) in all dogs and 80 % of dogs underwent CSF sampling 3 or more days after the last seizure. No association was found between CSF protein concentration and time of CSF collection and the occurrence of cluster seizures was not associated with any significant change in CSF WBC or protein concentration [35]. The pathophysiology of seizure-induced CSF pleocytosis remains unclear. It is possible that a transient disturbance of the blood–brain barrier function (which has been demonstrated after seizures in experimental animals) and release of chemotactic substances into the CSF during the seizures result in these CSF abnormalities [40]. Repeated CSF sampling after a seizure free interval reveals no abnormalities [38].

Recommendation on when to perform MRI of the brain The dog's age at seizure onset and the presence of interictal neurological abnormalities have been evaluated in an attempt to predict the probability of identifying structural cerebral disorders in epileptic dogs. In a study in a non-referral canine population, structural epilepsy was statistically more probable in dogs <1 year or > 7 years of age at seizure onset, whereas IE was statistically more probable in dogs aged 1 to 5 years at first seizure and when the interictal period was longer than 4 weeks [41]. In a retrospective study on a referral population of 240 dog with epileptic seizures, seizure onset between 1 and 5 years of age was associated with a 3.25 times greater likelihood for idiopathic epilepsy than structural epilepsy and reactive seizures [6]. One study reported brain MRI abnormalities in 22 % (14/63) and 90 % (47/52) of epileptic dogs with normal and abnormal neurological examination, respectively [42]. Results of CSF analysis (normal versus abnormal) were significantly associated with the results of the MRI study (normal versus abnormal), in dogs with both normal and abnormal neurological examination [42]. Another study reported clinically significant MRI abnormalities, including olfactory or frontal lobe neoplasia, in 2.2 % (1/46) and 26.7 % (8/30) of inter-ictally normal epileptic dogs younger and older than 6 years of age, respectively [43]. In a study including dogs whose first seizure occurred below the age of one year, 26 % (6/23) of dogs with a normal neurological examination had an underlying structural brain disease identified with MRI and CSF analysis [44]. Another study including dogs whose first seizure occurred ≥7 years of age identified an underlying CNS structural disease in 59 % (53/90) of dogs with an unremarkable inter-ictal neurologic examination [45]. A retrospective study including 99 dogs ≥ 5 years of age at epileptic seizure onset reported that an abnormal neurologic examination had 74 % sensitivity and 62 % specificity to predict structural epilepsy with positive and negative predictive values of 79 %, and 55 %, respectively [46]. Of the 53 dogs with an abnormal neurological examination, 42 (79 %) had a lesion detected by MRI or had abnormal findings on CSF analysis (some dogs had both CSF and MRI abnormalities). Fifteen of the 33 (45 %) dogs with normal neurological examination had structural epilepsy diagnosed on the basis of MRI or CSF analysis results [46]. Another recent study demonstrated that age at seizure onset and neurological examination findings were both significantly associated with type of brain disease (functional versus structural) [24]. In this study, 89 % (230/258) of dogs with IE had an age at seizure onset < 6 years and 84 % (217/258) of dogs with IE were neurologically normal inter-ictally. Dogs that

were older at seizure onset were significantly more likely to have an asymmetrical structural cerebral lesion (mean age at seizure onset 7.6 ± 3.4 years) than IE (3.3 ± 2.1 years). The odds of identifying an asymmetrical structural cerebral lesion rather than IE increased 1.6-fold with each additional year of age at seizure onset. Dogs with neurological abnormalities inter-ictally were 16.5 times more likely to have an asymmetrical structural cerebral lesion and 12.5 times more likely to have a symmetrical structural cerebral lesion than IE. Dogs with single seizures rather than cluster seizures were more likely to have IE than an asymmetrical structural cerebral lesion [24]. In another study, of 51 dogs presenting with status epilepticus as the first manifestation of seizure disorder, 45.1 % had structural epilepsy, 31.4 % had reactive seizures and 23.5 % had IE [23]. Dogs with IE had a reduced risk of developing status epilepticus at seizure onset compared to dogs with structural epilepsy or reactive seizures [23].

To further investigate the predictive value of age at epileptic seizure onset to differentiate between idiopathic and structural epilepsy, the data from the studies performed by Pakozdy [6] and Armaşu [24] have been combined and analysed. There were 372 dogs with IE and 236 dogs with structural epilepsy. There was a significant association between age of onset and cause of epilepsy for dogs under 6 years of age at epileptic seizure onset (Chi-squared = 5.136, n = 431, p = 0.023) when the cut-off was set at 6 months (Fig. 1). Dogs between 6 months and 6 years were significantly more likely to be affected by idiopathic than symptomatic epilepsy compared to dogs under 6 months. Whereas, there was no significant association between age of onset and cause of epilepsy for dogs under 6 years of age at epileptic seizure onset (Chi-squared = 2.95, n = 431, p = 0.086) when the cut-off was set at 1 year (Fig. 2). A binary logistic regression demonstrated that dogs aged between 6 months and 6 years at epileptic seizure onset were 2.65 times more likely to be affected by IE than SE (p = 0.03) than those under 6 months of age at epileptic seizure onset. Whereas, a binary logistic regression demonstrated that there was no significant association between age of onset and cause of epilepsy for dogs under 6 years of age at epileptic seizure onset (p > 0.05) when the cut-off was set at 1 year. When comparing the 5 versus 6 years of age at epileptic seizure onset as upper cut off, the 6 year cut off was a better predictor (77.3 % accuracy versus 74.5 %) and had a better model fit with a lower Akaike Information Criteria (AIC) value. A binary logistic regression demonstrated that dogs under 6 at age at epileptic seizure onset were 10.89 times more likely to be affected by IE than structural epilepsy (p < 0.001). Whereas, a binary logistic regression demonstrated that dogs under 5 of age at epileptic seizure onset were 8.00 times more likely to be affected by IE than structural epilepsy (p < 0.001).

Based on the information described above, the authors' recommendation is to perform MRI of the brain (using the veterinary epilepsy-specific MRI protocol) and routine CSF analysis, after exclusion of reactive seizures, in dogs with:

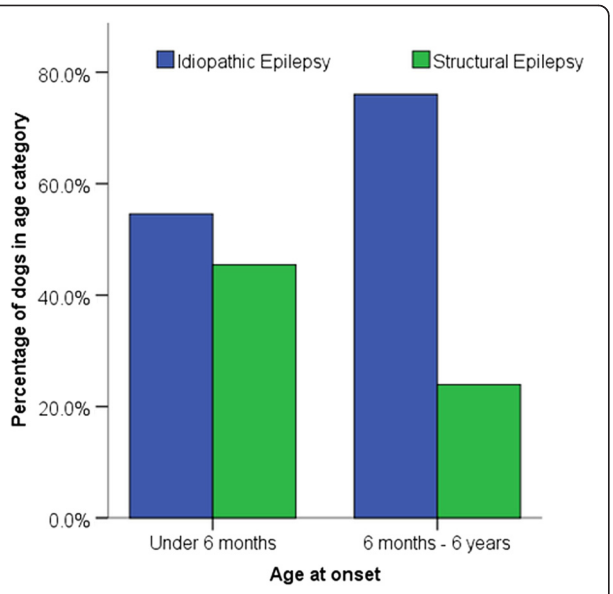

Figure 1 Proportion of dogs with idiopathic and structural epilepsy stratified by age at epileptic seizure onset (< 6 months versus 6 months to 6 years)

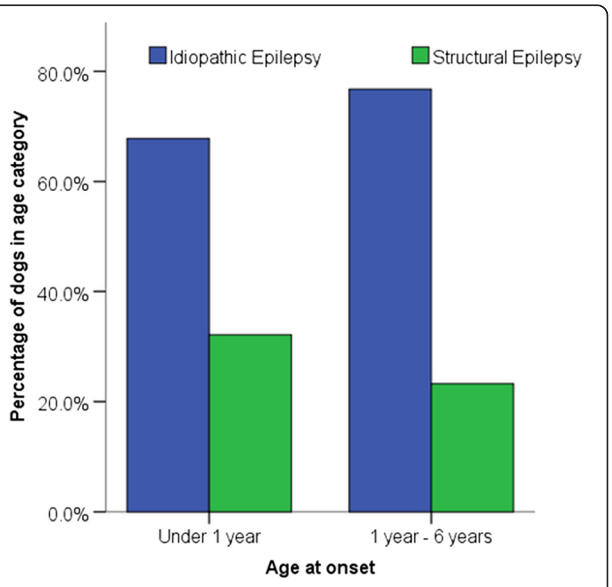

Figure 2 Proportion of dogs with idiopathic and structural epilepsy stratified by age at epileptic seizure onset (< 1 year versus 1 to 6 years)

- age at epileptic seizure onset <6 months or >6 years
- interictal neurological abnormalities consistent with intracranial neurolocalisation
- status epilepticus or cluster seizure
- a previous presumptive diagnosis of IE and drug-resistance with a single AED titrated to the highest tolerable dose.

Conclusions

The recommendations presented in this article represent the basis of a more standardised diagnostic approach to the seizure patient. These guidelines are likely to evolve over time with advances in structural and functional neuroimaging, EEG, and molecular genetics of canine epilepsy.

Additional file

Additional file 1: Standardised epilepsy investigation questionnaire.

Abbreviations

IE: Idiopathic epilepsy; ILAE: International League Against Epilepsy; MRI: Magnetic resonance imaging; CSF: Cerebrospinal fluid; EEG: Electroencephalography; AED: Antiepileptic drug; MDB: Minimum data base; CK: Creatine kinase; PCR: Polymerase chain reaction.

Competing interests

Following reimbursements, fees and funding have been received by the authors in the last three years and have been declared in the competing interest section. CR, RGF, HAV, KM, MP and JP have received fees for acting as a consultant for Boehringer Ingelheim (KM, MP: consultancy during development and approval of imepitoin; CR: pain consultancy; RGF, JP, HAV: consultancy pre and post launch of imepitoin). AT has been an advisor for Boehringer Ingelheim. SFMB, HAV and AT have been responsible principal investigator of several research studies concerning imepitoin financed by Boehringer Ingelheim. SFMB, HAV, JP, HP, MB, CR and AF received speaking fees from Boehringer Ingelheim. HP received consulting and speaking fees and funding for a collaborative project from Eisai Co. LTD. HAV received funding for a collaborative project from Desitin and Nestlé Purina Research. AF and LDR received reimbursements from Boehringer Ingelheim. LDR has received consulting and speaking fees from Vetoquinol. MP has received consultant fees for Aratana. The other authors declared that they have no competing interests.

Author's contributions

LDR chaired and SFMB co-chaired the diagnosis working group (LDR, SFMB, KM, JP, SVM, AT) and LDR wrote the first draft of the consensus paper with the help of SFMB, KM, JP, SVM, AT and HAV. RMAP re-analysed the data from AP and HAV. All authors read, critiqued, commented and approved the final manuscript.

Authors' information

Luisa De Risio chair of diagnosis working group.
Sofie Bhatti co-chair of diagnosis working group.
Karen Muñana, Jacques Penderis, Veronika Stein and Andrea Tipold members of the diagnosis working group (alphabetically listed).
Holger A Volk chair of IVETF.
All other co-authors are members of IVETF and are list alphabetically and have approved the consensus statements.

Acknowledgements

The authors are grateful to all owners of epileptic pets and veterinary colleagues who have inspired the group to create consensus statements. The authors also would like to thank the research office for assessing the manuscript according to the Royal Veterinary College's code of good research practice (Authorisation Number – CCS_ 01025). This study was not financially supported by any organization or grant.

Author details

[1]Animal Health Trust, Lanwades Park, Kentford, Newmarket, CB8 7UU Suffolk, UK. [2]Department of Small Animal Medicine and Clinical Biology, Faculty of Veterinary Medicine, Ghent University, Salisburylaan 133, Merelbeke 9820, Belgium. [3]Department of Clinical Sciences, College of Veterinary Medicine, North Carolina State University, 1052 William Moore Drive, Raleigh, NC 27607, USA. [4]Vet Extra Neurology, Broadleys Veterinary Hospital, Craig Leith Road, Stirling FK7 7LE, Stirlingshire, UK. [5]Department of Small Animal Medicine and Surgery, University of Veterinary Medicine Hannover, Bünteweg 9, 30559 Hannover, Germany. [6]Department of Veterinary and Clinical Sciences, Faculty of Health and Medical Sciences, University of Copenhagen, Frederiksberg C, Denmark. [7]Fernside Veterinary Centre, 205 Shenley Road, Borehamwood SG9 0TH, Hertfordshire, UK. [8]Centre for Clinical Veterinary Medicine, Ludwig-Maximilians-University, Veterinärstr. 13, 80539 Munich, Germany. [9]University of Melbourne, 250 Princes Highway, Weibee 3015, VIC, Australia. [10]Department of Clinical Sciences of Companion Animals, Utrecht University, Yalelaan 108, 3583 CM Utrecht, The Netherlands. [11]Section of Clinical & Comparative Neuropathology, Centre for Clinical Veterinary Medicine, Ludwig-Maximilians-University, Veterinärstr. 13, 80539 Munich, Germany. [12]Department of Clinical Science and Services, Royal Veterinary College, Hatfield AL9 7TA, Hertfordshire, UK. [13]Clinical Unit of Internal Medicine Small Animals, University of Veterinary Medicine, Veterinärplatz 1, 1210 Vienna, Austria. [14]University of Minnesota College of Veterinary Medicine, D426 Veterinary Medical Center, 1352 Boyd Avenue, St. Paul, MN 55108, USA. [15]College of Veterinary Medicine, University of Georgia, 501 DW Brooks Drive, Athens, GA 30602, USA. [16]Chicago Veterinary Neurology and Neurosurgery, 3123 N. Clybourn Avenue, Chicago, IL 60618, USA. [17]Department of Pharmacology, Toxicology and Pharmacy, Ludwig-Maximillians-University, Königinstr. 16, 80539 Munich, Germany. [18]Department of Animal Medicine and Surgery, Veterinary Faculty, Universitat Autònoma de Barcelona, Campus UAB, Bellaterra, 08193 Barcelona, Spain. [19]Fitzpatrick Referrals, Halfway Lane, Eashing, Godalming GU7 2QQ, Surrey, UK. [20]School of Veterinary Medicine, Faculty of Health & Medical Sciences, University of Surrey, Guildford GU2 7TE, Surrey, UK.

Received: 4 June 2015 Accepted: 29 June 2015
Published online: 31 December 2015

References

1. Fisher RS, van Emde BW, Blume W, Elger C, Genton P, Lee P, et al. Epileptic seizures and epilepsy: definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). Epilepsia. 2005;46:470–2.
2. Fisher RS, Acevedo C, Arzimanoglou A, Bogacz A, Cross JH, Elger CE, et al. ILAE official report: a practical clinical definition of epilepsy. Epilepsia. 2014;55:475–82.
3. Berg AT, Berkovic SF, Brodie MJ, Buchhalter J, Cross JH, van Emde BW, et al. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005-2009. Epilepsia. 2010;51:676–85.
4. Mariani CL. Terminology and classification of seizures and epilepsy in veterinary patients. Top Companion Anim Med. 2013;28:34–41.
5. Shorvon S. The concept of symptomatic epilepsy and the complexities of assigning cause in epilepsy. Epilepsy Behav. 2014;32:1–8.
6. Pákozdy A, Leschnik M, Tichy AG, Thalhammer JG. Retrospective clinical comparison of idiopathic versus symptomatic epilepsy in 240 dogs with seizures. Acta Vet Hung. 2008;56:471–83.
7. Hülsmeyer V, Zimmermann R, Brauer C, Sauter-Louis C, Fischer A. Epilepsy in Border Collies: Clinical manifestation, outcome, and mode of inheritance. J Vet Intern Med. 2010;24:171–8.
8. Fredsø N, Koch BC, Toft N, Berendt M. Risk factors for survival in a University Hospital population of dogs with epilepsy. J Vet Intern Med. 2014. doi:10.1111/jvim.12443.
9. Thomas WB. Evaluation of veterinary patients with brain disease. Vet Clin North Am Small Anim Pract. 2010;40:1–19.
10. Urkasemsin G, Olby NJ. Canine paroxysmal movement disorders. Vet Clin North Am Small Anim Pract. 2014;44:1091–102.
11. Platt SR. Mimics of seizure activity: Disorders confused with epilepsy. In: De Risio L, Platt S, editors. Canine and feline epilepsy: diagnosis and management. Wallingford: CABI; 2014. p. 244–76.

12. Brauer C, Kästner SB, Rohn K, Schenk HC, Tünsmeyer J, Tipold A. Electroencephalographic recordings in dogs suffering from idiopathic and symptomatic epilepsy: diagnostic value of interictal short time EEG protocols supplemented by two activation techniques. Vet J. 2012;193:185–92.
13. Forman OP, Penderis J, Hartley C, Hayward LJ, Ricketts SL, Mellersh CS. Parallel mapping and simultaneous sequencing reveals deletions in BCAN and FAM83H associated with discrete inherited disorders in a domestic dog breed. PLoS Genet. 2012. doi:10.1371/journal.pgen.1002462.
14. Gill JL, Tsai KL, Krey C, Noorai RE, Vanbellinghen JF, Garosi LS, et al. A canine BCAN microdeletion associated with episodic falling syndrome. Neurobiol Dis. 2012;45(1):130–6.
15. Erro R, Sheerin UM, Bhatia KP. Paroxysmal dyskinesias revisited: a review of 500 genetically proven cases and a new classification. Mov Disord. 2014;29:1108–16. doi:10.1002/mds.25933.
16. Ekenstedt KJ, Oberbauer AM. Inherited epilepsy in dogs. Top Companion Anim Med. 2013;28(2):51–8.
17. Wolf M, Bruehschwein A, Sauter-Louis C, Sewell AC, Fischer A. An inherited episodic head tremor syndrome in Doberman pinscher dogs. Mov Disord. 2011;26:2381–6.
18. Guevar J, De Decker S, Van Ham LM, Fischer A, Volk HA. Idiopathic head tremor in English bulldogs. Mov Disord. 2014;29(2):191–4.
19. Packer RMA, Berendt M, Bhatti S, Charalambous M, Cizinauskas S, De Risio L, et al. Inter-observer agreement of canine and feline paroxysmal event semiology and classification by veterinary neurology specialists and non-specialists. BMC Vet Res. 2015;1:39. doi:10.1186/s12917-015-0356-2.
20. James F. Introduction to electroencephalography. In: De Risio L, Platt S, editors. Canine and feline epilepsy: diagnosis and management. Wallingford: CABI; 2014. p. 325–46.
21. Poma R, Ochi A, Cortez MA. Absence seizures with myoclonic features in a juvenile Chihuahua dog. Epileptic Disord. 2010;12:138–41.
22. Brauer C, Jambroszy M, Tipold A. Metabolic and toxic causes of canine seizure disorders: a retrospective study of 96 cases. Vet J. 2011;187:272–5.
23. Zimmermann R, Hülsmeyer V, Sauter-Louis C, Fischer A. Status epilepticus and epileptic seizures in dogs. J Vet Intern Med. 2009;23:970–6.
24. Armaşu M, Packer RMA, Cook S, Solcan G, Volk HA. An exploratory study using a statistical approach as a platform for clinical reasoning in canine epilepsy. Vet J. 2014;202:292–6.
25. Schwartz M, Lamb CR, Brodbelt DC, Volk HA. Canine intracranial neoplasia: clinical risk factors for development of epileptic seizures. J Small Anim Pract. 2011;52:632–7.
26. Berendt M, Gullov CH, Fredholm M. Focal epilepsy in the Belgian shepherd: evidence for simple Mendelian inheritance. J Small Anim Pract. 2009;50:655–61.
27. Licht BG, Lin S, Luo Y, Hyson LL, Licht MH, Harper KM, et al. Clinical characteristics and mode of inheritance of familial focal seizures in Standard Poodles. J Am Anim Hosp Assoc. 2007;231:1520–8.
28. Patterson EE, Mickelson JR, Da Y, Roberts MC, McVey AS, O'Brien DP, et al. Clinical characteristics and inheritance of idiopathic epilepsy in Vizslas. J Vet Intern Med. 2003;17:319–25.
29. Patterson EE, Armstrong PJ, O'Brien DP, Roberts MC, Johnson GS, Mickelson JR. Clinical description and mode of inheritance of idiopathic epilepsy in English springer spaniels. J Am Vet Med Assoc. 2005;226:54–8.
30. De Risio L. Clinical and diagnostic investigation of the seizure patient. In: De Risio L, Platt S, editors. Canine and feline epilepsy: diagnosis and management. Wallingford: CABI; 2014. p. 274–324.
31. De Risio L. Reactive seizures. In: De Risio L, Platt S, editors. Canine and feline epilepsy: diagnosis and management. Wallingford: CABI; 2014. p. 54–100.
32. De Risio L. Structural epilepsy. In: De Risio L, Platt S, editors. Canine and feline epilepsy: diagnosis and management. Wallingford: CABI; 2014. p. 101–6.
33. Shihab N, Bowen J, Volk HA. Behavioral changes in dogs associated with the development of idiopathic epilepsy. Epilepsy Behav. 2011;21:160–7.
34. Lin JJ, Mula M, Hermann BP. Uncovering the neurobehavioural comorbidities of epilepsy over the lifespan. Lancet. 2012;29(380):1180–92.
35. Gonçalves R, Anderson TJ, Innocent G, Penderis J. Effect of seizures on cerebrospinal fluid analysis in dogs with idiopathic epilepsy. Vet Rec. 2010;166:497–8.
36. Mellema LM, Koblik PD, Kortz GD, LeCouter R, Chechowitz MA, Dickinson PJ. Reversible magnetic resonance imaging abnormalities in dogs following seizures. Vet Radiol Ultrasound. 1999;40:588–95.
37. Huang YC, Weng HH, Tsai YT, Huang YC, Hsiao MC, Wu CY, et al. Periictal magnetic resonance imaging in status epilepticus. Epilepsy Res. 2009;86:72–81.
38. Edwards R, Schmidley JW, Simon RP. How often does a CSF pleocytosis follow generalized convulsions? Ann Neurol. 1983;13:460–2.
39. Devinsky O, Nadi S, Theodore WH, Porter RJ. Cerebrospinal fluid pleocytosis following simple, complex partial, and generalized tonic-clonic seizures. Ann Neurol. 1988;23:402–3.
40. Schmidley JW, Simon RP. Postictal pleocytosis. Ann Neurol. 1981;9:81–4.
41. Podell M, Fenner WR, Powers JD. Seizure classification in dogs from a nonreferral-based population. J Am Vet Med Assoc. 1995;206:1721–8.
42. Bush WW, Barr CS, Darrin EW, Shofer FS, Vite CH, Steinberg SA. Results of cerebrospinal fluid analysis, neurologic examination findings, and age at the onset of seizures as predictors for results of magnetic resonance imaging of the brain in dogs examined because of seizures: 115 cases (1992-2000). J Am Vet Med Assoc. 2002;220:781–4.
43. Smith PM, Talbot CE, Jeffery ND. Findings on low-field cranial MR images in epileptic dogs that lack interictal neurological deficits. Vet J. 2008;176:320–5.
44. Arrol L, Penderis J, Garosi L, Cripps P, Gutierrez-Quintana R, Gonçalves R. Aetiology and long term outcome of juvenile epilepsy in 136 dogs. Vet Rec. 2012;170:335.
45. Schwartz M, Muñana KR, Nettifee-Osborne J. Assessment of the prevalence and clinical features of cryptogenic epilepsy in dogs: 45 cases (2003-2011). J Am Vet Med Assoc. 2013;42:651–7.
46. Ghormle TM, Feldman DG, Cook JR. Epilepsy in dogs five years of age and older: 99 cases (2006–2011). J Am Vet Med Assoc. 2015;246:447–50.

Hülsmeyer et al. BMC Veterinary Research (2015) 11:175
DOI 10.1186/s12917-015-0463-0

BMC Veterinary Research

CORRESPONDENCE Open Access

International Veterinary Epilepsy Task Force's current understanding of idiopathic epilepsy of genetic or suspected genetic origin in purebred dogs

Velia-Isabel Hülsmeyer[1*], Andrea Fischer[1], Paul J.J. Mandigers[2], Luisa DeRisio[3], Mette Berendt[4], Clare Rusbridge[5,6], Sofie F.M. Bhatti[7], Akos Pakozdy[8], Edward E. Patterson[9], Simon Platt[10], Rowena M.A. Packer[11] and Holger A. Volk[11]

Abstract

Canine idiopathic epilepsy is a common neurological disease affecting both purebred and crossbred dogs. Various breed-specific cohort, epidemiological and genetic studies have been conducted to date, which all improved our knowledge and general understanding of canine idiopathic epilepsy, and in particular our knowledge of those breeds studied. However, these studies also frequently revealed differences between the investigated breeds with respect to clinical features, inheritance and prevalence rates. Awareness and observation of breed-specific differences is important for successful management of the dog with epilepsy in everyday clinical practice and furthermore may promote canine epilepsy research. The following manuscript reviews the evidence available for breeds which have been identified as being predisposed to idiopathic epilepsy with a proven or suspected genetic background, and highlights different breed specific clinical features (e.g. age at onset, sex, seizure type), treatment response, prevalence rates and proposed inheritance reported in the literature. In addition, certain breed-specific diseases that may act as potential differentials for idiopathic epilepsy are highlighted.

Keywords: Idiopathic epilepsy, Dog, Breed, Epilepsy prevalence, Epileptic seizure

Introduction

Canine idiopathic epilepsy is a common neurological disease and has been recently defined as two or more unprovoked seizures at least 24 h apart with no identifiable underlying etiology other than a suspected genetic origin. Idiopathic epilepsy still represents a diagnosis of exclusion and an appropriate diagnostic workup is essential as a correct diagnosis impacts treatment and breeding decisions [1]. Affected dogs most often require life-long antiepileptic medication and regular control visits. Consequently, the daily lives of many owners are affected by concerns related to their pet's seizures and the changes in daily routine [1–4]. Furthermore, canine idiopathic epilepsy is a disease, which is characterised by a broad array of clinical signs, age of onset, and at least in part underlying genetic backgrounds (see also Tables 1 and 2) [5, 6]. In recent years, idiopathic epilepsy with a proven or suspected genetic background has been reported for a number of purebred dogs with most studies focusing on clinical characteristics and genetic aspects. However, most studies have not yet identified causative gene mutations, suggesting that, either the research group in question did not have resources or availability to go from clinical to genetic identification of monogenic epilepsy-causing genes or that inheritance may be complex, involving several or many susceptibility genes, and be reflective of additional environmental interactions similar to what is proposed for many human genetic epilepsies [5–7]. The individual dog's response to antiepileptic treatment may also be complex and in some individuals, successful antiepileptic drug treatment presents a time- and cost-consuming challenge with an increased risk for poor quality of life, premature death or euthanasia when seizures cannot be adequately

* Correspondence: v.huelsmeyer@medizinische-kleintierklinik.de
[1]Centre for Clinical Veterinary Medicine, Ludwig-Maximilians-University, Veterinärstr. 13, 80539 Munich, Germany
Full list of author information is available at the end of the article

Table 1 Depicting breed-specific data regarding age of seizure onset

Breed	Age at seizure onset	Reference
Australian Shepherd	2.5 years (median)	Weissl et al. 2012 [9]
Belgian Shepherd	3.3 years (mean)	Berendt et al. 2008 [23]
	3.3 years (mean)	Seppala et al. 2012 [34]
Bernese Mountain dog	26.5 months (mean)	Kathmann et al. 1999 [45]
Border Collie	2.5 years (median)	Hülsmeyer et al. 2010 [8]
Border Terrier	3.2 years (mean)	Kloene et al. 2008 [56]
Dalmatian	2.9 years (median), 3.2 years (mean)	Licht et al. 2002 [65]
English Springer Spaniel	3 years (median)	Patterson et al. 2005 [74]
Finnish Spitz	3 years (median)	Viitmaa et al. 2013 [82]
Golden Retriever	27.5 months (mean)	Srenk et al. 1994 [84]
	24.9 months (mean)	Lengweiler&Jaggy 1999 [86]
Hungarian (Magyar) Vizsla	3 years (median)	Patterson et al. 2003 [87]
Irish Wolfhound	by the age of 3 years in 73 % of dogs	Casal et al. 2006 [24]
Italian Spinone	38 months (mean)	De Risio et al. 2015 [93]
Labrador Retriever	30.6 months (mean)	Jaggy et al. 1998 [95]
	34 months for males and 28 months for females (mean)	Heynold et al. 1997 [94]
	by the age of 4 years in 76 % of dogs	Berendt et al. 2002 [26]
Lagotto Romganolo	6.3 weeks (mean)	Jokinen et al. 2007 [105]
Petit Basset Griffon Vendeen	2 years (median)	Gulløv et al. 2011 [25]
Shetland Sheepdog	predominantly between 1 and 1.5 years	Morita et al. 2002 [109]
Standard Poodle	3.7 years (median)	Licht et al. 2007 [113]
	2.4 years (median), 2.8 years (mean)	Licht et al. 2002 [65]

controlled [8–13]. Estimated prevalence data among the general dog population have been reported with variable results [14–17]. The true prevalence of epilepsy in dogs is unknown and has been estimated to be 0.6–0.75 % in general dog population [16, 18]. However, prevalence rates may differ considerably when looking at hospital populations with prevalence rates of 0.5 – 5 % in non-referral population and of 1–2.6 % in referral hospital population [14–17, 19–22]. In breeds, which are predisposed to idiopathic epilepsy, considerable higher prevalence rates are reported [23–26] than the prevalence estimated for the general dog population (see Table 3.), which is one of the reasons a genetic component is suspected in certain canine breeds. Current data show that the clinical courses, seizure semiology, treatment responses and heritability may differ substantially between dog breeds and also between geographically distinct populations of the same breed, which further highlights the complexity of the disease. In summary, knowledge and consideration of these breed-specific (or even population-specific) differences is important, as this may potentially impact the choice of treatment regimen, prognosis for the patient and advice given to owners of an epileptic dog. In the future breed-specific knowledge and epileptic syndromes may be defined in further detail which may not only advance future research in identifying causative gene mutations but also may support the development of "personalised" or "breed-specific" treatment concepts. The following manuscript reviews dog breeds, which have been identified as being predisposed to idiopathic epilepsy, with a special focus on different epilepsy phenotypes regarding clinical features, treatment response and inheritance. In addition, certain breed-specific diseases that may act as potential differentials for idiopathic epilepsy are highlighted. The seizure terminology used in the original studies has been adapted and uniformed (as far as possible) in line with the new Guidelines for Epilepsy Definition, Classification and Terminology in Companion Animals throughout the manuscript.

Australian Shepherd

In the current literature, there is one specific study of idiopathic epilepsy in Australian Shepherds available [9]. This longitudinal German cohort study was published in 2012 and includes detailed data for 50 affected Australian Shepherds (from Germany, Switzerland and Austria). Fifty unaffected Australian Shepherds served as control dogs. Idiopathic epilepsy was defined as recurrent seizures (≥2 seizures ≥ 4 weeks apart), age at onset ≤ 5 years,

Table 2 Depicting breed-specific data regarding seizure type and seizure remission

Breed	Seizure type	History of cluster seizures or status epilepticus	Remission rate	Reference
Australian Shepherd	36 % generalised epileptic seizures	20 % cluster seizures	12 %	Weissl et al. 2012 [9]
	26 % focal epileptic seizures evolving into generalised seizures	12 % status epilepticus		
	38 % both seizure types	48 % history of both		
	52 % showed also focal epileptic seizures (in addition to their generalised epileptic seizures or focal			
	epileptic seizures evolving into generalised seizures)			
Belgian Shepherd	18 % generalised epileptic seizures	n.s.	n.s.	Berendt et al. 2008 [23]
	25 % focal			
	53 % focal epileptic seizures evolving into generalised seizures			
	4 % unclassified			
	6 % generalised epileptic seizures	n.s.	n.s.	Berendt et al. 2009 [41]
	83 % focal epileptic seizures or focal epileptic seizures evolving into generalised seizures			
	11 % unclassified			
	n.s.	33 % cluster seizures	13.7 %	Gulløv et al. 2012 [37]
	18 % generalised epileptic seizures	33 % cluster seizures	n.s.	Seppala et al. 2012 [34]
	7 % focal epileptic seizures			
	37 % focal epileptic seizures evolving into generalised epileptic seizures			
	34 % generalised epileptic seizures with unknown onset			
	4 % unclassified			
Bernese Mountain dog	98 % generalised epileptic seizures	n.s.	n.s.	Kathmann et al. 1999 [45]
	2 % focal epileptic seizures			
	Distinction between (primary) generalised epileptic seizures and focal epileptic seizures evolving into generalised seizures was not performed.			
Border Collie	8 % generalised epileptic seizures	45 % cluster seizures	18 %	Hülsmeyer et al. 2010 [8]
	78 % focal epileptic seizures evolving into generalised seizures	4 % status epilepticus		
	14 % unclassified	49 % history of both		
	45 % showed also focal epileptic seizures (in addition to their generalised epileptic seizures or focal epileptic seizures evolving into generalised seizures)			
Border Terrier	68 % generalised epileptic seizures	n.s.	n.s.	Kloene et al. 2008 [56]
	32 % focal epileptic seizures			
	Distinction between (primary) generalised epileptic seizures and focal epileptic seizures evolving into generalised seizures was not performed.			
Cavalier King Charles	39 % generalised epileptic seizures	n.s.	n.s.	Driver et al. 2013 [59]
	36 % focal epileptic seizures			
	25 % focal epileptic seizures evolving into generalised seizures			

Table 2 Depicting breed-specific data regarding seizure type and seizure remission *(Continued)*

Collie (rough and smooth)	Predominantly generalised	35 % cluster seizures	n.s.	Munana et al. 2012 [64]
	Distinction between (primary) generalised epileptic seizures and focal epileptic seizures evolving into generalised seizures was not performed.			
Dalmatian	20 % generalised epileptic seizures	63.6 % cluster seizures	n.s.	Licht et al. 2002 [65]
	80 % focal epileptic seizures or focal epileptic seizures evolving into generalised seizures			
English Springer Spaniel	47 % generalised epileptic seizures	38 % cluster seizures	n.s.	Patterson et al. 2005 [74]
	33 % focal epileptic seizures			
	20 % focal epileptic seizures evolving into generalised seizures			
Finnish Spitz	1 % generalised epileptic seizures	16.2 % cluster seizures	n.s.	Viitmaa et al. 2013 [82]
	54 % focal epileptic seizures			
	31 % focal epileptic seizures evolving into generalised seizures			
	7 % generalised with unknown onset			
	7 % completely unclassified			
Golden Retriever	83 % generalised epileptic seizures	n.s.	n.s.	Lengweiler&Jaggy 1999 [86]
	Distinction between (primary) generalised epileptic seizures and focal epileptic seizures evolving into generalised seizures was not performed.			
	92 % generalised epileptic seizures	n.s.	n.s.	Srenk et al. 1994 [84]
	Distinction between (primary) generalised epileptic seizures and focal epileptic seizures evolving into generalised seizures was not performed.			
Hungarian (Magyar) Vizsla	21 % generalised epileptic seizures	n.s.	n.s.	Patterson et al. 2003 [87]
	62 % focal epileptic seizures			
	17 % focal epileptic seizures evolving into generalised seizures			
Irish Wolfhound	Predominantly generalised epileptic seizures	n.s.	n.s.	Casal et al. 2006 [24]
	Distinction between (primary) generalised epileptic seizures and focal epileptic seizures evolving into generalised seizures was not performed.			
Italian Spinone	23 % generalised epileptic seizures		n.s.	DeRisio et al. 2015 [93]
	51 % focal epileptic seizures evolving into generalised seizures			
	26 % generalised epileptic seizures with unknown onset			
Labrador Retriever	24 % generalised epileptic seizures	n.s.	n.s.	Berendt et al. 2002 [26]
	70 % focal epileptic seizures or focal epileptic seizures evolving into generalised seizures			
	91 % generalised epileptic seizures	n.s.	n.s.	Heynold et al. 1997 [94]
	9 % focal epileptic seizures			
	Distinction between (primary) generalised epileptic seizures and focal epileptic seizures evolving into generalised seizures was not performed.			

Table 2 Depicting breed-specific data regarding seizure type and seizure remission *(Continued)*

	96 % generalised epileptic seizures	n.s.	n.s.	Jaggy et al. 1998 [95]
	Distinction between (primary) generalised epileptic seizures and focal epileptic seizures evolving into generalised seizures was not performed.			
Lagotto Romagnolo	Mainly focal epileptic seizures	n.s.	by 8–13 weeks of age	Jokinen et al. 2007 [105]
Petit Baset Griffon Vendeen	5 % generalised epileptic seizures	n.s.	n.s.	Gulløv et al. 2011 [25]
	41 % focal epileptic seizures			
	52 % focal epileptic seizures evolving into generalised seizures			
	2 % unclassified			
Shetland Sheepdog	Predominantly generalised epileptic seizures	n.s.	n.s.	Morita et al. 2002 [109]
	Distinction between (primary) generalised epileptic seizures and focal epileptic seizures evolving into generalised seizures was not performed.			
Standard Poodle	3.5 % generalised epileptic seizures	n.s.	n.s.	Licht et al. 2007 [113]
	33 % focal epileptic seizures			
	60 % focal epileptic seizures evolving into generalised seizures			
	3.5 % generalised epileptic seizures with unknown onset			
	Predominantly focal epileptic seizures or focal epileptic seizures evolving into generalised seizures	34 % cluster seizures	n.s.	Licht et al. 2002 [65]

n.s. not specified

unremarkable laboratory results (CBC, biochemical profile, pre- and postprandial serum bile acids concentration), and normal interictal neurologic examination performed by the study investigators or a specialist in veterinary neurology. Magnetic resonance imaging (MRI) and cerebrospinal fluid (CSF) analysis were strongly recommended and obligatory if the age of onset was < 6 months. Dogs with a history of head trauma or structural brain disease were excluded. Advanced diagnostic imaging and CSF analysis were performed in 42 % of affected dogs [9]. Prevalence data for this breed yet are not reported. The median age at seizure onset was 2.5 years [9]. Among epileptic dogs, 64 % were males and 36 % females. The seizure type was specified as (primary) generalised epileptic seizures in 36 % of dogs and as focal epileptic seizures evolving into generalised seizures in 26 % of dogs; the remaining dogs (38 %) showed both seizure types [9]. In addition to their (primary or secondary) generalised seizures, 52 % of dogs also experienced focal seizures [9]. Focal seizures often presented with focal tremors, salivation, dilated pupils, and lateral head turn. Concomitant or solitary episodes with variable states of awareness and behavioural changes like panic attacks, sporadic aggressiveness, pacing, staring, or adverse reactions to emotive words were common [9]. Exclusively discrete seizures (single seizure per day) occurred in 20 % of dogs; of the remaining dogs 20 % had a history of cluster seizures, 12 % had a history of status epilepticus, and 48 % of dogs had a history of both. In summary, 68 % of dogs had a history of cluster seizures and 60 % of dogs a history of status epilepticus [9]. An important observation was that in 28 % of dogs the first seizure event presented as a cluster seizure or status epilepticus. Although severe clinical courses (high incidence of cluster seizures and status epilepticus) were frequently reported among Australian Shepherds, seizure remission was obtained in 12 % of dogs (6 % with and 6 % without antiepileptic treatment) [9], which is in line with remission rates reported in other canine epilepsy studies [8, 10, 11, 27]. The treatment response was reported to be poor (≥1 seizure day/month) in 56 % of Australian Shepherds (treatment response was only assessed for dogs that were treated sufficiently with phenobarbital alone or in combination with other AEDs; which was the case in 70 % of the study population) [9]. Phenobarbital serum concentrations did not differ between dogs with good seizure control and dogs with poor seizure control [9]. Among the deceased dogs (30 % of the population) the median age at death

Table 3 Depicting breed-specific epilepsy prevalence estimates

Breed	Prevalence	Country	Number of dogs	Study information/Epilepsy definition	Reference
Belgian Tervueren	17 %	USA	Complete records of 997 dogs containing 170 epileptic dogs. Data collection late 1980s.	Dogs were included as epilepsy cases when they experienced at least one seizure. Only dogs, which were at least five years of age at the time of the survey were included in the analysis to avoid censoring those individuals, which may have had their first seizure later in life.	Famula et al. 1997 [38]
Belgian Shepherd (Tervueren and Groenendael)	9.5 %	Denmark	1.248 registered dogs in the Danish Kennel Club, representative sample with interview of 516 dog owners identifying 49 epileptic dogs. Data collection 1995–2004.	Dogs that had experienced two or more seizures were defined as epilepsy cases.	Berendt et al. 2008 [23]
Belgian Shepherd (Tervueren and Groenendael) One large family	33 %	Denmark	199 family members (152 Groenendael and 47 Tervueren) containing 66 epileptic dogs (53 Groenendael & 13 Tervueren). Data collection 1988–2005.	Dogs that had experienced two or more seizures were defined as epilepsy cases.	Berendt et al. 2009 [41]
Border Terrier	13,1 %	Germany	Records of 365 dogs containing 47 epileptic individuals. Data collection from 1986–2000.	Not provided	Kloene et al. 2008 [56]
Irish Wolfhound	18.3 %	USA	796 Irish Wolfhounds from 115 litters with 146 identified epilepsy cases.	Dogs that had experienced more than 2 seizures. Average inbreeding coefficient (calculated throughout 10 generations) for all the dogs entered into the study was 0.156.	Casal et al. 2006 [24]
Labrador Retriever	3.1 %	Denmark	29.602 Danish Labrador retrievers registered in the Danish Kennel Club in a 10-year period. From the reference population a representative sample of 550 dogs were selected for by random sampling stratified by year of birth. After questionnaire interviews of all 550 dog-owners and clinical investigation of epilepsy suspected dogs, 17 dogs were finally identified with idiopathic epilepsy. Data collection 1989–1999.	Dogs that had experienced two or more recurrent seizures.	Berendt et al. 2002 [26]
Petit Basset Griffon Vendeen (PBGV)	8.9 %	Denmark	876 PBGV dogs registered in the Danish Kennel Club (56 dogs were exported), 471 owner interviews identified 42 epileptic individuals. Data collection 1999–2008.	Dogs that had experienced at least 2 seizures with a minimum interval of 24 h.	Gulløv et al. 2011 [25]
Finnish Spitz Dog	5.4 %	Finland	The epilepsy prevalence was calculated for the dogs that were living when their owners answered a questionnaire (111 epilepsy cases/2.069 total dogs). The questionnaire was sent to all owners of 1- to 10-year-old dogs during the period from June 2003 to July 2004.	Dogs that had experienced at least 2 seizure episodes without interictal neurologic abnormalities.	Viitmaa et al. 2013 [82]
Italian Spinone	5.3 %	UK	The owners of all UK Kennel Club registered Italian Spinoni born between 2000 and 2011 ($n = 3331$) were invited to participate in the study. Of these, 1192 returned the phase I questionnaire and 63 dogs (5.3 %) were identified with idiopathic epilepsy. Of the remaining dogs 0.6 % were identified with structural epilepsy, 0.6 % were identified with reactive epileptic seizures and 1.5 % had unclassified epilepsy.	Recurrent seizures (≥2 seizures occurring >24 h apart) with an onset between 6 months and 6 years of age in dogs with normal interictal physical and neurologic examinations and results of a CBC and biochemistry profile within the normal reference range.	DeRisio et al. 2015 [93]

was 3.1 years [9]. The identification of a causative gene mutation has not yet been reported, but a common founder of 29 affected Australian Shepherds and a clustering manifestation in littermates, full or half siblings was detected [9]. An important observation of this study was, that during the case recruitment phase, a large subset of dogs were reported with recurrent episodes of altered mentation, bizarre behavioural activity and autonomic signs, which corroborated suspicion for potential focal seizures. None of those dogs experienced generalised seizures and in most cases diagnostic work-up was lacking because the neurological signs were mild. Thus, these animals were included as neither case nor control dogs. However,

based on those findings and in contrast to the above-mentioned frequent severe clinical courses a distinct mild and focal epilepsy course cannot be excluded for the Australian Shepherd breed and may need to be further elucidated in the future [9]. Identified risk factors: The median age of seizure onset was lower in non-merle-coloured (1.8 years) than in merle-coloured (2.8 years) dogs [9]. Seizure control was associated with age at seizure onset (older age with better seizure control) and coat colour (merle dogs with better seizure control) but appeared unrelated to the ABCB1 (MDR1) genotype (when interpreting the latter finding, it needs to be considered that out of all the epilepsy cases only one dog was determined to be homozygous for the ABCB1-1Δ mutation) [9]. Seizure remission occurred independently of the clinical course and seizure frequency [9]. No association was found between seizure control, phenobarbital serum concentration and the number of administered drugs, indicating that there may be a subcategory of severe intrinsic epilepsy in Australian Shepherd dogs [9]. Reduced survival times were found in dogs with poor seizure control, in dogs <2 years of age at seizure onset, in dogs experiencing ≥ 10 seizure days within the first six months after seizure onset and in non-merle coloured dogs [9]. However, in a multivariable COX regression analysis only a high initial seizure frequency (≥10 seizure days/6 months after seizure onset) and poor seizure control remained statistically significant with respect to reduced survival times. Overall, dogs with good seizure control had a lower risk of death than dogs with poor seizure control [9]. Potential breed-specific diseases that may mimic idiopathic epilepsy: Neuronal ceroid lipofuscinosis (NCL), a neurodegenerative storage disorder, may also manifest with epileptic seizures and/or fly-biting episodes and therefore may present a potential differential in young Australian Shepherds with seizures. However, NCL usually manifests with concurrent severe neurological and/or cognitive abnormalities and seizures usually occur late in the disease course [28]. A gene test for NCL in Australian Shepherds is available (missense mutation in the CLN6 gene) [29]. One study from 2011, diagnosed two Australian Shepherds with exercise-induced collapse (EIC), which also may mimic a seizure event, and therefore should be considered as a potential differential to epileptic seizures. However, a dynamin-1 (DNM1)-gene-mutation was not detected in those two Australian Shepherds [30]. EIC usually is triggered by strenuous physical exercise and consciousness usually remains preserved during episodes, which may help to clinically differentiate between epileptic seizures and EIC [30]. Furthermore, the Australian Shepherd breed has a high frequency of the ABCB1-gene mutation (nt230 (del4)) that results in non-functional P-glycoprotein (P-gp) expression and neurotoxicity to drugs, which are P-gp substrates [31, 32]. This may need to be considered as a differential for idiopathic epilepsy in Australian Shepherd dogs that present with acute epileptic seizures and potential previous exposure to neurotoxic P-gp substrates. The frequency of dogs homozygous for the mutant allele is reported to range between 1.7 – 25 % depending on the respective study and geographic area [33].

Belgian Shepherd (mainly Groenendal and Tervueren variants)

There are ten different studies available that focus specifically on idiopathic epilepsy in the Belgian Shepherd (mainly Groenendal and Tervueren variants) [23, 34–42]. This relatively high number of studies leaves the Belgian Shepherd as one of the most intensively studied dog breeds in the field of canine epilepsy. Interestingly, an inheritance of idiopathic epilepsy in this breed was first suggested in 1968 [42]. All of the available studies respectively focus on seizure semiology, prevalence, mode of inheritance and gene mutation identification; and have been conducted mainly in Denmark [23, 37, 41], the United States [35, 36, 38–40] and Finland [34]. The variability in results between individual studies may be attributed to the examination of geographically and genetically distinct populations and variable study designs and inclusion and exclusion criteria being applied. One Danish study published in 2008 was an epidemiological study of a larger population of Belgian Shepherds registered in the Danish Kennel Club in a 10-year period. Prevalence was estimated at 9.5 % based on interviews of 516 dog owners, which identified 49 dogs with idiopathic epilepsy [23]. Mean age at seizure onset was 3.3 years. However, 39 % of all affected dogs did not experience their first seizure until after four years of age. Of the investigated epileptic dogs, 63.3 % were females and 36.7 % were male; however, a significant gender predisposition was not detected. The seizure type was reported to be focal in 25 % of dogs, focal evolving into generalisation in 53 % of dogs and (primary) generalised in 18 % of dogs (in 4 % of dogs seizures could not be classified). The most commonly reported focal seizure phenomenology included ataxia, crawling, swaying, behaviour suggesting fear, salivation, excessive attention seeking and disorientation. The median survival time from seizure onset was 2.5 years among deceased dogs [23]. In 2009 the same authors investigated a selected large Danish Belgian Shepherd family including 199 individuals with 66 idiopathic epilepsy affected dogs [41]. The epilepsy prevalence in this selected family was estimated at 33 % [41], which showed that accumulation of epileptic individuals within certain breeding lines can result in substantially higher prevalence estimates than in the breed in general (as reflected by the two Danish studies) [23]. As found in the Danish breed study from 2008, the seizure type was predominantly (83 % of dogs) defined as

focal or focal epileptic seizures evolving into generalised seizures, while only 6 % of dogs experienced (primary) generalised epileptic seizures [41]. In 11 % of dogs, seizures could not be classified. Due to the high prevalence of focal seizures the authors discussed if this familial epilepsy could be compared to familial focal epilepsy in humans [41]. This large Danish Belgian shepherd family was further investigated with respect to survival and selected risk factors for premature death by a longitudinal observational study published in 2012 [37]. The life span of epileptic dogs was not significantly shortened by the presence of epilepsy. Epilepsy was the predominant cause of death in the population and epilepsy-related deaths accounted for 70 % of all deaths in the group of dogs with epilepsy. Two probable sudden unexpected deaths related to epilepsy occurred in dogs with generalised seizures. Cluster seizures occurred in 33 % but did not significantly influence the life span of epileptic dogs. Dogs with epilepsy had an epilepsy remission proportion of 13.7 % [37]. A 2012 genome wide-association study including Belgian Shepherd epilepsy cases from Denmark, Finland and USA (159 cases and 148 controls) identified a novel idiopathic epilepsy locus [34]. The mean age at seizure onset in the dogs participating in the study was 3.3 years [34], which is in line with findings of the Danish study [23]. The median seizure frequency was 5.25 seizures per year with some dogs experiencing less than one seizure per year and others up to 10 seizures per day. One third (33 %) of the affected dogs had a history of cluster seizures. The seizure type was defined as focal epileptic seizures evolving into generalised seizures in 37 % of dogs, as generalised seizures with unknown onset in 34 % of dogs, as (primary) generalised in 18 % of dogs and as focal in 7 % of the dogs. In 4 % of dogs the seizures remained unclassified [34]. Only 3 % of the dogs did not respond to antiepileptic drug treatment, while the remaining dogs all responded at least with some degree of seizure frequency reduction. A number of dogs participating in the study had an EEG examination and interictal EEG revealed epileptiform activity with variable foci in all examined dogs [34]. Multiple studies have been conducted with respect to potential modes of inheritance in this breed, however results were not always consistent and this again may reflect different study design, inclusion and exclusion criteria. In the Danish study from 2009 the mode of inheritance of epilepsy was based on segregation analysis reported to be simple mendelian with a segregation pattern resembling autosomal dominant inheritance but with possible incomplete penetrance [41]. These results contradict the findings from an older USA study in 2003, in which a polygenic mode of inheritance influenced by a single autosomal recessive locus was suggested [35]. Furthermore a study from 1997 found that a single locus model does not appear adequate as an explanation [38], but the same investigators in a 2000 study suggested a single locus with a large effect on the incidence of seizures [39]. The 1997 USA study estimated the heritability of epilepsy in the Belgian Shepherd dog at 0.77 [38], and the 1998 USA study predicted that the offspring of the mating of two non-epileptic dogs has a probability of 0.99 of never suffering from a seizure, while the offspring of the mating of two dogs who have each had one seizure has a predicted probability 0.58 of never suffering from a seizure [40]. Although, the clinical phenotype of idiopathic epilepsy in the Belgian shepherd is well described and extensive research efforts have been undertaken, it has not yet been possible to identify causative gene mutation(s) responsible for idiopathic epilepsy in the breed [34–36]. Identified risk factors: Intact dogs with idiopathic epilepsy had a significantly increased risk of being euthanised because of idiopathic epilepsy compared to neutered dogs with idiopathic epilepsy [23]. Recently, it was found that homozygosity for a two-SNP haplotype within the ADAM23 gene conferred the highest risk for idiopathic epilepsy among the investigated Belgian shepherds [34]. These data suggested that the identified ADAM23 variant is a polymorphism, but yet needs to be further confirmed. Potential breed-specific diseases that may mimic idiopathic epilepsy: In the authors' experience the most important differential to be excluded in the Groenendael and Tervueren is a (often exercise induced) episodic involuntary movement disorder similar to paroxysmal dyskinesia described in Chinook dogs [43] and Border terriers [44]. It is recommended that the paroxysmal episode be filmed. The paroxysmal movement disorder can be distinguished from seizures because the dogs remain responsive to stimuli and their environment, for example will continue to try to play. The episodes are typically longer in duration than epileptic seizures and characterised by dystonic limb lifting (all joints in flexion). The dog may become recumbent but often remains standing (personal communication Clare Rusbridge February 2015).

Bernese Mountain dog

In the current literature, one study about idiopathic epilepsy in Bernese Mountain dogs is available [45]. This study includes 50 affected dogs from Switzerland and was published in 1999. Idiopathic epilepsy was diagnosed when physical and neurological examination, haematology, serum biochemistry, urine and CSF analysis were unremarkable. Detailed data regarding definition of idiopathic epilepsy were not provided in this study [45]. Sixty-nine healthy Bernese Mountain dogs served as control dogs and a possible gender predisposition was analysed by the use of a non-preselected population containing 4005 Swiss Bernese Mountain dogs [45]. Prevalence data have not been reported for this breed [45]. The mean age of seizure onset was 2.2 years (26.5 months) with 62 % of dogs exhibited their first seizure between one to three years of age, 20 % had an age of seizure onset of less than one year and 18 %

experienced the first seizure at an age ≥ 3 years [45]. A gender predisposition for males (62 %) compared to females (38 %) was observed. The gender ratios (males to females) were 1.6:1 among epileptic dogs, 1:1.1 among non-epileptic control dogs and 1:1.4 among all dogs [45]. The seizure type was defined as generalised in 98 % of dogs and as focal in 2 % of dogs [45]. However, a detailed differentiation between (primary) generalised seizures and focal epileptic seizures evolving into generalised epileptic seizures was not conducted, hence some of the dogs may have experienced focal seizures evolving into generalisation rather than (primary) generalised seizures. The seizure frequency was not analysed in detail, but was reported to range from three seizures per week to one seizure every year, with 50 % of dogs experiencing more than one seizure every two months. The results of the pedigree analyses and binomial test were best compatible with a polygenic, recessive (possibly sex-modified) mode of inheritance [45]. The identification of a causative gene mutation has not yet been reported [45]. Identified risk factors: The age at seizure onset was significantly lower in dogs from affected parental animals than in dogs from healthy parental animals [45].

Border Collie

In the current literature, one specific study about idiopathic epilepsy in Border Collies is available [8]. This study – conducted in Germany – was published in 2010 and provides data regarding clinical characteristics and heritability of epilepsy among a German Border Collie population [8]. The latter study, included data of 49 Border Collies diagnosed with idiopathic epilepsy; no control dogs were included. Idiopathic epilepsy was defined as recurrent seizures (≥2 seizure days at least 4 weeks apart) with an onset between 6 months and 5 years of age in dogs with otherwise normal physical, laboratory, and neurological characteristics upon examination. Requested minimal laboratory investigations included a CBC and biochemical profile. MRI and CSF analysis were requested if age at seizure onset was < 6 months or > 5 years of age [8]. Detailed prevalence data have yet not been provided for this breed [8]. Although detailed prevalence data are not available, the Border Collie was among the most common affected breeds in several epidemiological canine epilepsy studies in the UK [17, 46, 47]. The median age at seizure onset in the German study was 2.4 years with 74 % of dogs experiencing their first seizure between 1 and 5 years. However 18 % experienced the first seizure at an age ≤ 1 year and 8 % of dogs had an age of ≥ 5 years. No gender predisposition was detected with 49 % males and 51 % females. The seizure type was defined as focal epileptic seizures evolving into generalised seizures in 78 % of dogs and as (primary) generalised in 8 % of dogs. In 14 % of dogs the seizures remained unclassified, as seizure onset was not clearly observed. In addition, 45 % of dogs also had sporadic focal epileptic seizures, which manifested as sudden uncontrolled head or facial twitching mostly associated with impaired consciousness. Active epilepsy (≥1 epileptic seizure in the last year of the study or in the year preceding death) was documented in 82 % of dogs and seizure remission was reported for 18 % of the Border Collies with idiopathic epilepsy, which is similar to reported remission rates in other dog populations [9, 11, 27, 47]. However, a recent canine epilepsy study which focussed on identification of clinical risk factors for remission revealed the Border Collie as the breed least likely to achieve seizure remission [47]. Of all affected dogs 45 % had a history of cluster seizures, 4 % had a history of status epilepticus and 49 % had a history of both. Overall, 94 % of all dogs included in the German study experienced at least one episode of cluster seizures and 60 % of all dogs had at least one episode of status epilepticus [8]. A high prevalence of cluster seizures among Border Collies was also found in a recent study about canine juvenile epilepsy in the UK [10], however, in contradiction to this data another UK study reported the Border Collie as being less affected by cluster seizures (>80 % not clustering) [46]. The median age at death among the deceased epileptic Border Collies (47 % of the study population) was 5.2 years [8], which is more than half that of the general UK Border Collie population (median age at death 13.5 years) found in another study [48]. The median survival time from seizure onset for deceased epileptic Border Collies was short being only 2.1 years in the German study [8]. This finding was supported by another study that also found a significant shorter mean survival time for Border Collies with idiopathic epilepsy (3.6 years) compared to a general dog population with idiopathic epilepsy (7.9 years) [10]. Treatment response was reported to be poor (≥1 seizure day/month) in 71 % of dogs that were treated adequately (67 % of the study population) with ≥ 2 antiepileptic drugs [8]. In summary, all above-mentioned clinical data suggest that this breed may generally have a severe epilepsy course and epileptic Border Collies are more likely to be euthanised than affected dogs of other breeds. Based on pedigree analysis, 29 affected dogs shared a common ancestor, indicating a strong genetic background for epilepsy in Border Collies. The identification of a causative gene mutation has yet to be achieved [8]. Identified risk factors: No positive impact of neutering on the course of epilepsy was detected. Comparison between dogs with active epilepsy and dogs in remission identified significant differences in age at seizure onset (older age at seizure onset in dogs that went into remission) and age at death (younger age at death for dogs with active epilepsy). Furthermore, initial seizure frequency (during the first 6 months) was

significantly lower in dogs that went into remission compared to dogs with continuing epilepsy. Reduced survival times were found in dogs with young age at seizure onset (≤2 years of age) and dogs with a severe epilepsy course (occurrence of status epilepticus) [8]. No significant association between survival time and sex, reproductive status or number of administered drugs was identified. A Swiss study identified a polymorphism in the ABCB1-gene that was found to be associated with antiepileptic drug resistance (T > G variation in intron 1) in Border Collies [49]. This ABCB1-polymorphism (T > G variant) was detected in a later Japanese study with a frequency of 9.8 % among a Japanese Border Collie population [50]. In contrast to a known "loss of function" for the nt230 (del4) mutation, the T > G variation is hypothesised to have an ABCB1 drug transporter"gain of function" and therefore potentially might contribute to drug resistance. However, future research is required to investigate those associations further and also to investigate the possible mechanisms of this ABCB1-polymorphism on drug resistant epilepsy in Border Collies. Potential breed-specific diseases that may mimic idiopathic epilepsy: NCL, a neurodegenerative disorder, may also manifest with epileptic seizures and therefore may present a potential differential in young Border Collies presenting with seizures [51–53]. However, NCL is reported to manifest between the age of 15 and 22 months [51, 53] with severe and rapidly progressive neurological signs (e.g. vision impairment, gait abnormalities, dementia, behavioural abnormalities, aggression). Affected Border Collis died before the age of 3 years and the latest they were euthanized after the onset of clinical signs was 6 months [51]. A causative gene mutation for NCL in Border Collies has been identified and a gene test is available (mutation in the CLN5 gene) [54]. One study from 2011 reported 20 Border Collies diagnosed with exercise-induced collapse, but a DNM1-gene-mutation was not observed in any of these Border Collies [30]. However, in contrast to epileptic seizures, EIC usually is triggered by strenuous exercise and consciousness usually remains preserved during episodes and the dog's behaviour suggests discomfort from heat (panting, seeking shade and/or water), which may help a clinician to differentiate between these two diseases [30]. The Border Collie breed is also affected by the ABCB1/MDR1-gene mutation (nt230 (del4)), which may need to be considered in dogs with acute seizures and potential previous exposure to neurotoxic P-gp substrates. The frequency of homozygous affected dogs is reported with 0.3 % [33]. There is one case report describing hyperammonemic encephalopathy (normal bile acids, but abnormal ammonia tolerance test) secondary to a hereditary selective cobalamin malabsorption in a juvenile Border Collie that presented with neurological signs, such as an abnormal mental state (stupor) [55]. However, although this particular dog did not seizure, hyperammonemia may carry a potential risk for reactive seizures in other Border Collies with such hyperammonemic encephalopathy.

Border Terrier

One specific study about epilepsy in Border Terriers that was conducted in Germany and published in 2008 is available in the current literature [56]. This study included 47 affected dogs and 318 non-affected control dogs collected by questionnaires send to owners of dogs registered in the German Terrier Club. Detailed data regarding epilepsy definition were not provided [56]. The prevalence of epilepsy was estimated at 13.1 % among the investigated population [56]. In line with this high prevalence, a UK epilepsy prevalence and risk factor study reported the Border Terrier with a 2.7 times increased odds of epilepsy compared with crossbred dogs [17]. A gender predisposition was not detected with 53 % males and 47 % females in the German study. The mean age at seizure onset was 3.2 years. The clinical course was assessed as mild in most of the dogs (70 %) with only occasional seizures per year; only 27 % of dogs suffered from multiple seizures per month. Cluster seizures were documented in 8.5 % of dogs. The seizure type was defined as generalised epileptic seizures in 68 % of dogs and as focal epileptic seizures in 32 % of dogs, however a differentiation between (primary) generalised epileptic seizures and focal epileptic seizures evolving into generalised seizures was not performed. In 17 % of dogs autonomic signs (urination, defecation) were reported during a seizure and some of the dogs (27.6 %) experienced preictal signs, such as restlessness, disorientation, behaviour suggesting fear or seeking owners' attention [57]. Hence, according to the new classification guidelines some of those dogs with a "preictal phase" (27.6 %) might be reclassified as having focal seizures evolving into generalised seizures. The seizures were defined as tonic in 46.8 % of dogs, as clonic in 14.9 % of dogs and as tonic-clonic in 38.3 % of dogs. In 51 % of dogs seizures occurred when they were in a resting position [57]. One important finding was that in most of the dogs (79 %) consciousness was assessed as preserved during a seizure, and only 21 % of dogs experienced an ictal loss of consciousness. Thirty per cent of dogs were treated with phenobarbital, and in 23.4 % of dogs, owners subjectively reported at least some clinical improvement [57]. The identification of a causative gene mutation has not yet been reported [56]. Potential breed-specific diseases that may mimic idiopathic epilepsy: Canine epileptoid cramping syndrome (CECS) is proposed as paroxysmal dyskinesia affecting Border Terriers. Recently, detailed data regarding typical clinical phenotypes of 29 CECS-affected Border Terriers have been published [44]. Based on the similarities regarding

clinical semiology and typical age of disease manifestation, CECS is an important differential to epileptic seizures in this breed; even for experienced clinicians CECS may mimic a seizure disorder and vice versa. Distinct phenotypic characteristic of the paroxysmal events in CECS are generalised tremor, dystonia and difficulty walking. Episodes were reported to last from 2–30 min in the majority of dogs and in some up to 150 min [44]. In addition, some owners report signs of gastrointestinal distress associated with the episodes, including borborygmi during the episode and vomiting and diarrhoea before or after the episode in almost 50 % of the dogs. From a clinical point of view, the assessment of consciousness and the occurrence of autonomic signs such as urination, defecation or salivation during an episode may help to differentiate between both diseases, with CECS usually being characterized by a normal conscious state and absence of above mentioned autonomous signs [44]. However, as 79 % of epileptic Border Terriers were reported to have preserved consciousness during an epileptic seizure in the German study [56] and 62 % of Border Terriers diagnosed with CECS showed some kind of "pre- and postcramping" signs (such as eating grass, vomiting, or seeking to be near owners) [44] diagnosis still may remain challenging and potential overlapping of both diseases needs to be further elucidated in the future (e.g. with ambulatory ictal EEG examinations). With regard to response to therapy, therapeutic trials with phenobarbital, potassium bromide, diazepam, butylscopolamin resulted in no improvement in the majority of CECS affected dogs, but 50 % of the owners felt improvement after a dietary change (e.g. change to hypoallergenic diet) [44].

