Epilepsy and movement disorders: localisation and diagnostics

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Epilepsy is, although it varies per country, seen in 0.5 to 1 % of all dogs (1). This percentage varies for several reasons. First of all, it depends on the type of breeds people tend to have in a country. For instance, the Belgian Shepherd is rarely seen in the UK whereas it is quite popular in the Netherlands. The Tervueren variant had and has a rather high frequency and as such this will influence the number of epilepsy cases in both countries (2). Secondly there is a huge difference within the various breeds. A survey performed in the Netherlands revealed that f.i. the Dutch shepherd hardly suffers from epilepsy (<0.2%) whereas the Dutch Partridge dog has a rather high frequency (>3%) (3). Thirdly the possibility exists that the incidence for a specific disease in a breed varies per country. American Tervueren Shepherds are most likely genetically not completely the same as Dutch Tervueren shepherds. Furthermore, with the introduction of the smartphone we are able to characterize more properly. Although the description of the owner is important we can better classify thanks to the film's owners provide to us (4). And last but not least there is always the issue of interpretation. A recent survey among fellow diplomates revealed that there is a clear interobserver variance (5). Hence, even among academics it is possible that we see things differently.
Epilepsy can be categorized based on aetiology as well as on how it looks (1). Epilepsy was defined as "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" (1). It is further subdivided into generalised and focal seizures.

Generalised seizures or epilepsy.
The hallmark is the fact that both hemispheres are involved. The most seen form is the so-called generalised tonic-clonic seizure. The animal is suffering from a clear loss of consciousness. The seizure may present itself with a pre-ictale phase which consists of two parts of which we veterinarians can only observe the prodrome. This is a phase in which the animal can be different (busier, quiet etc). The second phase cannot be observed as it is a symptom rather than a clinical sign (1). During the ictus the animal often falls to its side (or was already laying) and first will show a tonic period during which an ophistonus and extension of all four legs may occur. It is directly followed by so-called clonic seizure that presents itself with paddling or jerking movements with all legs. During the seizure the animal may be vocal, salivate, urinate and defecate. The ictale phase can last from seconds to minutes. After the ictus a post-ictal phase is seen which may take seconds up to days during which an animal can be for instance unable to walk, ataxic, drowsy, aggressive, restless, etc (6). Not rarely the animal may show some (temporarily) loss of memory. Both a long ictale phase as well as post-ictal phase are for both animals and owners a clear loss of quality of life (7). Besides this tonic-clonic seizure five other forms have been identified (1). Those are a 2) tonic seizure, 3) clonic seizure, 4) atonic seizures, 5) myoclonic seizure and an absence seizure which was formerly call petit mal. Just recently absence seizures were identified in a Rhodesian Ridgeback with Generalised Myoclonic Epilepsy using EEG monitoring (8).

Focal seizures were defined in a recent work (Berendt et al., 2015) as: "Focal epileptic seizures are characterized by lateralized and/or regional signs (motor, autonomic or behavioural signs, alone or in combination). Focal epileptic seizures can present as: 1) 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), 2) Autonomic (with parasympathetic and epigastric components e.g. dilated pupils, hypersalivation or vomiting) and 3) 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, restlessness, unexplainable fear reactions or abnormal attention seeking/'clinging' to the owner." And although this definition is clear it may be very difficult to distinguish focal seizures, without EEG's, from certain movement disorders. Hence much realise on the knowledge and experience of the veterinarian / neurologist (4). Several handbooks and manuscripts nowadays provide on-line film material which makes it possible to compare what we have observed (4, 8-11). We no longer tend to categorize focal seizure into simple and complex focal seizures as the inclusion criterium for the latter, a decreased conscious level, may be very hard to observe. Hence the recommendation was done to abolish this subdivision (1).
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We still use aetiology to further approach epilepsy as a syndrome. But the proposal has been made to classify them into primary idiopathic, primary presumably genetic, genetic, secondary and reactive (1). Whether the seizures are focal, generalised or the combination of focal and generalised is not a criterium to classify them although certain secondary causes tend present themselves as focal seizures (1, 12). The reader is referred for a detailed summary of the different types of epilepsy and breeds to a recent published overview (12).
In most cases it will be possible to distinguish secondary and reactive epilepsy from the primary aetiologies (13). And the discovery of a a small number of mutation causing epilepsy even some of the genetic forms can be identified and eradicated (8, 14, 15).

