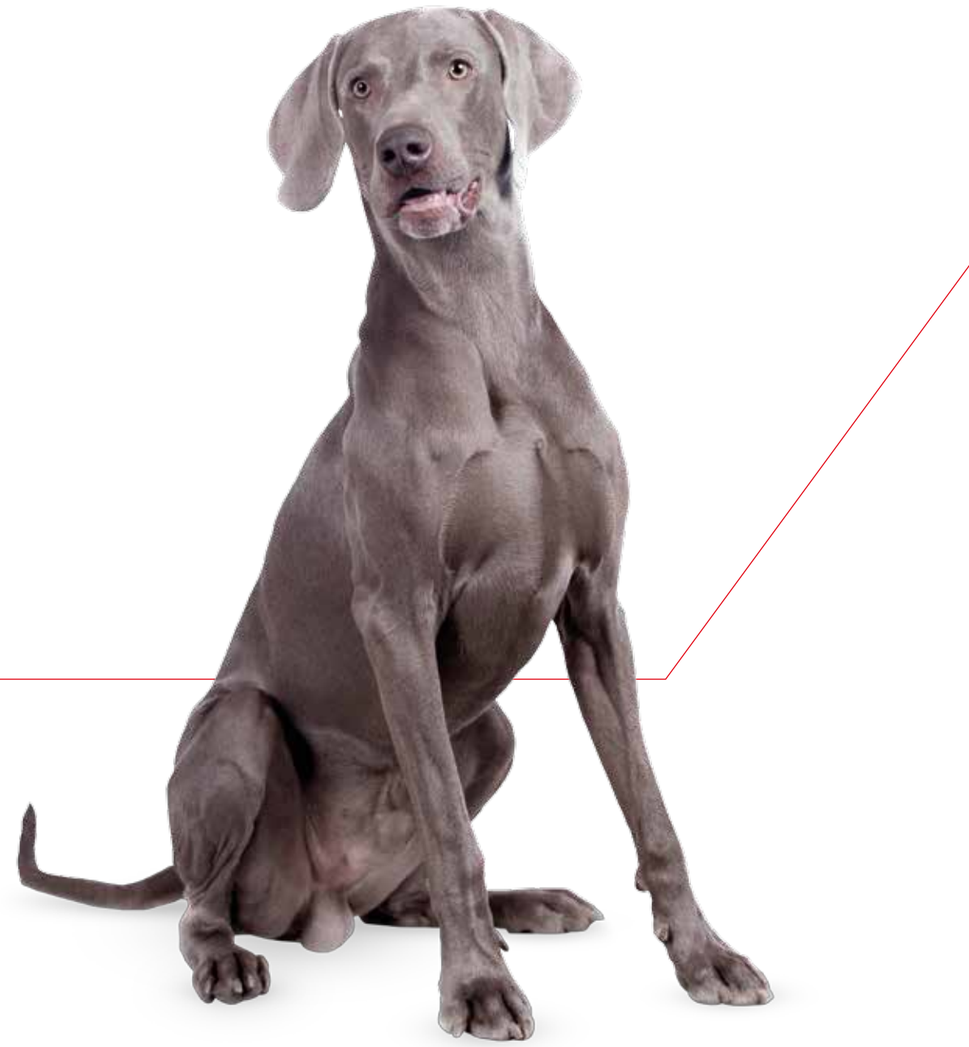
Canine Epilepsy:

Current Management and Nutritional Advances



Contents

Introduction

Canine epilepsy is frequently encountered in general practice, with refractory patients commonly being referred to specialists. Most veterinary practitioners share the experience that despite using a number of available antiepileptic drugs, many dogs continue to have seizures of varying frequency and suffer from side effects limiting their quality of life.

While antiepileptic drugs are the gold standard of treatment for canine epilepsy, nutrition can play a role in management of this condition. Recent research has shown that a diet containing medium chain triglycerides fed to epileptic dogs led to a significant decrease in seizure activity. This randomised, placebo-controlled, double-blinded, crossover study using a test diet with MCT oil confirmed that specially tailored nutrition containing MCTs should be considered as an adjunct to veterinary therapy for epileptic dogs.

Overview of epilepsy

Epilepsy is a common, chronic neurological disease affecting between 0.5 and 0.75% of dogs in the general population but affecting considerably more in at- risk breeds[1-4].

Epilepsy is typically characterised as two or more unprovoked epileptic seizures occurring at least 24 hours apart.[5,6] Idiopathic epilepsy (IE) is the most common form. It may be genetic, especially in certain breeds of dogs[1-4,7] **(Table 1)**, but also refers to seizures where the underlying cause is unknown. Other causes of epilepsy include intracranial or cerebral pathology including vascular, inflammatory, infectious, traumatic, neoplastic, degenerative or developmental lesions, collectively referred to as "structural epilepsy"[7,8]. A third cause of seizures often included within the area of epilepsy is reactive or induced seizures. These have extracranial causes such as metabolic or toxic aetiologies[1]. If none of these physical causes can be identified, the epilepsy is characterised as idiopathic.

Epilepsy is also a major risk to health and welfare in dogs. The disease predominantly has an early onset (most dogs have their first seizure between 1 and 3 years of age) and is lifelong[9], usually requiring chronic medication[10,11].

A recent review paper[12] highlighted that dogs with epilepsy are at risk not only for reduced quality but also quantity of life. In addition, quality of life (QoL) can be further impaired in some epileptics by the development of comorbidities such as anxiety and attention-deficit hyperactivity disorder (ADHD), antiepileptic drug (AED) side effects, complications from AED and early death[13-17]. Between 20% and 60% of dogs with idiopathic epilepsy (IE) are euthanised as a direct consequence of this disease and/or the side effects of AEDs[18]. In a subpopulation of dogs with IE, seizure severity and frequency progresses with time[19].

A very high seizure density and prolonged seizure activity (status epilepticus) is associated with a guarded prognosis and can potentially lead to brain damage and death.

Mean survival time following diagnosis of IE varied among studies, from 1.5 to 5.6 years, with individual survival after diagnosis ranging from 1 day to 9.2 years[3,14,20].

Complete remission from epileptic seizures, defined as no seizures for >3 years with or without antiepilepsy drugs, was achieved in only 10 of the 78 (13%) dogs with idiopathic epilepsy in one study[20] and in 15% of dogs in another study[14]. Although numerous drugs are available for treating epilepsy, further improvements in care options for epileptic dogs are needed.

Epileptic seizures are caused by abnormal hypersynchronisation of electrical activity of neurons in the brain ("an electrical storm in the brain"), affecting either a focal area within only one section of the brain (a focal seizure) or affecting multiple areas including both hemispheres of the brain (generalised seizure)[5]. The manifestation of seizures can be highly variable, but involve a transient occurrence of signs characterised by muscular, autonomic, cognitive or behavioural changes[5,7]. Muscular or motor seizures are perhaps the most recognisable type of seizure, but these can appear similar to manifestations of other episodic disorders[8]. In addition, there are other causes of seizures other than epilepsy. It is, therefore, important that appropriate diagnostic procedures be performed to confirm a diagnosis of epilepsy.