Cavalier King Charles Spaniel

For several years it has been suggested that idiopathic epilepsy may occur as an independent disease in this breed and may not be the consequence of the frequently occurring Chiari-like malformation [58]. This hypothesis was supported by a study from 2013 that did not find a significant association between the degree of the Chiari-like malformation, (such as degree of ventriculomegaly) and the occurrence of epileptic seizures [59]. However, an overlapping of the two diseases cannot be entirely excluded. According to the findings of the study published in 2013 the seizure type was defined as (primary) generalised epileptic seizures in 39 % of the dogs, as focal epileptic seizures in 36 % and as focal epileptic seizures evolving into generalised seizures in 25 % of dogs [59]. No detailed data regarding potential modes of inheritance are available; however, epilepsy was found more frequently in lines originating from whole-colour dogs [58]. Potential breed-specific diseases that may mimic idiopathic epilepsy: Cavalier King Charles Spaniels are also known to suffer from Episodic Falling (paroxysmal exercise-induced dyskinesia) [60]. Episodic falling is a movement disorder that typically manifests between the age of 4 months and four years. Falling episodes are induced by physical activity, stress and excitement and manifest with hypertonicity of the limbs resulting in inability to move or even complete collapse. In contrast to epileptic seizures consciousness usually is not affected during these episodes [60]. A gene test is available for episodic falling that is based on evidence of a BCAN (brevican) mutation [61, 62]. Older Cavalier King Charles spaniels (>5 years old) have a high prevalence of myoclonus, which manifests most commonly as a brief jerking of the head and forelimbs when the dog is standing or sitting. Initially the syndrome is relatively benign but can be progressive with affected dogs suffering frequent jerks which may interfere with function, for example cause the dog to fall or stumble [63]. The syndrome can be confused with focal epileptic seizures but generally does not respond to AEDs licenced for dogs although may respond to levetiracetam (personal communication Clare Rusbridge February 2015). The pathogenesis of the myoclonus is as yet undetermined.

Collie (rough and smooth coated; or Scottish sheepdog also known as Scottish Collie)

There is no specific epidemiological study for the Rough and Smooth coated Collie available, but one study has been published, which specifically focused on seizure control in association to the ABCB1/MDR1-genotype in epileptic Rough and Smooth coated Collies [64]. This study was conducted in the USA and included 29 Rough and Smooth Collies with suspected idiopathic epilepsy [64]. The investigated population consisted of 25 Rough coated Collies, 3 Smooth coated Collies, and 1 Collie cross. Collies with an age of seizure onset between 6 months and 5 years of age and a minimum 6-month history of AED administration were recruited for this cohort study [64]. All dogs had a presumptive diagnosis of idiopathic epilepsy, which was made by the primary veterinarian based on examination findings and laboratory analysis [64]. A good seizure control was defined as ≤ 1 seizure/month and no occurrence of cluster seizures; a poor seizure control was defined by > 1 seizure/month or the occurrence of cluster seizures [64]. Among the investigated population 66 % received one antiepileptic drug, 31 % received two antiepileptic drugs and 3 % received three antiepileptic drugs. Overall, 38 % of dogs were reported to have a poor seizure control, with a mean seizure frequency of 3.9 seizures/month; the remaining 62 % of dogs had a good seizure control with a mean seizure frequency of 0.29 seizures/month. Eighty-nine per cent of dogs with a good seizure control were managed with a single AED and 50 % of those dogs with a good seizure control became seizure free. Of

the dogs with a poor seizure control 91 % had a history of cluster seizures (=35 % of all dogs). Of all participating dogs, 48 % were homozygous for the ABCB1-/MDR1-gene mutation (nt230 (del4)) (M/M), 38 % were heterozygous for the mutation (M/N), and 14 % had the wild-type genotype (N/N). The M/M group had significantly better seizure control than the M/N or N/N groups. However, as the M/N and N/N groups suffered more frequently from antiepileptic drug adverse effects than dogs from the M/M group (with non-significant differences of antiepileptic drug serum concentrations among all groups), the authors concluded, that the association of the M/M genotype with better seizure control compared to the M/N or N/N (with poorer seizure control) does not support the transporter hypothesis of Pgp-mediated drug resistance in this breed. The authors rather considered the association between genotype and seizure outcome as an epiphenomenon, with the ABCB1/MDR1-gene mutation being associated with a less robust seizure phenotype that favours drug efficacy in accordance to the intrinsic disease severity theory [64]. However, Rough and Smooth coated Collies appear to have a less severe clinical manifestation of idiopathic epilepsy when compared with other breeds such as the Australian Shepherd or Border Collie. Potential breed-specific diseases that may mimic idiopathic epilepsy: As mentioned above Rough and Smooth Collies are breeds affected by ABCB1/MDR1-gene mutation, which needs to be considered for dogs with very acute seizures and potential previous exposure to neurotoxic P-gp substrates. The frequency of homozygous affected dogs is reported to range between 24 – 52 % depending on the respective study and geographic area [33].

Dalmatian

To date, there is no study available that has specifically evaluated idiopathic epilepsy in Dalmatians, but Short et al. found that the Dalmatian was in the "top 14" of dog breeds with epilepsy in the UK [46]. By contrast the Dalmatian was not listed in the "top 20" of dog breeds ranking in Kennel Club number registrations in 2011, which suggests a predisposition to epilepsy [46]. Furthermore, one study that reported clinical manifestations of naturally occurring canine epileptic seizures also included very detailed seizure data of 11 Dalmatians with probable idiopathic epilepsy [65], and hence this breed was included in the present manuscript. However, interpretation of these data should be made with caution due to the low number of investigated dogs. The latter study classified dogs as having probable idiopathic epilepsy if they had had at least 1 seizure without any evidence of an underlying cause. Specifically, the following conditions all had to be met: the owner's answers to health- related questions revealed no illnesses or events (e.g., head trauma) that could plausibly account for the seizures, at least 1 year had passed since seizure onset during which no interictal neurologic abnormalities were observed, and the dog was between 6 months and 7.5 years old when seizures began [65]. The median age at seizure onset among those eleven Dalmatians was 2.9 years. The number of Dalmatians was too small to reliably assess a potential gender predisposition, however, 36.4 % of the dogs were males and 63.6 % were females [65]. Among dogs, in which owners were able to reliably report the initial stages of an epileptic seizure, 20 % were reported to have (primary) generalised seizures and 80 % were reported to suffer from focal or focal seizures evolving into generalisation [65]. The mean seizure frequency was analysed with 9.7 seizures per year. At least one cluster seizure event was reported in 63.6 % of dogs; further analysis revealed that among dogs with cluster seizures the mean percentage of total episodes that were clusters was 17.8 % [65]. Mean duration of a generalised seizure was 3.3 min, whereas mean duration of a focal seizure was 4.7 min. Mean duration of a postictal phase after generalised seizures was 16 min and after a focal seizure 0.9 min [65]. The majority of dogs (72.7 %) received antiepileptic treatment, but treatment response could not be assessed reliably because few dogs provided enough seizure baseline data, making it impossible to evaluate their overall response to treatment [65].

Dutch breeds

There are nine different Dutch pedigree breeds. Although most of these breeds occur in the surrounding countries of the Netherlands, all nine breeds are small in number, increasing the risk of hereditary disorders [66, 67]. Recently all case-record logs from the nine Dutch breeders associations representing the nine Dutch breeds were reviewed [68]. Dogs presented with epileptic seizures were either classified as suffering from idiopathic generalised tonic-clonic seizures or classified as focal epilepsy based on their history, the clinical signs and diagnostic work-up. There are four breeds, 'Het Nederlandse Kooikerhondje' 'Drentse Patrijshond', 'Stabyhoun', and 'Saarlooswolfhond' with a higher incidence of idiopathic epilepsy [68]. Interestingly the incidence of idiopathic epilepsy is, within the other Dutch breeds, 'Hollandse Herder (also called Dutch Shepherd)', 'Smoushond', 'Het Nederlandse Markiesje, 'Wetterhoun', 'Nederlandse Schapendoes' remarkably low compared with most pedigree breeds. Hollandse herder: the incidence of generalised tonic-clonic epilepsy varied during the last ten years around 0.25 %. The affected dogs are presented between one to three years of age [68]. This breed, that originates to before 1890, may have a small common ancestry with the Belgian Shepherd dog [66] and like the Belgian Shepherd dog different hair coat varieties are recognised (shorthair, longhair and roughcoat).

However, in contrast with the Belgian Shepherd the incidence of idiopathic epilepsy is low in all varieties. Smoushond: the incidence of dogs presented with generalised tonic-clonic seizures was 0.7 % during the last 20 years. Another 0.7 % of the dogs were presented with signs suggestive of focal epilepsy but none of these dogs showed secondary generalisation As the frequency of these focal seizures remained low in these dogs it remains questionable how to classify these dogs [68]. Het Nederlandse Markiesje: the incidence of idiopathic epilepsy appears to be, with only 0.29 %. Within this breed a novel lethal neurological disorder has been identified in recently weaned pups, with an incidence of 1 %, that has been classified as a paroxysmal hyperekplexia [69]. Although affected dogs remain conscious, the tonic rigidity of this disorder may be confused with a myoclonic or tonic epilepsy [69]. Wetterhoun: this extremely small breed belongs to the group of Retrievers and Water dogs and originated from the Friesian area of the Netherlands. Although the number of Wetterhouns bred annually is too small (between 60 an 150) to maintain a healthy population, the incidence of generalised tonic-clonic epilepsy is extremely low: 0.1 %. Similar figures have been found in the Nederlandse Schapendoes (0.18 %) [68]. In contrast with these aforementioned five breeds that have a very low prevalence of epilepsy, there are four other Dutch breeds that are more greatly affected. The highest incidence has been found in the Drentse Patrijshond. Within the Drentse Patrijshond, a spaniel type of hunting dog, idiopathic epilepsy has been reported since 1986 [70]. In 1986 the incidence of idiopathic generalised epilepsy was at least 1.4 %. If the investigators excluded a group with missing data the incidence was calculated to be up to 9.4 %. Males and females were equally affected, and the dogs, were between 9 months and 5 years of age with a median of three years of age at onset of seizures [70]. Affected dogs did not have a higher inbreeding coefficient compared to the non-affected population [70]. The hereditary grade (h^2) was found to be between 0.33 and 0.47, which is highly suggestive for a genetic origin. Recently, the number of affected animals was again evaluated using the earlier described inclusion criteria [68]. The incidence, calculated over the last 20 years currently varies between 3 to 5 %. The majority of the affected dogs only have one to two seizures per time period but a small number (<10 %) suffered from clusters with more than three seizures per event [68]. In contrast with the earlier study of Bobbert and Reekers [70] , dogs could be presented up to 8 years of age before being identified as suffering from idiopathic epilepsy. As some of these affected dogs already had been bred from, the incidence of idiopathic epilepsy remains high. The Stabijhoun, a Friesian type of spaniel hunting dog (also called 'moles dog' as it is used to catch moles) had an average incidence of 1.5 % over the last 15 years. Dogs were presented between one and 5 years of age. Although not statistically significant males appeared to be more affected than females (59 % males to 41 % females). Typically, the dogs are presented with generalised tonic-clonic seizures. Het Nederlandse Kooikerhondje, also called 'Dutch Decoy Dog' as it is used as "decoy" to catch ducks [71] was re-established after the 2nd World War and subjected to a long period of intense inbreeding [72]. As a consequence several, hereditary, neurological disorders have been recognized in this breed [73]. The incidence of idiopathic epilepsy, calculated for the last 14 years is estimated to be 1.4 %. Males (71 %) appear to be overrepresented compared to females (29 %). The dogs are normally presented between the age of 1 and 3 years old [68]. The last breed, the Saarlooswolfhond, is a breed established from a German Shepherd and European wolf hybrid and was created just before the 2nd World War by Mr. Leendert Saarloos [66, 67]. The population is very small and highly inbred, with inbreeding coefficients varying between 25 to 60 %. A total of 37 dogs have been identified suffering from tonic-clonic seizures. The treatment response rate appears to be poor in this breed and up to 50 % suffer from cluster seizures. Up to 50 % of these dogs were euthanised, due too poor control of the seizures, within two years after their first seizure [68]. As the breed is highly inbred, selection against epilepsy is very challenging. Currently the breeders are using, with permission of the Dutch Kennel club, outcrossing to improve the genetic variation within this breed [68].

English Springer Spaniel

In the current literature, one specific study about epilepsy in English Springer Spaniels is available [74]. This study was published in 2005 and provides data regarding clinical characteristics and mode of inheritance of idiopathic epilepsy among an US English Springer Spaniel population [74]. The latter study included 45 dogs diagnosed with idiopathic epilepsy. Idiopathic epilepsy was defined as ≥2 seizures at least 1 month apart, without any evidence of toxin exposure or head trauma, and results of routine serum biochemical testing and interictal neurologic examinations were normal. Dogs in which seizures first began at < 6 months or > 5 years of age were considered to have idiopathic epilepsy only if CSF analysis and CT or MRI had been performed and no underlying cause of the seizures had been identified or if 2 years had lapsed since the onset of seizures without any interictal neurologic abnormalities [74]. The median age of seizure onset was reported as 3 years. A bimodal age distribution was detected with one peak at 1–3 years (60 %) and one peak at 5–6 years (20 %) [74]. There was no significant gender predisposition [74]. The seizure type was defined as (primary) generalised in 47 % of

dogs and as focal or focal epileptic seizures evolving into generalised seizures in 53 % of dogs. For the dogs with focal seizures, 58 % of dogs had simple focal seizures, 38 % had focal epileptic seizures evolving into generalised seizures, and 4 % had complex focal seizures characterized by stereotypic repetitive behaviours [74]. Applying the new seizure classification guidelines the seizure type distribution would be: 47 % generalised epileptic seizures, 33 % focal epileptic seizures and 20 % focal epileptic seizures evolving into generalised epileptic seizures. Seizure frequency ranged from 12 seizures per month to 1 seizure every 2 years (median 5 seizures per year). A history of cluster seizures was reported in 38 % of dogs [74]. Sixty-seven per cent of the dogs received an antiepileptic drug treatment. Treatment response was assessed subjectively based on the owners'opinion with a reported good response in 23 % of treated dogs, a moderate response in 47 % of dogs and a poor response in 30 % of dogs [74]. Detailed prevalence data have yet not been provided for this breed. However, one epidemiological study conducted in the UK reported 2.3 % English Springer Spaniels among 1260 dogs with epilepsy and reported a high incidence of cluster seizures [46]. Similarly, another UK study found that the English Springer Spaniel was one of the most commonly epilepsy affected purebreds [17]; however, it must be considered that the English Springer Spaniel is a popular breed in the UK, and thus may be overrepresented in this population in general. In contrast to the UK epidemiological studies, the English Springer Spaniel 2013 UK Breed Health survey found that the prevalence of epilepsy was 0.6 % (26 of 4327 dogs) [75]. Epilepsy was reported as occurring in young and middle aged dogs, of which 18 were male and 8 female. However in the mortality section of this survey (dogs which had died between 1st January 2008 and 31st July 2013) epilepsy was reported as the cause of 3.2 % of all deaths [75]. Many of the deaths were young dogs and consequently the UK breed club expressed concern about the disease and its impact. Pedigree analysis and results of segregation analysis of the US study were consistent with a partially penetrant autosomal recessive or polygenic inheritance [74]. The identification of a causative gene mutation has not yet reported [76]. Potential breed-specific diseases that may mimic idiopathic epilepsy: Fucosidosis is a lysosomal storage disease, which affects humans and English Springer Spaniels. The disease is autosomal recessively inherited in both species and results from a deficiency of the enzyme alpha-L-fucosidase [77, 78]. Affected English Springer Spaniels present with behavioural changes and signs of motor dysfunction that start at one to two years of age. Behavioural changes may manifest as bizarre behaviour patterns, aggression or unusually depressed mental state, and affected dogs appear to forget previously learned behaviours [77]. These behavioural changes may carry a risk of mistaking focal epileptic seizures as a potential differential in the early stage of the disease. However, Fucosidosis progresses rapidly, and death or euthanasia usually occurs within a few weeks from the onset of clinical signs [78]. A genetic test for Fucosidosis is available [79].

Finnish Spitz

Four specific studies about epilepsy in Finnish Spitz dogs are currently available [80–83], reporting prevalence, clinical characteristics, mode of inheritance, imaging findings and EEG findings. One prospective epidemiological study published in 2013 reported an epilepsy prevalence of 5.4 % among the Finnish Spitz dog population in Finland that were still alive [82]. This epidemiological study provided data regarding phenotype, inheritance and risk factors for idiopathic epilepsy of 141 affected Finnish Spitz dogs. For this study idiopathic epilepsy was defined as at least 2 seizure episodes without interictal neurologic abnormalities; with data collected by questionnaires and telephone interviews [82]. The latter study detected a significant gender predisposition with 60.1 % males and 39.9 % females compared to a control population [82]. The median age of seizure onset was 3 years [82]. The median seizure frequency was 2 seizures per year. A history of cluster seizures was reported for 16.2 % of dogs. The seizure type was defined as focal epileptic seizures in 54 % of the dogs, as focal epileptic seizures evolving into generalised seizures in 31 % of the dogs and as (primary) generalised epileptic seizures in 1 % of the dogs [82]. In 7 % of dogs the seizures were generalised but with unknown onset and in an additional 7 % of dogs the seizure type was unclassified. The median seizure duration was long at 11.75 min (occasionally ≥ 40 min). The disease course was reported as non-progressive in 67.8 % of the dogs and treatment response was assessed as good in 78.9 % of the dogs [82]. The heritability was estimated at 0.22 and, hence, a complex pattern of inheritance such as polygenic recessive or autosomal recessive with incomplete penetrance was suggested [82]. Another study conducted in 2006 focused on EEG and MRI findings in 11 affected Finnish Spitz dogs [81]. Among those dogs the seizure type again predominantly was defined as focal epileptic seizure or as focal epileptic seizure evolving into generalised epileptic seizures (in 73 % of the dogs), with the majority of dogs experiencing the latter seizure type [81]. In 23 % of dogs, episodic behavioural changes were present that lasted for only a few minutes such as disorientation, fear and compulsive walking. These episodes were classified as focal seizure activity, since consciousness was altered during these episodes [81]. Based on the predominant focal seizure type the term focal idiopathic epilepsy was proposed. On EEG

examination, focal epileptic activity was found in 64 % of dogs, and generalised epileptic activity was observed in 36 % of dogs [81]. On MRI examination, contrast enhancement was detected within the right parietal cortex in one of the dogs, but was suggested to be a reversible postictal finding, as such changes were not observed in repeated MRI examination of the same dog [81]. The remaining dogs showed no MRI abnormalities [81]. Another EEG study from 2007 – including 15 affected Finnish Spitz dogs – reported that paroxysmal activity seems to originate from a caudal-occipital location [80]. Furthermore, the EEGs of dogs with epilepsy exhibited a significant difference in background frequency bands compared with healthy control dogs; and beyond that, phenobarbital treatment in affected dogs was identified to markedly influence all background activity bands [80]. Recently, a FDG-PET-study has been published that investigated 11 affected Finnish Spitz dogs diagnosed with focal idiopathic epilepsy and six healthy controls [83]. This study identified that epileptic dogs had significantly lower standardized uptake values in numerous cortical regions, the cerebellum, and the hippocampus compared to the control dogs. The lowest standardized uptake values were found in the occipital lobe. Thus, the authors of this study suggested the use of FDG-PET as a diagnostic tool for Finnish Spitz dogs with suspected idiopathic epilepsy [83]. Identified risk factors: A generalised seizure phase was determined to be a risk factor for development of progressive disease [82]. Predisposing factors associated with the occurrence of seizure generalisation were the age of onset (≤3 years), duration of the seizure (1–10 min and ≥ 20 min), number of feeding times per day (only once per day), and when the dog was used for hunting [82].

Golden Retriever

Three studies focusing specifically on idiopathic epilepsy in Golden Retrievers –all conducted in Switzerland – have been published in the veterinary literature to date [84–86]. These studies provide information about clinical manifestation, heritability and EEG characteristics. Based on the study, 25 affected dogs [86], 36 affected dogs [84] or 5 affected dogs [85] were included, respectively. Prevalence data have not been reported to date, but the Golden Retriever was among the most common affected breeds in an UK epidemiological epilepsy study [17]; however, this may be due to the Golden Retriever being a very popular breed in the UK. Depending on the respective study the mean age at seizure onset ranged between 27.5 months (≈2.3 years) [84] and 24.9 months (≈2 years) [86]. The 1994 study, was a retrospective cohort study, that diagnosed idiopathic epilepsy when normal results on clinical, neurological, laboratory, CSF and EEG examinations were evident [84]. This study found a significant gender predisposition for male dogs (ratio 3.5:1), but only when a distribution of 1:1 for the general dog population was assumed [84]. Generalised epileptic seizures were reported as the most common seizure type among all of the studies with 83 % [86] and 92 % [84], respectively, but a detailed distinction between (primary) generalised epileptic seizures and focal epileptic seizures evolving into generalised epileptic seizures was not provided [84, 86]. Hence, a proportion of dogs may have suffered from focal epileptic seizures evolving into generalised epileptic seizures instead of (primary) generalised epileptic seizures. A long-term treatment study from 1999 included epileptic dogs when they had at least 2 epileptic seizures, normal clinical and neurological examination, normal routine blood work, normal urine analysis and normal CSF analysis. Dogs that were pre-treated with antiepileptic treatment were excluded from the study [86]. The mean seizure frequency was reported with one seizure every 16 days in the latter study [86]. A good initial treatment response to phenobarbital was observed in most of the dogs, however, after 4 years, treatment response was poor with almost half (43 %) of the dogs being euthanized [86]. The mean survival time after diagnosis was 46 months (≈3.8 years) among phenobarbital treated dogs [86]. A continuous positive impact of castration/neutering on seizure course was not found in any of the studies (although in few dogs a transient improvement was initially noted) [84, 86]. An EEG study from 1996 frequently identified spindles in all recordings of five examined epileptic Golden Retrievers [85]. Early data already suggested a genetic base for this breed, based on an increased idiopathic epilepsy prevalence of certain subpopulations and a repeated occurrence in different families of the same sires [84]. Based on pedigree analyses and binomial testing an autosomal multifactorial recessive mode of inheritance was suspected [84]. The identification of a causative gene mutation has not yet been reported. Identified risk factors: Treatment response was better the earlier an antiepileptic treatment was initiated and the lower the pretreatment seizure frequency [86]. Potential breed-specific diseases that may mimic idiopathic epilepsy: One study that investigated EIC among several dog breeds (Labrador Retrievers and non-Labrador retriever breeds) identified some Golden Retrievers diagnosed with EIC; however, a DNM1-gene mutation was not identified in any of the affected Golden Retrievers [30]. In contrast to epileptic seizures EIC usually is triggered by strenuous exercise and mental status predominantly remains normal during episodes, which may help a clinician to differentiate between both diseases.

Hungarian (Magyar) Vizsla

To date, one study about clinical characteristics and inheritance of idiopathic epilepsy in Hungarian (Magyar) Vizslas has been published in 2003 [87]. This study was

conducted in the United States and summarised information on 29 Hungarian (Magyar) Vizslas diagnosed with idiopathic epilepsy and 114 non-affected siblings and parents [87]. Idiopathic epilepsy was defined on the basis of a dog having 2 or more seizures occurring at least 1 month apart, no evidence of toxin exposure or head trauma, normal serum chemistry results, and a normal neurologic examination. For dogs with an age at seizure onset <6 months or >5 years, unremarkable findings on CT or MRI scans and CSF analysis were required [87]. Five dogs underwent CSF analysis and three dogs had brain-imaging studies [87]. Prevalence data are yet not reported for this breed, but among 1260 dogs with epilepsy in the UK 0.6 % were Hungarian (Magyar) Vizslas [46]. No significant gender predisposition was found with 59 % males compared to 41 % females [87]. The median age of seizure onset was 3 years. The seizure type was defined as focal epileptic seizures in 79 % of dogs and as generalised epileptic seizures in 21 % of dogs. In 22 % of those dogs with focal epileptic seizures, the seizures evolved into generalised epileptic seizures. In other words, 62 % of dogs had focal epileptic seizures, 17 % of dogs had focal epileptic seizures evolving into generalised seizures and 21 % had generalised epileptic seizures. Initial focal epileptic seizure signs consisted of a combination of limb or head tremors, staring, mydriasis, lip smacking, salivating, facial twitching and/or vomiting [87]. Two dogs, diagnosed with focal seizures, exhibited fly-biting episodes which responded to antiepileptic drugs [87]. The median seizure frequency for the study population was 9 seizures per year. Forty-eight per cent of the 29 epileptic dogs received antiepileptic drug treatment with 21 % of those being not well controlled based on their owners subjective opinion [87]. The segregation analysis was consistent with an autosomal recessive inheritance; however, polygenic inheritance could not be excluded [87]. Pedigree analysis revealed that all affected dogs could be traced back to a common sire. The identification of a causative gene mutation has not yet reported [76, 87].

Irish Wolfhound

In the current literature, one study is available that provides information regarding heritability and clinical characteristics of idiopathic epilepsy in Irish Wolfhounds [24]. The latter study was published in 2006 and conducted in the United States [24]. The diagnosis of idiopathic epilepsy was made based on a history of more than 2 seizures in the absence of other medical problems. Absence of other medical problems was confirmed for all affected dogs by normal physical and neurologic examination results, CBC, serum biochemical analysis, ammonia or bile acid values or both, and urine analysis. Dogs were considered unaffected if no seizure had been observed during the dog's lifetime. Seizure-free dogs that died before the age of 4 years and dogs who had seizures in the presence of seizure-associated conditions or diseases, compatible with metabolic seizures or structural epilepsy were excluded from the study [24]. Among a population that contained 796 Irish Wolfhounds, 146 dogs with idiopathic epilepsy were identified, leading to an estimated epilepsy prevalence of 18.3 % [24]. In 73 % of dogs the age at seizure onset was under three years old, with males having a later average age at seizure onset than females [24]. The seizure type was predominantly defined as generalised, but a precise description of seizure onset signs (e.g. focal epileptic seizures evolving into generalised seizures) was not provided. A gender predisposition towards males was found (61.6 % affected males versus 38.4 % affected females) compared to the control population [24]. The life expectancy of epileptic individuals compared to the general life expectancy of Irish Wolfhounds (provided by another study [88]) was reduced by two years [24]. The average inbreeding coefficient (calculated throughout 10 generations) for all the dogs entered into the study was 0.156 [24]. The heritability index for the affected dogs, their littermates, and unaffected parents was calculated at 0.87. Pedigree analysis and segregation analysis were best compatible with a complex pattern of inheritance such as an autosomal recessive trait with incomplete penetrance [24]. The identification of a causative gene mutation has not yet been reported. Potential breed-specific diseases that may mimic idiopathic epilepsy: Hyperekplexia (also known as startle disease), which has been described in Irish Wolfhounds is a disease characterized by noise- or touch-induced episodes of muscle stiffness and apnoea [89]. In affected pups clinical signs start 5–7 days postpartum and manifest with handling-evoked extensor rigidity and tremor. A micro-deletion of a presynaptic glycine-transporter-gene (GlyT2, *SLC6A5*) has been identified in affected Irish Wolfhound puppies [89]. Beside startle disease, a genetic predisposition for intrahepatic portosystemic shunts has been reported for the Irish Wolfhound [90]. Therefore potential hepatic encephalopathy needs to be considered in young Irish Wolfhounds that present with seizures [90]. In addition to portosystemic shunts a transient idiopathic hyperammonemia (with normal bile acid testing) due to urea cycle enzyme deficiency has been reported in Irish Wolfhound puppies [91, 92]. However, whether this transient and usually only moderate hyperammonemia may also contribute to seizures has not been investigated in detail, but may be considered in Irish Wolfhounds puppies with seizures and normal bile acid testing.

Italian Spinone

Very recently, the Italian Spinone was reported to be affected by idiopathic epilepsy [93]. A population study

was conducted to estimate the prevalence of idiopathic epilepsy in the Italian Spinoni in the UK and to investigate predictors of survival and seizure remission. The owners of all UK Kennel Club registered Italian Spinoni were invited to complete a phase I questionnaire. The phase I questionnaires, the primary veterinarian's, and, when available, the veterinary neurologist's medical records (including results of diagnostic investigations) were reviewed by the investigators to identify Italian Spinoni with idiopathic epilepsy and obtain data on treatment and survival. Additional information on various aspects of epilepsy (including seizure phenomenology and frequency) was obtained from owners of epileptic Italian Spinoni who completed the phase II questionnaire. The phase I questionnaire was returned for 1192 Italian Spinoni, of these, 63 Italian Spinoni were identified with idiopathic epilepsy. The prevalence of idiopathic epilepsy in the Italian Spinoni in the UK was estimated as 5.3 %. Mean age at first seizure was 38 months (median: 35 months). The gender distribution of the epileptic dogs was 67 % males and 33 % females (male to female ratio 2:1), but was not compared to the general Italian Spinone population. The phase II questionnaire was returned for 47 (75 %) of the 63 idiopathic epileptic Italian Spinoni. The most common seizure type was generalised tonic-clonic seizures with impaired consciousness and autonomic manifestations (e.g., increased salivation, urination, defecation) for all 47 Italian Spinoni. Focal epileptic seizures evolving into generalised epileptic seizures were consistently recognized by the owners of 24 Italian Spinoni (51 %). Cluster seizures and status epilepticus occurred anytime in life in 46 (73 %) and 13 (21 %) Italian Spinoni, respectively. Seizure remission occurred in 3 (6 %) of the 47 Italian Spinoni whose owners returned the phase II questionnaire. Successful antiepileptic drug treatment with good seizure control was reported to be challenging in many instances. The identification of a causative gene mutation has not yet reported, but genetic analyses are currently in progress [93]. Identified risk factors: Survival time was significantly shorter in Italian Spinoni euthanised because of poorly controlled epilepsy compared with epileptic Italian Spinoni that died of unrelated disorders. Survival was significantly longer in Italian Spinoni with no cluster seizures and in Italian Spinoni in which antiepileptic medication was initiated after the second seizure rather than after ≥3 seizures [93].

Labrador Retriever

Three studies investigating idiopathic epilepsy in the Labrador Retriever are currently available; two Swiss [94, 95] and one Danish [26] study. All three studies focus on different aspects of heritability and clinical characteristics. The Swiss studies were cohort studies and idiopathic epilepsy was defined by occurrence of more than one (or two) seizures (depending on study) and normal findings on physical examination, neurological examination, routine blood work, urine and CSF analysis [94, 95]. The two Swiss studies include 54 [94] and 55 [95]. Labrador Retrievers with idiopathic epilepsy, respectively, and they do not provide prevalence data [94, 95]. The Danish study [26] is an epidemiological cross sectional population study, which investigated a reference population of 29,602 Labrador retrievers registered in the Danish Kennel Club in a ten year period. From the reference population a representative sample of 550 dogs were selected for by random sampling stratified by year of birth. After questionnaire interviews of all 550 dog owners and clinical investigation of dogs, suspected with epilepsy, 17 dogs were finally identified with idiopathic epilepsy giving a prevalence of 3.1 % among the investigated Danish population [26]. No gender predisposition or positive effects of castration on epilepsy course was detected in the Swiss or the Danish studies [26, 94, 95]. The Danish study reported the seizure type as generalised epileptic seizures in 24 % of dogs and as focal epileptic seizures or focal epileptic seizures evolving into generalised seizures in 70 % of dogs. Among the latter 70 % of dogs focal epileptic seizures were rare, whereas focal epileptic seizures evolving into generalised seizures were predominant [26]. In both Swiss studies the seizure type was reported to be generalised in almost all the dogs (91 % [94] and 96 % [95], respectively) and only 9 % presented with focal epileptic seizures [94]. But, the latter two Swiss studies did not distinguish between (primary) generalised epileptic seizures and focal epileptic seizures evolving into generalised seizures; and preictal signs were reported in a substantial number of dogs (which were not considered as part/onset of a seizure), which may explain the discrepancy to the seizure type found in the Danish study. Age at seizure onset was reported with a mean age of 30.6 months in one of the Swiss studies [95], with a mean age of 34 months for males and 28 months for females in the other Swiss study [94], and with 76 % of dogs having the first seizure by the age of 4 years in the Danish study [26]. The average seizure frequency in one of the Swiss studies was one every 65 days in dogs with generalised seizures and one every 205 days in dogs with focal seizures, however, approximately half of the dogs had seizures more than once a month [94]. Pedigree analysis was best compatible with a polygenic, recessive inheritance according to one of the Swiss studies [95]. The identification of a causative gene mutation has not yet been reported. Identified risk factors: The 1997 Swiss study found that Labrador Retrievers with a higher age at seizure onset showed a good treatment response, even if treatment began late. Dogs with low seizure frequencies and low total numbers of seizures responded well to therapy if treated as early as possible. Untreated dogs mostly showed a progressive disease course [94]. One study that examined inhibitory and

excitatory neurotransmitters in the CSF of epileptic Labrador Retrievers, epileptic non-Labrador Retrievers and non-epileptic control dogs, identified that CSF concentrations of γ-aminobutyric acid (GABA) and glutamate (GLU) were significantly lower in Labrador Retrievers with idiopathic epilepsy than in a control-group of non-epileptic dogs as well as in non-Labrador Retriever dogs with idiopathic epilepsy [96]. However, the GLU to GABA ratio was significantly higher in epileptic Labrador Retriever than in epileptic non–Labrador Retriever dogs. It was suggested that an imbalance between GABAergic inhibition and excitation by glutamate (indicated by the high GLU-GABA ratio) in epileptic Labrador Retrievers may be involved in the epileptogenic processes in this breed [96]. However, whether those findings are the cause or the consequence of seizure activity or a combination of both cannot be concluded and still need to be further elucidated. Potential breed-specific diseases that may mimic idiopathic epilepsy: For the Labrador Retriever EIC, predominantly caused by a DNM1-gene mutation, needs to be considered as potential differentials for epileptic seizures. Several studies suggest the existence of another and "DNM-1-independent" EIC condition in Labrador Retrievers, as some of the EIC-affected Labrador Retrievers are negative or heterozygous for the DNM1-gene mutation (approximately 15–30 % of EIC affected Labrador Retriever) [97, 98]. Hence, two distinct terms have gained acceptance for Labrador Retrievers: d-EIC (homozygous DNM1-gene mutation) and non-d-EIC (negative or heterozygous for the DNM1-gene mutation) [30, 97, 98]. Apart from a suspected diverse genetic background for the latter two EIC types, clinical differences between d-EIC and non-d-EIC have been observed. However, in general, and in contrast to seizures, EIC-episodes are induced by strenuous exercise. Contrary to epileptic seizures muscle tone is initially decreased in the affected limbs and consciousness remains preserved in more than 80 % of the Labrador Retriever with d-EIC. Another study also reported a wide-based pelvic limb stance, crouched posture and falling to the side during d-EIC [99]. For non-d-EIC, the collapse episodes are reported to occur at an older age, furthermore abnormal mentation and involvement of all limbs are observed more frequently[58]. A gene test for d-EIC in Labrador Retrievers is available [30]. Narcolepsy with cataplexy, which may potentially mimic a seizure event, has also been reported in Labrador Retrievers [100, 101]. However, in contrast to seizures a clinical hallmark of narcolepsy, are sudden episodes of muscle atonia triggered by excitement such as presentation of food. Another disease that may mimic seizure episodes in Labrador Retriever puppies is familial reflex myoclonus, in which the affected puppies present with spasticity and opisthotonus at the age of 3 weeks [102], especially when handled or lifted up. In general, the Labrador Retriever breed is not known to be predisposed for NCL, however, one case report exists reporting an eight year old Labrador Retriever diagnosed with NCL on necropsy [103]. This dog had a 11-month history of progressive focal seizures with generalised seizures at the end stage of the disease [103]. Rapid eye movement (REM) sleep disorder is another potential differential when assessing an epileptic Labrador Retriever, with one case report of a 9-month-old Labrador retriever cross presenting with two morphologically distinct types of seizure episodes, one that occurred only during sleep and one that occurred only when awake. An EEG identified that the sleep-associated episodes occurred during REM sleep, consistent with a diagnosis of a REM behaviour disorder, which was improved with a tricyclic antidepressant medication. The waking episodes were diagnosed as epileptic seizures, as there was a clinical response to antiepileptic medication [104].

Lagotto Romagnolo

To date three studies about clinical signs, heritability and FDG-PET imaging findings in benign familial juvenile epilepsy in the Lagotto Romagnolo dog have been published [105–107]. The first study was published in 2007 and focused on clinical characteristics and clinical course, which both appeared to resemble the human form of benign familial juvenile epilepsy [105]. The latter study included 25 Lagotto Romagnolo puppies with (simple or complex) focal seizures and 3 adult Lagotto Romagnolo dogs exhibiting similar clinical signs [105]. However, prevalence data are yet not available. The mean age of seizure onset is reported as 6.3 weeks of age (with most puppies being affected by 1–2 month of age). The benign disease course is characterized by a spontaneous seizure remission by 8 to 13 weeks of age [105]. The epileptic seizures manifest with episodic stiffness, generalised tremor and a predominantly preserved consciousness. Although this seizure semiology is a rather uncommon presentation for epileptic seizures, epileptiform EEG activity was detected in affected puppies [105]. Puppies that were severely affected also suffered from interictal ataxia and hypermetria. The seizure frequency varied from multiple episodes per day to one episode per week. A gender-predisposition was not found. Histopathologic examination in one puppy and one adult dog, revealed Purkinje cell inclusions and vacuolation of axons restricted to the cerebellum [105]. A simple autosomal recessive inheritance was best compatible with pedigree analysis [105]. Using a genome-wide association study the disease locus was mapped to chromosome 3 where a protein-truncating mutation in the LGI2 gene was

identified in 2011 [106]. The latter study showed that LGI2, like the human analogue epilepsy gene LGI1, is neuronally secreted and acts on metalloproteinase-lacking members of the ADAM family of neuronal receptors, which function in synapse remodelling. It was identified that LGI2 truncation, like LGI1 truncations, prevents secretion and ADAM interaction [106]. LGI2 was highly expressed in the immediate post-natal period until halfway through pruning, unlike LGI1, which is expressed in the latter part of pruning and beyond. LGI2 acts at least in part through the same ADAM receptors as LGI1, but earlier, ensuring electrical stability during pruning time, preceding this same function performed by LGI1 later in life [106]. Hence, this functional LGI2-to-LGI1 transition may explain the benign and remitting course of epilepsy in the Lagotto Romagnolo breed. A genetic test is available for Lagotto Romagnolos. One study among a large Lagotto Romagnolo population from 3 different countries identified 32 % dogs as disease carriers [106]. It should be noted that in a small proportion of dogs seizures occurred at an adult age [105]. However, in almost all of these adult cases no LGI2 gene mutation was identified, suggesting that there might exist a second and distinct form of epilepsy in the Lagotto Romagnolo [106]. One recent study focussed on FDG PET-imaging in affected Lagotto Romagnolos [107]. Visual analysis revealed areas of hypometabolism interictally in five out of six dogs with juvenile epilepsy in the occipital, temporal, and parietal cortex. Epileptiform EEG activity occurred in three of these dogs in the same areas where PET showed cortical hypometabolism [107]. Visual analysis showed no abnormalities in cerebral glucose uptake of dogs with adult-onset epilepsy, which further supports the theory of another etiologically different form of genetic epilepsy in this dog breed [107]. Apart from the structural epilepsies that result from neurodegenerative diseases such as progressive myoclonus epilepsy or NCL, the Lagotto Romagnolo is the first dog breed where an idiopathic epilepsy causative gene mutation has been identified. Potential breed-specific diseases that may mimic idiopathic epilepsy: One report describes 2 Lagotto Romagnolo puppies diagnosed with cerebellar cortical abiotrophy, which might be considered as potential differential to benign familial juvenile epilepsy in this dog breed [108]. However, in cerebellar cortical abiotrophy the clinical (cerebellar) signs were reported as rapidly progressive or progressive followed by a static phase with no evidence of an episodic nature [108], which contrasts the episodic signs and remitting disease course evident in benign familial juvenile epilepsy [105]. In one of the cerebellar cortical abiotrophy affected puppies the cerebellum was slightly decreased in size on MRI examination of the brain [108].

Petit Basset Griffon Vendeen (PBGV)

One retrospective epidemiological population study investigating clinical characteristics and prevalence of epilepsy in PBGV dogs has been published in 2011 (including both living and deceased dogs) [25]. This study was conducted in Denmark and included all PBGV dogs (=820) registered in the Danish Kennel Club between 1999–2008. Idiopathic epilepsy was defined on the basis of a dog having at least 2 seizures with a minimum interval of 24 h and the dog having a typical epileptic seizure phenomenology [25]. All dogs that were defined as epilepsy positive after an interview validation and that were still alive, were invited to participate in a clinical evaluation at the study centre, which included clinical examination, neurological examination and blood samples analysed by CBC, serum biochemistry including thyroid hormone concentration and urinalysis, ECG and ultrasound of the heart by a cardiologist ($n = 19$). A few owners were offered an MRI of their dog's brain ($n = 3$) [25]. Forty-two dogs were evaluated to be true epilepsy cases and the epilepsy prevalence among the Danish PBGV population was estimated at 8.9 % [25]. The median age at seizure onset was 2 years. The gender distribution was 62 % males and 38 % females, but there was no significant gender predisposition detected (compared to the general PBGV population) [25]. The seizure type was defined as focal epileptic seizures in 41 % of dogs and as focal epileptic seizures evolving into generalised epileptic seizures in 52 % of dogs. In 5 % of dogs generalised epileptic seizures were identified and in 2 % of dogs the seizures remained unclassified. The most commonly reported focal seizure signs included motor signs such as ataxia and contractions of single muscle groups, autonomic signs such as vomiting and salivation and paroxysms of behavioural signs such as excessive attention seeking or standing with a blank stare not responding to external stimuli. The typical seizure duration varied from one to three minutes. A strong litter effect was demonstrated supporting the hypothesis of a hereditary component of epilepsy in the PBGV. Identification of a causative gene mutation has not been reported [25].

Shetland Sheepdog

Three reports about epilepsy in Shetland Sheepdogs are available in the current literature [109–111]. All studies were conducted in Japan. The first study was published in 2002 and reports about a large family of Shetland Sheepdogs with natural occurring familial frontal lobe epilepsy defined by EEG analysis and seizure semiology [109]. Two litters of one large family were produced deliberately for prospective examination in this study. A detailed definition for idiopathic epilepsy was not provided [109]. The age at seizure onset was predominantly

between 1 and 1.5 years of age. The average seizure frequency varied from one seizure every week to one every 6 months. The gender distribution was 79 % females compared to 21 % males. The seizure type was predominantly defined as generalised in almost all cases, but detailed classification of initial seizures signs was not conducted [109], hence a proportion of dogs might have experienced focal seizures evolving into generalised seizures instead of (primary) generalised seizures. EEG examination identified paroxysmal discharges predominantly in the frontal lobes [109]. Based on this, this epilepsy was postulated as familial frontal lobe epilepsy, however with prolonged disease duration also the parietal, temporal and occipital lobes showed epileptiform activity on EEG [109]. Pedigree analysis excluded potential mitochondrial or sex-linked inheritance and a multifactorial inheritance was suggested to be most likely [109]. Identification of a causative gene mutation has not yet reported. Additional findings of the latter study were increased aspartate and glutamate levels in the CSF in some of the epileptic dogs compared to control dogs [109]. Hence, another study that was published in 2005 focussed on intracerebral microdialysis and EEG recording as well as histopathological examination of epileptic Shetland Sheepdogs [110]. Intracerebral microdialysis and EEG – both conducted during hyperventilation – revealed increased extracellular glutamate and aspartate concentrations in the cerebral cortex of epileptic dogs. Coinciding with the increase in excitatory neurotransmitters, an increase in paroxysmal discharges on EEG was detected. On histopathological examination, dogs affected by status epilepticus showed a reduced density of glutamate receptors in the area of the lateral nucleus of the thalamus. In addition, glutamate positive granules were found within the perineural spaces of the cerebral cortex. It was considered possible that a decrease of glutamate receptor levels may induce an increase in extracellular glutamate concentration, which would evoke neuronal hyperexcitability and may contribute to a collapse of extracellular glutamate regulation during status epilepticus [110]. Another case report of a Shetland sheepdog with drug resistant epilepsy identified hippocampal and mesial temporal lobe sclerosis on necropsy. However, this finding was suggested as a secondary phenomenon induced by recurrent seizures rather than to be a primary seizure-causing finding [111]. Potential breed-specific diseases that may mimic idiopathic epilepsy: For the Shetland sheepdog a spongiform encephalopathy has been reported, which appears with neurological signs that may mimic a seizure event. However, clinical manifestation is early within the first weeks of life (between the 2– 9 weeks of life) and consists of tremors, ataxia, paresis, spasticity and loss of cranial nerve function. DNA sequencing of affected puppies showed a point mutation that resulted in an amino acid change of mitochondrial encoded cytochrome b [112]. The Shetland sheepdog is also a dog breed frequently affected by ABCB1/MDR1-gene mutation, with identified mutant allele frequencies between 1 – 12 % depending on the respective study and geographic area [33], which may need to be considered in Shetland sheepdogs with acute seizures and potential previous exposure to neurotoxic P-gp substrates.

Standard Poodle

In the current literature, there are two studies available that provide information about idiopathic epilepsy in the Standard Poodle [65, 113]. One study, that was published in 2007, reports clinical characteristics and mode of inheritance of epilepsy in a large family of Standard Poodles in the United States [113]. This study included 30 Standard Poodles diagnosed with probable idiopathic epilepsy and 90 healthy controls. Dogs were defined as having'probable idiopathic epilepsy' if they had had at least 1 seizure without any evidence of an underlying cause. Specifically, the following conditions all had to be met: the owner's answers to health-related questions revealed no illnesses or events (e.g., head trauma) that could plausibly account for the seizures, at least 1 year had passed since seizure onset during which no interictal neurologic abnormalities were observed, and the dog was between 6 months and 7.5 years old when seizures began [113]. The term'probable' was used because the medical work up was insufficient to definitely exclude other causes of epilepsy and because dogs that had experienced only a single seizure were also included [113]. No significant gender predisposition was detected between affected males (57 %) and females (43 %). The median age at seizure onset was 3.7 years, however, 20 % of all affected dogs had their first seizure after an age of five years [113]. The seizure type could be determined in 29 dogs and was defined as focal epileptic seizures in 33 % and as focal epileptic seizure evolving into generalised epileptic seizures in 60 % of dogs [113]. Overall 93 % of the dogs had focal epileptic seizures or focal epileptic seizures evolving into generalised seizures. In 3.5 % of dogs seizures were classified as (primary) generalised epileptic seizures; in another 3.5 % of dogs the epileptic seizures were generalised but the exact onset of seizures could not be determined precisely [113]. As the majority of dogs (93 %) among this family experienced focal epileptic seizures or focal epileptic seizures evolving into generalised seizures, familial focal epilepsy was suggested [113]. Focal epileptic seizures consisted of shaking, jerking, or shivering; incoordination characterized by staggering or an inability to stand; stiffness or rigidity; and unusual movements or body positions such as a head tilt or awkward limb lifting. Autonomic signs

included hypersalivation, panting, urination, and increased heart rate. Some dogs also presented with increased anxiety or automatisms such as licking, lip smacking, swallowing or circling [113]. Only 13 % of the dogs received antiepileptic drug treatment and all of them showed a good treatment response. The segregation analyses suggested a recessive autosomal inheritance with almost complete penetrance [113]. All examined Standard poodles in the latter study were closely related; hence, it is possible that there might be different epilepsy courses and modes of inheritance in geographically and genetically distinct standard poodle populations. However, a frequent occurrence of focal or focal epileptic seizures evolving into generalised seizures in Standard poodles was already reported in an earlier study from 2002 [65]; but the two studies (2002 and 2007) were conducted by the same authors and it was mentioned that few of the dogs were included in both studies. The study from 2002 reported a median age at onset of 2.4 years, a median seizure frequency of 2.8 seizures per year and a history of cluster seizures in 34.1 % of affected Standard Poodles [65]. Identification of a causative gene mutation has not yet been reported [65, 113]. Potential breed-specific diseases that may mimic idiopathic epilepsy: For the Standard Poodle, a neonatal encephalopathy with seizures (NEWS) has been reported that may play a role as potential differential in Standard poodle puppies with seizures [114]. However, NEWS manifests immediately after birth with ataxia, tremors and generalised tonic-clonic seizures. As a rule, affected puppies die within the first two months of life. A missense mutation in the canine orthologue of ATF2 has been identified in affected puppies [114]. Polymicrogyria is a rare malformation of the cerebrum characterized by an excessive number of small, histologically anomalous gyri and has been described in Standard Poodles [115, 116]. Affected dogs experience cortical blindness and other neurologic abnormalities including abnormal (hypermetria) gait and behavioural changes [115, 116] and may be considered as differential in young Standard Poodles that present with focal seizures or behavioural changes. Neurological signs predominantly start at a very young age (<4 months). MRI examination is consistent with multiple disorganized gyri, which especially may be seen on T2-weighted dorsal plane images [115]. EEG-examination of 1 dog revealed epileptiform discharges, including both spike and spike and wave discharges with voltage maximum potentials over the parietal/occipital region, which supported the repetitive behaviour as focal seizures [115].

German Shepherd, Beagle, Dachshund and Keeshond

There are a few older publications available that specifically focus on epilepsy in German Shepherds, Beagles, Dachshunds or Keeshonds [117–120]. Particularly for the Beagle, it should be mentioned that most of the earlier published data are based mainly on laboratory dog populations [117]. However, one recent epidemiological investigation and one genetic investigation support an increased risk for idiopathic epilepsy in Beagles at present [22, 76]. In Beagles, Dachshunds (miniature wirehaired) and Basset Hounds it is important to consider the occurrence of progressive myoclonus epilepsy (Lafora disease), as the latter is considered a neurodegenerative disorder and structural-metabolic epilepsy rather than idiopathic epilepsy [121–123]. In Dachshunds (and Bassett Hounds) a gene test for progressive myoclonus (Lafora) epilepsy is available [124]. Data from the Dachshund Breed council surveys in 2012 and 2015 suggest a epilepsy prevalence of approximately 1 % but rising to 3.7 % in miniature long haired Dachshunds (personal communication Clare Rusbridge February 2015). For the Keeshond, older studies proved a clear founder effect, which was most likely consistent with an autosomal recessive inheritance [120, 125], the median age at onset was reported with 2 years and some EEG examination has been made, however, further detailed clinical data are lacking. There are no up-to date studies available about idiopathic epilepsy in German Shepherds Dogs, but several current epidemiological canine epilepsy studies have been published that include interesting information for this breed. Most of those epidemiological studies have been conducted in the UK, and most of them identified the German Shepherd Dog among the most common epilepsy affected breeds [17, 46, 47]. Another epidemiological study revealed the German Shepherd Dog has an increased risk of cluster seizures compared to other breeds like the Labrador Retriever [126].

Finally, it is important to consider that in addition to the above mentioned dog breeds, there is strong clinical evidence that many more purebreds, such as the Siberian Husky, Staffordshire Bull Terrier, Boxer dog, Greater Swiss Mountain dog, Schipperke and many others appear to be affected by idiopathic epilepsy [10, 17, 22, 46, 47, 76]. It is only a matter of time until detailed data regarding the clinical characteristics and inheritance for those so far "suspected" breeds will be published. Furthermore, current epidemiological data suggest that beside purebred dogs, crossbreeds with idiopathic epilepsy present an increasing proportion among canine idiopathic epilepsy populations [46].

Conclusion and future perspectives

The present manuscript was conceived to review current knowledge of idiopathic epilepsy in purebreds with special interest on breed-specific phenotypes including clinical characteristics, disease course, seizure control and genetic transmission. Some differences, and in parts even contradicting findings became evident among breeds, and even – at least to some degree – between geographically distinct populations of the same breed. This may to some

Table 4 Depicting variable study design

Breed	Study	N	Study designs	Case selection	Inclusion criteria	Exclusion criteria	Investigations for confirmation of idiopathic epilepsy
Australian Shepherd	Weissl et al. 2012 [9]	50	Cohort, controls	Questionaire &phone interview	≥2 seizures ≥ 4 weeks apart, age at onset ≤ 5 years	History of skull trauma	PE, NE, laboratory with bile acid stimulation test MRI/CSF (47 %) Urinary organic/amino acids (20 %) Post mortem (4 %)
Belgian Shepherd	Berendt et al. 2008 [23]	49	Population survey (breed)	Questionnnaire (validated) &phone interview	≥2 seizures	n.s.	n.s.
	Seppala et al. 2012 [34]	94	Cohort, controls	Questionnaire	≥2 seizures	n.s.	Detailed examination (18 %) [35] PE, NE, laboratory MRI/CSF Descriptive: EEG (18 %)[b]
	Oberbauer et al. 2003 [35]	164	Cohort (family-based)	Owner-reported generalized seizures & questionnaire	≥2 seizures	n.s.	n.s.
	Oberbauer et al. 2010 [36]	74	Cohort, controls	Owner and veterinarian reported generalized seizures	≥2 seizures	n.s.	n.s.
	Gullov et al. 2012 [37]	51	Cohort, controls (family-based)	Questionnaire & phone interview	≥2 seizures	n.s.	PE, NE, laboratory with thyroid profile, ECG
	Berendt et al. 2009 [41]	66	Cohort (family-based)	Questionnaire & phone interview	≥2 seizures	History suggesting intracranial disease and progressive neurological signs.	PE, NE, laboratory with thyroid profile, ECG
	Famula et al. 1997 [38]	23	Population survey (breed)	Questionnaire	1 seizure	n.s.	n.s.
		142			≥2 seizures		
	Famula & Oberbauer 2000 [39]	21	Population survey (breed)	Questionnaire	1 seizure	n.s.	n.s.
		157			≥2 seizures		
Bernese Mountain Dog	Kathmann et al. 1999 [45]	50	Cohort	Questionnaire	History of epileptic seizures	n.s.	PE, NE, laboratory with bile acid stimulation test, CSF
Border Collie	Hülsmeyer et al. 2010 [8]	49	Cohort	Questionnaire & phone interview	≥2 seizures, at least 4 weeks apart	Presence of any initial precipitating event (eg, head trauma), an identified brain lesion, or observational data consisting of less than 10 h/day.	PE, NE, laboratory

Table 4 Depicting variable study design *(Continued)*

Border Terrier	Kearsley-Fleet et al. 2013 [17]	n.s.	Population survey (vet practice)	Electronic patient records	≥2 seizures for ≥ 1 year, or ≥4 prescript- ions of AEDs	Medical records documented disease that could have caused epilepsy including brain imaging abnormalities	PE, laboratory
	Kloene et al. 2008 [56]	47	Population survey (breed)	Questionnaire	n.s.	n.s.	PE, NE, laboratory with bile acid stimulation test[a] (10 %) CT/CSF (10 %) Urinary organic/amino acids (47 %)
Cavalier King Charles	Rusbridge&Knowler 2004 [58]	40	Cohort, controls (family investigation)	Owner-reported seizures	Diagnosis by veterinarian (generalized seizures, AED)	Clinical signs of CM	n.s.
	Driver et al. 2013 [59]	29	Cohort, controls	Medical record search CKCS with CM	History of epileptic seizures	MR lesions other than CM or ventriculomegaly Abnormal laboratory data	Laboratory with bile acid stimulation test, CSF, EEG[b]
Collie	Munana et al. 2012 [64]	29	Cohort	Questionnaire	Age of onset > 6 m/< 5 y, > 6 m prescription of AEDs		Laboratory
Dalmatian	Licht et al. 2002 [65]	11	Cohort	Questionnaire & phone interview	≥1 seizure	Evidence for structural epilepsy, seizures were not seen from the beginning	PE, NE, laboratory, bile acid stimulation test, tests for suspected toxin exposure
English Springer Spaniel	Patterson et al. 2005 [74]	45	Cohort	Questionnaire & phone interview	≥2 seizures, ≥ 4 weeks apart	Evidence for head trauma or toxin exposure	NE, laboratory age of onset < 6 m />5 y: MRI or CT WNL or > 2 y without interictal abnormalities
	Kearsley-Fleet et al. 2013 [17]	n.s.	Population survey (vet practice)	Electronic patient records	≥2 seizures for ≥ 1 year, or ≥4 prescriptions of AEDs	Medical records documented disease that could have caused epilepsy including brain imaging abnormalities	PE, CBC, biochemical profile
Finnish Spitz	Jeserevic et al. 2007 [80]	15	Cohort, controls		≥2 focal seizures		PE, NE, laboratory MRI/CSF (73 %), EEG[b]
	Viitmaa et al. 2006 [81]	11	Cohort, controls		≥2 focal seizures	Evidence for structural epilepsy	PE, NE, laboratory, MRI/CSF, EEG[b]
	Viitmaa et al. 2013 [82]	111	Population survey (breed)	Questionnaire & phone interview	≥2 seizure episodes	Interictal neurologic abnormalities, onset < 1 y, only 1 seizure episode	PE, NE, laboratory (27.8 %)
	Viitmaa et al. 2014 [83]	11	Cohort		≥2 focal seizures		PE, NE, laboratory
Golden Retriever	Srenk&Jaggy 1996 [85]	5	Cohort, controls	Questionnaire, medical records review	History of epileptic seizures, normal diagnostic tests	n.s.	EEG[b]
	Srenk et al. 1994 [84]	36	Cohort	Questionnaire, medical records review	History of epileptic seizures, normal diagnostic tests	n.s.	PE, NE repeatedly, laboratory with bile acids or ammonia, CSF, EEG

Table 4 Depicting variable study design *(Continued)*

	Lengweiler&Jaggy 1999 [86]	25	Cohort	Questionnaire	≥2 seizures	n.s.	PE, NE repeatedly, laboratory with bile acids or ammonia, CSF
Hungarian (Magyar) Vizsla	Patterson et al. 2003 [87]	29	Population survey (breed)	Questionnaire	≥2 seizures, ≥ 1 month apart	Evidence of toxin exposure or head trauma	NE, laboratory If < 6 m/ > 5 < y: CT /MRI/CSF
Irish Wolfhound	Casal et al. 2006 [24]	146	Population survey (families)	Questionnaire	≥2 seizures	Other medical problems	PE, NE, laboratory with bile acids or ammonia or both post mortem exam (10 %)
Italian Spinone	DeRisio et al. 2015 [93]	63	Population survey (breed)	Questionnaire	≥2 seizures, ≥ 24 h apart onset >6 m / <6y	n.s.	PE, NE, laboratory
Labrador Retriever	Heynold et al. 1997 [94]	54	Cohort (medical records)	Questionnaire	≥2 seizures video documentation (28 %)		PE, NE, laboratory with bile acids or ammonia, CSF
	Jaggy et al. 1998 [95]	55	Cohort, controls	Questionnaire	≥2 seizures	Other medical problems	PE, NE, laboratory with bile acids or ammonia, CSF at presentation and at 6 month follow-up
Lagotto Romagnolo	Jokinen et al. 2007 [105]	25	Cohort, case–control	Breeder-reported seizures families	Seizure episodes	n.s.	PE, NE, laboratory, MRI/CSF EEG/EMG/BAER[b] Post mortem ($n = 1$)
Petit Basset Griffon	Gullov et al. 2011 [25]	42	Population survey (breed)	Questionnaire (validated) & phone interview%	≥2 seizures, ≥ 24 h apart	n.s.	Laboratory, thyroid function, cardiac exam (45 %) bile acid stimulation test (21 %) MRI (7 %)
Shetland Sheepdog	Morita et al. 2002 [109]	11	Cohort (family)	Prospective investigation	Repeated seizures	n.s.	Laboratory EEG on repeated occasions[b] CSF (64 %) Post mortem (64 %)
Standard Poodle	Licht et al. 2007 [113]	30	Population survey (family)	Short questionnaire, & phone interview, 6 months follow-up	≥1 seizure	History of illness or head trauma that could account for seizures Age of onset <6 m/>7.5y	≥1 year unremarkable follow-up
	Licht et al. 2002 [65]	41	Cohort	Owner-reported seizures Questionnaire & phone interview	≥1 seizure	Evidence for structural epilepsy, seizures were not seen from the beginning	PE, NE, laboratory, bile acid stimulation test, tests for suspected toxin exposure

[a]some dogs with elevated bile acids; [b] EEG was used for descriptive purposes and not as a diagnostic test for IE

n.s. not specified, *PE* physical examination, *NE* neurological examination, *MRI* magnetic resonance imaging, *CSF* cerebrospinal fluid analysis, *EEG* electroencephalography, *ECG* electrocardiogram

degree reflect the development over time in our understanding of epilepsy, different study designs (see Table 4) and definitions for epilepsy and seizure terms that have been applied and furthermore genetic diversity between dog breeds and in some cases between geographically distinct populations of the same breed. Frequently, variable study designs were evident, with individual studies containing variable levels of disease-specific parameters (e.g. analysing occurrence of cluster seizures or not) and moreover data collections were performed in different ways (e.g. prospectively versus retrospectively). In human medicine, general guidelines and classification systems have long been established under the care of the International League Against Epilepsy. As these guidelines remain constantly under progress and are kept updated over the years, they have substantially promoted research and care for epilepsy patients, especially by diagnosis and treatment [127–133]. In recent years, strong efforts have been made to classify and define epilepsy terms in veterinary medicine, in particular, the clinical classification of different seizure types has been advanced by the application of human medicine classification systems [2, 65, 134–137]. However, direct comparability between canine epilepsy studies remains limited to some degree, due to the above mentioned issues, which point once more to the need for generally accepted concepts and guidelines for the conduct of epilepsy studies among the veterinary community, under guidance of a specialised veterinary epilepsy task force. The currently formed International Veterinary Epilepsy Task Force has crafted several consensus statements to help overcome these challenges in the area of Classification, Diagnosis, Treatment, Neuroimaging, Treatment outcomes, and Neuropathology. This might help establish new consistent studies of breed-specific canine epilepsy phenotypes and syndromes, which in turn may help to promote genetic analysis and to establish novel antiepileptic drug treatment strategies.

Abbreviations

ABCB1: ATP-binding cassette sub-family B; AED: Antiepileptic drug; CBC: Complete blood count; CECS: Canine epileptoid cramping syndrome; CSF: cerebrospinal fluid; CT: Computed tomography; DNM1: dynamin-1; ECG: Electrocardiogram; EEG: Electroencephalography; FDG: Fluorodeoxyglucose; GABA: Gamma-aminobutyric acid; GLU: Glutamate; MDR1: Multi-drug resistance protein 1; NCL: Neuronal ceroid lipofuscinosis; NEWS: Neonatal encephalopathy with seizures; REM: Rapid eye movement; PBGV: Petit Basset Griffon Vendeen; PET: Positron emission tomography; Pgp: P-glycoprotein EIC Exercise induced collapse, UK United Kingdome, DNA Deoxyribonucleic acid, LGI Leucine-rich glioma inactivated.

Competing interests

Following reimbursements, fees and funding have been received by the authors in the last three years and have been declared in the competing interest section. CR and HAV have received fees for acting as a consultant for Boehringer Ingelheim (CR: pain consultancy; HAV: consultancy pre and post launch of imepitoin). SFMB and HAV have been responsible principal investigator of several research studies concerning imepitoin financed by Boehringer Ingelheim. SFMB, HAV, MB, CR and AF received speaking fees from Boehringer Ingelheim. HAV received funding for a collaborative project from Desitin and Nestlé Purina Research. AF and LDR received reimbursements from Boehringer Ingelheim. LDR has received consulting and speaking fees from Vetoquinol. The other authors declared that they have no competing interests.

Authors' contributions

VIH lead the epilepsy breed working group and wrote the first draft of the consensus paper with the help of AF, PJJM, LDR, MB, CR, SFMB, AP, EEP, SP, RMAP and HAV. All authors read, critiqued, commented and approved the final manuscript.

Acknowledgements

The authors are grateful to all owners of epileptic pets and veterinary colleagues who have inspired the group to create consensus statements. We thank all the breeders and breed clubs for their support. The authors also would like to thank the research office for assessing the manuscript according to the Royal Veterinary College's code of good research practice (Authorisation Number – CSS_01013). This study was not financially supported by any organization or grant.