What other criteria can we use after excluding secondary or reactive causes to strengthen our diagnosis? According to the author it will be clearly be more prevalent in the pedigree dogs or look-alike dogs. And furthermore, we use the following checklist (1):
1) The first epileptic seizure is seen between the ages of 6 months and 5 years. Seizures seen at other ages usually have an underlying disorder although this is not always the case. There have been various reports in which the dogs were presented outside this frame (16-18).
2) Usually the seizures have for each breed a specific presentation (12).
3) The animal is healthy between seizures, and other disorders are not found.
4) A clear relation between the occurrence of a seizure and exercise and/or feeding does not exist. Again, it must be raised that in some cases the seizures are triggered by some type of excitement (as in f.i. cataplexy and narcolepsy) or emotional situations.
5) Normally no underlying disorders

Movement disorders
Although not new one could say that we veterinarians for years haven't recognized all neurological disorders correctly (4). In many cases we had to use the oral information an owner provided and how can we, for instance, reliably differentiate a myoclonus form a myoclonic epilepsy. Most likely it is thanks to the invention of the smart phone with a camera function that the field of veterinary movement disorders has developed itself this rapidly during the last 15 years.

The term movement disorders (MD) is used to group all involuntary movements such as tremors, twitches, fasciculations, myokymia, neuromyotonia and paroxysmal dyskinesias. The majority of movement disorders, tremors, paroxysmal dyskinesias, myoclonus are the result of a problem within the extrapyramidal system: the basal ganglia. Myotonia is of a muscular origin, myokymia and neuromyotonia peripheral of origin.

Most likely the most frequently observed MD is a tremor (10). Tremors can be subdivided into resting tremors and action-related tremors. In veterinary medicine a resting tremor has not been clearly identified but in humans the cause of a resting tremor is Parkinson. Parkinson, a neurodegenerative disorder arises from the slow degradation of the brainstem and several areas of the brain. When the substantia nigra gets affected a loss of dopamine arises with a.o. the clinical features of a resting tremor, stiff gait, bradykinesia, hypokinesia, akinesia as a result. Action tremors are seen in veterinary medicine and are further subdivided into kinetic tremors and postural tremors. Intention tremors arise when the animal is performing a purposeful movement and disappears at rest. The neurolocalisation is typically the cerebellum (10). Several toxic, metabolic, infectious and degenerative disorders of the cerebellum have been described causing this type of tremor. Action-related postural tremors are the orthostatic tremor in the Great Dane and Newfoundlander, the idiopathic head tremor often seen in Bulldogs (and several other type of dogs) and of course the benign idiopathic postural tremor in the (hind)legs of older dogs (10). Postural tremors disappear when the animal starts walking and this can be used to differentiate.
Cramps, twitches, fasciculation, myokymia, neuromyotonia, tetany and tetanus are all features of a peripheral nerve hyperexcitability (PNH) (10, 11, 19). In some cases hereditary channelopathies have been identified (11).
Paroxysmal dyskinesia's (PD's) may be a challenge to properly diagnose. By definition it is a group of conditions characterised by episodes of abnormal movement that are self-limiting (4). Furthermore the episodes are painless, autonomic signs are absent and consciousness is not impaired which would most likely be the case in epilepsy (4). Furthermore there is no post-ictal phase and the episodes last for seconds to hours (4). The latter will not be the case in epilepsy. PD's are caused by dysfunction of the basal ganglia. In a rare number of cases there may be some overlap with epilepsy. In humans PD's are classified into Paroxysmal Kinesigenic Dyskinesia (PKD), Paroxysmal Nonkinesigenic Dyskinesia (PNKD) and Paroxysmal Exertion-Induced Dyskinesia (PED) (20). Lowrie and Garosi (2017) proposed for veterinary medicine a altered classification: 1) genetic causes (Episodic falling CKCS; PD SCWT, PD in 'het Markiesje'), 2) dietary causes (Gluten in the Border Terrier), secondary causes (drugs such as propofol, encephalitis etc) and unidentified causes. A well-known typical example is Scotty Cramp is a.o. the Scottish terrier. Although presumably hereditary it has not been proven yet.

