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Important Aspects of
Canine Idiopathic and Symptomatic
Epilepsy

Thesis of PhD Dissertation

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Content

1. List of Abbreviations

AED   antiepileptic drug

CAP   cyclic alternating pattern

CNS   central nervous system

CS   cluster seizure

CSF   cerebrospinal fluid

CT   computed tomography

ECG   electrocardiography

ECoG   electrocorticography

EEG   electroencephalography

FLAIR   fluid attenuated inversion recovery

FSE   fast spin echo

GME   granulomatous meningoencephalomyelitis

GRE   gradient echo

IE   idiopathic epilepsy, primary epilepsy

IED   interictal epileptiform discharges

IGE   idiopathic generalized epilepsies

ILAE   international league against epilepsy

MRI   magnet resonance imaging

MUO   meningoencephalitis of unknown origin

NME   necrotising meningoencephalitis

PED   periodic epileptiform discharges

POST   positive occipital sharp transient

POSTS   positive occipital sharp transients of sleep

SE   symptomatic epilepsy, secondary epilepsy

STIR   short tau inversion recovery

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Canine Idiopathic and Symptomatic Epilepsy

2. Summary

This dissertation presents an overview of the research performed by the author in examining dogs with seizure disorders.

In the first study we summarized the clinical work-up and ictal analysis of 240 dogs with recurrent seizures. The aim was to examine the underlying aetiology and to compare idiopathic epilepsy (IE) with symptomatic epilepsy (SE) regarding signalment, history, ictal patterns and findings of the clinical and neurological examination. The diagnosis of symptomatic epilepsy was based on confirmed pathological changes in haematology, serum biochemistry, cerebrospinal fluid (CSF) analysis and morphological changes in the brain by CT/MRI or histopathological examinations. The seizure aetiologies were classified as idiopathic epilepsy in 115 (48%) dogs and symptomatic epilepsy in 125 (52%). Symptomatic epilepsy was mainly caused by intracranial neoplasia (39 dogs, 16%) and encephalitis (23 dogs, 10%). The following variables showed significant differences between the IE and SE groups: age, body weight, presence of partial seizures, cluster seizures, status epilepticus, ictal vocalization and neurological deficits. Status epilepticus, cluster seizures, partial seizures, vocalization during seizure and impaired neurological status were more readily seen in symptomatic epilepsy. If the first seizure occurred between 1 and 5 years of age or the seizures occurred during the resting condition the diagnosis was more likely to be IE than SE.

In the second study we investigated the clinical usefulness of EEG in dogs with seizures in a clinical setting in combination with other advanced diagnostic tools. We found that the interictal electroencephalographic (EEG) examination of epileptic dogs suffering from IE or

SE rarely showed epileptic discharges using chemical restraint with propofol (2-6mg/kg). Only 5 out of 40 (12.5%) dogs showed EEG changes, which were considered as epileptiform discharges (ED). The EEG changes identified were spikes in four cases and periodic epileptiform discharges in one case. We concluded that since epileptic discharges were infrequently detected the diagnostic value of EEG in such a work-up seemed to be rather low. Otherwise, we frequently found transient EEG phenomena (spindles, k-complexes, vertex waves, positive occipital sharp transients of sleep, cyclic alternating patterns), which were non-epileptic but their differentiation from epileptic phenomena was challenging and thus being aware of these patterns could reduce misinterpretation.

In the following studies possible therapy of two particularly difficult clinical conditions were evaluated.

In the third study we investigated the therapeutic effect of immunosuppressive cyclosporine on granulomatous meningoencephalomyelitis (GME), a condition that can cause seizures and which has a poor long-term prognosis. Fourteen dogs were included in this study and randomly divided into two groups. Seven dogs were treated with corticosteroids and seven dogs with corticosteroids in combination with cyclosporine. The median survival time of the seven dogs on immunosuppressive corticosteroid therapy was 28 days (range 3-63 days) while for the seven dogs with additional cyclosporine treatment it was 620 days (range 8-870). Four dogs were still alive at the time the study was completed. We concluded that cyclosporine combination therapy prolongs survival time in comparison with prednisolone therapy in dogs with granulomatous meningoencephalomyelitis. Total remission can also occur.

The fourth study evaluated the effect of gabapentin in the at-home treatment of 15 dogs with idiopathic refractory epilepsy, including cluster seizures (CS). When a CS started, additional gabapentin treatment was initiated PO at a dosage of 20 mg/kg TID for at least 3 days by the owner. In four dogs, a 49-100% reduction was reported in the seizures per cluster. The severity and duration of seizures were reduced in four and two dogs, respectively. The general interictal condition during CS was considerably ameliorated by gabapentin in four dogs. Eight out of fourteen owners considered that their dog's quality of life during a CS had been improved by the use of gabapentin. We concluded that gabapentin can be considered as an alternative at-home treatment for CS, although only a small proportion of dogs might experience considerable benefits.

3. 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 the ictal 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 CS in canine idiopathic epilepsy.

4. Introduction

Epilepsy was one of the earliest conditions to be identified in human medicine. It was mentioned in Babylonian and ancient Egyptian cultures, althoughat that time it was considered a supernatural phenomenon (Matthes and Schneble, 1992). In ancient Greece epilepsy was called the "sacred disease" as paroxysmal events were thought to be connected with God. The origin of the word epilepsy (epilambanein) means "to take over", emphasizing its supernatural origin. Hippocrates described it as the "holy disease" about 400 years BC and recommended healthy nutrition and gymnastics as therapy (Matthes and Schneble, 1992). Knowledge about epilepsy did not progress for a long period of time thereafter. The next big step was the introduction of the first antiepileptic drug in 1857: potassium bromide. John Hughlings Jackson (1870) explained that epileptic seizures were discharges at various hierarchical and functional levels in the cerebral cortex. In the twentieth century developments and scientific research within the field of epilepsy started to occur more rapidly. Important milestones were the discovery of phenobarbital (1912), the use of electroencephalography (EEG, 1924) and the introduction of phenytoin (1938). German chemists Emil Fischer and Joseph von Mering synthesized phenobarbital and brought it to market in 1912 via the drug company Bayer as a sedative and hypnotic drug; at this time its anticonvulsive effect was still unknown. Alfred Hauptmann treated first his epilepsy patients using this drug as a tranquilizer and discovered that their epileptic attacks were reduced. Hauptmann performed a study on his patients over a longer period. Most of these patients had used previously bromide, which, at that time, was the only effective drug available, although it had terrible side effects and limited efficacy. Hauptman observed that the withdrawal of phenobarbital led to an increase in seizure frequency; thus, it was not suitable for a cure (Matthes and Schneble, 1992) but it was quickly adopted as the first broadly effective anticonvulsant.

Two leading scientists were involved in the introduction of EEG. The presence of electrical currents in the brain was discovered by an English physician, Richard Caton, in 1875. This discovery gained clinical importance after 1924 when Hans Berger, a German neurologist, used his ordinary radio equipment to amplify the brain's electrical activity so that he could record it onto graph paper. Berger noticed that rhythmic changes (brain waves) varied with an individual's state of consciousness. Phenytoin (diphenylhydantoin) was first synthesized by a German chemist Heinrich Biltz in 1908. Biltz sold his discovery to Parke-Davis, who did not find an immediate use for it. In 1938, outstanding scientists including H. Houston Merritt

and Tracy Putnam discovered phenytoin's efficacyin controlling seizures, but without the sedative effects associated with phenobarbital (Matthes and Schneble, 1992).

Further cornerstones were the clinical implementation of computed tomography (CT, 1971) and magnetic resonance imaging (MRI, 1977). The English electrical engineer Godfrey Hounsfield and the South African-born Allan McLeod Cormack gradually developed the modality of CT. The first commercially available CT scanner was invented by Sir Godfrey Hounsfield in Hayes, United Kingdom. Hounsfield conceived his idea in 1967 and it was publicly announced in 1972. In Massachusetts (USA), Allan McLeod Cormack independently invented a similar process, and both Hounsfield and Cormack shared the 1979 Nobel Prize in Medicine. Felix Bloch and Edward Purcell independently discovered the magnetic resonance phenomenon in 1946, and were later awarded the Nobel Prize in 1952. Up until the 1970s, MRI was used for chemical and physical analyses. Then, in 1971, Raymond Damadian showed that nuclear magnetic relaxation times of tissues and tumours differed. Although with a certain delay, all of this knowledge served to benefit both humans and animals with epilepsy.

Despite these enormous developments in the field of epilepsy there is still a very large group of epileptic patients where the aetiology remains unknown.

The long process of developments in human thinking, technological progression and changes in society led to professional, specialized veterinary hospitals being able to diagnose and treat client-owned dogs and cats with epilepsy at the end of the twentieth century. The growing use of veterinary services with sophisticated diagnostic tools was the result of growing interest in the health of companion animals. In Europe, North-America and Australia high-tech medicine elaborated standard diagnostic procedures for dogs and cats. Laboratory examinations such as haematology, serum biochemistry, urine analysis, X-ray, sonography, computed tomography and even magnetic resonance imaging were not only available for dogs and cats at that time but they were in routine use.

Several different diseases in dogs can also cause recurrent seizures (Thomas, 2003). Idiopathic epilepsy is suspected to be the most frequent cause of recurrent seizures in dogs (Croft, 1965; Jaggy and Bernardini, 1998). 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. The treatment of two clinically challenging categories is evaluated in parts 3 and 4 of the current thesis. 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. This research was divided into four parts:

1. Clinical work-up and ictal analysis of epileptic dogs,
2. Electroencephalographic examination of epileptic dogs,
3. Cyclosporine therapy in dogs with granulomatous meningoencephalomyelitis,
4. Gabapentin therapy in dogs with cluster seizures.

5. Review of Literature and Aim of the Examination

5.1 Clinical work-up and ictal analysis of epileptic dogs

A seizure is a transient and involuntary change in behaviour or neurological status (March 1998). Epilepsies are conditions characterized by recurrent seizures over a longer period. Epilepsies are a group of diseases. It can be categorized in dogs as symptomatic, probable symptomatic (cryptogenic) or idiopathic (Podell, 2004). The underlying diseases for symptomatic epilepsy can be divided into intracranial and extra cranial disorders. Examples of intracranial disorders are intracranial neoplasia, encephalitis, trauma, vascular disorders and hydrocephalus (Fenner, 1981; Joseph et al., 1988; Oliver et al.; 1997; Thomas, 2003). Extracranial disorders that can cause seizures include hypoglycaemia, hepatic encephalopathy, uremic encephalopathy and electrolyte imbalances (Leifer et al., 1986; Maddison, 1992; Steffen and Jaggy, 1995; O'Brien, 1998). Probable symptomatic (cryptogenic) epileptic seizures are consequences of unidentified brain disease such as head trauma with normal imaging or undetected hypoxic events after anaesthesia (Podell, 2004). The reactive epileptic seizure is a reaction of the normal brain to toxic or metabolic insults. Some authors include reactive epileptic seizures with symptomatic extracranial disorders (Thomas, 2003).

Epilepsies is classified as idiopathic or primary epilepsy when no underlying cause can be identified: genetic mechanisms are presumed (Cunningham and Farnbach, 1987). Idiopathic epilepsy has been described in many breeds: Beagle (Koestner and Rehfeld, 1968), Tervueren (Van Der Velden, 1968; Famula et al., 1997), British Alsatian (Falco et al. 1974), Golden Retriever (Srenk et al., 1994), Keeshound (Hall and Wallace, 1996), Labrador Retriever (Heynold et al., 1997; Jaggy et al., 1998), Bernese Mountain Dog (Kathmann et al., 1999), Boxer (Nielen et al., 2001), Vizsla (Patterson et al., 2003), English Springer Spaniel (Patterson et al., 2005), Irish Wolfhound (Casal et al., 2006) and in mixed-breed dogs as well (Jaggy and Bernardini, 1998).

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 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.

