Small Animal *Review*

Summary: Canine epilepsy can follow circadian and multiday seizure cycles, and seizure clusters can be characterised over months-long time scales with ambulatory iEEG devices.

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Seizure periodicity in canine epilepsy

The onset of seizure activity in dogs with idiopathic epilepsy is thought of as a random event, with potential trigger factors often quoted. Human epileptics report that seizure activity is unpredictable, although apparent non-random and predictable circadian rhythms, multiday rhythms and weekly, monthly, 5-weekly, 3½ monthly and annual seizure periodicities have been described in human epileptics. However, there is an absence of data on the impact medication has on seizure periodicities, both in humans and dogs. When treating epileptics, it is best practice to adjust medication in response to continued seizures, but the impact of medication changes on seizure dynamics is unknown. There is also a need to deal with seizure clusters, the dynamics of which are unclear; they may arise as a result of an inherent self-triggering capacity in which one seizure promotes subsequent seizures, or seizure clusters may reflect variation in seizure risk, in which seizures recur in high-risk phases.

Understanding the temporal distribution of seizures helps with understanding seizure dynamics and seizure risk factors. Idiopathic canine epilepsy is similar to human epilepsy and dogs are large enough to accommodate long-term ambulatory intracranial EEG (iEEG) devices designed for humans. A study by Gregg et al (Circadian and multiday seizure periodicities, and seizure clusters in canine epilepsy (2020). Brain Communication 2(1): fcaa008) assessed the periodicity of seizures in dogs and whether there was co-occurrence of seizure periodicities and seizure clusters. The study comprised six dogs under treatment for idiopathic epilepsy who were implanted and monitored with long-term mobile iEEG for an average of 65 weeks.

Five of the dogs had statistically significant periodicity of seizure timing, with three dogs (dogs 1, 3 and 4) showing a circadian seizure periodicity, one dog (dog 6) a weekly seizure periodicity and two dogs (dogs 1 and 5) an approximately monthly seizure periodicity. Dog 5 had a trend towards a weekly periodicity, and dog 1 a trend towards monthly periodicity, although neither could be statistically confirmed. The timings of the daily and weekly seizures varied but in the five dogs with demonstrated periodicities, four occurred between 12.46 am and 8.34 am, with the fifth showing a weekly periodicity at 4 pm on a Friday. The periodicities must be considered in the context of when medication was administered. Dogs 1, 2, 5 and 6 received phenobarbitone twice daily, dog 4 received phenobarbitone, levetiracetam, zonisamide and potassium bromide, while dog 3 did not receive any anti-seizure medication. Some dogs received benzodiazepine rescue medication for prolonged seizures or seizure clusters. Dogs 1, 2, 5 and 6 developed seizure clustering (seizures that recurred within 24 hours of a preceding seizure) on 66%, 67%, 82% and 79% of occasions respectively, with the proportion of the lead seizures progressing to seizure clustering being 39%, 80%, 2.7%, 6.7%, 100% and 75% for dogs 1–6 respectively. For dogs 1, 2 and 6, within their seizure clusters, the longer each dog had gone since the prior seizure, the less likely it was to have a subsequent seizure. In contrast, dog 5 showed within-cluster seizure periodicity, with a median interseizure interval of 5.25 h. Dogs 3 and 4 had very few clustered seizures.

The authors have shown that non-random seizure temporal patterns with significant periodicities are present in dogs with idiopathic epilepsy, and that these circadian, weekly, and monthly rhythms, and seizure clustering are similar to those described for humans. Their conclusion is that seizure periodicities reflect endogenous rhythms of seizure risk, specific to the dog. The observation of a circadian seizure periodicity could inform owners whether to engage in activities with their dogs at specific times, and direct the timing of medication. The peak phase of circadian seizure cycles is subject specific but the observation in this small group of activity tending to be between 12 am and 9 am coincides with human data where there is a relative predominance for seizure activity in the 6–9 am period. In relation to the 7-day cycle identified in this study, the numbers of dogs is too low for the authors to identify a purely endogenous periodicity, or determine whether variable behaviourally driven and related activity and stress between weekday and weekend routines were the explanation. The explanation for the monthly periodicity in the dogs is unclear.

The authors conclude that the provision of anti-seizure medication or in the case of dog 3 no treatment, did not explain the circadian rhythm. Those dogs receiving treatment were receiving it twice a day and given the long half-life (72 hours) of phenobarbitone, small rises in serum levels post-dosing probably does not explain the periodicity. Dog 4 was treated with a mixture of drugs, and the influence of these on its periodicity is unclear particularly as levetiracetam has a half-life of 3.6 hours and zonisamide a half-life of 13 hours), although twice daily dosing and the lack of a peak of seizure activity at the opposite phase to drug serum levels peak suggests a purely medication associated periodicity is unlikely. Two potential mechanisms for seizure clustering are suggested: (1) a self-triggering mechanism whereby a single spontaneous seizure influences seizure-likelihood for a following period of time, and (2) fluctuations in seizure threshold producing sustained periods when conditions for a seizure are favourable. The results from these dogs suggest the second method as the more likely explanation, but the small number of cases preclude a definitive judgement. The dogs in this study were housed in a research kennel and exposed to regular cycles of light/dark, meal times and interactions with people. The environment was not considered to be a stimulus for seizure activity.

The authors have documented circadian and multi-day seizure periodicities, and seizure clusters in dogs with naturally occurring epilepsy. These observations may eventually guide recommendations on the management of affected dogs.