Nutritional intervention for an epileptic obese golden retriever with the inclusion of MCT-oil supplementation: A case report

Introduction

Epilepsy is a group of heterogeneous conditions sharing common features of chronic recurring seizures (Thomas 2010). It is the most common neurologic disorder in dogs affecting between 0.6% and 0.75% of the general population with a higher prevalence in some predisposed breeds (Molina et al. 2020, Packer et al. 2015). A family predisposition with an epidemiological prevalence of 3.1% has been recognized for Labradors and Golden Retrievers (Jaggy et al. 1998) with a multifactorial etiology, including genetic and environmental factors (Casal et al. 2006) and it has been described to comprise suspected polygenic autosomal recessive genetic basis (Ekenstedt & Oberbauer 2013). Epilepsy has a diverse, complex, and often-unknown etiology (Masino et al. 2019). The proposed canine classification for epilepsy is based on a modification of the one proposed by the International League against Epilepsy in human medicine as listed:

1) Primary/genetic (often termed as idiopathic) 2) Structural (symptomatic resulting from structural brain abnormalities) 3) Reactive (symptomatic resulting from metabolic or toxic abnormalities) and 4) unknown (Gardiner 2005, Thomas 2010, Molina et al. 2020). When chronic, recurring seizures without the detection of an underlying abnormality are distinguished, the syndrome is classified as primary (idiopathic) epilepsy presumed to be genetically regulated (Gardiner 2005).

Many anti-epileptic drugs are available on the market and are often prescribed alone or in combination to canines diagnosed with idiopathic epilepsy. More than one-third of these patients are recognized as drug-resistant; implicating that regardless of appropriate pharmacological treatment; suitable management of the seizure presentation remains unsuccessful and/or has severe unacceptable side effects (Han et al. 2021, Masino et al. 2019). One of the physiological factors known to influence the seizure presentation is cellular metabolism; taking into consideration that local metabolic derangements are the main characteristics in the brain epileptic foci (Masino & Roh 2019). Diverse nutritional strategies have been suggested to help to control seizure presentation in idiopathic epilepsy. Additional considerations for a comprehensive nutritional management plan include addressing concomitant diseases or nutrient-drug interactions (Larsen et al. 2014). Classic and modified ketogenic diets were first formulated for epileptic infants, to resemble fasting periods and

proved to modulate the progression of the disease, with decreasing the average presentation of seizures by forcing the metabolism to primary rely on ketone bodies rather than glucose (Masino & Roh 2019, Masino et al. 2019, Molina et al. 2020). Studies evaluating the effectiveness of these dietary approaches have failed to prove a substantial control for seizures on canine drug-resistant idiopathic epilepsy (Patterson et al. 2005). Latterly, diets with the inclusion of supplemental MCT-oils gained importance amongst the therapeutic strategies for drug-resistant seizures. MCTs act as an alternative energy source for the brain being able to cross the blood-brain barrier making them highly available for subsequent oxidation. Diets containing MCT-oils also seem to increase importantly the metabolic synthesis of polyunsaturated fatty acids (PUFAs) and their uptake in the brain tissue of dogs (Molina et al. 2020). Many studies have tested the efficiency of the inclusion of MCT-oils in nutritional protocols aiming to reduce seizure frequency. In a variety of studies an important percentage of dogs fed with diets containing MCT-oils experienced a reduction in overall and seizure-day frequency (Berk et al. 2018, Law et al. 2015).