5.2. Electroencephalographic examination of epileptic dogs

Electroencephalographic (EEG) examination became soon part of the routine diagnostic work-up in human medicine. After 1950 human epileptologists thought that dogs could be more susceptible to seizures than other animals, which led to investigations on canine seizure disease by human researchers (Gastaut et al., 1958). The interest of veterinary scientists in EEG increased too, particularly in electrode characteristics and arrangements, and in animal restraint (Klemm, 1964). In order to establish the validity of scalp leads for recording EEGs in dogs, it was found that surface recording and deep recording electrodes implanted in the skull (electrocorticogram) essentially provide the similar data (Redding and Colwell, 1964). However, Klemm and Mallo (1966) showed that anaesthesia provide advantages in animal restraint and in the reduction of artefacts, reducing errors in interpretation. A normal, alert, adult dog showed 8-20 Hz activity with 5-25 μV amplitude. When the dog is asleep the EEG pattern changes to 2-5 Hz, 25-100 μV. Even for encephalitis three distinguishable EEG patterns were found: slow frequency (3-6 Hz, 5-75μV) superimposed with high-frequency spikes (20-30 Hz) in the early stage, very high voltage, slow activity (1-3 Hz, 100-200 μV) in the acute stage and late encephalitis with a medium frequency and amplitude (4-7 Hz; 10-75 μV); however, this later study did not use chemical restraint (Redding et al., 1966). The first large study on the use of EEG in canine epilepsy was carried out by Holliday et al. (1970). Holliday examined 70 dogs with epilepsy of unknown origin and found that the interictal EEG was abnormalin 43 patients. The most frequent changes were diffuse or focal paroxysmal dysrhythmias followed by diffuse and focal persistent dysrhythmias. The interictal dysrhythmias consisted of single spikes, spike complexes, wave and spike complexes, sharp waves and slow waves. In the same year, Klemm and Hall (1970) found electroencephalographic signs for seizure disorders in 90 out of91 dogs with a history of convulsions. A few recent EEG studies on dogs with seizures indicated that some interictal EEG patterns are similar to the abnormalities seen in human epilepsy, at least on a general level (Holliday and Williams, 1998; Jaggy and Bernardini, 1998; Berendt et al., 1999).

Although the attempts to standardize veterinary EEG technique was emphasized over 40 years ago (Klemm 1968), there are still no generally accepted criteria among veterinary neurologists which EEG phenomena are likely to be associated with epilepsy.

Furthermore, there is no consensus regarding the type of electrodes, the number and position of electrodes and the restraint technique. Over the last 10 years almost nothing substantial was published on EEG in canine epilepsy. It seems that strong developments

inveterinary diagnostic imaging techniques led to a reduced use of EEG. A similar tendency was also found in human epileptology for a period of time but both diagnostic modalities are currently considered essential for the management of epileptic patients.

The aim of this study 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.

5.3. Cyclosporine therapy in dogs with granulomatous meningoencephalomyelitis (GME)

We realised at the beginning of our study that a unique inflammatory central nervous system disease (GME) causes secondary epilepsy and a fatal outcome. Granulomatous meningoencephalomyelitis (GME) is an inflammatory disease of the canine central nervous system (CNS) that is histologically characterized by an accumulation of mononuclear cells in the parenchyma and meninges of the brain and spinal cord (Braund et al., 1978). The aetiology of GME is currently unknown, but infectious, neoplastic and immune-mediated causes have been suggested. The most scientifically supported theory is immunemediated (Cuddon et al., 2002) and some authors have suggested a T cell-mediated delayed type of hypersensitivity of an organ-specific autoimmune disease (Kipar et al., 1998).

As the clinical signs of GME are not pathognomonic, a number of differential diagnoses should be considered such as: viral, protozoan and breed-specific encephalitides, as well as neoplastic brain disorders (Ryan et al., 2001; Pakozdy and Leschnik, 2005). The ante mortem diagnosis without a histopathological diagnosis is typically tentative, based on focal or multifocal CNS signs, cerebrospinal fluid (CSF) mononuclear or mixed pleocytosis and, mostly, multiple, intramedullary lesions with avariable intramedullary contrast-enhancement in computed tomography (CT) or magnetic resonance imaging (MRI) and negative infectious disease titres. Immunosuppressive doses of corticosteroids have commonly been recommended for the treatment of this disease, but the long-term prognosis is poor (Munana and Luttgen, 1998). Radiation therapy and other additional immunosuppressive drugs can improve survival time (Nuhsbaum et al., 2002; Zarfoss et al., 2006; Coates et al., 2007). Cyclosporine seemed to be beneficial in three dogs (Adamo and O'Brien, 2004), and since the first report only one other author has used this type of therapy (Gnirs, 2006). The

purpose of the current study was to investigate the effect of cyclosporine therapy on survival time in patients with GME and to compare it with standard corticosteroid therapy.

5.4. Gabapentin therapy in dogs with cluster seizures

A second therapeutic trial was carried out in patients with convulsive cluster seizures, which is also a challenging category. Cluster seizures (CS) are a severe form of seizure and are not uncommon in small animal practices. Cluster seizures are defined when two or more seizures occur over a 24-hour period and the patient regains consciousness between seizures (Bateman and Parent, 1999). Cluster seizures represent a medical emergency since animals with CS have a higher risk of developing status epilepticus (Parent, 1988; Kay, 1989; Dyer u. Shell, 1993; Thomas, 2003; Lorenz u. Kornegay, 2004). Some patients with IE tend to suffer from repetitive CS, which regularly requires emergency treatment and hospitalization. The resulting financial and emotional constraints are often the limiting factors in an owner's decision to continue medical treatment of their pet (Podell, 1998). The ability to manage CS in order to prevent status epilepticus without hospitalization is limited for owners. The rectal administration of diazepam is a well-known and accepted at-home therapy for the treatment of canine CS (Podell, 1995), but in some dogs it is insufficient. If the patient is able to swallow between seizures, peroral therapy could be carried out by the owner at home in order to avoid status epilepticus and hospitalization.

Gabapentin is approved in the United States in adults and children >3 years of age for adjunctive therapy in the treatment of partial seizures with and without secondary generalization (Radulovic et al., 1995; Morris, 1999; Laroche u. Helmers, 2004).

Gabapentin is a structural analogue of gamma-aminobutyric acid (GABA). It has an antiseizure effect, probably by enhancing the release of GABA in the brain, inhibiting neuronal sodium channels, specifically binding to the neutral L-amino acid transport carrier and modulating voltage-dependent calcium channels, although the exact mechanism is not fully understood (Gotz et al., 1993; Wamil, 1994; Morris, 1999). Although gabapentin can be successfully used in people for long-term treatment, its short half-life limits its usefulness in dogs. The elimination half-life of gabapentin in dogs (beagles and greyhounds) after oral administration is within the range of about 2.2-4 h (Vollmer et al., 1986; Radulovic et al., 1995; Rhee et al., 2008; Kukanich and Cohen, 2009). Only small amounts of gabapentin are bound to plasma proteins, at least, in rats, monkeys and humans (Radulovic et al., 1995). No significant changes in concomitant antiepileptic drug (AED) serum concentrations have been noted in humans (Hooper et al., 1991; Sivenius et al., 1991; McLean et al., 1993; Anhut et

al., 1994; Chadwick et al., 1996). In contrast to other species, about 34% of gabapentin is metabolized into N-methylgabapentin in the dog (Von Hodenberg u. Vollmer, 1983; Vollmer et al., 1986).

Gabapentin has already been reported to have some beneficial effects in dogs with seizures refractory to other drugs, and most dogs with CS clearly improved in these studies (Govendir et al., 2005; Platt et al., 2006).

In the emergency situation of a CS, the AED should rapidly achieve adequate serum concentrations and it should be easily administered by the owner. Due to its pharmacokinetic properties, gabapentin might, at least theoretically, meet these criteria. Such a temporally limited emergency therapy would have the advantage that there would be no further permanent exposure to another long-term medication for the patient. Furthermore, the application schedule of gabapentin would represent a lower financial burden for the owners of affected dogs.

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

6. Presentation of the Studies

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

A total of 406 dogs with histories of seizure were referred to the Clinic for Internal Medicine and Infectious Diseases at the University of Veterinary Medicine, Vienna, during the study period. In 166 cases the lack of accurate examination or incomplete follow-up information resulted in exclusion. Every patient 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 (CT, Type CT PaceTM Fa. General Electric, Milwaukee, USA) or magnetic resonance imaging (MRI, MR unit 0.23 Tesla, Outlook, Gold Performance®, Philips Medizinische Systeme, Vienna, Austria), or more than 2years 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 atour 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 impairments in neurological 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. A seizure was considered to be generalized when the motor activity involved the whole body. The diagnosis of SE was based on the history of seizures and confirmed pathological findings in haematology, serum biochemistry and CSF analysis and by morphological changes in the brain as observed on CT/MRI or histopathological examination. 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^{2}tests and t-tests were used. At-test for independent samples was performed in order to compare the mean values of the two groups. Chi^{2}tests 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.

6.1.2.Results

Aetiology

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 classification and cause of seizures are summarised in *Table 1*.

Table 1. **Classification and cause of seizures in dogs (n=240)**

Cause of seizures	Number of dogs	Percentage
Idiopathic epilepsy	115	48%
Intracranial neoplasma	39	16%
Encephalitis	23	10%
Brain anomaly	10	4.16%
Brain degeneration	9	3.75%
Toxicosis	9	3.75%
Hepathoencephalopathy	8	3.33%
Hypoglycaemia	7	2.91%
Brain vascular disorder	7	2.91%
Other extracranial disorder	5	2.08%
Head trauma	3	1.25%
Uremic encephalopathy	3	1.25%
Electrolyte imbalance	2	0.83%

Age, body weight, gender, breed

Table 2. **Number and breed distribution of dogs with idiopathic epilepsy**

Breed	Number/ Breed
Crossbreed	37
Golden Retriever	18
Beagle	9
Dachshound	5
Border Collie	4
German Shorthair, Labrador Retriever, Poodle	3
Bernese Mountain Dog, German Shepherd, Irish Setter, Jack Russel Terrier, Cavalier King Charles Spaniel, Münsterlander, Pekinese, St Bernard, Staffordshire Terrier	2
Alaskan Malamut, Bavarian Mountain Dog, Boxer, Bullterrier, Chihuahua, Collie, German Wirehair, Dobermann, Entlebucher Montain Dog, Kuvasz, Miniature Pinscher Tatradog, Tibetan Terrier, West Highland White Terrier, Yorkshire Terrier	1
Total number	**115**

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) (*Figure 1, Table 4*). 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) (Figure 1). 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. A regression analysis was performed in order to predict the probability of IE. A cubic regression resulted in an R^2 of 0.661, which provided a better fitting curve than a linear or quadratic regression. In order to predict the proportion of dogs aged 0.25 to 12 years with IE, the following formula was used: $Y = 19.27 + 26.96*x + -4.13*x^2 + 0.15*x^3$.
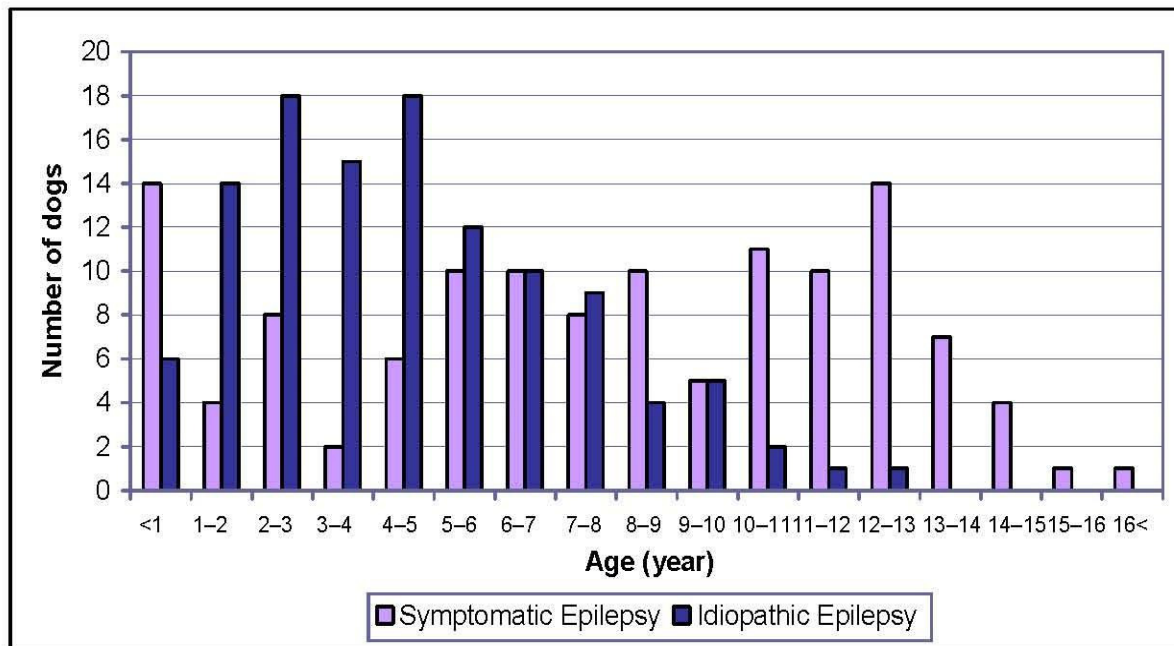
Figure 1. **Age of onset of first seizure and the number of dogs with idiopathic and symptomatic epilepsy**

