Szent István University
Postgraduate School of Veterinary Sciences
and
University of Veterinary Medicine Vienna

Important Aspects of Canine Idiopathic and Symptomatic Epilepsy

THESIS OF PHD DISSERTATION

Dr. PákozdyÁkos

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Co-supervisors and members of field committee:

The late Prof. Dr Péter Rudas
Supervisor
Department of Physiology and Biochemistry
Faculty of Veterinary Sciences
Szent István University

Prof. Dr Johann G. Thalhammer
Supervisor
Unit for Internal Medicine
Clinic for Companion Animal Medicine
University of Veterinary Medicine, Vienna, Austria

Prof. Dr Katalin Halasy
Co-supervisor
Department of Anatomy and Histology
Faculty of Veterinary Sciences
Szent István University

Prof. Dr Péter Halász
Consultant
Institute of Experimental Medicine, Budapest, Hungary

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Dr Pákozdy Ákos

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Aims and Scope

The general aim of this thesis was a better understanding of canine epilepsy. Diagnostic, differential diagnostic and therapeutic aspects were examined.
The particular aims of the thesis were:

- A comparison of idiopathic and symptomatic epilepsy regarding age, body weight, gender, breed, and clinical and neurological findings.
- An analysis of theictal and post-ictal parameters that could help to differentiate between idiopathic and symptomatic epilepsy.
- An investigation of the clinical usefulness of electroencephalography (EEG) in dogs with seizures in a clinical setting in combination with other advanced diagnostic tools.
- A description of interictal epileptiform discharges in a group of dogs with seizures of known aetiology (symptomatic epilepsy) and in dogs with idiopathic epilepsy.
- Identification of physiological sleep electroencephalographic phenomena that could lead to misinterpretation.
- An examination of the effect of cyclosporine therapy on survival time in patients with granulomatous meningoencephalomyelitis and a comparison of this with standard corticosteroid therapy.
- A presentation of the results of gabapentin usage as an at-home treatment of cluster seizures in canine idiopathic epilepsy.

Introduction

As epilepsy is one of the most common problems in veterinary neurology it is important to investigate large numbers of cases with this symptom in order to evaluate the clinical aspects of idiopathic epilepsy in dogs. Despite many references dealing with idiopathic epilepsy, only a few studies on symptomatic epilepsy are based on large amounts of case material (Croft, 1965; Palmer, 1972; Podell et al., 1995). In this part of our study 240 cases of symptomatic and idiopathic epilepsy were analysed in dogs. The primary aim of the first part of the research was to identify helpful ictal or post-ictal parameters to distinguish between idiopathic and symptomatic epilepsy. Another goal was to compare idiopathic epilepsy and symptomatic epilepsy regarding age, body weight, gender, breed and clinical signs in large case series.

The aim of second part of our research was to investigate the clinical usefulness of EEG in dogs with seizures in a clinical setting in combination with other advanced diagnostic tools. The primary aim was to identify interictal epileptiform discharges in a group of dogs with seizures of known aetiology (symptomatic epilepsy) and in dogs with idiopathic epilepsy. The second aim was to identify physiological sleep EEG phenomena that could lead to misinterpretation

The treatment of two clinically challenging categories is evaluated in parts 3 and 4 of the current thesis.

The purpose of the 3rd part was to investigate the effect of cyclosporine therapy on survival time in patients with granulomatous meningoencephalomyelitis (GME) and to compare it with standard corticosteroid therapy.

The main aim of the 4st part of the study was to analyse the results of gabapentin usage as an at-home treatment of CS in canine IE.

In summary, the major goals of our study were: to better understand epileptic aetiologies, their underlying pathophysiology and the use of electrophysiology, and to more precisely diagnose, classify and treat seizure symptoms.

Clinical work-up and ictal analysis of epileptic dogs
Materials and methods

Every dog included (240) underwent a physical and neurological examination. We used the following ancillary diagnostic tests for the work-up: routine serum biochemistry and haematology (n=231), dynamic bile acid test (n=38), urinanalysis (n=96), cerebrospinal fluid (CSF)

