Medium-chain triglycerides dietary supplement improves cognitive abilities in canine epilepsy.

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Summary – Abstract (200 words)

Objective: Cognitive impairments (CI) have recently been identified in canine epilepsy patients. A medium-chain triglyceride (MCT) enriched diet has been demonstrated to improve cognition in aged dogs and seizure control in canine epilepsy. This study evaluates the short-term effects of MCT oil consumption on cognitive abilities in dogs with epilepsy, a naturally occurring animal model.

Methods: A 6-month multi-center, prospective, randomized, double-blinded, controlled cross-over diet trial was conducted comparing dietary supplementation (DS) of MCT-oil to a control oil. Allocation to dietary oil supplements, consisting of 9% total caloric intake, was block-randomized and supplemented into each dogs' diet for three months followed by a respective switch of DS oil for a further three months. Non-invasive cognitive tests and a validated psychometric tool were utilized to evaluate cognitive function and perturbations associated with dietary intervention.

Results: Twenty-nine dogs completed the trial, of which 18 completed non-invasive cognitive testing. Spatial-working memory ($p=0.008$), problem-solving ability ($p=0.048$) and owner-reported trainability ($p=0.041$) were significantly improved during MCT-oil supplementation compared to control-DS.

Significance: MCT-oil DS improves cognition in dogs with epilepsy when compared to a control-DS. MCT supplementation may represent a promising option to address CI associated with epilepsy.

(180/200)

Introduction

The relationship between cognitive impairment (CI) and epilepsy has been extensively studied in people[1]. During the course of epilepsy, the occurrence of impaired cognitive function is very common. The enduring predisposition to epileptic seizures can trigger or exacerbate underlying CI in those patients. Approximately every second newly diagnosed child or adult with epilepsy has detectable cognitive or behavioural abnormalities. The degree of cognitive compromises (affecting learning ability, memory and attention), is diverse and depends on contributing factors such as seizure control, seizure type, age of onset and pharmacotherapy[1].

Canine epilepsy, a naturally occurring animal model, is associated with a higher risk of premature death, behavioural comorbidities[2, 3] and recently recognised cognitive deficits [4, 5]. Compared to healthy controls, dogs with epilepsy demonstrate dementia-like CI at a younger age[5], reduced trainability under polytherapy or specific anti-seizure drug (ASD) treatment[4] and exhibit impairments in their spatial-working memory[6]. Thus, the development of new or alternative treatment options that address CI as well as seizure control should be prioritised.

Diet has been shown to influence signs of age or disease related CI in both humans and dogs. One method of dietary intervention to improve CI is aimed at counteracting the undesirable age-associated reduction in cerebral glucose metabolism by providing alternative metabolites such as ketone bodies[7]. In epilepsy, it is hypothesized that the chronic condition of inefficient glycolysis can also initiate and promote epileptogenesis[7, 8]. Dietary intervention may therefore be simultaneously beneficial for CI and epilepsy[9]. Medium-chain triglycerides (MCT) are proposed to counter impaired utilization of glucose via increased ketone production

as one downstream metabolite[7], and are also reported to evoke anticonvulsant properties themselves[10]. Most recently, an MCT-enriched diet was shown to improve seizure control[11, 12] and anxiety[2] in dogs with epilepsy, but also cognition in aged dogs [13]. In veterinary medicine, two-third of patients continue to have seizures on ASDs with one-third of dogs continue to suffer from inadequate seizure control despite appropriately managed polypharmacotherapy. Veterinarians have a limited number of ASDs to choose from, often associated with adverse-effects that reduce quality of life, thus elevating the importance of non-drug therapies.

In human medicine, only one clinical study has assessed cognitive abilities in children and adolescents with epilepsy treated with a ketogenic diet (KD). In 2016, Ijff and colleagues reported a positive impact on cognitive functioning in children and adolescents after four months of KD consumption. An improved mood and cognitive activation with increased productivity were observed. 71% of the cases reported used an MCT based KD [14].

Consequently, MCTs are a promising dietary component to simultaneously address comorbid CI and a new management strategy for insufficient seizure control in dogs and humans with epilepsy.

The aim of this study was to investigate whether MCTs, when given as a daily dietary supplement (DS), can influence cognitive abilities in canine epilepsy.

