

The Magic Wand in Canine Epilepsy Management

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Abstract

Canine epilepsy is the most common chronic neurological condition seen in first opinion practice. Despite its frequency in occurrence and a battery of anti-epileptic drugs, the majority of dogs continue to seizure. New and more effective treatment strategies are needed. A newly developed ketogenic diet, based on medium-chain triglyceride supplementation, has been shown to be effective in improving seizure control and reducing behavioral comorbidities. Medium-chain triglyceride enriched diets not only improve brain metabolism but also have direct anti-seizure effects via blockage of AMPA receptors in the brain. Diets provide a new therapeutic option in the treatment of canine epilepsy.

Introduction

Epilepsy is the most common chronic neurological presentation in first opinion practice; however, it may be too easy to think of it as a simple disorder that can be controlled with anti-epileptic drugs. Epilepsy is more than just a seizure disorder,¹ it also is a brain disease² and a major risk to the health and welfare of dogs. In our recent review paper “Epilepsy Beyond Seizures,”³ we said that dogs with epilepsy have an increased risk for developing behavioral changes, such as anxiety and attention-deficit hyperactivity disorder (ADHD), and having reduced quality of life (QoL) from anti-epileptic drug (AED) side effects and complications of AED treatment and early death.^{4,7} Between 20 to 60% of dogs with idiopathic epilepsy (IE) die as a direct consequence of this disorder.⁸ The frequency and severity of the seizures may progress with time, with very frequent or prolonged seizures potentially leading to brain damage and death. The condition has an early onset (most dogs experiencing their first seizure between 1 to 4 years of age), is lifelong⁹ and requires chronic medication.

Medication with AEDs poses a fine balance between benefits and harms, with potentially adverse welfare consequences due to unpleasant side effects including excessive hunger, thirst, restlessness, lethargy, and ataxia.⁶ The impact

Glossary of Abbreviations

ADHD: Attention Deficit Hyperactivity Disorder
AED: Anti-Epileptic Drug
HRQoL: Health Related Quality of Life
IE: Idiopathic Epilepsy
KD: Ketogenic Diets
MCT: Medium-Chain Triglycerides
QoL: Quality of Life

of AEDs upon QoL may be considerable and cited by owners as the primary reason for decreased QoL in their dogs.⁶ In addition, drug resistance to AEDs can be a source of frustration for owners and veterinarians alike in the treatment of canine IE. Seizure freedom may not always be achievable, with over two-thirds of dogs with epilepsy continuing to have seizures long term^{5,10-12} and around 20 to 30% will remain poorly controlled (<50% reduction of seizure frequency) despite appropriate treatment with standard AEDs phenobarbital and/or

potassium bromide.¹³⁻¹⁵ Finding an effective AED that reduces seizure frequency to an acceptable level or results in seizure freedom can be a long process; several AEDs may need to be added before optimum treatment is reached. Our previous research has indicated that overall response rates (with response defined as >50% reduction in seizure frequency) to the first, second and third AEDs were 37.2%, 10.7% and 6.1%, respectively¹⁶; thus, many dogs continue to seizure chronically despite multiple therapies. New treatments for canine IE are urgently needed. The major problem in veterinary medicine is that many of the newer AEDs that are effective and well tolerated in humans¹⁷⁻¹⁹ are not efficacious in small animals due to inappropriate pharmacokinetics or life-threatening side effects.^{20,21} Their use is furthermore prohibited by cost. Finding new and alternative treatment options to improve seizure control is of utmost importance to allow dogs with IE to be treated with a reduced AED dosage or ideally no AED treatment to avoid their associated side effects.

The Influence of Diet on Seizures

Key to reducing stress and improving QoL for the owner and the dog is to consider the influence of the environment, diet, comorbidities and anti-epileptic treatment. Some reports have indicated the importance of diets, such as the ketogenic diet, 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 canine epilepsy. Food supplementation with omega-3 showed inconclusive results.²² There is some anecdotal evidence that a hypoallergenic diet might improve seizure control in dogs with gastrointestinal hypersensitivity.²³