analysis (n=108), computed tomography (n=28), magnetic resonance imaging (n=52) and a pathohistological examination (n=83). In some patients the diagnostic work-up included abdominal sonography (n=33), abdominal radiography (n=9) and thoracic radiography (n=26). Idiopathic epilepsy (IE) was considered when the results of the interictal neurological examination were normal and no underlying causes of the seizure had been identified in routine serum biochemistry, haematology, CSF analysis, computed tomography or magnetic resonance imaging, or more than 2 years had passed since the onset of seizures without any interictal neurological signs. All dogs with idiopathic epilepsy were re-evaluated at least 24 months after the initial examination by the author or another neurologist at our clinic and no abnormalities were identified on physical and neurological examination. Cluster seizures were considered if there was more than one seizure within 24 h and status epilepticus if the seizure lasted longer than 30 min or a series of seizures occurred with interictal impairmentsinneurological status. A partial seizure was characterized by motor activity in some muscles or muscle groups with or without generalization. More complex behaviour patterns without elementary motor seizures (psychomotor seizures, automotor seizures) were not included. Special emphasis was placed on signalment, history, the characteristics of ictal and post-ictal phases and the results of the clinical and neurological examinations. Data were analysed using SPSS 14.0 for Windows. For the statistical analysis between IE and SE groups, chi^2tests and t-tests were used. At-test for independent samples was performed in order to compare the mean values of the two groups. Chi^2tests were used to compare frequencies. A value of $P<0.05$ was considered significant. The following variables were analysed: age at first seizure, body weight, gender, breed, activity during seizure (partial seizure, generalized seizure, trembling, urination/defecation, salivation, vocalization), duration of seizure, presence of status epilepticus, post-ictal presence of polyphagia, polyuria/polydipsia, blindness, deafness, aggression, timing of seizures, possible trigger of seizures and the results of clinical and neurological examinations.

Results and discussion

In 125 dogs symptomatic epilepsy (SE), in 115 dogs idiopathic epilepsy (IE) was diagnosed. The most common aetiology of symptomatic epilepsy was intracranial neoplasia (n=39) and encephalitis (n=23). The proportion of intracranial neoplasia was more common than reported earlier. There are several possible explanations for this observation.

Newer diagnostic imaging techniques are better at detecting intracranial lesions. The increasing life expectancy of dogs as a result of improved veterinary services could explain the higher proportion of intracranial neoplasiafound in our study.

Different aetiologies of encephalitis were diagnosed: distemper (6), rabies (1), morbus Aujeszky (1) and cryptococcal encephalitis (1); in the majority of cases (14) meningoencephalitis of unknown origin (MUO) was suspected.

The mean age of patients at the onset of seizure was 4.11 years in the IE group (range: 4 months to 12 years). This differs significantly from the SE group, where the mean age at onset was 7.38 years (range: 2 months to 17 years).

Between 1 and 5 years of age the number of dogs with IE was significantly higher than those with SE (65/20); outside this range the proportions were reversed (50/105). If the onset of seizure was between 1 and 5 years of age the diagnosis was 3.25 times more likely to be IE than SE.

Partial seizures were observed significantly more often in the SE group (n=39) than in the IE group (n=12). When a partial seizure occurred, the diagnosis of SE was 3.25 times more likely than a diagnosis of IE. Partial seizures are frequently caused by intracranial pathological lesions (Barker, 1973; Berendt and Gram, 1999; Speciale, 2005). Similarly to the results of Kay (1989), we found that more than 90% of dogs in our study with idiopathic epilepsy exhibited generalized seizures that lasted 2–4 min and were bilaterally symmetrical from the start. On the other hand, Jaggy and Heynold (1996) observed unilateral cramping of the facial and head muscles in Labrador retrievers with IE and suggested that there is no pathognomicseizure pattern for IE and that it is not possible to differentiate between IE and SE based on the clinical picture alone. In our study, partial seizures were observed significantly more often (3.25 times) in the SE group. However, we agree with Jaggy and Heynold (1996) and Patterson et al. (2005) that the distinction between groups is not possible based on the clinical picture alone.

The occurrence of status epilepticus (IE/SE: 24/52) and cluster seizures (IE/SE: 52/82) was significantly higher in the SE group. Status epilepticusand cluster seizures were2.16 and1.57 times more likely in the SE group than in the IE group, respectivelywhich is similar to the findings of Bateman and Parent (1999) and Platt (2002) and supports Platt’s suggestion of the necessity of a complete diagnostic assessment of patients with status epilepticus and cluster seizures.

The seizures occurred significantly more often during sleep or the resting condition (97 cases) in the IE group than in the SE group (33). Seizures were only infrequently observed during periods of activity (IE/SE: 3/5).An increase in cortical neuronal synchronization is observed during sleep. This could decrease the seizure threshold (Tanaka and Naquet, 1975). This effect is probably less important when an underlying disease (SE) exists, because this disease could be changed independently from time of day and facilitate crossing the seizure threshold.