Author details

[1]Centre for Clinical Veterinary Medicine, Ludwig-Maximilians-University, Veterinärstr. 13, 80539 Munich, Germany. [2]Department of Clinical Sciences of Companion Animals, Utrecht University, Yalelaan 108, 3583 CM, Utrecht, The Netherlands. [3]Animal Health Trust, Lanwades Park, Kentford, Newmarket, CB8 7UU Suffolk, United Kingdom. [4]Department of Veterinary and Clinical Sciences, Faculty of Health and Medical Sciences, University of Copenhagen, Frederiksberg C, Denmark. [5]Fitzpatrick Referrals, Halfway Lane, Eashing, Godalming, GU7 2QQ Surrey, United Kingdom. [6]School of Veterinary Medicine, Faculty of Health & Medical Sciences, University of Surrey, Guildford, GU2 7TE Surrey, United Kingdom. [7]Department of Small Animal Medicine and Clinical Biology, Faculty of Veterinary Medicine, Ghent University, Salisburylaan 133, Merelbeke 9820, Belgium. [8]Clinical Unit of Internal Medicine Small Animals, University of Veterinary Medicine, Veterinärplatz 1, 1210 Vienna, Austria. [9]University of Minnesota College of Veterinary Medicine, D426 Veterinary Medical Center, 1352 Boyd Avenue, St. Paul, MN 55108, USA. [10]College of Veterinary Medicine, University of Georgia, 501 DW Brooks Drive, Athens, GA 30602, USA. [11]Department of Clinical Science and Services, Royal Veterinary College, Hatfield AL9 7TAHertfordshire, UK.

Received: 4 June 2015 Accepted: 29 June 2015
Published online: 28 August 2015

References

1. Moore SA. A clinical and diagnostic approach to the patient with seizures. Top Companion Anim Med. 2013;28(2):46–50.
2. Mariani CL. Terminology and classification of seizures and epilepsy in veterinary patients. Top Companion Anim Med. 2013;28(2):34–41.
3. Munana KR. Management of refractory epilepsy. Top Companion Anim Med. 2013;28(2):67–71.
4. Podell M. Antiepileptic drug therapy and monitoring. Top Companion Anim Med. 2013;28(2):59–66.
5. Ekenstedt KJ, Oberbauer AM. Inherited epilepsy in dogs. Top Companion Anim Med. 2013;28(2):51–8.
6. Ekenstedt KJ, Patterson EE, Mickelson JR. Canine epilepsy genetics. Mamm Genome. 2012;23(1–2):28–39.
7. Shorvon S. The concept of symptomatic epilepsy and the complexities of assigning cause in epilepsy. Epilepsy Behav. 2014;32:1–8.
8. Hulsmeyer V, Zimmermann R, Brauer C, Sauter-Louis C, Fischer A. Epilepsy in Border Collies: clinical manifestation, outcome, and mode of inheritance. Vet Intern Med. 2010;24(1):171–8.
9. Weissl J, Hulsmeyer V, Brauer C, Tipold A, Koskinen LL, Kyostila K, et al. Disease progression and treatment response of idiopathic epilepsy in Australian Shepherd dogs. Vet Intern Med. 2012;26(1):116–25.
10. Arrol L, Penderis J, Garosi L, Cripps P, Gutierrez-Quintana R, Goncalves R. Aetiology and long-term outcome of juvenile epilepsy in 136 dogs. Vet Rec. 2012;170(13):335.
11. Berendt M, Gredal H, Ersboll AK, Alving J. Premature death, risk factors, and life patterns in dogs with epilepsy. J Vet Intern Med. 2007;21(4):754–9.

12. Chang Y, Mellor DJ, Anderson TJ. Idiopathic epilepsy in dogs: owners' perspectives on management with phenobarbitone and/or potassium bromide. J Small Anim Pract. 2006;47(10):574–81.
13. Wessmann A, Volk HA, Parkin T, Ortega M, Anderson TJ. Evaluation of quality of life in dogs with idiopathic epilepsy. J Vet Intern Med. 2014;28(2):510–4.
14. Cunningham JGGCF. Inheritance and canine idiopathic epilepsy. J Am Anim Hosp Assoc. 1988;24:421–4.
15. Schwartz-Porsche. Epidemiological, clinical and pharmacokinetic studies in spontaneously epileptic dogs and cats. Am Coll Vet Intern Med. 1986;4:1161–3.
16. Heske L, Nodtvedt A, Jaderlund KH, Berendt M, Egenvall A. A cohort study of epilepsy among 665,000 insured dogs: incidence, mortality and survival after diagnosis. Vet J. 2014;202(3):471–6.
17. Kearsley-Fleet L, O'Neill DG, Volk HA, Church DB, Brodbelt DC. Prevalence and risk factors for canine epilepsy of unknown origin in the UK. Vet Record. 2013; 172(13):338.
18. Kearsley-Fleet L, O'Neill DG, Volk HA, Church DB, Brodbelt DC. Prevalence and risk factors for canine epilepsy of unknown origin in the UK. Vet Rec. 2013;172(13):338.
19. Zimmermann R, Hulsmeyer VI, Sauter-Louis C, Fischer A. Status epilepticus and epileptic seizures in dogs. J Vet Intern Med. 2009;23(5):970–6.
20. Podell M, Fenner WR, Powers JD. Seizure classification in dogs from a nonreferral-based population. J Am Vet Med Assoc. 1995;206(11):1721–8.
21. Fluehmann G, Doherr MG, Jaggy A. Canine neurological diseases in a referral hospital population between 1989 and 2000 in Switzerland. J Small Anim Pract. 2006;47(10):582–7.
22. Bellumori TP, Famula TR, Bannasch DL, Belanger JM, Oberbauer AM. Prevalence of inherited disorders among mixed-breed and purebred dogs: 27,254 cases (1995–2010). J Am Vet Med Assoc. 2013;242(11):1549–55.
23. Berendt M, Gullov CH, Christensen SL, Gudmundsdottir H, Gredal H, Fredholm M, et al. Prevalence and characteristics of epilepsy in the Belgian shepherd variants Groenendael and Tervueren born in Denmark 1995–2004. Acta Vet Scand. 2008;50:51.
24. Casal ML, Munuve RM, Janis MA, Werner P, Henthorn PS. Epilepsy in Irish Wolfhounds. J Vet Intern Med. 2006;20(1):131–5.
25. Gullov CH, Toft N, Baadsager MM, Berendt M. Epilepsy in the Petit Basset Griffon Vendeen: prevalence, semiology, and clinical phenotype. Vet Intern Med. 2011;25(6):1372–8.
26. Berendt M, Gredal H, Pedersen LG, Alban L, Alving J. A cross-sectional study of epilepsy in Danish Labrador Retrievers: prevalence and selected risk factors. J Vet Intern Med. 2002;16(3):262–8.
27. Saito M, Munana KR, Sharp NJ, Olby NJ. Risk factors for development of status epilepticus in dogs with idiopathic epilepsy and effects of status epilepticus on outcome and survival time: 32 cases (1990–1996). J Am Vet Med Assoc. 2001;219(5):618–23.
28. O'Brien DP, Katz ML. Neuronal ceroid lipofuscinosis in 3 Australian shepherd littermates. J Vet Intern Med. 2008;22(2):472–5.
29. Katz ML, Farias FH, Sanders DN, Zeng R, Khan S, Johnson GS, et al. A missense mutation in canine CLN6 in an Australian shepherd with neuronal ceroid lipofuscinosis. J Biomed Biotechnol. 2011;2011:198042.
30. Minor KM, Patterson EE, Keating MK, Gross SD, Ekenstedt KJ, Taylor SM, et al. Presence and impact of the exercise-induced collapse associated DNM1 mutation in Labrador retrievers and other breeds. Vet J. 2011;189(2):214–9.
31. Mealey KL, Meurs KM. Breed distribution of the ABCB1-1Delta (multidrug sensitivity) polymorphism among dogs undergoing ABCB1 genotyping. J Am Vet Med Assoc. 2008;233(6):921–4.
32. Swain MD, Orzechowski KL, Swaim HL, Jones YL, Robl MG, Tinaza CA, et al. P-gp substrate-induced neurotoxicity in an Abcb1a knock-in/Abcb1b knock-out mouse model with a mutated canine ABCB1 targeted insertion. Res Vet Sci. 2013;94(3):656–61.
33. Gramer I, Leidolf R, Doring B, Klintzsch S, Kramer EM, Yalcin E, et al. Breed distribution of the nt230(del4) MDR1 mutation in dogs. Vet J. 2011;189(1):67–71.
34. Seppala EH, Koskinen LL, Gullov CH, Jokinen P, Karlskov-Mortensen P, Bergamasco L, et al. Identification of a novel idiopathic epilepsy locus in Belgian Shepherd dogs. PloS one. 2012;7(3), e33549.
35. Oberbauer AM, Grossman DI, Irion DN, Schaffer AL, Eggleston ML, Famula TR. The genetics of epilepsy in the Belgian tervuren and sheepdog. J Hered. 2003;94(1):57–63.
36. Oberbauer AM, Belanger JM, Grossman DI, Regan KR, Famula TR. Genome-wide linkage scan for loci associated with epilepsy in Belgian shepherd dogs. BMC Genet. 2010;11:35.
37. Gullov CH, Toft N, Berendt M. A longitudinal study of survival in Belgian Shepherds with genetic epilepsy. J Vet Intern Med. 2012;26(5):1115–20.
38. Famula TR, Oberbauer AM, Brown KN. Heritability of epileptic seizures in the Belgian tervueren. J Small Anim Pract. 1997;38(8):349–52.
39. Famula TR, Oberbauer AM. Segregation analysis of epilepsy in the Belgian tervueren dog. Vet Rec. 2000;147(8):218–21.
40. Famula TR, Oberbauer AM. Reducing the incidence of epileptic seizures in the Belgian Tervuren through selection. Prev Vet Med. 1998;33(1–4):251–9.
41. Berendt M, Gullov CH, Fredholm M. Focal epilepsy in the Belgian shepherd: evidence for simple Mendelian inheritance. J Small Anim Pract. 2009;50(12):655–61.
42. van der Velden NA. Fits in Tervueren Shepherd dogs: a presumed hereditary trait. J Small Anim Pract. 1968;9(2):63–70.
43. Packer RA, Patterson EE, Taylor JF, Coates JR, Schnabel RD, O'Brien DP. Characterization and mode of inheritance of a paroxysmal dyskinesia in Chinook dogs. J Vet Intern Med. 2010;24(6):1305–13.
44. Black V, Garosi L, Lowrie M, Harvey RJ, Gale J. Phenotypic characterisation of canine epileptoid cramping syndrome in the Border terrier. J. Small Animal Prac. 2013; 55(2):102-7.
45. Kathmann I, Jaggy A, Busato A, Bartschi M, Gaillard C. Clinical and genetic investigations of idiopathic epilepsy in the Bernese mountain dog. J Small Anim Pract. 1999;40(7):319–25.
46. Short AD, Dunne A, Lohi H, Boulton S, Carter SD, Timofte D, et al. Characteristics of epileptic episodes in UK dog breeds: an epidemiological approach. Vet Rec. 2011;169(2):48.
47. Packer RM, Shihab NK, Torres BB, Volk HA. Clinical risk factors associated with anti-epileptic drug responsiveness in canine epilepsy. PLoS One. 2014;9(8), e106026.
48. O'Neill DG, Church DB, McGreevy PD, Thomson PC, Brodbelt DC. Longevity and mortality of owned dogs in England. Vet J. 2013;198(3):638–43.
49. Alves L, Hulsmeyer V, Jaggy A, Fischer A, Leeb T, Drogemuller M. Polymorphisms in the ABCB1 gene in phenobarbital responsive and resistant idiopathic epileptic Border Collies. J Vet Intern Med. 2011;25(3):484–9.
50. Mizukami K, Yabuki A, Chang HS, Uddin MM, Rahman MM, Kushida K, et al. High frequency of a single nucleotide substitution (c.-6-180 T > G) of the canine MDR1/ABCB1 gene associated with phenobarbital-resistant idiopathic epilepsy in Border Collie dogs. Dis Markers. 2013;35(6):669–72.
51. Studdert VP, Mitten RW. Clinical features of ceroid lipofuscinosis in border collie dogs. Aust Vet J. 1991;68(4):137–40.
52. Taylor RM, Farrow BR. Ceroid-lipofuscinosis in border collie dogs. Acta Neuropathol. 1988;75(6):627–31.
53. Taylor RM, Farrow BR. Ceroid lipofuscinosis in the border collie dog: retinal lesions in an animal model of juvenile Batten disease. Am J Med Genet. 1992;42(4):622–7.
54. Melville SA, Wilson CL, Chiang CS, Studdert VP, Lingaas F, Wilton AN. A mutation in canine CLN5 causes neuronal ceroid lipofuscinosis in Border collie dogs. Genomics. 2005;86(3):287–94.
55. Battersby IA, Giger U, Hall EJ. Hyperammonaemic encephalopathy secondary to selective cobalamin deficiency in a juvenile Border collie. J Small Anim Pract. 2005;46(7):339–44.
56. Kloene A, Sewell A, Hamann H, Distl O, Tipold A. Klinische Untersuchung zu Krampfanfällen bei Border Terriern. Kleintierpraxis. 2008;53(1):5–12.
57. Kurnatowski Jv. Klinische und genetische Untersuchungen zu Krampfanfällen bei Border Terriern. Doctorate thesis. elib.tiho-hannover.de/dissertations/kurnatowskij_ss07.pdf: TIHO Hannover; 2007.
58. Rusbridge C, Knowler SP. Inheritance of occipital bone hypoplasia (Chiari type I malformation) in Cavalier King Charles Spaniels. J Vet Intern Med. 2004;18(5):673–8.
59. Driver CJ, Chandler K, Walmsley G, Shihab N, Volk HA. The association between Chiari-like malformation, ventriculomegaly and seizures in cavalier King Charles spaniels. Vet J. 2013;195(2):235–7.
60. Herrtage ME, Palmer AC. Episodic falling in the cavalier King Charles spaniel. Vet Rec. 1983;112(19):458–9.
61. Gill JL, Tsai KL, Krey C, Noorai RE, Vanbellinghen JF, Garosi LS, et al. A canine BCAN microdeletion associated with episodic falling syndrome. Neurobiol Dis. 2012;45(1):130–6.
62. Forman OP, Penderis J, Hartley C, Hayward LJ, Ricketts SL, Mellersh CS. Parallel mapping and simultaneous sequencing reveals deletions in BCAN and FAM83H associated with discrete inherited disorders in a domestic dog breed. PLoS Genet. 2012;8(1), e1002462.
63. Rusbridge C. Neurological diseases of the Cavalier King Charles spaniel. J Small Anim Pract. 2005;46(6):265–72.

64. Munana KR, Nettifee-Osborne JA, Bergman Jr RL, Mealey KL. Association between ABCB1 genotype and seizure outcome in collies with epilepsy. J Vet Intern Med. 2012;26(6):1358–64.
65. Licht BG, Licht MH, Harper KM, Lin S, Curtin JJ, Hyson LL, et al. Clinical presentations of naturally occurring canine seizures: similarities to human seizures. Epilepsy Behav. 2002;3(5):460–70.
66. Bosch B. The Dutch Breeds. Raad van Beheer. 2002;19–193.
67. Patterson DF AG, Fyfe JC, Giger U, Green PL. Is this a genetic disease? The J Small Animal Prac. 1989; 30(12):127–139.
68. Mandigers PJJ. Epilepsie bij de Nederlandse hondenrassen, incidentie en aanbevelingen voor de fokkerij. Tijdschrift voor Diergeneeskunde 2015.
69. Mandigers PJJ. Nieuwe neurologische ziektes? UKG Nieuws. 2015;1:14.
70. Bobbert E, Reekers S. Epilepsie, toeval of erfelijk? Een onderzoek bij de Drentse Patrijshond. 1986.
71. Mandigers PJJ, van Nes J, Knol BW, Ubbink GJ, Gruys E. Hereditary necrotising myelopathy in Kooiker dogs. Res Vet Sci. 1993;54:118–23.
72. Mandigers PJJ, Vanden Broek J. Relationship between litter size and other reproductive traits in the Dutch Kooiker dog. VetQ. 1994;16:229–32.
73. Mandigers P.J.J. Neurological disorders within 'Het Nederlandse Kooikerhondje". In: International Symposium VHNK, Zutphen, The Netherlands, 2013. Netherlands; 2013.
74. Patterson EE, Armstrong PJ, O'Brien DP, Roberts MC, Johnson GS, Mickelson JR. Clinical description and mode of inheritance of idiopathic epilepsy in English springer spaniels. J Am Vet Med Assoc. 2005;226(1):54–8.
75. 2013 ESS UK Health Survey Report, page 20. 3rd july 2015.http://www.englishspringerhealth.org.uk.
76. Ekenstedt KJ, Patterson EE, Minor KM, Mickelson JR. Candidate genes for idiopathic epilepsy in four dog breeds. BMC Genet. 2011;12:38.
77. Herrtage ME. Canine fucosidosis. VetAnnual. 1988;28:223–7.
78. Skelly BJ, Sargan DR, Herrtage ME, Winchester BG. The molecular defect underlying canine fucosidosis. J Med Genet. 1996;33(4):284–8.
79. Skelly BJ, Sargan DR, Winchester BG, Smith MO, Herrtage ME, Giger U. Genomic screening for fucosidosis in English Springer Spaniels. Am J Vet Res. 1999;60(6):726–9.
80. Jeserevics J, Viitmaa R, Cizinauskas S, Sainio K, Jokinen TS, Snellman M, et al. Electroencephalography findings in healthy and Finnish Spitz dogs with epilepsy: visual and background quantitative analysis. J Vet Intern Med. 2007;21(6):1299–306.
81. Viitmaa R, Cizinauskas S, Bergamasco LA, Kuusela E, Pascoe P, Teppo AM, et al. Magnetic resonance imaging findings in Finnish Spitz dogs with focal epilepsy. J Vet Intern Med. 2006;20(2):305–10.
82. Viitmaa R, Cizinauskas S, Orro T, Niilo-Rama M, Gordin E, Lohi H, et al. Phenotype, inheritance characteristics, and risk factors for idiopathic epilepsy in Finnish Spitz dogs. J Am Vet Med Assoc. 2013;243(7):1001–9.
83. Viitmaa R, Haaparanta-Solin M, Snellman M, Cizinauskas S, Orro T, Kuusela E, et al. Cerebral glucose utilization measured with high resolution positron emission tomography in epileptic finnish spitz dogs and healthy dogs. Vet Radiol Ultrasound. 2014;55(4):453–61.
84. Srenk P, Jaggy A, Gaillard C, Busato A, Horin P. [Genetic basis of idiopathic epilepsy in the golden retriever]. Tierarztl Prax. 1994;22(6):574–8.
85. Srenk P, Jaggy A. Interictal electroencephalographic findings in a family of golden retrievers with idiopathic epilepsy. J Small Anim Pract. 1996;37(7):317–21.
86. Lengweiler C, Jaggy A. [Clinical, epidemiologic and therapeutic aspects of idiopathic epilepsy in 25 golden retrievers: results of a long term study]. Schweiz Arch Tierheilkd. 1999;141(5):231–8.
87. Patterson EE, Mickelson JR, Da Y, Roberts MC, McVey AS, O'Brien DP, et al. Clinical characteristics and inheritance of idiopathic epilepsy in Vizslas. J Vet Intern Med. 2003;17(3):319–25.
88. Bernardi G. Longevity and morbidity in the Irish wolf- hound in the United States from 1966–1986. AKC Gazette. 1986;105:70–8.
89. Gill JL, Capper D, Vanbellinghen JF, Chung SK, Higgins RJ, Rees MI, et al. Startle disease in Irish wolfhounds associated with a microdeletion in the glycine transporter GlyT2 gene. Neurobiol Dis. 2011;43(1):184–9.
90. van Steenbeek FG, Leegwater PA, van Sluijs FJ, Heuven HC, Rothuizen J. Evidence of inheritance of intrahepatic portosystemic shunts in Irish Wolfhounds. J Vet Intern Med. 2009;23(4):950–2.
91. Zandvliet MM, Rothuizen J. Transient hyperammonemia due to urea cycle enzyme deficiency in Irish wolfhounds. J Vet Intern Med. 2007;21(2):215–8.
92. Meyer HP, Rothuizen J, Tiemessen I, van den Brom WE, van den Ingh TS. Transient metabolic hyperammonaemia in young Irish wolfhounds. Vet Rec. 1996;138(5):105–7.
93. De Risio L, Newton R, Freeman J, Shea A: Idiopathic Epilepsy in the Italian Spinone in the United Kingdom: Prevalence, Clinical Characteristics, and Predictors of Survival and Seizure Remission. J Vet Intern Med 2015; 29(3):917-24.
94. Heynold Y, Faissler D, Steffen F, Jaggy A. Clinical, epidemiological and treatment results of idiopathic epilepsy in 54 labrador retrievers: a long-term study. J Small Anim Pract. 1997;38(1):7–14.
95. Jaggy A, Faissler D, Gaillard C, Srenk P, Graber H. Genetic aspects of idiopathic epilepsy in Labrador retrievers. J Small Anim Pract. 1998;39(6):275–80.
96. Ellenberger C, Mevissen M, Doherr M, Scholtysik G, Jaggy A. Inhibitory and excitatory neurotransmitters in the cerebrospinal fluid of epileptic dogs. Am J Vet Res. 2004;65(8):1108–13.
97. Furrow E, Minor KM, Taylor SM, Mickelson JR, Patterson EE. Relationship between dynamin 1 mutation status and characteristics of recurrent episodes of exercise-induced collapse in Labrador Retrievers. J Am Vet Med Assoc. 2013;242(6):786–91.
98. Patterson EE, Minor KM, Tchernatynskaia AV, Taylor SM, Shelton GD, Ekenstedt KJ, et al. A canine DNM1 mutation is highly associated with the syndrome of exercise-induced collapse. Nat Genet. 2008;40(10):1235–9.
99. Taylor SM, Shmon CL, Adams VJ, Mickelson JR, Patterson EN, Shelton GD. Evaluations of labrador retrievers with exercise-induced collapse, including response to a standardized strenuous exercise protocol. J Am Anim Hosp Assoc. 2009;45(1):3–13.
100. Foutz AS, Mitler MM, Cavalli-Sforza LL, Dement WC. Genetic factors in canine narcolepsy. Sleep. 1979;1(4):413–21.
101. Lin L, Faraco J, Li R, Kadotani H, Rogers W, Lin X, et al. The sleep disorder canine narcolepsy is caused by a mutation in the hypocretin (orexin) receptor 2 gene. Cell. 1999;98(3):365–76.
102. Fox JG, Averill DR, Hallett M, Schunk K. Familial reflex myoclonus in Labrador Retrievers. Am J Vet Res. 1984;45(11):2367–70.
103. Rossmeisl Jr JH, Duncan R, Fox J, Herring ES, Inzana KD. Neuronal ceroid-lipofuscinosis in a Labrador Retriever. J Vet Diagn Invest. 2003;15(5):457–60.
104. Bush WW, Barr CS, Stecker MM, Overall KL, Bernier NM, Darrin EW, et al. Diagnosis of rapid eye movement sleep disorder with electroencephalography and treatment with tricyclic antidepressants in a dog. J Am Anim Hosp Assoc. 2004;40(6):495–500.
105. Jokinen TS, Metsahonkala L, Bergamasco L, Viitmaa R, Syrja P, Lohi H, et al. Benign familial juvenile epilepsy in Lagotto Romagnolo dogs. J Vet Intern Med. 2007;21(3):464–71.
106. Seppala EH, Jokinen TS, Fukata M, Fukata Y, Webster MT, Karlsson EK, et al. LGI2 truncation causes a remitting focal epilepsy in dogs. PLoS Genet. 2011;7(7), e1002194.
107. Jokinen TS, Haaparanta-Solin M, Viitmaa R, Gronroos TJ, Johansson J, Bergamasco L, et al. FDG-pet in healthy and epileptic Lagotto Romagnolo dogs and changes in brain glucose uptake with age. Vet Radiol Ultrasound. 2014;55(3):331–41.
108. Jokinen TS, Rusbridge C, Steffen F, Viitmaa R, Syrja P, De Lahunta A, et al. Cerebellar cortical abiotrophy in Lagotto Romagnolo dogs. J Small Anim Pract. 2007;48(8):470–3.
109. Morita T, Shimada A, Takeuchi T, Hikasa Y, Sawada M, Ohiwa S, et al. Cliniconeuropathologic findings of familial frontal lobe epilepsy in Shetland sheepdogs. Can J Vet Res. 2002;66(1):35–41.
110. Morita T, Takahashi M, Takeuchi T, Hikasa Y, Ikeda S, Sawada M, et al. Changes in extracellular neurotransmitters in the cerebrum of familial idiopathic epileptic shetland sheepdogs using an intracerebral microdialysis technique and immunohistochemical study for glutamate metabolism. J Vet Med Sci. 2005;67(11):1119–26.
111. Hasegawa D, Fujita M, Nakamura S, Takahashi K, Orima H. Electrocorticographic and histological findings in a Shetland sheepdog with intractable epilepsy. J Vet Med Sci. 2002;64(3):277–9.
112. Li FY, Cuddon PA, Song J, Wood SL, Patterson JS, Shelton GD, et al. Canine spongiform leukoencephalomyelopathy is associated with a missense mutation in cytochrome b. Neurobiol Dis. 2006;21(1):35–42.
113. Licht BG, Lin S, Luo Y, Hyson LL, Licht MH, Harper KM, et al. Clinical characteristics and mode of inheritance of familial focal seizures in Standard Poodles. J Am Vet Med Assoc. 2007;231(10):1520–8.
114. Chen X, Johnson GS, Schnabel RD, Taylor JF, Johnson GC, Parker HG, et al. A neonatal encephalopathy with seizures in standard poodle dogs with a missense mutation in the canine ortholog of ATF2. Neurogenetics. 2008;9(1):41–9.
115. Jurney C, Haddad J, Crawford N, Miller AD, Van Winkle TJ, Vite CH, et al. Polymicrogyria in standard poodles. J Vet Intern Med. 2009;23(4):871–4.

116. Van Winkle TJJCF, Dayrell-Hart B, Aguirre GD, Acland GM, Patterson DF. Blindness due to polymicrogyria and asymmetrical dilation of the lateral ventricles in Standard Poodles. Prog Vet Neurol. 1995;5(2):66–71.
117. Bielfelt SW, Redman HC, McClellan RO. Sire- and sex-related differences in rates of epileptiform seizures in a purebred beagle dog colony. Am J Vet Res. 1971;32(12):2039–48.
118. Falco MJ, Barker J, Wallace ME. The genetics of epilepsy in the British Alsatian. J Small Anim Pract. 1974;15(11):685–92.
119. Holliday TA, Cunningham JG, Gutnick MJ. Comparative clinical and electroencephalographic studies of canine epilepsy. Epilepsia. 1970;11(3):281–92.
120. Wallace ME. Keeshonds: a genetic study of epilepsy and EEG readings. J Small Anim Pract. 1975;16(1):1–10.
121. Webb AA, McMillan C, Cullen CL, Boston SE, Turnbull J, Minassian BA. Lafora disease as a cause of visually exacerbated myoclonic attacks in a dog. Can Vet J. 2009;50(9):963–7.
122. Gredal H, Berendt M, Leifsson PS. Progressive myoclonus epilepsy in a beagle. J Small Anim Pract. 2003;44(11):511–4.
123. L.Swain AT, G.Key, J. Turnbull, B. Minassian, C. Rusbridge, : Lafora's disease in the miniature wirehaired dachshund. In: 27th Symposium ESV-ECVN: 2014; Madrid, Spain; 2014.
124. Lohi H, Young EJ, Fitzmaurice SN, Rusbridge C, Chan EM, Vervoort M, et al. Expanded repeat in canine epilepsy. Science. 2005;307(5706):81.
125. Hall SJ, Wallace ME. Canine epilepsy: a genetic counselling programme for keeshonds. Vet Rec. 1996;138(15):358–60.
126. Monteiro R, Adams V, Keys D, Platt SR. Canine idiopathic epilepsy: prevalence, risk factors and outcome associated with cluster seizures and status epilepticus. J Small Anim Pract. 2012;53(9):526–30.
127. Berg AT, Berkovic SF, Brodie MJ, Buchhalter J, Cross JH, van Emde Boas W, et al. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005–2009. Epilepsia. 2010;51(4):676–85.
128. Engel Jr J. ILAE classification of epilepsy syndromes. Epilepsy Res. 2006;70 Suppl 1:S5–10.
129. Flink R, Pedersen B, Guekht AB, Malmgren K, Michelucci R, Neville B, et al. Guidelines for the use of EEG methodology in the diagnosis of epilepsy. International League Against Epilepsy: commission report. Commission on European Affairs: Subcommission on European Guidelines. Acta Neurol Scand. 2002;106(1):1–7.
130. ILAE. Proposal for revised clinical and electroencephalographic classification of epileptic seizures. From the Commission on Classification and Terminology of the International League Against Epilepsy. Epilepsia. 1981;22(4):489–501.
131. ILAE. Proposal for revised classification of epilepsies and epileptic syndromes. From the Commission on Classification and Terminology of the International League Against Epilepsy. Epilepsia. 1989;30(4):389–99.
132. ILAE. Guidelines for epidemiologic studies on epilepsy. From the Commission on Epidemiology and Prognosis of the International League Against Epilepsy. Epilepsia. 1993;34(4):592–6.
133. Kwan P, Arzimanoglou A, Berg AT, Brodie MJ, Allen Hauser W, Mathern G, et al. Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. Epilepsia. 2010;51(6):1069–77.
134. Berendt M, Gram L. Epilepsy and seizure classification in 63 dogs: a reappraisal of veterinary epilepsy terminology. J Vet Intern Med. 1999;13(1):14–20.
135. Berendt M, Dam M. Re: clinical presentations of naturally occurring canine seizures: similarities to human seizures. Epilepsy Behav. 2003;4(2):198–9. author repyl 199–201.
136. Berendt M, Gredal H, Alving J. Characteristics and phenomenology of epileptic partial seizures in dogs: similarities with human seizure semiology. Epilepsy Res. 2004;61(1–3):167–73.
137. Podell M. Epilepsy and seizure classification: a lesson from Leonardo. J Vet Intern Med. 1999;13(1):3–4.

Bhatti et al. BMC Veterinary Research (2015) 11:176
DOI 10.1186/s12917-015-0464-z

BMC Veterinary Research

CORRESPONDENCE Open Access

International Veterinary Epilepsy Task Force consensus proposal: medical treatment of canine epilepsy in Europe

Sofie F.M. Bhatti[1*], Luisa De Risio[2], Karen Muñana[3], Jacques Penderis[4], Veronika M. Stein[5], Andrea Tipold[5], Mette Berendt[6], Robyn G. Farquhar[7], Andrea Fischer[8], Sam Long[9], Wolfgang Löscher[10], Paul J.J. Mandigers[11], Kaspar Matiasek[12], Akos Pakozdy[13], Edward E. Patterson[14], Simon Platt[15], Michael Podell[16], Heidrun Potschka[17], Clare Rusbridge[18,19] and Holger A. Volk[20]

Abstract

In Europe, the number of antiepileptic drugs (AEDs) licensed for dogs has grown considerably over the last years. Nevertheless, the same questions remain, which include, 1) when to start treatment, 2) which drug is best used initially, 3) which adjunctive AED can be advised if treatment with the initial drug is unsatisfactory, and 4) when treatment changes should be considered. In this consensus proposal, an overview is given on the aim of AED treatment, when to start long-term treatment in canine epilepsy and which veterinary AEDs are currently in use for dogs. The consensus proposal for drug treatment protocols, 1) is based on current published evidence-based literature, 2) considers the current legal framework of the cascade regulation for the prescription of veterinary drugs in Europe, and 3) reflects the authors' experience. With this paper it is aimed to provide a consensus for the management of canine idiopathic epilepsy. Furthermore, for the management of structural epilepsy AEDs are inevitable in addition to treating the underlying cause, if possible.

Keywords: Dog, Epileptic seizure, Epilepsy, Treatment

Background

In Europe, the number of antiepileptic drugs (AEDs) licensed for dogs has grown considerably over the last years. Nevertheless, the same questions remain, which include, 1) when to start treatment, 2) which drug is best used initially, 3) which adjunctive AED can be advised if treatment with the initial drug is unsatisfactory, and 4) when treatment changes should be considered. In this consensus proposal, an overview is given on the aim of AED treatment, when to start long-term treatment in canine epilepsy and which veterinary AEDs are currently in use for dogs. The consensus proposal for drug treatment protocols, 1) is based on current published evidence-based literature [17], 2) considers the current legal framework of the cascade regulation for the prescription of veterinary drugs in Europe, and 3) reflects the authors' experience. With this paper it is aimed to provide a consensus for the management of canine idiopathic epilepsy. Furthermore, for the management of structural epilepsy AEDs are inevitable in addition to treating the underlying cause, if possible.

At present, there is no doubt that the administration of AEDs is the mainstay of therapy. In fact, the term AED is rather inappropriate as the mode of action of most AEDs is to suppress epileptic seizures, not epileptogenesis or the pathophysiological mechanisms of epilepsy. Perhaps, in the future, the term anti-seizure drugs might be more applicable in veterinary neurology, a term that is increasingly used in human epilepsy. Additionally, it is known that epileptic seizure frequency appears to increase over time in a subpopulation of dogs with untreated idiopathic epilepsy, reflecting the need of AED treatment in these patients [63].

In our consensus proposal on classification and terminology we have defined idiopathic epilepsy as a disease in

* Correspondence: sofie.bhatti@ugent.be
[1]Department of Small Animal Medicine and Clinical Biology, Faculty of Veterinary Medicine, Ghent University, Salisburylaan 133, Merelbeke 9820, Belgium
Full list of author information is available at the end of the article

its own right, *per se*. A genetic origin of idiopathic epilepsy is supported by genetic testing (when available) and a genetic influence is supported by a high breed prevalence (>2 %), genealogical analysis and /or familial accumulation of epileptic individuals. However in the clinical setting idiopathic epilepsy remains most commonly a diagnosis of exclusion following diagnostic investigations for causes of reactive seizures and structural epilepsy.

Aims of AED treatment

The ideal goal of AED therapy is to balance the ability to eliminate epileptic seizures with the quality of life of the patient. Seizure eradication is often not likely in dogs. More realistic goals are to decrease seizure frequency, duration, severity and the total number of epileptic seizures that occur over a short time span, with no or limited and acceptable AED adverse effects to maximize the dog's and owner's quality of life. Clinicians should approach treatment using the following paradigm [23, 76, 91, 92, 120]:

- **Decide when to start AED treatment**
- **Choose the most appropriate AED and dosage**
- **Know if and when to monitor serum AED concentrations and adjust treatment accordingly**
- **Know when to add or change to a different AED**
- **Promote pet owner compliance**

When to recommend maintenance AED treatment?

Definitive, evidence-based data on when to start AED therapy in dogs based on seizure frequency and type is lacking. As such, extrapolation from human medicine may be possible to provide treatment guidelines. Clinicians should consider the general health of the patient, as well as the owner's lifestyle, financial limitations, and comfort with the proposed therapeutic regimen. Individualized therapy is paramount for choosing a treatment plan. As a general rule, the authors recommend initiation of long-term treatment in dogs with idiopathic epilepsy when any one of the following criteria is present:

- **Interictal period of ≤ 6 months** (i.e. 2 or more epileptic seizures within a 6 month period)
- **Status epilepticus or cluster seizures**
- **The postictal signs are considered especially severe** (e.g. aggression, blindness) **or last longer than 24 hours**
- **The epileptic seizure frequency and/or duration is increasing and/or seizure severity is deteriorating over 3 interictal periods**

In humans, the decision regarding when to recommend AED treatment is based on a number of risk factors (e.g. risk of recurrence, seizure type, tolerability, adverse effects) [42, 115]. In people, clear proof exists that there is no benefit initiating AED treatment after a single unprovoked seizure [42], but there is evidence to support starting treatment after the second seizure [43, 108]. In dogs, long-term seizure management is thought to be most successful when appropriate AED therapy is started early in the course of the disease, especially in dogs with a high seizure density and in dog breeds known to suffer from a severe form of epilepsy [12–14]. A total number of ≥ 10 seizures during the first 6 months of the disease appeared to be correlated with a poor outcome in Australian Shepherds with idiopathic epilepsy [132]. Furthermore, recent evidence exists that seizure density is a crucial risk factor, experiencing cluster seizures, and being male is associated with poor AED response [84].

A strong correlation exists in epileptic people between a high seizure frequency prior to AED treatment and poor AED response [16, 34, 59]. Historically, this has been attributed to kindling, in which seizure activity leads to intensification of subsequent seizures [117]. However, there is little clinical evidence that kindling plays a role in either dogs [54] or humans [111] with recurrent seizures. In humans, a multifactorial pathogenesis is suggested [14, 52]. Recent epidemiologic data suggest that there are differences in the intrinsic severity of epilepsy among individuals, and these differences influence a patient's response to medication and long-term outcome. Additionally, evidence for seizure-associated alterations that affect the pharmacodynamics and pharmacokinetics of AEDs have been suggested [99]. Breed-related differences in epilepsy severity have been described in dogs, with a moderate to severe clinical course reported in Australian Shepherds [132], Border Collies [49, 84], Italian Spinoni [24], German Shepherds and Staffordshire Bull Terriers [84], whereas a less severe form of the disease has been described in a different cohort of Collies (mainly rough coated) [77], Labrador Retrievers [7] and Belgian Shepherds [45]. Consequently, genetics may affect the success of treatment and may explain why some breeds are more predisposed to drug resistant epilepsy [3, 77].

Choice of AED therapy

There are no evidence-based guidelines regarding the choice of AEDs in dogs. When choosing an AED for the management of epilepsy in dogs several factors need to be taken into account (AED-specific factors (e.g. regulatory aspects, safety, tolerability, adverse effects, drug interactions, frequency of administration), dog-related factors (e.g. seizure type, frequency and aetiology, underlying pathologies such as kidney/hepatic/gastrointestinal problems) and owner-related factors (e.g. lifestyle, financial circumstances)) [23]. In the end, however, AED choice is often determined on a case-by-case basis.

Until recently, primary treatment options for dogs with epilepsy have focused mainly on phenobarbital (PB) and potassium bromide (KBr) due to their long standing history, widespread availability, and low cost. While both AEDs are still widely used in veterinary practice, several newer AEDs approved for use in people are also being used for the management of canine idiopathic epilepsy mainly as add-on treatment. Moreover, since early 2013, imepitoin has been introduced in most European countries for the management of recurrent single generalized epileptic seizures in dogs with idiopathic epilepsy.

Several AEDs of the older generation approved for humans have been shown to be unsuitable for use in dogs as most have an elimination half-life that is too short to allow convenient dosing by owners, these include phenytoin, carbamazepine, valproic acid, and ethosuximide [119]. Some are even toxic in dogs such as lamotrigine (the metabolite is cardiotoxic) [26, 136] and vigabatrin (associated with neurotoxicity and haemolytic anemia) [113, 131, 138].

Since the 1990s, new AEDs with improved tolerability, fewer side effects and reduced drug interaction potential have been approved for the management of epilepsy in humans. Many of these novel drugs appear to be relatively safe in dogs, these include levetiracetam, zonisamide, felbamate, topiramate, gabapentin, and pregabalin. Pharmacokinetic studies on lacosamide [68] and rufinamide [137] support the potential use of these drugs in dogs, but they have not been evaluated in the clinical setting. Although these newer drugs have gained considerable popularity in the management of canine epilepsy, scientific data on their safety and efficacy are very limited and cost is often prohibitive.

Phenobarbital

Efficacy

PB has the longest history of chronic use of all AEDs in veterinary medicine. After decades of use, it has been approved in 2009 for the prevention of seizures caused by generalized epilepsy in dogs. PB has a favourable pharmacokinetic profile and is relatively safe [2, 87, 97]. PB seems to be effective in decreasing seizure frequency in approximately 60–93 % of dogs with idiopathic epilepsy when plasma concentrations are maintained within the therapeutic range of 25–35 mg/l [10, 31, 74, 105]. According to Charalambous et al. (2014) [17], there is overall good evidence for recommending the use of PB as a monotherapy AED in dogs with idiopathic epilepsy. Moreover, the superior efficacy of PB was demonstrated in a randomized clinical trial comparing PB to bromide (Br) as first-line AED in dogs, in which 85 % of dogs administered PB became seizure-free for 6 months compared with 52 % of dogs administered Br [10]. This study demonstrated a higher efficacy of PB compared to Br as a monotherapy, providing better seizure control and showing fewer side effects.

Pharmacokinetics

PB is rapidly (within 2h) absorbed after oral administration in dogs, with a reported bioavailability of approximately 90 % [2, 87]. Peak serum concentrations are achieved approximately 4–8h after oral administration in dogs [2, 97]. The initial elimination half-life in normal dogs has been reported to range from 37–73h after multiple oral dosing [96]. Plasma protein binding is approximately 45 % in dogs [36]. PB crosses the placenta and can be teratogenic.

PB is metabolized primarily by hepatic microsomal enzymes and approximately 25 % is excreted unchanged in the urine. There is individual variability in PB absorption, excretion and elimination half-life [2, 87, 97]. In dogs, PB is a potent inducer of cytochrome P450 enzyme activity in the liver [48], and this significantly increases hepatic production of reactive oxygen species, thus increasing the risk of hepatic injury [107]. Therefore PB is contraindicated in dogs with hepatic dysfunction. The induction of cytochrome P450 activity in the liver can lead to autoinduction or accelerated clearance of itself over time, also known as metabolic tolerance, as well as endogenous compounds (such as thyroid hormones) [40, 48]. As a result, with chronic PB administration in dogs, its total body clearance increases and elimination half-life decreases progressively which stabilizes between 30–45 days after starting therapy [97]. This can result in reduction of PB serum concentrations and therapeutic failure and therefore, monitoring of serum PB concentrations is very important for dose modulation over time.

A parenteral form of PB is available for intramuscular (IM) or intravenous (IV) administration. Different PB formulations are available in different countries, it should be emphasized, however, that IM formulations cannot be used IV and *vice versa*. Parenteral administration of PB is useful for administering maintenance therapy in hospitalized patients that are unable to take oral medication. The pharmacokinetics of IM PB have not been explored in dogs, however, studies in humans have shown a similar absorption after IM administration compared to oral administration [135]. The elimination half-life in dogs after a single IV dose is approximately 93h [87].

Pharmacokinetic interactions

In dogs, chronic PB administration can affect the disposition of other co-administered medications which are metabolized by cytochrome P450 subfamilies and/or bound to plasma proteins [48]. PB can alter the pharmacokinetics and as a consequence may decrease the therapeutic effect of other AEDs (levetiracetam, zonisamide, and benzodiazepines) as well as corticosteroids, cyclosporine,

metronidazole, voriconazole, digoxin, digitoxin, phenylbutazone and some anaesthetics (e.g. thiopental) [23, 33, 72, 82, 130]. As diazepam is used as first-line medicine for emergency use (e.g. status epilepticus) in practice it should be emphasized to double the IV or rectal dose of diazepam in dogs treated chronically with PB [130]. Concurrent administration of PB and medications that inhibit hepatic microsomal cytochrome P450 enzymes such as cimetidine, omeprazole, lansoprazole, chloramphenicol, trimethoprim, fluoroquinolones, tetracyclines, ketoconazole, fluconazole, itraconazole, fluoxetine, felbamate and topiramate may inhibit PB metabolism, increase serum concentration and can result in toxicity [10].

Common adverse effects

Most of the adverse effects due to PB are dose dependent, occur early after treatment initiation or dose increase and generally disappear or decrease in the subsequent weeks due to development of pharmacokinetic and pharmacodynamic tolerance [35, 121] (Table 1). The adverse effects include sedation, ataxia, polyphagia, polydipsia and polyuria. For an in-depth review on the adverse effects of PB, the reader is referred to comprehensive book chapters [23, 32, 91].

Idiosyncratic adverse effects

These effects occur uncommonly in dogs and include hepatotoxicity [13, 22, 39, 75], haematologic abnormalities (anaemia, and/or thrombocytopenia, and/or neutropenia) [51, 56]), superficial necrolytic dermatitis [66], potential risk for pancreatitis [38, 46], dyskinesia [58], anxiety [58], and hypoalbuminaemia [41] (Table 1). Most of these idiosyncratic reactions are potentially reversible with discontinuation of PB. For an in-depth review on the idiosyncratic adverse effects of PB the reader is referred to comprehensive book chapters [23, 32, 91].

Laboratory changes

Laboratory changes related to chronic PB administration in dogs include elevation in serum liver enzyme activities [39, 41, 75], cholesterol and triglyceride concentrations [41]. Alterations in some endocrine function testing may occur (thyroid and adrenal function, pituitary-adrenal axis) [21, 41, 128]. For an in-depth review on these laboratory changes the reader is referred to comprehensive book chapters [23, 32, 91].

Dose and monitoring (Fig. 1)

The recommended oral starting dose of PB in dogs is 2.5–3 mg/kg BID. Subsequently, the oral dosage is tailored

Table 1 Most common reported adverse effects seen in dogs treated with PB, imepitoin and KBr (rarely reported and/or idiosyncratic adverse effects are indicated in grey

AED	Adverse effects in dogs
PB	Sedation
	Ataxia
	Polyphagia
	Polydipsia/polyuria
	Hepatotoxicity
	Haematologic abnormalities
	Superficial necrolytic dermatitis
	Potential risk of pancreatitis
	Dyskinesia and anxiousness
	Hypoalbuminaemie
Imepitoin	Polyphagia (often transient)
	Hyperactivity, apathy, polyuria, polydipsia, hypersalivation, somnolence,
	vomiting, ataxia, apathy, diarrhoea, prolapsed nictitating membrane,
	decreased sight and sensitivity to sound
KBr	Sedation
	Ataxia and pelvic limb weakness
	Polydipsia/polyuria
	Polyphagia
	Nausea, vomiting and/or diarrhea
	Personality changes (aggression, irritability, hyperactivity)
	Megaoesophagus
	Persistent cough
	Increased risk of pancreatitis

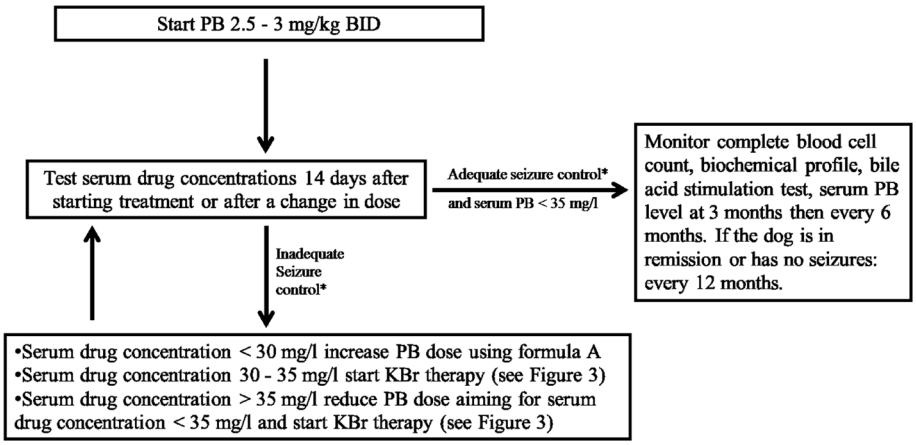

Fig. 1 PB treatment flow diagram for decision making during seizure management in an otherwise healthy dog. The authors advise to start with PB (and add KBr if inadequate seizure control after optimal use of PB (Fig. 3)): in dogs with idiopathic epilepsy experiencing recurrent single generalised epileptic seizures; in dogs with idiopathic epilepsy experiencing cluster seizures or status epilepticus; in dogs with other epilepsy types. *Criteria for (in)adequate seizure control with regard to efficacy and tolerability (see Consensus proposal: Outcome of therapeutic interventions in canine and feline epilepsy [94]). 1. Treatment efficacious: a: Achievement of complete treatment success (i.e. seizure freedom or extension of the interseizure interval to three times the longest pretreatment interseizure interval and for a minimum of three months (ideally > 1 year); b: Achievement of partial treatment success (i.e. a reduction in seizure frequency including information on seizure incidence (usually at least 50 % or more reduction defines a drug responder), a reduction in seizure severity, or a reduction in frequency of seizure clusters and/or status epilepticus). 2. Treatment not tolerated i.e. appearance of severe adverse effects necessitating discontinuation of the AED

to the individual patient based on seizure control, adverse effects and serum concentration monitoring.

Because of considerable variability in the pharmacokinetics of PB among individuals, the serum concentration should be measured 14 days after starting therapy (baseline concentration for future adjustments) or after a change in dose. To evaluate the effect of metabolic tolerance, a second PB serum concentration can be measured 6 weeks after initiation of therapy. Recommendations on optimal timing of blood collection for serum PB concentration monitoring in dogs vary among studies [23]. Generally, serum concentrations can be checked at any time in the dosing cycle as the change in PB concentrations through a daily dosing interval is not therapeutically relevant once steady-state has been achieved [62, 70]. However, in dogs receiving a dose of 5 mg/kg BID or higher, trough concentrations were significantly lower than non-trough concentrations and serum PB concentration monitoring at the same time post-drug dosing was recommended, in order to allow accurate comparison of results in these dogs [70]. Another study recommended performing serum PB concentration monitoring on a trough sample as a significant difference between peak and trough PB concentration was identified in individual dogs [10]. The therapeutic range of PB in serum is 15 mg/l to 40 mg/l in dogs. However, it is the authors' opinion that in the majority of dogs a serum PB concentration between 25–30 mg/l is required for optimal seizure control. Serum concentrations of more than 35 mg/l are associated with an increased risk of hepatotoxicity and should be avoided [22, 75]. In case of inadequate seizure control, serum PB concentrations must be used to guide increases in drug dose. Dose adjustments can be calculated according to the following formula (Formula A):

$$\begin{aligned}&\text{New PB total daily dosage in mg}\\&= (\text{desired serum PB concentration}/\text{actual serum PB concentration})\\&\times \text{actual PB total daily dosage in mg}\end{aligned}$$

A dog with adequate seizure control, but serum drug concentrations below the reported therapeutic range, does not require alteration of the drug dose, as this serum concentration may be sufficient for that individual. Generally, the desired serum AED concentration for individual patients should be the lowest possible concentration associated with >50 % reduction in seizure frequency or seizure-freedom and absence of intolerable adverse effects [23].

In animals with cluster seizures, status epilepticus or high seizure frequency, PB can be administered at a loading dose of 15–20 mg/kg IV, IM or PO divided in multiple doses of 3–5 mg/kg over 24–48h to obtain a therapeutic brain concentration quickly and then sustain it [10]. Serum PB concentrations can be measured 1–3 days after loading. Some authors load as soon as possible (over 40 to 60 min) and start with a loading dose of 10 to 12 mg/kg IV followed by two further boluses of 4 to 6 mg/kg 20 min apart.

Complete blood cell count, biochemical profile (including cholesterol and triglycerides), and bile acid stimulation

test should be performed before starting PB treatment and periodically at 3 months and then every 6 months during treatment. In case of adequate seizure control, serum PB concentrations should be monitored every 6 months. If the dog is in remission or has no seizures, a periodical control every 12 months is advised.

Imepitoin

Efficacy

Imepitoin was initially developed as a new AED for humans, but, the more favourable pharmacokinetic profile of imepitoin in dogs versus humans led to the decision to develop imepitoin for the treatment of canine idiopathic epilepsy [102]. Based on randomized controlled trials that demonstrated antiepileptic efficacy, high tolerability and safety in epileptic dogs, the drug was approved in 2013 for this indication in Europe [64, 98, 122]. It has been recommended to use imepitoin in dogs with idiopathic epilepsy experiencing recurrent single generalized epileptic seizures, however, its efficacy has not yet been demonstrated in dogs with cluster seizures or status epilepticus [30]. In a recent randomized controlled study [122], the efficacy of imepitoin was compared with PB in 226 client-owned dogs. The administration of imepitoin twice daily in incremental doses of 10, 20 or 30 mg/kg demonstrated that the majority of dogs with idiopathic epilepsy were managed successfully with imepitoin without significant difference to the efficacy of PB. The frequency of adverse events (e.g. sedation, polydipsia, polyphagia) was significantly higher in the PB group [122]. In a study by Rieck et al. (2006) [98], dogs with chronic epilepsy not responding to PB or primidone received imepitoin (in its initial formulation) or KBr as adjunct AED and the seizure frequency improved to a similar degree in both groups. According to Charalambous et al. (2014) [17], there is good evidence for recommending the use of imepitoin as monotherapy in dogs with recurrent single generalized epileptic seizures, but insufficient evidence for use as adjunct AED. At present, scientific data and evidence-based guidelines on which AED can best be combined with imepitoin are lacking, and further research is needed. Nevertheless, at this moment, the authors recommend the use of PB as adjunct AED in dogs receiving the maximum dose of imepitoin and experiencing poor seizure control. According to the authors, in case of combined therapy with imepitoin and PB, it is advised to slowly wean off imepitoin over several months if seizure control appears successful on PB and/or to reduce the dose of imepitoin if adverse effects (e.g. sedation) occur (Fig. 2).

Pharmacokinetics

Following oral administration of imepitoin at a dose of 30 mg/kg in healthy Beagle dogs, high plasma levels were observed within 30 min, but maximal plasma levels were only reached after 2–3h following a prolonged absorption time [101]. The elimination half-life was found to be short; approximately 1.5 to 2h. However, in another study in Beagle dogs, a longer half-life (~6 h) was found after higher doses of imepitoin, and accumulation of plasma levels was seen during chronic BID treatment [64]. Also, it has to be considered that Beagle dogs eliminate AEDs more rapidly than other dog strains [122]. Despite the short half-life in healthy Beagle dogs, this pharmacokinetic profile is reported as adequate to maintain therapeutically active concentrations with twice daily dosing in dogs [64, 122]. Imepitoin is extensively metabolized in the liver prior to elimination. In dogs, imepitoin is mainly excreted via the faecal route rather than the urinary route. Neither reduced kidney function nor impaired liver function is likely to greatly influence the pharmacokinetics of imepitoin [122].

Pharmacokinetic interactions and adverse reactions

There is no information on pharmacokinetic interactions between imepitoin and other medications. Although, imepitoin is a low affinity partial agonist for the benzodiazepine binding site of the $GABA_A$ receptor it has not prevented the pharmacological activity of full benzodiazepine agonists such as diazepam in the clinical setting (e.g. in dogs with status epilepticus) [122]. Consequently, because the affinity of diazepam for the $GABA_A$ receptor is much higher than imepitoin, care should be taken in the emergency setting [122]. Therefore, dogs with idiopathic epilepsy treated with imepitoin and presented in status epilepticus might require, in addition to diazepam, an additional AED parenterally (e.g. PB, levetiracetam).

Mild and most commonly transient adverse reactions (Table 1) have been reported in dogs administered 10–30 mg/kg BID of imepitoin in its initial formulation; polyphagia at the beginning of the treatment, hyperactivity, polyuria, polydipsia, somnolence, hypersalivation, emesis, ataxia, lethargy, diarrhoea, prolapsed nictitating membranes, decreased vision and sensitivity to sound [64, 98].

As part of the development of imepitoin for the treatment of canine epilepsy, a target animal safety study in dogs was conducted [96]. Under laboratory conditions, healthy Beagle dogs were exposed to high doses (up to 150 mg/kg q12h) of imepitoin for 6 months. Clinical signs of toxicity were mild and infrequent and they were mostly CNS (depression, transient ataxia) or gastrointestinal system (vomiting, body weight loss, salivation) related. These clinical signs were not life-threatening and generally resolved within 24h if symptomatic treatment was given. These data indicate that imepitoin is a safe AED and is well tolerated up to high doses in dogs treated twice daily [96]. However, the safety of imepitoin has not been evaluated in dogs weighing less than 5 kg or in dogs with safety concerns such as renal, liver,

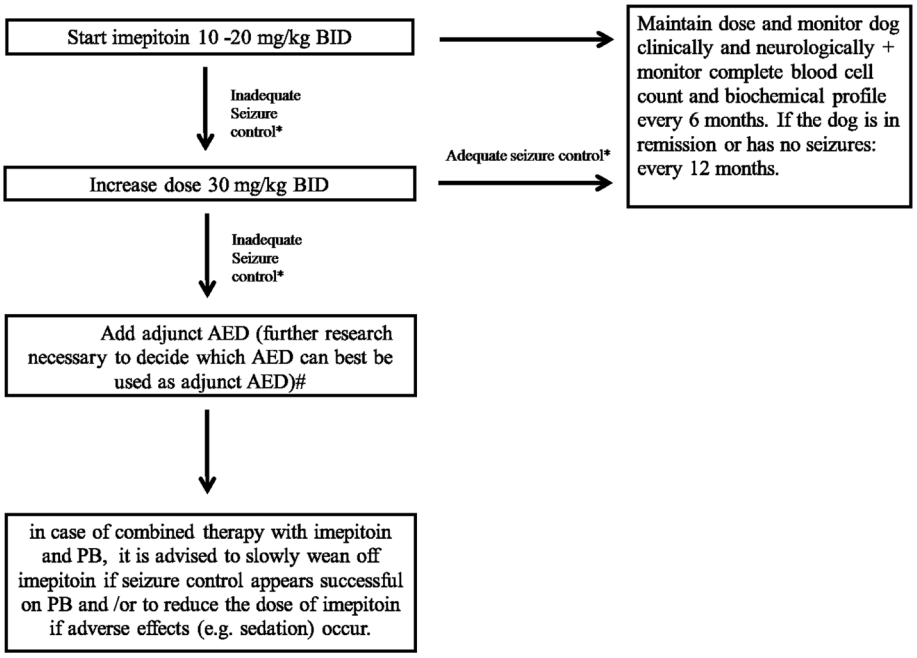

Fig. 2 Imepitoin treatment flow diagram for decision making during seizure management in an otherwise healthy dog. The authors advise to start with imepitoin in dogs with idiopathic epilepsy experiencing recurrent single generalised epileptic seizures. *Criteria for (in)adequate seizure control with regard to efficacy and tolerability (see Consensus proposal: Outcome of therapeutic interventions in canine and feline epilepsy [94]). 1. Treatment efficacious: a: Achievement of complete treatment success (i.e. seizure freedom or extension of the interseizure interval to three times the longest pretreatment interseizure interval and for a minimum of three months (ideally > 1 year), b: Achievement of partial treatment success (i.e. a reduction in seizure frequency including information on seizure incidence (usually at least 50 % or more reduction defines a drug responder), a reduction in seizure severity, or a reduction in frequency of seizure clusters and/or status epilepticus). 2. Treatment not tolerated i.e. appearance of severe adverse effects necessitating discontinuation of the AED. #Currently there are no data available on which AED should be added to imepitoin in case of inadequate seizure control. At this moment, the authors recommend the use of PB as adjunct AED in dogs receiving the maximum dose of imepitoin and experiencing poor seizure control

cardiac, gastrointestinal or other disease. No idiosyncratic reactions have been demonstrated so far. The routinely measured liver enzymes' activity do not appear to be induced by imepitoin [96]. Compared with the traditional benzodiazepines, such as diazepam, which acts as full agonists at the benzodiazepine site of the $GABA_A$ receptor, partial agonists such as imepitoin show less sedative adverse effects and are not associated with tolerance and dependence during long-term administration in animal models [122]. Also in epileptic dogs, tolerance did not develop and no withdrawal signs were observed after treatment discontinuation [64].

Dose and monitoring (Fig. 2)

The oral dose range of imepitoin is 10–30 mg/kg BID. The recommended oral starting dose of imepitoin is 10–20 mg/kg BID. If seizure control is not satisfactory after at least 1 week of treatment at this dose and the medication is well tolerated, the dose can be increased up to a maximum of 30 mg/kg BID. Reference range of plasma or serum imepitoin concentrations is unknown and there are no therapeutic monitoring recommendations for imepitoin from the manufacturer. Pharmacokinetic studies in dogs suggest variability in plasma imepitoin concentrations among individuals and sampling times. However, no correlation between plasma imepitoin concentration and seizure frequency reduction was identified [64] therefore and because of its wide therapeutic index, serum imepitoin monitoring is not needed.

The authors recommend a complete blood cell count and biochemical profile before starting imepitoin treatment and periodically every 6 months during treatment. If the dog is in remission or has no seizures, a periodical control every 12 months is advised.

Bromide

Efficacy

Br is usually administered as the potassium salt (KBr). The sodium salt form (NaBr) contains more Br per gram of compound, therefore, the dose should be approximately 15 % less than that calculated for KBr [124]. In most EU countries, KBr is approved only for add-on treatment in dogs with epilepsy drug-resistant to first-line AED therapy. PB and KBr have a synergistic effect and add-on treatment with KBr in epileptic dogs improves seizure control in dogs that are poorly controlled with PB alone [46, 93, 126]. A recent study showed that

KBr was less efficacious and tolerable than PB as first-line drug [10]. According to Charalambous et al. (2014) [17] there is fair level of evidence for recommending the use of KBr as a monotherapy, but less as adjunct AED.

Pharmacokinetics

The bioavailability of Br after oral administration in normal dogs is approximately 46 %. The elimination half-life is long and ranges from 25–46 days in dogs, consequently, it can take several months (approximately 3 months) before steady-state concentrations after treatment initiation at maintenance dose are reached [46, 67, 90, 125]. KBr is unbound to plasma proteins and can diffuse freely across cellular membranes. KBr is not metabolised in the liver and is therefore a good alternative in dogs with hepatic dysfunction. KBr is excreted unchanged in the urine and undergoes tubular reabsorption in competition with chloride. Therefore, dietary factors affecting chloride levels can alter serum KBr concentrations [123]. High (low) dietary chloride concentrations increase (decrease) the excretion of KBr and shorten (prolong) its half-life. Dogs administered KBr should be maintained on a constant diet (and chloride intake) to prevent fluctuations in serum KBr concentrations, which could result in therapeutic failure or toxicity. If dietary changes are necessary they should be made gradually (over at least 5 days) and serum concentrations of KBr should be monitored following dietary changes, especially if the dog becomes sedated or has unexpected seizures. On biochemistry profiles serum chloride concentrations are often falsely elevated ("pseudohyperchloraemia") because the assays cannot distinguish between chloride and Br ions [123].

Pharmacokinetic interactions and adverse effects

Pharmacokinetic interactions of KBr are limited as KBr is not metabolized or protein-bound. The main interactions are associated with alterations in the renal excretion of KBr. As already mentioned, the rate of elimination of KBr varies proportionally and inversely to chloride intake. Loop diuretics such as furosemide may enhance KBr elimination by blocking KBr reabsorption through renal tubular chloride channels. KBr should be avoided in dogs with renal dysfunction to prevent toxicity secondary to reduced renal elimination [80].

Common, dose-dependent adverse effects of KBr in dogs include sedation, ataxia and pelvic limb weakness, polydipsia/polyuria, and polyphagia with weight gain [4, 25, 46, 124] (Table 1). These effects occur in the initial weeks of treatment and may be magnified by concurrent PB administration. These adverse effects subside (partly or completely), once KBr steady-state concentrations are reached [125]. Gastrointestinal irritation and clinical signs can be prevented or minimized by administering Br with food and dividing the daily dose into 2 or more doses [4].

Uncommon idiosyncratic reactions of KBr in dogs include personality changes (aggressive behaviour, irritability, hyperactivity), persistent cough, increased risk of pancreatitis and megaoesofagus [4, 46, 67, 106] (Table 1). Kbr may cause skin problems (bromoderma) in humans [106], but no reports exist currently in dogs. For an in-depth review on the adverse effects of Br the reader is referred to comprehensive book chapters [23, 32, 91].

Dose and monitoring (Fig. 3)

The recommended oral starting dose of KBr is 15 mg/kg BID when used as an add-on drug. An oral dose of 20 mg/kg BID is advised when used as a monotherapy. Because of the long elimination half-life, KBr can be administered once daily (preferably in the evening), however, twice daily dosing as well as administration with food can help to prevent gastrointestinal mucosa irritation [123]. Twice daily dosing is also recommended if excessive sedation is present. Therapeutic ranges have been reported as approximately 1000 mg/l to 2000 mg/l when administered in conjunction with PB and 2000mg/l to 3000mg/l when administered alone [126]. Br has a long half-life, consequently, reaching a steady-state serum concentration may require several months (approximately 3 months). Due to this long half-life, timing of blood sample collection relative to oral administration is not critical [123].