The mean body weight of the IE group was 24.93 kg (range 3 to 74). This was significantly higher than the mean body weight of the SE group, which was 19.28 kg (range 2 to 85) (Table 4). The IE group was made up of 69 males and 46 females, while the SE group consisted of 62 males and 63 females, which did not differ significantly. Forty-nine animals were neutered in the IE group and thirty-nine were neutered in the SE group (Table 5). There was a substantial difference in the representation of certain breeds in the IE and SE groups (*Tables 2* and *3*). The low numbers of each breed studied did not allow precise statistical analyses for breed predisposition in all breeds: a comparison with clinical breed distribution was performed when n>7. Golden Retrievers (n=18, 7.5%) and Beagles (n=9, 3.75%) were overrepresented in the IE group in comparison to the breed distribution in our clinic (Golden Retriever: 5.25%, Beagle: 2.27%). Boxers (n=9, 7.2%) were overrepresented in the SE group according to the distribution in our clinic (1.62%).

Table 3. **Number and breed distribution of dogs with symptomatic epilepsy**

Breed	Number/ Breed
Crossbreed	43
Boxer	9
Maltese, German Shepherd	6
Chihuahua	5
Yorkshire Terrier, Coccer Spaniel	4
Staffordshire Terrier, Samojede, Miniature Pinscher	3
Golden Retriever, West Highland White Terrier, Siberian Husky, Rottweiler, Dachshound, Pappillon, Jack Russel Terrier, Irisch Setter	2
Alaskan Malamut, Belgian Shepherd, Boston Terrier, Bouvier, Canadian Shepherd, Dalmatian, Dobermann, France Bulldog, Foxterrier, German Shorthair, German Hunting Terrier, Beagle, Havaneser, Howavart, Lhasa apso, Labrador Retriever, Mastino, Puli, Poodle, Portugesic Shepherd, Pekinese, Pug, Shitzu	1
Total number	**125**

Characteristics of the ictal phase

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. No significant difference was found in generalized seizures between the IE group (n=112) and the SE group (n=116). The presence of trembling (IE/SE: 63/80), ictal urination (IE/SE: 27/28), defecation (IE/SE: 14/19) and salivation (IE/SE: 51/68) did not differ between the groups (*Table 5*).

Vocalization occurred in some cases in combination with other ictal signs. Ictal vocalization was observed significantly more often in the SE group (n=15) than in the IE group (n=6) (Table 5).

The mean duration of the seizures did not differ significantly between the groups: it was 3.06 min (range 0.1 to 30) in the IE group and 4.8 min (range 0.1 to 120) in the SE group (Table 4). The occurrence of status epilepticus (IE/SE: 24/52) and cluster seizures (IE/SE: 52/82) was significantly higher in the SE group. Status epilepticus and cluster seizures were2.16 and1.57 times more likely in the SE group than in the IE group (Table 5), respectively.

Postictal Phase

Presence of polyphagia (IE/SE: 7/5), polyuria/polydypsia (IE/SE: 14/7), blindness or deafness (IE/SE: 29/27) and ataxia (IE/SE: 66/67) was not different between the groups. Aggression was detected only occasionally in the postictal phase (IE/SE: 3/1) (*Table 5*).

Timing of the 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) (Table 5).

Seizure triggers
No correlations between seizures and oestrus (IE/SE: 2/0), a full moon (IE/SE: 3/0) or stress and excitement (IE/SE: 6/3) were found (Table 5).

Clinical and neurological findings
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 (Table 5).

Table 4.**Results and t-teststatistics for the IE and SE groups**

Variable	IE group (n=115)		SE group (n=125)		t	P
	M	**SD**	**M**	**SD**		
Age	4.11	2.64	7.38	4.30	7.13	0.001
Bodyweight	24.93	12.67	19.28	12.94	3.402	0.001
Duration	3.06	3.30	4.80	11.27	1.575	0.117

Yellow field: statistically significant results

Table 5. **Results and chi^2 test statistics for the IE and SE groups**

Variable	IE group (n=115)		SE group (n=125)		x^2	P
	N	%	N	%		
Male	69	60	62	49.6	0.374	0.541
Female	46	40	63	50.4	2.370	0.124
Partial seizure	12	10	39	31.2	13.520	0.001
Generalized seizure	112	97.39	116	92.8	0.07	0.791
Trembling	63	54.7	80	64	2.021	0.155
Urination	27	23.4	28	22.4	0.018	0.893
Defecation	14	12.1	19	15.2	0.758	0.384
Salivation	51	44.3	68	54.4	2.429	0.119
Vocalization	15	13	6	4.8	3.857	0.05
Status epilepticus	24	20.8	52	41.6	10.316	0.001
Cluster seizure	52	45.2	82	65.6	6.716	0.01
Polyphagia	7	6	5	4	0.333	0.564
PU/PD	14	12.1	7	5.6	2.333	0.127
Blindness/deafness	29	25.2	27	21.6	0.071	0.789
Ataxia	66	57.39	67	53.6	0.008	0.931
Aggression	3	2.6	1	0.8	1.000	0.317
During sleep or resting	97	84.34	33	26.4	27.904	0.001
Period of activity	3	2.6	5	4	0.5	0.48
Oestrus	2	1.73	0	0	0.511	0.475
Full moon	3	2.6	0	0	0.610	0.435
Stress	6	5.2	3	2.4	0.231	0.628
Neurological abnormalities	2	1.7	80	64	87.044	0.001

Yellow fields: statistically significant results

6.1.3. Discussion

In our study, 115 out of 240 dogs (48%) were suffering from idiopathic epilepsy (IE). Croft (1965) found a much higher percentage, 167/260 (64%), of IE among dogs with seizures. Jaggy and Bernardini (1998) reported only a slightly higher proportion of IE: 125/235 (53%). The development and wider use of modern diagnostic tools during the last decade, particularly CT and MRI, has undoubtedly permitted a more precise diagnosis, resulting in a

lower proportion of IE. CT/MRI was used in one third (80/240) of our cases in the diagnostic work-up, whereas in Croft's study advanced imaging was not available and in the study by Jaggy and Bernardini (1998), between 1989 and 1994, diagnostic imaging was only occasionally carried out (personal communication with A. Jaggy). This development in diagnostic imaging could be the cause of the lower proportion of IE.

We included cases in the IE group without full diagnostic work-up, where more than two years had passed since the onset of seizures without any evidence of interictal neurological signs on the repeated neurological examinations. If we excluded dogs from the IE group based on the lack of full diagnostic work-up we would loose a very important group of patients often seen in the practice: dogs that have occasional seizures but are otherwise in good clinical condition with or even without any antiepileptic drug treatment. Thus we think that the exclusion of these patients would falsify the results. Even neurological textbooks do not define idiopathic epilepsy necessarily based on the full diagnostic work-up (Thomas, 2003; Podell, 2004).

Golden Retrievers and Beagles were the most common pure breeds suffering from IE. This is not surprising in the light of previous reports (Bielefelt et al., 1971; Srenk et al., 1994) which showed the higher prevalence of idiopathic epilepsy in these breeds. Boxers were overrepresented in the SE group; this is also not surprising since this breed has an increased predisposition for brain neoplasia and SE (Heidner et al., 1999; Pakozdy et al., 2006).

The age of onset of epileptic seizure is an important piece of information and helpful for the diagnosis. The first seizure of IE typically occurs between one and five years of age (Podell, 1996; Thomas 2003) or between six months and five years (Cunningham, 1971; Oliver et al. 1997). In our study, if the seizure onset was between one and five years of age, there was 3,25 times greater likelihood for IE than SE, supporting the previous observations.

Body weight seemed to be an identifiable risk factor in dogs with idiopathic epilepsy to develop status epilepticus. Dogs with a higher body weight were more likely to have episodes of status epilepticus (Saito et al., 2001). In our study, the body weight was higher in the IE group. Despite this significant difference between the two groups, which was already reported by Podell (1996), the body weight allows limited clinical use in the determination of the cause of diseases. Another important aspect is that high number of large dogs like Golden Retriever in the IE group may cause this result.

In our patients there were more male than female dogs in the IE group. This is comparable to other reports (Bielfelt et al., 1971; Falco et al., 1974; Jaggy and Bernardini, 1998), although the number of male and female dogs does not differ significantly between the IE and SE groups.

The most common cause of secondary epilepsy in our study was intracranial neoplasia (39/125) (*Table 1*), which was more common than reported by Croft (1965). There are several possible explanations for this observation. (1) Newer diagnostic imaging techniques are better at detecting intracranial lesions. (2) In the study by Croft (1965), only a few old dogs were included, whereas in the present study 48/125 were older than 10 years of age (*Figure 1*). The increasing life expectancy of dogs as a result of improved veterinary services could explain the higher proportion of intracranial neoplasia found in our study.

Inflammatory brain disease represented the second most frequent aetiologic group. 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 clinical management of dogs with MUO is difficult; not just the diagnosis but also the therapy is challenging. Immunosuppressive treatment is commonly recommended for the treatment of this disease, as an immune-mediated aetiology is suspected, but the long-term prognosis is poor (Munana and Luttgen, 1998). We decided to investigate these patients in more detail and test a new treatment modality (part 3).

Partial seizures are frequently caused by intracranial pathological lesions (Barker, 1973; Berendt and Gram, 1999; Speciale, 2005). Similarly to the results of another report (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 pathognomic seizure pattern for IE and that it is not possible to differentiate between IE and SE based on the clinical picture alone. Similar suggestions were made by Lengweiler and Jaggy (1999) for Golden Retriever and by Patterson et al. (2005) who investigated an English Springer Spaniel population with idiopathic epilepsy. 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: partial seizures are more suggestive of SE. This criterion has two more limitations: (1) a partial attack may become generalized so rapidly that its true nature is obscured and the seizure may then be classified as primary generalized epilepsy (Barker, 1973; Berendt and Gram, 1999; Speciale, 2005), thus the objective difference is underestimated; (2) seizure classification was based on the owners' observations, which were certainly not accurate in every case.

Status epilepticus and cluster seizures were 2.16 times and 1.57 times more likely to occur in the SE group, respectively, which 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.

Other ictal signs observed by the owners such as trembling, urination, defecation, salivation, and post-ictal signs (like polyphagia, polyuria/polydypsia, blindness or deafness, ataxia and aggression) did not differ between two groups. Therefore, these symptoms did not allow any differentiation between IE and SE.