In 80 cases in the SE group (64%) clinical or neurological signs other than seizures were found or reported by the owner, whereas in the IE group only 2 cases showed other symptoms that were not evidently linked to the ictal or post-ictal phases.

Although it was not possible to differentiate between IE and SE based on ictal clinical signs, indications such as status epilepticus, cluster or partial seizures and altered interictal neurological status more frequently predict symptomatic epilepsy. Seizure onset between 1 and 5 years of age or seizures during resting condition predict more likely a diagnosis of IE than SE.

Electroencephalographic examination of epileptic dogs
Materials and Methods

Dogs were included if they fulfilled the following criteria: (1) history of recurrent seizures (more than one seizure) in the medical history, (2) the diagnosis was idiopathic or symptomatic epilepsy, (3) EEG recordings with standard settings.

Stainless steel needle electrodes were used for the EEG recordings. The electrodes were subcutaneously placed over the right/left frontal and the right/left occipital lobe and vertex and an 8-channel bipolar montage was used according to the method of Redding and Knecht (1984). Chemical restraint was used in all dogs. Propofol was used for induction, until the animalbecame intubatable (2–6 mg/kg); oxygen was administeredafter intubation. Some other drugs (diazepam, midazolam, phenobarbital, pentobarbital, gabapentin, isofluran) were occasionally given for clinical indications. Each EEG recording was made until the patient woke up and movement artefacts made interpretation impossible. During the EEG analysis we looked for possible epileptiform discharges, particularly interictal epileptiform discharges (IED) representing the basic elements of EEG diagnosis of epilepsy (Niedermeyer, 2005).

Accordingly, we searched for the following IEDs: spike, sharp waves, and a spike-wave complex.

Results and discussion

In the present study the interictal electroencephalographic (EEG) examination of dogs suffering from idiopathic (IE) and symptomatic epilepsy (SE) rarely showed epileptic discharges. We only found EEG changes that could be considered epileptiform discharges (EDs) in 5 out of 40 (12.5%) dogs. The EEG changes identified were spikes in four cases and periodic epileptiform discharges in one case. All EDs were seen in the SE group. No dog in the IE group showed EEG changes that were considered to be epileptiform. As the EDs in our epileptic dogs were rarely detected, the diagnostic value of the EEG in the work-up appeared to be very low. In our study spikes were the most frequently identified ED; similar results were found by several previous investigators (Holliday et al., 1970; Klemm and Hall, 1970). We detected spikes in four patients with space-occupying lesions (oligodendroglioma 2, meningioma 2).

We found a considerably lower portion of epileptiform discharges (12.5%) among the epileptic dogs compared to previous researchers (20-100%).

There are several possible explanations for this remarkable discrepancy: (1) different drugs were used for restraint; (2) different dose regimes; (3) the possible misinterpretation of epileptiform-like but normal sleep phenomena.

Based on our results, it is likely that with this propofol regime only very strong epileptic discharges can be detected that are possibly more likely to be associated with severe neoplastic and inflammatory diseases. An additional problem could be the influence of previous anticonvulsant therapy as in the majority of cases (31/40) other drugs (diazepam, midazolam, phenobarbital, pentobarbital, gabapentin) were used within 24 h of the EEG recording. Jaggy and Bernardini (1998) observed that 60% of dogs with IE showing noepileptiform EEG phenomena because of anticonvulsant therapy. The influence of anticonvulsant therapy on EEG recordings of epileptiform discharges was not examined in other studies.

To the best of our knowledge we observed, for first time in dogs, an EEG pattern that closely resembles periodic epileptic discharges (PED) in humans.

Periodic epileptic discharges in humans are usually associated with acute or subacute cortical pathologies. Stroke, neoplasia, and infections are the most common aetiologies. In Creutzfeldt-Jacob disease the majority of patients demonstrate PED at least for a period of time during the disease course. Usually, the PED indicates a poor prognosis if it is associated with seizures. The one patient with a PED-like EEG pattern in our study had also a malignant disease and died during hospitalization. A disseminated form of necrotizing meningoencephalitis was confirmed by pathohistology, which is a disease with a poor prognosis (Talarico and Schatzberg, 2009).

Based on our study, EEG seems to have a low sensitivity for detectingepileptiform discharges in this clinical setting. The author believes that using restraint techniques that do not artificially alter electricalbrain activity, as found with methohexital, or recording with telemetry during natural sleep are the most promising methods. The complexity of this research area underlines the need to establish specific research groups. Only systematic studies by multicentres on various aspects of electroencephalography will result in conclusions that can be recommended for practical clinical use. These steps are essential in order to reduce misinterpretation and to develop veterinary electroencephalography. Only after such a progression can EEG have a relevant role in veterinary clinical epileptology.