Breed	Incidence, per 10,000 dog-years at risk
Boxer	60.3
Border terrier	37.2
Cavalier King Charles Spaniel	31.1
Labrador Retriever	29.3
Poodle, medium and miniature	27.5
Yorkshire terrier	25.4
Rottweiler	24.3
Papillon	23.4
Beagle	22.6
Miniature schnauzer	22.5
Bernese mountain dog	20.9
Standard poodle	20.9
Border collie	20.0
Shetland sheepdog	19.6
Flat-coated retriever	19.2

Table 1: Incidence rate for epilepsy by breed among 665,249 insured dogs, showing the 15 breeds with the highest incidence rate. (adapted from Heske 2014[3])

Diagnosis of epilepsy

The diagnosis of epilepsy starts by an owner describing to their veterinary surgeon the classic clinical signs of a seizure in their dog. Muscular or motor seizures are perhaps the most recognisable form of epilepsy, but these can sometimes be confused with other episodic disorders[8]. In addition, there are other underlying causes of seizures; therefore, it is important to perform appropriate diagnostic procedures before arriving at a diagnosis of epilepsy.

A preliminary diagnosis of epilepsy can be based on patient history, signalment and neurological examination findings. A genetic predisposition to idiopathic epilepsy occurs in numerous breeds and a familial history of epilepsy increases risk; however, this alone should not be considered diagnostic[8]. Most dogs with idiopathic epilepsy experience their first seizure between 1 and 7 years of age and often experience their first seizure while at rest[1]. Dogs with idiopathic epilepsy are more likely to have generalised seizures, with focal seizures occurring less commonly[1].

Of utmost importance in the diagnosis is confirmation that an epileptic seizure has occurred, and not another event, such as syncope, narcolepsy, or peripheral tremors[1,8]. Generalised epileptic seizures typically last less than 5 minutes and are usually followed by a post-ictal period of disorientation, thirst, hunger, restlessness or behaviour changes[8]. Impaired consciousness, oro-facial muscle tremoring, autonomic signs and convulsions are typically seen during a seizure[8]. In some cases it may be helpful to have the owner record a video during an event. A standardised questionnaire for owners of dogs with seizure disorders has been created by the International veterinary epilepsy task force[8] and is available for download through a link at:

➤ http://bmcvetres.biomedcentral.com/articles/10.1186/s12917-015-0462-1.

Once it is determined a seizure has occurred, a complete blood count, serum chemistry profile and a complete urinalysis should be performed to help rule out underlying metabolic causes[1,8]. Additional testing, such as bile acids, a thyroid profile, and/or glucose: insulin ratios, may also be recommended[8]. A thorough neurological examination is also important. Key components include evaluation of gait and posture, mentation, spinal and cranial nerve reflexes and spinal palpation[1]. This can help rule in or out possible causes of seizure activity. Dogs with structural lesions usually have abnormalities during neurological examination, which may be symmetrical or asymmetrical depending on location of the lesion[8]. Dogs with reactive or metabolic seizures often show evidence of diffuse, bilateral and sometimes symmetrical forebrain involvement[8]. Dogs with idiopathic epilepsy usually have normal neurological examinations during the interictal period, but may show significant defects for up to 48 hours following a seizure so it is important to evaluate or re-evaluate at least 48 hours following cessation of seizure-related behaviours[1].

If neurologic abnormalities are present outside the seizure and post-ictal phase, a structural lesion may be suspected. In these cases, magnetic resonance imaging (MRI) or cerebrospinal fluid analysis may be indicated. If a patient is refractory to therapy, additional testing, including MRI, should be recommended[1,8]. Finally, for any dog that experiences a first epileptic seizure younger than 6 months of age or older than 6 years of age, or that has experienced an episode of status epilepticus or cluster seizures, an MRI is necessary[8].

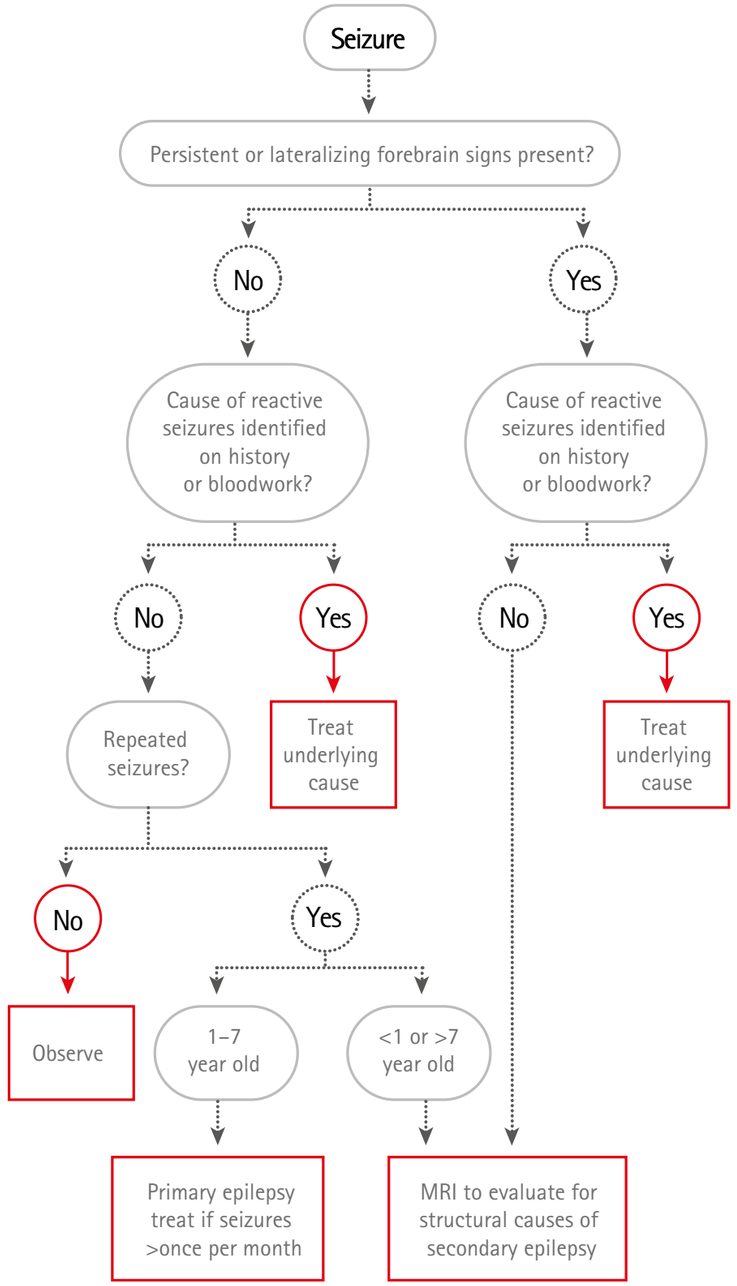


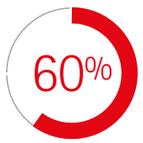
Fig 1: A diagnostic algorithm for the patient with seizure

Treatment of epilepsy

The goal of epilepsy treatment is to reduce or eliminate seizure activity and to improve quality of life for the patient and pet owners[21].

From a medical perspective, a reduction in seizure frequency of at least 50% is considered successful treatment[2,22]. Unfortunately, only about 60% to 80% of patients respond adequately to treatment[21]. The reasons for the refractory seizure activity can be divided into 3 main variables: disease-related, drug-related and patient-related problems[21]. Examples of these include undiagnosed brain disease, such as related to physical trauma; development of drug tolerance or changes in drug uptake over time; and patient-related differences such as genetic polymorphisms. Each of these must be considered in a patient that either does not respond to therapy or stops responding over time.

>50% resolution = positive response to treatment:



Approximately two-thirds of dogs with IE continue to have seizures despite AED treatment. [24-26]

Around 20% to 30% remain inadequately controlled (<50% reduction of seizure frequency) despiteuse of the standard AEDs phenobarbital and/or potassium bromide. [27-29]

An ideal anti-epilepsy drug (AED) would have excellent efficacy, a high therapeutic index, a low potential for side effects, and pharmacokinetics allowing it to be dosed once or twice daily[2]1. Although there are numerous AEDs available for treating canine epilepsy, there are no "ideal" drugs currently available. Instead, veterinary surgeons must balance the benefits and side effects of each drug and responsiveness to treatment when deciding the best protocol for each patient[11].