Methods

Study Design and recruitment

Cognitive abilities were assessed as part of a 6-month prospective, randomised, double-blinded, controlled, multicentre dietary crossover trial comparing an MCT-DS to a standardised control oil DS for the management of canine epilepsy. The clinical trial study design protocol has previously been reported in detail and the study results for seizure control showed an overall significant reduction in the MCT-DS phase of the study[12, 15]. Briefly, dogs diagnosed with idiopathic epilepsy (International Veterinary Epilepsy Task Force tier II level diagnosis) and not responding with 50% seizure frequency reduction to at least one appropriately chosen and administered ASD were recruited. Dogs were block randomised and assigned a DS-1, either the MCT- or control-DS, alongside their normal diet and fed initially for three months (day 1 to day 90 ± 2), followed by a 7-day washout phase and switch to the alternative DS-2 for another three months (day 90 to day 187 ± 2). Concomitant changes of ASD medication or diet during the study resulted in exclusion.

Assessment methods for cognitive abilities

Depending on the study centre's facilities, two cognitive tasks and a psychometric tool were conducted to assess cognitive function during each DS phase:

Cognitive performance tasks **(N =18)**:

Dogs underwent two validated, non-invasive tests to measure different aspects of cognition (task 1: spatial-working memory, task 2: problem-solving [6, 16]). The cognitive assessments were performed in an empty standardized examination room with reduced sensory distractions. Dogs were live scored during the tasks (Figure 1). Each dog received an overall mean

performance score for four consecutive repeats for each of the two tasks. The percentage change relative to baseline scores (positive = improvement, negative = deterioration) for MCT and control-DS were compared. Not every facility had the set-up to perform the cognitive tests and thus data are not available for all dogs.

Canine Cognitive Dysfunction Rating scale (CCDR) (N = 29):

The CCDR rating system is a psychometrically validated and well-established veterinary questionnaire tool to quantify signs of canine dementia [17]. Questions on thirteen behavioral traits are used to calculate the overall CCDR score out of 80 for each dog (0-39 = normal; 40-49 = at risk; >50 = CCD). Individual scores were subsequently compared between both study phases normalized to baseline. As level of canine training, age and number of ASD may influence signs of CI, these effects were taken into account in statistical analyses and reported, where relevant.

Canine Behavioral Assessment & Research Questionnaire (C-BARQ) (N = 29):

Trainability was evaluated with the C-BARQ[18] which was designed to provide standardized evaluations of canine behavior. The trainability subscale consists of eight items, the scores of which are averaged to derive an overall change in trainability score relative to baseline. This overall score was compared between both dietary periods.

Ketone Body Measurements

Pre- and post-prandial beta-hydroxybutyrate (BHB) concentrations were analyzed on each visit day (V1-V3). Pre-prandial blood samples were collected in the morning after fasting for at least 12h, while post-prandial samples were taken two hours after consumption of their usual diet with the prescribed amount of DS. Collected serum was then shipped for subsequent analysis

to two local laboratories.

Statistics

Statistical analysis was performed on SPPS V24 (IBM Deutschland GmbH, Germany) and Prism® (GraphPad Software 8.1, USA). Normally distributed data are presented as mean ±standard deviation, and non-normally distributed data are presented as median (25th–75th percentile). Data are presented relative to baseline. Comparisons of normalized data between the control and MCT group were made using paired t-test for normally distributed data and Wilcoxon test for non-normally distributed data. The relationships between continuous variables were analysed using Pearson's correlation coefficient for normally distributed data and Spearman test for non-normally distributed data. $P < 0.05$ was considered significant.

Results

Study Population

Thirty-six dogs were recruited onto this study of which twenty-nine dogs completed at least one element of the cognition assessment. The multicenter trial was carried out at five different study sites in three different countries (UK [Royal Veterinary College (RVC) (N=13, 45%) and Pride Veterinary Centre (N=4, 14%)], Germany [Tierarztpraxis Dr. A. Bathen-Nöthen (N=4, 14%), University of Veterinary Medicine Hannover (N=3, 10%) and Tierarztpraxis Strassenheim (N=4, 14%)] and Finland [University of Helsinki, (N=1, 3%)]). All twenty-nine dogs had the CCDR and Trainability (C-BARQ) scored, while eighteen of those dogs underwent two cognitive tests (UK [RVC, N=13, 72%], Germany [Tierarztpraxis Strassenheim (N=4, 22%)], Finland [University of Helsinki, (N=1, 3%)]). All 29 dogs were drug-resistant to at least one of the ASD given with less than 50% reduction in seizure frequency. Two dogs

received imepitoin only, the rest were under chronic ASD combination polytherapy (N=27). Twenty-six (89%) of the 29 dogs received phenobarbital, and the predominant combination therapy in over half of cases was phenobarbital, potassium bromide and levetiracetam (N=15). For the acute treatment of more than one seizure within 24 hours (cluster seizures) rectal diazepam (N = 29) and levetiracetam as a pulse therapy (N=3) were used by owners.