Clinical history

An overweighed, neutered 7-year old, male, Golden Retriever with a bodyweight of 39.5 kg (ideal weight: 30-33 kg) was referred to the Institute of Animal Nutrition and Dietetics of the Vetsuisse Faculty University of Zurich with a diagnosis of Idiopathic epilepsy for a nutritional consultation. After the patient's neutering and with the prescription of the anti-epileptic drug therapy, (Phenobarbital 100 mg BID) the patient's weight had great variability and the BCS ranged between 7-8/9. At the time of the patient's nutritional consultation, the BCS assessment was 8 on a 9-point scale where 1 is emaciated and 9 is morbidly obese (WSAVA, 2013). The patient was subsequently admitted to the neurological department of the animal hospital in Zurich, for clarification of epileptic seizures that first emerged, at 7 years of age. Initially, the seizures occurred as individual incidents at intervals of about 3-4 weeks. After the second seizure, the aforementioned anti-epileptic drug therapy protocol was established. A phenobarbital level in the blood (active substance of the drug) was determined, without an exacerbation of the recommended ranges. After the presentation of cluster seizures (more than 2 seizures within 24 hours) more generalized, epileptic seizures continued to take place. The seizures were reported to occur at home and under unaltered circumstances. The patient would initially exhibit a blank stare, generalized rigidity, and dystonic head movements to the right. During the ictal period, the patient would sag and display classic, generalized tonic-clonic owing movements with strong salivation, without micturition or defecation. The average

seizure length was on average 3.5 minutes where the patient remained unresponsive. During the post-ictal period, the patient seemed disoriented and restless for about an hour. The seizures were not associated with feeding or long periods of fasting. After the cluster seizure presentation, the phenobarbital dose was adjusted from 100 mg to 150 mg BID. Since the pharmacological adjustment, the presentation of seizures decreased importantly, however, the patient continued to endure seizures (around one to two episodes a month) before the nutritional consultation. Aside from the reported seizures, no other abnormalities were found during clinical examinations. Seriated blood works were performed, where only an increased serum cholesterol level was found (Table 1). Hypertriglyceridemia may be a common finding in epileptic dogs undergoing phenobarbital pharmacological treatment. The mechanism remains unclear; however, phenobarbital may increase hepatic production of very-low-density lipoproteins and decrease lipase activity (Bauer 1995). Other parasitic causes of neurological symptoms were ruled out (Toxoplasma and Neospora infection). A magnetic resonance imaging (MRI) examination showed a morphologically normal brain, additionally, a cerebrospinal fluid analysis (CSF) collected from the atlanto-occipital region revealed in addition to a few erythrocytes, isolated small and mature lymphocytes, and very few monocytic cells without the presence of infectious agents. The unremarkable cytological findings closed the final diagnosis of primary or idiopathic epilepsy.

Nutritional approach

The nutritional contents of the patient's subsequent diets are specified in Table 2 and were estimated with Diet Check Munich ©2005 Version 3.0 (RV Software; based on NRC 2006, modified by Dobenecker and Kienzle). The Diet A fed to the patient before the nutritional consultation consisted of one commercial extruded grain-free maintenance adult dry food supplemented with vitamin-amino acid-mineral tablets. Around 59% of the total amount fed daily consisted of commercial chewing material. The data on the mineral content of some of the commercial chewing material was not fully available. A complete diet check to review if the entire patient's nutritional requirements were met was therefore not possible. Nevertheless, an estimated diet check was performed based on the products that did provide a complete nutritional analysis profile to proffer a comparison criterion. (Diet A, Table 2). The department of Neurology of the Animal Hospital of the Vetsuisse Faculty University of Zurich recommended to the owners a nutritional consultation, considering the patient's severe overweight and the inclusion of supplemental MCT-oils in the diet since regardless of the pharmacological treatment, the patient continued to present sporadic seizures. According to

these remarks, diet B was established for the patient. It consisted of commercial dry food (at the request of the owner) formulated for neurological care and balanced with the inclusion of oats, beef dried muscle meat, vegetables, salmon and walnut oil, MCT-oil, trace-mineral supplement, and cellulose for satiety stimulation (Table 3) since the patient exhibited an uncontrolled appetite behavior. Based on the calculated nutritional composition of the initial diet A and the recommended diet B (Table 2), the energy supply of the dietary recommendation was initially calculated with a 30% reduction in the energetic supply when compared to the initial energetic calculation in the diet check. Starting points for caloric restriction may differ; however, it has been proposed that if current intake can be estimated from a comprehensive dietary history, a 20 to 30% energetic restriction is an optimal initial approach (Burkholder & Bauer 1998).