Cyclosporine therapy in dogs with granulomatous meningoencephalomyelitis
Materials and Methods

Dogs were evaluated for the following criteria: (1) focal or multifocal neuroanatomical localization; (2) CSF pleocytosis (> 5 cells/µl); (3) CT/MRI of the brain consistent with focal or multifocal disorders suggestive of GME; (4) pathohistological post-mortem confirmation of GME. Patients were included in this study if they fulfilled criteria 1 and 4 (eight cases) or 1, 2 and 3 (six cases).

Seven dogs were treated by corticosteroids only (ST group) before 2004. Since Adamo (2004) reported successful treatment using cyclosporine, we prospectively used it in our clinic in seven other dogs (CY group). The minimum information included in the database for the dogs consisted of a complete blood count (13), serum biochemistry profile (13) including liver enzymes, creatinine, total protein and potassium. The inclusion criteria for the histological diagnosis of GME

were the characteristic perivascular inflammation of mononuclear cells and the absence of infectious agents based on routine histopathology, immunohistochemistry and special stainings.

The treatment was performed using cyclosporine; the starting dosage was 3 mg/kg perorally twice a day. Survival time was designed as the time from the onset of the first clinical signs to death or to the end of the study. The clinical responses to and adverse effects of the treatment were determined through follow-up examinations, telephone conversations with the owner and referring veterinarians. Descriptive statistics were used to evaluate the distribution of data between the ST and CY groups. The dependent variable was survival time, described in days. The independent variables included: age, gender, body weight, lesion distribution based on neurological examination, CSF white blood cell count, CSF protein concentration, and lesion distribution based on diagnostic imaging. For the statistical analyses between the ST and CY groups chi^2 tests (gender, lesion distribution) U-tests (age, survival time) and T-tests (body weight) were performed. A value of $P<0.05$ was considered significant.

Results and discussion

A total of 14dogs with granulomatous meningoencephalomyelitis were studied: 7 dogs in the ST group and 7 dogs in the CY group. The median survival time of620 days (range 8–870) in the CY group was significantly longer (Mann-Whitney test, u=5.5; P=0.011) than the 28 days (range: 3–63) found in the ST group. Full remission occurred only in CY group (4 out of 7).

To the best of our knowledge this was the first study to evaluate the efficacy of cyclosporine/corticosteroid versus corticosteroid therapy in GME and showed clear difference between these two therapeutic options.

Cyclosporine was generally well tolerated in our study. This was not surprising because this treatment is frequently used in dogs with different indications. Our findings were comparable with those of a previous report where cyclosporine-treated dogs showed short periods of diarrhoea, vomiting and in appetence as adverse effects (Radowicz and Power, 2005; Gnirs, 2006; Adamo et al., 2007).

The lack of histopathological diagnoses in surviving cases hindered definitive diagnoses in the present study, as was also found in other clinical studies (Zarfoss et al., 2006). Despite this limitation, the authors of the present study believe that the two groups are comparable.

Cyclosporine treatment has advantages compared toprocarbazine and cytosine arabinoside treatment. First, it is well tolerated and, second, cyclosporine has been in longer veterinary usage, thus there is more experience with its long-term treatment. It may be that one drug which is superior to all others in all cases simply does not exist, but cyclosporine seems to be a reasonable choice in dogs with meningoencephalomyelitis of unknown origin.

We concluded that combination therapy using cyclosporine/prednisolone increases the survival time in dogs with GME and full remission can occure.

Gabapentin therapy in dogs with cluster seizures

Materials and Methods

Dogs with a history of cluster seizures (CS) due to suspected IE were included in this part of our trial. Cluster seizures were considered if there was more than one convulsive seizure within a 24-h period (Bateman and Parent, 1999). For the CS, additional at-home gabapentin treatment was started perorally at 20 mg/kg TID for at least 72 h until a seizure-free day was achieved.

The following parameters were evaluated with and without the use of gabapentin: duration of a CS, number of seizures per CS, severity and duration of single seizures, autonomic ictal signs, changes in the seizure type, general interictal conditions during a CS, quality of life, cost reductions and adverse effects. These parameters were mostly evaluated via a questionnaire and/or phone contacts with the owner. The questionnaire was formulated in cooperation with the Department of Marketing, Institute for International Marketing & Management, Vienna University of Economics and Business.

Statistical analysis was performed using SPSS 17.0. The chi^2test, Mann-Whitney U-test and Wilcoxon test were used to test for statistical significance.