Baseline complete blood cell count, biochemical profile (including cholesterol and triglycerides) should be performed before starting KBr treatment and periodically every 6 months during treatment. Serum KBr concentrations should be monitored 3 months after treatment initiation (or dose change). In the long term, in dogs with adequate seizure control, serum KBr concentrations should be monitored every 6 months. If the dog is in remission or has no seizures, a periodical control every 12 months is advised.

A loading dose may be recommended to achieve steady-state therapeutic concentrations more rapidly (e.g. in dogs with frequent or severe seizures, or when PB must be rapidly discontinued because of life-threatening adverse effects). Different protocols have been reported. Oral loading can be performed by administering KBr at a dose of 625 mg/kg given over 48h and divided into eight or more doses. A more gradual loading can be accomplished giving 125 mg/kg/day divided in three to four daily administrations for 5 consecutive days. Daily phone contact with the owners is advised. Loading can be associated with adverse effects (e.g. nausea, vomiting, diarrhoea, sedation, ataxia and pelvic limb weakness, polydipsia, polyuria and polyphagia) and the dog should be hospitalized if loading takes place over 48h (7,85). It is advised to stop loading when serious adverse effects occur. Consider that dogs in which

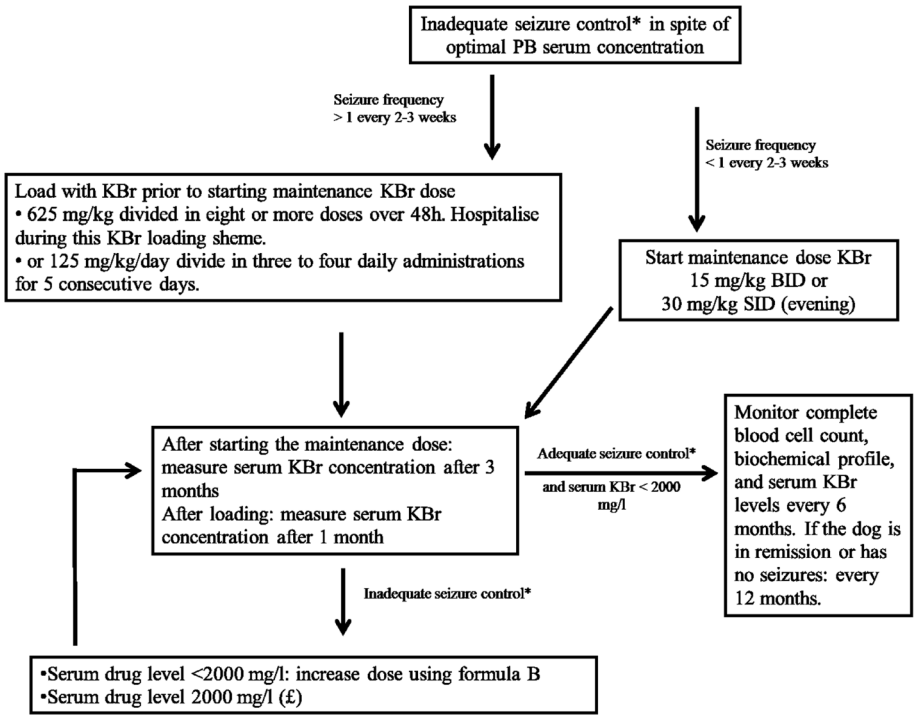

Fig. 3 KBr adjunct treatment flow diagram for decision making during seizure management in an otherwise healthy dog. *Criteria for (in)adequate seizure control with regard to efficacy and tolerability (see Consensus proposal: Outcome of therapeutic interventions in canine and feline epilepsy [94]). 1. Treatment efficacious: a: Achievement of complete treatment success (i.e. seizure freedom or extension of the interseizure interval to three times the longest pretreatment interseizure interval and for a minimum of three months (ideally > 1 year), b: Achievement of partial treatment success (i.e. a reduction in seizure frequency including information on seizure incidence (usually at least 50 % or more reduction defines a drug responder), a reduction in seizure severity, or a reduction in frequency of seizure clusters and/or status epilepticus). 2. Treatment not tolerated i.e. appearance of severe adverse effects necessitating discontinuation of the AED

KBr is used as adjunct AED to PB may be more prone to adverse effects. In these cases, a PB dose decrease of 25 % may be needed. Serum KBr levels should be monitored 1 month after loading.

Dose increases can be calculated according to the following formula

Formula B:

For concomitant PB and KBr treatment, the new maintenance dose can be calculated as follows:

$$(2000\ \text{mg/l} - \text{actual serum KBr steady-state concentration}) \times 0.02 = \text{mg/kg/day added to existing dose}$$

Formula C:

In case of monotherapy KBr, the new maintenance dose can be calculated as follows:

$$(2500\ \text{mg/l} - \text{actual serum KBr steady–state concentration}) \times 0.02 = \text{mg/kg/day added to existing dose}$$

Only PB and imepitoin are approved as first-line treatment of canine epilepsy in the EU. In most EU countries, KBr is only approved as add-on treatment in dogs resistant to first-line treatments. None of the drugs discussed in the following section are approved for treatment of dogs with epilepsy, thus, according to EU drug laws, these drugs can only be used as adjunctive treatment if monotherapy or polytherapy with the approved treatments have failed. Furthermore, except for levetiracetam, none of the AEDs discussed in the following section have been evaluated in randomized controlled trials in epileptic dogs, so that the evidence for their efficacy is very limited [17].

Levetiracetam

So far, three studies evaluated the efficacy of levetiracetam as an adjunct to other AEDs [79, 114, 127]. In all these studies, the majority of the dogs were treated successfully by oral levetiracetam as adjunct AED. The use of oral levetiracetam was evaluated in an open-label study and a response rate of 57 % was reported in dogs with drug resistant epilepsy [127]. In a recent randomized placebo-controlled study by Muñana et al. (2012) [79], the use of levetiracetam was evaluated in dogs with drug resistant epilepsy. A significant decrease in seizure frequency was reported compared with baseline, however, no difference was detected in seizure frequency when

levetiractam was compared with placebo. However, the divergence in group size and the small sample size (due to the high dropout rate) may have contributed to this result. Nevertheless, a trend towards a decrease in seizure frequency and increase in responder rate during levetiracetam administration compared to placebo warrants further evaluation in a larger scale study. According to the study of Charalambous et al., (2014) [17], there is a fair evidence for recommending the use of levetiracetam as an adjunct AED. Recently, a retrospective study provided further evidence that administering levetiracetam as an adjunct AED is well tolerated, and suppresses epileptic seizures significantly in dogs with idiopathic epilepsy [83]. The authors also confirmed that if seizure frequency increases, an extra AED may be beneficial and they added the possibility of administering levetiracetam as pulse treatment for cluster seizures.

Levetiracetam possesses a favourable pharmacokinetic profile in dogs with respect to its use as an add-on AED. It has rapid and complete absorption after oral administration, minimal protein binding, minimal hepatic metabolism and is excreted mainly unchanged via the kidneys. In humans and dogs, renal clearance of levetiracetam is progressively reduced in patients with increasing severity of renal dysfunction [85], thus, dosage reduction should be considered in patients with impaired renal function. As levetiracetam has minimal hepatic metabolism [85], this drug represents a useful therapeutic option in animals with known or suspected hepatic dysfunction. However, its short elimination half-life of 3–6 h necessitates frequent administration. The recommended oral maintenance dose of levetiracetam in dogs is 20 mg/kg TID-QID. The same dose can be administered parenterally in dogs (SC, IM, IV) when oral administration is not possible [86]. In a previous study [127] it was shown that some dogs develop a tolerance to levetiracetam when used chronically. This phenomenon, the 'honeymoon effect', has been documented for other AEDs, e.g. zonisamide and levetiracetam in dogs with epilepsy [127, 129]. Therefore, the introduction of the pulse treatment protocol (an initial dose of 60 mg/kg orally or parenterally after a seizure occurs or preictal signs are recognized by the owner, followed by 20 mg/kg TID until seizures do not occur for 48h) was developed, in order to start treatment only in case of cluster seizures when therapeutic levetiracetam concentrations need to be reached rapidly. The results in the recent study by Packer et al., 2015 [83] supports this clinical approach. Pulse treatment was, however, associated with more side effects compared to maintenance levetiracetam therapy [83]. Levetiracetam is well tolerated and generally safe in dogs. Except for mild sedation, ataxia, decreased appetite and vomiting adverse effects are very rarely described in dogs [79, 127] (Table 2). Levetiracetam has also a different mode of action compared to other AEDs and therefore may be advantageous when polytherapy is instituted. It selectively binds to a presynaptic protein (SVA2), whereby it seems to modulate the release of neurotransmitters [86]. As, in dogs there is no information available regarding a therapeutic range [79], the human target range of 12–46 μg/l can be used as guidance regarding effective concentrations.

Table 2 Most common reported adverse effects seen in dogs treated with levetiracetam, zonisamide, felbamate, topiramate, gabapentin, and pregabalin (rarely reported and/or idiosyncratic adverse effects are indicated in grey

AED	Adverse effects in dogs
Levetiracetam	Sedation
	Ataxia
	Decreased appetite or anorexia
	Vomiting
	Behavioural changes
Zonisamide	Sedation
	Ataxia
	Vomiting
	Inappetence
	Acute hepatopathy/hepatomegaly
	Renal tubular acidosis
Felbamate	Keratoconjunctivitis sicca
	Thrombocytopenia
	Lymphopenia and leucopenia
Topiramate	Sedation
	Ataxia
	Weight loss
Gabapentin	Sedation
	Ataxia
Pregabalin	Sedation
	Ataxia
	Weakness

Studies in humans have shown that concomitant administration of AEDs that induce cytochrome P450 metabolism such as PB, can alter the disposition of levetiracetam [19]. Recently, it has been demonstrated that PB administration significantly alters the pharmacokinetics of levetiracetam in normal dogs [73]. Thus, levetiracetam oral dose may need to be increased or dosing time interval may need to be shortened when concurrently administered with PB [73]. Also in dogs with epilepsy, concurrent administration of PB alone or in combination with KBr increases levetiracetam clearance compared to concurrent administration of KBr alone [78]. Thus, dosage increases might be indicated when utilizing levetiracetam as add-on treatment with PB in dogs [78], preferably guided by levetiracetam serum concentration measurement.

Zonisamide

There are few reports on the use of zonisamide in dogs, despite it being licensed for treatment of canine epilepsy in Japan. One report evaluated the efficacy of oral zonisamide as a monotherapy [18]. Two studies have been described evaluating zonisamide as an add-on treatment in dogs with drug resistant epilepsy [28, 129]. Based on the results of these studies, Charalambous et al. (2014) [17] concluded that, at present, there is insufficient evidence to recommend the use of zonisamide either as a monotherapy or as an adjunct AED in dogs. Larger studies are required to evaluate zonisamide as a monotherapy or as an adjunctive AED in dogs. Adverse effects in dogs include sedation, vomiting, ataxia, and loss of appetite [18, 28, 129] (Table 2). Additionally, recently hepatotoxicity has been described in 2 dogs receiving zonisamide monotherapy which is believed to be an idiosyncratic reaction to the drug [69, 104] (Table 2). Renal tubular acidosis has also been described in a dog receiving zonisamide monotherapy [20] (Table 2). Thus, zonisamide should be used with caution in dogs with renal or hepatic impairment. Both, hepatic and renal failures have been described in humans receiving zonisamide as well. Currently, zonisamide is not available in every country and when available, it can be very expensive.

Zonisamide is a sulphonamide-based anticonvulsant approved for use in humans. The exact mechanism of action is unknown, however, blockage of calcium channels, enhancement of GABA release, inhibition of glutamate release, and inhibition of voltage-gated sodium channels might contribute to its anticonvulsant properties [61]. In dogs, zonisamide is well-absorbed after oral administration, has a relatively long elimination half-life (approximately 15h), and has low protein binding so that drug interactions are minimized. The drug mainly undergoes hepatic metabolism via the cytochrome P450 system before excretion by the kidneys [11].

The recommended oral starting dose of zonisamide in dogs is 3–7 mg/kg BID and 7–10 mg/kg BID in dogs co-administered hepatic microsomal enzymes inducers such as PB [11, 28]. Serum concentrations of zonisamide should be measured minimally 1 week after treatment initiation or dosage adjustment to allow steady state concentrations be reached. Care should be taken to avoid haemolysis, as falsely elevated serum zonisamide concentrations from lysed red blood cells may occur. The human target range of 10–40 mg/l can be used as guidance regarding effective concentrations. [28]. Baseline complete blood cell count and biochemical profile should be performed before starting zonisamide treatment and periodically every 6 months during treatment.

Felbamate

One veterinary study evaluated the efficacy of felbamate as an adjunct to PB in 6 dogs with focal idiopathic epilepsy [100]. According to Charalambous et al. (2014) [17], the study demonstrated overall moderate/high risk of bias. On this basis it was concluded that there is currently insufficient evidence to recommending the use of felbamate as an add-on AED. Felbamate should be reserved for dogs refractory to the other more thoroughly investigated and safer AEDs in this species and as such this is a 4^{th} or 5^{th} line option. In the clinical study by Ruehlmann et al., (2001) [100] adverse effects noted included keratoconjunctivitis sicca and mild blood dyscrasias (Table 2).

Felbamate is a dicarbamate AED released for use in humans in 1993 for the control of focal seizures. Its mechanism of action is multiple such as inhibition of glycine-enhanced NMDA-induced intracellular calcium currents [134], blockade of voltage-gated sodium channels and inhibition of voltage –gated calcium currents [133].

In 1993, felbamate was marketed as a safe AED, which lacked demonstrable toxic side effects and did not require laboratory monitoring in humans. However, within a year of its release it became evident that felbamate was associated with an unacceptable incidence of life-threatening side effects [12], such as anorexia, weight loss, vomiting, headache, irritability. Moreover, aplastic anemia and fatal hepatotoxicity were also described [55, 134].

Pharmacokinetic interactions between felbamate and other AEDs have been well described. E.g. felbamate raises concurrent PB serum levels in a dose-dependent manner [12], and the elimination of felbamate was noted to be strikingly reduced when given with gabapentin [50]. Felbamate is mainly metabolized by the liver [88] and should therefore not be used in dogs with pre-existing hepatic disease. Felbamate has an elimination half-life of 5–7h.

The recommended oral starting dose in dogs is 20 mg/kg TID, increasing to 400–600mg/day every 1–2 weeks [1]. Haematologic evaluations and biochemistry panels (esp. liver enzyme concentrations) should be performed before felbamate therapy is initiated and during therapy. This is especially important in animals receiving concurrent PB. In humans, the signs of aplastic anaemia and liver failure are usually seen during the first 6–12 months of therapy. In dogs, a minimum of monthly blood tests should be performed for this period of time, following-up every 6–12 months after this. Currently, felbamate is not available in every country.

Topiramate

In 2013, one sudy evaluated the efficacy of topiramate as an adjunct to PB, KBr, and levetiracetam in 10 dogs [57]. The dose was titrated (2–10 mg/kg) two to three times daily. Sedation, ataxia and weight loss were the most common adverse effects in dogs (Table 2). According to Charalambous et al. (2014) [17], the study demontsrated

an overall moderate/high risk of bias. Thus, there is currently insufficient evidence to recommend the use of topiramate as an adjunct AED [17].

In humans, topiramate has served both as a monotherapy and adjunctive therapy to treat focal and generalised seizures [29, 71]. It is a sulphamate-substituted monosaccharide that acts on multiple signalling mechanisms enhancing GABA-ergic activity and inhibiting voltage-sensitive sodium and calcium channels, kainate-evoked currents and carbonic anhydrase isoenzymes [118, 139].

From the available human data, topiramate is not metabolized extensively once absorbed, with 70–80 % of an administered dose eliminated unchanged in the urine [65]. Topiramate has an elimination half-life of 2–4h. Clearance of topiramate is reduced in patients with renal impairment, necessitating dosage adjustments [37]. In dogs, topiramate is not extensively metabolized and is primarily eliminated unchanged in the urine. However, biliary excretion is present following topiramate administration in dogs [15]. The drug has a relatively low potential for clinically relevant interactions with other medications [8, 53]. The most commonly observed adverse effects in humans are somnolence, dizziness, ataxia, vertigo and speech disorders [110]. No adverse reactions were reported in healthy Beagle dogs administered 10–150 mg/kg daily oral doses for 15 days [116].

Gabapentin

Two prospective studies evaluated the efficacy of oral gabapentin as an adjunct to other AEDs, giving a combined sample size of 28 dogs [44, 89]. According to Charalambous et al. (2014) [17], one study demonstrated an overall moderate/high risk of bias and the other one demonstrated an overall high risk of bias. None of the studies demonstrated an increased likelihood that the majority of the dogs were treated successfully by oral administration of gabapentin. Accordingly, there is currently overall insufficient evidence for recommending the use of gabapentin as an adjunct AED [17]. If used, the recommended oral dosage of gabapentin in dogs is 10 to 20 mg/kg TID, although dose reduction may be necessary in patients with reduced renal function [9]. Sedation and ataxia were the most common side effects reported in dogs [44, 89] (Table 2).

Gabapentin has been approved in people in Europe and by the US Food and Drug Administration (FDA) since 1993 for adjunctive treatment of focal seizures with or without secondary generalisation and for the treatment of post-herpetic neuralgia [9]. Its precise mechanism of action is unclear, but is believed that much of its anticonvulsant effect is because of its binding to a specific modulatory protein of voltage-gated calcium channels, which results in decreased release of excitatory neurotransmitters [112]. In humans, gabapentin is entirely excreted by the kidneys. In dogs, renal excretion occurs after a partial hepatic metabolism. The elimination half-life is 3–4h.

Although information in veterinary medicine is limited, pharmacokinetic interactions of gabapentin are unlikely to occur as the drug has negligible protein binding and does not induce hepatic cytochrome P450 family enzymes [95]. In humans, the elimination of felbamate was noted to be significantly reduced when given with gabapentin [50]. The most common adverse effects in humans include dizziness, somnolence and fatigue [9]. These effects seem to be dose-dependent and resolve within the first few weeks of treatment. No serious idiosyncratic reactions or organ toxicities have been identified in humans or animals [60].

Pregabalin

There is limited data on the use of pregabalin in dogs. In a study by Dewey et al., (2009), the efficacy of oral pregabalin as an adjunct to PB and KBr was evaluated in 9 dogs [27]. According to Charalambous et al. (2014) [17], this study demonstrated an overall moderate/high risk of bias. Consequently, there is currently insufficient evidence to recommend the use of pregabalin as an adjunct AED [17]. If used, the recommended oral dose in dogs is 3–4 mg/kg BID-TID. The most common adverse effects (Table 2) in the study of Dewey et al., (2009) included sedation, ataxia and weakness, and to minimize these, treatment could be initiated at a dose of 2 mg/kg two to three times daily and escalated by 1 mg/kg each week until the final dose is achieved [27]. As pregabalin clearance is highly correlated with renal function, dose reduction is necessary in patients with reduced renal function [5, 9].

Pregabalin is a GABA analogue that is structurally similar to gabapentin. Pregabalin was approved in 2004 for the treatment of adults with peripheral neuropathic pain and as adjunctive treatment for adults with focal seizures with or without secondary generalization. Pregabalin is more potent than gabapentin owing to a greater affinity for its receptor [112]. Pharmacokinetic studies have been performed in dogs, with a reported elimination half-life of approximately 7 h [103]. In humans, pregabalin does not bind to plasma proteins and is excreted virtually unchanged by the kidneys [9]. Pregabalin does not undergo hepatic metabolism and does not induce or inhibit hepatic enzymes such as the cytochrome P450 system [5]. No clinically relevant pharmacokinetic drug interactions have been identified in humans to date. The most commonly reported adverse effects in humans are dose-related and include dizziness, somnolence and ataxia [9].

Discontinuation of AEDs

Two main reasons for discontinuation of an AED are remission of seizures or life-threatening adverse effects. Generally, treatment for idiopathic epilepsy involves lifelong AED administration. However, remission has been

reported in dogs. Remission rates between 15–30 % have been described in hospital based populations [6, 7, 47, 49]. In a study by Packer et al. (2014) 14 % of dogs were in remission on PB [84]. When ≥50 % reduction in seizure frequency was used as the outcome measure, success rates were markedly higher with 64,5 % of dogs achieving this level of seizure reduction. Several factors were associated with an increased likelihood of achieving remission, namely: being female, neutered, no previous experience of cluster seizures and an older age at onset of seizures. The same four factors were associated with an increased likelihood of achieving a ≥50 % reduction in seizure frequency [84]. The breed least likely to go into remission or have an ≥50 % reduction in seizure frequency was the Border Collie (0 and 40 %, respectively), the German Shepherd (11 and 35 %, respectively) and Staffordshire Bull Terrier (0 and 57 %, respectively) [84]. In a study by Hülsmeyer et al. (2010) the remission rate was 18 % in Border Collies independent of disease severity [49]. The decision to gradually taper the dose of an AED should be taken on a case-by-case basis, but seizure freedom of at least 1–2 years is advised. In people with prolonged seizure remission (generally 2 or more years), the decision to discontinue AED treatment is done on an individual basis considering relative risks and benefits. Individuals with the highest probability of remaining seizure-free are those who had no structural brain lesion, a short duration of epilepsy, few seizures before pharmacological control, and AED monotherapy [81, 109]. In dogs, however, little information on risk factors associated with seizure relapse exist, thus the pet owner must be aware that seizures may recur anytime during AED dose reduction of after discontinuation. To prevent withdrawal seizures or status epilepticus it is advised to decrease the dose with 20 % or less on a monthly basis.

In case of life-threatening adverse effects, instant cessation of AED administration under 24h observation is necessary. In these cases, loading with an alternative AED should be initiated promptly in order to achieve target serum concentrations before serum PB concentration decreases. Loading with KBr (see section on KBr) or levetiracetam (see section on levetiracetam) is possible. If hepatic function is normal, starting imepitoin or zonisamide at the recommended oral starting dose may be another alternative.

Pet owner education

In order to promote a successful management of an epileptic pet, owners need to be educated thoroughly on [23, 32, 91]:

- The disease of their pet and the influence on their daily life (considerations regarding e.g. leaving the dog alone, what to do if travelling and leaving the dog in a kennel, fears of behavioural comorbidities, …)
- The need for AED therapy and the understanding that this often is a lifetime commitment
- The aim of AED therapy
- The importance of regular administration of AEDs
- The fact that dose adjustments should only be made after consulting a veterinarian
- Potential adverse effects of AED therapy
- The importance of maintaining a detailed seizure diary
- The importance of regular check-ups to monitor AED blood concentrations as well as haematology/serum biochemistry where appropriate
- The need for treatment modulation to achieve optimal seizure control
- The possibility of occurrence of status epilepticus and cluster seizures and the administration of additional AEDs at home
- Costs involved
- The fact that drug interactions might occur when combined with other AEDs or non-AEDs
- The understanding that abrupt drug withdrawal might be detrimental
- The fact that diet (e.g salt content), diarrhoea and vomiting may affect the absorption of AEDs. It should be advised to keep the diet constant or to make changes gradually and seek veterinary advice if gastrointestinal signs occur.

Abbreviations

AED: Antiepileptic drug; PB: Phenobarbital; KBr: Potassium bromide; Br: Bromide; IM: Intramuscular; IV: Intravenous; PO: Orally; SC: Subcutaneously; SID: Once daily; BID: Twice daily; TID: Three times daily; QID: Four times daily.

Competing interests

Following reimbursements, fees and funding have been received by the authors in the last three years and have been declared in the competing interest section. WL, CR, RGF, HAV, KM, MP and JP have received fees for acting as a consultant for Boehringer Ingelheim (WL, KM, MP: consultancy during development and approval of imepitoin; CR: pain consultancy; RGF, JP, HAV: consultancy pre and post launch of imepitoin). AT has been an advisor for Boehringer Ingelheim. SFMB, HAV and AT have been responsible principal investigator of several research studies concerning imepitoin financed by Boehringer Ingelheim. SFMB, HAV, JP, HP, MB, CR and AF received speaking fees from Boehringer Ingelheim. HP received consulting and speaking fees and funding for a collaborative project from Eisai Co. LTD. HAV received funding for a collaborative project from Desitin and Nestlé Purina Research. AF and LDR received reimbursements from Boehringer Ingelheim. LDR has received consulting and speaking fees from Vetoquinol. MP has received consultant fees for Aratana. The other authors declared that they have no competing interests.

Authors' contributions

SFMB chaired and LDR co-chaired the treatment working group (LDR, SFMB, KM, JP, SVM, AT) and wrote the first draft of the consensus paper with the help of LDR, KM, JP, SVM, AT and HAV. All authors read, critiqued, commented and approved the final manuscript.

Authors' information

Co-chair of the medical treatment of canine epilepsy working group: Luisa De Risio. Chair of IVETF: Holger A. Volk.

Acknowledgements
The authors are grateful to all owners of epileptic pets and veterinary colleagues who have inspired the group to create consensus statements. The authors also would like to thank the research office for assessing the manuscript according to the Royal Veterinary College's code of good research practice (Authorisation Number – CCS_ 01027). This study was not financially supported by any organization or grant.

Author details
[1]Department of Small Animal Medicine and Clinical Biology, Faculty of Veterinary Medicine, Ghent University, Salisburylaan 133, Merelbeke 9820, Belgium. [2]Animal Health Trust, Lanwades Park, Kentford, Newmarket, CB8 7UU Suffolk, United Kingdom. [3]Department of Clinical Sciences, College of Veterinary Medicine, North Carolina State University, 1052 William Moore Drive, Raleigh, NC 27607, USA. [4]Vet Extra Neurology, Broadleys Veterinary Hospital, Craig Leith Road, Stirling FK7 7LEStirlingshire, United Kingdom. [5]Department of Small Animal Medicine and Surgery, University of Veterinary Medicine Hannover, Bünteweg 9, 30559 Hannover, Germany. [6]Department of Veterinary and Clinical Sciences, Faculty of Health and Medical Sciences, University of Copenhagen, Frederiksberg C, Denmark. [7]Fernside Veterinary Centre, 205 Shenley Road, Borehamwood, SG9 0TH Hertfordshire, United Kingdom. [8]Clinical Veterinary Medicine, Ludwig-Maximillians-University, Veterinärstr. 13, 80539 Munich, Germany. [9]University of Melbourne, 250 Princes Highway, Weibee 3015VIC, Australia. [10]Department of Pharmacology, Toxicology and Pharmacy, University of Veterinary Medicine Hannover, Bünteweg 17, 30559 Hannover, Germany. [11]Department of Clinical Sciences of Companion Animals, Utrecht University, Yalelaan 108, 3583 CM Utrecht, The Netherlands. [12]Section of Clinical & Comparative Neuropathology, Centre for Clinical Veterinary Medicine, Ludwig-Maximilians-University, Veterinärstr. 13, 80539 Munich, Germany. [13]Clinical Unit of Internal Medicine Small Animals, University of Veterinary Medicine, Veterinärplatz 1, 1210 Vienna, Austria. [14]University of Minnesota College of Veterinary Medicine, D426 Veterinary Medical Center, 1352 Boyd Avenue, St. Paul, MN 55108, USA. [15]College of Veterinary Medicine, University of Georgia, 501 DW Brooks Drive, Athens, GA 30602, USA. [16]Chicago Veterinary Neurology and Neurosurgery, 3123 N. Clybourn Avenue, Chicago, IL 60618, USA. [17]Department of Pharmacology, Toxicology and Pharmacy, Ludwig-Maximillians-University, Königinstr. 16, 80539 Munich, Germany. [18]Fitzpatrick Referrals, Halfway Lane, Eashing, Godalming, GU7 2QQ Surrey, United Kingdom. [19]School of Veterinary Medicine, Faculty of Health & Medical Sciences, University of Surrey, Guildford, GU2 7TE Surrey, United Kingdom. [20]Department of Clinical Science and Services, Royal Veterinary College, Hatfield AL9 7TAHertfordshire, UK.

Received: 4 June 2015 Accepted: 29 June 2015
Published online: 28 August 2015

References

1. Adusumalli VE, Gilchrist JR, Wichmann JK, Kucharczyk N, Sofia RD. Pharmacokinetics of felbamate in pediatric and adult beagle dogs. Epilepsia. 1992;33:955–60.
2. Al-Tahan F, Frey HH. Absorption kinetics and bioavailability of phenobarbital after oral administration to dogs. J Vet Pharmacol Ther. 1985;8:205–7.
3. Alves L, Hülsmeyer V, Jaggy A, Fischer A, Leeb T, Drögemüller M. Polymorphisms in the ABCB1 gene in phenobarbital responsive and resistant idiopathic epileptic Border Collies. J Vet Intern Med. 2011;25:484–9.
4. Baird-Heinz HE, Van Schoick AL, Pelsor FR, Ranivand L, Hungerford LL. A systematic review of the safety of potassium bromide in dogs. J Am Vet Med Assoc. 2012;240:705–15.
5. Ben-Menachem E. Pregabalin pharmacology and its relevance to clinical practice. Epilepsia. 2004;45.
6. Berendt M, Gredal H, Ersbøll AK, Alving J. Premature death, risk factors, and life patterns in dogs with epilepsy. J Vet Intern Med. 2007;21:754–9.
7. Berendt M, Gredal H, Pedersen LG, Alban L, Alving J. A cross-sectional study of epilepsy in Danish Labrador Retrievers: prevalence and selected risk factors. J Vet Intern Med. 2002;16:262–8.
8. Bialer M, Doose DR, Murthy B, Curtin C, Wang SS, Twyman RE, et al. Pharmacokinetic interactions of topiramate. Clin Pharmacokinet. 2004;43:763–80. Review.
9. Bockbrader HN, Wesche D, Miller R, Chapel S, Janiczek N, Burger P. Clin Pharmacokinet. A comparison of the pharmacokinetics and pharmacodynamics of pregabalin and gabapentin. 2010;49:661-9.
10. Boothe DM, Dewey C, Carpenter DM. Comparison of phenobarbital with bromide as a first-choice antiepileptic drug for treatment of epilepsy in dogs. J Am Vet Med Assoc. 2012;240:1073–83.
11. Boothe DM, Perkins J. Disposition and safety of zonisamide after intravenous and oral single dose and oral multiple dosing in normal hound dogs. J Vet Pharmacol Ther. 2008;31:544–53.
12. Bourgeois BF. Felbamate. Semin Pediatr Neurol. 1997;4:3–8.
13. Bunch SE, Castleman WL, Hornbuckle WE, Tennant BC. Hepatic cirrhosis associated with long-term anticonvulsant drug therapy in dogs. J Am Vet Med Assoc. 1982;181:357–62.
14. Cahan LD, Engel Jr J. Surgery for epilepsy: a review. Acta Neurol Scand. 1986;73:551–60.
15. Caldwell GW, Wu WN, Masucci JA, McKown LA, Gauthier D, Jones WJ, et al. Metabolism and excretion of the antiepileptic/antimigraine drug, Topiramate in animals and humans. Eur J Drug Metab Pharmacokinet. 2005;30:151–64.
16. Chadwick DW. The treatment of the first seizure: the benefits. Epilepsia. 2008;49:26–8.
17. Charalambous M, Brodbelt D, Volk HA. Treatment in canine epilepsy–a systematic review. BMC Vet Res. 2014;10:257.
18. Chung JY, Hwang CY, Chae JS, Ahn JO, Kim TH, Seo KW, et al. Zonisamide monotherapy for idiopathic epilepsy in dogs. N Z Vet J. 2012;60:357–9.
19. Contin M1, Albani F, Riva R, Baruzzi A. Levetiracetam therapeutic monitoring in patients with epilepsy: effect of concomitant antiepileptic drugs. Ther Drug Monit. 2004;26:375–9.
20. Cook AK, Allen AK, Espinosa D, Barr J. Renal tubular acidosis associated with zonisamide therapy in a dog. J Vet Intern Med. 2011;25:1454–7.
21. Daminet S, Ferguson DC. Influence of drugs on thyroid function in dogs. J Vet Intern Med. 2003;17:463–72.
22. Dayrell-Hart B, Steinberg SA, VanWinkle TJ, Farnbach GC. Hepatotoxicity of phenobarbital in dogs: 18 cases (1985-1989). J Am Vet Med Assoc. 1991;199:1060–6.
23. De Risio L. Chapter 12-20. In: De Risio L, Platt S, editors. Canine and feline epilepsy. Diagnosis and Management. 2014. p. 347–475.
24. De Risio L, Freeman J, Shea A. Proceedings of the 27th Symposium of the European College of Veterinary Neurology, Madrid, 18-20 September 2014, and Journal of Veterinary Internal Medicine 2015; Prevalence and clinical characteristics of idiopathic epilepsy in the Italian Spinone in the UK.
25. Dewey CW. Anticonvulsant therapy in dogs and cats. Vet Clin North Am Small Anim Pract. 2006;36:1107–27.
26. Dewey CW, Barone G, Smith K, Kortz GD. Alternative anticonvulsant drugs for dogs with seizure disorders. Vet Med. 2004;99:786–93.
27. Dewey CW, Cerda-Gonzalez S, Levine JM, Badgley BL, Ducoté JM, Silver GM, et al. Pregabalin as an adjunct to phenobarbital, potassium bromide, or a combination of phenobarbital and potassium bromide for treatment of dogs with suspected idiopathic epilepsy. J Am Vet Med Assoc. 2009;235:1442–9.
28. Dewey CW, Guiliano R, Boothe DM, Berg JM, Kortz GD, Joseph RJ, et al. Zonisamide therapy for refractory idiopathic epilepsy in dogs. J Am Anim Hosp Assoc. 2004;40:285–91.
29. Elterman RD, Glauser TA, Wyllie E, Reife R, Wu SC, Pledger G. A double-blind, randomized trial of topiramate as adjunctive therapy for partial-onset seizures in children. Topiramate YP Study Group. Neurology. 1999;52:1338–44.
30. European Medicines agency http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/veterinary/medicines/002543/vet_med_000268.jsp&mid=WC0b01ac058008d7a8 http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/veterinary/002543/WC500140840.pdf
31. Farnbach GC. Serum concentrations and efficacy of phenytoin, phenobarbital, and primidone in canine epilepsy. J Am Vet Med Assoc. 1984;184:1117–20.
32. Fischer A, Jurina K, Potschka H, Rentmeister K, Tipold A, Volk HA, et al. Hoofdstuk 4: Therapie. In: Enke Verlag, Stuttgart, editor. Idiopathische epilepsie bij de hond. 2013. p. 69–115.
33. Forrester SD, Wilcke JR, Jacobson JD, Dyer KR. Effects of a 44-day administration of phenobarbital on disposition of clorazepate in dogs. Am J Vet Res. 1993;54:1136–8.
34. Freitag H, Tuxhorn I. Cognitive function in preschool children after epilepsy surgery: rationale for early intervention. Epilepsia. 2005;46:561–7.
35. Frey HH. Use of anticonvulsants in small animals. Vet Rec. 1986;118:484–6.
36. Frey HH, Göbel W, Löscher W. Pharmacokinetics of primidone and its active metabolites in the dog. Arch Int Pharmacodyn Ther. 1979;242:14–30.

37. Garnett WR. Clinical pharmacology of topiramate: a review. Epilepsia. 2000;41:61–5.
38. Gaskill CL, Cribb AE. Pancreatitis associated with potassium bromide/ phenobarbital combination therapy in epileptic dogs. Can Vet J. 2000;41:555–8.
39. Gaskill CL, Miller LM, Mattoon JS, Hoffmann WE, Burton SA, Gelens HC, et al. Liver histopathology and liver and serum alanine aminotransferase and alkaline phosphatase activities in epileptic dogs receiving phenobarbital. Vet Pathol. 2005;42:147–60.
40. Gieger TL, Hosgood G, Taboada J, Wolfsheimer KJ, Mueller PB. Thyroid function and serum hepatic enzyme activity in dogs after phenobarbital administration. J Vet Intern Med. 2000;14:277–81.
41. Gieger TL, Hosgood G, Taboada J, Wolfsheimer KJ, Mueller PB. Thyroid function and serum hepatic enzyme activity in dogs after phenobarbital administration. J Vet Intern Med. 2000;14:277–81.
42. Glauser T, Ben-Menachem E, Bourgeois B, Cnaan A, Chadwick D, Guerreiro C, et al. ILAE treatment guidelines: evidence-based analysis of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes. Epilepsia. 2006;47:1094–120.
43. Glauser TA, Loddenkemper T. Management of childhood epilepsy. Epilepsy. 2013;19:568.
44. Govendir M, Perkins M, Malik R. Improving seizure control in dogs with refractory epilepsy using gabapentin as an adjunctive agent. Aust Vet J. 2005;83:602–8.
45. Gulløv CH, Toft N, Berendt M. A Longitudinal Study of Survival in Belgian Shepherds with Genetic Epilepsy. J Vet Int Med. 2012;26:1115–20.
46. Hess RS, Kass PH, Shofer FS, Van Winkle TJ, Washabau RJ. Evaluation of risk factors for fatal acute pancreatitis in dogs. J Am Vet Med Assoc. 1999;214:46–51.
47. Heynold Y, Faissler D, Steffen F, Jaggy A. Clinical, epidemiological and treatment results of idiopathic epilepsy in 54 labrador retrievers: a long-term study. J Small Anim Pract. 1997;38:7–14.
48. Hojo T, Ohno R, Shimoda M, Kokue E. Enzyme and plasma protein induction by multiple oral administrations of phenobarbital at a therapeutic dosage regimen in dogs. J Vet Pharmacol Ther. 2002;25:121–7.
49. Hülsmeyer V, Zimmermann R, Brauer C, Sauter-Louis C, Fischer A. Epilepsy in Border Collies: clinical manifestation, outcome, and mode of inheritance. J Vet Intern Med. 2010;24:171–8.
50. Hussein G, Troupin AS, Montouris G. Gabapentin interaction with felbamate. Neurology. 1996;47:1106.
51. Jacobs G, Calvert C, Kaufman A. Neutropenia and thrombocytopenia in three dogs treated with anticonvulsants. J Am Vet Med Assoc. 1998;212:681–4.
52. Janszky J, Janszky I, Schulz R, Hoppe M, Behne F, Pannek HW, et al. Temporal lobe epilepsy with hippocampal sclerosis: predictors for long-term surgical outcome. Brain. 2005;128:395–404.
53. Johannessen SI. Pharmacokinetics and interaction profile of topiramate: review and comparison with other newer antiepileptic drugs. Epilepsia. 1997;38:18–23.
54. Jull P, Risio LD, Horton C, Volk HA. Effect of prolonged status epilepticus as a result of intoxication on epileptogenesis in a UK canine population. Vet Rec. 2011;169:361.
55. Kaufman DW, Kelly JP, Anderson T, Harmon DC, Shapiro S. Evaluation of case reports of aplastic anemia among patients treated with felbamate. Epilepsia. 1997;38:1265–9.
56. Khoutorsky A, Bruchim Y. Transient leucopenia, thrombocytopenia and anaemia associated with severe acute phenobarbital intoxication in a dog. J Small Anim Pract. 2008;49:367–9.
57. Kiviranta AM, Laitinen-Vapaavuori O, Hielm-Björkman A, Jokinen T. Topiramate as an add-on antiepileptic drug in treating refractory canine idiopathic epilepsy. J Small Anim Pract. 2013;54:512–20.
58. Kube SA, Vernau KM, LeCouteur RA. Dyskinesia associated with oral phenobarbital administration in a dog. J Vet Intern Med. 2006;20:1238–40.
59. Kwan P, Brodie MJ. Early identification of refractory epilepsy. N Engl J Med. 2000;342:314–9.
60. La Roche SM, Helmers SL. The new antiepileptic drugs: scientific review. JAMA. 2004;291:605–14.
61. Leppik IE. Zonisamide: chemistry, mechanism of action, and pharmacokinetics. Seizure. 2004;13:5–9.
62. Levitski RE, Trepanier öA. . Effect of timing of blood collection on serum phenobarbital concentrations in dogs with epilepsy. J Am Vet Med Assoc. 2000;15(217):200–4.
63. Löscher W, Potschka H, Rieck S, Tipold A, Rundfeldt C. Anticonvulsant efficacy of the low-affinity partial benzodiazepine receptor agonist ELB 138 in a dog seizure model and in epileptic dogs with spontaneously recurrent seizures. Epilepsia. 2004;45:1228–39.
64. Löscher W, Potschka H, Rieck S, Tipold A, Rundfeldt C. Anticonvulsant efficacy of the low-affinity partial benzodiazepine receptor agonist ELB 138 in a dog seizure model and in epileptic dogs with spontaneously recurrent seizures. Epilepsia. 2004;45:1228–39.
65. Lyseng-Williamson KA, Yang LP. Topiramate: a review of its use in the treatment of epilepsy. Drugs. 2007;67:2231–56.
66. March PA, Hillier A, Weisbrode SE, Mattoon JS, Johnson SE, DiBartola SP, et al. Superficial necrolytic dermatitis in 11 dogs with a history of phenobarbital administration (1995-2002). J Vet Intern Med. 2004;18:65–74.
67. March PA, Podell M, Sams RA. Pharmacokinetics and toxicity of bromide following high-dose oral potassium bromide administration in healthy Beagles. J Vet Pharmacol Ther. 2002;25:425–32.
68. Martinez SE, Bowen KA, Remsberg CM, Takemoto JK, Wright HM, Chen-Allen AV, et al. High-performance liquid chromatographic analysis of lacosamide in canine serum using ultraviolet detection: application to pre-clinical pharmacokinetics in dogs. Biomed Chromatogr. 2012;26:606–9.
69. Miller ML, Center SA, Randolph JF, Lepherd ML, Cautela MA, Dewey CW. Apparent acute idiosyncratic hepatic necrosis associated with zonisamide administration in a dog. J Vet Intern Med. 2011;25:1156–60.
70. Monteiro R, Anderson TJ, Innocent G, Evans NP, Penderis J. Variations in serum concentration of phenobarbitone in dogs receiving regular twice daily doses in relation to the times of administration. Vet Rec. 2009;165:556–8.
71. Montouris GD, Biton V, Rosenfeld WE. Nonfocal generalized tonic-clonic seizures: response during long-term topiramate treatment. Topiramate YTC/ YTCE Study Group. Epilepsia. 2000;41:77–81.
72. Moore SA, Muñana KR, Papich MG, Nettifee-Osborne JA. The pharmacokinetics of levetiracetam in healthy dogs concurrently receiving phenobarbital. J Vet Pharmacol Ther. 2011;34:31–4.
73. Moore SA, Muñana KR, Papich MG, Nettifee-Osborne JA. The pharmacokinetics of levetiracetam in healthy dogs concurrently receiving phenobarbital. J Vet Pharmacol Ther. 2011;34:31–4.
74. Morton DJ, Honhold N. Effectiveness of a therapeutic drug monitoring service as an aid to the control of canine seizures. Vet Rec. 1988;9(122):346–9.
75. Müller PB, Taboada J, Hosgood G, Partington BP, VanSteenhouse JL, Taylor HW, et al. Effects of long-term phenobarbital treatment on the liver in dogs. J Vet Intern Med. 2000;14:165–71.
76. Muñana KR. Update: seizure management in small animal practice. Vet Clin North Am Small Anim Pract. 2013;43:1127–47.
77. Muñana KR, Nettifee-Osborne JA, Bergman Jr RL, Mealey KL. Association between ABCB1 genotype and seizure outcome in Collies with epilepsy. J Vet Intern Med. 2012;26:1358–64.
78. Muñana KR, Nettifee-Osborne JA, Papich MG. Effect of chronic administration of phenobarbital, or bromide, on pharmacokinetics of levetiracetam in dogs with epilepsy. J Vet Intern Med. 2015. In press.
79. Muñana KR, Thomas WB, Inzana KD, Nettifee-Osborne JA, McLucas KJ, Olby NJ, et al. Evaluation of levetiracetam as adjunctive treatment for refractory canine epilepsy: a randomized, placebo-controlled, crossover trial. J Vet Intern Med. 2012;26:341–8.
80. Nichols ES, Trepanier LA, Linn K. Bromide toxicosis secondary to renal insufficiency in an epileptic dog. J Am Vet Med Assoc. 1996;208:231–3.
81. O'Dell C, Shinnar S. Initiation and discontinuation of antiepileptic drugs. Neurol Clin. 2001;19:289–311.
82. Orito K, Saito M, Fukunaga K, Matsuo E, Takikawa S, Muto M, et al. Pharmacokinetics of zonisamide and drug interaction with phenobarbital in dogs. J Vet Pharmacol Ther. 2008;31:259–64.
83. Packer RMA, Nye G, Porter SE, Vok HA. Assessment into the usage of levetiracetam in a canine epilepsy clinic. BMC Vet Res. 2015. In press.
84. Packer RM, Shihab NK, Torres BB, Volk HA. Clinical risk factors associated with anti-epileptic drug responsiveness in canine epilepsy. PLoS One. 2014;25:9.
85. Patsalos PN. Clinical pharmacokinetics of levetiracetam. Clin Pharmacokinet. 2004;43:707–24.
86. Patterson EE, Goel V, Cloyd JC, O'Brien TD, Fisher JE, Dunn AW, et al. Intramuscular, intravenous and oral levetiracetam in dogs: safety and pharmacokinetics. J Vet Pharmacol Ther. 2008;31:253–8.

87. Pedersoli WM, Wike JS, Ravis WR. Pharmacokinetics of single doses of phenobarbital given intravenously and orally to dogs. Am J Vet Res. 1987;48:679–83.
88. Pellock JM, Faught E, Leppik IE, Shinnar S, Zupanc ML. Felbamate: consensus of current clinical experience. Epilepsy Res. 2006;71:89–101.
89. Platt SR, Adams V, Garosi LS, Abramson CJ, Penderis J, De Stefani A, et al. Treatment with gabapentin of 11 dogs with refractory idiopathic epilepsy. Vet Rec. 2006;59:881–4.
90. Podell M. Antiepileptic drug therapy. Clin Tech Small Anim Pract. 1998;13:185–92.
91. Podell M. Chapter 7. In: Platt S, Olby N, editors. BSAVA Manual of Canine and Feline Neurology. 3rd ed. 2010. p. 97–112.
92. Podell M. Antiepileptic drug therapy and monitoring. Top Companion Anim Med. 2013;28:59–66.
93. Podell M, Fenner WR. Bromide therapy in refractory canine idiopathic epilepsy. J Vet Intern Med. 1993;7:318–27.
94. Potschka H, Fischer A, Löscher W, Patterson EE, Bhatti SFM, Berendt M, De Risio L, Farquhar RG, Long S, Mandigers PJJ, Matiasek K, Muñana K, Pakozdy A, Penderis J, Platt S, Podell M, Pumarola MB, Rusbridge C, Stein VM, Tipold A, Volk HA[21]. International Veterinary Epilepsy Task Force Consensus Proposal: Outcome of therapeutic interventions in canine and feline epilepsy. BMC Vet Res; 2015.
95. Radulovic LL, Türck D, von Hodenberg A, Vollmer KO, McNally WP, DeHart PD, et al. Disposition of gabapentin (neurontin) in mice, rats, dogs, and monkeys. Drug Metab Dispos. 1995;23:441–8.
96. Ravis WR, Nachreiner RF, Pedersoli WM, Houghton NS. Pharmacokinetics of phenobarbital in dogs after multiple oral administration. Am J Vet Res. 1984;45:1283–6.
97. Ravis WR, Pedersoli WM, Wike JS. Pharmacokinetics of phenobarbital in dogs given multiple doses. Am J Vet Res. 1989;50:1343–7.
98. Rieck S, Rundfeldt C, Tipold A. Anticonvulsant activity and tolerance of ELB138 in dogs with epilepsy: a clinical pilot study. Vet J. 2006;172:86–95.
99. Rogawski MA, Johnson MR. Intrinsic severity as a determinant of antiepileptic drug refractoriness. Epilepsy Curr. 2008;8:127–30.
100. Ruehlmann D, Podell M, March P. Treatment of partial seizures and seizure-like activity with felbamate in six dogs. J Small Anim Pract. 2001;42:403–8.
101. Rundfeldt C, Gasparic A, Wlaź P. Imepitoin as novel treatment option for canine idiopathic epilepsy: pharmacokinetics, distribution, and metabolism in dogs. J Vet Pharmacol Ther. 2014;37:421–34.
102. Rundfeldt C, Löscher W. The pharmacology of imepitoin: the first partial benzodiazepine receptor agonist developed for the treatment of epilepsy. CNS Drugs. 2014;28:29–43.
103. Salazar V, Dewey CW, Schwark W, Badgley BL, Gleed RD, Horne W, et al. Pharmacokinetics of single-dose oral pregabalin administration in normal dogs. Vet Anaesth Analg. 2009;36:574–80.
104. Schwartz M, Muñana KR, Olby NJ. Possible drug-induced hepatopathy in a dog receiving zonisamide monotherapy for treatment of cryptogenic epilepsy. J Vet Med Sci. 2011;73:1505–8.
105. Schwartz-Porsche D, Löscher W, Frey HH. Therapeutic efficacy of phenobarbital and primidone in canine epilepsy: a comparison. J Vet Pharmacol Ther. 1985;8:113–9.
106. Scola N, Kaczmarczyk J, Möllenhoff K. Infantile bromoderma due to antiepileptic therapy. J Dtsch Dermatol Ges. 2012;10:131–2.
107. Shaik IH, Mehvar R. Cytochrome P450 induction by phenobarbital exacerbates warm hepatic ischemia-reperfusion injury in rat livers. Free Radic Res. 2010;44:441–53.
108. Shih JJ, Ochoa JG. A systematic review of antiepileptic drug initiation and withdrawal. Neurologist. 2009;15:122–31.
109. Shih JJ, Ochoa JG. A systematic review of antiepileptic drug initiation and withdrawal. Neurologist. 2009;15:122–31.
110. Shorvon SD. Safety of topiramate: adverse events and relationships to dosing. Epilepsia. 1996;37:18–S22.
111. Shorvon S, Luciano AL. Prognosis of chronic and newly diagnosed epilepsy: revisiting temporal aspects. Curr Opin Neurol. 2007;20:208–12.
112. Sills GJ. The mechanisms of action of gabapentin and pregabalin. Curr Opin Pharmacol. 2006;6:108–13.
113. Speciale J, Dayrell-Hart B, Steinberg SA. Clinical evaluation of c-vinyl-c-aminobutyric acid for control of epilepsy in dogs. J Am Vet Med Assoc. 1991;198:995–1000.
114. Steinberg MFD. Levetiracetam therapy for long-term idiopathic epileptic dogs. J Vet Intern Med. 2004;18:410.
115. Stephen LJ, Brodie MJ. Selection of antiepileptic drugs in adults. Neurologic Clinics. 2009;27:967–92.
116. Streeter AJ, Stahle PL, Holland ML, Pritchard JF, Takacs AR. Pharmacokinetics and bioavailability of topiramate in the beagle dog. Drug Metab Dispos. 1995;23:90–3.
117. Sutula TP, Hagen J, Pitkänen A. Do epileptic seizures damage the brain? Curr Opin Neurol. 2003;16:189–95.
118. Taverna M, Nguyet TT, Valentin C, Level O, Merry T, Kolbe HV, et al. A multi-mode chromatographic method for the comparison of the N-glycosylation of a recombinant HIV envelope glycoprotein (gp160s-MN/LAI) purified by two different processes. J Biotechnol. 1999;68:37–48.
119. Thomas WB. Seizures and narcolepsy. In: Dewey CW, editor. A practical guide to canine and feline neurology. Ames (IA): Iowa State Press (Blackwell Publishing); 2003. p. 193–212.
120. Thomas WB. Idiopathic epilepsy in dogs and cats. Vet Clin North Am Small Anim Pract. 2010;40:161–79.
121. Thurman GD, McFadyen ML, Miller R. The pharmacokinetics of phenobarbitone in fasting and non-fasting dogs. J S Afr Vet Assoc. 1990;61:86–9.
122. Tipold A, Keefe TJ, Löscher W, Rundfeldt C, de Vries F. Clinical efficacy and safety of imepitoin in comparison with phenobarbital for the control of idiopathic epilepsy in dogs. J Vet Pharmacol Ther. 2015;38:160–8.
123. Trepanier LA. Use of bromide as an anticonvulsant for dogs with epilepsy. J Am Vet Med Assoc. 1995;207:163–6.
124. Trepanier LA, Babish JG. Effect of dietary chloride content on the elimination of bromide by dogs. Res Vet Sci. 1995;58:252–5.
125. Trepanier LA, Babish JG. Pharmacokinetic properties of bromide in dogs after the intravenous and oral administration of single doses. Res Vet Sci. 1995;58:248–51.
126. Trepanier LA, Van Schoick A, Schwark WS, Carrillo J. Therapeutic serum drug concentrations in epileptic dogs treated with potassium bromide alone or in combination with other anticonvulsants: 122 cases (1992-1996). J Am Vet Med Assoc. 1998;213:1449–53.
127. Volk HA, Matiasek LA, Luján Feliu-Pascual A, Platt SR, Chandler KE. The efficacy and tolerability of levetiracetam in pharmacoresistant epileptic dogs. Vet J. 2008;176:310–9.
128. von Klopmann T, Boettcher IC, Rotermund A, Rohn K, Tipold A. Euthyroid sick syndrome in dogs with idiopathic epilepsy before treatment with anticonvulsant drugs. J Vet Intern Med. 2006;20:516–22.
129. von Klopmann T, Rambeck B, Tipold A. Prospective study of zonisamide therapy for refractory idiopathic epilepsy in dogs. J Small Anim Pract. 2007;48:134–8.
130. Wagner SO, Sams RA, Podell M. Chronic phenobarbital therapy reduces plasma benzodiazepine concentrations after intravenous and rectal administration of diazepam in the dog. J Vet Pharmacol Ther. 1998;21:335–41.
131. Weiss KL, Schroeder CE, Kastin SJ, Gibson JP, Yarrington JT, Heydorn WE, et al. MRI monitoring of vigabatrin-induced intramyelinic edema in dogs. Neurology. 1994;44:1944–9.
132. Weissl J, Hülsmeyer V, Brauer C, Tipold A, Koskinen LL, Kyöstilä K, et al. Disease progression and treatment response of idiopathic epilepsy in Australian Shepherd dogs. J Vet Intern Med. 2012;26:116–25.
133. White HS. Comparative anticonvulsant and mechanistic profile of the established and newer antiepileptic drugs. Epilepsia. 1999;40.
134. White HS, Harmsworth WL, Sofia RD, Wolf HH. Felbamate modulates the strychnine-insensitive glycine receptor. Epilepsy Res. 1995;20:41–8.
135. Wilensky AJ, Friel PN, Levy RH, Comfort CP, Kaluzny SP. Kinetics of phenobarbital in normal subjects and epileptic patients. Eur J Clin Pharmacol. 1982;23:87–92.
136. Wong IC, Lhatoo SD. Adverse reactions to new anticonvulsant drugs. Drug Saf. 2000;23:35–56.
137. Wright HM, Chen AV, Martinez SE, Davies NM. Pharmacokinetics of oral rufinamide in dogs. J Vet Pharmacol Ther. 2012;35:529–33.
138. Yarrington JT, Gibson JP, Dillberger JE, Hurst G, Lippert B, Sussman NM, et al. Sequential neuropathology of dogs treated with vigabatrin, a GABA-transaminase inhibitor. Toxicol Pathol. 1993;21:480–9.
139. Zhang X, Velumian AA, Jones OT, Carlen PL. Modulation of high-voltage-activated calcium channels in dentate granule cells by topiramate. Epilepsia. 2000;41.

Potschka et al. BMC Veterinary Research (2015) 11:177
DOI 10.1186/s12917-015-0465-y

BMC Veterinary Research

CORRESPONDENCE Open Access

International veterinary epilepsy task force consensus proposal: outcome of therapeutic interventions in canine and feline epilepsy

Heidrun Potschka[1*], Andrea Fischer[2*], Wolfgang Löscher[3], Ned Patterson[4], Sofie Bhatti[5], Mette Berendt[6], Luisa De Risio[7], Robyn Farquhar[8], Sam Long[9], Paul Mandigers[10], Kaspar Matiasek[11], Karen Muñana[12], Akos Pakozdy[13], Jacques Penderis[14], Simon Platt[15], Michael Podell[16], Clare Rusbridge[17,18], Veronika Stein[19], Andrea Tipold[19] and Holger A Volk[20]

Abstract

Common criteria for the diagnosis of drug resistance and the assessment of outcome are needed urgently as a prerequisite for standardized evaluation and reporting of individual therapeutic responses in canine epilepsy. Thus, we provide a proposal for the definition of drug resistance and partial therapeutic success in canine patients with epilepsy. This consensus statement also suggests a list of factors and aspects of outcome, which should be considered in addition to the impact on seizures. Moreover, these expert recommendations discuss criteria which determine the validity and informative value of a therapeutic trial in an individual patient and also suggest the application of individual outcome criteria. Agreement on common guidelines does not only render a basis for future optimization of individual patient management, but is also a presupposition for the design and implementation of clinical studies with highly standardized inclusion and exclusion criteria. Respective standardization will improve the comparability of findings from different studies and renders an improved basis for multicenter studies. Therefore, this proposal provides an in-depth discussion of the implications of outcome criteria for clinical studies. In particular ethical aspects and the different options for study design and application of individual patient-centered outcome criteria are considered.

Keywords: Dog, Epileptic seizure, Epilepsy, Treatment

Background

Therapeutic management of canine and feline patients with epilepsy poses a particular challenge for the practitioner. The challenge is related to the multitude of etiologies as well as the high inter-individual variance in the clinical picture of canine and feline epilepsies. Moreover, the response to standard therapeutic regimes differs tremendously between individual patients.

Standardization in the assessment and reporting of outcome of therapeutic interventions is essential for several reasons. In individual patients, standardized procedures in the evaluation of therapeutic responses will guide practitioners in the diagnosis of drug resistance as a basis for the decision to continue with an alternate therapeutic regime. Moreover, expert consensus based recommendations render a basis for common reporting schemes, which can significantly improve the information content of patient history documents e.g. in the case of referral to a veterinary neurology specialist. Thus, one aim of this consensus proposal is to provide expert recommendations for the assessment of outcome in individual patients focusing on the impact on seizures but also considering other relevant aspects of outcome. In addition, we provide and discuss a list of criteria that determine whether a therapeutic trial in an individual patient can be considered adequate and informative. Respective guidelines will also help to exclude pseudo-resistance (defined as lack of a response due to an inadequate dosing or treatment regime) in individual patients.

* Correspondence: potschka@pharmtox.vetmed.uni-muenchen.de; andreafischer@lmu.de
[1]Department of Pharmacology, Toxicology and Pharmacy, Ludwig-Maximillians-University, Königinstr. 16, 80539 Munich, Germany
[2]Service Neurology at the Centre for Clinical Veterinary Medicine, Ludwig-Maximilians-University, Veterinärstr. 13, 80539 Munich, Germany
Full list of author information is available at the end of the article

Standardized assessment and reporting of therapeutic outcome in individual patients also is a prerequisite for the realization of scientifically proven clinical studies. In general, it is of particular relevance for the informative value of the study that strict inclusion and exclusion criteria are considered in the enrolment of patients for clinical studies evaluating a particular therapeutic regime. For instance if the study plan is to enrol patients, in which epilepsy proved to be resistant to monotherapy with a specific antiepileptic drug, a common definition of resistance as well as common criteria for an adequate and informative trial are needed urgently. Thus, universal recommendations provided in this proposal will render a basis for an improved consideration of inclusion and exclusion criteria, will help reduce study population variance, and will thereby increase the significance of study data sets and findings.

Considering the diversity of etiologies and phenotypes of canine and feline epilepsy and considering the fact that data from human patients indicate that therapeutic responses differ tremendously between patient subgroups depending on etiology, epilepsy and seizures types, there is a pressing need to perform clinical studies in respective subgroups of canine and feline patients. Studies focusing on epilepsy with a specific etiology will only be feasible in the form of multicenter studies, which require common schemes for outcome assessment. Thus, one purpose of this consensus paper is to provide the scientific, practical and ethical aspects to be considered in different types of epilepsy study designs.

Assessment of outcome in individual patients

Impact on seizures: definition of drug resistance and of therapeutic success in individual patients

Despite a high number of studies dealing with the clinical issue of drug resistance, a common definition of drug resistant epilepsy is lacking. In 2010, a Task Force established by the International League against Epilepsy (ILAE) has proposed a working definition for drug resistance in human patients, which since then has been assessed in clinical practice: "*Drug resistant epilepsy is defined as failure of adequate trials of two tolerated, appropriately chosen and used antiepileptic drug schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom*" [1]. This definition has been the source of much debate in relation to human epilepsy, and is intended mainly for epidemiological work rather than to guide individual practice. A recent study evaluated and confirmed the reliability and validity of the criteria provided by the definition [2]. The question for veterinary neurology is whether this definition is suitable for the specific conditions in clinical veterinary practice and whether it can be applied to classify the outcome in canine and feline patients.

There is agreement that *seizure freedom* is the *primary treatment goal* in the therapeutic management of canine and feline epilepsy patients (Fig. 1; Table 1). Striving for

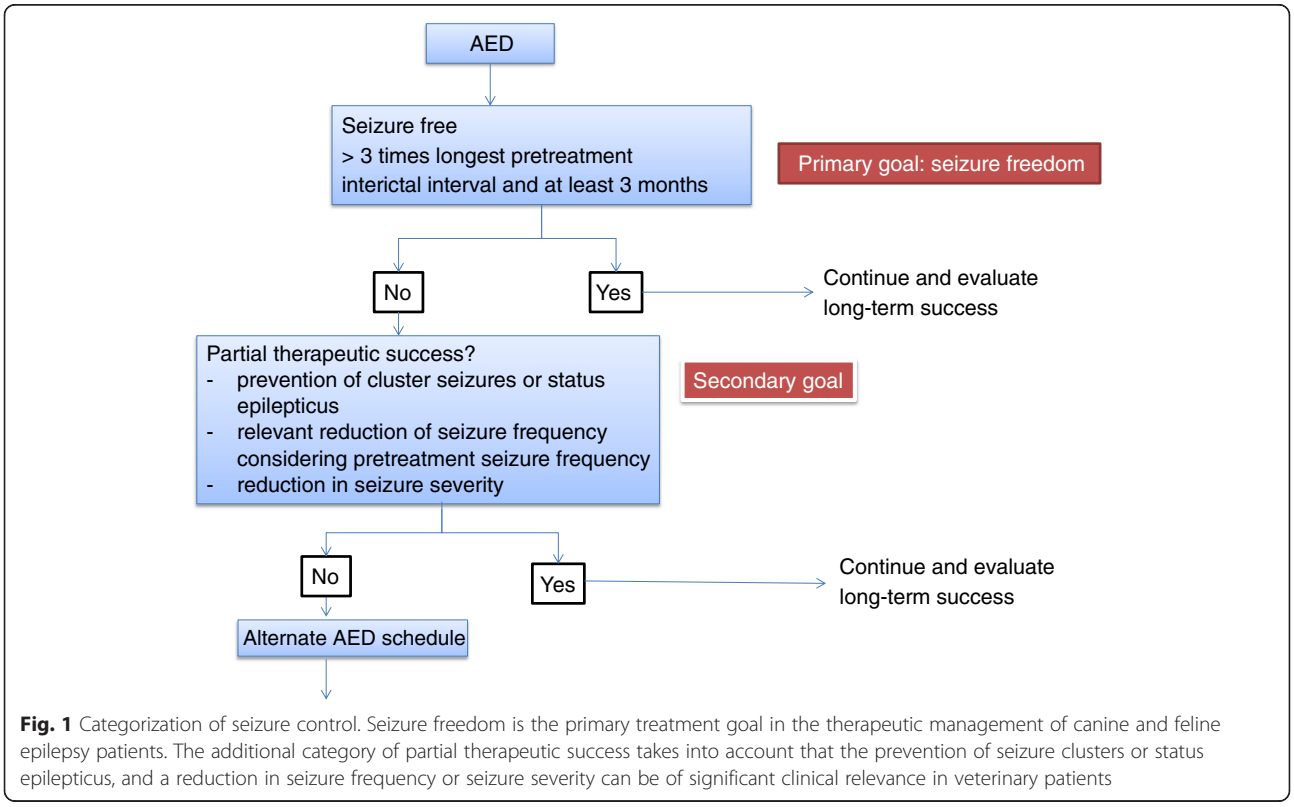

Fig. 1 Categorization of seizure control. Seizure freedom is the primary treatment goal in the therapeutic management of canine and feline epilepsy patients. The additional category of partial therapeutic success takes into account that the prevention of seizure clusters or status epilepticus, and a reduction in seizure frequency or seizure severity can be of significant clinical relevance in veterinary patients

Table 1 Categorization of outcome in individual patients

Categories: seizure control
1. Seizure-free
2. Seizures continue with partial therapeutic success (specified: reduction in seizure frequency including information on seizure incidence, seizure severity, or reduction in frequency of seizure clusters and status epilepticus)
3. Seizures continue without partial therapeutic success
4. Undetermined (specify reason)
Categories: tolerability
A. No adverse effects
B. Adverse effects
C. Treatment not tolerated (substantial adverse effects resulting in discontinuation)
D. Undetermined (specify reason)
Consider that short-term and long-term success should be evaluated and should be indicated as discussed in the text. As outlined in the text respective outcome information should always include information about the drug regime. Table modified from [1].

complete seizure control is of utmost importance considering the consequences of recurrent seizures. Repeated epileptic seizures can result in neuronal cell loss, persistent neuro-inflammation, disturbance of blood-brain barrier function, and functional alterations in neurotransmitter receptors and ion channels [3–5]. Respective alterations can contribute to the development of behavioral comorbidities, can contribute to a progressively increasing intrinsic disease severity, and a declining responsiveness to therapeutic interventions [6].