With this energetic adjustment, a minimum of 1% or a maximum of 2% weekly weight loss rate was anticipated, down to a target weight of about 33 kg (Figure 1). A slow introduction to the new recommended diet (during 14 days) was encouraged to allow the patient's gastrointestinal tract to get used to the novel ingredients, especially oils.

In the dietary recommendation, the classic nutritional approach of the ketogenic diets (high fat, low protein, low carbohydrate) designed to simulate the biochemical changes of fasting to potentiate mitochondrial-dependent energy metabolism (Clanton et al. 2016) was partially included. The total amount of fat supply was increased and the protein supply was decreased in contrast to the previously fed diet. Since the owners requested a mixed diet (composed partially of fresh ingredients and mainly of dry commercial food) (Table 3) an approach of a medium-chain triglyceride (MCT)-supplemented diet was formulated. The diet included 6.5% MCTs on the dry matter basis on the commercial neurological diet and an additional 4 g of an MCT-oil formulation (100% MCT-oil, 55% C8, or octanoic acid, and 40% C10 or decanoic acid). A new approach with a higher dosage of MCT oils on a dry matter basis was pursued in this case. The recommended diet was higher in fat (22.6 % on a dry matter basis) but not a ketogenic diet and not lower in the total nitrogen-free extract (33.7% on a dry matter basis). It was, however, a calorically restricted controlled diet with a high proportion of whole food components replacing the high proportion of commercial chewing materials. Fresh components were adjusted according to availability and the owner's preference. Despite the only marked shift in macronutrient composition being the fat and protein content.

The fatty acid and essential fatty acid requirements were balanced according to the recommendations provided by the NRC, 2006. The estimated Omega 6:3 ratio of the recommended diet was estimated in 2.5

Follow up

The dietary adjustment was highly beneficial and there was a clear relationship between the dietary change and the monthly seizure presentation following the adjustment of the pharmacological anti-epileptic drug therapy. This case also provides a clear positive control of the relationship between supplemental MCT-oils, seizure presentation and an intermediate amount of carbohydrates present in the diet. Regardless of a 33.7% Nfe on the dry matter basis, there was a reported 9-month free seizure period without further adjustments required on the anti-seizure drug dosage protocol.

After the nutritional consultation, the follow-up was limited, we contacted the owner to update the weight loss rate and document the presence of seizures. The weight loss appeared slower than the minimal expected weight loss of 1% weekly (Figure 1) being the patient 1.2 kg heavier than the calculated expected weight (Current weight: 36 kg). The owner reported to feed slightly larger amounts of beef and oats as rewards but agreed to comprise the recommended amounts of ingredients in the future and to follow a further energetic adjustment if the patient fails to reach the expected target body weight. Regarding the seizure presentation, the owner reported that since the establishment of the nutritional recommendation the patient was completely seizure-free for 9 months without further adjustment of the anti-seizure drug dosage and without any veterinary check-up. The owner reported the patient to accept very well the nutritional recommendation especially since it is partly homemade. No adverse gastrointestinal symptoms were reported with the implementation of the nutritional recommendation.

Discussion

In this case, an initial prompt diagnosis of the disease was achieved. Due to the recurrence of the symptoms despite an anti-epileptic drug therapy protocol, the patient was forwarded to the Neurology department, wherein concordance to what is described in the literature a suitable diagnostic pathway was conducted. (Thomas, 2010). With the introduction of the dietary recommendation the patient lost weight, but not on the speed nor the amount desired (Figure 1). Anti-epileptic drugs have many known side effects and are considered one of the major contributions to a reduction in the life quality of patients with idiopathic epilepsy. Side effects such as polyphagia, polydipsia, polyuria, weight gain, ataxia, increased sleeping, vomiting, and