Whining, crying or other ictal vocalizations were rarely noticed; to the extent that when they were noticed they were more often reported in the IE group. The pathophysiology of vocalization may have a different origin: it could be related to convulsions of laryngeal or intercostal muscles, or be a consequence of limbic system or frontal lobe involvement (Penfield and Rasmussen, 1949). Ictal non-speech vocalization is characteristic of almost 50% of human patients with frontal lobe epilepsy (Janszky, 2000). Frontal lobe epilepsy has been reported in dogs based on EEG analysis (Morita et al., 2002); however, vocalization was not observed. We hypothesized that the ictal vocalization observed in dogs in IE and SE might also be related to the involvement of frontal lobe structures. In patients of the SE group that exhibited vocalization the causes varied: toxic or metabolic (7), intracranial neoplasia localized in the temporal lobe, frontal lobe or rhinencephalon (4), hydrocephalus (2) and encephalitis (2). The real connection between seizure aetiology and ictal vocalization should be identified using ictal video-EEG monitoring, as in human medicine.

We found that seizures were more frequently reported during the resting condition in IE; previous studies commonly reported theoccurrence of seizures during sleep or under resting conditions (Podell, 1995; Jaggy and Bernardini, 1998; Lengweiler and Jaggy, 1999; Thomas, 2003). 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. Podell (1995) reported that the first seizure in dogs with symptomatic epilepsy was frequently observed between midnight and 08:00; conversely, dogs with IE were unlikely to experience their first seizure during this time period. However, we were not able to support this observation.

Anecdotal reports from clients suggest that some dogs with IE have seizures that are related to lunar cycles and oestrus. We were not able to statistically support this because of the low number of dogs affected (n=3); however, all patients reported to have seizures in connection

with a full moon had IE. Similarly, we could not statistically confirm that female dogs exhibited an increasing frequency of seizures during oestrus.

Clinical and neurological examinations are the most important indicators that enableus to distinguish between IE and SE (Jaggy, 1997). In our study, the clinical neurological examination was suggestive of SE in 64% of cases in the SE group. In the IE group, the clinical and neurological examinations were typically unremarkable, but post-ictal behavioural changes were occasionally observed. Like Bagley et al. (1999), we found that, in many cases of SE, the clinical status was unremarkable when patients presented for the first time, especially if the seizures were caused by intracranial tumours. Since the analysis of the ictus was based on owners' reports, it should be considered with caution. A more precise semiology of seizures based on video observations needs to be carried out in the future.

We concluded that idiopathic epilepsy (IE) and symptomatic epilepsy (SE) were approximately equally distributed (48/52%). Symptomatic epilepsy was mostly caused by intracranial tumours (16%) and encephalitis (10%), similar to the results of previous reports. 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. If the first seizure occurred between 1and 5years of age or the seizures occurred during resting condition, vocalization during the seizure was more likely to predict a diagnosis of IE than SE.

6.2. Electroencephalographic examination of epileptic dogs

6.2.1 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.

Idiopathic epilepsy was considered when the result of the interictal neurological examination was normal and no underlying cause of the seizure was identified in routine serum biochemistry, haematology, CSF analysis, computed tomography (CT) or magnetic resonance imaging (MRI, MR unit 0,23 Tesla, Outlook, Gold Performance®, Philips Medizinische Systeme, Vienna, Austria), or when more than two years had passed since the onset of seizures without any interictal neurological signs. All dogs with idiopathic epilepsy (IE) were re-evaluated at least 24 months after diagnosis by the author or another neurologist in our clinic and no abnormalities were identified in physical orneurological examinations. Symptomatic epilepsy (SE) was considered when the clinicopathological diagnostic work-up revealed severe cerebral morphological changes, which are very likely to be an aetiologic factor for seizure recurrence.

Stainless steel needle electrodes were used (Viasys Healthcare, Subdermal Needle, 12mm, 0.4 mm diameter, Netherlands) 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) (Figure 2). Chemical restraint was used in all dogs. Propofol was used for induction, until the animal became intubatable (2–6 mg/kg); oxygen was administered after 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.

The basic terminology regarding basic epileptiform EEG graphoelements was reviewed by the International Federation of the Society for Electroencephalography and Clinical Neurology (IFSECN, 1974), whose terminology is currently accepted (Nordli et al., 2011). According to the IFSECN "spike is a transient, clearly distinguished from the background

activity, with pointed peak at conventional paper speed and a duration from 20 to under 70 msec; the main component is generally negative. Amplitude is variable."

"A sharp wave is a transient, clearly distinguished from the background activity, with pointed peak at conventional paper speed and a duration from 70 to 200 msec; the main component is generally negative relative to the areas" (IFSECN, 1974).

The spike wave-complex definition of the IFSECN (1974) is simple: "a pattern consisting of a spike followed by slow wave".

Very soon after beginning of EEG analysis we found that there are several other EEG patterns which are clearly distinguishable from the background activity. Some of them are characteristic sleeping phenomena but may be misinterpreted as IED. So we also identified EEG changes which are however transient but not epileptic. The following further terms were used through the manuscript according to IFSECN (1974):

Pattern – "Any characteristic EEG activity". Background activity – "Any EEG activity representing the setting in which a given normal or abnormal pattern appears and from which such pattern is distinguished". Transient – "Any isolated wave or complex, distinguished from the background activity".

The EEG analysis was carried out with the assistance of human epileptologist and encephalographer (HP).
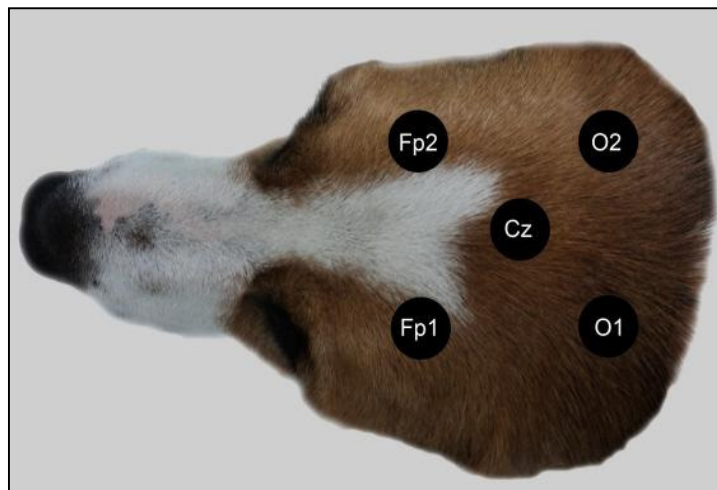

Figure 2. **The electrodes were positioned according to Redding and Knecht (1984). Fp1 is the frontal left, Fp2 frontal right, Cz represents vertex, O1 left and O2 right occipital electrodes. Ground and reference electrodes were placed in the neck and noise respectively. The following leads were used throughout the manuscript: (1) Fp1-Fp2, (2) Fp1-Cz, (3) Fp2-Cz, (4) Fp1-O1, (5) Fp2-O2, (6) Cz-O1, (7) Cz-O2, (8) O1-O2, (9-ECG) ECG2+ECG2, (10-Mark) MKR+MKR-100μV.**

6.2.2 Results

Patients

Twenty dogs in the SE group and 20 in the IE group fulfilled the inclusion criteria. The following diagnostic groups were identified among dogs with SE: brain neoplasia (12), brain anomaly (4), encephalitis (3), and brain hemorrhage (1).

Epileptiform discharges
Spikes

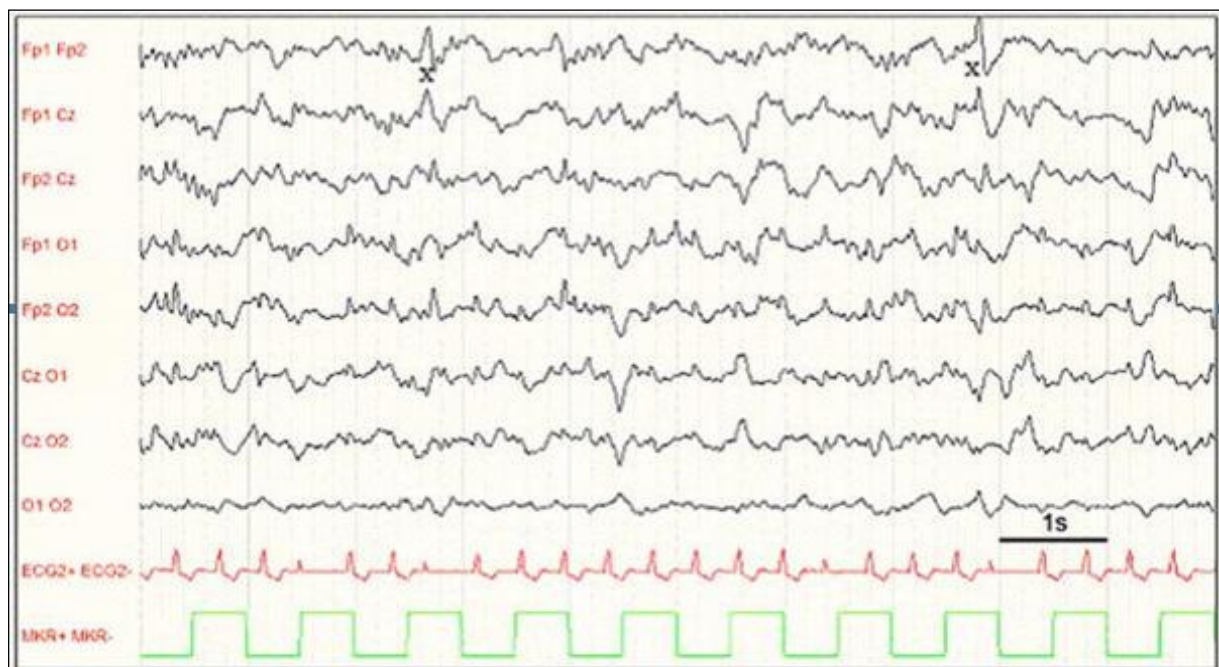Spikes were found in 4/20 dogs in the SE group; none of the patients in the IE group showed spikes (*Figure 3*).

Figure 3.**Spike (X) in the Frontal region with highest negative amplitude in the FP1. Post mortem examination showed oligodendroglioma in the right (contralateral) frontal lobe**

Sharp waves and spike-wave complex

None of patients showed sharp waves or a spike-wave complex.

Periodic epileptiform discharges

One patient in the SE group with severe necrotizing encephalitis (NME, Pug-encephalitis) showed periodic spike-like discharges every second, similar to periodic epileptiform discharges (PEDs) in humans (Figure 4). Periodic epileptiform discharges are classically triphasic; the total duration is usually 100-300ms and, as the term periodic indicates, PED recurs: the frequency is usually 0.5–4 s.

