Management of Canine Epilepsy Beyond Drugs

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KEYWORDS

• Epilepsy • Seizure • Drug Resistance • Medium Chain Triglycerides
• Fatty Acids

ABSTRACT

Seizures and epilepsy in the dog are frequently encountered in first opinion practice. Most veterinary practitioners share the experience that despite an ever-increasing number of available antiepileptic drugs, most dogs continue to have seizures and suffer from quality of life (QOL)–limiting side effects. Epilepsy is a multifactorial brain disease, and new treatment strategies should reflect this in a more multimodal (holistic) approach to epilepsy management. The "right mix" in epilepsy management usually needs to include antiepileptic drug(s) medication tailored to the individual case, a balanced and potentially specialized nutrition plan, a reduction of potential seizure triggers and stress factors, and a treatment plan for comorbidities. Until recently, there was only anecdotal evidence that nutrition could play a role in epilepsy treatment. A newly developed diet based on medium chain triglycerides (MCTs) has been shown to be effective not only in significantly improving seizure control but also in reducing behavioral comorbidities in most dogs with idiopathic epilepsy, when fed as an adjunct to antiepileptic drug treatment. This was shown in a recent double-blind, randomized, controlled, cross-over design study in dogs nonresponsive to standard antiepileptic medication(s). Fourteen percent of dogs became seizure free when on an MCT diet, and 48% of dogs showed a 50% or greater reduction in seizure frequency. Diets provide a new therapeutic angle in the treatment of canine epilepsy and should be considered as an additional treatment option in this challenging brain disease.

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INTRODUCTION

Epilepsy is known to be the most common chronic neurological brain disease seen in first opinion practice,[1] but thinking of it as a simple seizure disorder that can be controlled with antiepileptic drugs would be far too simple. Epilepsy is more than just a seizure disorder.[2] Epilepsy is a brain disease.[3] Epilepsy is also a major risk to health and welfare in dogs. A recent review paper[4] highlighted that dogs with epilepsy are at risk not only of reduced quality but also quantity of life, with threats to quality of life (QOL) including an increased risk of developing comorbidities such as anxiety and attention-deficit hyperactivity disorder (ADHD), antiepileptic drug (AED) side effects, complications of AED treatment and early death.[5-9] Between 20% and 60% of dogs with idiopathic epilepsy (IE) are euthanized as a direct consequence of this brain disease and the side effects of AEDs.[10] In a subpopulation of dogs with IE, seizure severity and frequency progresses with time, especially in those with high seizure density (cluster seizures) or severity (status epilepticus).[11] A very high seizure density and prolonged seizure activity (status epilepticus) can potentially lead to brain damage and death. The disease is of early onset (most dogs have their first seizure between 1 and 4 years of age) and is lifelong,[12] usually requiring chronic medication.[13,14]

With AEDs, there is a fine line between benefit and harm, with potentially adverse welfare consequences due to unpleasant side effects, including polyphagia and weight gain, polydipsia, polyuria, restlessness, lethargy, and ataxia.[7,15] These side effects, especially sedation and ataxia, can impact an owner's QOL considerably, with this being one of the top reasons cited by owners for a decreased QOL.[7,9] A high seizure frequency and treatment with a third AED is significantly associated with a reduced QOL in dogs with IE.[9] In addition, drug resistance to AEDs can be a source of frustration for owners and veterinarians alike in the treatment of canine IE. Seizures can be perceived by the owners as "unpredictable" and "uncontrollable" and have been associated with a stress response in form of a postictal cortisol spike in dogs with IE and owners alike (personal communication, H. Volk). The ultimate aim in the management of IE is the complete cessation of seizures without causing clinically significant side effects.[16] It is, however, difficult to achieve seizure remission. Around two-thirds of dogs with IE continue to have seizures despite AED treatment,[6,17-19] with around 20% to 30% remaining inadequately controlled (<50% reduction of seizure frequency) despite adequate and appropriate medication with the standard AEDs phenobarbital and/or potassium bromide.[20-22] Finding an effective AED that reduces seizure frequency to an acceptable level or results in seizure freedom can be a long process, with several AEDs tried and added before optimum treatment is reached. Recent research has indicated that overall response rates (defined as >50% reduction in seizure frequency) to successive AED treatments are 37% (first), 11% (second), and 6% (third) AEDs, respectively.[23] Many dogs therefore continue to have seizures long term despite polytherapy. New treatments for canine IE are urgently required. The use of recently developed, effective, and well-tolerated AEDs for people with epilepsy for pets[24-26] is limited due to cost, inappropriate