diarrhea are included on the list (Wessmann et al. 2014). As highlighted in the presented case, the anti-epileptic drugs can predispose affected dogs to obesity; this concomitant disease might hinder a dog's ability to behave properly and has a deep impact on the quality of life. (German 2006, Linder & Mueller, 2014). The drawback from this perspective could be attributed first to a lack of owner compliance, related to the increased appetite behavior mediated by the introduction of anti-epileptic drugs and the reduced amount of feed per meal provided compared with the initial feeding regime. This might explain why overall was difficult for the owner to adapt strictly to the dietary recommendation, consequently leading to higher amounts of food fed to the patient. The patient presented in this case report suffered from obesity before the diagnosis with idiopathic epilepsy, nonetheless, the weight gain increased dramatically with the onset of the anti-epileptic drug protocol. With the nutritional recommendations, the patient did lose weight (Figure 1). In accordance, it is important to observe that the estimated volume of distribution of anti-epileptic drugs may be impacted by obesity to different degrees. Phenobarbital has a high lipid solubility and a large volume of distribution, meaning that the body composition (excess of adipose tissue or muscle atrophy) plays an important role in determining the efficacy of the dosage regimens (Larsen et al. 2014). The hypothesis in this context could be that, as the patient underwent a relative loss of adipose tissue, the efficacy of the already adjusted phenobarbital dose increased. Aiding to the final observations of a prolonged seizure-free period without further increment required on the dosage protocol. Additional scientific evidence is still required to determine if these pharmacokinetic principles also have importance in the canine idiopathic epilepsy treatment and therapeutic outcome.

In addition, the long-term phenobarbital treatment has been associated with hepatotoxicity, suspected to be dose-dependent (Gaskill et al. 2005). Since the diagnosis of this case is relatively recent, no compromise of the liver has been yet observed. Additional complications reported with the use of phenobarbital such as pancreatitis (Hess et al. 1999) are as well to be discarded in this case at the moment. Nevertheless, no additional control blood work has been performed since the pharmacological treatment was adjusted so that these observations are merely symptomatic. If additional compromises of the liver or pancreas are established in the future, the dietary recommendation might require further adaptations.

In this case, a dosage regimen of almost 10% MCTs supplementation on the dry matter basis was achieved, with the combination of the commercial neurological care dog food and the supplemented MCT-oil without any reported adverse effects. Congruent with what has been described in the literature, the inclusion of MCT-oil improved the seizure control and free

seizure interval, on the hand of an appropriate anti-epileptic drug therapeutic protocol. MCTs not only possess the already mentioned ketogenic yield, improving brain metabolism but also, have direct antiepileptic effects (such as valproic acid). There is also strong evidence to support that the MCT decanoic acid has antiseizure effects due to its mechanism of action, being a non-competitive receptor antagonist, directly capable of inhibiting excitatory neurotransmission (Chang et al. 2015). Other possible pathways for the seizure inhibition of the oral MCT supplementation may be the elevation of ketone BHB (Beta-hydroxybutyrate) concentrations (Law et al. 2016). In contrast to most of the anti-epileptic drugs prescribed to canine idiopathic epileptic patients, which work on increasing the function of the inhibitory brain pathways, this might also explain as well the undesired effects such as ataxia, sedation, and reduction of life quality (Podell et al. 2016).

The relatively high-dosage regimen of MCT oils implemented in this case, might be one of the reasons why such a long seizure-free period was achieved without additional manipulation of the anti-epileptic drug protocol. Congruent with the results of several efficacy studies including the addition of MCT-oils to decrease the seizure presentation in idiopathic epileptic dogs. (Packer et al. 2016, Molina et al. 2020). In this case, no gastrointestinal side effects with the administration of MCT oils and no negative drug interaction was observed, consistent with the literature remarks (Berk et al 2019, 2020, 2021, Masino et al. 2019). The outcome of the present case report, also complies with the results of another case report where one dog without seizure reduction on standard phenobarbital and bromide anti-epileptic therapy, was reported to be seizure-free for 33 weeks with supplementation of MCT oils. (Masino et al. 2019).

For this case, the addition of omega-3 was aimed to aid the subjacent mild hyperlipidemia and obesity. Doses of 120-125 mg EPA+DHA per kg body weight have been recommended for dogs with hyperlipidemia or inflammatory diseases diagnosed with idiopathic epilepsy. (Bauer 2011). According to Bourre's studies in 2014, fish oils contribute to the risk reduction of neurological disorders such as epilepsy via modulation of ion channels and reduction of the excitability in the central nervous system. There is enough evidence of the described mechanism in human chronic epilepsy (Yuen et al. 2005). However, in dogs, there is little evidence that supports that the addition of omega-3 fatty acids has a positive impact on seizure occurrence and a subjective improvement of life quality in dogs with idiopathic epilepsy. It is not possible to distinct in this case if the supplementation with omega-3 played a role in the overall positive results, notwithstanding the possibility of synergistic effects of the combination of the different dietary measures established in this case, should not be ruled out.