Figure 4. **Periodic epileptiform discharges with an interval about 1 second. Note the different frequency compared with ECG channel. The pattern is similar to human Creutzfeldt-Jakob Disease (severe "Pug Dog Encephalitis" with cortical and thalamic involvement)**

Non-epileptic sleep phenomena that could cause misinterpretation
Spindle

EEG phenomena were observed in all patients that showed clear similarities to human spindles (*Figures 5* and *6*). The frequency was between 5 and 12Hz and the duration was 0.5-2 s. Spindles in humans are physiological rhythmic bursts that represent thalamocortical oscillations that occur at the vertex or in the parietal region in different stages of sleep. Their amplitudes characteristically change: during spindles with the lowest amplitudes at the

beginning and end, the maximal amplitude at about the midpoint forms a "spindle". Spindles start and end suddenly and contain a single unchanged frequency that is typically between 11 and15 Hz; they commonly last from 2 to 4 s. Spindles typically have a lower amplitude than the surrounding background activity.
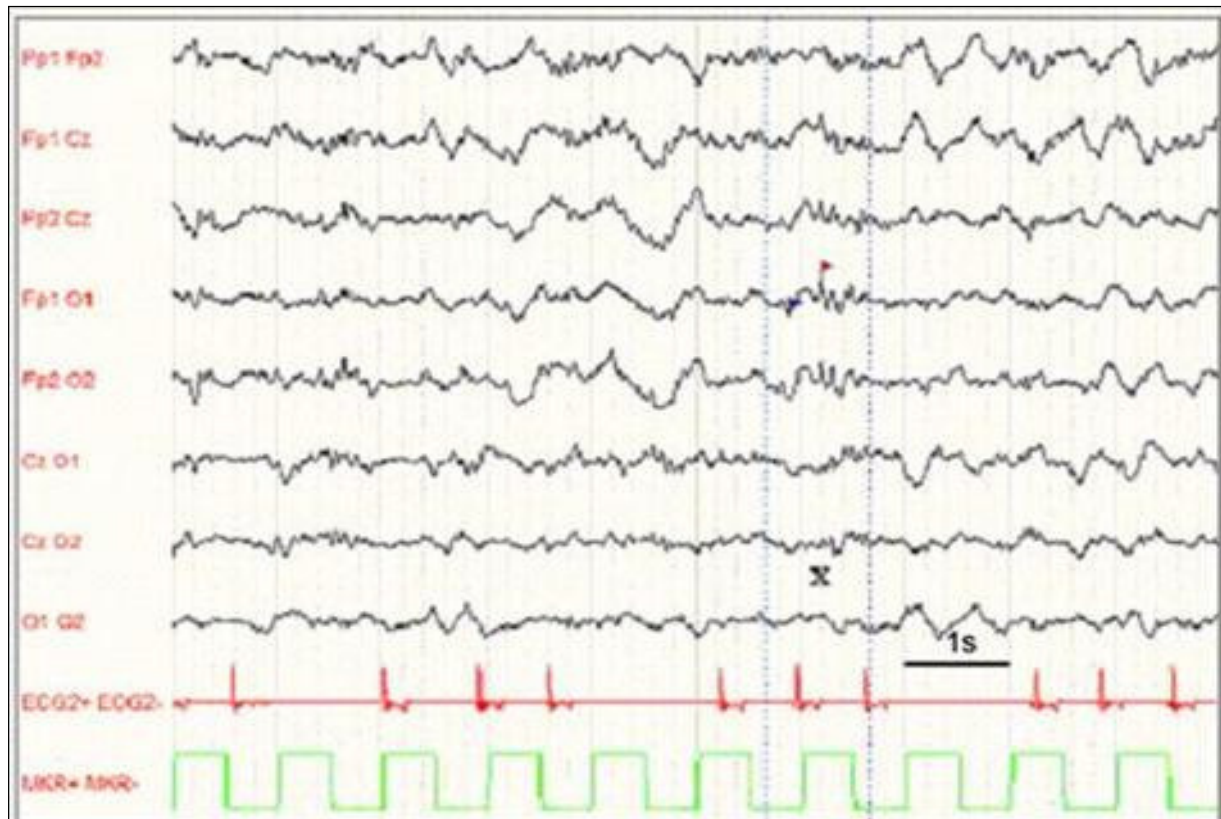

Figure 5. **Small spindles can be recognized with a frequency of about 10 Hz and duration of 0.5 s in all but the occipital (O1O2) channels**
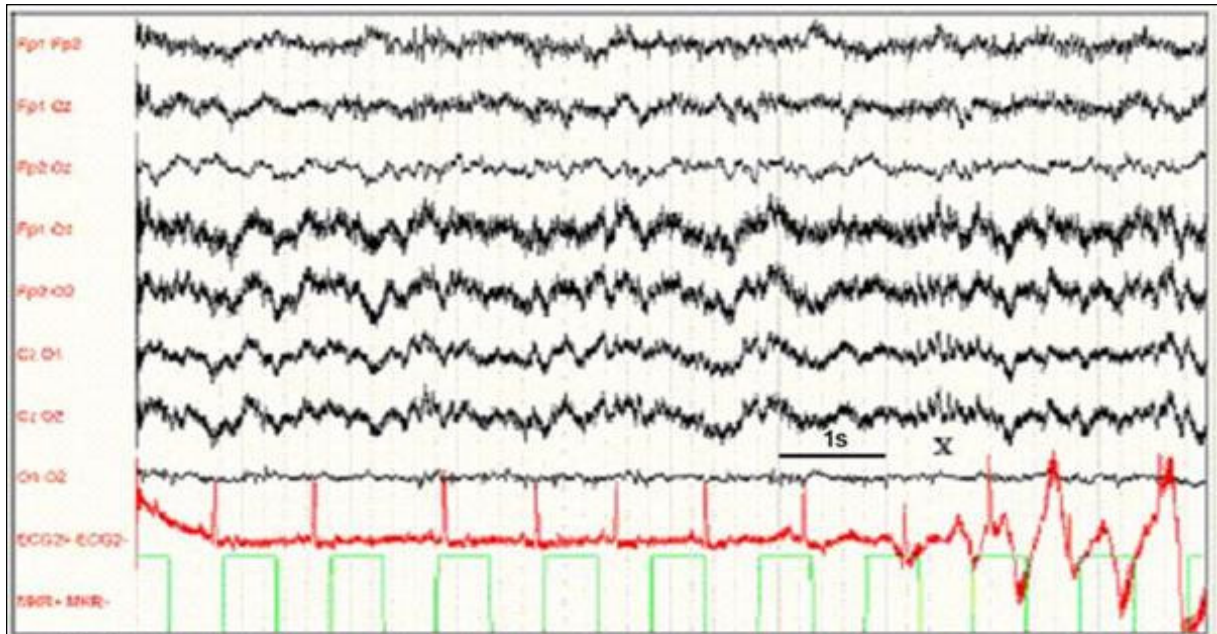
Figure 6. **Despite of severe muscle artefact in FP1 and in both occipital channels, spindles can be recognized with frequency about 10,5 Hz and duration of 0,5 seconds in all leads but occipital (O1O2) channels**

Vertex-waves and K-complex

Vertex waves and K-complex were observed in almost all of the patients in both (18/17 in IE/SE respectively) groups (*Figure 7*). Vertex waves (vertex sharp transient, V wave, biparietal hump) in humans are physiological EEG phenomenon during sleep. They represent evoked potentials by different modalities. They can be most easily elicited by auditory stimulation. Although they are often found together with K-complexes (Figure 8), vertex waves are distinct from K-complexes (Figure 9). Vertex-waves occur in light sleep but K-complexes are associated with deeper sleep. Vertex waves are at a maximum in the central midline and are usually visible on both sides; however, K-complexes are more of a frontal phenomenon. K-complexes are often triphasic; however, di- and monophasic variants also occur, and K-complexes can also be associated with spindles (*Figure 8*).
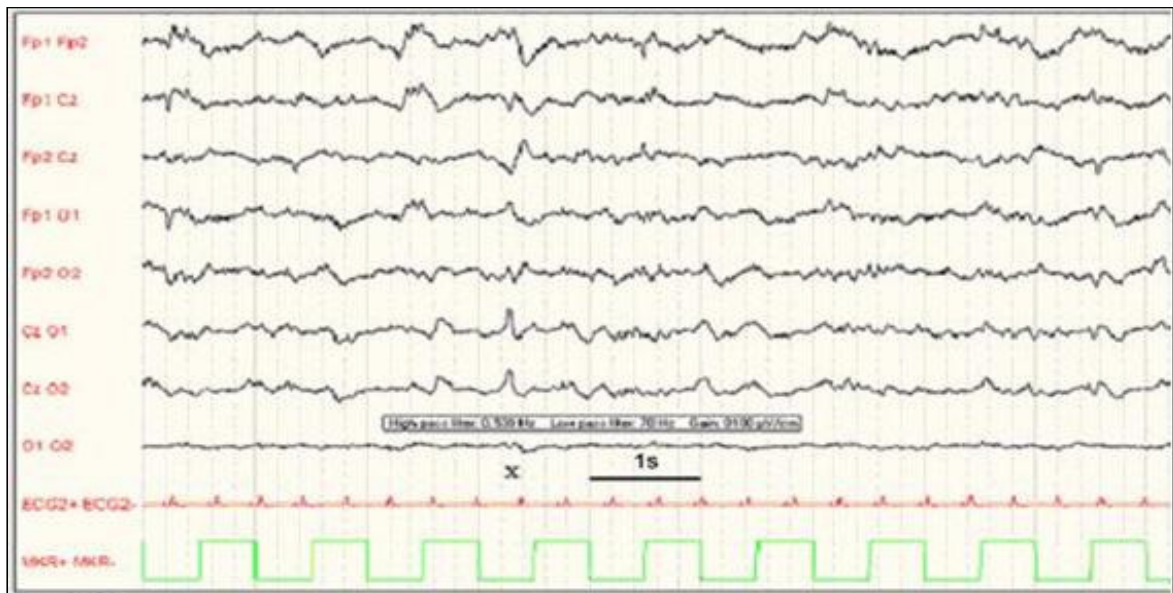
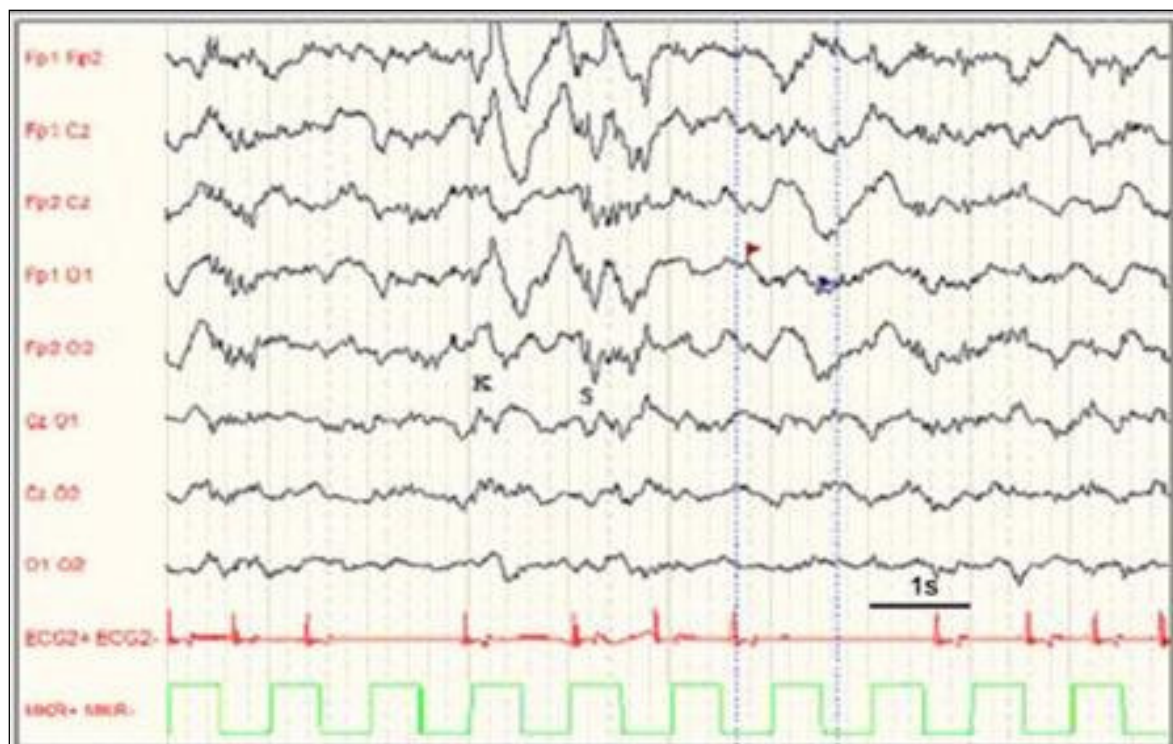Figure 7. **The vertex waves (X) are biphasic in channels 1,2,3, and 5 and monophasic in channels 4, 6 and 7**