pharmacokinetics, and sometimes life-threatening side effects.[27,28] Finding new and alternative treatment options to improve seizure control is of utmost importance, to allow dogs with IE to either be treated with a reduced AED dosage or ideally no AED treatment to avoid associated side effects.

THE INFLUENCE OF DIET ON SEIZURES

Key for reducing stress and improving QOL for the owner and the dog is to consider the influence of the environment, diet, comorbidities and antiepileptic treatment (**Figs. 1 and 2**; it is beyond the scope of this article to discuss appropriate antiepileptic drug treatment and the diagnosis of IE, and the interested reader should consider the recent consensus statements published by the International Veterinary Epilepsy Task Force and American College of Veterinary Internal Medicine[3,13,14,16,29]). It is long known that salt content in the diet can influence bromide serum concentration, potentially leading to poorer seizure control. Therefore, a balanced and consistent diet has been recommended for years in dogs receiving AEDs. Newer reports have indicated the importance of specialized nutrition, such as the ketogenic diet (KD), hypoallergenic diet, and fatty acid supplementation as new or alternative treatment strategies for canine epilepsy. Anecdotally, canine epilepsy support groups commonly report the importance of diets for the control of the disease. Food supplementation with omega-3 fatty acids showed inconclusive results.[30] There is some anecdotal evidence that a hypoallergenic diet might improve seizure control in dogs with gastrointestinal hypersensitivity.[31]

Ketogenic diets have shown their efficiency in reducing seizure frequency in people with epilepsy and animal models of epilepsy. Ketone bodies (acetone, acetoacetate, and β-hydroxybutyrate) can support 60% of the brain's energy requirements and have been shown to be increased in the brain of patients consuming a KD.[32] Changing brain metabolism has been one explanation why KDs can improve seizure control. The original KD, characterized by its high fat and low carbohydrate content, has been used for many years successfully in children with drug-resistant epilepsy, even allowing reduction or cessation of AEDs in some patients.[33,34] The diet is also efficacious in adult patients, but compliance to the traditional KD is poor due to the high fat and low carbohydrate content of the diet. The original human KD can induce ketosis in people, but not as easily in dogs.[35] Its effect in dogs was therefore questionable. A traditional high fat low carbohydrate/protein KD failed to improve seizure control in dogs.[36] A more promising KD is based on medium chain triglycerides (MCTs), which improved seizure control in the majority of cases.[37] MCTs have a high ketogenic yield that can improve brain metabolism. Furthermore, valproic acid—an AED—is an MCT, and it is thought that its metabolites and other MCTs might have a similar antiepileptic effect. There is also now robust evidence that the MCT decanoic acid (capric acid; C10) has antiseizure effects, with a recent ground-breaking study revealing its mechanism of action. Decanoic acid was found to be a noncompetitive AMPA receptor antagonist at therapeutically relevant concentrations, in a voltage- and subunit-dependent manner, that results in direct