Sudden unexpected death in epilepsy (SUDEP) is a rare event, which however puts the patient at risk with each single seizure event [7, 8]. Although an overall decreased life-span has not been confirmed in a recent study focusing on idiopathic epilepsy [9], several other reports acknowledge a decreased life-span in canine patients with idiopathic and structural (=symptomatic) epilepsy [10–12]. These reports indicate that euthanasia is the major risk factor contributing to a decreased life-span due to uncontrolled seizures [10–12], but sudden unexpected death in epilepsy (SUDEP) and seizure-related falls, injuries, or asphyxiation are also risk factors in the management of canine patients contributing to increased mortality rates [11, 13]. To our knowledge no information is available yet about SUDEP and life expectancy in feline epilepsy patients.

The ILAE Task Force has acknowledged in their proposal that "a therapeutic intervention may lead to a clinically meaningful reduction in seizure frequency (or severity) that stops short of seizure freedom" [1]. In view of the fact that complete vs. incomplete seizure control does not have the same implications and consequences in veterinary patients as it has in human patients due to the socioeconomic impact on daily lifestyles, and that therapeutic decisions have thus to be balanced with costs and adverse effects, we included the category of *partial therapeutic success* as a *secondary treatment goal* in the classification scheme that we suggest in this proposal (see 2.4) (Fig. 1; Table 1). This decision also takes into consideration that in the past AED induced remission for 1–3 years has only been reported in 15 – 24 % of dogs with idiopathic epilepsy in a wide range of studies focusing on different dog breeds with epilepsy of various severity [11, 12, 14].

The additional category of *partial therapeutic success* takes into account that a reduction in seizure frequency, seizure severity, and the prevention of seizure clusters or status epilepticus can be of significant clinical relevance in veterinary patients (Fig. 1; Table 1). Regarding an impact on seizure frequency it is difficult to set a %-based limit for partial success, because the baseline seizure frequency needs to be taken into consideration. Experience of veterinary neurologists suggests that patient caregivers, the owners, often consider less than one seizure in 3 months acceptable [15]. Thus, depending on the pretreatment seizure frequency a reduction of seizure density to a respective seizure interval e. g. one seizure every 3 months can be considered as a relevant effect. In addition, a reduction in seizure severity can result in a clinically meaningful success, if for instance spread of seizure activity e. g. generalization of focal onset seizures is prevented so that seizures remain focal. Moreover, the prevention of seizure clusters or status epilepticus can significantly affect the quality of life of the patient and the pet owner.

Partial therapeutic success can have a significant clinical relevance in canine and feline patients also affecting the owner's decision for euthanasia. Nevertheless, we propose to apply the ILAE Task Force definition for veterinary patients thereby drug-resistant epilepsy is diagnosed if seizure freedom is not achieved with two therapeutic trials. However, we suggest indicating for each patient in which drug-resistant epilepsy has been diagnosed if there was evidence for a partial therapeutic success as outlined above.

Moreover, consideration should be given to the fact that there might still be reasonable hope to achieve seizure freedom in patients in which several therapeutic trials have failed. Respective evidence has been reported by different groups performing studies in human patients [16–18]. Neligan et al [17] concluded that about half of the patients with apparent drug resistant epilepsy can have relevant improvements in seizure control with further drug changes. Based on these findings they discussed that the proposed ILAE Task Force definition might be too restrictive [17]. Another study indicated that childhood-onset epilepsy might require specific considerations as 51 % of the patients with drug-resistant epilepsy entered 5-year terminal remissions [18]. Despite

the lack of respective, comprehensive data sets in veterinary medicine, we feel that it is important to avoid an early classification of drug resistant epilepsy having a negative impact on the clinician's efforts to continue with therapeutic trials in individual patients. Thus, we suggest that the term *drug resistant is always used along with the specification 'to which antiepileptic drugs'*, e.g. phenobarbital resistant, imepitoin resistant and/or bromide resistant [19, 20].

The ILAE task force definition lists an 'appropriately chosen antiepileptic drug schedule' as a presupposition for outcome conclusions [1]. In human patients knowledge about pathophysiological mechanisms as well as the outcome of clinical studies rendered the basis for treatment guidelines, which list first line antiepileptic drugs, adjunctive antiepileptic drugs, second line antiepileptic drugs, and antiepileptic drugs that may worsen seizures for different seizure types and epilepsy syndromes [21, 22]. Unfortunately, there is a lack of knowledge about drug responsiveness of different seizure types and of epilepsies with different etiologies in veterinary medicine. Despite this fact we propose to keep the term 'appropriately chosen' in the definition (see consensus statement on treatment for recommendations [23]), when applying it to veterinary patients, as we expect a gain in knowledge in the near future and as it should also motivate to study differential responsiveness in patient subgroups and canine vs. feline patients in more detail.

Please note that criteria for an adequate and informative trial in individual veterinary patients are discussed under 2.4.

Other criteria and aspects of outcome

Impact on neurobehavioral comorbidities

Experimental studies as well as studies in human patients point to a bidirectional link between epileptic seizures and psychological symptoms [24]. In human epilepsy patients the increased prevalence of psychiatric disorders including attention deficit hyperactivity disorder, depression, and anxiety disorders has been attributed to the psychosocial burden of epilepsy but also to epilepsy-associated molecular, cellular, and network alterations. Also, it is postulated that in some instances, the epilepsy and the co-morbidities are both the result of similar underlying mechanisms. A direct impact of pathophysiological mechanisms of epilepsy on neurobehavioral comorbidities is further confirmed by findings in animal models [25]. So far only limited information is available about epilepsy-associated neurobehavioral alterations in veterinary medicine. In drug-naïve dogs diagnosed with idiopathic epilepsy the development of the disease resulted in an increase in the behavioral scores for Fear/Anxiety, Defensive Aggression, and Abnormal Perception [26]. Following onset of medication Defensive Aggression was attenuated, whereas other behavioral alterations became evident including Abnormal Reactivity, Attachment Disorder, Demented Behavior, and Apathetic Behavior [26]. These data underline the need to evaluate the effect of a therapeutic regime on patient's behavior with a particular focus on a beneficial impact on neurobehavioral comorbidities. Therefore, it is necessary to further develop behavioral scoring systems validated for the assessment of *epilepsy-specific behavioral comorbidities*. The efforts by Shihab et al [26] and Wessmann et al [27] render an important basis for respective score sheets, which are needed urgently for different types of epilepsy in canine and feline patients. In this context the questionnaire developed for the analysis of behavior in Cavalier King Charles Spaniels with neuropathic pain due to Chiari-like malformation should be considered as an example questionnaire tailored for a specific neurological disease [28].

It is emphasized that data need to be collected before the initiation of therapy, because only this baseline information will allow distinguishing between disease-associated alterations as well as beneficial or detrimental effects of antiepileptic drugs. Moreover, despite the fact that controversial findings exist, it is recommended to thoroughly investigate the endocrine status in particular considering that thyroid function might be altered in association with epilepsy development and antiepileptic drug treatment, and that the functional state of the thyroid gland has a major impact on neurobehavior and brain function [29–32].

Adverse effects

Tolerability issues constitute an important limiting factor in the therapeutic management of epilepsy in human and veterinary patients [27, 33, 34]. As further discussed below they can significantly contribute to the patient's burden and can thereby determine drug retention rates. Thus, the extent and the course of adverse effects should be closely monitored when assessing the overall outcome of a therapeutic trial in an individual patient (Table 1). In general, it is important to distinguish between dose-related effects and idiosyncratic effects as well as between transient and long-term effects. Repeated evaluation of adverse effects is necessary during titration phases but also during chronic therapy. It needs to be considered that adjustment and selective tolerance to specific adverse effects can occur, and that aging or development of multimorbidities might alter the predisposition of individual patients.

Pharmacological targeting of central nervous system hyperexcitability is of course prone to be associated with central nervous system adverse effects. However, pronounced inter-individual differences exist in the susceptibility to respective effects. Sedation or apathy and

other behavioral alterations as well as a disturbance of motor function [35, 36], sleep patterns, and cognition [37] are among the dose-dependent central nervous system effects, which should be considered in a patient's evaluation. In addition, systemic effects need to be assessed including gastrointestinal effects. Moreover, it is well known that the exposure to specific antiepileptic drugs can increase the risk to develop pancreatitis [38, 39], hepatopathy, blood dyscrasias [40, 41] and skin reactions. Specific attention to the following introduction of a new antiepileptic drug should be drawn to the potential development of antiepileptic drug hypersensitivity syndrome [42–45] which may evolve into a life-threatening situation and requires immediate modification of the drug regimen.

Food intake, water intake, body weight gain or loss can be affected by both, central and peripheral effects of antiepileptic drugs. The introduction of standardized validated questionnaires based on Likert or VAS scores which comprise a respective list of frequent and rare adverse effects allowing repeated comparison during drug treatment are highly recommended. Comparison with the pre-drug baseline condition, data, and antiepileptic drug levels is of particular relevance. Evaluation should also include pre-drug baseline and post-drug laboratory evaluation which should ideally include CBC, extended biochemical serum profile, urine and adequate evaluation of liver function (pre- and postprandial bile acids or ammonia). Evaluation of thyroid function is also recommended but faces specific challenges.

In case of polytherapy, putative drug interactions require specific considerations when assessing the tolerability of an antiepileptic drug regime. Despite a controversial discussion, we recommend that the endocrine status is carefully controlled as thyroid function might be affected by the disease as well as its treatment, and might in turn affect the general condition with a pronounced impact on behavior as well as body weight.

In case of severe adverse effects resulting in discontinuation of a specific therapeutic approach, this fact should be documented in the patient's files with the classification *'treatment-not-tolerated'* with information about the specific drug or other approach tested e.g. *'Phenobarbital not tolerated'*.

Assessment of the impact on quality of life

The impact of a treatment regime on quality of life (QoL) must be considered as a major factor for the evaluation of outcome. Thereby, therapeutic management can affect QoL in a dichotomous manner. Whereas improved seizure control can exert beneficial effects on QoL, adverse effects can contribute to the patient's burden.

The World Health Organization (WHO) has defined QoL as the individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns [46]. The International Society for QoL Research considers health-related QoL as the functional effect of a medical condition and/or its consequent therapy upon a patient (http://www.isoqol.org). They emphasize that health-related QoL is subjective and multidimensional, encompassing physical and occupational function, psychological state, social interaction and somatic sensation. It is a matter of course that the assessment of health-related quality of life in veterinary medicine is limited to just some selected dimensions and aspects from the list of those considered in human medicine.

Whereas the development of standardized tools can render a basis for patient-reported outcomes measurement in human patients, assessment of the QoL of veterinary patients poses an even greater challenge to veterinary practitioners regardless of the indication. On the other hand it is well known that the perception of a veterinary patient's QoL by the owner plays a major role in important decisions regarding the therapeutic management of epilepsy or the decision for euthanasia of a patient with difficult-to-treat or drug-resistant epilepsy.

Problems are associated with the fact that the owner's QoL can constitute a bias in the owner-based evaluation of the QoL of veterinary patients with epilepsy. In this context, it needs to be considered that caring for a dog with idiopathic epilepsy proved to have a major impact on the carer's QoL [10, 27]. Thus, it is of particular relevance to not only assess the patient's QoL with owner-based questionnaires but also to assess the carer's QoL, and consider both in interpretations. In this context, it is of interest that the owner's perception of their dog's quality of life proved to negatively correlate with the amount of work required to care for the dog [47].

QoL evaluation should ideally be performed before treatment onset, following treatment initiation, following treatment adjustments regarding dose titration or drug choice, and should be repeated on an annual basis. Whereas patient-related questions in the questionnaire developed by Wessmann et al [27] focused on the control of seizures and adverse effects of antiepileptic drugs, owner-related key questions dealt with restrictions on the carer's life, frustrations of the carer, the owner's distaste of antiepileptic drug adverse effects, the carer's anxiety around the seizure event, and the perception of rectal diazepam use. The efforts by Wessmann et al [27] rendered a validated tool specific for canine idiopathic epilepsy. Muñana et al [48] have applied a QoL assessment in the evaluation of adjunctive levetiracetam efficacy and tolerability. The questionnaire used in this study was adapted from one previously described by Lord and Podell [47]. Respective standardized QoL assessment tools need to be evaluated and if necessary

further specified for symptomatic epilepsies, and need to be developed for feline patients.

Adequate and informative therapeutic trial – criteria

In order to allow valid conclusions about the individual outcome, each therapeutic trial should have been used at optimal doses to exclude pseudoresistance defined as the lack of a response due to an inadequate dosing or treatment regime. As in human medicine, pseudoresistance can have multiple reasons in veterinary patients. First of all the compliance of the patient's owner should be considered and if in doubt should be controlled by plasma concentration analysis. As also emphasized by Kwan et al [1] for human patients, it is of particular relevance to guarantee an adequate dosing with sufficient duration including efforts for optimization of dosing and titration to clinically efficacious and still tolerated doses. If relevant based on the mechanism of action of an antiepileptic drug, it is recommended to control steady-state concentrations in veterinary patients with plasma sampling and analysis of trough levels before the next drug administration. Standardized drug level monitoring schemes are in general highly recommended. In a recent study comparing the effect of timing of blood collection on serum phenobarbital concentrations in dogs, no difference was evident between trough, 3-hour and 6-hour concentrations indicating that timing of blood sampling is not as important when phenobarbital is administered twice daily [49, 50]. However, timing of sampling is likely to be of relevance, when antiepileptic drugs marketed for veterinary patients have failed to achieve seizure control resulting in the use of drugs developed and marketed for human patients. The pharmacokinetic features of respective antiepileptic drugs are often suboptimal for dogs and cats, and have often not been studied in detail in veterinary patients. Thus, the choice of adequate administration intervals requires careful consideration and control by determining trough levels. Determining trough concentrations is also of particular interest, if seizures predominantly occur during the night. Moreover, it needs to be considered that small changes in plasma concentrations might adversely affect outcome in an individual patients, while no statistical effect might be observed in a larger study population.

This however also requires valid knowledge about the therapeutic plasma concentration range in dogs and cats, which is not available for all antiepileptic drugs, which have been used in canine and feline patients. Moreover, putative drug interactions need to be considered with polytherapeutic regimens. Muñana et al [51] have recently reported that concurrent administration of phenobarbital alone or together with bromide significantly alters the disposition of the antiepileptic drug levetiracetam compared to co-administration of bromide alone. In line with previous findings from healthy dogs [52], the findings pointed to the fact that phenobarbital lowers maximum plasma concentrations reached and accelerates the clearance of levetiracetam in epileptic dogs [51]. A similar interaction with phenobarbital has been shown for zonisamide [53, 54].

As pointed out above, seizure freedom is the primary goal in the therapeutic management of epilepsy patients. An intense discussion has dealt with the minimum duration of a therapeutic trial allowing conclusions about seizure-freedom in the course of an intervention trial. Being considered seizure-free has major implications for a human epilepsy patient for instance affecting the allowance to drive or to work in specific environments. In veterinary medicine the main question is whether the duration of a trial has been long enough to be informative, so that one can decide about continuing with another intervention trial in the case of therapeutic failure. Moreover, trial duration also has significant implications for the design of clinical studies, which require specific ethical as well as trial validity considerations as further discussed below.

A task force established by the ILAE has proposed that a patient should be considered seizure-free in response to a new intervention once no seizure occurred "during a phase of at least three times the duration of their longest pre-intervention interseizure interval in the preceding 12 months or during 12 months, whichever is longer" [1]. Evaluation during a time span of at least three times the duration of their longest preintervention interseizure interval has been reported to result in a 95 % certainty that the patient's seizure frequency has at very least been decreased [1]. However, it has also been emphasized that this certainty is only reached in patients with a high seizure frequency. The ILAE task force proposal is based on the statistical principle referred to as the 'Rule of Three', which dealt with the issue to calculate confidence intervals for zero events [55, 56]. The minimum duration of seizure freedom for 12 months has been added by the Task Force in order to obtain information, if a clinically relevant sustained effect occurred [1]. If seizure freedom of at least three times the longest preintervention seizure interval has been reached but for less than 12 months, the outcome regarding seizure control is considered "undetermined" until seizure freedom lasts for at least 12 months [1]. More recently, Westover et al [57] have stated that the "Rule of Three" as an operational definition of seizure freedom might be reasonable in many cases, but that in other common cases a longer waiting time might be necessary. The authors suggested a revised criterion for seizure freedom which they termed the 'Rule of Three-to-Six' [57]. This suggestion considers the pre-intervention probability for therapeutic success, which for instance can be significantly reduced in patients with a history of multiple failed therapeutic trials. In veterinary medicine valid data

is lacking so that it is not possible to reliably conclude about pre-intervention probability. Thus, it is recommended to consider the ILAE Task Force proposal as a basis for seizure outcome classification in veterinary patients. However, the statistical limitations, which are most pronounced in patients with low seizure frequencies, need to be considered when drawing conclusions.

In this context, it is important to note that the development of tolerance has been reported in canine patients during the course of a chronic antiepileptic drug treatment regime. Thereby, one needs to distinguish between metabolic tolerance related to accelerated drug metabolism and elimination rates and functional tolerance related to alterations in drug targets sites. Whereas metabolic tolerance might be overcome by adjustment of dosing or administration intervals, this might not be possible with functional tolerance.

The phenomenon of tolerance also referred to as the 'honeymoon effect' can result in relapse after prolonged periods of a pharmacological treatment. Tolerance development has for instance been suggested by studies with zonisamide or levetiracetam add-on regimens [58, 59]. However, in these studies the relapse or impairment of seizure control occurred within 2 and 8 months following initiation of the new therapeutic regime [58, 59]. Thus, the fact that the seizure-free period should last at least 12 months according to the ILAE Task Force proposal should account for most of the cases with tolerance development in canine patients rather avoiding a bias of the 'honeymoon effect' on seizure outcome conclusion. However, it is also emphasized that relapse is possible later on, and that a continued follow up of seizures during subsequent years is crucial in order to conclude about clinically relevant long-term success. In this context, it is also important to consider that seizure reoccurrence during therapy might also reflect 'regression to the mean' as patients often enter trials, when seizure frequency is high, and for the first few months seizure frequency might just be reduced due to the natural course of individual seizure frequency fluctuation. Please note that the definition of short term and long term therapeutic success is discussed in detail below (see subchapter on *Outcome criteria for clinical studies*).

Several issues can result in the owners' and practitioners' decision for discontinuation of a specific intervention. In these cases, it is of utmost importance to document the reasons for discontinuation in the patient's files indicating whether tolerability issues, lack of efficacy, lack of compliance, financial considerations or other reasons resulted in the decision. Respective information will be of relevance for future therapeutic management decisions throughout the patient's life, and will be of particular significance if the patient is enrolled in future clinical studies.

Assessment of outcome: implications for clinical studies

Ethical and general aspects

There is a great interest of owners of epileptic dogs to participate in trials of new antiepileptic drugs and regimens. This interest is driven by failures of available antiepileptic drugs in a proportion of epileptic dogs and concerns about possible side effects of antiepileptic drug treatment [12, 60–62]. There is general consensus that an informative clinical trial of antiepileptic drugs should be conducted in a controlled, blinded and randomized manner in order to achieve a high level of evidence [63] and to adjust for placebo effects which may average up to 30 % [64], and which have been explained by natural fluctuations in seizure frequency; but underreporting of seizures towards the end of the trial or improper patient selection may also increase clinical outcome variability [65, 66].

This raises several ethical issues which are of relevance to epileptic dogs and their owners. In particular, there are concerns that participation in placebo-controlled clinical studies may withhold the chance for successful treatment by the next individual therapeutic trial, either due to the use of placebo or because of the requirements to stay on an ineffective drug regime for prolonged time periods in order to complete the study with a sufficient number of subjects and to assess monthly seizure frequency within a fixed treatment period.

These issues may be approached by the use of direct comparison head-to-head trials and application of outcome parameters which allow individual study end points. Comparative head-to-head trials compare the effectiveness of the drug under investigation against another drug, usually a licensed drug with proven effectiveness against placebo considered the gold standard for the specific indication (active control; e. g. phenobarbital) [67]. This approach should provide each study participant with a highly effective antiepileptic drug, but has the draw-back that the differences between the interventional group and the control group are smaller than if compared to placebo and that higher numbers of participants are required for demonstration of smaller effects. Assessment of outcome in clinical studies requires definition of clearly defined primary outcome measures. The primary outcome measure in AED trials is efficacy defined by the drug's influence on seizure occurrence, but tolerability, quality of life, compliance and retention rates should also be assessed in informative clinical trials [65].

The use of individual outcome parameters in clinical trials which define individual study end points will be possible if clinical studies aim at seizure freedom [1]. This has been suggested in human medicine for a long time (e. g. time to first seizure, time to n^{th} seizure, or individual patient-centered outcome criteria including tolerability issues), but clinical studies utilizing these

outcome parameters are rarely found and validation for veterinary patients would be required [65, 66, 68].

A more detailed discussion about general aspects regarding the design of clinical studies is beyond the scope of this paper. In this consensus statement we will focus on outcome parameters, and will just shortly introduce the different types of clinical studies because study design and inclusion criteria will affect assessment of outcome.

Types of clinical studies

Clinical studies of AED therapy should clearly describe the study goal and the study population in focus. The two different types of AED treatment trials are: (1) Evaluation of AED monotherapy, or (2) evaluation of adjunctive AED add-on therapy. The study populations in focus for the two study designs differ by chronicity and likelihood of a positive outcome: Evaluation of AED monotherapy focusses on patients with new onset epilepsy, while the study population for evaluation of AED add-on therapy is more likely to be composed of epilepsy patients with a history of recurrent seizures for prolonged time periods up to several years and proven refractoriness to several AEDs. Controlled randomized clinical studies with inclusion of control groups provide higher levels of evidence and are preferred to uncontrolled open label pilot studies of antiepileptic drug efficacy. In the latter each patient serves as its own control and seizure frequency during the intervention period is compared to a comparable baseline period. Uncontrolled open label studies cannot differentiate between drug effects, natural disease fluctuations (placebo response) and systemic influences e. g. intensified patient care during the treatment period which might affect seizure frequency. Still, open label pilot studies allow preliminary conclusions as to the potential efficacy of the drug under investigation, and can provide baseline statistical data for calculation of the necessary group sizes to conduct meaningful controlled clinical studies with adequate statistical power. The major reason why controlled randomized clinical studies fail to show an existing effect is inadequate statistical power, caused by high drop-out rates, insufficient patient numbers in the intervention and control group to show an effect of a given size, or high placebo responses [48, 64]. Patient selection contributes to the variance within and between treatment groups and will be further outlined below as part of the inclusion criteria. Clinical studies in epilepsy also differ significantly by the types of controls, which are used in the respective studies. These should be clearly described to facilitate interpretation of the results. Four different types of controls are distinguished: (1) placebo, which should have a similar appearance as the drug, (2) pseudoplacebo, meaning that the active drug is provided to the control group in a low dose which may not be effective (3) active control (positive control, treatment with an effective drug provided to the control group, head-to-head trial) (4) pseudocontrol (control group without any treatment; also termed negative control) [69]. Often, for ethical reasons the only choice for a trial in patients with new onset epilepsy can be an active control trial [67]. In line with this concept, Boothe et al [70] have performed a head-to-head trial comparing the efficacy and tolerability of phenobarbital and bromide as an initial monotherapy. During the development of imepitoin as a new AED for canine epilepsy, several trial types have been used in epileptic dogs [19]: (1) an open (non-controlled) trial, comparing imepitoin with phenobarbital and primidone in newly diagnosed dogs with epilepsy; (2) an open (non-controlled) trial, comparing add-on with imepitoin with add-on with potassium bromide in dogs resistant to treatment with phenobarbital and primidone; (3) a randomized controlled trial with imepitoin vs. pseudoplacebo (low dose of imepitoin); (4) a randomized controlled trial with imepitoin vs. primidone; and (5) a randomized controlled trial with imepitoin vs. phenobarbital. The last trial type was used in a pivotal field trial for approval of imepitoin by the European Medicines Agency [20]. A randomized placebo-controlled trial for approval in the U.S. is in progress. As an alternative the use of historic controls is intensely discussed in human medicine [71, 72]. However, due to alterations in study populations, and placebo response rates over time and due to a pronounced impact of study sites on outcome, the use of historic controls also faces major issues. In veterinary medicine, the paucity of well-controlled studies represents another limitation. In general, patients should be assigned to the intervention and control groups in a blinded and randomized manner to avoid any bias in patient selection. However, stratification of treatment groups for disease severity and further parameters (e.g. diagnosis, seizure type, appearance of cluster seizures, age of onset, duration of seizures prior to treatment, breed) may be warranted. Moreover, strict inclusion and exclusion criteria need to be applied considering respective parameters and clearly defining the study population (Table 2).

In this context it should be mentioned that the preferred type of study varies by the intention of the respective investigators e. g. regulatory ministries, drug companies, or clinicians treating the respective patients. The U.S. Food and Drug Administration (FDA) often requires statistical proof of superiority to a drug with known efficacy, European Medicines Agency (EMEA) requires proof of noninferiority.

Outcome criteria for clinical studies

In human patients huge differences exist between epilepsies of different etiologies and seizure types regarding

Table 2 Important inclusion criteria which may affect outcome

Criteria for the diagnosis of epilepsy	How exclusion of other episodic events (paroxysmal dyskinesias, tremors, episodic collapse etc.) is achieved, which are likely not to respond to interventions with AEDs
Criteria to restrict the study population under investigation to specific patient groups, breed-specific epilepsies, specific etiologies	E. g. if restriction to patients with idiopathic epilepsy, implies to define specific measures and examinations undertaken to exclude other causes of epilepsy that are known to influence outcome in a significant manner. These criteria should follow the requirements for the diagnosis of idiopathic epilepsy as defined in a separate consensus statement.
	Description of the specific pharmacoresistance pattern of the study population under investigation e. g. resistance to phenobarbital, potassium bromide, imepitoin, levetiracetam etc. Definition of pharmacoresistance should follow previous consensus in this paper, which may include definition of minimum serum concentrations, requirements for measurement of trough levels and definition of steady state periods as deemed necessary based on mechanism of action for the specific drug for which pharmacoresistance is defined.
Criteria to restrict the study population to a specific disease stage	Criteria to restrict the study population under investigation either to
	• trials of AEDs in patients with new onset epilepsy, or
	• trials of AEDs in patients with chronic refractory epilepsy
Criteria for pre-drug assessment in trials of AEDs in patients with chronic epilepsy	Definition of baseline data (e.g. written seizure diary, prospective, retrospective) and duration of baseline period for assessment of median pre-treatment seizure frequency, cluster seizure frequency or assessment of the longest seizure-free interval in the year preceding study inclusion
Criteria to restrict the study population to patients without severe systemic disease which will likely affect outcome	E. g. exclude severe preexisting hepatic, renal, endocrine disease

responsiveness to different interventions, while only limited data are available in veterinary neurology with regard to different types of epilepsies or breed-specific epilepsy syndromes. It is generally agreed that a gain in knowledge can only be obtained by applying stringent inclusion criteria and defined endpoints, which define the patient groups under investigation and, furthermore, set the base for large multicenter studies with adequate statistical power. Inclusion criteria and outcome parameters must be identical for the intervention and control group, in order to avoid any bias which may influence outcome assessment. Important inclusion criteria which may influence outcome of clinical studies are outlined shortly in Table 2, while the further discussion focuses on the specific outcome parameters.

Regarding outcome criteria it is recommended to consider all categories discussed above for individual patients, and to apply standardized evaluation tools for assessment. Thus, the outcome assessment should not only consider the impact on seizures (efficacy), but also a detailed evaluation of adverse effects (tolerability) and of the impact of the intervention on behavioral comorbidities, and on quality of life of the patient and caretaker (Table 3). With regard to tolerability detailed data on reasons for study drop-out should be provided for each patient that exits prematurely. Furthermore retention rate is a clinical relevant parameter which reflects

Table 3 Summary of primary outcome endpoints which are applicable to clinical studies and highlight different aspects of outcome; modified from [65, 66, 73]

Outcome parameters	
Efficacy	
Conventional endpoints	fixed treatment period
Seizure free rate (percentage seizure freedom)[a]	no baseline data required
Short-term	24 weeks
Long-term	48 weeks – 3 years
Median seizure frequency reduction	baseline data required
Responder rate (percentage responders)	baseline data required
(≥50 % reduction median seizure frequency often not clinically relevant)	
Individual endpoints	
Time to first seizure	based on interseizure interval
Time to second seizure	
Time to n-th seizure	
Pre-defined patient-centered outcome criteria	individually assessed
Tolerability	
Adverse events	to be assessed, also assess number and reasons for drop-outs
Quality of life	
Patient's QOL score	validated scores needed
Owner's QOL score	control groups important
Retention rate	applicable to long-term studies

[a] Need to specify reliability of assessment: (A) freedom of generalized seizures only or (B) freedom of generalized and focal seizures

the percentage of patients adhering to the drug after prolonged treatment periods and thus is considered a useful parameter for combined assessment of efficacy, tolerability and even quality of life. Regarding the intervention's impact on seizures as many data should be collected as possible. These should include total number of seizures, seizure days allowing calculation of median seizure frequency and seizure day frequency and seizure free intervals (days). Additional parameters that assess severity (occurrence of clusters and average number of seizure per cluster, status epilepticus, focal seizures vs. generalized seizures, severity and duration of post ictal signs) should be included. This would allow assessment of outcome in concordance with current recommendations in human medicine. Conventional primary outcome parameters in humans are seizure free rate, median seizure frequency, and responder rate, whereby a drug responder is defined by a > 50 % reduction in seizures compared to baseline. However, this is generally considered a very weak endpoint, also reached by placebo in many patients, so that many clinical studies prefer at least 75 % reduction in seizure frequency. It should be noted that responder rate may not be a clinically meaningful outcome parameter, while assessment of the seizure free rate (percentage) is a hard outcome parameter which is independent from baseline data and is clinically relevant. Current ILAE guidelines request a ≥ 20 % absolute difference in between treatment groups for ascertainment of a clinically relevant positive outcome [73, 74]. It remains debatable whether a 20 % difference in outcome constitutes a clinically relevant difference in veterinary patients. A summary of outcome criteria which highlight different aspects of the disease and are currently discussed in human medicine is provided in Table 2. Study protocols and assessment schemes should also collect information about putative seizure precipitating events or factors (e.g. owner leaving, excessive activity, transfer to kennel).

A consensus was reached within the group that defined individual study end points based on individual pretreatment seizure frequency are preferred and that respective study designs should be further developed and validated in accordance to suggestions for AED trials in human patients [1]. Preferred endpoint was the definition of short term success as seizure freedom for a time-span exceeding three times the longest interseizure interval (days) in the year preceding the study and for a minimum of three months (time to 1st seizure) [1, 65, 66]. Thus, if seizure freedom is not achieved time to the 2nd or nth seizure was considered as an alternative outcome parameter for add-on trials in patients with chronic refractory epilepsy [1, 65]. In this setting, any patient with continued seizures following a titration phase will be classified as treatment failure and allowed to exit the study. Consequently, patients with complete freedom of seizures or extension of the interseizure interval to three times the longest interseizure interval and a minimum of three months will be considered treatment success and treatment should thereafter be continued to assess the seizure free rate e. g. the percentage of patients with short-term or long-term freedom of seizures [67].

The use of seizure freedom as a primary outcome parameter follows current ILAE recommendations and has been successfully applied as primary outcome parameter in one veterinary study focusing on new onset epilepsy (outcome described as percentage seizure freedom, short term) [70]. With this approach differences in seizure frequency, seizure days, seizure severity, clusters or status epilepticus during a fixed time period between groups should be considered secondary outcome parameters in clinical studies which can define and describe partial treatment success in patients with chronic epilepsy participating in add-on trials of AEDs in which seizure freedom may be difficult to achieve.

Open questions remain as to the definition of short term or long term treatment success and whether seizure freedom can be a realistic goal in chronic epileptic patients with AED drug polytherapy. Consensus exists that the minimum duration of 24 weeks for studies in human patients only assesses short term response to AEDs, is subject to the so-called honeymoon effect, and does not adequately predict long-term outcome after 1 year, 2 years or 5 years of treatment. Thus, follow-up of patients for up to one year or even longer is warranted. Besides seizure frequency, dogs' QoL, owners' QoL, adverse effects affecting tolerability, retention rate of AED, survival rates and number and costs of veterinary visits are other outcome parameters which may be specifically applicable to long-term clinical studies in veterinary patients due to the shortened life span of dogs and cats compared to humans and the specific human-animal-bond, which is affected by the disease. Open questions remain also to the reliable assessment of focal seizures in clinical studies in veterinary patients. Can these be reliably counted and assessed in clinical studies in veterinary patients without use of invasive EEG based recording tools? Should improvement in generalized but not in focal seizures be rated as a positive outcome e. g. partial treatment success? These thoughts are especially important if seizure freedom is applied as the primary outcome parameter.

Further important points to be discussed are whether stratification of treatment and control groups for appearance of cluster seizures, breed and age of onset should be attempted. Specifically the frequent appearance of cluster seizure events appears to characterize a difficult to treat subpopulation in veterinary patients with

idiopathic epilepsy [12, 62, 75]. Differences between certain dog breeds appear to exist in regard to the natural course of the epilepsy, while the impact of other factors (e. g. previous head trauma) on outcome needs yet to be defined. However, a more detailed discussion about general aspects regarding the design of clinical studies and the influence of study design on outcome assessment is beyond the scope of this paper and will be provided in a separate publication.

Abbreviations

SUDEP: Sudden unexpected death in epilepsy; ILAE: International League against Epilepsy; QoL: Quality of life; AED: Antiepileptic drug; FDA: Food and drug administration.

Competing interests

Following reimbursements, fees and funding have been received by the authors in the last three years and have been declared in the competing interest section. WL, CR, RGF, HAV, KM, MP and JP have received fees for acting as a consultant for Boehringer Ingelheim (WL, KM, MP: consultancy during development and approval of imepitoin; CR: pain consultancy; RGF, JP, HAV: consultancy pre and post launch of imepitoin). AT has been an advisor for Boehringer Ingelheim. SFMB, HAV and AT have been responsible principal investigator of several research studies concerning imepitoin financed by Boehringer Ingelheim. SFMB, HAV, JP, HP, MB, CR and AF received speaking fees from Boehringer Ingelheim. HP received consulting and speaking fees and funding for a collaborative project from Eisai Co. LTD. HAV received funding for a collaborative project from Desitin and Nestlé Purina Research. AF and LDR received reimbursements from Boehringer Ingelheim. LDR has received consulting and speaking fees from Vetoquinol. MP has received consultant fees for Aratana. The other authors declared that they have no competing interests.

Authors' contributions

HP and AF chaired the treatment outcome working group (HP, AF, WL, EEP) and wrote the first draft of the consensus paper with the help of WL and EEP. All authors read, critiqued, commented and approved the final manuscript.

Authors' information

Wolfgang Löscher and Ned Patterson: Other members of the outcome of therapeutic interventions in canine and feline epilepsy.
Holger A Volk: Chair of IVETF.
All other co-authors are members of IVETF, are list alphabetically and have approved the consensus statements.

Acknowledgements

The authors are grateful to all owners of epileptic pets and veterinary colleagues who have inspired the group to create consensus statements. We would especially like to thank Professor Simon Shorvon for the critical review of the consensus statements. His great insight has been immensely helpful. The authors also would like to thank the research office for assessing the manuscript according to the Royal Veterinary College's code of good research practice (Authorisation Number – CCS_ 01026). This study was not financially supported by any organization or grant.

Author details

[1]Department of Pharmacology, Toxicology and Pharmacy, Ludwig-Maximillians-University, Königinstr. 16, 80539 Munich, Germany. [2]Service Neurology at the Centre for Clinical Veterinary Medicine, Ludwig-Maximilians-University, Veterinärstr. 13, 80539 Munich, Germany. [3]Department of Pharmacology, Toxicology and Pharmacy, University of Veterinary Medicine Hannover, Bünteweg 17, 30559 Hannover, Germany. [4]University of Minnesota College of Veterinary Medicine, D426 Veterinary Medical Center, 1352 Boyd Avenue, St. Paul, MN 55108, USA. [5]Department of Small Animal Medicine and Clinical Biology, Faculty of Veterinary Medicine, Ghent University, Salisburylaan 133, Merelbeke 9820, Belgium. [6]Department of Veterinary and Clinical Sciences, Faculty of Health and Medical Sciences, University of Copenhagen, Frederiksberg C, Denmark. [7]Animal Health Trust, Lanwades Park, Kentford, Newmarket, CB8 7UU Suffolk, UK. [8]Fernside Veterinary Centre, 205 Shenley Road, Borehamwood SG9 0THHertfordshire, UK. [9]University of Melbourne, 250 Princes Highway, Weibee 3015VIC, Australia. [10]Department of Clinical Sciences of Companion Animals, Utrecht University, Yalelaan 108, 3583 CM Utrecht, The Netherlands. [11]Section of Clinical & Comparative Neuropathology, Centre for Clinical Veterinary Medicine, Ludwig-Maximilians-University, Veterinärstr. 13, 80539 Munich, Germany. [12]Department of Clinical Sciences, College of Veterinary Medicine, North Carolina State University, 1052 William Moore Drive, Raleigh, NC 27607, USA. [13]Clinical Unit of Internal Medicine Small Animals, University of Veterinary Medicine, Veterinärplatz 1, 1210 Vienna, Austria. [14]Vet Extra Neurology, Broadleys Veterinary Hospital, Craig Leith Road, Stirling FK7 7LEStirlingshire, UK. [15]College of Veterinary Medicine, University of Georgia, 501 DW Brooks Drive, Athens, GA 30602, USA. [16]Chicago Veterinary Neurology and Neurosurgery, 3123 N. Clybourn Avenue, Chicago, IL 60618, USA. [17]Fitzpatrick Referrals, Halfway Lane, Eashing, Godalming, GU7 2QQ Surrey, UK. [18]School of Veterinary Medicine, Faculty of Health & Medical Sciences, University of Surrey, Guildford GU2 7TESurrey, UK. [19]Department of Small Animal Medicine and Surgery, University of Veterinary Medicine Hannover, Bünteweg 9, 30559 Hannover, Germany. [20]Department of Clinical Science and Services, Royal Veterinary College, Hatfield AL9 7TAHertfordshire, UK.

Received: 5 June 2015 Accepted: 29 June 2015
Published online: 28 August 2015

References

1. Kwan P, Arzimanoglou A, Berg AT, Brodie MJ, Allen Hauser W, Mathern G, et al. Definition of drug resistant epilepsy: consensus proposal by the *ad hoc* Task Force of the ILAE Commission on Therapeutic Strategies. Epilepsia. 2010;51(6):1069–77.
2. Tellez-Zenteno JF, Hernandez-Ronquillo L, Buckley S, Zahagun R, Rizvi S. A validation of the new definition of drug-resistant epilepsy by the International League Against Epilepsy. Epilepsia. 2014;55(6):829–34.
3. Balosso S, Liu J, Bianchi ME, Vezzani A. Disulfide-containing high mobility group box-1 promotes N-methyl-D-aspartate receptor function and excitotoxicity by activating Toll-like receptor 4-dependent signaling in hippocampal neurons. Antioxid Redox Signal. 2014;21(12):1726–40.
4. Balosso S, Maroso M, Sanchez-Alavez M, Ravizza T, Frasca A, Bartfai T, et al. A novel non-transcriptional pathway mediates the proconvulsive effects of interleukin-1beta. Brain. 2008;131(Pt 12):3256–65.
5. Librizzi L, Noe F, Vezzani A, de Curtis M, Ravizza T. Seizure-induced brain-borne inflammation sustains seizure recurrence and blood-brain barrier damage. Ann Neurol. 2012;72(1):82–90.
6. Wilcox KS, Vezzani A. Does brain inflammation mediate pathological outcomes in epilepsy? Adv Exp Med Biol. 2014;813:169–83.
7. Ryvlin P, Nashef L, Lhatoo SD, Bateman LM, Bird J, Bleasel A, et al. Incidence and mechanisms of cardiorespiratory arrests in epilepsy monitoring units (MORTEMUS): a retrospective study. Lancet Neurol. 2013;12(10):966–77.
8. Shankar R, Cox D, Jalihal V, Brown S, Hanna J, McLean B. Sudden unexpected death in epilepsy (SUDEP): development of a safety checklist. Seizure. 2013;22(10):812–7.
9. Fredso N, Koch BC, Toft N, Berendt M. Risk factors for survival in a university hospital population of dogs with epilepsy. J Vet Intern Med. 2014;28(6):1782–8.
10. Berendt M, Gredal H, Ersboll AK, Alving J. Premature death, risk factors, and life patterns in dogs with epilepsy. J Vet Intern Med. 2007;21(4):754–9.
11. Gullov CH, Toft N, Berendt M. A longitudinal study of survival in Belgian Shepherds with genetic epilepsy. J Vet Intern Med. 2012;26(5):1115–20.
12. Hülsmeyer V, Zimmermann R, Brauer C, Sauter-Louis C, Fischer A. Epilepsy in Border Collies: clinical manifestation, outcome, and mode of inheritance. J Vet Intern Med. 2010;24(1):171–8.
13. Scorza CA, Calderazzo L, Cavalheiro EA, Scorza FA, Cysneiros RM. Sudden unexpected death in dogs with epilepsy: risks versus benefits of omega-3 fatty acid supplementation for man's best friend. Epilepsy Behav. 2013;27(3):508–9.
14. Berendt M, Gredal H, Pedersen LG, Alban L, Alving J. A cross-sectional study of epilepsy in Danish Labrador Retrievers: prevalence and selected risk factors. J Vet Intern Med. 2002;16(3):262–8.
15. Chang Y, Mellor DJ, Anderson TJ. Idiopathic epilepsy in dogs: owners' perspectives on management with phenobarbitone and/or potassium bromide. J Small Anim Pract. 2006;47(10):574–81.

16. Callaghan B, Schlesinger M, Rodemer W, Pollard J, Hesdorffer D, Allen Hauser W, et al. Remission and relapse in a drug-resistant epilepsy population followed prospectively. Epilepsia. 2011;52(3):619–26.
17. Neligan A, Bell GS, Elsayed M, Sander JW, Shorvon SD. Treatment changes in a cohort of people with apparently drug-resistant epilepsy: an extended follow-up. J Neurol Neurosurg Psychiatry. 2012;83(8):810–3.
18. Sillanpaa M, Schmidt D. Is incident drug-resistance of childhood-onset epilepsy reversible? A long-term follow-up study. Brain. 2012;135(Pt 7):2256–62.
19. Rundfeldt C, Loscher W. The pharmacology of imepitoin: the first partial benzodiazepine receptor agonist developed for the treatment of epilepsy. CNS Drugs. 2014;28(1):29–43.
20. Tipold A, Keefe TJ, Loscher W, Rundfeldt C, de Vries F. Clinical efficacy and safety of imepitoin in comparison with phenobarbital for the control of idiopathic epilepsy in dogs. J Vet Pharmacol Ther. 2015;38(2):160–8.
21. Cross HJ, Kurlemann G. Current Recommendations for Children. Bremen: UNI-MED Verlag AG; 2013.
22. Klamer S, Singh A, Gil-Nagel A, Krämer G, French J, Lerche H. Current Recommendations, Guidlines, and Expert Views of Practical Anticonvusant Therapy. Bremen: UNI-MED Verlag AG; 2013.
23. Bhatti S, De Risio L, Muñana KR, Penderis J, Stein V, Tipold A, *et al.* International Veterinary Epilepsy Task Force consensus proposal: medical treatment of canine epilepsy in Europe. BMC Vet Res. 2015.
24. Tang V, Michaelis R, Kwan P. Psychobehavioral therapy for epilepsy. Epilepsy Behav. 2014;32:147–55.
25. Stafstrom CE. Epilepsy comorbidities: how can animal models help? Adv Exp Med Biol. 2014;813:273–81.
26. Shihab N, Bowen J, Volk HA. Behavioral changes in dogs associated with the development of idiopathic epilepsy. Epilepsy Behav. 2011;21(2):160–7.
27. Wessmann A, Volk HA, Parkin T, Ortega M, Anderson TJ. Evaluation of quality of life in dogs with idiopathic epilepsy. J Vet Intern Med. 2014;28(2):510–4.
28. Rutherford L, Wessmann A, Rusbridge C, McGonnell IM, Abeyesinghe S, Burn C, et al. Questionnaire-based behaviour analysis of Cavalier King Charles spaniels with neuropathic pain due to Chiari-like malformation and syringomyelia. Vet J. 2012;194(3):294–8.
29. Olmez I, Moses H, Sriram S, Kirshner H, Lagrange AH, Pawate S. Diagnostic and therapeutic aspects of Hashimoto's encephalopathy. J Neurol Sci. 2013;331(1-2):67–71.
30. Pancotto T, Rossmeisl Jr JH, Panciera DL, Zimmerman KL. Blood-brain-barrier disruption in chronic canine hypothyroidism. Vet Clin Pathol. 2010;39(4):485–93.
31. von Klopmann T, Boettcher IC, Rotermund A, Rohn K, Tipold A. Euthyroid sick syndrome in dogs with idiopathic epilepsy before treatment with anticonvulsant drugs. J Vet Intern Med. 2006;3:516–22.
32. Yilmaz U, Yilmaz TS, Akinci G, Korkmaz HA, Tekgul H. The effect of antiepileptic drugs on thyroid function in children. Seizure. 2014;23(1):29–35.
33. Eddy CM, Rickards HE, Cavanna AE. Behavioral adverse effects of antiepileptic drugs in epilepsy. J Clin Psychopharmacol. 2012;32(3):362–75.
34. Zaccara G, Franciotta D, Perucca E. Idiosyncratic adverse reactions to antiepileptic drugs. Epilepsia. 2007;48(7):1223–44.
35. Steinmetz S, Tipold A, Bilzer T, Schenk HC. Transient neuromyopathy after bromide intoxication in a dog with idiopathic epilepsy. Ir Vet J. 2012;65(1):19.
36. Baird-Heinz HE, Van Schoick AL, Pelsor FR, Ranivand L, Hungerford LL. A systematic review of the safety of potassium bromide in dogs. J Am Vet Med Assoc. 2012;240(6):705–15.
37. Kube SA, Vernau KM, LeCouteur RA. Dyskinesia associated with oral phenobarbital administration in a dog. J Vet Intern Med. 2006;20(5):1238–40.
38. Gaskill CL, Cribb AE. Pancreatitis associated with potassium bromide/ phenobarbital combination therapy in epileptic dogs. Can Vet J. 2000;41(7):555–8.
39. Dewey CW, Cerda-Gonzalez S, Levine JM, Badgley BL, Ducote JM, Silver GM, et al. Pregabalin as an adjunct to phenobarbital, potassium bromide, or a combination of phenobarbital and potassium bromide for treatment of dogs with suspected idiopathic epilepsy. J Am Vet Med Assoc. 2009;235(12):1442–9.
40. Bersan E, Volk HA, Ros C, De Risio L. Phenobarbitone-induced haematological abnormalities in idiopathic epileptic dogs: prevalence, risk factors, clinical presentation and outcome. Vet Rec. 2014;175(10):247.
41. Jacobs G, Calvert C, Kaufman A. Neutropenia and thrombocytopenia in three dogs treated with anticonvulsants. J Am Vet Med Assoc. 1998;212(5):681–4.
42. Schwartz M, Munana KR, Olby NJ. Possible drug-induced hepatopathy in a dog receiving zonisamide monotherapy for treatment of cryptogenic epilepsy. J Vet Med Sci. 2011;73(11):1505–8.
43. Miller ML, Center SA, Randolph JF, Lepherd ML, Cautela MA, Dewey CW. Apparent acute idiosyncratic hepatic necrosis associated with zonisamide administration in a dog. J Vet Intern Med. 2011;25(5):1156–60.
44. March PA, Hillier A, Weisbrode SE, Mattoon JS, Johnson SE, DiBartola SP, et al. Superficial necrolytic dermatitis in 11 dogs with a history of phenobarbital administration (1995-2002). J Vet Intern Med. 2004;18(1):65–74.
45. Neuman MG, Cohen L, Nanau RM, Hwang PA. Genetic and immune predictors for hypersensitivity syndrome to antiepileptic drugs. Transl Res. 2012;159(5):397–406.
46. WHOQOL-Group T. The World Health Organization Quality Of Life Assessment (WHOQOL): position paper from the World Health Organization. Soc Sci Med. 1995;41(10):1403–9.
47. Lord LK, Podell M. Owner perception of the care of long-term phenobarbital-treated epileptic dogs. J Small Anim Pract. 1999;40(1):11–5.
48. Munana KR, Thomas WB, Inzana KD, Nettifee-Osborne JA, McLucas KJ, Olby NJ, et al. Evaluation of levetiracetam as adjunctive treatment for refractory canine epilepsy: a randomized, placebo-controlled, crossover trial. J Vet Intern Med. 2012;26(2):341–8.
49. Levitski RE, Trepanier LA. Effect of timing of blood collection on serum phenobarbital concentrations in dogs with epilepsy. J Am Vet Med Assoc. 2000;217(2):200–4.
50. Monteiro R, Anderson TJ, Innocent G, Evans NP, Penderis J. Variations in serum concentration of phenobarbitone in dogs receiving regular twice daily doses in relation to the times of administration. Vet Rec. 2009;165(19):556–8.
51. Munana KR, Nettifee-Osborne JA, Papich MG. Pharmacokinetics of levetiracetam in epileptic dogs when administered concurrently with phenobarbital, bromide, or phenobarbital and bromide in combination. J Vet Intern Med. 2014;28:1358.
52. Moore SA, Munana KR, Papich MG, Nettifee-Osborne JA. The pharmacokinetics of levetiracetam in healthy dogs concurrently receiving phenobarbital. J Vet Pharmacol Ther. 2011;34(1):31–4.
53. Orito K, Saito M, Fukunaga K, Matsuo E, Takikawa S, Muto M, et al. Pharmacokinetics of zonisamide and drug interaction with phenobarbital in dogs. J Vet Pharmacol Ther. 2008;31(3):259–64.
54. Chung JY, Hwang CY, Chae JS, Ahn JO, Kim TH, Seo KW, et al. Zonisamide monotherapy for idiopathic epilepsy in dogs. N Z Vet J. 2012;60(6):357–9.
55. Hanley JA, Lippman-Hand A. If nothing goes wrong, is everything all right? Interpreting zero numerators. JAMA. 1983;249(13):1743–5.
56. Jovanovic BD, Levy PS. A look at the rule of three. Am Stat. 1997;51:137–9.
57. Westover MB, Cormier J, Bianchi MT, Shafi M, Kilbride R, Cole AJ, et al. Revising the "Rule of Three" for inferring seizure freedom. Epilepsia. 2012;53(2):368–76.
58. Volk HA, Matiasek LA, Lujan Feliu-Pascual A, Platt SR, Chandler KE. The efficacy and tolerability of levetiracetam in pharmacoresistant epileptic dogs. Vet J. 2008;176(3):310–9.
59. Von Klopmann T, Rambeck B, Tipold A. Prospective study of zonisamide therapy for refractory idiopathic epilepsy in dogs. J Small Anim Pract. 2007;48(3):134–8.
60. Potschka H, Fischer A, von Ruden EL, Hulsmeyer V, Baumgartner W. Canine epilepsy as a translational model? Epilepsia. 2013;54(4):571–9.
61. Rossmeisl JH, Inzana KD. Clinical signs, risk factors, and outcomes associated with bromide toxicosis (bromism) in dogs with idiopathic epilepsy. J Am Vet Med Assoc. 2009;234(11):1425–31.
62. Weissl J, Hulsmeyer V, Brauer C, Tipold A, Koskinen LL, Kyostila K, et al. Disease progression and treatment response of idiopathic epilepsy in Australian Shepherd dogs. J Vet Intern Med. 2012;26(1):116–25.
63. Charalambous M, Brodbelt D, Volk HA. Treatment in canine epilepsy–a systematic review. BMC Vet Res. 2014;10:257.
64. Munana KR, Zhang D, Patterson EE. Placebo effect in canine epilepsy trials. J Vet Intern Med. 2010;24(1):166–70.
65. Ben-Menachem E, Sander JW, Privitera M, Gilliam F. Measuring outcomes of treatment with antiepileptic drugs in clinical trials. Epilepsy Behav. 2010;18(1-2):24–30.
66. Faught E. Antiepileptic drug trials: the view from the clinic. Epileptic Disord. 2012;14(2):114–23.
67. Löscher W, Schmidt D. Modern antiepileptic drug development has failed to deliver: ways out of the current dilemma. Epilepsia. 2011;52(4):657–78.

68. French JA, Cabrera J, Emir B, Whalen E, Lu F. Designing a new proof-of-principle trial for treatment of partial seizures to demonstrate efficacy with minimal sample size and duration-a case study. Epilepsy Res. 2013;106(1-2):230–6.
69. European-Medicines-Agency. International Conference on Harmonisation of Technocal Requirement of Pharmaceuticals for Human Use (ICH) Topic E10 Note for Guidance on Choice of Control Group in Clinical Trials, vol. 96. London: CPMP/ICH; 2001.
70. Boothe DM, Dewey C, Carpenter DM. Comparison of phenobarbital with bromide as a first-choice antiepileptic drug for treatment of epilepsy in dogs. J Am Vet Med Assoc. 2012;240(9):1073–83.
71. French JA, Wang S, Warnock B, Temkin N. Historical control monotherapy design in the treatment of epilepsy. Epilepsia. 2010;51(10):1936–43.
72. Perucca E. When clinical trials make history: demonstrating efficacy of new antiepileptic drugs as monotherapy. Epilepsia. 2010;51(10):1933–5.
73. Glauser T, Ben-Menachem E, Bourgeois B, Cnaan A, Chadwick D, Guerreiro C, et al. ILAE treatment guidelines: evidence-based analysis of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes. Epilepsia. 2006;47(7):1094–120.
74. Glauser T, Ben-Menachem E, Bourgeois B, Cnaan A, Guerreiro C, Kalviainen R, et al. Updated ILAE evidence review of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes. Epilepsia. 2013;54(3):551–63.
75. Packer RM, Shihab NK, Torres BB, Volk HA. Clinical risk factors associated with anti-epileptic drug responsiveness in canine epilepsy. PLoS ONE. 2014;9(8):e106026.

Rusbridge et al. BMC Veterinary Research (2015) 11:194
DOI 10.1186/s12917-015-0466-x

BMC Veterinary Research

CORRESPONDENCE Open Access

International Veterinary Epilepsy Task Force recommendations for a veterinary epilepsy-specific MRI protocol

Clare Rusbridge[1,2*], Sam Long[3], Jelena Jovanovik[1], Marjorie Milne[3], Mette Berendt[4], Sofie F. M. Bhatti[5], Luisa De Risio[6], Robyn G. Farqhuar[7], Andrea Fischer[8], Kaspar Matiasek[9], Karen Muñana[10], Edward E. Patterson[11], Akos Pakozdy[12], Jacques Penderis[13], Simon Platt[14], Michael Podell[15], Heidrun Potschka[16], Veronika M. Stein[17], Andrea Tipold[17] and Holger A. Volk[18]

Abstract

Epilepsy is one of the most common chronic neurological diseases in veterinary practice. Magnetic resonance imaging (MRI) is regarded as an important diagnostic test to reach the diagnosis of idiopathic epilepsy. However, given that the diagnosis requires the exclusion of other differentials for seizures, the parameters for MRI examination should allow the detection of subtle lesions which may not be obvious with existing techniques. In addition, there are several differentials for idiopathic epilepsy in humans, for example some focal cortical dysplasias, which may only apparent with special sequences, imaging planes and/or particular techniques used in performing the MRI scan. As a result, there is a need to standardize MRI examination in veterinary patients with techniques that reliably diagnose subtle lesions, identify post-seizure changes, and which will allow for future identification of underlying causes of seizures not yet apparent in the veterinary literature.

There is a need for a standardized veterinary epilepsy-specific MRI protocol which will facilitate more detailed examination of areas susceptible to generating and perpetuating seizures, is cost efficient, simple to perform and can be adapted for both low and high field scanners. Standardisation of imaging will improve clinical communication and uniformity of case definition between research studies. A 6–7 sequence epilepsy-specific MRI protocol for veterinary patients is proposed and further advanced MR and functional imaging is reviewed.

Keywords: Canine, Feline, Seizure, Imaging, Hippocampus

Background

Canine epilepsy has an estimated prevalence of 0.62–0.75 % in primary veterinary practice [1, 2] and as such is one of the most common chronic neurological diseases. Magnetic resonance imaging (MRI) is regarded as an essential diagnostic test however the specificity is limited because the diagnosis of idiopathic epilepsy is one of exclusion and the reliability of diagnosis is limited by available technology and expertise in interpretation. The International League against Epilepsy (ILAE) defines idiopathic epilepsy as *an epilepsy of predominately genetic or presumed genetic origin and in which there is no gross neuroanatomic or neuropathologic abnormality* [3]. Therefore by default, MRI examination of an animal with idiopathic epilepsy should be "normal" (in human epilepsy termed MRI–negative). However the ability to detect lesions depends on many factors that affect the quality of the MRI examination (Table 1). Some of these factors can be controlled, such as optimal slice thickness and sequence. Other factors are less easy to influence. For example, the ideal epilepsy protocol in humans (Table 2) would include a gradient echo or similar technique for detecting haemorrhage or calcification. However this sequence is sensitive to susceptibility artefacts arising from the skull bones for example the mastoid area of the temporal bone, which are a more significant problem in veterinary patients that have a greater bone:brain ratio

* Correspondence: ClareR@fitzpatrickreferrals.co.uk
[1]Fitzpatrick Referrals, Halfway Lane, Eashing, Godalming GU7 2QQ, Surrey, UK
[2]School of Veterinary Medicine, Faculty of Health & Medical Sciences, University of Surrey, Guildford GU2 7TE, Surrey, UK
Full list of author information is available at the end of the article

Table 1 Factors that have an effect on the ability to detect epileptic lesions on MRI

Type	Example	Notes
Protocol	Slice thickness	Thinner slices give more chance of lesion detection. A routine scan with 5 mm thick slices and 0.5 mm interslice gaps with T1W and T2W transverse image acquisitions and gadolinium contrast enhancement may be adequate to evaluate gross cerebral abnormalities such as large tumours or malformations but may not detect subtle epileptic lesions. Slice thickness of 3 mm or less in at least 2 orientations is recommended for examination of the epileptic brain and larger slice size risks missing lesions less than 5 mm [38]. However MRI machines of 1 T or less cannot provide thin slices with sufficient SNR within reasonable time. For this reason machines under 1.5 T are considered insufficient for the imaging of human epilepsy patients unless there is no alternative [38].
	Sequence	Failure or inability to select the appropriate sequences to detect lesions. For example in humans, high resolution, volumetric and 3D MRI acquisition is recommended to obtained detailed information on hippocampal anatomy, cortical gyral patterns, improve grey and white matter contrast and to enable co-registration with other modalities or sequential MRI examinations [13, 38]. This requires a good quality machine (1.5 T or more) and careful orientation of slice plane relative to patient position. FLAIR sequence is regarded as the most useful image for detecting epileptic lesions in humans [38] however many low field machines produce FLAIR with low resolution.
Magnetic field strength	Low field versus high field 1.5 T versus 3 T	Imaging with higher magnetic field-strength provides improved signal-to-noise ratio and spatial resolution which allows shorter imaging times for a given resolution and/or higher resolution for a given imaging time. Higher signal-to-noise ratio allows better resolution with smaller voxel size and thinner slice thickness [7].
Coil	Type of coil used (for example Knee vs Head coil)	Coils with minimum distance between receiving coil and brain surface and minimal diameter increase SNR and therefore image quality. Some coils (for example brain coils) may limit the field of view that can be imaged before significant signal drop-off occurs. The lack of availability of dog-specific coils and variation in dog head size makes coil selection challenging in some cases.
	Available channels	An 8 channel brain coil is usual in veterinary MRI but a 32 channel brain coil will provide much better SNR and contrast resolution.
Operator factors	Inexperience / lack of training	A fully trained radiography technician understands the physics of MRI and anatomy allowing them to create images with excellent contrast and clarity and target the brain structures to be studied. Typically, a trained MRI technician has undertaken a 3-year radiography degree plus an additional 2–3 years of post-graduate MRI training. A poorly trained or unqualified operator may not be able to achieve optimal results from the machine that they have. In veterinary medicine it is possible to operate a MRI service without a specialist qualification.
	Diligence	There are ways of improving image quality, for example increasing the number of averages (NEX) however these tend to increase the acquisition time. Out with other reasons for decreasing imaging time (economic / duration of anaesthesia), operator motivation is a factor. Bearing this in mind any recommended epilepsy-specific MRI protocol should not be overly onerous in order to improve compliance. A basic protocol of 6 sequences is recommended [38].
Interpreter factors	Inexperience / lack of training	Failure to recognise significant lesions or over-interpretation of other features. A study in humans found that 61 % of epileptogenic lesions remained undetected following "non-expert" reports of "standard" MRI scans. The failure rate dropped to 9 % using an epilepsy tailored MRI protocol with interpretation by experienced neuro-radiologists [39].
Patient factors	Skull and air interface	In some machines may cause susceptibility artefacts on gradient echo and T1W 3D imaging
	Small brain	Slice thickness should be proportional to the brain volume to achieve images with diagnostic quality i.e. animals with smaller brain volume require thinner slices.
	Brain conformation	Changes in skull shape, in particular brachycephaly have resulted in changes in brain conformation [40].
	General anaesthetic	Increased time under general anaesthesia may increase risk to patient.
Economic factors	Time	Increased time of scanning increases cost and risks of anaesthesia. It is important to consider the balance between time of acquisition and image quality in an animal under general anaesthesia.
	Machine costs (purchase of hardware, software, housing and maintenance)	Imaging with higher magnetic field-strength allows for superior images in a shorter imaging time but at a greater cost.
	Relevance	Identification and localisation of epileptic lesion is vital in humans with drug-resistant epilepsy, who may be candidates for potentially curative resective epilepsy surgery. Whether this is applicable for dogs with idiopathic epilepsy remains to be seen. Technology that is only capable of detecting large structural pathology such as tumours may be sufficient if it does not alter the management. However acquisition of high quality scans may enable future identification of resectable lesions that are currently hypothesised.

Table 2 Epilepsy-specific MRI protocol for humans This "essential" 6 sequence protocol allows the detection of virtually all common epileptogenic lesion in humans and was proposed after systemic analysis of 2740 patients in a epilepsy pre-surgery program [13, 38, 41]

Human epilepsy-specific MRI protocol
Slice thickness 3 mm or less
➢ T2W - 2 sequence orientations for hippocampal angulation
• Perpendicular to the long axis of the hippocampus
• Along the long axis of the hippocampus
➢ FLAIR - 2 sequence orientations for hippocampal angulation
• Perpendicular to the long axis of the hippocampus
• Along the long axis of the hippocampus
➢ T1W
• 3D volume with 1 mm isotropic voxel size
➢ Hemosiderin/calcification sensitive sequences e.g. gradient echo

than humans. The interface between bone and air can cause inhomogeneity in the magnetic field and signal void (susceptibility) artefact, particularly noticeable on special sequences such as diffusion-weighted imaging (DWI) and which can interfere with MR spectroscopic techniques.