Conclusion

The outcome of this case supports the scientific evidence stating that the use of MCT-oils as adjuvants for pharmacological anti-epileptic drug treatment of canine idiopathic and drug-resistant epilepsy might be beneficial and provide synergistic effects. The inclusion of MCTs in higher safe doses, therefore, may implicate a good choice in contrast to restrictive dietary regimens such as the classic ketogenic diets. A comprehensive nutritional approach is additionally recommendable in order to address risk factors for the presentation of drug interactions such as obesity and possible side effects of the administration of anti-epileptic drugs. Further work is required to fully understand the findings here enlightened and to establish exact dosage regimens of MCT-oil inclusion in nutritional recommendations for dogs with idiopathic epilepsy.

Tables and Figures

Figure 1: Summary of the weight history of the patient with an initial weight of 39.5 kg, compared with the expected weight loss rate of minimum 1% and maximum 2% per week after the nutritional adaptation (week 1) further to the target weight for the initial weight-loss stage of approximately 33 kg (week 12). Note that with the expected weight loss of minimum 1% per week the end expected weight of 33 Kg would be reach slower.

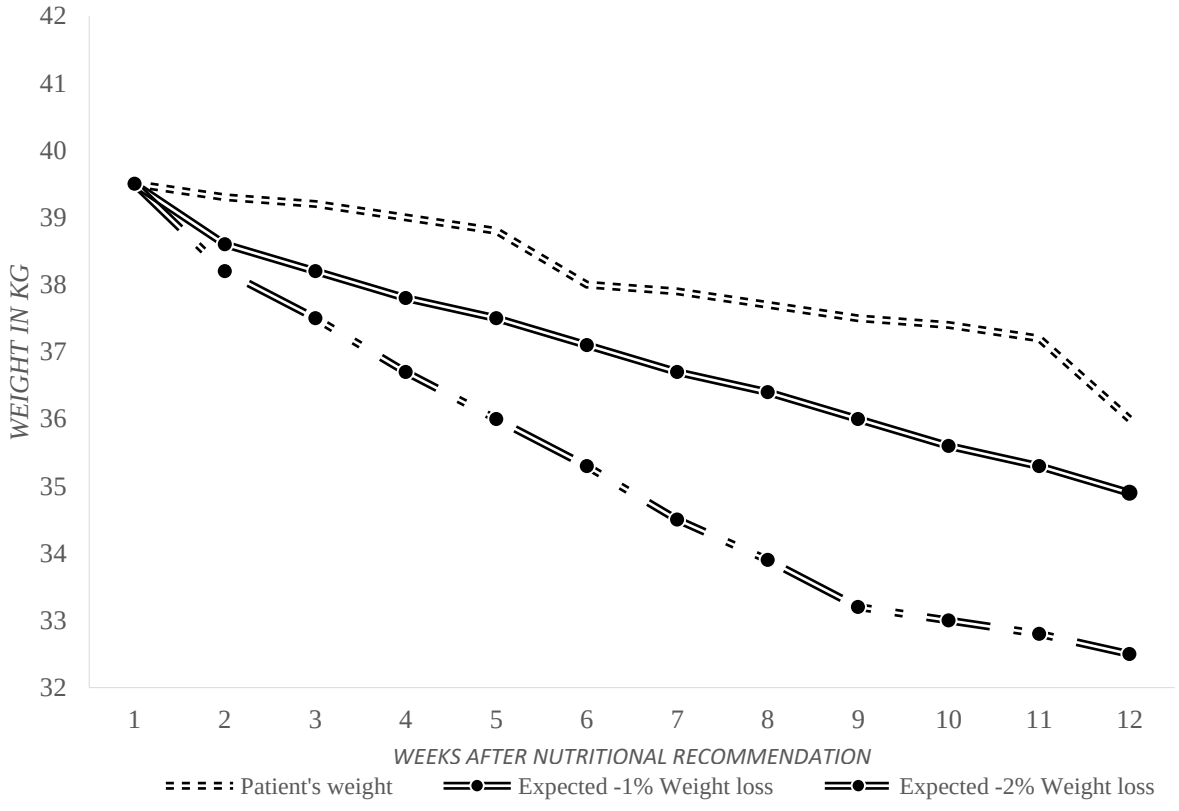

Table 1: Summary of the available laboratory test results performed initially, with the onset of the seizures, and completed before the adjustment of the anti-epileptic drug treatment.

Comprehensive metabolic panel	**12.04.2021**	**01.11.2021**	**08.11.2021**	**Reference Values**
Albumin	-	39	-	25-44 g/l
ALP	-	94 U/L		
ALT	-	95	-	10-118 U/L
Amylase	-	400	-	200-1200 U/L
Bilirubin	-	5	-	2-10 µmmol/l
Blood urea nitrogen	6.5	6.9	-	2.5-8.9 mmol/l
Creatine-kinase	-	-	86	51-191 U/l
Calcium	2.4	2.53	-	2.15-2.95 mmol/L
Phosphorus	1.4	1.35	-	0.94-2.13 mmol/l