Drugs may be used singly (mono-therapy) or used in conjunction with other AEDs in an attempt to control refractory epilepsy or to reduce dosages in order to control side effects. Two recent reviews regarding canine AEDs indicated that oral phenobarbital, imepitoin, and potassium bromide are likely to be effective for the treatment of idiopathic epilepsy, and that data for other drugs was either insufficient or suggested the drugs were ineffective[2,11]. Successful treatment for idiopathic epilepsy, defined as greater than 50% reduction in seizure activity, was achieved in 82% of dogs treated with phenobarbital, while 31% became seizure-free but 15% showed no improvement[11]. A single study with potassium bromide indicated 74% of epileptic dogs showed >50% reduction in seizures and 52% were seizure- free during the 6-month study. Imepitoin, which is approved for use in dogs in Australia and Europe, but not in the USA, was shown to be as effective as phenobarbital but with a higher incidence of side effects such as somnolence, ataxia, polydipsia and hyperphagia[11].

All AEDs currently available have adverse effects, such as polyphagia, weight gain, polydipsia, polyuria, restlessness, lethargy, and ataxia[15,23]. Side effects can be transient or persistent, can be life threatening and can reduce quality of life. In fact undesirable effects of AEDs are one of the top reasons cited by owners for a decreased QoL[15,17].

High seizure frequency and treatment with a third AED is also significantly associated with a reduced QoL in dogs with IE[17]. In addition, drug resistance to AEDs can be a source of frustration for owners and veterinary surgeons.

Use of secondary treatments, e.g. two or more AEDs, are often used to increase treatment efficacy and/or reduce side effects in some dogs. Good quality studies confirming this benefit are limited. The ACVIM Consensus Committee on seizure management in dogs suggests value in add-on AEDs when used appropriately. They specifically suggest that combinations with phenobarbital, potassium bromide, levetiracetam or zonisadmide may be beneficial in refractory cases[11].

The decision to add a second AED should be based on seizure frequency and severity, while selection of the specific AEDs should be based on mechanisms of action, avoiding or minimizing drug-drug interactions and additive toxicities, as well as considerations for the impact on quality of life[11]. Approximately two-thirds of dogs with IE continue to have seizures despite AED treatment[7, 24-26] and around 20% to 30% remain inadequately controlled (<50% reduction of seizure frequency) despite use of the standard AEDs phenobarbital and/or potassium bromide[27-29].

Finding an effective AED combination that reduces seizure frequency to an acceptable level or results in seizure freedom can be a long process. Recent research has indicated that overall response rates to successive AED treatments are 37% (first), 11% (second), and 6% (third) AEDs, respectively[22].

Treatment of epilepsy (Cont)

(Fig. 2) Unfortunately, many dogs continue to have seizures despite polytherapy.

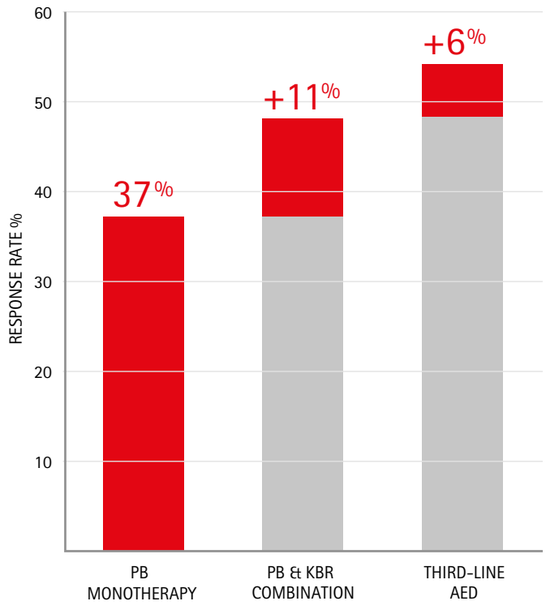


Fig 2: Drug responsiveness of dogs receiving a combination of phenobarbital (PB), potassium bromide (KBr) and/or a third-line anti-epileptic drug (AED).

Modes of Action of Common Anti- Epileptic Drugs

PHENOBARBITAL increases synaptic inhibition by acting on GABA receptors. It increases the action of GABA (inhibitory neurotransmitter) and appears to also inhibit the release of glutamate (excitatory neurotransmitter). This helps to elevate the seizure threshold and reduces the spread of seizure activity from a seizure focus. Phenobarbital may also block calcium channels, resulting in a reduction in excitatory transmitter release.

POTASSIUM BROMIDE'S mechanism of action is not fully defined. Bromide appears to be preferentially moved across neuronal membranes via GABA- activated chloride channels thereby hyperpolarising neuronal cell membranes. This leads to stabilisation, a reduction in epileptic discharge and decreased sensitivity to epileptic foci with a resulting increase in seizure threshold.

IMEPITOIN potentiates the GABA- mediated inhibitory effect on the neuron by targeting the benzodiazepine binding site of the post-synaptic neuron. This suppresses the formation of an action potential by causing Chloride ions to flood into the neuron- thus preventing seizure activity from occurring.

LEVETIRACETAM can be used alone or in combination with other AEDs such as phenobarbital. Its mechanism of action is poorly understood but it is known to bind to a synaptic vesicle glycoprotein, SV2A in the brain leading to modulation of synaptic neurotransmitter release. It also inhibits presynaptic calcium channels reducing neurotransmitter release and acting as a neuromodulator. By preventing excessive synchronisation of nerve engagement and depressing excitability of neurons within the brain it reduces seizure activity.

Finding new and alternative treatment options to improve seizure control is therefore of utmost importance. The ACVIM Consensus Committee on seizure management in dogs therefore considered the option of dietary treatment as an adjunct therapy for epileptic dogs.

The best known dietary treatment for epileptic humans is a ketogenic diet, consisting of a high fat diet that is low in carbohydrates and protein. When a diet of this description was fed to dogs with drug-resistant idiopathic epilepsy, no beneficial effect was observed. Rather, 3 of the 9 dogs fed the high fat, ketogenic diet developed pancreatitis. Likewise, when omega-3 fatty acid supplementation was provided for dogs with idiopathic epilepsy, no effect was seen on seizure frequency or severity. In contrast, a ketogenic diet based on medium chain triglycerides (MCTs) was shown to decrease both seizure frequency and total seizure days per month compared to a control diet.(Podell 2016; Law 2015) More details about diet and the potential benefit of MCTs are provided in the section on medium-chain triglyceride ketogenic diet for management of epilepsy.

Effect of epilepsy on quality of life

Canine epilepsy can have a significant negative effect on both the dog's and owner's quality of life.

According to a survey of owners of epileptic dogs, the frequency of seizure days had a greater impact on measures of QoL compared to severity of seizures, with higher seizure frequency associated with a decrease in the dog's QoL[17]. Tolerance by dog owners regarding seizure frequency varied among studies. A seizure frequency of one seizure every 3 to 6 months was acceptable to most owners of epileptic dogs in one study, (Chang 2006) but in another, only a seizure-free state as acceptable[17].

Another factor shown to affect perceived QoL are the side effects caused by the AEDs. AED-induced side effects of increased drinking, sleeping or restlessness, or loss of coordination (being wobbly) while walking all were associated with a reduced QoL. Of these, loss of coordination and more time spent sleeping had the greatest negative impact on perceived QoL. The use of different AEDs had little impact on perceived QoL, but the use of multiple AEDs (3 or more) had a negative impact on perceived QoL[17].

