Canine epilepsy: separating the wood from the trees

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Editorial

Every 100th patient appearing on the doorstep of a busy first opinion practice will be presented with seizures and two thirds of these patients will have epilepsy (Heske and others 2014; Kearsley-Fleet and others 2013). Despite the frequency in occurrence and a plethora of studies been published in the field, the clinician remains puzzled of what terminology is the correct one to use, how to diagnose the different types of epilepsy, how and when to treat best and when change in treatment is necessary?

In 2015, a group of Veterinary Neurology Specialists and Non-specialists came together to form the International Veterinary Epilepsy Task Force (IVETF). The IVETF's 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"(Volk 2015). The IVETF wants to represent the "chain of care" involving a broad range of stakeholders (veterinary and human neurologists and neuroscientists, practitioners, neuropharmacologists and neuropathologists) to ensure that the produced consensus statements are pragmatic and 'user-friendly' for daily use. More than 25 co-authors were involved in the process of developing seven consensus statements:

1. International Veterinary Epilepsy Task Force consensus report on epilepsy definition, classification and terminology in companion animals (Berendt and others 2015)
2. International Veterinary Epilepsy Task Force Consensus Proposal: Diagnostic approach to epilepsy in dogs (De Risio and others 2015)
3. International Veterinary Epilepsy Task Force current understanding of idiopathic epilepsy of genetic or suspected genetic origin in purebred dogs (Huelsmeyer and others 2015)
4. International Veterinary Epilepsy Task Force consensus proposal: Medical treatment of canine epilepsy in Europe (Bhatti and others 2015)

5. International Veterinary Epilepsy Task Force Consensus Proposal: Outcome of therapeutic interventions in canine and feline epilepsy (Potschka and others 2015)
6. International Veterinary Epilepsy Task Force recommendations for a veterinary epilepsy-specific MRI protocol (Rusbridge and others 2015)
7. International Veterinary Epilepsy Task Force recommendations for systematic sampling and processing of brains from epileptic dogs and cats (Matiasek and others 2015)

In 2016, a complimentary consensus statement about seizure management was published under the umbrella of the American College of Veterinary Internal Medicine (ACVIM) (Podell and others 2016). The ACVIM's and IVETF's consensus statements are based on evidence-based medicine, but also consider collective expertise where such evidence is conflicting or lacking. All the consensus statements are freely available online for the interested reader[1]. A potted version of some of the highlights can be found below:

What terminology is the correct one to use (Berendt and others 2015)?

How best to talk the talk in Epilepsy - the IVETF proposed to differentiate between the term seizure and epileptic seizure. The term seizure can be used for any sudden occurring, brief and transient episode and does not necessarily imply that the event is epileptic. It is therefore better to use the term epileptic seizure when you are certain of the nature of the episode. Epileptic seizures are defined as "manifestations of excessive synchronous, usually self-limiting epileptic activity of neurons in the brain. This results in a transient occurrence of signs which may be characterised 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"(Berendt and others 2015).

[1] http://www.biomedcentral.com/bmcvetres/series/IVETF_consensus_reports; http://onlinelibrary.wiley.com/doi/10.1111/jvim.13841/abstract

Epileptic seizures can be differentiated into focal and generalised epileptic seizures, and focal epileptic seizures can evolve into generalised epileptic seizures. Focal epileptic seizures originate within a neural network of one cerebral hemisphere. The onset and the resulting clinical signs are consistent from one epileptic seizure to another. An example could be the animal presents with epileptic seizures which always start with a twitching of its right facial muscles. Focal epileptic seizures are often asymmetrical in presentation. On the other hand, a generalised epileptic seizure is characterised by major involvement of both cerebral hemispheres. Epileptic seizures can further be described depending on their expression(s) of autonomic, motor or behavioural features.

The IVETF defined epilepsy conceptually as a brain disease which is "characterised by an enduring predisposition to generate epileptic seizures", however, realised that a more practical definition was needed. The definition for epilepsy which can be used in daily practice is that epilepsy is defined as "at least two unprovoked epileptic seizures >24 h apart". The IVETF proposed not to use the term epilepsy for epileptic seizures which are secondary or reactive to a metabolic or toxic transient disturbance in function, which when rectified will result in a cessation of epileptic activity. The term reactive seizures should be used for these.

How to diagnose the different types of epilepsy (Berendt and others 2015; De Risio and others 2015)?