Creatinine	-	77	-	27-124 µmmol/l
Glucose	4.4	5.7	-	3.3-6.1 mmol/l
Sodium	-	146	-	138-160 mmol/l
Potassium	-	4	-	3.7-5.8 mmol/l
Total Protein	-	64	-	54-82 g/L
Globulin	-	25	-	23-52 g/l
Bile acids	7.78	-	-	<20 µmmol/l
Bile acids (Pre prandial)	-	-	1	1-6.5 µmmol/l
Thyroxine	-	16	-	14-52 nmol/L
Cholesterol	-	8.8	-	3.2-7.0 mmol/l

Table 2: Comparison of subsequent diets nutritional content, calculated with Diet Check Munich © 2005 Daily values of Nutrient content of the diets provided. CRA = Calculated Recommended allowance; Diet A = diet fed during the onset of clinical disease; Diet B = completely balanced mixed diet, prescribed by the Institute of Animal Nutrition and Dietetics of the Vetsuisse Faculty, University of Zurich

	CRA	**Diet A**	**Diet B**
Energy (MJ ME)	3.9	5.6	3.9
Crude Protein (g)	70	36	72
Nitrogen free extract (g)	/	45	33.7
Fat (g)	/	20	47
Fat (% Dry Matter)	/	16.9	22.6
Calcium (mg)	1669	1394	2800
Phosphorus (mg)	1251	1011	1984
Magnesium (mg)	250	146	251
Potassium (mg)	1669	1971	1925
Sodium (mg)	334	643	492
Iron (mg)	12.5	45.7	42.8
Copper (mg)	2.5	2.2	4.5
Zinc (mg)	25	34.0	40
Manganese (mg)	2.0	4.5	8.6
Chloride (mg)	501	320	1129
Iodine (µg)	367	458	541
Vitamin A (IU)	2108	2857	3647
Vitamin D (IU)	227	395	330
Vitamin E (mg)	13	36	78
Vitamin B1 (mg)	0.93	3.07	3.65
Vitamin B12 (µg)	15	48	37

Table 3: Composition of diet B. Quantity of ingredients in the daily ration of Diet B as recommended by the Institute of Animal Nutrition and Dietetics of the Vetsuisse Faculty, University of Zurich for an obese dog with 33kg ideal body weight with epilepsy

Ingredient	**Diet B**
Purina Proplan Canine Neurocare (g)	120
Oats (raw weight) (g)	30
Dried beef muscle meat (g)	45
Carrots (raw weight) (g)	40
Zucchini (raw weight) (g)	40
Walnut oil (g)	10
MCT-oil(g)	4
Trace element supplement	3
EPA & DHA in salmon oil (g)	5
Feed cellulose	30

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