Most dogs with IE experience some behavioural changes, such as increased fear or anxiety, attachment disorders, abnormal perception, or defensive aggression[13,22]. Affected dogs acted more anxiously in unfamiliar settings or when exposed to unfamiliar people or other dogs; and they acted more aggressively under these circumstances. These negative emotional states and reduced social interactions suggest an adverse effect on QoL[22].

In addition to the effect of epilepsy on the dog's QoL, research shows that the QoL of the dog's owner/caregiver is directly related to the perceived QoL of the dog. Caregivers reporting a decreased QoL in their epileptic dogs were more likely to report a decrease in their own QoL[17]. From the owner's perspective, the dog's QoL, acceptable seizure frequency and acceptable side effects of AEDs were the 3 greatest concerns for owners of epileptic dogs[15]. Thus, optimising seizure control and AED therapy will not only affect the perceived QoL of the epileptic dog, but also the QoL of the dog's caregiver[17].

The 3 greatest concerns for owners of epileptic dogs are:

- The dog's Quality of Life
- Achieve an acceptable seizure frequency
- Achieve reduced/absence of AEDs side effects.

Effect of epilepsy on brain energy metabolism

Under normal physiological conditions, the brain is unique as it is almost completely dependent on glucose for energy and requires a continuous supply. Glucose metabolism allows for production of ATP as well as substrates for the generation of neurotransmitters[30]. **(Fig. 3)**

Brain glucose metabolism is disrupted in patients with epilepsy and other conditions associated with seizure activity[31-36]. Although increased energy is used during a seizure, glucose hypometabolism has been consistently demonstrated during the interictal period in human focal epileptic patients[35-37]. The hypometabolic regions detected using 2-deoxy-2-[18F] fluoro-D-glucose positron emission tomography (18F-FDG PET) correlate with epileptogenic zones in human patients[35,37]. Although there is often a widespread area with reduced glucose metabolism, the interictal onset zones typically are located at the sites with the most severe hypometabolism. Likewise, dogs with idiopathic or juvenile onset epilepsy demonstrate reduced glucose utilisation in various locations of the brain during the interictal period, as detected by 18F-FDG PET[31,32]. As with human patients, the localisation of glucose hypometabolism seemed to indicate epileptic foci.

Numerous theories have been proposed to explain the hypometabolism observed in epileptic brains. Among these are neuronal loss caused by chronic seizure activity, reduced synaptic activity due to a reduction in neuronal connections, a reduction in synaptic density in the pathways that are associated with seizure onset and spread, and interictal inhibitory processes[32,38]. At this time, however, no theories have been adequately confirmed[37,39]. Recently, a strong association between glucose hypometabolism and mitochondrial cellular energy function was described[39].

In children undergoing surgical treatment for their epilepsy, there was a significant reduction in complex IV and a trend ($p < 0.10$) for reduced complex II and III within the mitochondria of the hypometabolic areas[39].

The severity of hypometabolism detected via[18] F-FDG PET is dependent on time lapsed since the last seizure[37,40]. The volume of affected areas is influenced by the type of seizure, with larger areas of hypometabolism detected following generalised seizures. Further, the volume of hypometabolic areas increase with increasing numbers of seizures and increasing duration of epilepsy, strongly suggesting progressive damage[37,41]. The areas of glucose hypometabolism beyond the ictal zones may contribute to functional deficits in cognition and behaviour in epileptic patients[42-44].

Successful treatment of epilepsy with an AED, levetiracetam, resulted in increased regional brain glucose metabolism, although the same AED in non-responsive patients showed no increase in metabolism[45]. Whether the increased metabolism was a cause or consequence of the clinical improvement is not yet known, but it suggests value in therapies that may correct glucose hypometabolism or provide alternative energy sources.

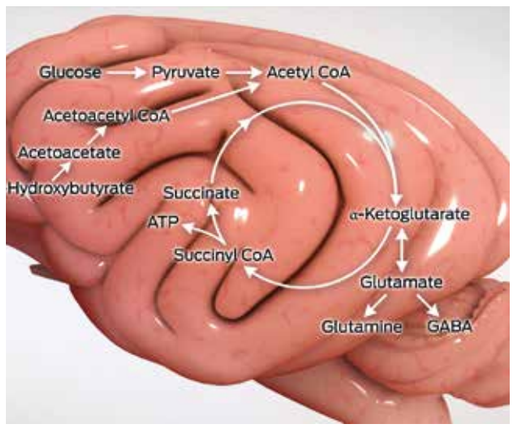


Fig 3. Representation of the glucose metabolism in the brain.

Medium chain triglycerides – an alternate energy source for brain energy metabolism

In the face of compromised glucose metabolism, neurons may need an alternate source of energy. Fat is the most concentrated energy source, providing over twice as much energy per gram compared to glucose or proteins.

However, in contrast to other organs, the brain is limited in its ability to use long chain fatty acids as an energy source. At one time, this was thought to be due to an inability of fatty acids to cross the blood brain barrier but this has since been disproven: both saturated and unsaturated non-esterified fatty acids can readily pass through the blood brain barrier[46]. Rather, it appears that the mitochondria of neurons have low enzymatic capacity for beta-oxidation of long chain fatty acids[46]. Another contributing factor is oxygen tension. Oxidation of fatty acids requires more oxygen than oxidation of glucose.

The oxygen tension in the brain is relatively low and non-uniform, being higher in grey matter than in white matter. The greater oxygen consumption associated with fatty acid oxidation increases the risk for neural hypoxia, and also is a limiting factor during neuronal electrical activity. During periods of brain activity with sustained neuronal firing, energy needs exceed the oxidative ATP generation and anaerobic glycolytic ATP generation becomes important[46]. Fatty acids are simply unable to meet this energy demand in a timely manner. In addition to these limitations, evidence suggests that beta-oxidation of long-chain fatty acids also increases the risk for increased oxidative stress[46].

Despite these limitations from long chain fatty acids, medium chain fatty acids (MCFAs) can be readily oxidised in astrocytes[47] and provide an alternative energy source. **Research suggests that MCFAs have anti-convulsant effects and, in addition, dietary MCFAs provide a source of liver-derived ketone bodies which can provide an alternate energy source**[48-50].

Ketone bodies can replace a large portion of the glucose demand, providing up to 60% of the brain's energy requirement during prolonged fasting[46]. The liver-derived ketones readily cross the blood-brain barrier where they can be converted into acetyl-coA and enter the citric acid cycle for oxidation. Neural cells can oxidize ketone bodies with a 7- to 9-fold greater rate than glucose[46]. **(Fig 4)**

Lactate is another metabolite that can provide small amounts of energy for brain tissue. This has been most studied using an exercise model, which results in increased blood concentrations of lactate. Brain uptake and oxidation of lactate increase, while glucose uptake decreases, in this scenario[51,52]. In addition, neurons are now known to utilise lactate produced by astrocytes in the brain[53]. However, lactate accumulates during seizures, contributing to acidosis[54], and supplementation with lactate does not appear to be a viable option for feeding the brain. **(Fig 5)**