The ability to detect epileptogenic lesions is further limited by economics. For example, imaging with a 3 tesla (3 T) MRI system gives better anatomical detail and is superior for detecting subtle lesions such as mesial temporal sclerosis [4] and migration disorders [5, 6]. However the initial and on-going cost of this technology is prohibitive for many institutions and indeed much of veterinary MRI is performed on low field (1 T or less) scanners, which have decreased spatial resolution and signal-to-noise ratio (SNR) [7].

Other technology may need to be employed to detect lesions in MRI–negative patients. Methods of processing MRI data post-acquisition have identified previously undetectable or overlooked abnormalities in humans [8, 9]. One such example is employed to improve hippocampal volumetric measurements in the sparsely myelinated and small brain of neonatal humans. To achieve this, contrast is optimised by combining dual echo T2W and proton density images [10]. In large part this is based upon the fact that discovery of a surgically resectable lesion significantly improves the prognosis in human drug-resistant focal epilepsy, including abnormalities of the hippocampus in the region of the mesial temporal lobe. As a result, if the MRI is negative then further work-up, for example with functional MR imaging, is engaged to help localize the epileptogenic lesion [11–13]. Table 3 details examples of the modalities used, none of which are established as routine in animals. However before making recommendations for advanced imaging, the veterinary surgeon and the owner must be clear about what is to be gained. Unless the diagnostic procedure changes the outcome or management there may be little achieved by subjecting an animal to invasive and/or expensive procedures. For example, Smith and others found that if an epileptic dog was less than six years old and had a normal inter-ictal neurological examination then there was a 97 % confidence of a unremarkable low field brain MRI, making diagnosis of idiopathic epilepsy very likely [14]. At present, given the lack of surgical or other therapeutic techniques available to improve prognosis over standard antiepileptic therapy, more research is required to improve the diagnostic sensitivity of MRI and establish the value of such therapeutic techniques.

The purpose of this article is to propose an epilepsy-specific MRI protocol that will optimise detection of lesions ruling out idiopathic epilepsy as a diagnosis, standardise the diagnosis for entry into clinical trials and facilitate detection of lesions which develop as a consequence of epilepsy, as well as provide high quality data for future studies investigating the pathophysiology of epilepsy.

Aim of advanced diagnostic imaging for animals with epilepsy

There are three main aims of advanced diagnostic imaging of the epileptic animal: 1) to rule out causes of epileptic seizures which may be treatable with means other than antiepileptic therapy only (e.g. inflammatory or infectious brain disease) 2) to identify lesions which are caused by seizures but are not themselves the source of seizures for example hippocampal sclerosis and 3) to provide data to further advance the field of research into the pathogenesis and/or treatment of epilepsy. Importantly, MRI must always be preceded by a thorough investigation including a good clinical history with clinical and neurological examination (see Consensus Proposal on the diagnostic approach to epilepsy in dogs). In addition, the absence of lesions identifiable on MRI examination does not indicate prognosis or which drugs are most appropriate. However MRI may enable the detection of lesions that may be associated with drug-resistance such as hippocampal sclerosis [5]. High resolution imaging of the hippocampus is therefore paramount in humans but the value of this remains undetermined in animals [15, 16].

Identification of the epileptogenic lesion

Most veterinary hospitals that offer advanced diagnostic imaging use the same protocol for the epileptic brain as for detection of gross intracranial pathology such as tumours. This reflects the aim of the procedure, namely to identify those lesions that have a different prognosis or treatment to idiopathic epilepsy. In human medicine, different MRI protocols are performed depending on whether the patient is expected to have idiopathic or structural epilepsy. Some might recommend that epileptic

Table 3 Novel imaging modalities for identifying epileptic foci

Modality	Principle	Veterinary application
Magnetoencephalography (MEG) and magnetic source imaging (MSI)	MEG – non-invasive functional imaging recording magnetic flux on the head surface associated with electrical currents in activated sets of neurons. MSI - created when MEG data is superimposed on a MRI [42].	Has been performed experimentally in anaesthetised non-epileptic dog [43]. May be limited by requirement for anaesthesia [44]. Identity microchip may interfere with recording [45]. Requires a magnetically shielded room and other expensive equipment [12].
Positron Emission Tomography (PET)	Functional representational of brain activity (dependent of the radionuclide tracer utilised) e.g. local glucose utilisation (fluorine-18 fluorodeoxyglucose - FDG). Brain regions containing the epileptogenic zone have hypometabolism on inter-ictal FDG-PET [12]. PET and MRI co-registration or integrated PET/MR with simultaneous acquisition is considered superior [8].	FDG-PET may be useful as a diagnostic test for idiopathic epilepsy in the dog [46, 47]
Ictal and inter-ictal single-photon emission computed tomography (ictal/inter-ictal SPECT)	Injection of a radiolabeled tracer during ictus and inter-ictus. Statistical comparison of the blood flow changes. Ideally co-registered to MRI (SISCOM) [48, 49].	Practical difficulties of performing in ictus. Has been performed in inter-ictus and in one study demonstrated subcortical hypoperfusion in epileptic dogs [50]
Diffusion tensor imaging (DTI)	Detects tissue microstructural pathology that influences freedom of water molecular diffusion. Has been used to detect hippocampal and temporal lobe pathology in TLE and DTI tractography has been used in surgical planning [12]. Has demonstrated microstructural alterations in large white matter tracts in idiopathic generalised epilepsy [51]	Experimental studies suggest DTI is feasible in dog [52–54] and structural abnormalities have been identified in a compulsive behaviour disorder [55]. No application for epilepsy yet.
Functional magnetic resonance imaging (fMRI)	Utilises the different magnetic susceptibilities of deoxygenated and oxygenated haemoglobin (blood oxygenation level dependent (BOLD) contrast). Deoxygenated haemoglobin is paramagnetic leading to distortion of magnetic fields and a shorter T2 relaxation time. Areas of increased brain activity have greater metabolic demand and more oxygenated haemoglobin and a prolonged T2 relaxation time. The difference in BOLD at rest and during a specific task (such as language and memory) indicates the areas of the brain activated by the task [12].	Laboratory experimental studies, none relating to epilepsy [56]. Has been used in trained awake dogs to assess cognition [57–59].
fMRI-EEG	EEG is acquired using a specialized system in the MRI machine while acquiring a blood oxygenation level dependent (BOLD) sequence. The EEG is analysed for epileptiform discharges spikes and the corresponding BOLD fMRI change is evaluated [12].	None as yet
Functional connectivity MRI (FcMRI)	Utilizes the principles of fMRI to demarcate brain networks. It evaluates the structural changes distant from the epileptic focus. Main application is in pathophysiology of the epilepsy but has the potential to guide surgery [12].	None as yet
Near infra-red spectroscopy (NIRS)	Probe transmits near infra-red spectrum wavelength rays that passed through the cranium to a depth of approximately 2 cm and is absorbed by haemoglobin in the tissue. Reflected rays are detected by a sensor probe. The strength of reflected rays is inversely related to the concentration of haemoglobin in the brain tissue. The resulting images are co-registered to the MRI to lateralize and localize the signal changes [12].	Pilot studies performed assessing positive emotional states in dogs [60] Limited to superficial brain structures. May have limited application in dogs with thicker skulls and muscle. However can be performed in awake animals.
Magnetic resonance spectroscopy (MRS)	MRS can be used to measure creatine (Cr), N-acetyl aspartate (NAA), choline (Cho), lactate, myo-inositol and GABA non-invasively in the brain tissue [12]. Reduced NAA/Cho and NAA/Cr was found in the lesional temporal lobe in TLE [61] and in the epileptogenic/irritative zone in frontal lobe epilepsy [62]. These MRS changes were most likely due to cell dysfunction than cell loss [12]	Studies in healthy dogs [63], laboratory canine model of seizures [64] and in some disease states [65].

Table 3 Novel imaging modalities for identifying epileptic foci *(Continued)*

Arterial spin labelling (ASL)	ASL is a non-invasive MRI technique to assess brain perfusion and therefore image functional areas of the brain. Arterial blood is magnetically labelled using a 180° radio frequency (RF) inversion pulse prior to imaging the region of interest (ROI). The labelled blood flows into the ROI and reduces the MR signal and image intensity at this area. Subtracting this image from the baseline MRI creates the perfusion image which reflects the amount of blood delivered to each voxel [12, 66]. It has been used to show mesial temporal hypometabolism [67] and hippocampal volume loss [68]	None as yet

Table 4 Differentials for idiopathic epilepsy that may require high resolution imaging to identify

Condition	Imaging features	References
Congenital and developmental causes		
Nodular heteroptopia/ focal cortical dysplasia	Abnormal location or thickness of deep grey matter, commonly periventricular or interspersed amongst white matter.	[69]
L2-hydroxyglutaric aciduria	Poor distinction between grey and white matter throughout cerebral hemispheres and deep grey matter. Bilateral grey matter hyperintensity, especially the thalamus and cerebellum	[70]
Infectious and inflammatory causes		
Distemper encephalitis	Patchy, asymmetric T2-weighted hyperintensities with mild or no contrast enhancement on T1W scans. Lesions are usually asymmetric, large, round to ovoid in shape throughout different parts of the forebrain, especially in grey matter of the temporal lobe, as well as the brainstem, cerebellum and subcortical white matter.	[71]
Rabies encephalitis	Very mild lesions - bilaterally symmetrical T2W hyperintensities in temporal lobes, hippocampus, hypothalamus, midbrain and pons with little or no contrast enhancement.	[72]
Metabolic, endocrine and nutritional causes		
Hepatic encephalopathy	Bilaterally symmetrical T1W hyperintensities in caudate nuclei, thalamus, not associated with contrast enhancement	[73]
Thiamine deficiency	Bilateral, symmetric T2W hyperintensities in caudate nuclei, lateral geniculate nuclei, red nucleus, caudal colliculi, facial and vestibular nuclei	[74]

animals that are not expected to have idiopathic epilepsy (for example those animals younger than 6 months or older than 6 years or those patients with abnormal interictal neurological examination) could be examined using an MRI protocol that does not require as high a resolution imaging of the brain while those patients expected to have idiopathic epilepsy could be examined using a higher resolution protocol. However in practice the expense and risk associated with general anaesthesia in veterinary patients makes it unlikely that more than one protocol be used for scanning an animal with epileptic seizures. Therefore any protocol developed for animals must be capable of diagnosing both types of epilepsy.

For animals with a probable diagnosis of idiopathic epilepsy (i.e. those animals that fulfil Tier 1 level of confidence for diagnosis - see Consensus Proposal: Diagnostic approach to epilepsy in dogs), many of the differential diagnoses associated with structural epilepsy, in particular large malformations and neoplastic causes, are relatively straightforward to identify [6, 17, 18]. However, several are associated with subtle changes that may be easily missed without adequate resolution scanning and careful interpretation. The most common of these are listed in Table 4. It must also be remembered that any lesion identified is not automatically epileptogenic in nature and other evidence (e.g. EEG, seizure history) may be required to demonstrate this [19].

Identification of lesions which are the consequence of seizures

Longitudinal studies of epileptic humans suggest that 10 % of newly diagnosed patients and 25 % of those with chronic active epilepsy develop significant cerebral, hippocampal or cerebellar atrophy over 3.5 years [20]. More acute changes secondary to seizures have also been reported (Fig. 1) and it is important that imaging techniques are able to differentiate these resultant, reversible changes from those that may be the cause of seizures. Most commonly, changes that are the result of seizures are found as T2-weighted hyperintensities predominantly in

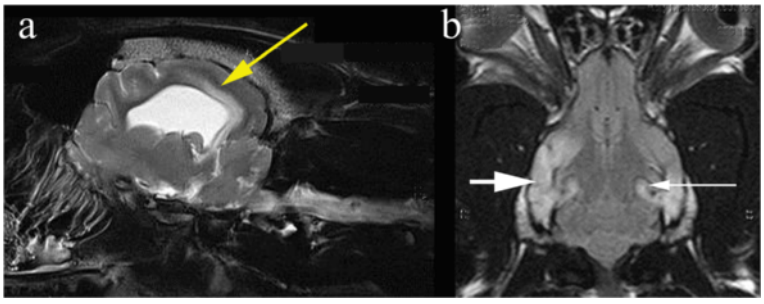

Fig. 1 Post-ictal changes in the temporal and parietal lobe. Images obtained in a 1.5 T Siemens Symphony, Erlangen, Germany. Post-ictal oedema in the temporal lobe (*short white arrow*), hippocampus (*long white arrow*) and cingulate gyrus (*yellow arrow*) in a 2 year male English Bulldog that presented in status epilepticus

the piriform and temporal lobes, as well as the cingulate gyrus and hippocampus [21]. These changes resemble those reported in humans and are likely to represent a mixture of cytotoxic oedema and gliosis [21]. In some cases mild contrast uptake may also be apparent [22]. In general these changes are diffuse, relatively extensive, and their characteristic location makes it straightforward to distinguish them from epileptogenic lesions with either high-field or low-field scanners. However sometimes in can be difficult to ascertain if the changes are cause or effect for example in VGKC-complex/LGI1 antibody-associated limbic encephalitis in cats (Fig. 2) [23]. Cerebrospinal fluid analysis can be unhelpful because post-ictal pleocytosis can occur [24]. In ideal circumstances it would be preferred to repeat imaging in the post ictal period and also assess changes in brain volume/ atrophy however available finances can limit this opportunity. In those patients with whom some doubt may remain, however, the most useful procedure for identifying post-ictal MRI changes is to repeat the scan at a later date, since these changes resolve usually within 16 weeks [21].

Providing data for further research into the pathogenesis and treatment of seizures

In humans, much attention has focussed on the hippocampus because temporal lobe epilepsy (TLE) is the most common cause of complex focal epilepsy, and mesial temporal sclerosis (i.e. severe neuronal cell loss and gliosis in the medial portion of the temporal lobe and particularly in the hippocampus) is a major pathological finding, occurring in roughly 50 % of TLE patients [25]. The pathogenesis of mesial temporal sclerosis is multifactorial and includes genetic factors and molecular events such as channelopathies, activation of NMDA receptors, and other conditions related to Ca(2+) influx into neurons and imbalance of Ca(2+)-binding proteins [26]. There has been much debate as to whether these changes are the cause or the effect of seizures. Most significantly, the surgical removal of these regions in patients with an electroencephalographic (EEG) diagnosis that confirms their location as the source of seizure activity results in significant improvement in seizure control in up to 80 % of patients [27, 28]. The current diagnosis of hippocampal sclerosis in humans requires specific positioning of slices in order to define the hippocampus accurately, together with a considerable body of research defining the range of normal volumes in healthy individuals. These techniques for hippocampal measurement have been established for many years and TLE is one of the more common homogenous forms of epilepsy, so adequate numbers of patients are available for studies [20].

Whether hippocampal volume loss and mesial temporal sclerosis is a parameter that should be assessed in dog has yet to be established (Fig. 1). Hippocampal atrophy has been demonstrated in rodent models [29] and in familial spontaneous epileptic cats where EEG features suggested TLE [16]. Reduced volume of the hippocampus / hippocampal atrophy has been demonstrated in epileptic dogs [15]. Furthermore histopathological changes consistent with hippocampal sclerosis have been well described in epileptic cats [28, 30, 31] (Figs. 2, 3). For these reasons, as well as the recognition that hippocampal sclerosis represents a common surgical target in the treatment of human epilepsy, it appears prudent to evaluate the hippocampus accurately in animal patients with epilepsy. Therefore routine MR evaluation of the epileptic subject should at least include a visual assessment of the hippocampus for atrophy, asymmetry in size, loss of defined morphologic structure, increased T2W or T2W Fluid Attenuated Inversion Recovery (FLAIR) signal and decreased T1W signal [15, 32]. Hippocampal T2W hyperintensity is well correlated with pathology and hippocampal sclerosis and measurement of the T2 relaxation time (T2 relaxometry) can provide an objective measure in humans but has not been assessed in dogs or cats [32]. There is an argument that volumetric studies should be performed in veterinary patients (Table 5) and recent studies have defined the range in normal animals [33]. However making volumetric measurements is a labour intensive process requiring high resolution MRI

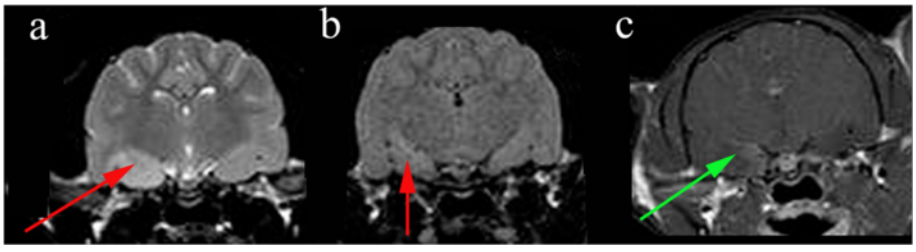

Fig. 2 Hippocampal changes in an 8 month male neutered Oriental Shorthair presented with status epilepticus. **a** Transverse TW2 at level of pituitary gland. There is hyperintensity of the right temporal lobe (red arrow) (**b**) Transverse FLAIR at level of pituitary gland also demonstrating hyperintensity of the right temporal lobe (red arrow) (**c**) Transverse TW1 at level of pituitary gland. There is slight gadolinium contrast enhancement in the mesial temporal lobe. Images reproduced with the kind permission of Dr Ane Uriarte . The cat was suspected to have limbic encephalitis

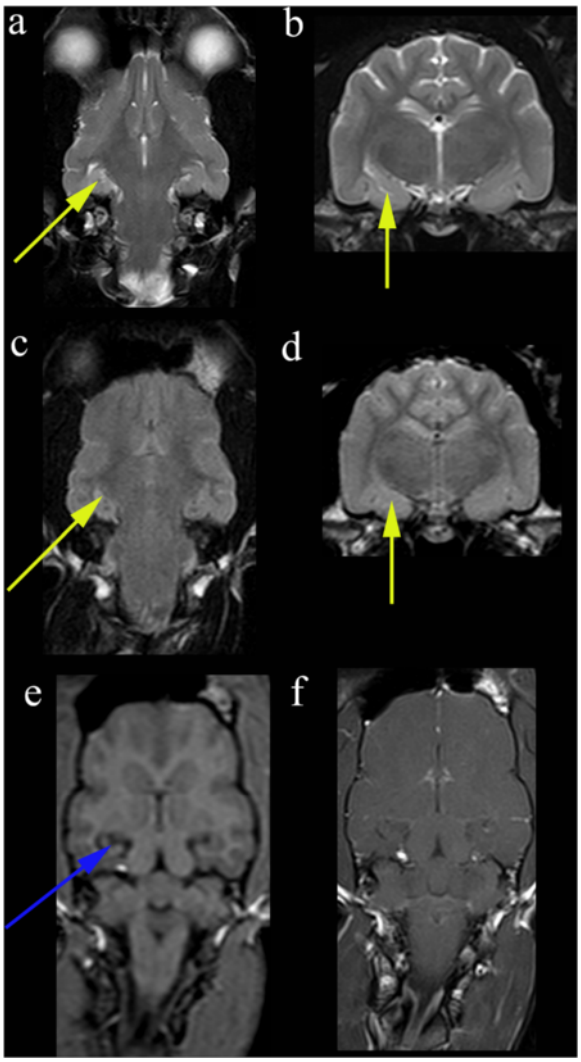

Fig. 3 Hippocampal changes in a 22 month male neutered Oriental Shorthair with drug-resitant epilepsy. Images obtained in a 1.5 T MRI (Siemens Symphony, Erlangen, Germany) 12 months after the images in Fig. 2. Despite an initial course of corticosteroids and polypharmacy with multiple anti-convulsants the cat seizured on an almost daily basis. **a** Dorsal T2W orientated perpendicular to long axis of the hippocampus. **b** Transverse T2W orientated parallel to the long axis of the hippocampus. **c** Dorsal FLAIR orientated perpendicular to long axis of the hippocampus. **d** Transverse FLAIR orientated to long axis of the hippocampus. **e** Dorsal T1W 3D images 1 mm slice thickness orientated perpendicular to long axis of the hippocampus. **f** Dorsal T1W orientated perpendicular to long axis of the hippocampus post gadolinium. On FLAIR and T2W images there is reduction in volume and a hyperintensity of the hippocampus (*yellow arrows*). With the TIW 3D images it is possible to appreciate loss in definition between the white and grey matter in addition to reduction in volume of the hippocampus (*blue arrow*) There is no abnormal enhancement with gadolinium contrast

and personnel training [33]. Currently this is only used as a research tool, although in the future automated atlas-based segmentation may make hippocampal volumetry more routine. Even in humans where hippocampal volumetry has established utility, the time demands and required technical skills mean that it has been difficult to integrate into clinical practice [34]. Consequently patients with a surgically resectable lesion may be missed. This has led to the development of automated software which will

Table 5 Reasons why it may be appropriate to perform volumetric studies on hippocampus or other potentially epileptogenic areas

Rationale for volumetric analysis
➢ **To establish normative date**
• Breed and size variations
• Age
• Gender
• Within subject functional and anatomical asymmetry [75]
➢ **To provide a baseline**
• At initial diagnosis and for serial comparison, for example, if develops drug-resistant epilepsy
➢ **To identify patients with poor prognosis / less likely to respond to treatment**
• Volume compared to normative data
• Within subject asymmetry in volume
➢ **Improving cohort selection for entry into clinical trials evaluating**
• Antiepileptic drugs
• Neuro-protective agents that may modulate the consequences of epilepsy on cognition and behaviour [76]
• Novel treatment modalities

Table 6 Proposed epilepsy-specific MRI protocol for a high field machine

Veterinary epilepsy-specific protocol for 1.5 T MRI
Slice thickness 3 mm or less
➢ **T2W – 3 sequence orientations**
• Sagittal enabling identification long axis of the hippocampus
• Dorsal, perpendicular to the long axis of the hippocampus
• Transverse, parallel to the long axis of the hippocampus
➢ **FLAIR 1–2 sequence orientations for hippocampal angulation**
• Dorsal, perpendicular to the long axis of the hippocampus
• Transverse, parallel to the long axis of the hippocampus (optional)
➢ **T1W**
• 3D technique at 1 mm isotropic voxel size (if possible) or routine T1W dorsal, perpendicular to long axis of the hippocampus
• T1W post paramagnetic contrast injection enhancement if indicated by other pathology / desired by clinician
➢ **Hemosiderin / calcification sensitive sequences e.g. gradient echo**
• Transverse, parallel to the long axis of the hippocampus

Table 7 Proposed epilepsy specific MRI protocol for a low field machine

Veterinary epilepsy-specific protocol for 0.2 T MRI
Slice thickness 4 mm or less
➢ **T1W – 3 sequence orientations**
• Sagittal enabling identification of the long axis of the hippocampus
• Dorsal, perpendicular to the long axis of the hippocampus
• Transverse, parallel to the long axis of the hippocampus
➢ **T2W - 2 sequence orientations for hippocampal angulation**
• Dorsal, perpendicular to the long axis of the hippocampus
• Transverse, parallel to the long axis of the hippocampus
➢ **FLAIR 1–2 sequence orientations for hippocampal angulation**
• Dorsal, perpendicular to the long axis of the hippocampus
• Transverse parallel to the long axis of the hippocampus (optional)
➢ **T1W post paramagnetic contrast enhancement**
• If indicated by other pathology / desired by clinician
• Number of sequences determined by pathology

compare an individual patient's regional brain volumes with a normative database, correcting for sex, head size, and age [34]. Establishing automated software in veterinary patients is challenging due to difficulties in automatic brain extraction algorithms arising from the great variation is head shape and brain size and conformation. Establishment of reference ranges for the three basic canine brain shapes (dolicocephalic, mesaticephalic and brachycephalic) may represent a suitable compromise. Before making a recommendation of measurement of hippocampal volumes in veterinary patients it should be remembered that hippocampal sclerosis is not applicable to all idiopathic generalised epilepsies in humans especially if the epileptogenic focus is not the temporal lobe [35]. Repeated seizures will affect other structures pathologically including the amygdala, cerebral neocortex and the cerebellum [20].

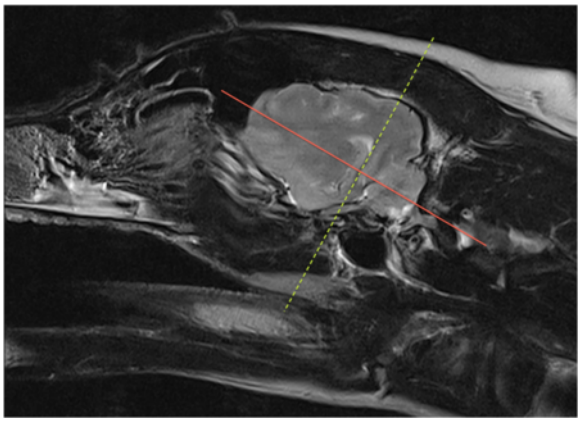

Fig. 4 Parasaggital slice in a veterinary epilepsy-specific protocol for 1.5 T MRI scanner. T2W parasagittal image of the brain demonstrating a planned sequence parallel (*yellow dotted line*) and perpendicular (*red solid line*) to the long axis of the hippocampus. Images obtained in a 1.5 T MRI (Siemens Symphony, Erlangen, Germany)

Existing MRI protocols

Current protocols vary substantially between institutions. Polling of members of the international veterinary epilepsy task force determined that all protocols currently include imaging in at least two orientations (transverse and sagittal) and the majority in three planes (dorsal, typically orientated parallel to hard palate rather than perpendicular to the long axis of the hippocampus). T2W, T2W FLAIR and T1W images pre and post paramagnetic contrast (gadolinium based) are included as standard in most protocols used by specialists who are active in the veterinary field. This differs from human epilepsy-specific MRI protocols where routine administration of gadolinium contrast is considered to provide little advantage for idiopathic or TLE and is reserved for patients in whom there is concern for tumour, vascular malformations, inflammation, and infectious disease or when these are suspected based on review of non-contrast studies [35]. Routine administration of gadolinium contrast in veterinary medicine has been questioned [36]. Other sequences currently included in "veterinary brain protocols" vary between institutions and may include Gradient Echo (GE), T1 weighted Inversion Recovery (T1WIR), Diffusion Weighted Imaging (DWI) and Short Tau Inversion Recovery (STIR) or other fat suppression techniques.

This variation between institutions suggests a need for a uniform veterinary epilepsy-specific MRI protocol that can provide a solid platform for clinical communication and comparability of case definition between research studies. There is also an argument for an MRI protocol that is optimized for epilepsy evaluation facilitating more detailed examination of areas susceptible to generating and perpetuating seizures such as the frontal and temporal lobes and other structures likely to be evaluated at post-mortem in patients who have died. Such a protocol must acknowledge financial constraints, be tailored for low or high field machines and also complement pathological studies.

Consensus on epilepsy-specific MRI protocol

There is a need for a standardized veterinary epilepsy-specific MRI protocol which will facilitate more detailed examination of areas susceptible to generating and perpetuating seizures, complement pathological studies, is economical, simple to perform and can be adapted for both low and high field machines. Standardisation of

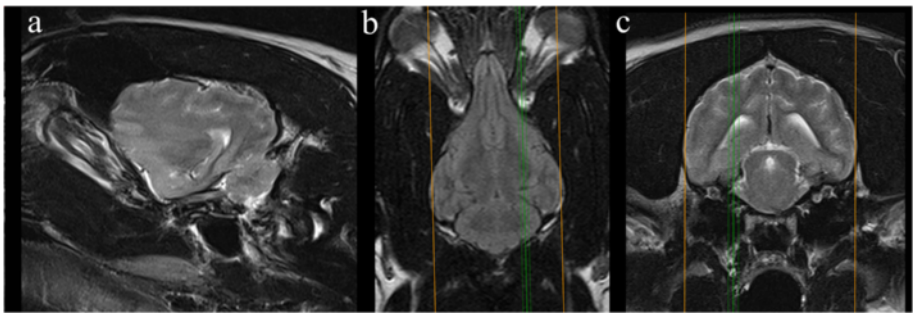

Fig. 5 Veterinary epilepsy-specific protocol for high field MRI. Images obtained in a 1.5 T MRI (Siemens Symphony, Erlangen, Germany). Triplet of MR images illustrating the positon of the parasagittal slice containing the hippocampus. *Left*. T2W parasagittal section demonstrating the hippocampus for sequences orientated relative to the long axis. *Middle*. Dorsal FLAIR of the brain at the level of the orbits illustrating the position of the parasagittal slice (*green line*). *Right* T2W transverse of the brain at the level of the hippocampus illustrating the position of the parasagittal slice (*green line*)

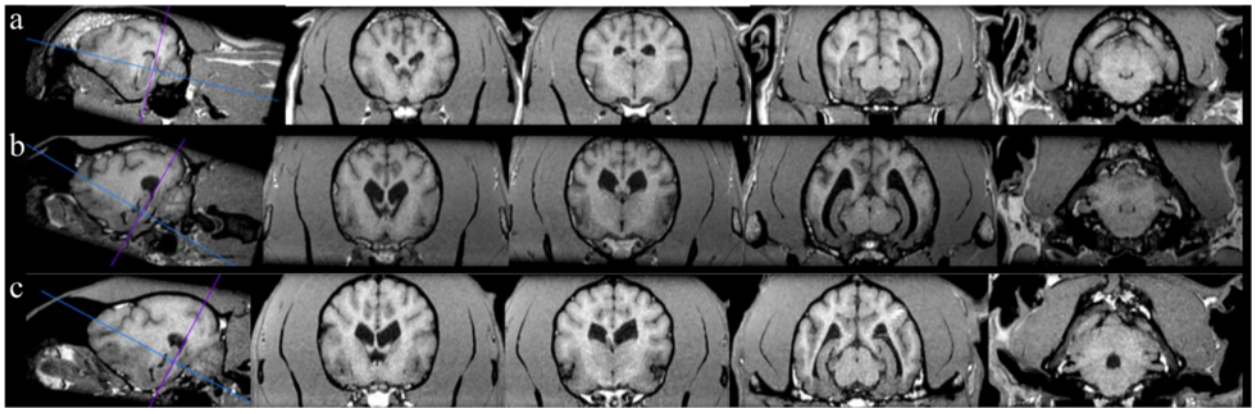

Fig. 6 Variation in appearance of the hippocampus in different skull shapes. **a** brachycephalic vs (**b**) mesocephalic vs (**c**) dolicocephalic with orientation of transverse scans parallel to the long axis of the hippocampus

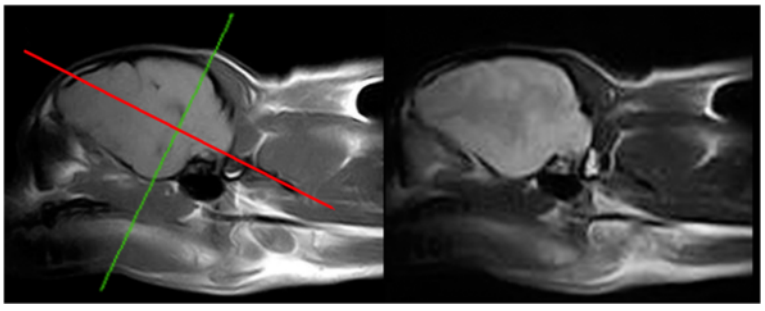

Fig. 7 Veterinary epilepsy-specific protocol for low field MRI. T1W parasagittal image (*left*) of the brain demonstrating a planned sequence orientated parallel (*green line*) and perpendicular (*red solid line*) to the long axis of the hippocampus. It is easier to identify the hippocampus in T1W images from a low field machine. For comparison the corresponding T2W parasagittal images are included (*right*). Images obtained in 0.2 T MRI (Esaote Grande, Genova, Italy)

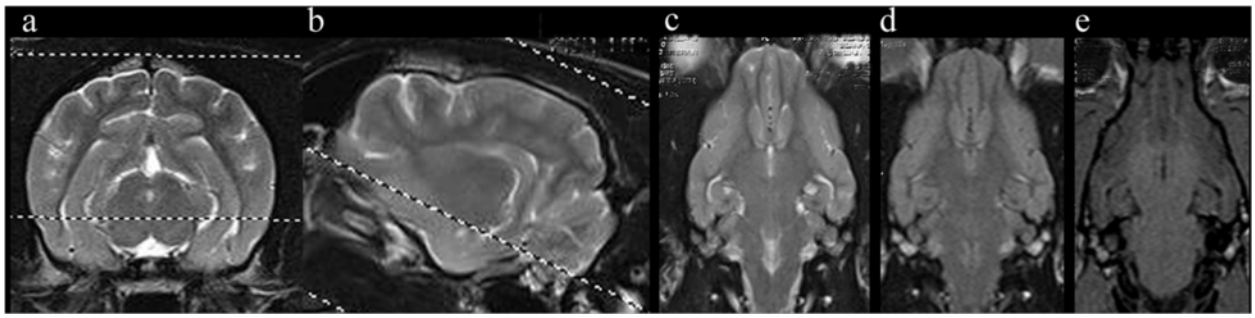

Fig. 8 Veterinary epilepsy-specific protocol for high field MRI. The imaging time for 6 sequences (Figs. 8 and 9) on a 1.5 T MRI was 45 min. The subject was an epileptic 16 month female Cocker spaniel (**a**) and (**b**) Transverse and parasagittal T2W image illustrating slice orientation. **c** Dorsal T2W orientated perpendicular to long axis of the hippocampus (**d**) Dorsal FLAIR orientated perpendicular to long axis of the hippocampus (**e**) Dorsal T1W 3D images1mm slice thickness orientated perpendicular to long axis of the hippocampus

imaging will improve clinical communication and uniformity of case definition between research studies. We propose the following protocols (Tables 6 and 7). During protocol set-up, it is recommended that different parameters (such as flip angle) are trialed in order to obtain the optimal balance between grey-white matter contrast and SNR (for information on MR parameters for 0, 2, 1.5 and 3T see Additional files 1, 2 and 3). Both protocols start with obtaining a sagittal sequence. Due to the difference in anatomical definition this is a T2W sequence in high field machines and T1W sequence in low field machines. In addition to identifying gross structural pathology the sagittal images allow assessment of cerebellar atrophy according to the protocol described by Thames and others [37]. Using parasagittal images the long axis of the hippocampus is identified (Figs. 4, 5, 6, 7, 8 and 9). The hippocampus forms the medial wall of the temporal horn of the lateral ventricle and is delineated on parasagittal images by the contrasting cerebrospinal fluid. After identification of the hippocampus, T2W and sequences are orientated parallel and perpendicular to the long axis of the hippocampus (Figs. 4 and 7). T2W and FLAIR are acknowledged to be optimal for detection of epileptic lesions in humans in particular hippocampal changes (Figs. 2 and 3) and therefore in humans two FLAIR sequences would be obtained [38], however, it is recognized that performing two FLAIR sequences may increase scanning time significantly therefore we recommend that at a minimum a dorsal FLAIR sequence perpendicular to the long axis of the hippocampus is obtained with an option for an additional transverse sequence parallel to the long axis of the hippocampus. In high field scanners a transverse gradient echo or similar sequences sensitive to detection of hemosiderin and / or calcification should be obtained. Like the other images this transverse image is also orientated parallel to the hippocampus. In low field scanners additional T1W sequences are recommended (Table 5). Some high field machines may be able to obtain good resolution 3D TW1 images (Figs. 3, 8 and 10). For these the acquired slice thickness is 1 mm or less giving improved chance of lesion detection, better white and grey matter definition and can be processed after imaging into any anatomical plane including oblique. Furthermore this will facilitate volumetric measurements and to enable co-registration with other modalities or sequential MRI examinations [13, 38]. If this is not possible then a dorsal T1W sequence oriented along the long axis of the hippocampus is suggested. As indicated above there is an argument against routine paramagnetic

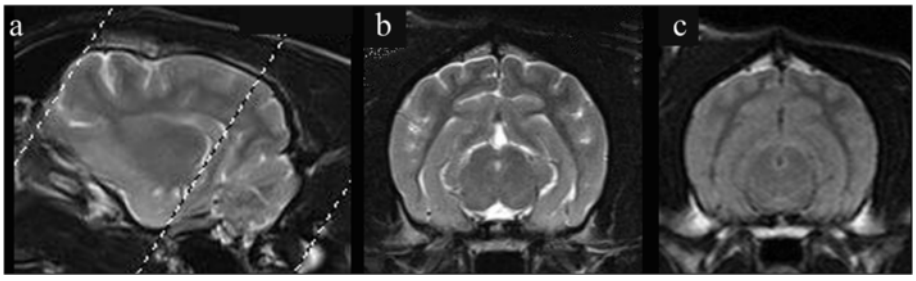

Fig. 9 Veterinary epilepsy-specific protocol for high field MRI. **a** parasagittal T2W image illustrating slice orientation. **b** Transverse T2W orientated parallel to the long axis of the hippocampus. **c** Transverse FLAIR orientated parallel to the long axis of the hippocampus. Images obtained in a 1.5 T MRI (Siemens Symphony, Erlangen, Germany)

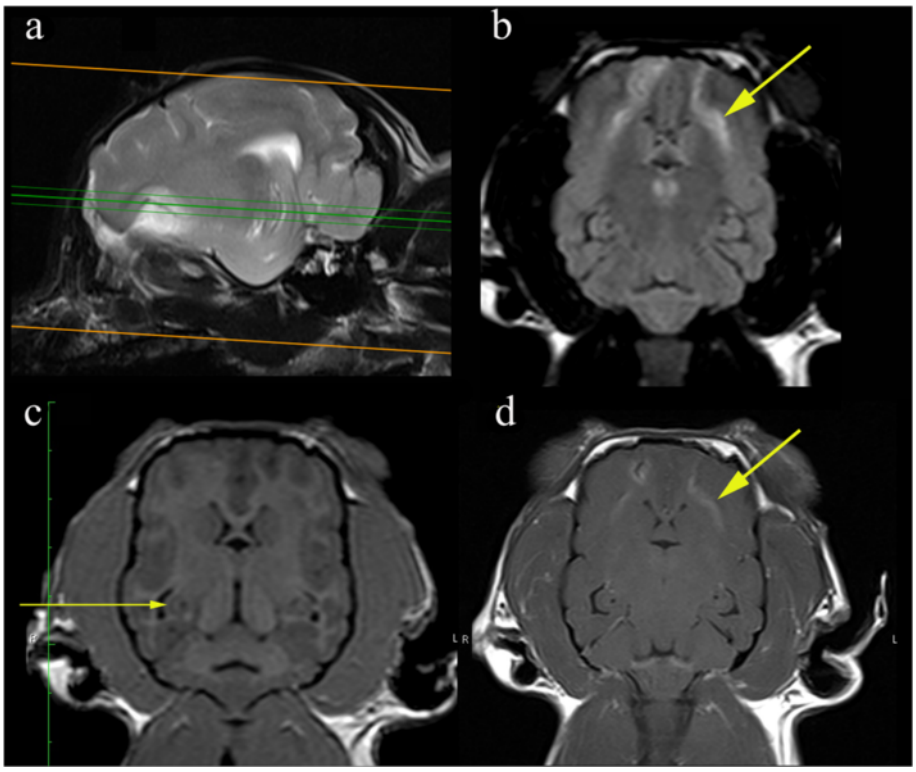

Fig. 10 Representative MRI from a 2.95 kg 5 year female entire Chihuahua dog that underwent a diagnostic investigation for cluster seizures. **a** Parasagittal image demonstrating the hippocampus and the planned imaging perpendicular to the long axis (**b**) Dorsal FLAIR images orientated perpendicular to long axis of the hippocampus demonstrating hyperintensity in the frontal lobe (*short arrow*). Although this protocol is optimised for detection of hippocampal lesions visualisation of other pathology is not compromised. **c** Dorsal T1W 3D images 1 mm slice thickness orientated perpendicular to long axis of the hippocampus. The scrolled structure of the hippocampus is clearly defined despite the small patient size. Furthermore the demarcation between white and grey matter can be appreciated (*long arrow*). **d** Post gadolinium T1W images are obtained in further investigation of the frontal lobe pathology. The patient was diagnosed subsequently with necrotising encephalitis. Images obtained in a 1.5 T MRI (Siemens Symphony, Erlangen, Germany)

contrast administration however it is acknowledged that many veterinary neurologists would feel a MRI study of an epileptic patient was incomplete without this therefore these sequences are an optional extra. However if pathology was detected in the unenhanced study, post-gadolinium sequences would be indicated (Fig. 10). Recommended slice thickness is 3 mm or less for high field machines and 4 mm or less for low field machines. Such a protocol would give 6–7 sequences for a high field machine and 6–7 sequences on a low field machine (not including optional paramagnetic contrast enhancement).

Additional files

Additional file 1: MRI Parameters for epilepsy-specific protocol on a 0.2 T machine.

Additional file 2: MRI Parameters for epilepsy-specific protocol on a 1.5 T machine.

Additional file 3: MRI Parameters for epilepsy-specific protocol on a 3 T machine.

Abbreviations

MRI: Magnetic resonance imaging; MR: Magnetic resonance; ILAE: International League Against Epilepsy; IVETF: International Veterinary Epilepsy Task Force; SNR: Signal-to-Noise-Ratio; TLE: Temporal lobe epilepsy; FLAIR: Fluid attenuated inversion recovery; GE: Gradient echo; T1WIR: T1 weighted inversion recovery; DWI: Diffusion weighted imaging; STIR: Short tau inversion recovery.

Competing interests

Following reimbursements, fees and funding have been received by the authors in the last three years and have been declared in the competing interest section. CR, RGF, HAV, KM, MP and JP have received fees for acting as a consultant for Boehringer Ingelheim (KM, MP: consultancy during development and approval of imepitoin; CR: pain consultancy; RGF, JP, HAV: consultancy pre and post launch of imepitoin). AT has been an advisor for Boehringer Ingelheim. SFMB, HAV and AT have been responsible principal investigator of several research studies concerning imepitoin financed by Boehringer Ingelheim. SFMB, HAV, JP, HP, MB, CR and AF received speaking fees from Boehringer Ingelheim. HP received consulting and speaking fees and funding for a collaborative project from Eisai Co. LTD. HAV received funding for a collaborative project from Desitin and Nestlé Purina Research. AF and LDR received reimbursements from Boehringer Ingelheim. LDR has received consulting and speaking fees from Vetoquinol. MP has received consultant fees for Aratana. The other authors declared that they have no competing interests.

Authors' contributions
CR chaired and SL co-chaired the neuroimaging working group (CR, SL, JJ, MM) and wrote the first draft of the consensus paper with the help of JJ and MM. All authors read, critiqued, commented and approved the final manuscript.

Authors' information
Chair of neuroimaging working group: Clare Rusbridge, Fitzpatrick Referrals, Halfway Lane, Eashing, Godalming, GU7 2QQ, Surrey, United Kingdom and School of Veterinary Medicine, Faculty of Health & Medical Sciences, University of Surrey, Guildford, GU2 7TE, Surrey, United Kingdom; ClareR@fitzpatrickreferrals.co.uk.
Co-chair of neuroimaging working group: Sam Long, University of Melbourne, 250 Princes Highway, Weibee 3015, Victoria, Australia; snlong@unimelb.edu.au.
Jelena Jovanovik and Marjorie Milne; Rest of the members of the neuroimaging working group (alphabetically listed).
Chair of IVETF: Holger A Volk, Department of Clinical Science and Services, Royal Veterinary College, Hatfield, Hertfordshire, UK; hvolk@rvc.ac.uk.
All other co-authors are members of IVETF, are listed alphabetically and have approved the consensus statements.

Acknowledgements
The authors are grateful to all owners of epileptic pets and veterinary colleagues who have inspired the group to create consensus statements. The authors wish to thank Penny Knowler for help in creating the images. The authors also would like to thank the research office for assessing the manuscript according to the Royal Veterinary College's code of good research practice (Authorisation Number – CCS_ 01024). This study was not financially supported by any organization or grant.

Author details
[1]Fitzpatrick Referrals, Halfway Lane, Eashing, Godalming GU7 2QQ, Surrey, UK. [2]School of Veterinary Medicine, Faculty of Health & Medical Sciences, University of Surrey, Guildford GU2 7TE, Surrey, UK. [3]University of Melbourne, 250 Princes Highway, Weibee 3015VIC, Australia. [4]Department of Veterinary and Clinical Sciences, Faculty of Health and Medical Sciences, University of Copenhagen, Frederiksberg C, Denmark. [5]Department of Small Animal Medicine and Clinical Biology, Faculty of Veterinary Medicine, Ghent University, Salisburylaan 133, Merelbeke 9820, Belgium. [6]Animal Health Trust, Lanwades Park, Kentford, Newmarket, CB8 7UU Suffolk, UK. [7]Fernside Veterinary Centre, 205 Shenley Road, Borehamwood SG9 0THHertfordshire, UK. [8]Centre for Clinical Veterinary Medicine, Ludwig-Maximilians-University, Veterinärstr. 13, 80539 Munich, Germany. [9]Section of Clinical & Comparative Neuropathology, Centre for Clinical Veterinary Medicine, Ludwig-Maximilians-University, Veterinärstr. 13, 80539 Munich, Germany. [10]Department of Clinical Sciences, College of Veterinary Medicine, North Carolina State University, 1052 William Moore Drive, Raleigh, NC 27607, USA. [11]University of Minnesota College of Veterinary Medicine, D426 Veterinary Medical Center, 1352 Boyd Avenue, St. Paul, MN 55108, USA. [12]Clinical Unit of Internal Medicine Small Animals, University of Veterinary Medicine, Veterinärplatz 1, 1210 Vienna, Austria. [13]Vet Extra Neurology, Broadleys Veterinary Hospital, Craig Leith Road, Stirling FK7 7LEStirlingshire, UK. [14]College of Veterinary Medicine, University of Georgia, 501 DW Brooks Drive, Athens, GA 30602, USA. [15]Chicago Veterinary Neurology and Neurosurgery, 3123 N. Clybourn Avenue, Chicago, IL 60618, USA. [16]Department of Pharmacology, Toxicology and Pharmacy, Ludwig-Maximillians-University, Königinstr. 16, 80539 Munich, Germany. [17]Department of Small Animal Medicine and Surgery, University of Veterinary Medicine Hannover, Bünteweg 9, 30559 Hannover, Germany. [18]Department of Clinical Science and Services, Royal Veterinary College, Hatfield AL9 7TAHertfordshire, UK.

Received: 5 June 2015 Accepted: 29 June 2015
Published online: 28 August 2015

References

1. Kearsley-Fleet L, O'Neill DG, Volk HA, Church DB, Brodbelt DC. Prevalence and risk factors for canine epilepsy of unknown origin in the UK. Vet Rec. 2013;172(13):338.
2. Heske L, Nodtvedt A, Jaderlund KH, Berendt M, Egenvall A. A cohort study of epilepsy among 665,000 insured dogs: incidence, mortality and survival after diagnosis. Vet J. 2014;202(3):471–6.
3. Shorvon SD. The etiologic classification of epilepsy. Epilepsia. 2011;52(6):1052–7.
4. Craven I, Griffiths PD, Hoggard N. Magnetic resonance imaging of epilepsy at 3 Tesla. Clin Radiol. 2011;66(3):278–86.
5. Kuzniecky R, Garcia JH, Faught E, Morawetz RB. Cortical dysplasia in temporal lobe epilepsy: magnetic resonance imaging correlations. Ann Neurol. 1991;29(3):293–8.
6. Raymond AA, Fish DR, Sisodiya SM, Alsanjari N, Stevens JM, Shorvon SD. Abnormalities of gyration, heterotopias, tuberous sclerosis, focal cortical dysplasia, microdysgenesis, dysembryoplastic neuroepithelial tumour and dysgenesis of the archicortex in epilepsy. Clinical, EEG and neuroimaging features in 100 adult patients. Brain. 1995;118(Pt 3):629–60.
7. Konar M, Lang J. Pros and cons of low-field magnetic resonance imaging in veterinary practice. Vet Radiol Ultrasound. 2011;52(1 Suppl 1):S5–14.
8. So EL, Lee RW. Epilepsy surgery in MRI-negative epilepsies. Curr Opin Neurol. 2014;27(2):206–12.
9. Vasta R, Caligiuri ME, Labate A, Cherubini A, Mumoli L, Ferlazzo E, et al. 3-T magnetic resonance imaging simultaneous automated multimodal approach improves detection of ambiguous visual hippocampal sclerosis. Eur J Neurol. 2015;22(4):725–e47.
10. Thompson DK, Ahmadzai ZM, Wood SJ, Inder TE, Warfield SK, Doyle LW, et al. Optimizing hippocampal segmentation in infants utilizing MRI post-acquisition processing. Neuroinformatics. 2012;10(2):173–80.
11. Ding YS, Chen BB, Glielmi C, Friedman K, Devinsky O. A pilot study in epilepsy patients using simultaneous PET/MR. Am J Nucl Med Mol Imaging. 2014;4(5):459–70.
12. Haneef Z, Chen DK. Functional neuro-imaging as a pre-surgical tool in epilepsy. Ann Indian Acad Neurol. 2014;17 Suppl 1:S56–64.
13. Shah AK, Mittal S. Evaluation of magnetic resonance imaging-negative drug-resistant epilepsy. Ann Indian Acad Neurol. 2014;17 Suppl 1:S80–8.
14. Smith PM, Talbot CE, Jeffery ND. Findings on low-field cranial MR images in epileptic dogs that lack interictal neurological deficits. Vet J. 2008;176(3):320–5.
15. Kuwabara T, Hasegawa D, Kobayashi M, Fujita M, Orima H. Clinical magnetic resonance volumetry of the hippocampus in 58 epileptic dogs. Vet Radiol Ultrasound. 2010;51(5):485–90.
16. Mizoguchi S, Hasegawa D, Kuwabara T, Hamamoto Y, Ogawa F, Fujiwara A, et al. Magnetic resonance volumetry of the hippocampus in familial spontaneous epileptic cats. Epilepsy Res. 2014;108(10):1940–4.
17. Schwartz M, Lamb CR, Brodbelt DC, Volk HA. Canine intracranial neoplasia: clinical risk factors for development of epileptic seizures. J Small Anim Pract. 2011;52(12):632–7.
18. Hecht S, Adams WH. MRI of brain disease in veterinary patients part 2: Acquired brain disorders. Vet Clin North Am Small Anim Pract. 2010;40(1):39–63.
19. Rosenow F, Luders H. Presurgical evaluation of epilepsy. Brain. 2001;124(Pt 9):1683–700.
20. Duncan JS. Neuroimaging methods to evaluate the etiology and consequences of epilepsy. Epilepsy Res. 2002;50(1–2):131–40.
21. Mellema LM, Koblik PD, Kortz GD, LeCouteur RA, Chechowitz MA, Dickinson PJ. Reversible magnetic resonance imaging abnormalities in dogs following seizures. Vet Radiol Ultrasound. 1999;40(6):588–95.
22. Viitmaa R, Cizinauskas S, Bergamasco LA, Kuusela E, Pascoe P, Teppo AM, et al. Magnetic resonance imaging findings in Finnish Spitz dogs with focal epilepsy. J Vet Intern Med. 2006;20(2):305–10.
23. Pakozdy A, Glantschnigg U, Leschnik M, Hechinger H, Moloney T, Lang B, et al. EEG-confirmed epileptic activity in a cat with VGKC-complex/LGI1 antibody-associated limbic encephalitis. Epileptic Disord. 2014;16(1):116–20.
24. Goncalves R, Anderson TJ, Innocent G, Penderis J. Effect of seizures on cerebrospinal fluid analysis in dogs with idiopathic epilepsy. Vet Rec. 2010;166(16):497–8.
25. Goldberg H, Weinstock A, Bergsland N, Dwyer MG, Farooq O, Sazgar M, et al. MRI segmentation analysis in temporal lobe and idiopathic generalized epilepsy. BMC Neurol. 2014;14:131.
26. Cendes F, Sakamoto AC, Spreafico R, Bingaman W, Becker AJ. Epilepsies associated with hippocampal sclerosis. Acta Neuropathol. 2014;128(1):21–37.
27. McIntosh AM, Kalnins RM, Mitchell LA, Fabinyi GC, Briellmann RS, Berkovic SF. Temporal lobectomy: long-term seizure outcome, late recurrence and risks for seizure recurrence. Brain. 2004;127(Pt 9):2018–30.
28. Fiest KM, Sajobi TT, Wiebe S. Epilepsy surgery and meaningful improvements in quality of life: results from a randomized controlled trial. Epilepsia. 2014;55(6):886–92.

29. Ebert U, Brandt C, Loscher W. Delayed sclerosis, neuroprotection, and limbic epileptogenesis after status epilepticus in the rat. Epilepsia. 2002;43 Suppl 5:86–95.
30. Klang A, Thaller D, Schmidt P, Kovacs GG, Halasz P, Pakozdy A. Bilateral Dentate Gyrus Structural Alterations in a Cat Associated With Hippocampal Sclerosis and Intraventricular Meningioma. Vet Pathol. 2015.
31. Wagner E, Rosati M, Molin J, Foitzik U, Wahle AM, Fischer A, et al. Hippocampal sclerosis in feline epilepsy. Brain Pathol. 2014;24(6):607–19.
32. Singh P, Kaur R, Saggar K, Singh G, Kaur A. Qualitative and quantitative hippocampal MRI assessments in intractable epilepsy. BioMed Res Int. 2013;2013:480524.
33. Milne ME, Anderson GA, Chow KE, O'Brien TJ, Moffat BA, Long SN. Description of technique and lower reference limit for magnetic resonance imaging of hippocampal volumetry in dogs. Am J Vet Res. 2013;74(2):224–31.
34. Farid N, Girard HM, Kemmotsu N, Smith ME, Magda SW, Lim WY, et al. Temporal lobe epilepsy: quantitative MR volumetry in detection of hippocampal atrophy. Radiology. 2012;264(2):542–50.
35. Gaillard WD, Chiron C, Cross JH, Harvey AS, Kuzniecky R, Hertz-Pannier L, et al. Guidelines for imaging infants and children with recent-onset epilepsy. Epilepsia. 2009;50(9):2147–53.
36. Ives EJ, Rousset N, Heliczer N, Herrtage ME, Vanhaesebrouck AE. Exclusion of a brain lesion: is intravenous contrast administration required after normal precontrast magnetic resonance imaging? J Vet Intern Med. 2014;28(2):522–8.
37. Thames RA, Robertson ID, Flegel T, Henke D, O'Brien DP, Coates JR, et al. Development of a morphometric magnetic resonance image parameter suitable for distinguishing between normal dogs and dogs with cerebellar atrophy. Vet Radiol Ultrasound. 2010;51(3):246–53.
38. Wellmer J, Quesada CM, Rothe L, Elger CE, Bien CG, Urbach H. Proposal for a magnetic resonance imaging protocol for the detection of epileptogenic lesions at early outpatient stages. Epilepsia. 2013;54(11):1977–87.
39. Von Oertzen J, Urbach H, Jungbluth S, Kurthen M, Reuber M, Fernandez G, et al. Standard magnetic resonance imaging is inadequate for patients with refractory focal epilepsy. J Neurol Neurosurg Psychiatry. 2002;73(6):643–7.
40. Knowler SP, McFadyen AK, Freeman C, Kent M, Platt SR, Kibar Z, et al. Quantitative analysis of Chiari-like malformation and syringomyelia in the griffon bruxellois dog. PLoS One. 2014;9(2), e88120.
41. Wellmer J, Parpaley Y, von Lehe M, Huppertz HJ. Integrating magnetic resonance imaging postprocessing results into neuronavigation for electrode implantation and resection of subtle focal cortical dysplasia in previously cryptogenic epilepsy. Neurosurgery. 2010;66(1):187–94. discussion 194–185.
42. Wheless JW, Castillo E, Maggio V, Kim HL, Breier JI, Simos PG, et al. Magnetoencephalography (MEG) and magnetic source imaging (MSI). Neurologist. 2004;10(3):138–53.
43. Jantti V, Baer G, Yli-Hankala A, Hamalainen M, Hari R. MEG burst suppression in an anaesthetized dog. Acta Anaesthesiol Scand. 1995;39(1):126–8.
44. Szmuk P, Kee S, Pivalizza EG, Warters RD, Abramson DC, Ezri T. Anaesthesia for magnetoencephalography in children with intractable seizures. Paediatr Anaesth. 2003;13(9):811–7.
45. Velmurugan J, Sinha S, Satishchandra P. Magnetoencephalography recording and analysis. Ann Indian Acad Neurol. 2014;17 Suppl 1:S113–9.
46. Viitmaa R, Haaparanta-Solin M, Snellman M, Cizinauskas S, Orro T, Kuusela E, et al. Cerebral glucose utilization measured with high resolution positron emission tomography in epileptic Finnish Spitz dogs and healthy dogs. Vet Radiol Ultrasound. 2014;55(4):453–61.
47. Jokinen TS, Haaparanta-Solin M, Viitmaa R, Gronroos TJ, Johansson J, Bergamasco L, et al. FDG-PET in healthy and epileptic Lagotto Romagnolo dogs and changes in brain glucose uptake with age. Vet Radiol Ultrasound. 2014;55(3):331–41.
48. De Ciantis A, Lemieux L. Localisation of epileptic foci using novel imaging modalities. Curr Opin Neurol. 2013;26(4):368–73.
49. von Oertzen TJ, Mormann F, Urbach H, Reichmann K, Koenig R, Clusmann H, et al. Prospective use of subtraction ictal SPECT coregistered to MRI (SISCOM) in presurgical evaluation of epilepsy. Epilepsia. 2011;52(12):2239–48.
50. Martle V, Peremans K, Audenaert K, Vermeire S, Bhatti S, Gielen I, et al. Regional brain perfusion in epileptic dogs evaluated by technetium-99 m-ethyl cysteinate dimer SPECT. Vet Radiol Ultrasound. 2009;50(6):655–9.
51. Focke NK, Diederich C, Helms G, Nitsche MA, Lerche H, Paulus W. Idiopathic-generalized epilepsy shows profound white matter diffusion-tensor imaging alterations. Hum Brain Mapp. 2014;35(7):3332–42.
52. Anaya Garcia MS, Hernandez Anaya JS, Marrufo Melendez O, Velazquez Ramirez JL, Palacios Aguiar R. In Vivo study of cerebral white matter in the dog using diffusion tensor tractography. Vet Radiol Ultrasound. 2015;56(2):188–95.
53. Wei PT, Leong D, Calabrese E, White L, Pierce T, Platt S, et al. Diffusion tensor imaging of neural tissue organization: correlations between radiologic and histologic parameters. Neuroradiol J. 2013;26(5):501–10.
54. Jacqmot O, Van Thielen B, Fierens Y, Hammond M, Willekens I, Van Schuerbeek P, et al. Diffusion tensor imaging of white matter tracts in the dog brain. Anat Rec (Hoboken). 2013;296(2):340–9.
55. Ogata N, Gillis TE, Liu X, Cunningham SM, Lowen SB, Adams BL, et al. Brain structural abnormalities in Doberman pinschers with canine compulsive disorder. Prog Neuropsychopharmacol Biol Psychiatry. 2013;45:1–6.
56. Hall AJ, Brown TA, Grahn JA, Gati JS, Nixon PL, Hughes SM, et al. There's more than one way to scan a cat: imaging cat auditory cortex with high-field fMRI using continuous or sparse sampling. J Neurosci Methods. 2014;224:96–106.
57. Berns GS, Brooks AM, Spivak M. Functional MRI in awake unrestrained dogs. PLoS One. 2012;7(5), e38027.
58. Cook PF, Spivak M, Berns GS. One pair of hands is not like another: caudate BOLD response in dogs depends on signal source and canine temperament. Peer J. 2014;2, e596.
59. Berns GS, Brooks AM, Spivak M. Scent of the familiar: an fMRI study of canine brain responses to familiar and unfamiliar human and dog odors. Behav Processes. 2015;110:37–46.
60. Gygax L, Reefmann N, Pilheden T, Scholkmann F, Keeling L. Dog behavior but not frontal brain reaction changes in repeated positive interactions with a human: a non-invasive pilot study using functional near-infrared spectroscopy (fNIRS). Behav Brain Res. 2014;281C:172–6.
61. Hammen T, Kerling F, Schwarz M, Stadlbauer A, Ganslandt O, Keck B, et al. Identifying the affected hemisphere by (1)H-MR spectroscopy in patients with temporal lobe epilepsy and no pathological findings in high resolution MRI. Eur J Neurol. 2006;13(5):482–90.
62. Guye M, Ranjeva JP, Le Fur Y, Bartolomei F, Confort-Gouny S, Regis J, et al. 1H-MRS imaging in intractable frontal lobe epilepsies characterized by depth electrode recording. Neuroimage. 2005;26(4):1174–83.
63. Ono K, Kitagawa M, Ito D, Tanaka N, Watari T. Regional variations and age-related changes detected with magnetic resonance spectroscopy in the brain of healthy dogs. Am J Vet Res. 2014;75(2):179–86.
64. Neppl R, Nguyen CM, Bowen W, Al-Saadi T, Pallagi J, Morris G, et al. In vivo detection of postictal perturbations of cerebral metabolism by use of proton MR spectroscopy: preliminary results in a canine model of prolonged generalized seizures. AJNR Am J Neuroradiol. 2001;22(10):1933–43.
65. Stadler KL, Ober CP, Feeney DA, Jessen CR. Multivoxel proton magnetic resonance spectroscopy of inflammatory and neoplastic lesions of the canine brain at 3.0 T. Am J Vet Res. 2014;75(11):982–9.
66. Deibler AR, Pollock JM, Kraft RA, Tan H, Burdette JH, Maldjian JA. Arterial spin-labeling in routine clinical practice, part 1: technique and artifacts. AJNR Am J Neuroradiol. 2008;29(7):1228–34.
67. Lim YM, Cho YW, Shamim S, Solomon J, Birn R, Luh WM, et al. Usefulness of pulsed arterial spin labeling MR imaging in mesial temporal lobe epilepsy. Epilepsy Res. 2008;82(2–3):183–9.
68. Wolf RL, Alsop DC, Levy-Reis I, Meyer PT, Maldjian JA, Gonzalez-Atavales J, et al. Detection of mesial temporal lobe hypoperfusion in patients with temporal lobe epilepsy by use of arterial spin labeled perfusion MR imaging. AJNR Am J Neuroradiol. 2001;22(7):1334–41.
69. Casey KM, Bollen AW, Winger KM, Vernau KM, Dickinson PJ, Higgins RJ, et al. Bilaterally symmetric focal cortical dysplasia in a golden retriever dog. J Comp Pathol. 2014;151(4):375–9.
70. Abramson CJ, Platt SR, Jakobs C, Verhoeven NM, Dennis R, Garosi L, et al. L-2-Hydroxyglutaric aciduria in Staffordshire Bull Terriers. J Vet Intern Med. 2003;17(4):551–6.
71. Bathen-Noethen A, Stein VM, Puff C, Baumgaertner W, Tipold A. Magnetic resonance imaging findings in acute canine distemper virus infection. J Small Anim Pract. 2008;49(9):460–7.
72. Laothamatas J, Wacharapluesadee S, Lumlertdacha B, Ampawong S, Tepsumethanon V, Shuangshoti S, et al. Furious and paralytic rabies of canine origin: neuroimaging with virological and cytokine studies. J Neurovirol. 2008;14(2):119–29.
73. Torisu S, Washizu M, Hasegawa D, Orima H. Brain magnetic resonance imaging characteristics in dogs and cats with congenital portosystemic shunts. Vet Radiol Ultrasound. 2005;46(6):447–51.
74. Garosi LS, Dennis R, Platt SR, Corletto F, de Lahunta A, Jakobs C. Thiamine deficiency in a dog: clinical, clinicopathologic, and magnetic resonance imaging findings. J Vet Intern Med. 2003;17(5):719–23.

75. Guadalupe T, Zwiers MP, Teumer A, Wittfeld K, Vasquez AA, Hoogman M, et al. Measurement and genetics of human subcortical and hippocampal asymmetries in large datasets. Hum Brain Mapp. 2014;35(7):3277–89.
76. Fernandes MJ, Carneiro JE, Amorim RP, Araujo MG, Nehlig A. Neuroprotective agents and modulation of temporal lobe epilepsy. Front Biosci (Elite Ed). 2015;7:90–106.

Matiasek et al. BMC Veterinary Research (2015) 11:216
DOI 10.1186/s12917-015-0467-9

BMC Veterinary Research

CORRESPONDENCE Open Access

International veterinary epilepsy task force recommendations for systematic sampling and processing of brains from epileptic dogs and cats

Kaspar Matiasek[1*], Martí Pumarola i Batlle[2], Marco Rosati[1], Francisco Fernández-Flores[2], Andrea Fischer[3], Eva Wagner[1], Mette Berendt[3], Sofie F. M. Bhatti[4], Luisa De Risio[5], Robyn G. Farquhar[6], Sam Long[7], Karen Muñana[8], Edward E. Patterson[9], Akos Pakozdy[10], Jacques Penderis[11], Simon Platt[12], Michael Podell[13], Heidrun Potschka[14], Clare Rusbridge[15,16], Veronika M. Stein[17], Andrea Tipold[17] and Holger A. Volk[18]

Abstract

Traditionally, histological investigations of the epileptic brain are required to identify epileptogenic brain lesions, to evaluate the impact of seizure activity, to search for mechanisms of drug-resistance and to look for comorbidities. For many instances, however, neuropathological studies fail to add substantial data on patients with complete clinical work-up. This may be due to sparse training in epilepsy pathology and or due to lack of neuropathological guidelines for companion animals.