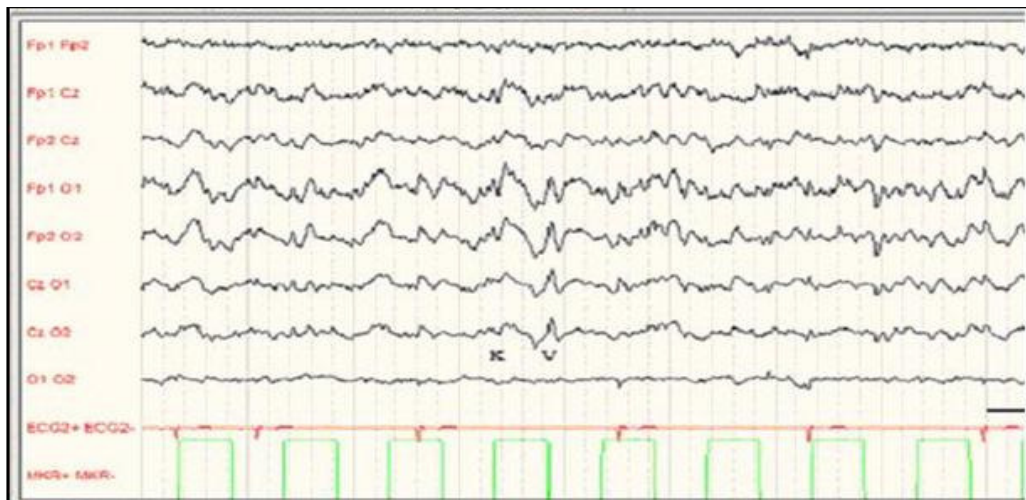Figure 8. **K complexes (K) are present in channels 1,2,4 and 5, followed by a spindle (S)**

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Figure 9. A **K-complex (K) is visible in channels 2-7 followed by a vertex wave (V) in channels 4-7**

Positive occipital sharp transient (POST)

Positive occipital sharp transient (POST) was detected in three dogs (1/2 in the IE/SE groups, respectively) and is characterized by a train composed of a positive-polarity, triangular sharp wave with phase reversal at occipital electrodes. They have triangular shape with symmetric rising and falling phase. Amplitudes are typically 20-75µV, the duration 80-200ms, and POST can only be identified during sleep but not during wakefulness. These waves represent a functional "playback" of visual experiences and are absent in individuals with severely impaired vision (*Figure 10*).
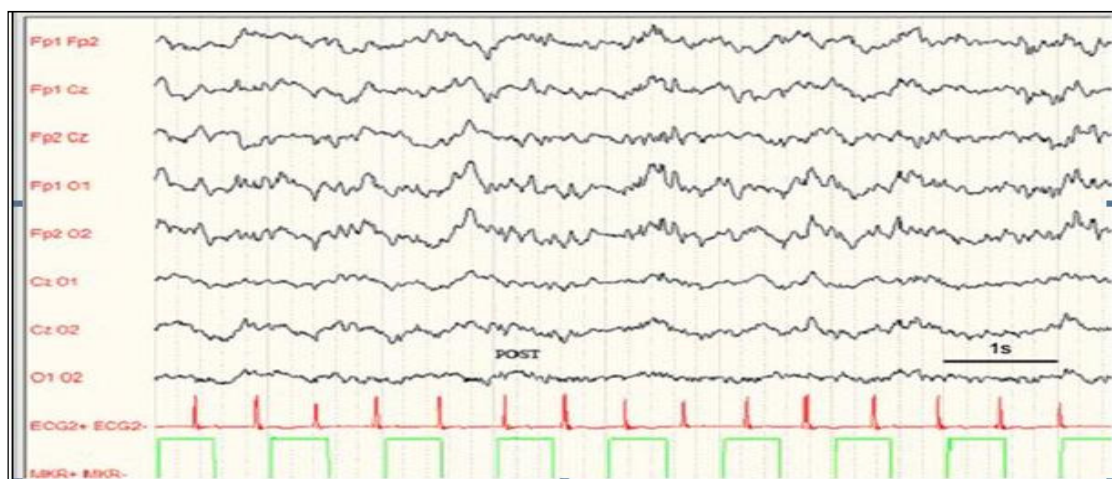

Figure 10. **POST in a dog with SE (melanoma)**

Cyclic alternating pattern

In 16 patients (7/9 in the IE/SE groups, respectively) repetitive EEG patterns that lasted about 2 s, followed by 4-20 s background activity (Figure 11), were found. This phenomenon was most likely consistent with the human cyclic alternating pattern (CAP),which is characterized by repetitive stereotyped EEG patterns lasting about several seconds and separated by time-equivalent intervals of background activity (Gaches, 1971).

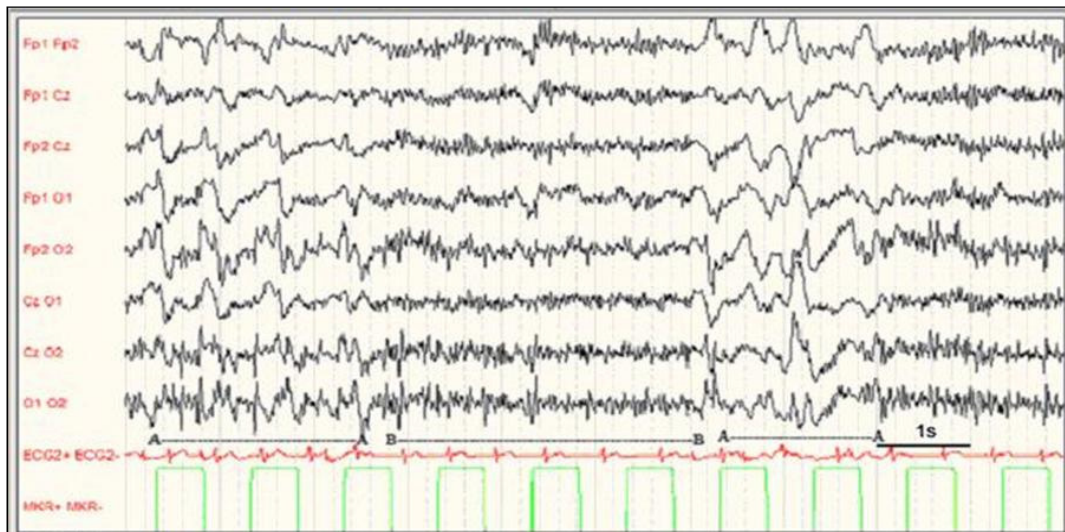Figure 11. **Cyclic alternating pattern is a normal sleeping phenomenon but may be misinterpreted as epileptiform. Phase A (A) represents the excitatory state and phase B (B) the inhibitory state during sleep oscillations**

ECG artefacts

We frequently observed ECG artefacts, which could also have caused misinterpretation (Figure 12). Distinguishing these waves is straightforward when an ECG channel (channel 9) is present.
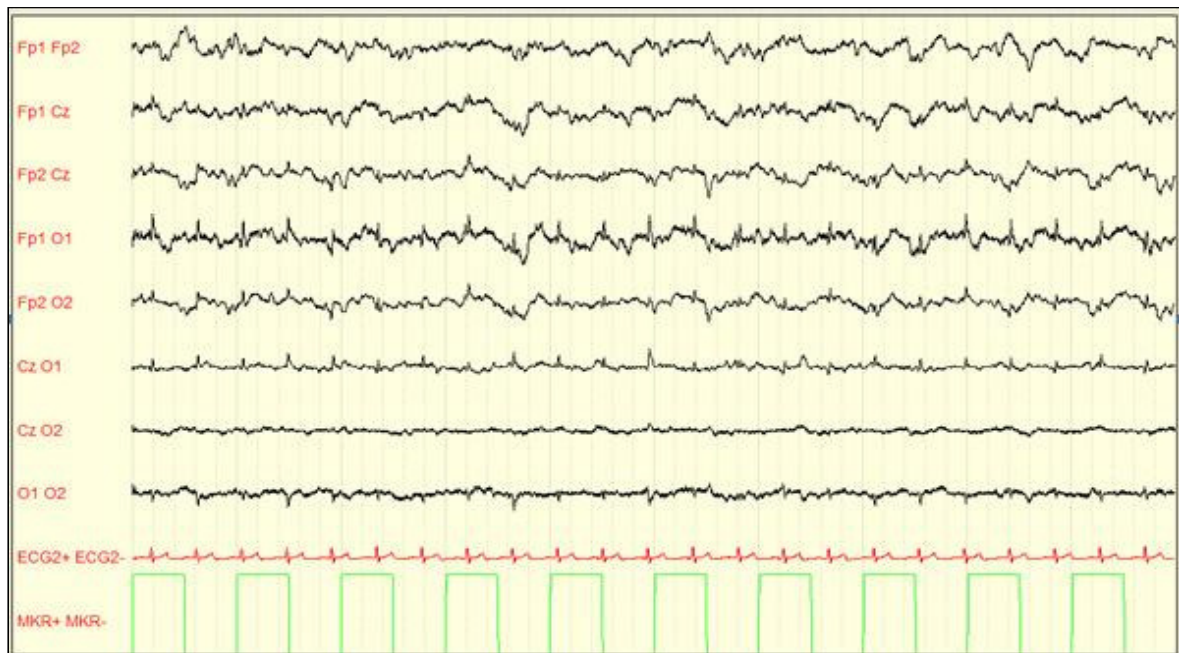
Figure 12. **ECG artefacts are clearly visible in almost all channels of the EEG compared to the ECG (lowest channel). The EEG changes occur simultaneously with the QRS complex**

6.2.3. 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. We frequently found transient non-epileptic EEG phenomena but their differentiation from epileptic phenomena can be challenging.

A comparison of different veterinary studies
We found a considerably lower portion of epileptiform discharges (12.5%) among the epileptic dogs compared to previous researchers (20-100%) (*Table 6*).

Table 6. **Clinical EEG studies of canine epilepsy**

Study	n	Restraint technique/number of channels/electrode placement	Recording time	Portion of epileptiform discharges	Other important information
Holliday et al., 1970	70	Physical/6 channels bipolar/subcutaneous	1–2h	43/70 (61%)	Photic stimulation (13), chlorpromazine (43)
Klemm and Hall, 1970.	91	Pentobarbital, thiopental/8 channels monopolar and bipolar/subcutaneous	15–30min	90/91 (99%)	
Knecht et al., 1984	46	DNA	DNA	10/46 (22%)	
Srenk and Jaggy, 1996	5	Medetomodine, propofol/ 8 channels/monopolar and bipolar/subcutaneous	DNA	5/5 (100%)	
Berendt et al., 1999	23	Acepromazine,pethidine/14 channels/ subcutaneous	30–45 min	15/23 (65%)	
Jaggy and Bernardini, 1998	37	Medetomidine, propofol/ 8 channels, monopolar and bipolar/subcutaneous	10 min	32/37 (86%)	
Morita et al., 2002	11	Xylazine/12channels, bipolar and monopolar/subcutan	DNA	9/9 (100%);no detailsareavailable	Shetland sheepdogs
Pellegrino and Sica, 2004	9	Xylazine/12 channels, bipolar/subcutaneous	Minimum 30 min	5/9 (55%); no detailsareavailable	
Jeserevics et al. 2007	15	Medetomidine/17 channels, bipolar/ subcutaneous	20 min	3/15 (20%)	Finnish Spitz dogs
Brauer et al. 2011	89	Propofol/8 channels, bi-, and monopolar/subcutaneous	16 min	23/89	15/61 (25%) in IE, 8/28 (29%) in SE
Present Study	40	Propofol/8 channels, bipolar/subcutaneous	At least 7 min	5/40 (12.5%)	

DNA: data not available

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. We used propofol as it can safely be used in epileptic patients. Propofol is characterized by a rapid onset with a smooth and rapid recovery (Glen, 1980). The effects of propofol are at least partly mediated by the GABAa

receptor complex (Trapani et al., 2000). Fiset et al. (1999) proposed a role of the dopaminergic pathway and effects of propofol on the reticulothalamic system. Propofol's anticonvulsant effect was confirmed in animal models (Lowson et al., 1990) and in clinical veterinary use (Steffen and Grasmuek, 2000). It has also been used in EEG recordings of epileptic canine patients without suppressing epileptic activity (Jaggy and Bernardini, 1998). However, pro-convulsant properties were also reported for this drug (Committee on Safety of Medicine, 1989). It seems that these converse effects are dose-dependent. In humans, low-dose propofol was successfully used to increase EEG spike activity in patients with epilepsy (Leijten et al., 2001). This could be one of the reasons for the large difference between the results of Jaggy and Bernardini (1998) and those from our study regarding the occurrence of epileptic discharges in dogs with epilepsy. We used higher doses of propofol (2-6mg/kg), which may have been why we detected fewer epileptiform discharges compared to Jaggy and Bernardini (1998) (2mg/kg) (Table 6.). In the future, researchers are advised to take into consideration these findings when using propofol for EEG recordings in epileptic patients.