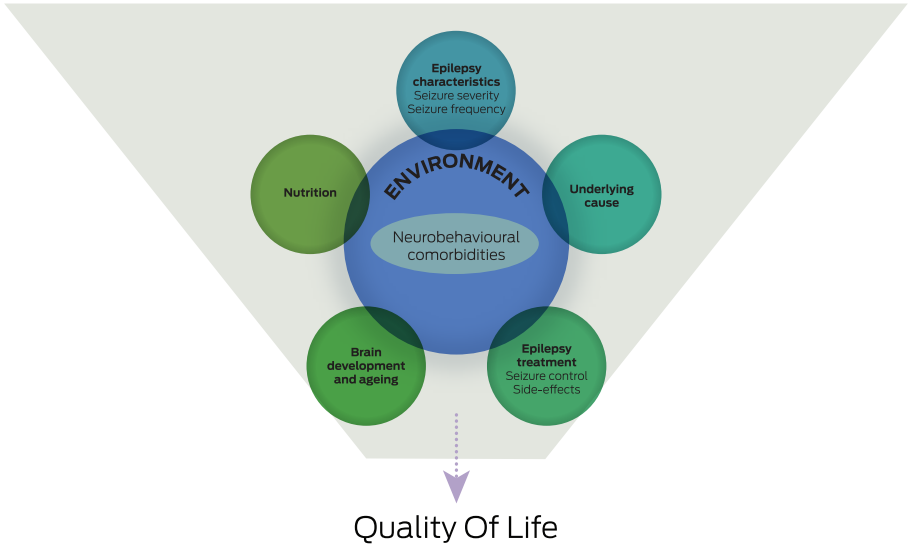

Fig. 1. Quality of life (QOL) influencing factors in dogs with idiopathic epilepsy. Reductions in perceived canine QOL scores are associated with reductions in caregiver QOL, and vice versa.[9] It is therefore important in epilepsy management to consider the QOL of the canine patient and its caregiver, the owner.

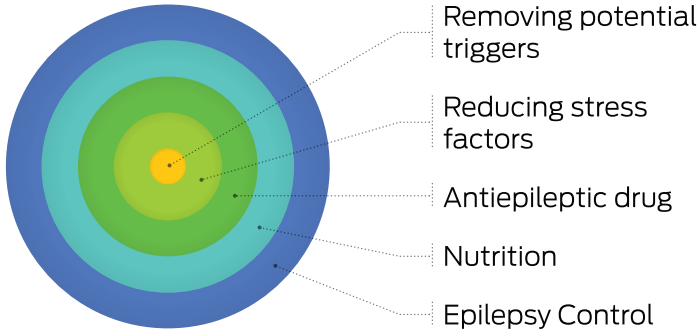

Fig. 2. Targeted epilepsy control. Epilepsy control can usually only be achieved fully when targeted and tailored to the individual patient.

inhibition of excitatory neurotransmission, and thus has an anticonvulsant effect.[38] This is especially interesting, as most AEDs used in veterinary medicine work on increasing the function of the inhibitory brain pathways, which can also explain the side effects frequently seen such as sedation and ataxia.[13,14] Decanoic acid has been shown to readily pass the blood–brain barrier, with 60% to 80% of its serum concentration arriving in the brain.[39] Interestingly, in experimental seizure models in which the direct seizure-reducing effect of decanoic acid has been shown to be effective, high concentration of acetone or β-hydroxybutyrate has no effect.[38] This could suggest that the effect on the AMPA receptor is the main mechanism of action for an MCT diet. Another interesting potential mechanism could be explained by decanoic acid regulating mitochondrial proliferation[40] and therefore protecting against mitochondrial dysfunction, which can be seen with intensive seizure activity.

The MCT diet was tested in a 6-month prospective, randomized, double-blind, placebo-controlled crossover dietary trial in chronically antiepileptic drug-treated dogs with IE.[37] The dogs were randomized to either start on the MCT or placebo diet and were switched over to the other diet after a 3-month period, respectively. Seizure frequency, severity, physical and neurological examination findings, drug serum concentrations, and clinical pathology data were recorded and analyzed for all dogs with IE completing the study. The overall seizure frequency was significantly reduced by 13% on the MCT diet compared with the placebo diet; 71% of dogs showed a reduction in seizure frequency, 48% of dogs showed a 50% or greater reduction in seizure frequency, and 14% of dogs achieved cessation of seizures. Because many dogs experienced cluster seizures, the number of seizure days also was assessed, which also significantly decreased on the MCT diet. The MCT diet resulted in significant elevation of blood β-hydroxybutyrate concentrations compared with the placebo diet, but no significant differences were found for AED serum concentrations, visual analogue scores for sedation, ataxia, QOL, weight, and most laboratory values (there was only a mild decrease in creatinine and mean cell Hb concentration on the MCT diet).