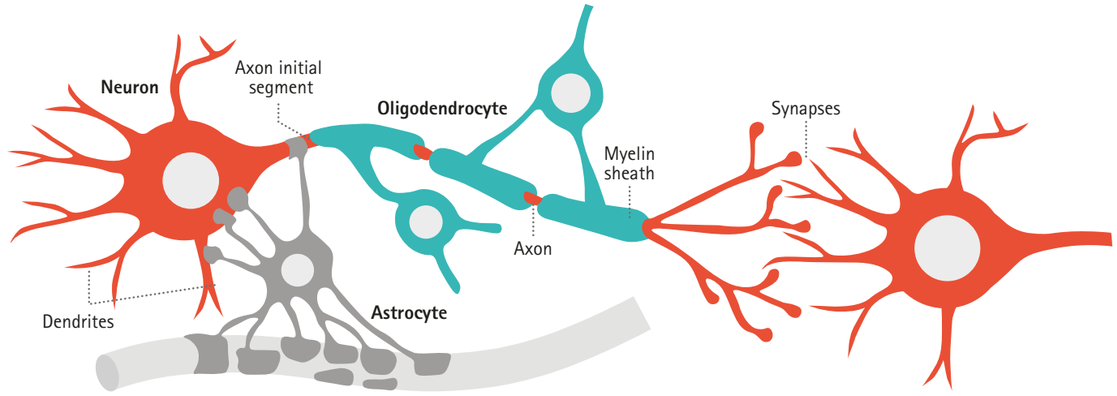


Fig 4. Different cell types in brain and relative relationship of energy

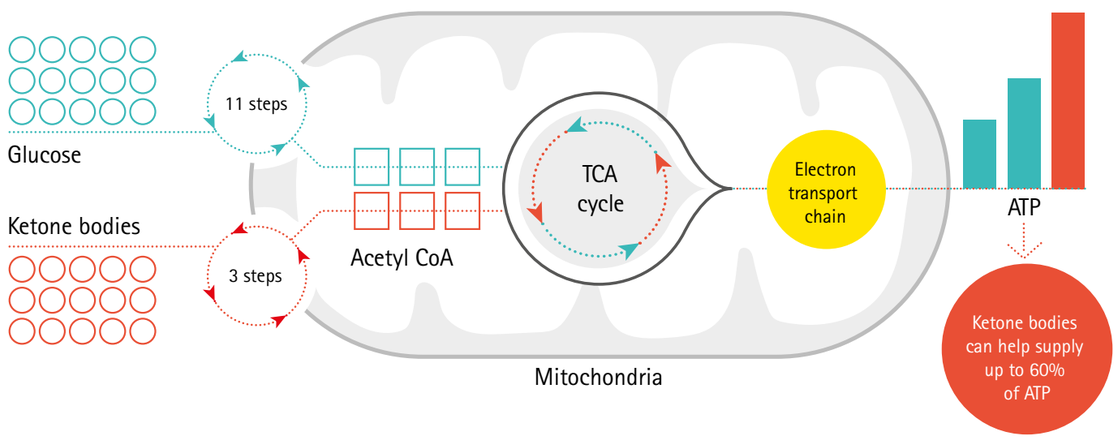


Fig 5: Metabolism of glucose and ketone bodies in neuronal mitchondria

Medium chain triglyceride diet for management of epilepsy

The benefit of ketones for the management of epilepsy was first identified over 90 years ago as a means to mimic the benefits of fasting on seizure control[55]. Either fasting or consumption of high fat, low carbohydrate, low protein diets stimulate hepatic production of ketones. Classic ketogenic diets used for management of epilepsy contain fat to carbohydrate plus protein in a ratio of 4:1 to 3:1, and these are fed to provide only 75% to 80% of daily calorie requirements[56]. When carbohydrate or other glucose precursors (e.g. amino acids) are lacking, the liver increases production of ketone bodies, releasing them into circulation for use as an energy source by various tissues including the brain and neural tissues.

Multiple studies and clinical trials in human epileptic patients have demonstrated efficacy of ketogenic diets against epileptic seizures although widely differing response rates have been reported[55,57]. In one clinical trial, 27% of children had greater than 50% reduction of seizure frequency within 3 months including 5% that had greater than 90% reduction on the ketogenic diets. Among the children still on the study after 12 months, there was a median reduction in seizure frequency of approximately two thirds[55]. Other studies reported freedom from seizure rates as high as 55% and reductions in seizure frequency as high as 85%[57]. Ketogenic diets are not without their own problems, however, as side effects are frequently reported. The most commonly reported side effects were gastrointestinal problems, and attrition rates are high in published studies of ketogenic diets due to dietary intolerance and lack of observed efficacy[57]. In one controlled clinical trial in epileptic children, side effects reported during the first 3 months of the trial included vomiting (27%), diarrhoea and/or abdominal pain (15%), constipation (39%) lack of energy (26%), hunger (29%) and taste problems (19%)[55]. Ketogenic diets are highly restrictive and, in some patients, the psychosocial costs of following such as strict diet outweighed the benefits observed: 46% of the study subjects had discontinued the diet by the end of one year[55]. Similar to other highly restrictive diets, ketogenic diets also have been associated with nutritional deficiencies[56].

Although ketogenic diets have been used with good clinical success for many decades, their mechanism of action is still poorly understood[58]. Recent research suggests that ketogenic diets not only influence energy metabolism but also modify brain neurotransmitter amino acids. Brain gamma-amino-butyric acid (GABA), an inhibitory neurotransmitter was increased and glutamate, an amino acid that serves as an excitatory neurotransmitter, was decreased in rats fed a ketogenic diet. In addition, the ketogenic branched chain amino acids leucine and isoleucine, long thought to be beneficial in hepatic encephalopathy and other central nervous system disorders, were increased in the brain of rats fed the ketogenic diet[59]. Any of these metabolic changes may contribute to the anti-epileptic benefits attributed to ketogenic diets.

High fat ketogenic diets have been used for managing refractory seizures in children for many years. However, few studies have evaluated ketogenic diets for dogs. Dogs do not easily become ketotic due to efficient utilisation of ketones. When ketone precursors were administered to dogs, they were quickly metabolised and ketosis was not achieved[56]. One small study evaluated the use of a classic ketogenic diet for epileptic dogs. Although an increase in serum BHB was documented, differences in seizure activity based on the ketogenic diet were not seen[60]. On the contrary, 3 of the 9 dogs fed the high fat, ketogenic diet developed pancreatitis[11]. More recently, a ketogenic diet based on inclusion of medium chain triglycerides (MCTs) was evaluated in epileptic dogs. MCT are more ketogenic in both humans and dogs, compared to traditional long chain fatty acids[61].

Medium chain triglycerides – a novel mechanism of action for epilepsy

Medium chain triglycerides (MCTs) such as decanoic acid have been utilised for their anti-seizure effects. A recent ground-breaking study revealed decanoic acid's mechanism of action is as a non-competitive AMPA receptor antagonist **(Fig.6)**. At therapeutic concentrations, this results in direct inhibition of excitatory neurotransmission, and thus an anticonvulsant effect[62].

This is in stark contrast to most AEDs used in veterinary medicine that function to increase inhibitory brain pathways, which unfortunately also contributes to side effects such as sedation and ataxia[10,11]. Decanoic acid has been shown to readily pass the blood– brain barrier, at 60% to 80% of serum concentration[63]. Another interesting potential mechanism could be explained by decanoic acid upregulating mitochondrial proliferation[64] and therefore protecting against mitochondrial dysfunction, which can be seen with intensive seizure activity.