Cognitive Tasks Data

Sixteen purebred and two cross breed dogs were included in cognitive testing, with ten males and eight females, of which were 83% (N=15) neutered and 17% (N=3) intact. The mean age was 5.5±2.5 years and mean weight was 21.9±12.9 kilograms at the start of the trial. In over 70% of dogs (N=13), a reduction in seizure frequency was observed during MCT supplementation, which was previously reported[12]. Comparing as % change relative to baseline between DS phases, dogs performed significantly better during the MCT-DS phase for both the spatial-memory task (MCT: +33.3% [+16.1 – +43.3%] v. Control: +20.8% [0 – +43.2%]; P = 0.049) (Figure 1.a) or the problem-solving task (MCT: +10% [0 – +33%] v. Control: 0% [-14.3 – +66.70 %]; P = 0.008) (Figure 1.b). Additionally, a significant, positive correlation between postprandial BHB serum concentration and improved performance in the problem-solving task was identified ($p = 0.048$, $r = 0.45$, $X^2 = 0.46$). The higher the change in postprandial BHB serum concentration, the better the improvement seen in the problem-solving task performance.

CCDR and C-BARQ data

The study population for which CCDR and C-BARQ data were analyzed consisted of twenty-one purebred and eight cross breeds with seventeen males and twelve females, of which 79% were neutered. The mean age was 5.5±2.57 years of age and mean weight was 25.2±13.35

kilograms at the start of the trial.

There was no difference in CCDR score between groups ($P > 0.05$). The change in C-BARQ trainability score relative to baseline was significantly improved when MCT DS was given compared to Control-DS (MCT: +20.5% [+0.5 – +49.8%]; Control: +2% [-27.5 – +30.5%] ($P = 0.041$) (Figure 2). When trainability score was broken down into its eight sub-components, only two of the eight measures were significantly improved in dogs under MCT-DS: Dogs consumed MCT were (i) more likely to be able to learn new tricks ($P = 0.038$) and (ii) faster in responding to punishment or 'correction' ($P = 0.034$).

Discussion

The objective of this clinical trial was to investigate the effects of an MCT oil DS on cognition in dogs with epilepsy, who were also chronically treated with medication. Twenty-nine dogs with epilepsy completed this 6-month multi-center, randomized, controlled, cross-over prospective trial, of which eighteen underwent cognitive assessment. Both DS were added as an 9% of their metabolic energy to the base diet.

Cognitive enhancing effects were observed in two cognitive tasks comparing MCT oil to control. Spatial working memory and problem-solving ability significantly differed between diets, which was confirmed in a standardised and validated questionnaire (C-BARQ), showing improved trainability scores in the MCT trial phase. Although evidence for the direct impact of CI on canine welfare is lacking, CI has the potential to alter dog-owner relationship and interactions (e.g. by cognitively impaired dogs being considered 'naughty' or 'disobedient' and thus subject to inappropriate and aversive training techniques[4]), and has a bidirectional

243 relationship with epilepsy[19], which compromises the quality of life for both dogs and their
244 owners via seizures themselves, behavioural comorbidities and adverse effects of treatment
245 [20-24]. For maintenance of a healthy and positive dog-owner relationship, including avoiding
246 relinquishment of dogs to rescue centres, trainability plays an important role [25] and should
247 thus be improved where possible.
248
249 The overall changes reported here have been small, and are mainly due to some individual dogs
250 having a greater improvement than others during the MCT treatment phase. Future studies need
251 to identify the reason for the individual varied response seen here. However, in regards to
252 canine epilepsy management, even small improvement, as here reported, in the cognitive
253 abilities could strengthen the human animal bond. CCDR a tool developed for detecting canine
254 dementia did not differ between diet phases. This may reflect the small sample size of this
255 cohort leading to a lack of power to detect effects, or as has previously been discussed, it is
256 possible that CCDR is not the ideal tool to sensitively capture epilepsy-specific cognitive
257 impairments in dogs[17].
258
259 A limitation of this study is that the changes in cognition were only assessed in ASD treated
260 dogs. In people, combination therapies have been shown to negatively influence cognitive
261 functioning in a dose-dependent manner [26]. Furthermore, commonly reported side-effects of
262 ASDs in dogs are polyphagia, lethargy and ataxia. While polyphagia might be able to influence
263 the motivation for finding a food reward, ataxia could lead to a slower reaction time and
264 coordination within the test room. Both may be relevant and should be also considered as
265 limiting factors when trying to objectively study cognitive impairments in dogs with epilepsy.
266 Further studies would ideally assess cognition in drug naïve dogs with epilepsy to remove these
267 effects.