Results and discussion

The mean numbers of seizures per cluster without and with gabapentin were 5.81 (SD: 4.39) and 7.27 (SD: 6.97), respectively, with no significant difference between them (P=0.65). The mean duration of cluster seizures without gabapentin was shorter than with gabapentin: 27.8 and 37 hours. This differed not signifficantly (P=0.23). The type of seizure was not significantly affected by gabapentin usage (P=0.17). The

severity of seizures was reduced in 4 dogs (out of 14, as not all of the owners answered all of the questions), 2 owners reported “weaker” seizures and another 2 “much weaker” seizures. The duration of seizures was reported to be “shorter” in one dog and “much shorter” in another dog. The general interictal condition during the cluster seizures was ameliorated by gabapentin in four dogs. Eight owners (out of fourteen) considered that the quality of life of their dogs was better with gabapentin. Lethargy, ataxia, polyphagia, polydipsia and irritation were the most frequently reported adverse effects.

The most important finding in our study was that the response to gabapentin varied from dog to dog. Considerable individual differences were found regarding both the duration of CS and the number of seizures per CS. After the initiation of gabapentin, CS ceased completely in two dogs and in another two dogs the duration of CS was reduced. Furthermore, after the application of gabapentin, two dogs stopped having seizures completely, and a further three dogs showed reductions in seizures of 11, 49 and 58%. In one dog, the application of gabapentin in the aura prevented seizures on most occasions; in contrast, when the first seizure had already occurred, gabapentin increased the number of seizures per CS; these findings underline the potential pre-ictal use of gabapentin.

A total of 28.6% of owners reported that their dogs’ seizures appeared to be less violent following the initiation of gabapentin. We did not find any influence of gabapentin on seizure duration. This finding is consistent with the findings of a recent study by Platt et al. (2006), whereas another study found that 47% of dogs showed a reduction in seizure intensity and duration in response to gabapentin (Govendir et al., 2005).

Fifty-seven percent of owners noted that gabapentin improved their dogs’ quality of life during a CS. The owner’s quality of life was improved in 39% of cases.

The effect of gabapentin was not statistically significant in the study group, which is not surprising as we treated refractory cases. After receiving two or three AEDs, an additional AED in human refractory cases only showed about a 10% success rate (Kwan et al., 2004; Karceski, 2005).

The subjectivity regarding the owners’ evaluations of their dogs and the low case numbers make our results debatable. Furthermore, due to the lack of a placebo control it would be incorrect to conclude that each change was the consequence of the medication.

It seems that add-on at-home gabapentin is useful in the treatment of CS after the identification of responders. However, based on the results of our study, it is not possible to select responders other than by trying drugs in each individual patient.

Although we were unable to confirm a significant positive effect on CS following the use of gabapentin in the study group, a clear amelioration was reported in some dogs.

New Scientific Findings

1. Idiopathic epilepsy (IE) is the most frequent aetiology for repeated seizures in dogs and is responsible for approximately half of all cases (48%) when a large amount of case material is investigated.
2. Symptomatic epilepsy was mostly caused by intracranial tumours (16%) and encephalitis (10%).
3. We concluded that it is not possible to differentiate between idiopathic and symptomatic epilepsy based on ictal clinical signs alone. Indications such as status epilepticus, cluster or partial seizures, vocalization during seizures, and altered interictal neurological status were more common predictors of symptomatic epilepsy. If the first seizure occurred between one and five years of age or if the seizures occurred during the resting condition, the diagnosis was more likely to be IE than SE.
4. Interictal electroencephalographic examinations of propofol anaesthetized dogs suffering from idiopathic and symptomatic epilepsy rarely show epileptic discharges.
5. We concluded that the diagnostic value of such EEGs in the work-up for epilepsy seems to be low as epileptic discharges were unlikely to be detected.
6. We found frequent, transient EEG phenomena (spindles, k-complexes, vertex waves, positive occipital sharp transients of sleep, cyclic alternating patterns), which are non-epileptic but their differentiation from epileptic phenomena can be challenging.
7. Cyclosporine/prednisolone combination therapy increases survival time in dogs with granulomatous meningoencephalitis compared to prednisolone alone, and even long-term remission can occur.
8. We were unable to confirm a significant positive effect on cluster seizures following the use of gabapentin in the study group; however, a clear amelioration was reported in some dogs.

The candidate's publications related to the present dissertation

1.) Full lenght peer-rewieved papers, case reports and short communications:

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Dr Akos Pakozdy

author