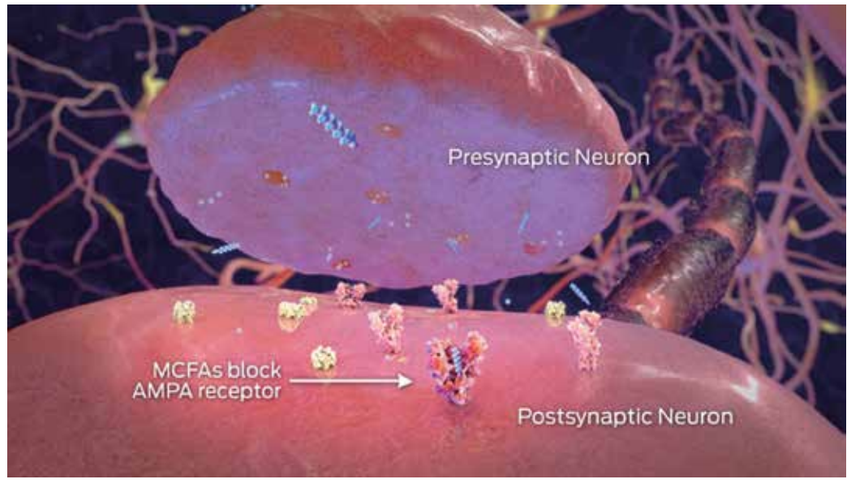


Fig 6: Proposed novel mechanism of action of MCTs as blockers of the AMPA receptor in the post-synaptic neuron.

Clinical study

Thirty-one dogs of various breeds with idiopathic epilepsy were enrolled into a randomised, placebo-controlled, double-blinded, crossover study to evaluate the impact of a diet containing MCT oil[61]. Dogs entered into the study were required to have experienced at least 3 seizure episodes in the 3-month period before the start of the study, despite use of at least one AED. Dogs accepted into the study were randomly assigned to be fed the diet with 5.5% MCT oil or a very similar diet made with lard (containing long-chain triglycerides) instead of MCTs. Dogs were fed their assigned diet for 3 months, then switched to the alternate diet for 3 additional months. Dogs not completing the study (n=10) were equally divided between the MCT and the placebo diet, leaving 21 dogs completing both phases of the crossover study.

The data showed the diet with 5.5% MCT oil resulted in fewer seizure episodes and fewer seizure days during the 3-month treatment period, compared to the control diet[61] **(Fig.7)**. 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 complete seizure freedom. Because many dogs experienced cluster seizures, the number of seizure days also was assessed, which also significantly decreased on diet with MCT oil. The diet with MCT oil resulted in significant elevation of blood β-hydroxybutyrate (a ketone body) concentration compared with the placebo diet. Of interest was the time to response, which began immediately on day 1 after introducing the MCT diet.

Based on this data, a diet with MCT oil may be a useful adjunct in the management of dogs with idiopathic epilepsy. **(Fig.8)**

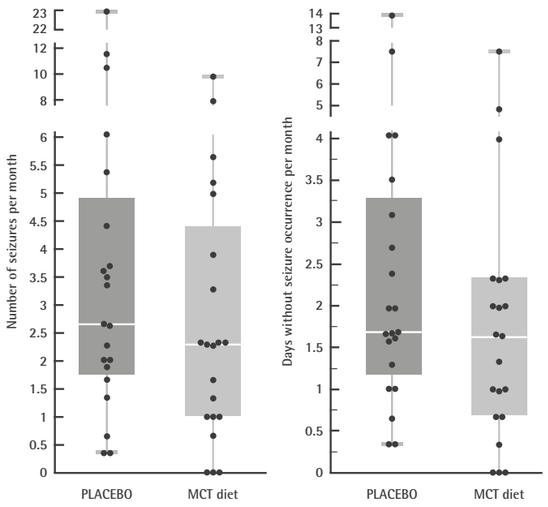
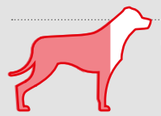


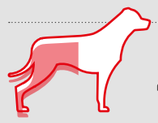
Fig 7:. Extracted from: Law TH, *et al.* A randomised trial of a medium-chain TAG diet as treatment for dogs with idiopathic epilepsy. *Br J Nutr.* 2015 Nov 14;114(9):1438-47.

The results showed that the dogs fed with a diet enriched in MCTs have a reduction in the number of seizures per month and the seizure days per month.

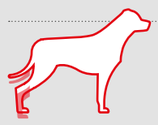
Most dogs with idiopathic epilepsy showed a reduction in seizure frequency in 90 days when fed a test diet with MCT oil, as an adjunct to veterinary therapy



71% of dogs showed a reduction in seizure frequency



48% of dogs showed a 50% or greater reduction in seizure frequency



14% of dogs achieved complete seizure freedom

In addition to seizures, the impact of this MCT-based ketogenic diet on the neurobehavioral comorbidities of canine IE was evaluated[65].
In addition to seizures, epilepsy is strongly associated with neurobehavioural changes in both people and dogs. It has previously been recognized that dogs with IE experience behavioural changes such as increased fear or anxiety, attachment disorders, abnormal perception, or defensive aggression[12,13]. Psychiatric disorders are common in people with epilepsy, with depression, anxiety and attention-deficit/hyperactivity disorder (ADHD) being the most common[65].

Nearly 20% of adults with IE had ADHD, which was associated with increased psychosocial morbidity and lower QoL[6]6. Hyperactivity is more than 5 times more prevalent in children with epilepsy compared to control children[65]. ADHD-like behaviours also occur in animals with epilepsy. In dogs, ADHD-like behaviours are recognised as excitability/impulsivity and inattention[67,68]. In Lagotto Romagnolo dogs, the ADHD-like behaviours were worse among those dogs with a history of juvenile epilepsy[68].

Concurrent with evaluating the impact of an MCT-based ketogenic diet on epileptic seizures, the impact on neurobehavioural comorbidities was assessed[65]. **The MCT diet resulted in a significant improvement in ADHD-related behaviours with a reduction in chasing and in stranger-directed fear. Trainability, which was very low for all the epileptic dogs, also improved with the MCT diet although this did not reach statistical significance within this small study.** It was suggested that the improvements in ADHD-like behaviours may be related to potentially anxiolytic effects of ketogenic diets[65].

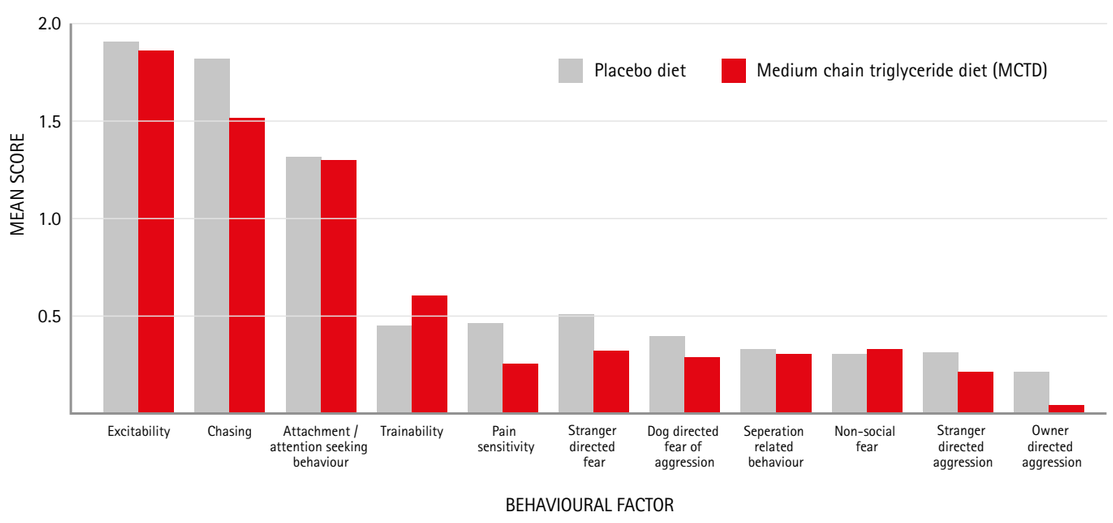


Fig 8: Comparison of behavioural scores for C-BARQ behavioural factors between a placebo and a MCTD diet. Significant reductions were observed in the behavioural factors, namely, chasing and stranger-directed fear ($p<0.05$)

RMA Packer *et al / Epilepsy & Behaviour* 55 (2016) 62-68

Summary

Idiopathic epilepsy (IE) is the most common form of canine epilepsy. Although multiple anti-epilepsy drugs (AEDs) are available, many dogs do not show adequate resolution of seizure activity. Brain energy metabolism is disrupted in IE, leading to reduced glucose metabolism. Ketones, derived from fatty acids, provide an alternative energy source for the brain. Ketogenic diets have been used to help manage IE in children for decades but traditionally high fat ketogenic diets do not appear efficacious in dogs. Recent research demonstrated that an MCT-based ketogenic diet can be used to improve management of IE in dogs. This diet was associated with significant improvements in seizure frequency as well as in related neurobehavioural comorbidities, in dogs with refractory IE. Based on this data, a MCT-based ketogenic diet may be a useful adjunct in the management of dogs with IE.