The higher the postprandial BHB serum concentration was the better the dogs performed in the problem-solving task. An association between BHB-levels and improvement in cognitive performance has been reported in human medicine[27], but this is a novel finding in veterinary medicine. The exact mechanism mediating ketones' effects on cognition remains unclear, but it has been speculated that ketones can serve as a better alternative fuel source for cerebral neurons[7]. The correction of metabolic alteration, the improvement of mitochondrial function and the support of neuronal health are major targets for the use of different nutritional strategies[7]. Although glucose remains the primary energy source for the brain, ketone bodies provide an alternative, especially in the aged or diseased brain. MCTs have a high ketogenic yield and can increase ketone concentrations in the blood. Neurons use the ketone bodies as alternative energy source and compensate for the impaired glucose metabolism[27], and thus potentially improve brain function. MCTs were also found to influence neuronal signal transmission via direct receptor interaction [10]. Cognition in older dogs was positively affected, when fed with MCT-enriched diet[13], and the same diet was associated with increased BHB levels in canine epilepsy . The improved cognitive abilities reported here may be due to continuously increased BHB levels serving as alternative energy supply[27] and/or positively altered neuronal transmission via medium-chain fatty acid receptor-interactions in the brain[10].

Conclusion

Previous literature reported that spatial-working memory is particularly impaired in dogs with epilepsy compared to healthy individuals [6]. This novel clinical trial provides evidence that the daily supplementation of MCTs in addition to standard ASD treatment is a promising dietary intervention to address CI in canine epilepsy. Response to MCTs was variable and it is likely that the heterogeneity of this population (e.g. age of seizure onset, seizure severity and

ASD treatment) may influence both the degree of initial cognitive impairment in this population[4, 5] and correspondingly the success of dietary interventions. Potential mechanisms of how MCT enhances cognition in dogs are proposed; however, further work is needed to fully understand these findings and highlight dogs that may benefit from MCT supplementation.

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Disclosure of Conflicts of Interest

None of the authors has any conflict of interest to disclose.

Ethical Publication Statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. This trial was conducted in accordance with the guidelines of the International Cooperation of Harmonization of Technical Requirements for Registration of Veterinary Products (VICH) GL9 Good Clinical Practices (GCP) and the European Agency for the evaluation of Medical Products (EMEA). The study protocol and design were approved by the Clinical Research Ethical Review Board (CRERB) and ethical approval has been granted (URN 2016 1558). The data collected in this trial are collated and stored at the Royal Veterinary College in London. All data are anonymised as appropriate, and only used for analysis. All patient's personal information are held and used in accordance with the GDPR 2018 and will not be disclosed to any unauthorized person or body.

No financial and non-financial competing interests exists.

List of abbreviations

ABBREVIATIONS	
ASD	Anti-seizure drug
B	Baseline
BHB	Beta-hydroxybutyrate
CBARQ	Canine Behavioral Assessment & Research Questionnaire
CCDR	Canine Cognitive Dysfunction Rating scale
CI	Cognitive impairment
DS	Dietary supplement
IE	Idiopathic epilepsy
MCT	Medium chain triacylglyceride
RVC	Royal Veterinary College

Figure legends

Figure 1.: Effects of the medium chain TAG dietary supplement (MCT, white) or control dietary supplement (control-DS, dark-grey) on (a) spatial working memory and (b) problem solving ability compared (light-pointed) (N=18). Mean scores were used to calculate the rate of change from baseline to each DS. The performance in (b) solving a problem ($P = 0 \cdot 0078$) and finding a food dropped on the floor improved significantly to baseline under MCT-intake ($P = 0 \cdot 0488$). The percentage change relative to baseline scores (positive = improvement, negative = deterioration) for MCT and control-DS were compared relative to baseline. Data are shown as box-and-whisker plots (central lines of the box represent the median, lower and upper limits of the box represent the 25th and 75th percentiles and whiskers represent the minimum and maximum). Wilcoxon test were conducted to compare rate of change between control and MCT-DS group. * $P < 0 \cdot 05$

Figure 2: Effects of the medium chain TAG dietary supplement (MCT, white) or control dietary supplement (control-DS, dark-grey) on trainability (N=29). Mean scores were used to calculate the rate of change from baseline to each DS. The percentage change relative to baseline scores (positive = improvement, negative = deterioration) for MCT and control-DS were compared. The overall trainability score was found significantly improved between MCT DS compared to Control-DS (MCT: +20.5% [0.5 – 49.8%]; Control: +2% [-27.5 – 30.5%], P = 0 · 0418): (i) Dogs consumed MCT were more likely to learn new tricks (P = 0 · 03812) and were (ii) much faster in responding to punishment or correction (P = 0 · 0345). Data are shown as box-and-whisker plots (central lines of the box represent the median, lower and upper limits of the box represent the 25th and 75th percentiles and whiskers represent the minimum and maximum). Wilcoxon test were conducted to compare rate of change between control and MCT-DS group. * P < 0 · 05

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