The correct recognition of all these syndromes may be very difficult but with our growing knowledge also in veterinary medicine we have been able to categorize most reported syndromes

Literatuur

1. Berendt M, Farquhar RG, Mandigers PJ, Pakozdy A, Bhatti SF, De Risio L, et al. International veterinary epilepsy task force consensus report on epilepsy definition, classification and terminology in companion animals. BMC Vet Res. 2015;11:182.
2. Hulsmeyer VI, Fischer A, Mandigers PJ, DeRisio L, Berendt M, Rusbridge C, et al. International Veterinary Epilepsy Task Force's current understanding of idiopathic epilepsy of genetic or suspected genetic origin in purebred dogs. BMC Vet Res. 2015;11:175.
3. Mandigers PJJ. Het voorkomen van epilepsie bij de Nederlandse hondenrassen. Tijdschrift voor diergeneeskunde. 2017(2):28-32.
4. Lowrie M, Garosi L. Classification of involuntary movements in dogs: Paroxysmal dyskinesias. Vet J. 2017;220:65-71.
5. 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;11:39.
6. Packer RMA, Volk HA, Fowkes RC. Physiological reactivity to spontaneously occurring seizure activity in dogs with epilepsy and their carers. Physiol Behav. 2017;177:27-33.
7. Hamers MFN, Diaz-Espineira M, Mandigers PJJ. Canine epilepsy: a survey on the owners' perspective of quality of life. Voorjaarsdagen; The Hague2017.
8. Wielaender F, Sarviaho R, James F, Hytonen MK, Cortez MA, Kluger G, et al. Generalized myoclonic epilepsy with photosensitivity in juvenile dogs caused by a defective DIRAS family GTPase 1. Proc Natl Acad Sci U S A. 2017;114(10):2669-74.
9. Bagley RS, Platt SR. Tremors, involuntary movements and paroxysmal disorders. Platt SR, Olby NJ, editors. Gloucester: BSAVA; 2013. 232-51 p.
10. Lowrie M, Garosi L. Classification of involuntary movements in dogs: Tremors and twitches. Vet J. 2016;214:109-16.
11. Vanhaesebrouck AE, Bhatti SF, Franklin RJ, Van Ham L. Myokymia and neuromyotonia in veterinary medicine: a comparison with peripheral nerve hyperexcitability syndrome in humans. Vet J. 2013;197(2):153-62.
12. Hulsmeyer V, Fischer A, Mandigers PJJ, L. D, Berendt M, C.R. R, et al. International Veterinary Epilepsy Task Force's current understanding of idiopathic epilepsy of genetic or suspected genetic origin in purebred dogs. BMC Veterinary Research. 2015;11.
13. Bhatti SF, De Risio L, Munana K, Penderis J, Stein VM, Tipold A, et al. International Veterinary Epilepsy Task Force consensus proposal: medical treatment of canine epilepsy in Europe. BMC Vet Res. 2015;11:176.
14. 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.
15. Jokinen TS, Metsahonkala L, Bergamasco L, Viitmaa R, Syrja P, Lohi H, et al. Benign familial juvenile epilepsy in Lagotto Romagnolo dogs. Journal of veterinary internal medicine / American College of Veterinary Internal Medicine. 2007;21(3):464-71.
16. Jaggy A, Bernardini M. Idiopathic epilepsy in 125 dogs: a long-term study. Clinical and electroencephalographic findings. The Journal of small animal practice. 1998;39(1):23-9.
17. Kathmann I, Jaggy A, Busato A, Bartschi M, Gaillard C. Clinical and genetic investigations of idiopathic epilepsy in the Bernese mountain dog. The Journal of small animal practice. 1999;40(7):319-25.
18. Lengweiler C, Jaggy A. [Clinical, epidemiologic and therapeutic aspects of idiopathic epilepsy in 25 golden retrievers: results of a long term study]. Schweizer Archiv fur Tierheilkunde. 1999;141(5):231-8.
19. Vanhaesebrouck A, Granger N, Garosi L. Extreme generalised muscular stiffness in young labrador retrievers. The Veterinary record. 2012;170(6):161-2.
20. Jankovic J, Demirkiran M. Classification of paroxysmal dyskinesias and ataxias. Advances in neurology. 2002;89:387-400.