The sensitivity of EEG for recording epileptic discharges in IE is even worse; the detection of epileptic discharges by EEG was not possible in any of the dogs in the IE group. In the light of previous investigations it seems likely that the suppressant effect of propofol is at least partly responsible for this result. It seems that our original idea, namely to connect the EEG with other diagnostic procedures (e.g. CSF tap, diagnostic imaging) and to use the same narcosis protocol with propofol, was associated with a low sensitivity for epileptic EEG changes. We did consider this possible effect at the beginning, but as propofol is a short-acting anaesthetic drug we expected it to have less of a suppressant effect on the EEG soon after stopping propofol administration. 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 but without epileptiform EEG phenomena had already been on anticonvulsant therapy. The influence of anticonvulsant therapy on EEG recordings of epileptiform discharges was not examined in other studies.

EEG activation by drugs

The activation of epileptiform discharges by drugs was considered by Holliday et al. (1970). These authors used chlorpromazine in 43 dogs; 17 showed paroxysmal activity before the

drug was administered but more showed paroxysmal activity after the drug was administered and 5 showed EEG abnormalities only after chlorpromazine was administered. Earlier investigators confirmed that chlorpromazine increases epileptic activity in humans (Fabish 1957; Logothetis 1967).

Klemm and Hall (1970), using pentobarbital and thiopental, found that the use of anaesthesia did not mask epileptic EEG changes and encouraged such methods.

Experiments by Wiederholt (1974) on epileptic dogs found that by using thiopental and methohexital spike discharges were seen arising from the temporal lobe, but no such discharges were detected in control dogs. Methohexital was used to induce sleep in human out-patients as it is very short-acting and does not suppress epileptic discharges (Fenton and Scotton, 1967). Furthermore, methohexital caused the selective activation of the epileptogenic focus during acute electrocorticography (ECoG) in the majority of human patients. This activation seemed to be specific for the epileptogenic focus and did not cause epileptiform spiking from other non-epileptogenic cortical regions (Whyler et al., 1987). Such activation methods could have the advantage of sleep without the disadvantage of the suppressant effect of most anaesthetics and should be considered for diagnostic use in veterinary medicine. However, such non-established and potentially dangerous clinical applications should be used with caution and with the agreement of the owner and the ethics committee of the institution as well.

Recording technique

Another important topic in electroencephalography is the recording technique used, which has a great influence on the diagnostic value. Surface electrodes (i.e. scalp-EEG) are used in clinical veterinary medicine because of their simplicity, although activity can only be detected only if they penetrate the scalp. This means that even ictal EEGs might be normal if the epileptic discharges occurin deeper brain structures. In human mesial temporal lobe epilepsy, which is one of the most frequent and most examined forms of epilepsy, ictal scalp-EEGs might be normal or inconclusive in 60% of cases (Wieser et al., 2004).

Several techniques have been developed for humans in order to increase the diagnostic value of routine 20-min EEGs. Some important techniques are: tape cassette systems with off-head amplifiers, short video-EEGs, hospitalized video-EEGs, implanted intracranial or intracerebral electrodes, and increasing the number of channels up to 128 (Halasz, 2010). Sleep deprivation, photostimulation and medication withdrawal are further well-established methods of increasing EEG sensitivity. The prolongation of EEG recording could have resulted in higher sensitivity in our study; however, Jaggy and Bernardini (1998) also used

short 10 min-recording sessions. Increasing the number of electrodes contributed towards improving the diagnostic value, although the exact localization of the ED is not essential in canine epilepsy, in contrast to humans where EEG findings are fundamental for surgical treatment (Wieser et al., 2004).

Limitations in the accuracy of electrode placement in dogs

The small brain size of dogs and their different skull formations limit the accuracy of electrode placement and the number of electrodes that can be used. Another limitation is the movement of skin, which, in dogs, results in movement of the electrodes due to different subcutaneous structures, unlike in humans. A further problem is the high diversity in shape and size of the brain and skull in dogs and large variations in the sinus frontalis. These limitations hindered the very similar electrode placements in all of the dogs examined but this effect on the results of the EEG could not be analysed due to the low number of cases in our study.

Spikes, spindles, K-complexes, vertex waves, PED, POST

Spikes represent the basic element of epileptiform activity in the EEG. In our study spikes were the most frequently identified ED; similar results were found by several previous investigators, although sharp waves were found as well (Holliday et al., 1970; Klemm and Hall, 1970). We detected spikes in four patients with space-occupying lesions (oligodendroglioma 2, meningioma 2) with localization contralateral to the lesion in two cases.

At the beginning of the disease spikes are temporally linked to the so-called primary lesion; however, with time, spikes may develop in the contralateral homotopic cortex. These contralateral spikes have been called the mirror focus. If ablation of the primary cortex is performed at the onset of disease, the contralateral spikes will disappear. However, if the primary lesion remains active, later excision of the primary lesion may not abolish the interictal spikes in the homotopic cortex (Morell, 1985).

Some other studies suggested that the relationship between scalp EEG spikes and the seizure focus is not reliable enough to determine the location of the side of epileptic dysfunction, while others found scalp spikes to be a useful component of the pre-surgical evaluation (Blume et al., 1993, 2001; Janszky et al., 2001; Ray et al., 2007). Either the previous so-called mirror focus (also called secondary epileptogenesis) or the propagation of epileptic discharges could have been associated with contralateral spiking in our study. We think that other mechanisms should be considered as our cases were related to space-

occupying lesions. In both cases the lesion caused a mass effect and a midlineshift on diagnostic imaging, thus neuronal destruction could have occurred in the contralateral hemisphere and neither the mirror focus phenomenon nor the propagation of epileptic dysfunction was necessary to produce contralateral spiking.

Spikes have several unique characteristics but remarkable inter- and intra-individual variations can also occur. Spikes are defined by the IFSECN (1974) (see Materials and Methods); however, in practice they are not always that obvious. The usual characteristics area minor positive (downwards), a major negative (upwards), and a second minor positive (downwards) component. A slow negative component may trail the spike and reach the same amplitude as the main negative component of the spike. This should not be regarded as a spike-wave complex (Niedermeyer, 2005). We conclude that, based on the location of the spike on the single scalp-EEG, it is not possible to localize the primary epileptogenetic lesion in dogs.

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).

There is another specific aspect of the EEG evaluations in dogs: as EEG recording was performed during sleep, different physiological sleep phenomena were observed. Some of these have been well described previously, others only sparsely. Researcher sought to be aware of these graphoelements as they can present differential diagnosis difficulties.

Different kinds of spindle activity were observed in all of the patients. In humans, spindles are accompanied by other signs of stage II non-REM (NREM) sleep, including vertex sharp transients and positive occipital sharp transients of sleep (POSTS). Human EEG spindles do not occur in stage I or REM sleep (Stern and Engel, 2005). The K-complexes are also normal phenomena and are usually provoked by external stimulation during sleep, most frequently by external auditory stimulation. The K-complexes are usually polyphasic and often precede a sleep spindle (Figure 6). They include a couplet of two waves of opposite polarity that are greater in amplitude than the surrounding background activity. The K-complexes can occur

together with vertex waves; the latter has a sharper form (Figure 7). Bergamasco et al. (2003) observed the same sleep phenomenon in dogs and they connected it to propofol usage. Spindles, K-complexes and vertex waves should be differentiated from ED; however, the morphology in some vertex waves is really challenging although their localization (i.e. vertex) can help to distinguish them from ED.

POSTs are normal and common findings in humans with intact vision. The physiological basis of POST is a functional playback of visual experiences during sleep; POST is absent in individuals with severely impaired vision, and POST only occurs during sleep, not during wakefulness. This can help to differentiate POST from sharp waves (ED). POST was previously detected in normal dogs during propofol anaesthesia (Bergamasco et al., 2003).

We observed graphoelements that were very similar to the cyclic alternating pattern (CAP). The CAP is a physiological sleep phenomenon and is independent of the presence of epileptic activity. However, this physiological rhythm modulates certain pathological events and seizures. Epileptic discharges occur during sleep, usually in the same CAP phase. The CAP sequences are composed of a repetitive transient EEG pattern that lasts for several seconds (Phase A) divided by a period (Phase B) of background activity of 15-20 s. Phase A represents the excitatory state and phase B the inhibitory state during sleep oscillations. In some forms of epilepsy it has been confirmed that activation of the epileptic mechanism takes place during phase A (Parrino et al., 2000).

Reviewing different veterinary studies about the use of EEG in epileptic dogs (*Table 6*) a large discrepancy was noticed: the occurrence of epileptiform activity was reported to be 20-100%. We suspect that this was not just due to the different clinical settings but that it was also due to other important factors too.

(1) The influence of all anaesthetic drugs on brain activity is inhibitory, which reduces the likelihood of epileptiform activity.

(2) The lack of detailed knowledge on sleep phenomena can cause misinterpretation. This can be reduced with the assistance of an epileptologist; however, the interpretation of sleep phenomena can be challenging.

(3) There is a lack of good veterinary education on the use of electroencephalography. Some universities and reference clinics with otherwise high medical standards do not use EEG in the work-up of epileptic patients. Even veterinary neurologists can be poorly trained in EEG interpretation and thus do not see the need to employ it.

(4) The lack of knowledge on healthy canine sleep EEG patterns makes the assessment of individual patient EEGs more difficult.

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Based on our study, EEG seems to have a low sensitivity for detecting epileptiform discharges in this clinical setting. The author believes that using restraint techniques that do not artificially alter electrical brain 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.

6.3. Cyclosporine therapy in dogs with granulomatous meningoencephalomyelitis

6.3.1. 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.

MRI was performed using an MR unit (described earlier). Imaging included T1-weighted spin echo, dorsal T1-weighted gradient echo (GRE), transverse T1-weighted GRE, and transverse T2-weighted fast spin echo (FSE) sequences. The T1-weighted images were repeated after the intravenous administration of gadodiamide (Omniscan, Nycomed, Oslo, Norway) or gadobenate dimeglumine (MultiHance®; Bracco Östereich GmbH, Vienna, Austria) at a dose rate of 0.15 mmol/kg body weight (T1+C). If considered necessary, additional sequences, such as dorsal fluid attenuated inversion recovery (FLAIR) and FSE short tau inversion recovery (STIR) were acquired. The CT scans consisted of a plain series and a contrast series after the intravenous administration of contrast medium (Scanlux, Sanochemia AG) at a dose of 555 mg/kg body weight. The technical settings were 80–120 kV and 80–120 mAs. The matrix was 512×512 cm and the field of view was 11–16 cm.

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.

6.3.2. Results

A total of 14dogs were studied: 7 dogs in the ST group and 7 dogs in the CY group. The following breeds were represented: poodle (1), Staffordshire terrier (1), Lhasa apso (1), pinscher (1), French bulldog (1), chihuahua (1), cocker spaniel (1), collie (1), wire-haired fox terrier (1), Maltese (1) Rottweiler (2) and mixed-breed dogs (2). The mean age of all patients at the time of diagnosis was 5.61 years (range: 1-10); in the ST group the mean age was 5.29 years old (range: 11-10) while in the CY group it was 5.86 years old (range: 1-11); this difference was not statistically significant (P=0.699). In the ST group there were three males and four females, while in the CY group there were four males and three females; this difference was not statistically significant(P=0.28). Body weight was measured in all of the dogs included and ranged from 1-37 kg (mean: 15) in the ST group and 5-37 kg (mean: 18) in the CY group; this difference was not statistically significant(t=0.527; P=0.609). In the ST group the neuroanatomical localizations were focal in three cases and multifocal in four cases; in the CY group they were focal in four cases and multifocal in three cases; this difference was not statistically significant (P=0.593). We observed the following neurological signs in the ST/CY group: ataxia (3/3), tetraparesis (2/3), seizures (2/2), central vestibular signs (1/3), compulsive walking (1/1), and cervical pain (1/1).