Ketogenic diets (KDs) have shown to be efficient in reducing seizure frequency in human patients and rodent models of epilepsy. The ketogenic diet, which was originally characterized by a high fat and low carbohydrate diet, has been a highly efficacious anti-epileptic treatment in children for several decades. KDs can decrease seizure activity or lead to seizure freedom in children refractory to AED therapy allowing reduction or cessation of medication.^{24,25} With the original human diet, it was more difficult to induce ketosis in dogs than in humans,²⁶ and so it was unknown whether the ketogenic diet would prove to be an effective anti-epileptic treatment in dogs. A traditional high fat and low carb/protein ketogenic diet failed to improve seizure control in dogs.²⁷ A more promising ketogenic diet is based on the addition of medium-chain triglycerides (MCT), which improved seizure control in the majority of cases.²⁸ 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 may have a similar anti-epileptic effect. There also is robust evidence that the MCT decanoic acid (capric acid; C10) has anti-seizure effects, as reported in a recent study revealing mechanism of action. Decanoic acid was found to be a noncompetitive AMPA receptor antagonist at therapeutically relevant concentrations that results in direct inhibition of excitatory neurotransmission, and thus has an anticonvulsant effect.²⁹

In a six-month prospective, randomized, double-blinded, placebo-controlled crossover dietary trial, we recently compared the aforementioned MCT diet to a standardized placebo diet in chronically anti-epileptic drug-treated dogs with IE.²⁸ Dogs were fed either the MCT or a placebo diet for three months followed by a subsequent respective switch of diet for an additional three months. Seizure frequency and clinical and laboratory data were collected and evaluated for 21 dogs completing the study. Seizure frequency was significantly lower when dogs were fed the MCT diet (2.31/month, 0-9.89/month) in comparison to placebo diet (2.67/month, 0.33-22.92/month); 3 dogs achieved seizure freedom, 7 dogs had $\geq 50\%$ reduction in seizure frequency, 5 had an overall $< 50\%$ -reduction in seizures (38.87%, 35.68-43.27%), and 6 showed no response. Seizure day frequency was also significantly lower when dogs were fed the MCT diet (1.63/month, 0-7.58/month) in comparison to the placebo diet (1.69/month, 0.33-13.82/month). Consumption of the MCT diet also resulted in significant elevation of blood beta-hydroxybutyrate concentrations in comparison to the placebo 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 documented behavioral comorbidities of canine epilepsy. In humans, pilot study results have shown reductions in some of the behavioral, social communication and cognitive deficits seen in children with autism on a KD.³⁰ Diet-induced behavioral modifications in dogs have been reported in peer-reviewed literature and anecdotal notes.³¹ For example, a low-protein diet has been shown to reduce certain types of aggression in dogs,^{32,33} and supplementation of caseozepine or the proportion of protein in a given diet may reduce anxiety-related behavior.³⁴ A similar ketogenic MCT diet used in our study has previously been demonstrated to improve the cognitive function of aged dogs, hypothesized to be due to the diet providing the brain with a more effective energy source.³⁵

The prevalence of psychiatric disorders in people with epilepsy is higher than in the general population or patients with other chronic medical diseases,³⁶⁻³⁸ with the most common disorders being depression and anxiety disorders followed by psychoses and attention-deficit disorders.^{37,39-42} A bidirectional relationship between epilepsy and psychiatric disorders such as depression has been considered, with potentially common operant pathogenic mechanisms in the disorders that facilitate the occurrence of one in the presence of the other.⁴³ This is supported by people with epilepsy being at greater risk of developing depressive disorders, but patients with depressive disorders also being at higher risk of epilepsy.^{44,45}

Behavioral comorbidities of epilepsy should be taken seriously due to their potential to decrease QoL. In a study of HRQoL in people with epilepsy, inter-ictal anxiety and depression were found to have adverse effects on HRQoL, with their effects greater than those of seizure frequency, severity and chronicity.⁴⁶ 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 our research group, in which we found that at least one behavior had changed since the onset of IE in 71% of dogs studied.⁴ Drug-resistant dogs were found to have greater behavioral changes than drug responders in that study,⁴ a finding also seen in rodent models of epilepsy where drug-resistant rats had greater behavioral changes.⁴⁷ 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. We documented a significant reduction in chasing behavior (a potential indicator of canine ADHD-like behavior) during the MCT diet period compared to the

placebo diet phase, and a reduction in stranger-directed fear, which may indicate anxiolytic properties of the MCT.⁴⁸

Pet Owner Education

Finally, pet owner education is another key to successful management of the patient with epilepsy. The better educated the pet owner is about epilepsy, its comorbidities and anti-epileptic treatment (side effects, pharmacodynamics and pharmacokinetic aspects), the greater likelihood the owner will learn to live with the condition successfully and help the veterinarian in the care of the patient, e.g., 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>)).⁴⁹ The owner also can help to reduce environmental stress factors and help with the individualization of the drug treatment depending on the seizure status of the dog.⁵⁰ The principle of holistic epilepsy care is that “every little bit helps” to increase the seizure threshold and, therefore, improve the management of epilepsy.

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