INFLUENCE OF DIET ON BEHAVIOR IN CANINE EPILEPSY

In addition to the demonstrated benefits of MCTs on seizure frequency, there are potentially beneficial effects on the behavioral comorbidities seen in canine epilepsy. A pilot study in children with autism showed an improvement in some of the social interaction, behavioral, and cognitive insufficiencies seen in these patients.[41] In dogs, diets have been reported to modify certain types of behaviors,[42] for example, certain types of aggression can improve on a low protein diet.[43,44] Interestingly, a similar MCT diet as used in the aforementioned epilepsy trial in dogs[37] previously was shown to support cognitive health of aging dogs.[45]. The authors hypothesized that the improvement in cognitive function can be explained by the diet providing the aged brain with a more effective energy source.[45]

The prevalence of psychiatric disorders is increased in people with epilepsy. It is higher than in either the general background population or patients with

other chronic medical disorders.[46-48] Depression and anxiety disorders, followed by psychoses and attention-deficit disorders, are the most frequently reported psychiatric disorders.[47,49-52] A bidirectional relationship between psychiatric disorders such as depression and epilepsy has been suggested, with potentially mutual operant pathophysiological mechanisms.[53] This observation is supported by patients with epilepsy being at greater risk of developing depression, but patients with depression are also at higher risk of developing epilepsy.[54,55]

Behavioral comorbidities of epilepsy should be taken seriously due to their potential to decrease QOL. In a study of health-related QOL (HRQOL) in people with epilepsy, interictal anxiety and depression were found to have adverse effects on HRQOL, with their effects greater than those of seizure frequency, severity, and chronicity.[56] To date, few studies have considered the possibility of psychiatric comorbidities in dogs with IE. The first study of this topic was successfully carried out by a research group from London, where it was found that at least one behavior had changed since the onset of IE in 71% of all dogs studied.[5] Drug-resistant dogs were found to have greater amounts of unfavorable behavioral changes than drug responders in that study,[5] a finding also seen in rodent models of epilepsy, where drug-resistant rats had greater behavior changes.[57] As such, finding appropriate treatments to reduce the effects of behavioral comorbidities alongside seizure frequency in dogs with epilepsy (if present) should be a further goal of epilepsy treatment. A significant reduction in chasing behavior (a potential indicator of canine ADHD-like behavior) was documented during the MCT diet period compared with the placebo diet phase as well as a reduction in stranger-directed fear, which may indicate anxiolytic properties of the MCT.[58]

PET OWNER EDUCATION

Finally, pet owner education is another key to successful management of the patient with epilepsy. The better the pet owner is educated about epilepsy, its comorbidities, nutritional and antiepileptic treatment (side effects, pharmacodynamics, and pharmacokinetic aspects), the more the owner will learn to live with the condition successfully and help the veterinarian in the care of the patient—for example, active monitoring of seizure frequency (e.g., paper or electronic seizure diary using an APP [http://www.rvc.ac.uk/news-and-events/press-office/rvc-creates-a-dog-epilepsy-smart-phone-app-to-help-manage-mans-best-friend-s-fits]).[13] The owner can also help to identify and reduce environmental stress factors, keep daily routines, and help with the individualization of the diet and drug treatment, depending on the seizure status of the dog.[59] The principle of holistic epilepsy care is based on the concept that "every little bit helps" to increase the seizure threshold and therefore improve the management of epilepsy.

CONCLUSION

As a busy clinician, one can easily not see the forest for the trees in canine epilepsy and its management. Epilepsy is a complex disease process that can be difficult

to treat with AEDs alone, but working together with the owner and having a holistic approach will not only provide the best chance of treatment success but also improve the QOL of the patients and their owners.

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