References

1. Moore SA. A clinical and diagnostic approach to the patient with seizures. *Topics Compan An Med* 2013;28:46-50.
2. Charalambous M, Brodbelt D, Volk HA. Treatment in canine epilepsy--a systematic review. *BMC Vet Res* 2014 Oct 22;10:257.
3. Heske L, Nodtvedt A, Jaderlund KH, *et al.* A cohort study of epilepsy among 665,000 insured dogs: incidence, mortality and survival after diagnosis. *Vet J* 2014;202:471-476.
4. Hulsmeyer VI, Fischer A, Mandigers PJJ, *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.
5. Mariani CL. Terminology and classification of seizures and epilepsy in veterinary patients. *Topics Compan An Med* 2013;28:34-41.
6. Fisher RS, Acevedo C, Arzimanoglou A, *et al.*. ILAE official report: a practical clinical definition of epilepsy. *Epilepsia* 2014;55:475-482.
7. Berendt M, Farquhar RG, Mandigers PJJ, *et al.*. International veterinary epilepsy task force consensus report of epilepsy definition, classification and terminology in companion animals. *BMC Vet Res* 2015;11:182.
8. De Risio L, Bhatti S, Muñana K, *et al.* International veterinary epilepsy task force consensus proposal: diagnostic approach to epilepsy in dogs. *BMC Vet Res* 2015 Aug 28;11:148
9. Skerritt G. Canine Epilepsy. *In Practice* 1988;10:27-30.
10. Bhatti S, De Risio L, Muñana KR, *et al.* International Veterinary Epilepsy Task Force consensus proposal: Medical treatment of canine epilepsy in Europe. *BMC Vet Res* 2015.
11. Podell M, Volk HA, Berendt M, *et al.* 2015 ACVIM Small Animal Consensus Statement on Seizure Management in Dogs. *J Vet Intern Med* 2016;30:477-490.
12. Packer RMA, Volk HA. Epilepsy beyond seizures: a review of the impact of epilepsy and its comorbidities on health-related quality of life in dogs. *Vet Rec* 2015;177:306-315.
13. Shihab N, Bowen J, Volk HA. Behavioral changes in dogs associated with the development of idiopathic epilepsy. *Epilepsy & Behavior* 2011;21:160-167.
14. Berendt M, Gredal H, Ersbøll AK, *et al.* Premature Death, Risk Factors, and Life Patterns in Dogs with Epilepsy. *J Vet Intern Med* 2007;21:754-759.
15. Chang Y, Mellor DJ, Anderson TJ. Idiopathic epilepsy in dogs: owners' perspectives on management with phenobarbitone and/or potassium bromide. *J Small Anim Pract* 2006;47:574-581.
16. Wessmann A, Volk H, Parkin T, *et al.* Living with canine idiopathic epilepsy: a questionnaire-based evaluation of quality of life. Proceedings of the 24th Symposium ESVN-ECVN. *J Vet Intern Med* 2012;26:823-852.
17. Wessmann A, Volk HA, Packer RM, *et al.* Quality-of-life aspects in idiopathic epilepsy in dogs. *Vet Rec* 2016.
18. Mellersh CS. Genetic Testing in Canine and Feline Epilepsy. In: British Small Animal Veterinary Association Congress, Birmingham, UK 2010.
19. Packer RMA, Shihab NK, Torres BBJ, *et al.* Clinical risk factors associated with anti-epileptic drug responsiveness in canine epilepsy. *PLoS ONE* 2014;
20. Fredso N, Koch BC, Toft N, Berendt M. Risk factors for survival in a university hospital population of dogs with epilepsy. *J Vet Intern Med* 2014;28:1782-1788.
21. Podell M. Antiepileptic drug therapy and monitoring. *Topics Compan An Med* 2013;28:59-66.
22. Packer RMA, Shihab NK, Torres BBJ, *et al.* Responses to successive anti-epileptic drugs in canine idiopathic epilepsy. *Vet Rec* 2015.
23. Suiter EJ, Packer RM, Volk HA. Comparing the effects of first-line antiepileptic drugs on the gait of dogs with idiopathic epilepsy. *Vet Rec* 2016;178:652.
24. Heynold Y, Faissler D, Steffen F, *et al.* Clinical, epidemiological and treatment results of idiopathic epilepsy in 54 Labrador Retrievers: a long-term study. *J Small Anim Pract* 1997;38:7-14.
25. Arrol L, Penderis J, Garosi L, *et al.* Aetiology and long-term outcome of juvenile epilepsy in 136 dogs. *Vet Rec 2012*;170:335.
26. Berendt M, Gredal H, Pedersen LG, *et al.* A Cross-Sectional Study of Epilepsy in Danish Labrador Retrievers: Prevalence and Selected Risk Factors. *J Vet Intern Med* 2002;16:262-268.
27. Trepanier L, Schwark W, Van Schoick A, *et al.* Therapeutic serum drug concentrations in epileptic dogs treated with potassium bro¬mide alone or in combination with other anticonvulsants: 122 cases (1992-1996). *J Am Vet Med Assoc* 1998;213:1449-1453.
28. Schwartz-Porsche D, Löscher W, Frey H. Therapeutic efficacy of phenobarbital and primidone in canine epilepsy: a comparison. *J Vet Pharmacol Ther* 1985;8:113-119.
29. Podell M, Fenner W. Bromide therapy in refractory canine idiopathic epilepsy. *J Vet Intern Med* 1993;7:318-327.
30. Mergenthaler P, Lindauer U, Dienel GA, Meisel A. Sugar for the brain: the role of glucose in physiological and pathological brain function. *Trends Neurosci* 2013;36:587-597.
31. Viitmaa R, Haaparanta-Solin M, Snellman M *et al.* Cerebral glucose utilization measured with high resolution positron emission tomography in epileptic Finnish Spitz dogs and healthy dogs. *Vet Radiol Ultrasound* 2014;55:453-461.
32. Jokinen TS, Haaparanta-Solin M, Viitmaa R *et al.* FDG-PET in healthy and epileptic Lagotto Romagnolo dogs and changes in brain glucose uptake with age. *Vet Radiol Ultrasound* 2014;55:331-341.
33. Eom KD, Lim CY, Gu SH *et al.* Positron emission tomography features of canine necrotizing meningoencephalitis. *Vet Radiol Ultrasound* 2008;49:595-599.
34. Kang BT, Kim SG, Lim CY *et al.* Correlation between fluorodeoxy¬glucose positron emission tomography and magnetic resonance imaging findings of non-suppurative meningoencephalitis in 5 dogs. *Can Vet J* 2010;51:986-992.
35. Kim YK, Lee DS, Lee SK, *et al.* Differential features of metabolic abnormalities between medial and lateral temporal lobe epilepsy: quantitative analysis of 18F-FDG PET using SPM. *J Nucl Med* 2003;44:1006-1012.
36. Galazzo IB, Mattoli MV, Pizzini FB, *et al.* Cerebral metabolism and perfusion in MR-negative individuals with refractory focal epilepsy assessed by simultaneous acquisition of 18F-FDG PET and arterial spin labeling. *Neuroimage Clin* 2016;11:648-657.