The protocols introduced herein shall facilitate systematic sampling and processing of epileptic brains and therefore increase the efficacy, reliability and reproducibility of morphological studies in animals suffering from seizures.

Brain dissection protocols of two neuropathological centres with research focus in epilepsy have been optimised with regards to their diagnostic yield and accuracy, their practicability and their feasibility concerning clinical research requirements.

The recommended guidelines allow for easy, standardised and ubiquitous collection of brain regions, relevant for seizure generation. Tissues harvested the prescribed way will increase the diagnostic efficacy and provide reliable material for scientific investigations.

Keywords: Canine, Feline, Seizures, Hippocampus, Ictogenic, Epileptogenic, Processing, Neuropathology

Background

Paroxysmal seizure-like events are one of the most common causes of admission to neurological services in small animal practice. With a prevalence ranging between 0.5 % and 5.0 % amongst a general non-referral population of dogs, with higher number of dogs being affected in specific breeds [1–4], epilepsy is a major health issue that severely affects the performance, cognition and behaviour of pets with recurrent seizures and thereby the quality of life of the animals and owners, the owners' economy as well as their range of social activities [5–7].

Hence, the clinical and socioeconomical impact of epilepsy, more than its semiological and pathomechanistic resemblance to human epilepsy has been a trigger of clinical research in that field ever since. However, the most recent advances of imaging, video electroencephalography and telemetry, pharmacotherapy and neurogenetics kicked-off a new wave of enthusiasm in epileptology amongst veterinary neurologists [1, 8–13].

With some exceptions [14, 15], the pace of clinical achievements in diagnostics, classification and management of epilepsy patients in veterinary practice has not been paralleled by comparable insights into epilepsy-associated tissue changes and, in particular, those underlying drug resistance.

Brain tissue studies in clinically affected animals often are anecdotal and rarely comprise investigations for causative changes and biomarkers. If tissue studies represent the mainstay of rodent models of epilepsy, research in

* Correspondence: kaspar.matiasek@neuropathologie.de
[1]Section of Clinical and Comparative Neuropathology, Centre for Clinical Veterinary Medicine, Ludwig-Maximilians-University, Veterinärstr. 13, 80539 Munich, Germany
Full list of author information is available at the end of the article

Table 1 Skill level thresholds in brain pathology with special reference to epilepsy pathology

Level	Experience	Anatomical baseline skills	Semiological baseline skills & clinical neurolocalisation	Neuropathology baseline skills	Achievement
0	None: *1st year student (veterinary & human medicine, neurobiology)* *Untrained technician*	none	none	none	n.a.
I	Basic: *2nd year student,* *Trained technician*	External: Recognition of cerebrum, cerebellum, brain stem and frontal/parietal/temporal/ occipital regions. Internal: Distinction of white vs grey matter.	Distinction of clinical forebrain, cerebellar and brainstem signs.	Macro: Spotting malacia, gross malformations, mass lesions, haemorrhage. Micro: None to basic neurohistology.	Easy, Single training, Within weeks
II	Advanced: *Pathology & neurology residents* *PhD students* *General pathologist*	Recognition of brain lobes, major brain regions (e.g. hippocampus thalamus, basal nuclei), tracts and of regions containing expected nuclei.	General: Specific neurolocalisation based on clinical signs. Epilepsy-specific: Distinction and localisation of seizure types.	General: Recognition of basic malformations, mass effects, haemorrhage, infiltrative lesions and basic neurodegeneration. Epilepsy-specific: Histological recognition of stereotypic seizure-associated changes.	Demanding, Repeated training, Within months
III	Expert: A. broad-based *Neurology-trained pathologist* *Pathology-trained neurologist* B. topic-based *Neuroscientist*	Detailed knowledge of the species-specific topographic and functional anatomy of the brain including gyri and folia organisation, distinct nuclei, cortical areas and their patterning as well as fibre connections, neurotransmitter maps, cell markers and the vascularity.	Capable of subregional and nuclear neuro-localisation.	Recognition and classification of the above named entities, plus of microanomalies, distinct cytopathologies, brain specific disease markers and neurodegenerative disorders. Knowledge and experience in comparative neuropathology including human disorders.	Demanding, Cont´ training, Within years

Table 2 Important epilepsy-related brain zones and definitions (adapted from [59])

Epileptogenic zone	Region of cortex that can generate epileptic seizures and removal or disconnection of which should lead to seizure freedom
Epileptogenic lesion	Distinct brain lesion, capable of generating and sustaining epileptic seizures
Excitable zone	Region susceptible to excitation spreading from a primary focus
Irritative zone	Region of cortex that generates interictal epileptiform discharges on EEG
Seizure/ictal onset zone	Region where a clinical seizure originates
Symptomatogenic zone	Region of cortex that generates the initial seizure presentation (signs)
Functional deficit zone	Region of cortex that in the interictal period is clinically and/or electrophysiologically abnormal
Ictal/postictal changes	Nonspecific tissue changes due to local excitotoxicity

veterinary medicine appears to focus mainly on advancing the genetic characterisation and less so on brain pathology and anatomical changes.

One of the drawbacks that impacts negatively on the neuropathological contribution to advancing the field of canine and feline epilepsy is the lack of consensus guidelines for brain sampling, tissue processing, candidate areas, stains and algorithms. Instead, most studies employ empirical and inconsistent sampling modes and algorithms that preclude external reproducibility and therefore limit the scientific impact of the data obtained.

A standardised evaluation of brains from patients with epilepsy should provide the basis for an informed dialogue between clinicians and pathologists, and therefore requires a certain level of confidence and expertise in that specific field (Table 1).

As we learned from the dichotomous evolution of epilepsy pathology in humans, the advancement of surgical therapy specifically promoted research and training in focal epilepsies and produced a diaspora of neuropathologists with exceptional skills in reading biopsies from lobectomy. Some of these diagnosticians influentially contribute to the activities of the International League Against Epilepsy (ILAE) and proved successful in implementing tissue studies to the forefront of epilepsy research [16–21].

In stark contrast, the interest in extra-focal pathologies appears generally limited and attempts to foster retrospective post-mortem analyses in human epileptics are sparse unless driven by forensic aspects [22, 23]. Naturally, in veterinary medicine pathologists most commonly face a post-mortem setting with incomplete data sets but with the fortune of the entire brain being available for examination. Due to paucity of centres with specific expertise in epilepsy pathology, however, a dedicated curriculum is difficult to acquire and experts are not easily at hand for aiding processing and evaluation of clinical cases in loco.

This limitation holds true for human autopsies as well. Most requested post-mortem examinations are conducted either by the coroner or hospital pathologists [23]. There is a general perception that neuropathologists do not necessarily have to be involved into examination of epilepsy cases until histological slides are available [23, 24]. This view bears the risk of missing essential information on the brain as prescriptions for sampling roughly propose guidance by macroscopic changes, which requires a keen eye, or from localising clinical, electrophysiological and/or imaging data, which requires special training [25].

Sending-off animal carcasses or unfixed post-mortem tissues for remote examination by specialists is impractical, expensive and, hence, not feasible. Consequently, a meaningful progress in veterinary epilepsy pathology regarding diagnosis, classification and research can be achieved only if procedures and protocols are broadly available and manageable in a para-clinical setting.

Detailed and standardised descriptions are required in particular for immediate procedures, such as harvesting of the brain, sampling from the fresh brain and fixation that can be carried out by training level 0 personnel (Table 1) but in the same vein may pose essential limits to the adjacent work-up, diagnostic yield and accuracy.

Fixed tissues do not underlie the same time pressures. Hence, investigators may acquire the neuro-anatomical knowledge necessary to sample putatively epileptogenic areas (for definition see Table 2) and those likely to carry secondary changes [23, 24] during the fixation period.

Since “the obvious” poses the biggest obstacle to sustaining the diagnostic effort, data on the seizuring brain

Table 3 Neuropathological sampling schemes

Type	Determinant	Subtype	Reproducibility	Required skill levels
1	Evidence	A: structural (MRI, gross pathology)	Good	0-I
		B: functional/symptomatogenic	Good to fair	II-III
2	Systematic	A: disease-dependent, e.g. epilepsy	Good	II
		B: disease-independent	Good	I
3	Random	A: systematic (random sampling of distinct regions)	Fair to poor	I
		B: non-systematic	Poor	0

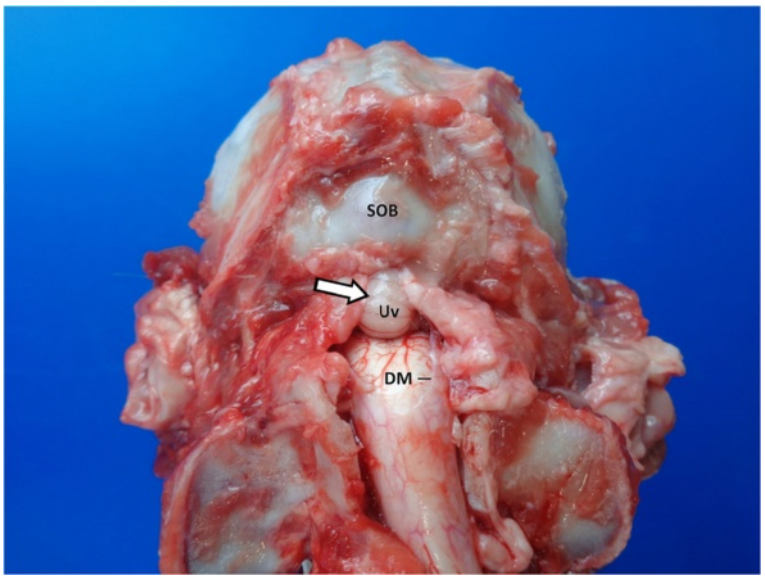

Fig. 1 Caudodorsal view of the ventroflexed craniospinal junction in a dog after removal of paraxial muscles and laminectomie. Note the coning of the cerebellum in the foramen magnum. DM: Dura mater; SOB: supraoccipital bone; Uv: Uvula

are poor in particular for patients with extensive structural brain lesions identified on magnetic resonance imaging (MRI), brain surgery or autopsy. It further needs to be emphasised that the trigger of epilepsy (epileptogenic lesion) and the perilesional brain tissue may not necessarily segregate or be contiguous with the perpetuating epileptogenic zone which becomes evident through incomplete seizure control after lesionectomy [1]. Restriction of the neuropathological examination to these areas, therefore, may not offer an insight into the pathobiology of an epileptic syndrome or the mechanisms of drug resistance.

Even with obvious structural lesions the diagnostician should follow the same procedures and sample the same areas as one would in cases presented with reactive epileptic seizures and idiopathic or genetic epilepsy.

Not to miss relevant information on the nature of seizures, their possible causes and consequences, and on related or unrelated comorbidities, there are three sampling schemes to consider: (1) evidence-based sampling, (2) systematic sampling and, for large brain volumes, (3) random sampling (Table 3).

Scheme 1 comprises two different confidence levels. For obvious reasons, sampling lesions identified via MRI or on gross examination (type 1A) rarely poses a problem. In contrast, symptomatogenic approaches to brain sampling (type 1B) very much rely on both the accuracy of the neurological history (see below) and the clinical understanding of the pathologist. Inexperienced investigators go easily with scheme 1A and are inclined to sample brain regions at random (type 3A,B), regardless.

Apart from the above mentioned claim for evidence-based sampling, autopsy guidelines for epilepsy by The Royal College of Pathologists advertise simple and reproducible systematic sampling from cingulate gyrus, hippocampus, parahippocampal gyrus, middle frontal gyrus,

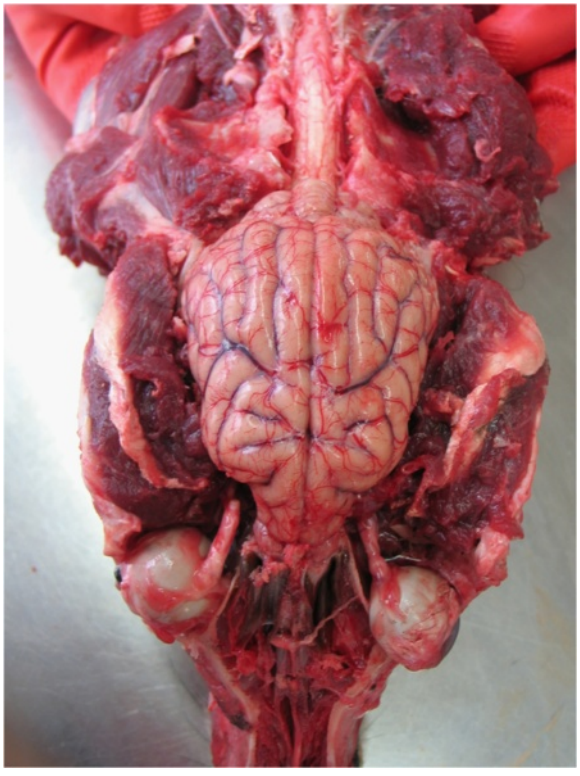

Fig. 2 Canine brain exposed via extensive craniectomy

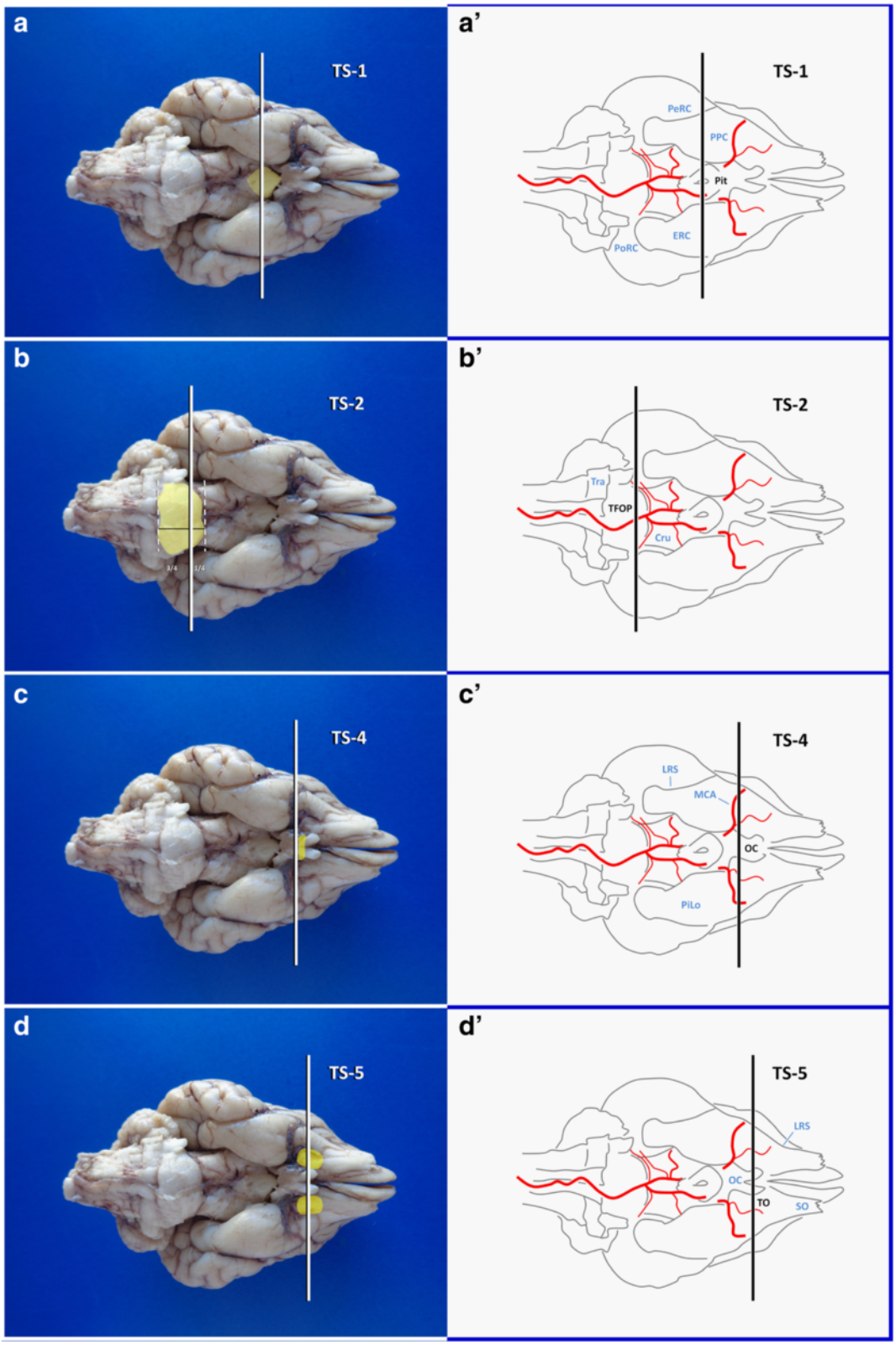

Fig. 3 Landmarks of the ventral brain surface in a dog (Fixed brain **a**, **b**, **c**, **d**; schematic illustration **a´**, **b´**, **c´**, **d´**). Cru: crura cerebri; ERC: entorhinal cortex; LRS: lateral rhinal sulcus; MCA: middle cerebral artery; OC: optic chiasm; PeRC: perirhinal cortex; Pit: pituitary stalk; PiLo: piriform lobe; PoRC: postrhinal cortex; PPC: prepiriform cortex; SO: stria olfactoria; TFOP: transverse fibres of pons; TO: tuberculum olfactorium; Tra: trapezoid body; TS: transverse section

superior and middle temporal gyri, caudate nucleus, putamen, globus pallidus, cerebellar vermis and cerebellar hemispheres [24]. This selection is based on protocols available for assessment of human neurodegenerative disorders [26] and it is expected to facilitate identification of (1) structural causes of epilepsy; (2) epilepsy-induced changes; and (3) lethal consequences of seizures, such as in Sudden Unexpected Death in Epilepsy (SUDEP) [23]. Likewise, it has been the consensus of the International Veterinary Epilepsy Task Force (IVETF) to encourage and facilitate systematic sampling of epilepsy brains in dogs and cats in order to enable standardised diagnostic approaches and to obtain tissues adequately for epilepsy research. The following protocol thus is driven by both diagnostic motives and neurobiological considerations. We hope, in particular, to facilitate studies on the involvement and role of specific brain regions for seizure propagation and semiology in dogs and cats since our current understanding derives from suspected analogies to human and rodent seizures.

Determination of a structural brain abnormality in epilepsy patients to be considered epileptogenic is based on its type, neuroanatomical localisation and seizure phenomenology. The term "epileptogenic" recently has been restricted to a set of distinctive pathologies (e.g. dysembryoplastic neuroepithelial tumours, focal cortical dysplasia, cavernoma and hippocampal sclerosis). Other pathologies more accurately are referred to as "typically epileptogenic" [2].

The fact that lesionectomy does not necessarily abolish seizures [1] should increase the awareness that the principal lesion may just elicit a process in the excitable cortex that may become an epileptogenic zone or focus itself. The area where discharges convert into clinical seizures is called seizure-onset or ictal-onset zone and may not be contiguous to the symptomatogenic zone, excitation of which determines the clinical type of seizures (Table 2).

In brain surgery of focal epilepsy, the goal is to remove the epileptogenic zone, localised by electroencephalography or functional MRI. The semiology and course,

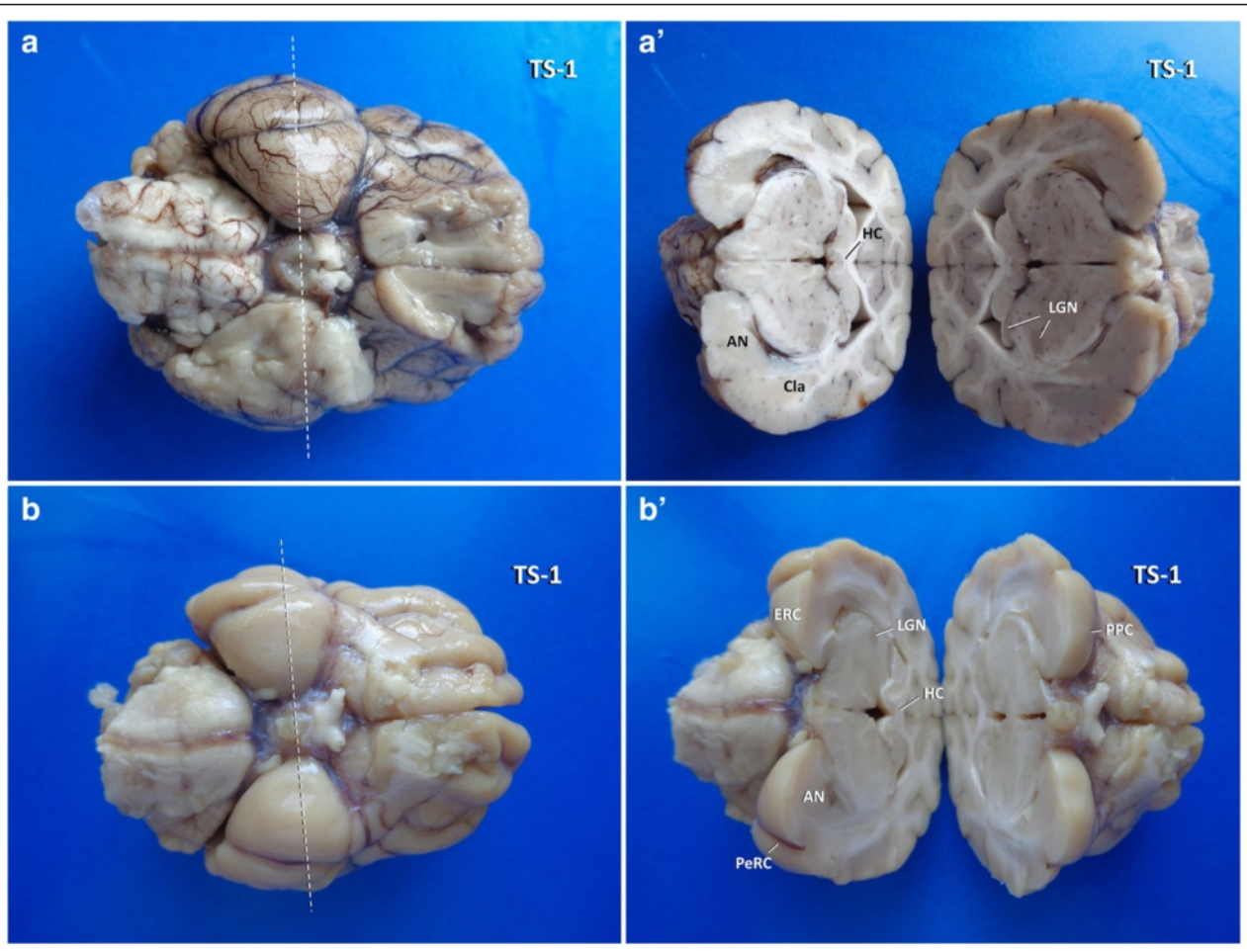

Fig. 4 Insights into the three-dimensional orientation of the hippocampus after TS-1 (dashed line) in dog (**a**, **a´**) and cat (**b**, **b'**). AN: amygdaloid nucleus; Cla: claustrum; ERC: entorhinal cortex; HC: hippocampal commissure; LGN: lateral geniculate nucleus; PeRC: perirhinal cortex; PPC: pre-piriforme cortex

however, may be influenced by brain regions that act as seizure modifiers (e.g. claustrum) or propagators (e.g. hippocampus). Those regions should not be left unseen, even in straightforward focal structural epilepsy, to enable retrospective pathomechanistic and correlative studies. If the primary or any mirror epileptic focus cannot be excised completely, drug therapy should be continued [1].

With all understanding of required speed and efficacy of post-mortem examination as well as of ubiquitous financial constraints that affect the number of slides which can be processed, complete sampling and tissue banking constitutes the base of good research practice and of future scientific encounters that are expected to impact on the management of epileptic patients.

Short overview of principal candidate areas

Epilepsy sampling should be guided by the acknowledgment of possible mimicry and overlap with compulsive and behavioural disorders, sleep disorders and movement disorders [3, 4]. Sampling therefore extends from the ascending reticular activating system (ARAS), via thalamocortical areas to extrapyramidal motor centres of the forebrain [5]. Little is known yet about the involvement of certain brain regions in distinct forms of canine and feline epilepsy, apart from orofacial seizures in cats [6]. Broad sampling schemes are necessary at this stage to acquire the respective data.

In most species, postictal and epileptogenic changes predominantly involve grey matter of the forebrain [5] and also Purkinje cells laden with glutamatergic synapses [7, 8]. Neurochemistry and metabolic demands determine the irritability and hence the intrinsic vulnerability to excitotoxicity. Minor local changes may translate into convulsive activity and from there spread to adjacent or remotely connected excitable areas via extra-synaptic migratory excitation or neurotransmission. Certain areas such as frontal cortex and temporal lobe are particularly susceptible to generating and perpetuating seizures and therefore should comprise the main regions of interest when sampling brain tissue [9, 10].

Amongst irritable areas, the hippocampus resembles the brain structure most commonly involved in seizures, either primarily or secondarily. Thereby, its involvement

Table 4 Macroscopic examination of the unfixed brain

Unfixed brain—checklist		
UB-1	Changes to Cerebrum-cerebellum-brainstem size and volume ratios	
UB-2	Abnormalities of shape and patterning—tissue	
	a. lobes	
	b. lobules	
	c. gyri	
	d. folia	
UB-3	Abnormalities of shape and patterning—spaces (FISS)	
	a. fissures	
	b. sulci	
	c. interfolia spaces	
UB-4	Meningeal features	
	1. Dura mater	a. thickness/appearance
		b. venous sinuses
	2. Leptomeninx	a. transparency & thickness
		b. meningeal blood vessels
		1. filling
		2. pattern & branching
UB-5	Supracollicular features	
	1. Tentorium cerebelli	
	a. position/impingement	
	b. thickness	
	2. Perimesencephalic cisterns/rostrocerebellar space	
	3. Lamina quadrigemina	
UB-6	Cranial nerve roots	
	a. appearance	
	b. course	

Table 5 Macroscopic examination of the trimmed brain

Trimmed brain—checklist	
TB-1	FISS base
	a. depth
	b. width
	c. course
TB-2	Cortical ribbon—subcortical white matter
	a. thickness
	b. symmetry
	c. delineation
	d. white-grey ratio
TB-3	Large white matter tracts, capsules and interposed nuclei
	a. volume & ratios
	b. symmetry
	c. delineation
	d. misplaced grey matter
TB-4	Periventricular features
	a. subependyma/glia limitans interna
	b. periventricular white matter
TB-5	Ventricular features
	a. ventricular size, symmetry, contents and communications
	b. ependymal lining and vela
	c. circumventricular organs
	d. choroid plexuses

goes with essential regional, functional and interspecies differences. In kindled and pilocarpine-treated rats, for example, the ventral hippocampus presents with the earliest discharges and most extensive neuronal losses, amongst the septotemporal hippocampal axis [11, 12]. Likewise the temporoventral body (TVB), is the key area for orofacial seizures amongst temporal lobe epilepsy in cats; it is the main target of limbic encephalitis in humans and cats and it is more susceptible to hippocampal sclerosis (HS) than the dorsal parts of hippocampus [12–15].

HS is defined as pyramidal cell loss with gliosis and resembles one of the most important acquired epilepsy-promoting changes in humans [16]. It can result from necrotising and non-necrotising hippocampal lesions and thus should not be used synonymously with hippocampal necrosis. HS is subclassified according to the affected cornu ammonis segments that can be evaluated properly only in perpendicular sections of the hippocampus [17]. Currently, the high prevalence of recurrent feline epilepsy suggests a role in disease propagation in this species [13]. Its occurrence in epileptic dogs awaits further elucidation. Thus, suspected HS from hippocampal scans [18] and volumetry require to be substantiated by tissue studies [19]. Other forms of epilepsy-associated sclerosis occur in entorhinal cortex, amygdala and the subpial molecular layer [20, 21]. Their occurrence and relevance in feline and canine epilepsy remains to be clarified.

It should be noted that coexistence of HS with other epileptogenic lesions (usually outside of the hippocampus) is called “dual pathology” whereas “double pathology” refers to two epileptogenic principal lesions, other than HS [17]. If the latter occurs together with HS, this situation is referred to as “triple pathology” [22].

Depending on the cause of epilepsy and animal species, the flexure and dorsomedial tip of the hippocampal tail may contribute to the epileptic syndrome. It is important to stick to the perpendicular section throughout the longitudinal (septotemporal) axis of the hippocampus to allow for proper evaluation of the cornu ammonis (CA) segments and the dentate gyrus and for comparison in between the different hippocampal localisations. The same holds true for the subiculum and parahippocampal gyrus that may clarify whether HS is associated with reactive encephalopathy such as in hypoglycaemia [23].

Even though our insights on this topic are incomplete, temporal lobe involvement in canine epilepsy appears to differ greatly from cats [24] and predominantly affects the piriform cortex and amygdala, just rostral to the hippocampal head. Hemispheric transverse sections of the temporal lobe also allow for evaluation of entorhinal, perirhinal and postrhinal cortices, insular cortex and the claustrum, none of which has been systematically investigated in seizuring animals yet.

Table 6 Brain lesion types

Pathological lesion category	Type & underlying pathology	
PL-1: Discolouration	Pallor	a. oedema
		b. gliosis, sclerosis, fibrosis
		c. coagulation necrosis
		d. mineralisation
		e. infiltrative disease
	Greyish	a. oedema
		b. colliquative necrosis
		c. infiltrative disease
	Yellow	a. pus
		b. caseous necrosis
		c. nuclear jaundice
	Brown	a. lipofuscinergic
		b. siderosis
	Black	a. melanin
		b. blood
	Red	blood
	Pink	carbon monoxide
PL-2: Loss & gain of tissue	Architecture sparing: disproportion & asymmetry	
	1. Gain	a. regional oedema/ inflammation
		b. malformation (e.g. macrogyria)
		c. harmatoma
		d. low grade glioma
	2. Loss	a. atrophy/ neurodegeneration
		b. hypoplasia
	With architectural changes	
	1. Gain	a. oedema
		b. infiltrative disease
	2. Loss	a. atrophy
		b. degeneration/necrosis
	3. Topographical	a. misplacement (e.g. heterotopia)
		b. disorganisation (dysplasia)
PL-3: Textural change	Induration	a. glial/sclerosis
		b. neoplasia
		c. fibrosis
		d. mineralisation
	Softening	a. oedema
		b. collequative necrosis
		c. inflammation
		d. neoplasia

Table 7 Systematic trimming of the occipitotemporal region (Block A)

Cuts	Time	View/specimen	Landmarks and cutting levels	Orientation of sections	Aim/harvest	Difficulty
TS-1	0 min	Ventral view of whole brain	Transverse line through centre of pituitary stalk and the broadest laterolateral extension of the piriform lobe	*2D knife axis*: laterolateral.	Standard transverse section of the diencephalon.	Easy
				Plane: transverse.	Exposes the amygdaloid nucleus, thalamus and often lateral geniculate nucleus, piriform cortex.	
				Blade movement: ventrodorsal.	Allows for localisation of rostral tip of hippocampal tail and head/TVB.	
TS-2	2 min	Ventral view of brainstem	Transverse line 2 mm caudal to the rostral border of TFOP	*2D knife axis*: ventrodorsal.	Standard transverse section of the midbrain.	Easy
				Plane: transverse.	Prerequisite for TVB section	
				Blade movement: laterolateral		
TILT-1	4 min	Caudal view of occipital lobe and rostral mesencephalic stump	Horizontal line just dorsal to transverse fibres of the pons	*2D knife axis*: laterolateral.	Epilepsy-specific sections of TVB.	Easy but requires some practice
				Plane: oblique, transverse with rostral inclination so that the blade cuts the caudal temporal lobe flexure at right angle.	Also shows prepiriform cortex, peri/entorhinal cortex.	
				Blade movement: from caudoventral to rostodorsal.		
HOR-1	7 min	Same as before	Horizontal line through the upper mesencephalic aquaeduct	*2D knife axis*: laterolateral.	Epilepsy-specific section.	Easy
				Plane: horizontal.	Exposes CV of both hippocampi, parahippocampal gyri, postrhinal and caudal perirhinal cortex as well as lateral geniculate nucleus.	
				Blade movement: caudorostral.		
TILT-2L/R	9 min	Same as previous two steps	Lines perpendicularly set through the vertex of both occipitotemporal flexures.	*2D knife axis*:	Epilepsy-specific sections of both hippocampal OV and associated parahippocampal gyri, rostral colliculi, optic radiations and main visual cortices.	Easy but requires some practice
				2R: dextroventral to sinistrodorsal.		
				2L: sinistroventral to dextrodorsal		
				Plane: oblique, longitudinal, with lateral inclination (45° and 135°).	Also, standard procedure in transtentorial herniation.	
				Blade movement: caudorostral.		
TS-3	11 min	Lateral view of dorsal wedge remaining from tissue Block A	Transverse line just 1–2 mm caudal to the level of the dorsomedial tip of hippocampus.	*2D knife axis*: laterolateral.	Epilepsy-specific section of dorsomedial hippocampal tail and hippocampal commissure, corpus callosum, occipitomesial cortex including cingulate gyrus and associated subcortical white matter.	Moderately difficult as the rostrocaudal range is very small
				Plane: transverse.		
				Blade movement: dextrodorsal to sinistroventral or vice versa.		

Being a thalamocortical syndrome, epilepsy frequently affects thalamus and lateral geniculate nucleus (own observations), which is synaptically connected to the occipital cortex. Investigation of this axis also may help to differentiate between primary versus secondary occipital lobe changes, due to forebrain enlargement and impingement by the tentorium cerebelli.

Concerning the rostral pole of the brain, the diagnostic interest in epileptic patients should carry on throughout frontal lobe rostral to lamina terminalis and include the precallosal fronto-olfactory region which is another area with low-threshold excitability.

As the frontal lobe carries the motor cortex and major extrapyramidal motor nuclei, it is the home of non-ataxic movement disorders but also resembles an important symptomatogenic zone in motor seizures with stereotypic movement pattern.

Naturally, the plethora of candidate areas for seizure development and perpetuation is intimidating. The good news is, all above mentioned areas and structures are "mutually" sampled by a rather simple trimming protocol within less than 30 min by inexperienced staff (see Additional file 1) and about 10 min by experienced investigators. Throughout all levels of expertise, regular consultation of anatomical textbooks and articles featuring topographic brain anatomy is inevitable (for useful examples see [25–28]). Thereby, the examiner needs to be aware of some terminological inconsistencies and the incompleteness of the Nomina Anatomica Veterinaria [27].

Guidelines for brain processing

Macro dissection and immediate post mortem procedures

Removal of the brain in epileptic patients employs a standard approach via removal of the skin and of the muscles of head and neck, mobilisation and dislocation of orbital contents, frontonasal osteotomy and extensive craniectomy. Before further preparation of the atlantooccipital junction, preceding decapitation or supraoccipital osteotomy, attention should be paid to possible cerebellar coning and transforaminal herniation as a consequence to intracranial pressure elevation (Fig. 1) [29].

Upon removal of the calvaria and dorsal (mid sagittal) or ventrolateral (bilateral) durotomy, the exposed brain is inspected in situ (Fig. 2). Thereafter, the olfactory bulbs are explored and mobilised from the cribrosal lamina, the brain is lifted and cranial nerves and the pituitary stalk are transected avoiding unnecessary tearing.

The relief of having extracted the brain in one piece all too often leads to premature immersion in formalin. As a rule, a tiny piece of fresh brain tissue, deriving from a clinically or macroscopically affected target area, should be placed in RNA later® (Qiagen Inc, Hilden) or snap-frozen and stored at −80 °C for possible molecular analyses. Cerebrospinal fluid, brain swabs for culture and other case-sensitive samples for microbiological and virological testing also require to be harvested from the unfixed brain. If it comes to sampling fresh tissue for an "-omics" approach (genomic, transcriptomic, proteomic, metabolomic) to epilepsy or cryohistology, prefixation sampling protocols can be quite sophisticated

Table 8 Systematic trimming of the frontoparietal region (Block B)

Cuts	Time	View/specimen	Landmarks and cutting levels	Orientation of sections	Aim/harvest	Difficulty
TS-4	13 min	Ventral view of the frontal lobe	Transverse line through or just rostral to optic chiasm	*2D knife axis*: laterolateral. *Plane*: transverse. *Blade movement*: ventrodorsal.	Standard section of the frontal lobe. Boundary between thalamus and basal nuclei; also shows septal nuclei, body of fornix, rostral commissure parietofrontal cortex.	Easy
TS-5	15 min	Ventral (or dorsal) view of the frontal lobe	Transverse midline section of olfactory tuberculum	*2D knife axis*: laterolateral. *Plane*: transverse. *Blade movement*: ventrodorsal.	Standard section of the frontal lobe providing the best view of the basal nuclei and capsules	Easy
HOR-2	17 min	Rostral view of the still connected hemispheres of olfactoryfrontal brain	2: Horizontal midline section through proreus gyrus. 2′,2″:..followed by parallel sections of the ventral block with 3 mm slice thickness.	*2D knife axis*: laterolateral. *Plane*: horizontal. *Blade movement*: rostrocaudal.	Epilepsy-specific section of the susceptible olfactoryfrontal cortex. Standard section in ethmoidal pathologies.	Easy
SAG-1L/R	19 min	Rostral view of the dorsal block of the olfactoryfrontal brain	1L/R: Sagittal lines through lateral third of proreus gyrus. 1 L′/R′/1 L″/R″:..followed by parallel sections with 3 mm slice thickness	*2D knife axis*: rostrocaudal. *Plane*: sagittal. *Blade movement*: rostrodorsal to caudoventral.	Epilepsy-specific sections exposing motor cortex	Easy

and vary in accordance to the objectives of the respective study [30, 31].

If sampling is aspired from specific hippocampal regions of the autopsied brain, the dissection protocol mentioned below may apply even though the morphology is preserved better if trimmed after fixation [32]. Detection of pathological changes by less experienced staff increases significantly if gross examination is carried out on the fixed brain [32, 33]

In surgically resected epileptogenic foci, tissue is lamellated and slabs for "omics" and cryohistology are sandwiched in between slices, undergoing routine formalin-fixation and paraffin-embedding (FFPE) [32].

For a standard autopsy setting with an uncertain location of the epileptogenic focus, it still may be worth to snap-freeze a small section of hippocampus. Without risking the accuracy of the standard sections, mentioned below, one single transverse section at the level of infundibular recess of the third ventricle rostral to the mammillary bodies (Figs. 3 and 4) may allow for tissue-sparing identification of the dorsomedial tail of the hippocampus from which bilateral samples can easily be taken. Once, this has been achieved, the brain is immersed in a sufficient volume of 10 % neutral buffered formalin and fixed for 48 h prior to further trimming and gross examination [33].

Post-fixation examination and trimming protocol

Preamble

Sampling of the different aspects of the hippocampus with sections taken perpendicularly to the longitudinal axis of the pyramidal cell band comprises the single most critical step of trimming the epileptic brain.

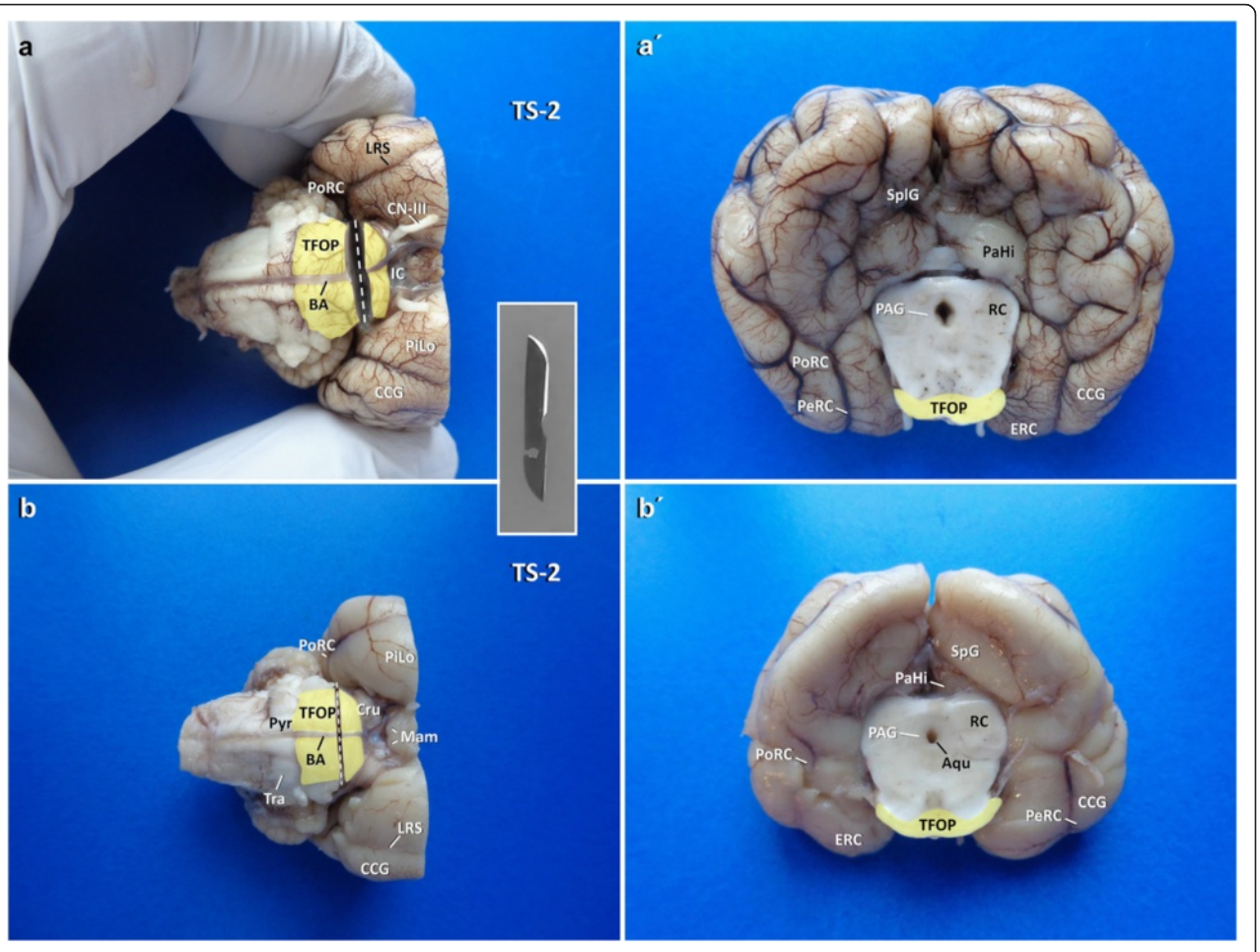

Fig. 5 Planning of TS-2 (**a**, **b**) and inspection of the occipitotemporal brain and mesencephalon (**a'**, **b'**) in dog (**a'**, **a'**) and cat (**b**, **b'**). Transection is performed by a tipped blade (inlet). Aqu: mesencephalic aqueduct; BA: basilar artery; CCG: caudal composite gyrus; CN-III: cranial nerve III; Cru: crura cerebri; IF: intercrural cistern; LRS: lateral rhinal sulcus; Mam: mammillary bodies; PAG: periaqueductal gray matter; ParaH: parahippocampal gyrus; PeRC: perirhinal cortex; PiLo: piriform lobe; PoRC: postrhinal cortex; Pyr: pyramis. RC: rostral colliculus; SplG: splenial gyrus; TFOP: transverse fibres of pons; Tra: trapezoid body

Nearly all other regions can be retrospectively collected and identified from fixed and trimmed pieces of brain ("bits in a bottle"). A reliable investigation of the hippocampus, however, requires both the correct angle of section and its physical connection to adjacent and connected structures such as the parahippocampal gyrus. Thus, hippocampal sampling represents the centre of efforts at this stage. However, the brain should not be cut without prior evaluation! Essential information may be

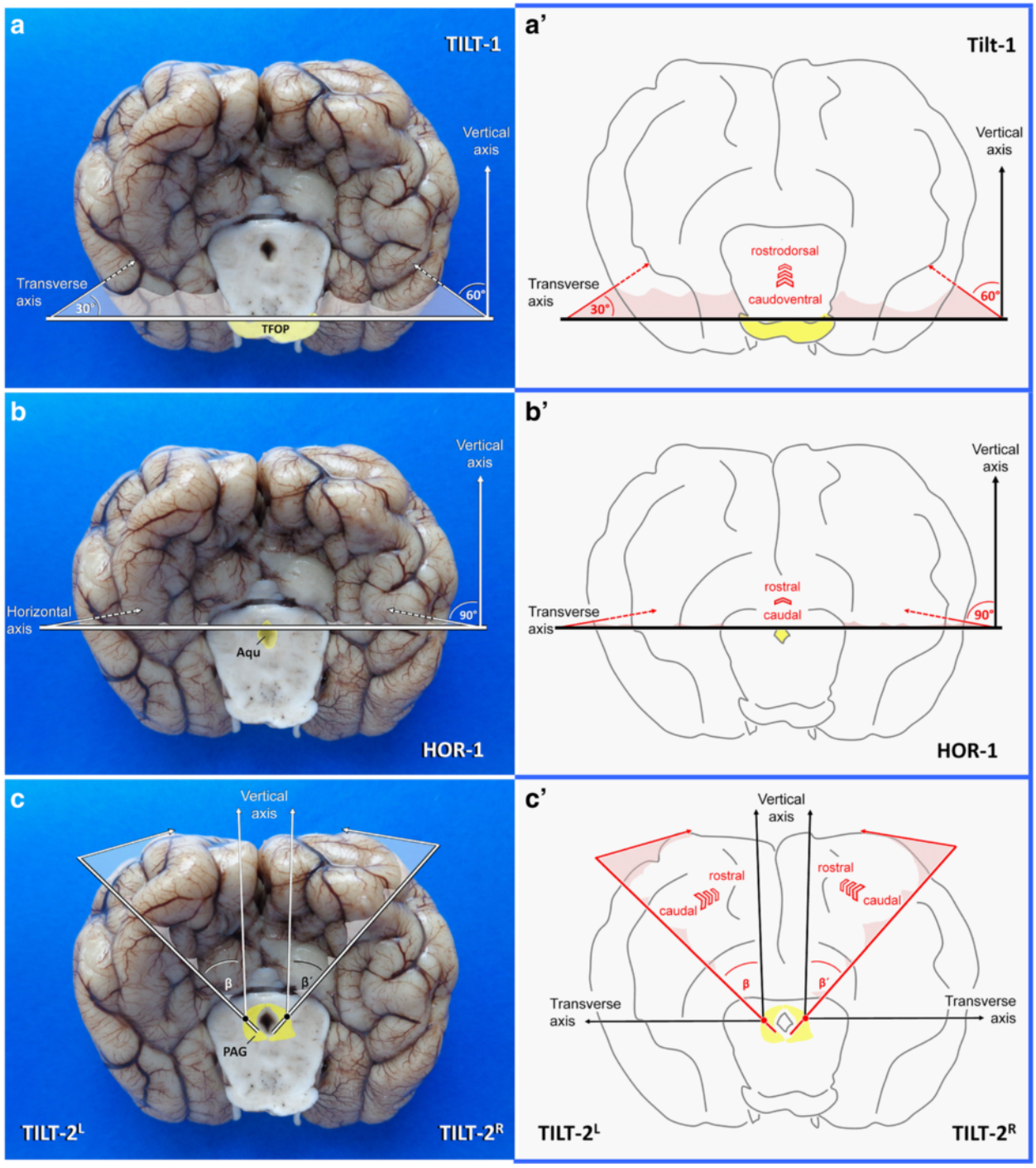

Fig. 6 Planning of occipitotemporal brain dissection in three steps. TFOP: transverse fibres of pons; Aqu: mesencephalic aqueduct; PAG: periaqueductal gray matter. Canine brain

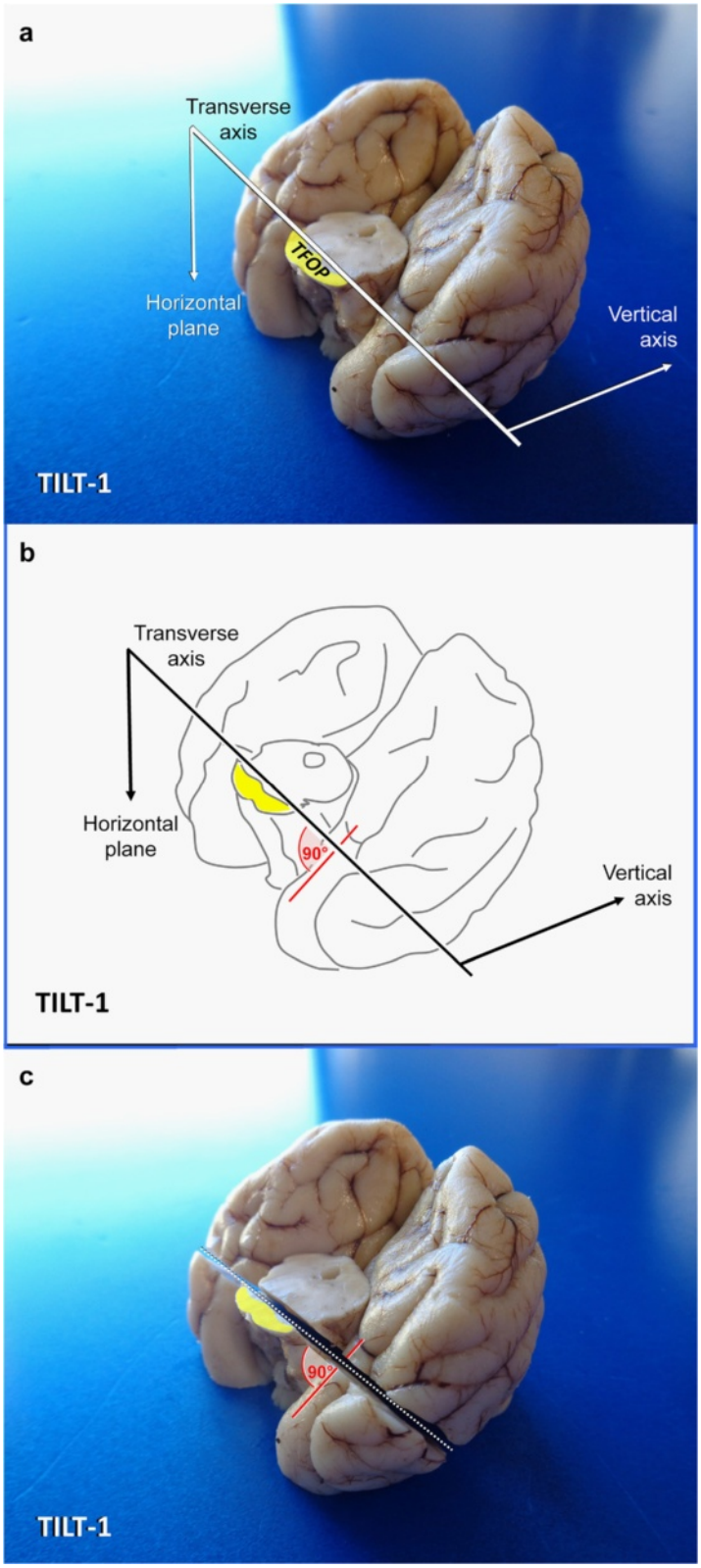

Fig. 7 Dissection of the temporoventral body of the hippocampus via TILT-1 in a dog. MA: mesencephalic aqueduct PAG: periaqueductal grey matter; TFOP: transverse fibres of pons

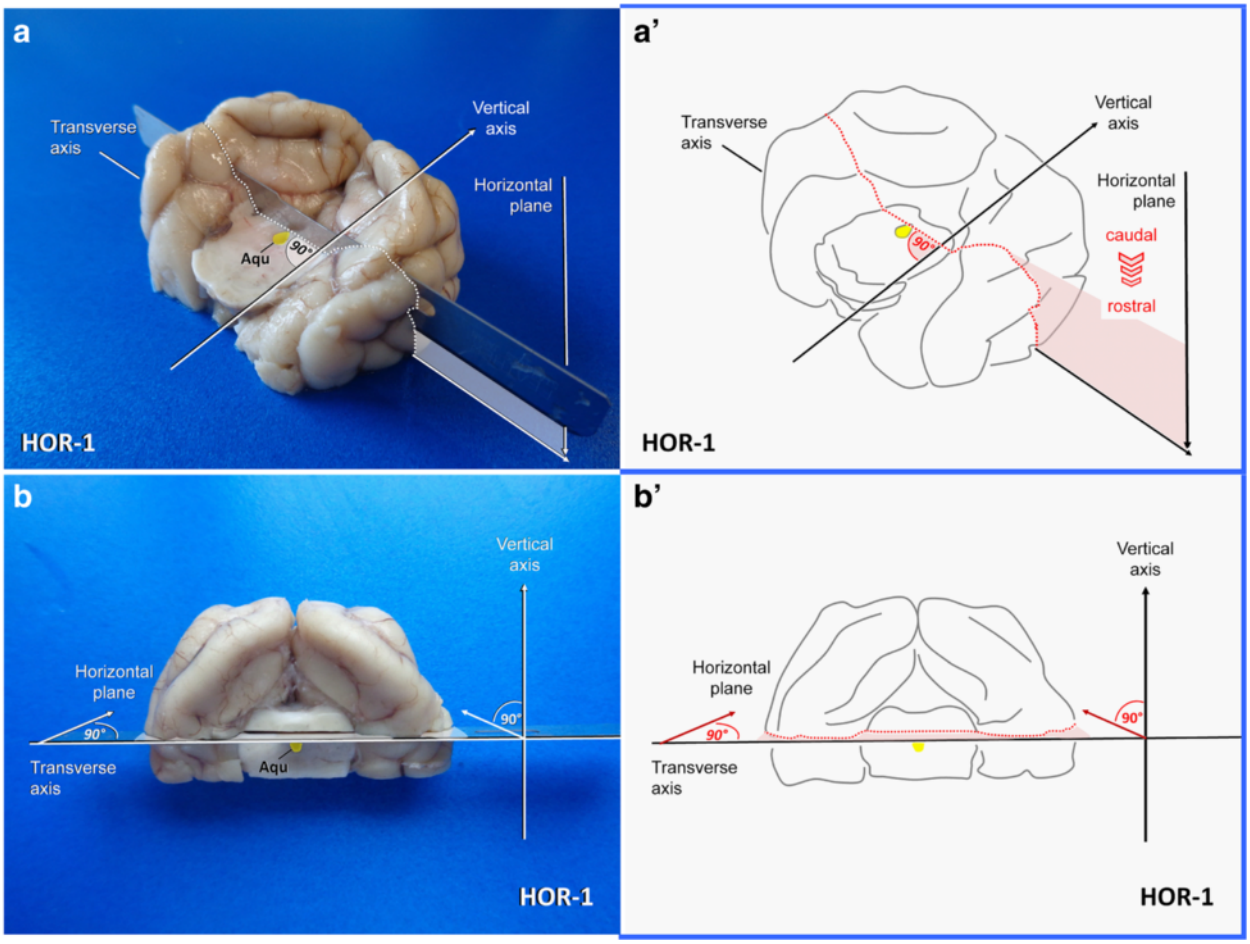

Fig. 8 Dissection of the caudal vertex of hippocampus via HOR-1 in a dog illustrated before (**a**, **a´**) and after (**b**, **b´**) procurement of the temporoventral body. Aqu: mesencephalic aqueduct

missed and irreplaceably lost if macroscopic examination has been skipped.

As in a general setting, the brain should be constantly evaluated for anatomical abnormalities (Tables 4 and 5) and distinct lesions (Table 6). Concerning the untrimmed brain (Tables 4), this in particular refers to (UB-1) changes to cerebrum-cerebellum-brain stem ratio, (UB-2) abnormal brain shape and external patterning (lobes, lobules, gyri, folia), (UB-3) increased orifical width of fissures, interfolia spaces and sulci (FISS), (UB-4) leptomeningeal

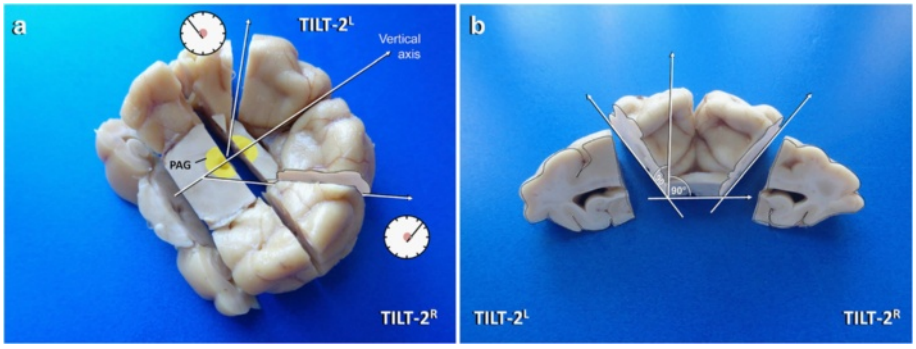

Fig. 9 Dissection (**a**) and inspection (**b**, dashed line) of the occipital vertex of the hippocampus in a dog. PAG: periaqueductal gray matter

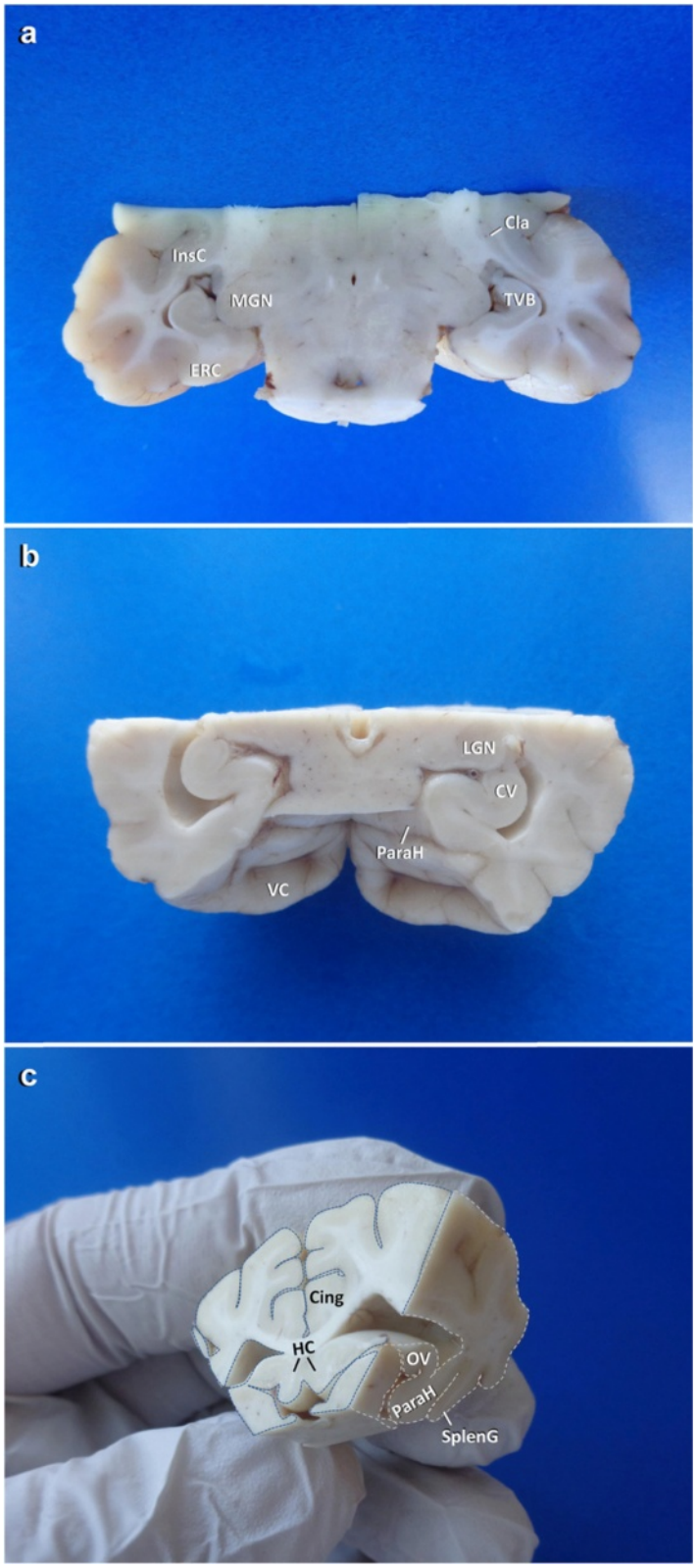

Fig. 10 Overview of dissected temporoventral body (**a**: TVB), caudal vertex (**b**: CV), occipital vertex (**c**: OV) and commissure of hippocampus (**c**: HC). Cing: cingulate gyrus; Cla: claustrum; ERC: entorhinal cortex; InsC: insular cortex; LGN: lateral geniculate nucleus; MGN: medial geniculate nucleus; ParaH: parahippocampal gyrus; SplG: splenial gyrus; VC: visual cortex

transparency and vascular pattern, (UB-5) changes in the rostrocerebellar space/quadrigeminal area and (UB-6) to the appearance of cranial nerve roots.

Trimmed brain examination (Table 5), on the other hand, checklists (TB-1) course, depth and width of FISS base, (TB-2) volume, ratio, symmetry and delineation of cortical ribbon and subcortical white matter, (TB-3) visibility and symmetry of major white matter tracts and prosencephalic nuclei, (TB-4) preservation of periventricular white matter, (TB-5) appearance of the ventricular surfaces, plexuses and vela, the ventricular size, symmetry and contents.

Pathological lesions throughout the trimming process may become evident simply by (PL-1) discolouration, (PL-2) loss or gain of tissue and (PL-3) changes to the texture (Table 6).

Specific procedures

Trimming of the occipito-temporal region (tissue block A)

Orientation and planning after transverse section through the pituitary stalk or mammillary bodies

If the brain has been removed in toto, this cut (Fig. 6) should be performed with a long blade to enable fresh sampling of the dorsomedial hippocampus. It also resembles a scout section that allows for rostrocaudal localisation of the dorsomedial and ventrolateral hippocampal boundaries and of the hippocampal (syn. fornical) commissure. The insight gained from this section enables controlled sampling of the hippocampus independent of topographic variations in position and extension of the hippocampus across cats and dogs and different skull types.