After the clinician has determined that the animal has recurrent epileptic seizures, the cause of the epileptic seizures need to be determined. Broadly speaking, the IVETF proposed to differentiate idiopathic epilepsy from structural epilepsy. The former term cryptogenic (possible symptomatic) epilepsy has been heavily discussed in human medicine, as some of them were identified later to be genetic in origin and this resulted human medicine to move away from this term and use the term epilepsy of unknown cause for epilepsy in which an

underlying cause could not be identified. This term was also listed in the IVETF statement as a "bucket term" for all the epilepsies which cannot be classified as idiopathic or structural epilepsy.

Structural epilepsy is caused by any disease which alters the brain structure such as vascular, inflammatory/infectious, traumatic, anomalous/developmental, neoplastic and degenerative diseases. After long debate the IVETF continues to recommend to use the term idiopathic epilepsy as it is well established. However, idiopathic epilepsy should be seen as a framework term which can be further differentiated into

1. "Idiopathic epilepsy (genetic epilepsy)—a causative gene for epilepsy has been identified/confirmed genetic background" (Berendt and others 2015).
2. "Idiopathic epilepsy (suspected genetic epilepsy)" – this applies for those cases where you have family or breed history of epilepsy (see also Huelsmeyer and others 2015).
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".

The IVETF also provided guidelines of how to confirm idiopathic epilepsy diagnostically and introduced a three tier level of confidence for the diagnosis of idiopathic epilepsy (De Risio and others 2015). In brief, the first tier can be diagnosed by any first opinion practitioner if an animal has "≥ 2 unprovoked epileptic seizures occurring ≥ 24h apart, age at epileptic seizure onset 6 months to 6 years, unremarkable inter-ictal physical and neurological examination, no clinically significant abnormalities on minimum database blood tests and urinalysis". A family history of epilepsy adds strength to the diagnosis. The next level of confidence can be reached (tier 2) by having also an unremarkable dynamic

bile acid test, MRI (epilepsy-specific MRI protocol (Rusbridge and others 2015)) and CSF analysis. The highest level of confidence (tier 3) can be reached when in addition to the requirements fulfilled in tier 1 and 2 characteristic EEG changes are present.

How and when to treat best and when change in treatment is necessary (Bhatti and others 2015; Podell and others 2016)?

The ACVIM's and IVETF's consensus statements agree in most parts of when medical treatment should be initiated. Treatment should be started when structural epilepsy is present, the period between seizures is equal or less than 6 months, the frequency of seizures is increasing over the last 3 inter-ictal periods, the animal had a status epilepticus, cluster seizures, severe or debilitating postictal signs. Both also agree that the evidence (Charalambous and others 2014; Charalambous and others 2016) is strongest for starting an otherwise healthy dog with epilepsy on Imepitoin or Phenobarbital. The IVETF, however, pointed out that in Europe, Imepitoin should only be prescribed for dogs with idiopathic epilepsy which have single generalised epileptic seizures.

The IVETF's aim is to ideally achieve seizure freedom or at least an "extension of the inter-seizure interval to three times the longest pre-treatment inter-seizure interval and for a minimum of three months"(Bhatti and others 2015; Potschka and others 2015). The IVETF does recognizes partial treatment success which is characterized by an at least 50% reduction in seizure frequency and/or seizure severity. It is known that a risk factor for poorer seizure control is a high seizure density (Packer and others 2014) and patients with cluster seizures might need to be treated more aggressively sooner. If treatment is not successful and/or treatment is not well tolerated treatment might need to be altered. Other factors apart from treatment success which might need to be considered when selecting a second anti-epileptic drug is the selection of a drug with a different mechanism of action,

potential harmful drug-interactions and a risk-benefit analysis of polypharmacy versus quality of life (Podell and others 2016).

The IVETF mainly recommends potassium bromide as an add-on medication, considering also local legal frameworks (Bhatti and others 2015). The ACVIM provides only a moderate level of recommendation of which drug best to chose from for second line treatment; Drugs mentioned are Phenobarbital, potassium bromide, Levetiracetam and Zonisamide (Podell and others 2016). The ACVIM also provides recommendations about non-pharmacological treatment options and the potential of novel diets for the management of epilepsy (Podell and others 2016), which might improve seizure control and reduce behavioural comorbidities(Law and others 2015; Packer and others 2016). Both groups highlight the importance of owner education and the importance of considering quality of life in the successful management of epilepsy.

In conclusion, as a busy clinician one can easily not see the forest for the trees in epilepsy. Epilepsy is a rather complex disease and can be challenging to diagnose and treat. The recent published consensus statements are useful resources to help give an expert overview of what is relevant.

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