37. Henry TR, Votaw JR. The role of positron emission tomography with [18F] fluorodeoxyglucose in the evaluation of the epilepsies. N*euroimag Clin N Am* 2004;14:517-535.
38. Casse R, Rowe CC, Newton M, Berlangieri SU, Scott AM. Positron emission tomography and epilepsy. *Mol Imaging Biol* 2002;4:338-351.
39. Tenney JR, Rozhkov L, Horn P, Miles L, Miles MV. Cerebral glucose hypometabolism is associated with mitochondrial dysfunction in patients with intractable epilepsy and cortical dysplasia. *Epilepsia* 2014;55:1415-1422.
40. Tepmongkol S, Srikijvalaikul T, Vasavid P. Factors affecting bilateral temporal lobe hypometabolism on 18F-FDG PET brain scan in unilateral medial temporal lobe epilepsy. *Epilepsy Behav* 2013;29:386-389.
41. Akman CI, Ichise M, Olsavsky A, et al. Epilepsy duration impacts on brain glucose metabolism in temporal lobe epilepsy: results of voxel-based mapping. *Epilepsy Behav* 2010;17:373-380.
42. Tang Z, Chen Z, Zhai Q, *et al.*Correlation between interictal cerebral gluocse hypometabolism and IQ in children with epilepsy. *Epilepsy Behav* 2014;31:15-18.
43. Juhasz C, Behen ME, Muzik O, *et al.*Bilateral medial prefrontal and temporal neocortical hypometabolism in children with epilepsy and aggresion. *Epilepsia* 2001;42:991-1001.
44. Ferrie CD, Madigan C, Tilling K, *et al.*Adaptive and maladaptive behaviour in children with epileptic encephalopathies: correlation with cerebral glucose metabolism. *Dev Med Child Neurol* 1997;39:588-595.
45. Kim SH, Lim S-C, Kim W, *et al.*Changes in background electroencephalography and regional cerebral glucose metabolism in focal epilepsy patients after 1-month administration of levetiracetam. *Neuropsychiatric Disease and Treatment.* 2015;11:215-223.
46. Schonfeld P, Reiser G. Why does brain metabolism not favor burn¬ing of fatty acids to provide energy? – Reflections on disadvantages of the use of free fatty acids as fuel for brain. *J Cerebral Blood Flow Metabol* 2013;33:1493-1499.
47. Ebert D, Haller RG, Walton ME. Energy contribution of octanoate to intact rat brain metabolism measured by 13C nuclear magnetic resonance spectroscopy. *J Neurosci* 2003; 23: 5928–5935.
48. Wlaz P, Socala K, Nieoczym D, *et al.* Acute anticonvulsant effects of capric acid in seizure tests in mice. *Prog Neuro-Psychopharmacol Biolog Psychiatry* 2015;57:110-116.
49. Chang P, Terback N, Plant N, *et al.* Seizure control by ketogenic di¬et-associated medium chain fatty acids. *Neuropharm* 2013;69:105-114.
50. Pan Y, Larson B, Araujo JA, *et al.* Dietary supplementation with medium-chain TAG has long-lasting cognition-enhancing effects in aged dogs. *Brit J Nutr* 2010;103:1746-1754.
51. Quistorff B, Secher NH, VanLieshout JJ. Lactate fuels the human brain during exercise. *FASEB J* 2008;22:3443-3449.
52. Kemppainen J, Aalto S, Fujimoto T, *et al.* High intensity exercise decreases global brain glucose uptake in humans. *J Physiol* 2005 DOI: 10.1113/jphysiol.2005.091355.
53. Occhipinti R, Somersalo E, Calvetti D. Astrocytes as the glucose shunt for glutamatergic neurons at high activity: an in silico study. *J Neurophysiol* 2009;101:2528-2538.
54. Yang H, Wu J, Guo R, *et al.*Glycolysis in energy metabolism during seizures. *Neural Regen Res* 2013;8:1316-1326.
55. Neal EG, Chaffe H, Schwartz RH, *et al.* A randomized trial of classical and medium-chain triglyceride ketogenic diets in the treatment of childhood epilepsy. *Epilepsia* 2009;50:1109-1117.
56. Larsen JA, Owens TJ, Fascetti AJ. Nutritional management of idiopathic epilepsy in dogs. J *Am Vet Med Assoc.* 2014
57. Martin K , Jackson CF, Levy RG, Cooper PN. Ketogenic diet and other dietary treatments for epilepsy. *Cochrane Database Syst Rev.* 2016.
58. Ruskin DN, Masino SA. The nervous system and metabolic dysregulation: emerging evidence converges on ketogenic diet therapy. *Frontiers Neurosci* 2012. DOI: 10.3389/ fnins.2012.00033.
59. Roy M, Beauvieux MC, Naulin J, *et al.*Rapid adaptation of rat brain and liver metabolism to a ketogenic diet: an integrated study using 1H- and 13C-NMR spectrscopy. *J Cerebral Blood Flow Metabol* 2015;35:1154-1162.
60. Patterson EE, Munana KR, Kirk CA, *et al.* Results of a ketogenic food trial for dogs with idiopathic epilepsy. *J Vet Intern Med* 2005;19:421.
61. Law TH, Davies ES, Pan Y, *et al.*A randomised trial of a medium-chain TAG diet as treatment for dogs with idiopathic epilepsy. *Br J Nutr.* 2015 Nov 14;114(9):1438-47.
62. Chang P-S, Augustin K, Boddum K, *et al.*Seizure control by decanoic acid through direct AMPA receptor inhibition. *Brain* 2015;25:1-13.
63. Wlaz P, Socala K, Nieoczym D, *et al.* Anticonvulsant profile of caprylic acid, a main constituent of the medium-chain triglyceride (MCT) ketogenic diet, in mice. *Neuropharmacology* 2012;62:1882-1889.
64. Hughes SD, Kanabus M, Anderson G, *et al.* The ketogenic diet com¬ponent decanoic acid increases mitochondrial citrate synthase and complex I activity in neuronal cells. *J Neurochem* 2014;129:426-433.
65. Packer RMA, Law TH, Davies E, *et al.* Effects of a ketogenic diet on ADHD-like behavior in dogs with idiopathic epilepsy. *Epilepsy Behav* 2016;55:62-68.
66. Ettinger AB, Ottman R, Lipton RB, *et al.* Attention-deficit/hyperactivity disorder symptoms in adults with self-reported epilepsy: results from a national epidemiological survey of epilepsy. *Epilepsia* 2015;56:218-224.
67. Vas J, Topal J, Pech E, Miklosi A. Measuring attention deficit and activity in dogs: a new application and validation of a human ADHD questionnaire. *Appl Anim Behav Sci* 2007;103:105-117.
68. Jokinen TS, Tiira K81-1087., Metsahonkala L, *et al.*Behavioral abnormalities in Lagotto Romagnolo dogs with a history of benign familial juvenile epilepsy: a long-term follow-up study. *J Vet Intern Med* 2015;29:10

For more information

Contact: XXXXXXXXXX
Or visit : XXXXXXXXX

PURINA® Your Pet, Our Passion.®