In addition to providing a good overview of the middle diencephalon, this section reveals the amygdaloid nucleus that is positioned just rostral to the TVB; this should be included, as it is the second most vulnerable

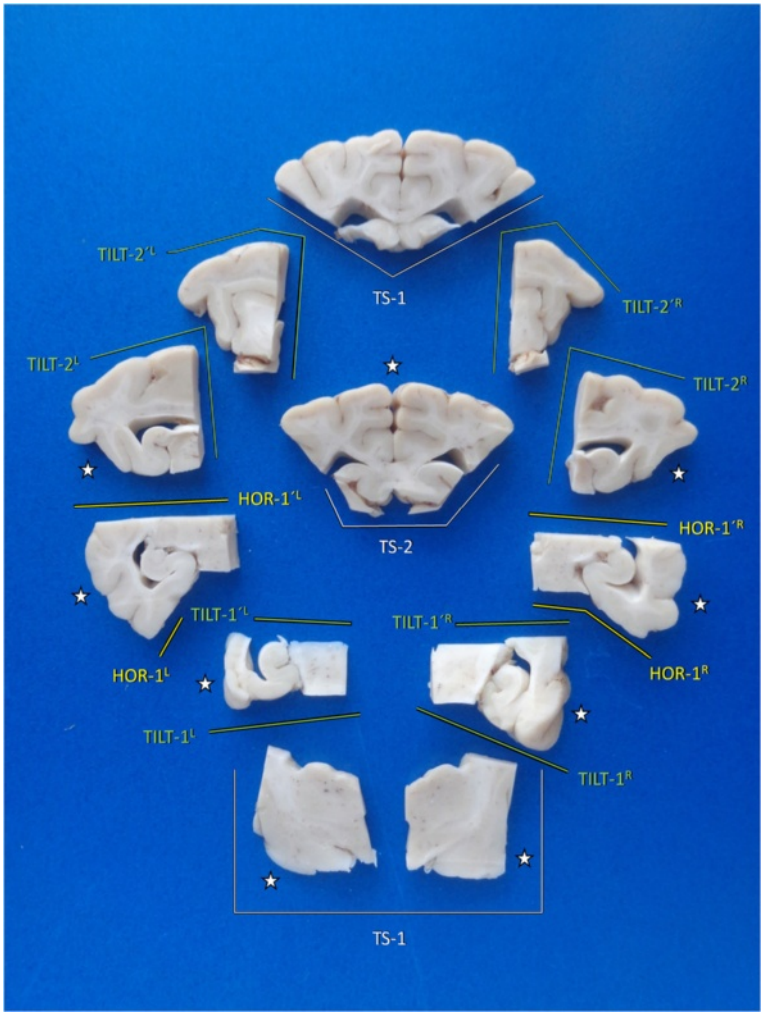

Fig. 11 Overview of main brain slabs of Block A in correct angle of section. A selection of these may be further processed for histology. Asterisks mark our recommendation for systematic epilepsy pathology studies

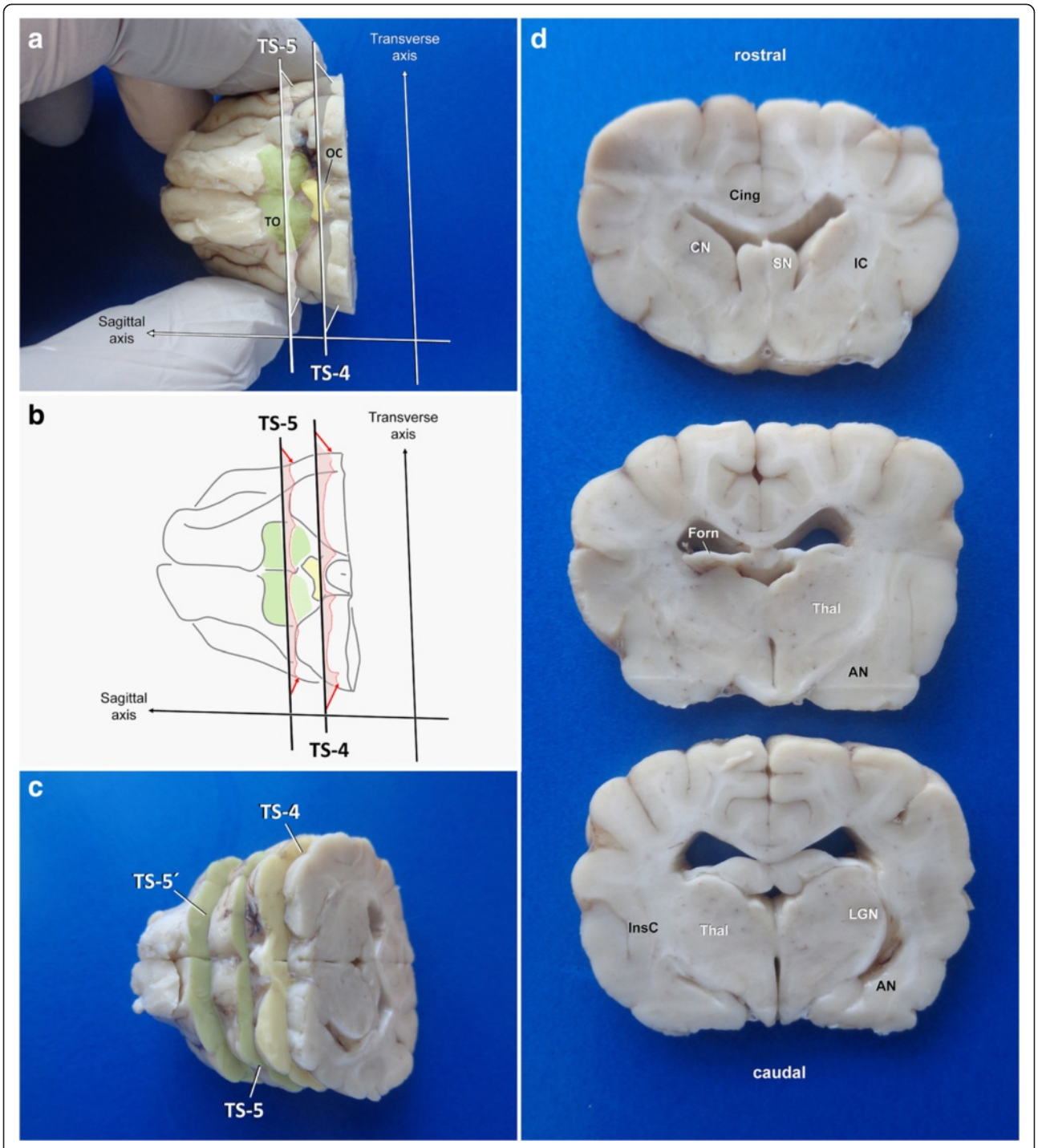

Fig. 12 Planning (**a**, **b**) and performance (**c**, **d**) of dissection of the caudal and middle capsular region. AN: amygdaloid nucleus; Cing: cingulate gyrus; CN: caudate nucleus; Forn: fornix; IC: internal capsule; InsC: insular cortex; LGN: lateral geniculate nucleus; OC: optic chiasm; SN: septal nuclei; Thal: thalamus; TO: tuberculum olfactorium

area for seizure-associated sclerosis, in particular in temporal lobe epilepsy identified clinically or on MRI, as well as in epilepsy patients with behavioural abnormalities and in unexplained drug resistance [34–36].

In particular in brachycephalic dogs and in cats, the ventrodorsal axis of the hippocampus is very steep and its concave plane is tilted towards the midline. Meaning that there is no way to obtain perpendicular CA sections by conventional transverse sections of the brain. The

sectioning protocol should be tailored with regards to the three-dimensional placement of the hippocampus within the hemispheres (Table 7).

For epilepsy-related research the following segments should be obtained bilaterally from the temporal lobe and hippocampus:

1. amygdaloid nucleus with piriform cortex;
2. temporoventral body (TVB) with entorhinal cortex;
3. caudal vertex of hippocampal flexure (CV) with post-rhinal cortex;
4. occipital vertex of hippocampal flexure (OV) with parahippocampal gyrus and visual cortex
5. dorsomedial tail at hippocampal commissure (HC) with cingulate gyrus.

Procurement of these regions is manageable for training level I personnel (Table 1) in 10 min or less if the protocol is strictly followed (Tables 7, 8, 9).

Procurement of the temporoventral body of the hippocampus

For the second section (**TS-2**; Fig. 3), the caudal part of the brain is approached ventrally. The transverse fibres of the pons (TFOP) are easily recognised in between the convergence of both crura cerebri (rostral) and the origin of the pyramis (caudal). A transverse section of the brain stem is performed with a pointed blade (e.g. scalpel blades no. 11 (cats) or 22 (dogs)), pointed ventrodorsally, just separating the rostral quarter of TFOP from its caudal three quarters (Fig. 5). That way, the caudal surface of the rostral mesencephalic stump ventrally reveals the TFOP, the dorsal border of which serves as the next landmark (Figs. 6 and 7).

Insert a long blade at the horizontal laterolateral axis (0° angle), where the TFOP border the tegmentum and lower the back edge of the blade ventrally until the sharp

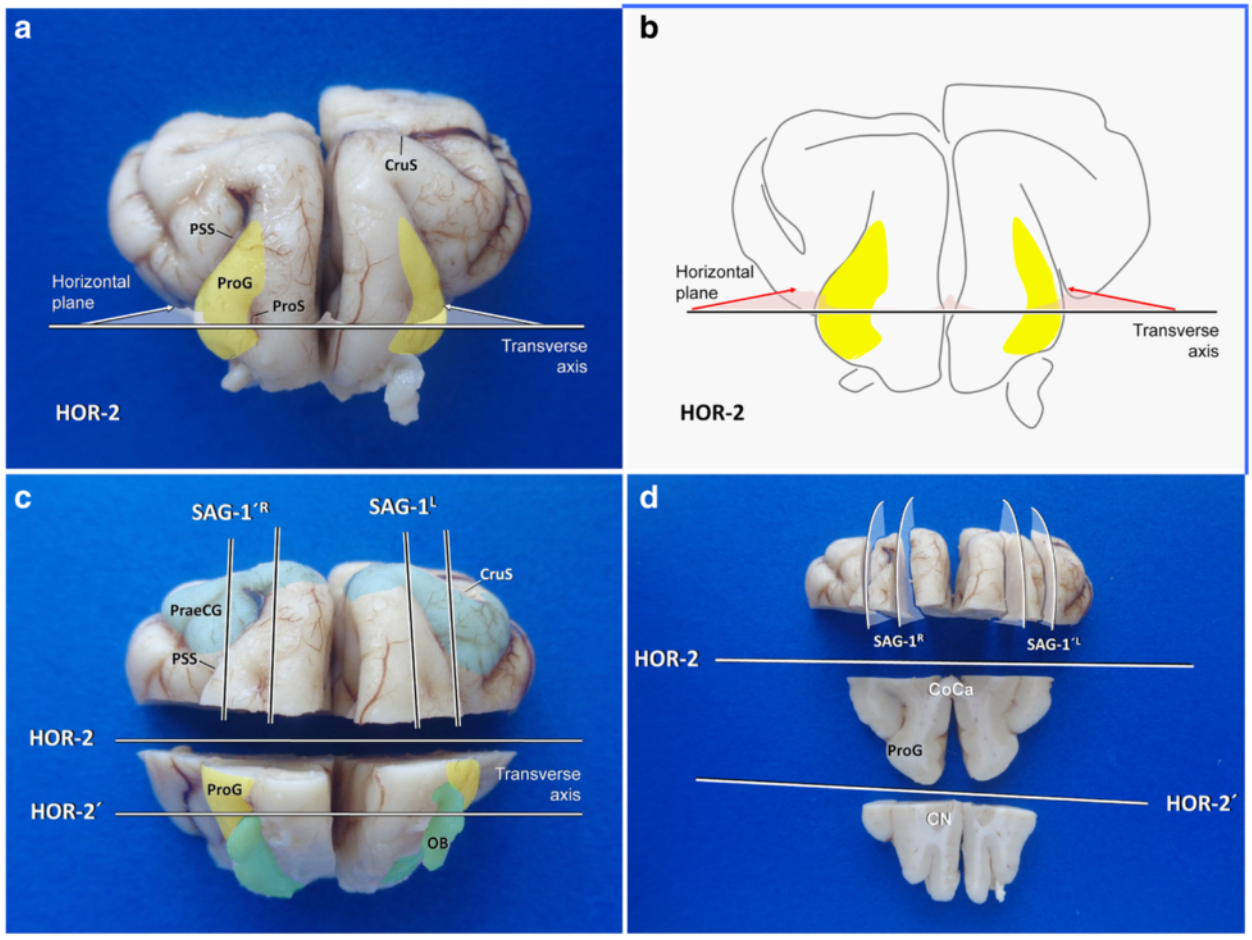

Fig. 13 Planning and performance of fronto-olfactory dissection in a dog; rostral view. CN: caudate nucleus; CoCa: corpus callosum. CruS: cruciate sulcus; OB: olfactory bulb; PraeCG: praecruciate gyrus; ProG: proreus gyrus; ProS: prorean sulcus PSS: presylvian sulcus

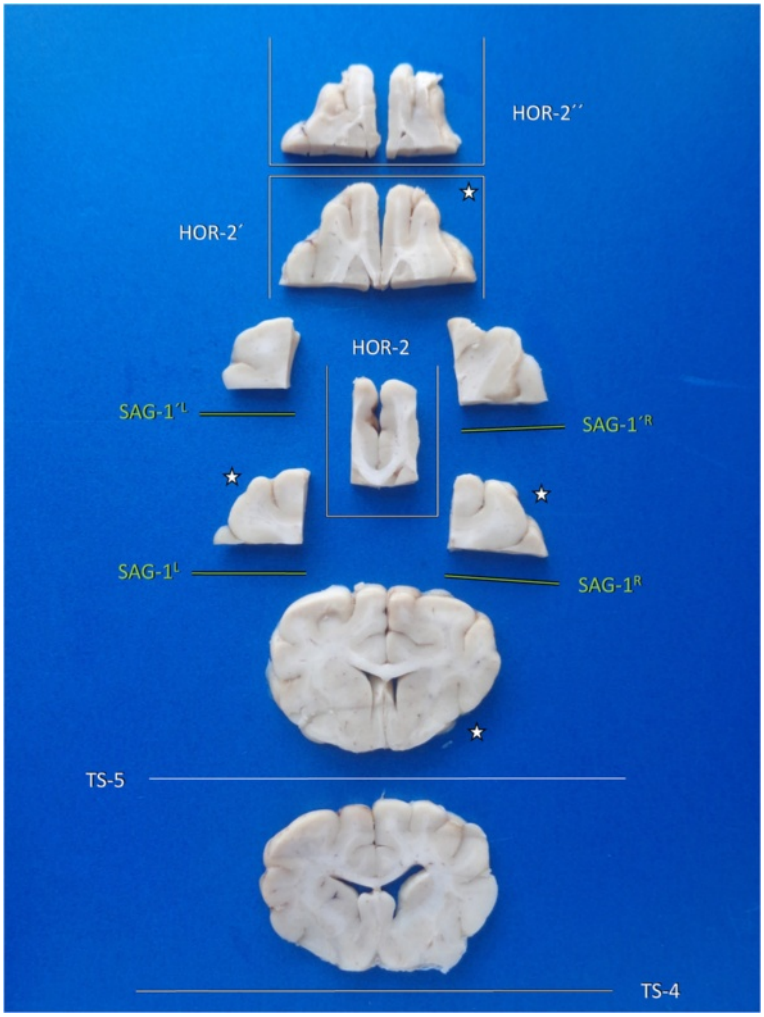

Fig. 14 Overview of main brain slabs of Block B in correct angle of section. A selection of these may be further processed for histology. Asterisks mark our recommendation for systematic epilepsy pathology studies

edge points towards the caudoventral curvature of the temporal lobes (caudal composite gyrus and base of piriform lobes) at a right angle (Fig. 7).

If you perform the section in this tilted caudoventral to rostrodorsal fashion (**TILT-1**), you will create a perpendicular section of the entorhinal cortex and TVB; differential evaluation of individual CA segments (e.g. for HS) or evaluation of the dentate gyrus and subiculum pathology will be easy and reliable.

Adequate slices will be ready to be put in standard cassettes after another section is made parallel to the surface of the wedge (**TILT-1′**) and a longitudinal cut is made through the attached brain stem (see Additional file 1).

Obtainment of the caudal vertex of hippocampal flexure

At the level of lateral geniculate nuclei (LGN), MR investigation of the hippocampus in angled horizontal plane (or coronal in humans) may allow for assessment of hippocampal atrophy and HS [37]. Even though histopathological changes usually are more advanced in TVB, this adjacent region should be sampled for correlative investigations and for changes to the postrhinal and perirhinal cortices [38–40].

It can be easily approached from caudal aspect again (Fig. 6). A long blade is positioned horizontally at the dorsal border of the mesencephalic aqueduct (Fig. 8). This section (**HOR-1**) simply is conducted perpendicular to the transectional surface of the mesencephalic stump in a caudorostral fashion (horizontal plane). If the level has been correctly chosen, the LGN are seen just opposite to the hippocampi at the other side of the choroidal fissure (Fig. 10).

Procurement of the occipital vertex of hippocampal flexure

Additional sections of brain block A allow for a contextual evaluation of the hippocampal OV, the parahippocampal

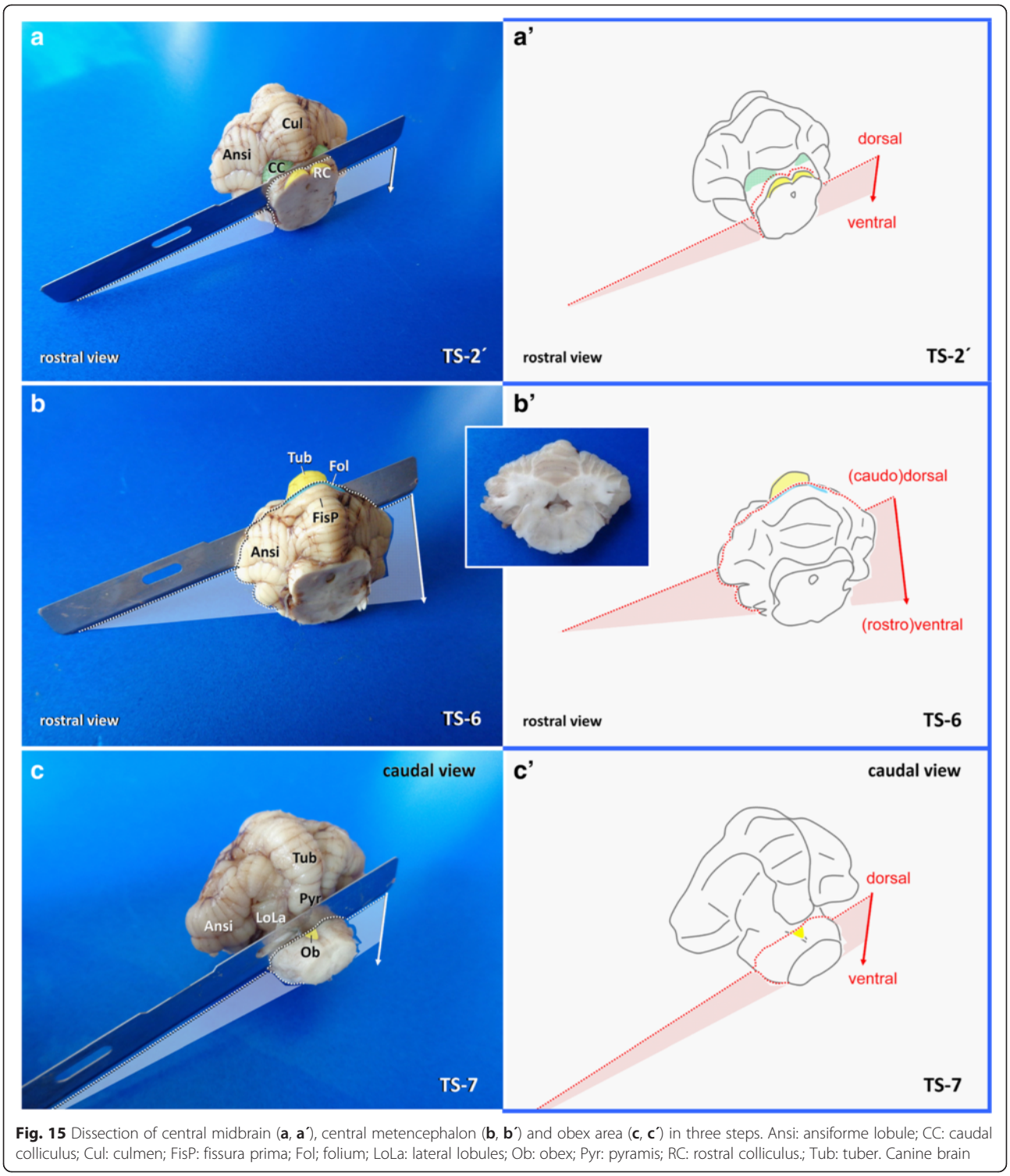

Fig. 15 Dissection of central midbrain (**a**, **a´**), central metencephalon (**b**, **b´**) and obex area (**c**, **c´**) in three steps. Ansi: ansiforme lobule; CC: caudal colliculus; Cul: culmen; FisP: fissura prima; Fol; folium; LoLa: lateral lobules; Ob: obex; Pyr: pyramis; RC: rostral colliculus.; Tub: tuber. Canine brain

and splenial gyri, both directly exposed to the tentorium and, hence, prone to impingement during herniation [29].

On caudal view of the left occipital lobe, the blade is directed rostrally while the knife points clockwise to 10.30 and the pivot is set slightly left to mesencephalic aequeduct, where the periaquaeductal grey matter dorsolaterally is expected to border the tegmentum (**TILT-2**^{L} Fig. 6; Fig. 9).

That way, the blade is supposed to cut the parahippocampal gyrus and hippocampus perpendicularly. For

the right hemisphere the procedure is repeated just mirror inverted (**TILT-2R**; Figs. 6 and 9).

Procurement of the dorsomedial hippocampal tail and hippocampal commissure

Longitudinal variations of pathological lesions along the septotemporal axis are frequently seen but have been rarely associated to distinct aetiologies. Exceptions are toxicopathological studies and rodent models of epilepsy [11]. Respecting the varying connectivities, functions and metabolism, and in particular our lack of knowledge regarding selective vulnerabilities and involvement, the dorsomedial hippocampus should not be omitted.

After obtainment of the occipital vertices, a wedge shaped piece of block A remains containing the occipitomesial cortex, marginal and ectomarginal gyri bilaterally. Rostral inspection of this wedge allows for judgement of the rostral tip of the hippocampal tail in the midline, ventrally attached to the fornix. A transverse section (**TS-3**) should be performed just about 1 mm caudal to this point. This level usually provides a perpendicular view of the dorsal CA segments and DG and of the hippocampal commissure (Figs. 4 and 10) that may be one of the pathways wiring excitations to the contralateral side of the brain.

A survey on the brain slides possibly sampled by trimming of tissue block A is provided in Fig. 11.

Trimming of the parieto-frontal region (tissue block B)

Essential parts of parietal cortex will have already been collected at the thalamic level. For gross inspection, further transverse sections should be performed from ventral at or just proximal of the optic chiasm (**TS-4**; Figs. 3 and 12) to investigate septal nuclei, fornical body, rostral commissure and basal nuclei. Depending on the size of the brain, a parallel transverse section through the middle part of the olfactory tuberculum (**TS-5**) provides a representative view of the frontal lobe, including the caudal parts of frontal cortex, striatum and the capsules (Figs. 3 and 12).

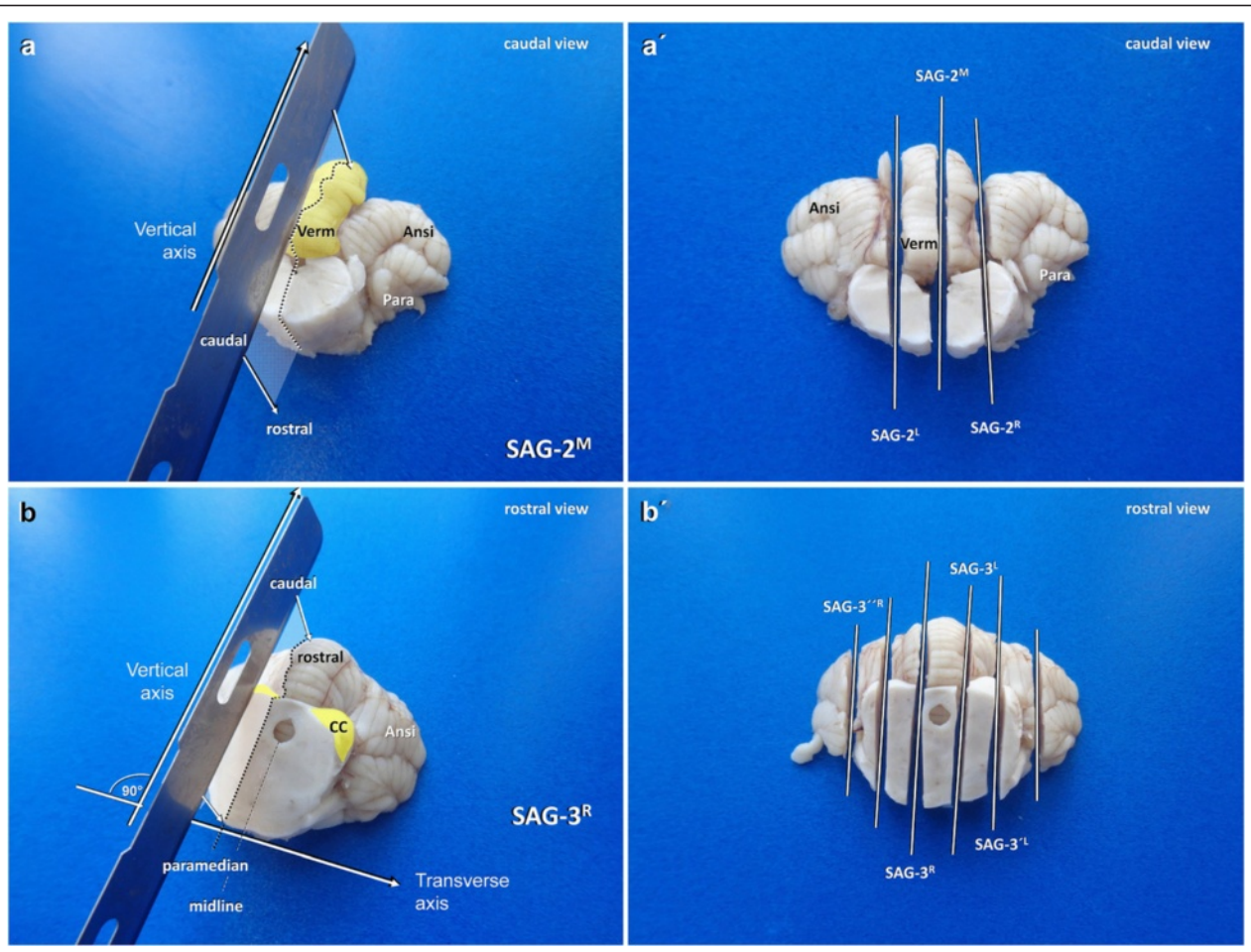

Fig. 16 Sagittal dissection of the caudal (**a**, **a´**) and rostral (**b**, **b´**) cerebellar lobes and the associated brain stem in a dog. Ansi: ansiform lobule; CC: caudal colliculus; Para: paraflocculus; Verm: vermis

Fig. 17 Overview of main brain slabs of Block C in correct angle of section. A selection of these may be further processed for histology. Asterisks mark our recommendation for systematic epilepsy pathology studies

Further trimming of the remaining tissue block B (Table 8) mainly is dedicated to explore motor areas of frontal cortex and the olfactory lobe, which resembles another low threshold area for seizure generation and lesions of which are rarely associated with neurological signs in dogs and cats other than seizures.

It proves useful to approach the olfactory bulb and cortex, its connections to the periventricular brain and subventricular zones using horizontal sections. To conduct the first horizontal section (**HOR-2**), the blade is inserted in laterolateral axis at the proreus gyrus and the tissue is cut in rostrocaudal direction (Fig. 13). With the previous transverse cut, set caudal to the genu of the corpus callosum, both hemispheric parts stay connected, which facilitates cutting and processing. Depending on the brain size, one or two further horizontal sections (**HOR-2′, −2″**) are performed at 3–4 mm interslice distances ventral to **HOR-2** (Fig. 13).

Having achieved this, two sagittal sections through the lateral third of the proreus gyrus (**SAG-1Left/Right**) and again about 3 mm lateral to these (**SAG-1′L/R**) allow for inspection of and sampling of motor cortex, flanking the cruciate sulcus rostrally (pre-cruciate) and caudally (post-cruciate) (Fig. 13). Further sagittal sections in vertical plane (**SAG-1″ L/R**) may be taken if for diagnostic purposes.

An example of the tissue slabs achieved by trimming of tissue block B is provided in Fig. 14.

Trimming of the hindbrain (tissue block C)

Brainstem and cerebellar seizures have not been reported in domestic animals yet but there is some histological evidence that epilepsy in dogs maybe associated with cerebellocortical abnormalities [8]. Likewise, cerebellar atrophy is observed in about 25 % of human epileptics presented at autopsy [41] with some

Table 9 Trimming and sampling of midbrain and hindbrain (Block C)

Cut	Time	View/specimen	Landmarks and cutting levels	Orientation of section	Aim/harvest	Difficulty
TS-2′	21 min	Lateral view of the midbrain	Transverse line through the intercollicular area (small brains) or caudal colliculi (large brains)	*2D knife axis*: ventrodorsal. *Plane*: transverse. *Blade movement*: laterolateral.	Standard section of the midbrain	Easy
TS-6	22 min	Dorsal view of the cerebellum	6: Transverse line just caudal to the primary fissure. 6′..followed by a parallel section with 3 mm slice thickness	*2D knife axis*: laterolateral. *Plane*: transverse. *Blade movement*: dorsoventral along the midline axis of cerebellar hemispheres.	Standard cross section of cerebellum and medulla oblongata. Shows central vermis, hemispheres, paraflocculus, flocculonodular lobe, cerebellar roof, caudal/middle peduncles and medulla oblongata.	Easy
TS-7	24 min	Caudodorsal view of the medullary stump	Transverse line close to the obex	*2D knife axis*: laterolateral. *Plane*: transverse. *Blade movement*: dorsoventral.	Standard section of the lower brainstem. Shows spinal tracts, vagal and associated nuclei, proprioceptive nuclei.	Easy
SAG-2M	25 min	Caudal view of cerebellum and medulla	Sagittal midline section through caudal cerebellar vermis and underlying medulla.	*2D knife axis*: ventrodorsal. *Plane*: sagittal, midline. *Blade movement*: caudorostral.	Standard section of cerebellar caudal lobe and in particular useful in suspected foramen magnum herniation. Shows caudal vermis and midline medulla.	Easy
SAG-2′L/R & SAG-2″L/R	27 min	Caudal view of cerebellum and medulla	2´L/R: Sagittal lines, lateral und parallel to SAG-2M on each side. 2″L/R: ..followed by parallel sections 3 mm lateral to 2′L/R.	*2D knife axis*: ventrodorsal. *Plane*: sagittal, paramedian. *Blade movement*: rostrocaudal.	Standard sections for evaluation of caudal cerebellar hemispheres. Shows in particular lobules ansiformis and dorsolateral proprioceptive and vestibular areas of medulla.	Easy
SAG-3′L/R & SAG-3″L/R	29 min	Rostral view of the caudal midbrain stump and the rostral cerebellar lobe	3′L/R: Sagittal lines through the lateral boundaries of periaqueductal grey matter, about 1–2 mm lateral to the aqueduct. 3″L/R: ..followed by parallel sections 3 mm lateral to 3′L/R.	*2D knife axis*: ventrodorsal *Plane*: sagittal, paramedian. *Blade movement*: rostrocaudal.	Standard sections for evaluation of rostral cerebellar lobe and in particular the effects of transtentorial herniation, as well as of pontomesencephalic transition, including caudal colliculi, leminiscus and lateral tegmental nuclei	Easy

variabilities between anterior versus posterior lobe involvement [42]. Cerebellar changes either are related to the seizure-syndrome [8], to antiepileptic drug toxicity [42] or to specific epileptogenic aetiologies, such as hypoxia, ischaemia, intoxication or mitochondrial disease [42, 43]. In contrast, there is no systematic interdependence between epilepsy and brainstem lesions.

Sampling of these areas pretty much underlies laboratory specific protocols with the basic requirement to obtain sections from the cerebellum in two planes and to investigate vital brainstem centres (Table 9).

In the following, one possible approach is illustrated which, based upon the experience gained at our own laboratories (LMU Munich, UAB Barcelona), has proven easy to perform and to standardise and is effective in picking-up lesions blindly.

Procurement of mesencephalon

After **TS-2**, a transversely oriented tissue section is taken from the caudal mesencephalic stump, either at the intercollicular level or the level of the rostral colliculi (**TS-2′**). The caudal colliculi are sampled later on

Table 10 Example of a CNS specific processing/embedding cycle [45]

Incubation time	Chemical	Temperature
6 h	70 % ethanol	40 °C
4 h	80 % ethanol	40 °C
4 h	90 % ethanol	40 °C
4 h	100 % ethanol	40 °C
4 h	100 % ethanol	40 °C
4 h	100 % ethanol	40 °C
2 h	xylene	40 °C
2 h	xylene	40 °C
2 h	xylene	40 °C
1 h	paraffin[a]	60 °C
1 h	paraffin[a]	60 °C
1 h	paraffin[a]	60 °C
3 h	paraffin[a]	60 °C

Cycle times differ if fixation is performed with higher concentrations of formalin as occasionally recommended for large specimens
[a]We recommend use of paraffin with 4 % DMSO (Paraplast®, Leica Biosystems, Nussloch)

via paramedian sagittal sections in vertical plane (see below).

Procurement of cerebellum and medulla oblongata at mid-cerebellar level

In order to obtain a representative transverse section, the cerebellum is approached from dorsal. After mesencephalic sampling, sectioning (**TS-6**; Fig. 15) is carried out in a dorsoventral direction along the dorsoventral axis of the cerebellar hemispheres, with the long blade being inserted 2–3 mm caudal to the primary fissure. The parallel section (**TS-6′**), necessary to obtain a tissue slice is then performed either on the rostral or caudal stump, depending on the placement of the cerebellar roof nuclei (Additional file 1).

This section provides a detailed view on the flocculonodular lobe, paraflocculus, paravermis and dorsal vermis, the cerebellar roof, including the associated nuclei, the caudal peduncles or lateral foramina, and the medulla at its largest laterolateral diameter that contains in particular the dorsolateral sensory nuclei and motor nuclei of CN-VI and CN-VII (Fig. 15).

Procurement of the caudal vermis and the autonomic centres of the caudal brainstem

Even though the last section being broadly considered representative of the cerebellum, it does not contain the essential spinocerebellar parts of the vermis, since the nodulus belongs to the vestibulocerebellum and the dorsal aspects of the vermis receive cortico-ponto-cerebellar inputs. Furthermore, the medulla being cut at mid rostocaudal level does not contain the respiratory control centre. In particular in combined (medullocerebellar) midline pathologies, such as in transforaminal cerebellar herniation [29], it is essential to study the micromorphology of these areas in detail.

Most of the vagal nerve nuclei and related parasympathetic nuclei are preserved by gathering a transversely oriented slab of brainstem from the obex area (**TS-7**; Fig. 15).

After that, the caudal part of the cerebellum and brain stem can be sectioned sagittally through the midline (**SAG-2 M**) and in sequential paramedian slides (**SAG-2′L/R**; Fig. 16).

Histological slides from these brain slices allow for inspection of the comb-like two dimensional organisation of the Purkinje cell dendrites, which is not possible on transverse sections. It further elucidates histopathological sequelae of transtentorial herniation, which may be subtle and restricted to the lingula or pyramis.

Obtainment of rostral cerebellar lobe and caudal mesencephalon

Concerning, the transtentorial border zone, the implied brain shifting and associated problems, the cerebellum may have suffered from descending occipital lobes. In contrast to transforaminal herniation, caudal transtentorial protrusion of the occipital lobes results in a lesion of the paravermal areas of the rostral cerebellum [29]. Midline sections, hence, do not necessarily reflect the effects of impingement. Evaluation of the rostral lobe

Table 11 Essential data (Level I) that are required to be collected for a meaningful post-mortem examination

I. Data on the animal and pedigree	# breed, age, gender
	# evidence of seizures or other paroxysmal and neurological diseases in the pedigree
	# usual food and treats, dietary changes
	# exposure to toxins/medications
II. Data on the events & clinical presentation	# possible triggers
	# seizure onset semiology and characteristics
	# evidence of automatisms
	# interictal neurological signs/ neurolocalisation
	# seizure frequency and duration
	# abnormal MRI and EEG findings
	# abnormalities on blood work, CSF and urine analysis
III. Epicrisis	# treatment scheme and response
	# changes to semiology
	# recently acquired medical problems
	# time span from last seizure to death
	# natural death or euthanasia
	# death in status epilepticus

further may pick-up the anterior type of epilepsy-related cerebellar atrophy [42].

Investigation of the brainstem underlying the rostral cerebellar lobe, on the other hand, could help to detect systemic ictogenic conditions such as global ischaemia [44]

There are two different assessment modes that may be applied, depending on the individual case scenario. The easier procedure (Table 9, Fig. 16) employs two parallel sagittal or slightly inwardly rotated paramedial sections in the rostrocaudal direction through caudal colliculi and/or rostral peduncles (CC/RP) and the caudally adjacent paravermis (**SAG-3 L/R**) as well as parallel sections (**SAG-3′L/R**) conducted 3 mm farther lateral (Fig. 16).

Figure 17 provides a summary of the possible tissue slabs generated through the described protocol for tissue block C trimming (Table 9).

An alternative option, used in distinct rostral compression of the cerebellum would be a horizontal section of the cerebellum just dorsal to the colliculi with subsequent bilateral sagittal sections through the "decapitated" CC/RP.

Post-Trimming procedures and histological staining

Independent of the sections necessary for the requested diagnosis, processing of the brain sections to paraffin blocks is advisable to prevent the brain tissue from formalin-induced, excessive aldehyde bridging and DNA fragmentation. Processing cycles vary slightly in between different labs and run on standard or, even better, dedicated CNS programs with or without dimethylsulfoxide permeabilisation [45]. Table 10 provides an example of a CNS adapted paraffin embedding cycle. It has to be made clear that any attempt to accelerate histoprocessing will impact negatively on the tissue quality and thereby compromise detection of degenerative cytopathological features. Identification of infiltrative changes will be less severe.

Staining protocols, in addition to haematoxylin-eosin (H.E.), are to be chosen in accordance to (1) the requirements of the individual case, (2) the investigational purpose and (3) financial constraints. Overviews on neuropathological standard stains are provided elsewhere [46]

For elucidation of epilepsy-related changes it proved beneficial to highlight the regional drop-out of nerve cells by cresyl violet-based stains such as Nissl stain (without myelin staining) or Kluver Barrera stain (with myelin staining). In very fresh samples taken via brain surgery or early post-mortem, NeuN immunohistochemistry may be superior for highlighting neurons [47] but this procedure also is far more expensive and immunoreactivity rapidly decreases post-mortem and with prolonged fixation periods.

Apart from providing an insight into nerve cell density neuronal stainings also facilitate the detection of histoarchitectural grey matter changes, such as dyslamination, and heterotopia [47]. Dysmorphic neurons, on the other hand, become most obvious on staining for microtubule associated protein 2 (MAP-2) and neurofilament staining. Just the interpretation requires some experience in neuronal cytoarchitecture [47].

In post-mortem samples, differentiation of post- and intra-ictal neuronal necrosis from terminal ischaemic changes can be problematic, in particular if prefinal seizure episodes might have gone unseen. In such cases, clarification of the fate of eosinophilic neurons can be achieved using FluoroJade-B® or -C® [48, 49]. Other, more specific markers of degeneration, necrosis and apoptosis may be used based on the aim of investigation and the experiences of the investigator.

Experience also comes into effect with evaluation of glial response. Reactive astroglial changes occur with or without preceding neuronal degeneration. Protoplasmatic astrogliosis may be missed if the examiner is not familiar with astroglial cytomorphological details. It becomes even more sophisticated to identify fibrillary astrogliosis and isomorphic astrocytosis, without cytoplasmic accumulation. Intraobserver's sensitivity can be increased for both fibrillary and protoplasmic astrogliosis by staining for the filament glial fibrillary acidic protein (GFAP) and by use of the overall available marker vimentin [17].

Most recently, the role of autoimmune mechanisms [14] and neuroinflammation have gained new attention in veterinary epileptology and led to introduction of immunosuppressive and anti-inflammatory treatment concepts [50]. With regards to autoimmune encephalitis, conventional markers for lymphocyte subsets, antibodies and complement factors may shed light on their specific involvement [14], while cellular infiltrates are seen on standard stains (e.g. H.E.).

With ionized calcium-binding molecule (Iba1), even subtle changes to the microglial activity can be nicely visualised in paraffin embedded tissues of different animal species [51] including the hippocampi of dogs [52]. In combination with CD-163, It has also proved to be a reliable marker for distinction of local microglial response and invasive macrophages in canine encephalitis [53].

Breakdown of the blood brain barrier due to seizures or their primary pathologies will lead to pervasive effects due to extravasation of fluid and possibly epilepsy promoting molecules [54]. Postictal brain oedema usually is quite prominent and its extension into the white matter remains visible for a prolonged period with proper brain processing (see above). In grey matter, however, reabsorption is quick and an oedema diagnosis may

require staining for the water channel molecule aquaporin 4 [55]. As surrogate for the possible influx of neuroactive agents immunohistochemical staining for albumin may be performed [54]

The list of histological tools could be further extended. The major diagnostic purpose, though, is to identify epileptogenic and postictal changes and to shed light on possibly epileptogenic pathologies. It rarely is the staining panel that limits the success of brain histology in clinical patients. Instead the relevant area may be easily missed. For most investigations, H.E. staining combined with Nissl's stain and GFAP will provide sufficient data for the clinician.

What the pathologist should know about the case?

Pathological studies on epilepsy brains in animals mainly aim to identify undiagnosed seizure aetiologies, comorbidities and the substrate of drug-resistance as well as to relate clinical findings, including the focality of seizures, to morphological changes.

For a meaningful investigation, a certain data set has to be obtained from the veterinarian and/or the owner (Table 11) that clarifies predisposing factors and pedigree data, the possibility of preceding or precipitating events, possible exposure to toxins, neurological signs, phenomenology and time course of the paroxysmal disorder, MRI and EEG data, concurrent medical problems and therapy response.

Clinical data can be stratified, as Level 1 data (basic) that are mandatory and Level 2 data (detailed) that are optional. The questionnaires very much benefit from requesting as much objective and binary parameters as possible.

If not even Level 1 data can be obtained, efforts should not be wasted, since pathological findings are not able to produce and replace clinical observations. Those patients must not be included in scientific studies as neither impact nor relevance of tissue findings can be reproduced. The same holds true for acquisition of control animals. Seizure freedom has to be sought with the same stringency as seizure histories in epilepsy patients.

Conclusions and outlook

Epilepsy is a highly prevalent disease in veterinary practice that demands to be investigated using a multi- and transdisciplinary approach. Unfortunately, brain pathology has been broadly perceived as a confirmative rather than investigative tool in the retrospective work-up of epileptic companion pets. This lack of enthusiasm may be due to the paucity of tissue changes even in severe clinical presentations [56], the sometimes overwhelming severity of non-specific ictal and postictal changes, and the elusive ambition to localise an epileptic focus in the huge brain without EEG and functional imaging data or a thorough sampling scheme.

Even though the advances in human epileptology are dominated by the activities on focal epilepsy, we may profit from the experiences in those cases and from paradigms that were brought to light by studies in rodents. In fact, natural epilepsy in dogs and cats resembles an ideal playground to test hypotheses originating from "mice and men". Comparative neuropathological concepts, indeed, have unravelled important pathobiological data that may impact on the clinical management and prognostic considerations of epileptic animals [13, 14].

It remains to be seen that in animals advances in EEG, functional imaging and brain surgery will translate into surgical removal of epileptogenic brain tissue, other than lesionectomy [1]. Until then we should benefit from the availability of post-mortem brains the offer a precious opportunity to study anatomical, neurochemical and molecular determinants for seizure progression and drug resistance, if the tissue has been stored and processed accurately and changes, on high resolution, can be attributed to specific functional brain regions. By application of the procedures illustrated herein the caseload of epilepsies of unknown cause may be further narrowed [57, 58].

Most hitherto published tissue studies in dogs and cats, however, underscore even baseline neuroanatomical accuracy and lack reproducible sampling schemes. That way, the relevance of published findings for a larger population of epileptic animals remains obscure, at best.

Even if the investigations may be high pitched and restricted to specialised laboratories, accurate sampling of epileptic brains can be performed at virtually any place with minimal training requirements. The true impact of the studies, on the other hand, very much depends on these, less appreciated early investigational steps.

Since the mission of this group is to foster diagnosis, research and clinical care of epilepsy in companion animals, this paper aims to ensure efficient brain sampling by pathologists and neurologists. The above described guideline rather has been tested in untrained staff and rapidly can be implemented into every pathology laboratory that wishes to contribute to the alliance against epilepsy.

Additional file

Additional file 1: Video featuring a real time demonstration of systematic brain trimming. Please note, that other approaches may be necessary for distinct lesions and neurological signs.

Abbreviations

AN: Amygdaloid nucleus; Ansi: Ansiform lobule; Aqu: Mesencephalic aqueduct; ARAS: Ascending reticular activating system; BA: Basilar artery; CA: Cornu ammonis; CC: Caudal colliculus; CCG: Caudal composite gyrus; Cing: Cingulate gyrus; Cla: Claustrum; CN: Caudate nucleus; CN-III/-VI/-

VII: Cranial nerves III/VI/VII; CNS: Central nervous system; CoCa: Corpus callosum; Cru: Crura cerebri; CruS: Cruciate sulcus; Cul: Culmen; CV: Caudal vertex; DM: Dura mater; DNA: Deoxyribonucleic acid; EEG: Electroencephalography; ERC: Entorhinal cortex; FFPE: Formalin-fixed paraffin embedded; FISS: Fissures, interfoliar spaces, sulci; FisP: Primary fissure; Fol: Folium; Forn: Fornix; GFAP: Glial fibrillary acidic protein; HC: Hippocampal commissure; HE: Haematoxylin eosin; HOR: Horizontal section; HS: Hippocampal sclerosis; IC: Internal capsule; IF: Intercrural fossa; ILAE: International League Against Epilepsy; InsC: Insular cortex; IVETF: International Veterinary Epilepsy Task Force; LGN: Lateral geniculate nucleus; LoLa: Lateral lobule; LRS: Lateral rhinal sulcus; Mam: Mammillary bodies; MAP: Microtubule-associated protein; MCA: Middle cerebral artery; MRI: Magnetic resonance imaging; OB: Olfactory bulb; Ob: Obex; OC: Optic chiasm; PAG: Periaqueductal gray matter; Para: Paraflocculus; ParaH: Parahippocampal gyrus; PeRC: Perirhinal cortex; OV: Occipital vertex; PiLo: Piriform lobe; Pit: Pituitary stalk; PL: Pathological lesion; PoRC: Postrhinal cortex; PPC: Prepiriform cortex; PraeCG: Praecruciate gyrus; ProG: Prorean gyrus; ProS: Prorean sulcus; PSS: Presylvian sulcus; Pyr: Pyramis; RC: Rostral colliculus; RP: Rostral peduncle; SAG: Sagittal section; SN: Spetal nuclei; SO: Stria olfactoria; SOB: Supraoccipital bone; SplG: Splenial gyrus; SUDEP: Sudden Unexpected Death in Epilepsy; TB: Trimmed brain; TFOP: Transverse fibres of pons; Thal: Thalamus; TILT: Tilted section; TO: Tuberculum olfactorium; Tra: Trapezoid body; TS: Transverse section; Tub: Tuber; TVB: Temporoventral body; UB: Unfixed brain; Uv: Uvula; Verm: Vermis; VC: Visual cortex.

Competing interests

Following reimbursements, fees and funding have been received by the authors in the last three years and have been declared in the competing interest section. CR, RGF, HAV, KM, MP and JP have received fees for acting as a consultant for Boehringer Ingelheim (KM, MP: consultancy during development and approval of imepitoin; CR: pain consultancy; RGF, JP, HAV: consultancy pre and post launch of imepitoin). AT has been an advisor for Boehringer Ingelheim. SFMB, HAV and AT have been responsible principal investigator of several research studies concerning imepitoin financed by Boehringer Ingelheim. SFMB, HAV, JP, HP, MB, CR and AF received speaking fees from Boehringer Ingelheim. HP received consulting and speaking fees and funding for a collaborative project from Eisai Co. LTD. HAV received funding for a collaborative project from Desitin and Nestlé Purina Research. AF and LDR received reimbursements from Boehringer Ingelheim. LDR has received consulting and speaking fees from Vetoquinol. MP has received consultant fees for Aratana. The other authors declared that they have no competing interests.

Authors' contributions

KM chaired the neuropathology working group (KMat, MPB, MR, FFF, AF, EW) together with MPB and wrote the first draft of the consensus paper. MPB, MR, FFF, AF, EW and HAV contributed essentially to the final draft. Reproducibility and reliability of the protocol were evaluated in laboratory practice by KMat, MPB, MR, FFF and EW. HAV chaired the IVETF. All other authors have read, critiqued, commented and approved the final manuscript.

Authors' information

Corresponding author and chair of neuropathology working group: Kaspar Matiasek, Section of Clinical & Comparative Neuropathology, Centre for Clinical Veterinary Medicine, Ludwig-Maximillians-University, Veterinärstr. 13, 80539 Munich, Germany.
Co-chair of neuropathology working group: Martí Pumarola Batlle, Department of Animal Medicine and Surgery, Veterinary Faculty, Universitat Autònoma de Barcelona, Campus UAB, Bellaterra, 08193 Barcelona, Spain.
Other members of the neuropathology working group
Chair of IVETF: Holger A Volk, Department of Clinical Science and Services, Royal Veterinary College, Hatfield, Hertfordshire, UK.
All other co-authors are members of IVETF, are list alphabetically and have approved the consensus statements.

Acknowledgements

This paper implements mutual experiences in epilepsy pathology collected by esteemed colleagues and coworkers. Many of the concepts have been based on comparative algorithms that Prof. Erwin Dahme, LMU Munich, addressed already fourty years ago. Individual approaches however would not have been intertwined to this systematic work-up without the groundbreaking efforts to clarify and standardise epilepsy pathology in humans by Prof. Ingmar Blümcke, German Epilepsy Registry and the Neuropathological Institute, University of Erlangen. The authors also would like to thank the research office for assessing the manuscript according to the Royal Veterinary College's code of good research practice (Authorisation Number – CCS_ 01029). The authors are grateful to all owners of epileptic pets and veterinary colleagues who have inspired the group to create consensus statements. This study was not financially supported by any organization or grant.

Author details

[1]Section of Clinical and Comparative Neuropathology, Centre for Clinical Veterinary Medicine, Ludwig-Maximilians-University, Veterinärstr. 13, 80539 Munich, Germany. [2]Department of Animal Medicine and Surgery, Veterinary Faculty, Universitat Autònoma de Barcelona, Campus UAB Bellaterra, 08193 Barcelona, Spain. [3]Department of Animal and Clinical Sciences, Faculty of Health and Medical Sciences, University of Copenhagen, Frederiksberg C, Denmark. [4]Department of Small Animal Medicine and Clinical Biology, Faculty of Veterinary Medicine, Ghent University, Salisburylaan 133, Merelbeke 9820, Belgium. [5]Animal Health Trust, Lanwades Park, Kentford, Newmarket CB8 7UUSuffolk, UK. [6]Fernside Veterinary Centre, 205 Shenley Road, Borehamwood SG9 0THHertfordshire, UK. [7]University of Melbourne, 250 Princes Highway, Weibee 3015VIC, Australia. [8]North Carolina State University, 1052 William Moore Drive, Raleigh, NC 27607, USA. [9]University of Minnesota College of Veterinary Medicine, D426 Veterinary Medical Center, 1352 Boyd Avenue, St. Paul, MN 55108, USA. [10]Clinical Unit of Internal Medicine Small Animals, University of Veterinary Medicine, Veterinärplatz 1, 1210 Vienna, Austria. [11]Vet Extra Neurology, Broadleys Veterinary Hospital, Craig Leith Road, Stirling FK7 7LEStirlingshire, UK. [12]College of Veterinary Medicine, University of Georgia, 501 DW Brooks Drive, Athens, GA 30602, USA. [13]Chicago Veterinary Neurology and Neurosurgery, 3123 N. Clybourn Avenue, Chicago, IL 60618, USA. [14]Department of Pharmacology, Toxicology and Pharmacy, Ludwig-Maximillians-University, Königinstr. 16, 80539 Munich, Germany. [15]Fitzpatrick Referrals, Halfway Lane, Eashing, Godalming GU7 2QQSurrey, UK. [16]School of Veterinary Medicine, Faculty of Health and Medical Sciences, University of Surrey, Guildford GU2 7TESurrey, UK. [17]Department of Small Animal Medicine and Surgery, University of Veterinary Medicine Hannover, Bünteweg 9, 30559 Hannover, Germany. [18]Department of Clinical Science and Services, Royal Veterinary College, Hatfield AL9 7TAHertfordshire, UK.

Received: 5 June 2015 Accepted: 29 June 2015
Published online: 28 August 2015

References

1. Shihab N, Summers BA, Benigni L, McEvoy AW, Volk HA. Novel approach to temporal lobectomy for removal of a cavernous hemangioma in a dog. Vet Surg. 2014;43(7):877–81.
2. Urbach H. The Term "Epileptogenic Lesion" and How to Use it. In: Urbach H, editor. MRI in Epilepsy. Heidelberg: Springer Berlin; 2013. p. 21–3.
3. Wolf M, Bruehschwein A, Sauter-Louis C, Sewell AC, Fischer A. An inherited episodic head tremor syndrome in Doberman pinscher dogs. Mov Disord. 2011;26(13):2381–6.
4. Packer RM, Berendt M, Bhatti S, Charalambous M, Cizinauskas S, De Risio L, et al. Inter-observer agreement of canine and feline paroxysmal event semiology and classification by veterinary neurology specialists and non-specialists. BMC Vet Res. 2015;11(1):39.
5. Seneviratne U, Cook M, D'Souza W. Focal abnormalities in idiopathic generalized epilepsy: a critical review of the literature. Epilepsia. 2014;55(8):1157–69.
6. Pakozdy A, Gruber A, Kneissl S, Leschnik M, Halasz P, Thalhammer JG. Complex partial cluster seizures in cats with orofacial involvement. J Feline Med Surg. 2011;13(10):687–93.
7. Lomoio S, Necchi D, Mares V, Scherini E. A single episode of neonatal seizures alters the cerebellum of immature rats. Epilepsy Res. 2011;93(1):17–24.
8. Jokinen TS, Metsahonkala L, Bergamasco L, Viitmaa R, Syrja P, Lohi H, et al. Benign familial juvenile epilepsy in Lagotto Romagnolo dogs. J Veterinary Internal Medicine / American College of Veterinary Internal Medicine. 2007;21(3):464–71.

9. Manford M, Fish DR, Shorvon SD. An analysis of clinical seizure patterns and their localizing value in frontal and temporal lobe epilepsies. Brain. 1996;119(Pt 1):17–40.
10. O'Muircheartaigh J, Richardson MP. Epilepsy and the frontal lobes. Cortex. 2012;48(2):144–55.
11. Toyoda I, Bower MR, Leyva F, Buckmaster PS. Early activation of ventral hippocampus and subiculum during spontaneous seizures in a rat model of temporal lobe epilepsy. J Neurosci. 2013;33(27):11100–15.
12. Cavazos JE, Das I, Sutula TP. Neuronal loss induced in limbic pathways by kindling: evidence for induction of hippocampal sclerosis by repeated brief seizures. J Neurosci. 1994;14(5 Pt 2):3106–21.
13. Wagner E, Rosati M, Molin J, Foitzik U, Wahle AM, Fischer A, et al. Hippocampal Sclerosis in Feline Epilepsy. Brain Pathology. 2014.
14. Klang A, Schmidt P, Kneissl S, Bago Z, Vincent A, Lang B, et al. IgG and complement deposition and neuronal loss in cats and humans with epilepsy and voltage-gated potassium channel complex antibodies. J Neuropathol Exp Neurol. 2014;73(5):403–13.
15. Pakozdy A, Halasz P, Klang A, Bauer J, Leschnik M, Tichy A, et al. Suspected limbic encephalitis and seizure in cats associated with voltage-gated potassium channel (VGKC) complex antibody. J Veterinary Internal Medicine/ American College of Veterinary Internal Medicine. 2013;27(1):212–4.
16. Thom M. Review: Hippocampal sclerosis in epilepsy: a neuropathology review. Neuropathol Appl Neurobiol. 2014;40(5):520–43.
17. Blumcke I, Thom M, Aronica E, Armstrong DD, Bartolomei F, Bernasconi A, et al. International consensus classification of hippocampal sclerosis in temporal lobe epilepsy: a Task Force report from the ILAE Commission on Diagnostic Methods. Epilepsia. 2013;54(7):1315–29.
18. Milne ME, Anderson GA, Chow KE, O'Brien TJ, Moffat BA, Long SN. Description of technique and lower reference limit for magnetic resonance imaging of hippocampal volumetry in dogs. Am J Vet Res. 2013;74(2):224–31.
19. Kuwabara T, Hasegawa D, Kobayashi M, Fujita M, Orima H. Clinical magnetic resonance volumetry of the hippocampus in 58 epileptic dogs. Vet Radiol Ultrasound. 2010;51(5):485–90.
20. Hudson LP, Munoz DG, Miller L, McLachlan RS, Girvin JP, Blume WT. Amygdaloid sclerosis in temporal lobe epilepsy. Ann Neurol. 1993;33(6):622–31.
21. Lahl R, Villagran R, Teixera W. Neuropathology of focal epilepsies. John Libbey Eurotext. 2003.
22. Cheong JY, Wong C, Bleasel A, Varikatt W, Ng T, Dexter MA. Late onset Rasmussen's encephalitis with triple pathology. J Clin Neurosci. 2009;16(12):1677–81.
23. Auer RN, Kalimo H, Olsson Y, Siesjo BK. The temporal evolution of hypoglycemic brain damage. II. Light- and electron-microscopic findings in the hippocampal gyrus and subiculum of the rat. Acta Neuropathol. 1985;67(1–2):25–36.
24. Potschka H, Fischer A, von Ruden EL, Hulsmeyer V, Baumgartner W. Canine epilepsy as a translational model? Epilepsia. 2013;54(4):571–9.
25. Singer M. The brain of the dog in section. Philadelphia: Saunders; 1962.
26. Reinoso-Suárez F. Topographischer Hirnatlas der Katze für experimental-physiologische Untersuchungen. E. Merck AG: Darmstadt; 1961.
27. Pakozdy A, Angerer C, Klang A, Konig EH, Probst A. Gyration of the Feline Brain: Localization, Terminology and Variability. Anatomia, Histologia, Embryologia. 2014.
28. Gil VA. Functional neuroanatomy of the dog. Bellaterra: Universitat Autònoma de Barcelona; 2012.
29. Kornegay JN, Oliver Jr JE, Gorgacz EJ. Clinicopathologic features of brain herniation in animals. J Am Vet Med Assoc. 1983;182(10):1111–6.
30. Masuo Y, Imai T, Shibato J, Hirano M, Jones OA, Maguire ML, et al. Omic analyses unravels global molecular changes in the brain and liver of a rat model for chronic Sake (Japanese alcoholic beverage) intake. Electrophoresis. 2009;30(8):1259–75.
31. Bando SY, Alegro MC, Amaro Jr E, Silva AV, Castro LH, Wen HT, et al. Hippocampal CA3 transcriptome signature correlates with initial precipitating injury in refractory mesial temporal lobe epilepsy. PLoS ONE. 2011;6(10):e26268.
32. Thom M. Neuropathology of Epilepsy. In: Rugg-Gunn F, Smalls J, editors. From Membranes to Mankind - A Practical Guide to Epilepsy. 14th ed. London: Epilepsy Society; 2013. p. 27–50.
33. Katelaris A, Kencian J, Duflou J, Hilton JM. Brains at necropsy: to fix or not to fix? J Clin Pathol. 1994;47(8):718–20.
34. Adamec RE, Stark-Adamec C. Partial kindling and emotional bias in the cat: lasting aftereffects of partial kindling of the ventral hippocampus. I. Behavioral changes. Behav Neural Biol. 1983;38(2):205–22.
35. Adamec RE. Partial kindling and behavioral pathologies. Int Rev Neurobiol. 2001;45:409–34.
36. Adamec R. Behavioral and epileptic determinants of predatory attack behavior in the cat. The Canadian J Neurological Sciences Le J Canadien des Sciences Neurologiques. 1975;2(4):457–66.
37. Sasaki M, Tohyama K, Matsunaga S, Nakamura M, Tomizawa N, Inoue T, et al. MRI identification of dorsal hippocampus homologue in human brain. Neuroreport. 2004;15(14):2173–6.
38. Witter MP, Groenewegen HJ. Laminar origin and septotemporal distribution of entorhinal and perirhinal projections to the hippocampus in the cat. J Comp Neurol. 1984;224(3):371–85.
39. Woznicka A, Kosmal A. Cytoarchitecture of the canine perirhinal and postrhinal cortex. Acta Neurobiol Exp. 2003;63(3):197–209.
40. Kowalska DM, Kusmierek P, Kosmal A, Mishkin M. Neither perirhinal/ entorhinal nor hippocampal lesions impair short-term auditory recognition memory in dogs. Neuroscience. 2001;104(4):965–78.
41. Margerison JH, Corsellis JA. Epilepsy and the temporal lobes. A clinical, electroencephalographic and neuropathological study of the brain in epilepsy, with particular reference to the temporal lobes. Brain. 1966;89(3):499–530.
42. Crooks R, Mitchell T, Thom M. Patterns of cerebellar atrophy in patients with chronic epilepsy: a quantitative neuropathological study. Epilepsy Res. 2000;41(1):63–73.
43. Baiker K, Hofmann S, Fischer A, Godde T, Medl S, Schmahl W, et al. Leigh-like subacute necrotising encephalopathy in Yorkshire Terriers: neuropathological characterisation, respiratory chain activities and mitochondrial DNA. Acta Neuropathol. 2009;118(5):697–709.
44. Fischer M, Hossmann KA. No-reflow after cardiac arrest. Intensive Care Med. 1995;21(2):132–41.
45. Oehmichen M, Auer RN, König HG. Methods in Forensic Neuropathology. In: Oehmichen M, editor. Forensic Neuropathology and Associated Neurology. Berlin: Springer; 2006. p. 83–94.
46. Jeans A, Esiri M. Brain histology. Pract Neurol. 2008;8(5):303–10.
47. Blumcke I, Thom M, Aronica E, Armstrong DD, Vinters HV, Palmini A, et al. The clinicopathologic spectrum of focal cortical dysplasias: a consensus classification proposed by an ad hoc Task Force of the ILAE Diagnostic Methods Commission. Epilepsia. 2011;52(1):158–74.
48. Pitkanen A, Nissinen J, Nairismagi J, Lukasiuk K, Grohn OH, Miettinen R, et al. Progression of neuronal damage after status epilepticus and during spontaneous seizures in a rat model of temporal lobe epilepsy. Prog Brain Res. 2002;135:67–83.
49. Wang L, Liu YH, Huang YG, Chen LW. Time-course of neuronal death in the mouse pilocarpine model of chronic epilepsy using Fluoro-Jade C staining. Brain Res. 2008;1241:157–67.
50. Kobow K, Auvin S, Jensen F, Loscher W, Mody I, Potschka H, et al. Finding a better drug for epilepsy: antiepileptogenesis targets. Epilepsia. 2012;53(11):1868–76.
51. Ahmed Z, Shaw G, Sharma VP, Yang C, McGowan E, Dickson DW. Actin-binding proteins coronin-1a and IBA-1 are effective microglial markers for immunohistochemistry. J Histochem Cytochem. 2007;55(7):687–700.
52. Hwang IK, Lee CH, Li H, Yoo KY, Choi JH, Kim DW, et al. Comparison of ionized calcium-binding adapter molecule 1 immunoreactivity of the hippocampal dentate gyrus and CA1 region in adult and aged dogs. Neurochem Res. 2008;33(7):1309–15.
53. Park ES, Uchida K, Nakayama H. Establishment of a rat model for canine necrotizing meningoencephalitis (NME). Vet Pathol. 2014;51(6):1151–64.
54. van Vliet EA, Aronica E, Gorter JA. Blood–brain barrier dysfunction, seizures and epilepsy. Seminars in cell & Developmental biology. 2014.
55. Isoardo G, Morra I, Chiarle G, Audrito V, Deaglio S, Melcarne A, et al. Different aquaporin-4 expression in glioblastoma multiforme patients with and without seizures. Mol Med. 2012;18:1147–51.
56. Buckmaster PS, Smith MO, Buckmaster CL, LeCouteur RA, Dudeck FE. Absence of temporal lobe pathology in dogs with medically intractable epilepsy. J Veterinary Internal Medicine / American College of Veterinary Internal Medicine. 2002;16(1):95–9.
57. Schriefl S, Steinberg TA, Matiasek K, Ossig A, Fenske N, Fischer A. Etiologic classification of seizures, signalment, clinical signs, and outcome in cats with

seizure disorders: 91 cases (2000–2004). J Am Vet Med Assoc. 2008;233(10):1591–7.
58. Wahle AM, Bruhschwein A, Matiasek K, Putschbach K, Wagner E, Mueller RS, et al. Clinical characterization of epilepsy of unknown cause in cats. J Veterinary Internal Medicine / American College of Veterinary Internal Medicine. 2014;28(1):182–8.
59. Lüders HO, Awad I. Conceptional considerations. In: Lüders HO, editor. Epilepsy Surgery. New York: Raven; 1992. p. 51–62.