Blood work showed leucocytosis (4/13), hypokalaemia (2/0), hyperproteinaemia (1/1), and hypoglycaemia (1/0). The CSF analysis exhibited mononuclear pleocytosis in nine cases, mixed pleocytosis in two cases and polymorphonuclear pleocytosis in one case. The white cell count (WCC) was within normal limits (<5 nucleated cells/µl) in one case. The mean WCC per µl was 284 (range: 0-1500) in the ST group and 169 (range: 28-700) in the CY group; this difference was not statistically significant (P=0.721). The CSF protein level was elevated (>48mg/dl) in 11/13 dogs. The mean CSF protein level was 148 mg/dl (range: 32-913) in all dogs, 212 mg/dl in the ST group (range: 32-913) and 95 mg/dl in the CY group (range: 34-234); this difference was not statistically significant (P=0.998).

Brain imaging was performed in 13 patients and consisted of 5 MR and 11 CT scans, including 3 control studies in 2 patients. The distribution of lesions (focal/multifocal) based on diagnostic imaging was 2/4 in the ST group and 3/4 in the CY group, although this difference

was not significant (P=0.797). The MRI revealed multifocal lesions in three dogs and a focal lesion in two dogs. All lesions were hyperintense on T2-weighted and post-contrast T1-weighted images. The CT showed multiple lesions in six patients and a single lesion in two dogs. The lesions were iso- to hypodense on the pre-contrast scan and hyperdense on the post-contrast scan.

All but one lesion showed irregular and diffuse margins with variable degrees of the distribution of contrast medium. The one lesion with different imaging characteristics had a homogenous contrast enhancement with sharp margins. Ring enhancement was seen in two patients and meningeal enhancement was detected in eight patients.

Control scans in two patients revealed resolution of the lesion in one patient and a relocation of the lesion from the brain stem to the forebrain in the other patient.

All patients in the ST group were initially treated with immunosuppressive doses of corticosteroids: 5-30mg/kg prednisolone (Solu-Dacortin, Merck) intramuscularly or intravenously or 1mg/kg dexamethasone in one dog (case 6). In the CY group prednisolone was used at the same doses in combination with peroral cyclosporine 3 mg/kg twice a day. Prednisolone therapy was gradually tapered over 2-3 months. It was possible to reduce the administration of cyclosporine after 6 months to 3 mg/kg every other day in four cases (cases 8, 9, 12, and 14). After 9 months cyclosporine therapy was stopped in two dogs (cases 8 and 9).

The median survival time of 620 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 (*Figure 10, Table 6*). Relapse was observed in two cases (cases 9 and 14) after tapered doses of cyclosporine. In these dogs the reintroduction of the original cyclosporine dosage resulted in amelioration of the clinical signs. Two dogs with seizures were additionally treated with 2-5mg/kg peroral phenobarbital twice a day (cases 2, 8, and 9).

In the ST group three dogs (cases 3, 4, and 7) were euthanized shortly after onset because the therapy failed. Four other cases in this group (cases 1, 2, 5, and 6) responded well to the initial therapy, but their relapse resulted in euthanasia (*Table 6*). In the CY group one dog (case 11) died in status epilepticus and one patient was euthanized (case 10) because of seizures. The other five dogs (cases 8, 9, 12, 13, and 14) were still alive upon completion of the study. Two dogs (cases 9 and 14) showed amelioration of clinical signs with a good quality of life. Three other patients (cases 8, 12, and 13) no longer exhibited any clinical signs; therefore, it was possible to taper and subsequently stop the treatment in these dogs, with no recurrence after 350, 300 and 250 days, respectively.

Three dogs (cases 12, 13, and 14) exhibited short episodes of vomitus and diarrhoea during cyclosporine therapy. One dog (case 8) developed pruritus and life-threatening gastrointestinal bleeding, which was treated by a blood transfusion. After cyclosporine treatment was stopped neither the gastrointestinal bleeding nor any clinical signs occurred again.

Cases for which a histopathological examination was performed (Table 6) showed lesions distributed throughout the CNS. The brain stem and cerebrum were most often affected and the cerebellum least frequently affected. In most cases the white matter suffered most severely. Alterations were characterized by perivascular and sometimes leptomeningeal infiltrates, as well as parenchymal granulomas. The dominant cell population was represented by varying numbers of macrophages, lymphocytes and some plasma cells. Sporadic epithelioid cells and neutrophil granulocytes were detected. Perivascular cuffs were a consistent finding in all cases. Granulomatous lesions in the neuropil were commonly present. In some cases, in adjacent areas, neuronal necrosis and/or malacia were also observed. In four cases (cases 1, 2, 3, and 6) diffuse inflammatory infiltration of the parenchyma was present. Neovascularization was also a common feature. The spinal cord, obtained in cases 1, 4, and 6 only, revealed a disseminated mild to severe inflammation of the leptomeninx and the parenchyma. In case 4 the inflammatory infiltrates had spread to the adjacent roots of some spinal nerves and focal myelomalacia could also be observed. The eyes were examined in one case (case 6) only, and showed a moderate chorioiditis and mild meningitis of the nervus opticus. Bacteria, fungi, and protozoan structures werenot detected by special stainings in any of the cases. Furthermore, immunohistochemistry revealed negative results for toxoplasmosis, neosporosis, canine distemper, and rabies (*Table 7*).
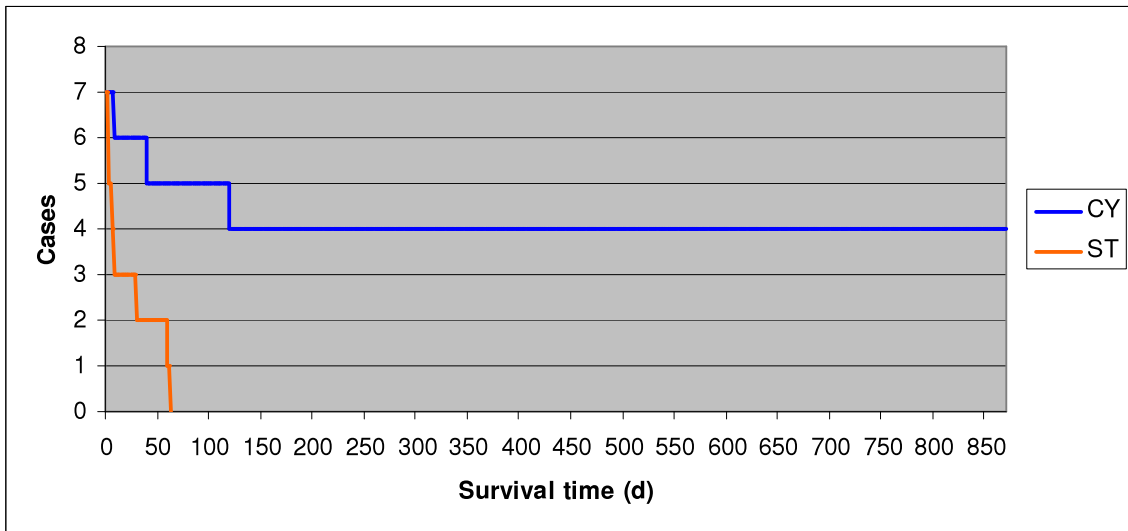
Figure 13.**Survival time in dogs with GME with and without cyclosporinetherapy**

(Graph of Kaplan-Meier)

CY: Treatment with Cyclosporine in combination with corticosteroids ST: treated only by corticosteroids

Table 7. Summary of signalment, clinical, diagnostic findings, therapy, survival time and outcome in dogs with GME.

Case	Breed	Age/Body weight	Sex	Neuroanatomical localisation: focal or multifocal	Blood work	CSF Cell count/µl cell typ	CSF Protein mg/dl	Lesion focal or multifocal by CT/MRI, Histology	Therapy	Survival Time	Outcome
1	Poodle	4/4,2	ME	multifocal	Hypokalaemia	85 – mononucleare	120	MRI: multifocal / Histo: multifocal	Pred	60	Euth
2	Staffordshire Terrier	4/28	MN	multifocal	TP:7.6g/dl	8 – mononucleare	72	MRI: multifocal / Histo: multifocal	Pred, Pheno	63	Euth
3	Lhasa Apso	10/8	FN	focal	WNL	50 – mononucleare	116	MRI: focal / Histo: multifocal	Pred	6	Euth
4	Pinscher	6/15	FN	multifocal	WNL	1500 – mononucleare	913	MRI: focal / Histo: multifocal	Pred	28	Euth
5	French Bulldog	5/12	FN	focal	Hypokalaemia, CK elevation	60 – mononucleare	norm	CT: multifocal / Histo: multifocal	Pred	30	Euth
6	Chihuahua	1/1	FN	multifocal	Hypoglycaemia	NA	NA	MRI/CT: NA / Histo: multifocal	Dexamethason	3	Euth
7	Rottweiler	7/37	ME	focal	WNL	WNL	32	MRI: multifocal / Histo: multifocal	Pred, Pheno	3	Euth
8	Mixed breed	11/18	MN	focal	WNL	230 – mononucleare	114	CT: focal / Histo: NA	Pred, CY, Pheno	870	Alive
9	Rottweiler	5/37	MN	focal	Leucocytosis	28 – mononucleare	34	CT: focal / Histo: NA	Pred, CY, Pheno	760	Alive
10	Mixed breed	10/18	FN	multifocal	Leucocytosis	80 – mixed cells	59	CT: multifocal / Histo: multifocal	Pred, CY	40	Euth
11	Cocker Spaniel	5/13	FN	multifocal	Leucocytosis	55 – mononucleare	234	CT: multifocal / Histo: multifocal	Pred, CY	8	Died
12	Collie	2/23	ME	multifocal	TP: 7.8g/dl	43 – mononucleare	52	CT: multifocal / Histo: NA	Pred, CY	650	Alive
13	Fox terrier	7/14	ME	focal	Leucocytosis	700 – polymorphonucleare	124	CT: multifocal / Histo: NA	Pred, CY	620	Alive
14	Maltese	1/5	ME	focal	WNL	50 mononucleare	50	CT focal / Histo: NA	Pred, CY	120	Euth

NA: not applicable, WNL: within normal limits, Pred: prednisolone, Pheno: phenobarbital, CY: cyclosporine, Euth: euthanized, TP: total protein, ME: male intact, MN: male neutered, FN: female neutered, yellow field: patients/dogsthat underwentcyclosporine therapy, yellow marked field: dogs with cyclosporin therapy

6.3.3. Discussion

To the best of our knowledge this was the first study to evaluate the efficacy of cyclosporine/corticosteroid versus corticosteroid therapy in GME. Cyclosporine is an immunosuppressive drug that mainly inhibits T-helper cells in the G0 or G1 phase of the cell cycle and reduces lymphokine production. The efficacy of cyclosporine has been reported for a variety of immunological disorders in dogs, such as canine atopic dermatitis (Fontaine and Olivry, 2001; Radowicz and Power, 2005), perianal fistulas (Mathews et al., 1997; Hardie et al., 2005), and inflammatory bowel disease (Allenspach et al., 2006) (*Figure 12*).

CSF analysis is an important diagnostic test for GME because the results are frequently abnormal when GME is present (Ryan et al., 2001). However, mild forms of the disease donot always cause the exfoliation of cells into the CSF (Cuddon et al., 2002). Pleocytosis is typically mononuclear with lymphocytes and macrophages, although polymorphonuclear cells are sometimes the main cell types elevated (Bailey and Higgins, 1986; Sarfaty et al., 1986; Munana and Luttgen, 1998). In our study, mononuclear pleocytosis was the most frequent CSF change in 11/13 dogs, which is similar to the results of previous reports. The CSF protein level was elevated in 10/13 cases and the value of 148 mg/dl was comparable to the results of previous studies (Bailey et al., 1986; Munana and Luttgen, 1998).

Advanced diagnostic imaging is important for the ante mortem diagnosis of GME (Speciale et al., 1992; Lamb et al., 2005; Cherubini et al., 2006; Higginbotham et al., 2007).

Cyclosporine was generally well tolerated in our study. This was not surprising because this treatment is frequently used in dogs with different indications. Vomiting, anorexia, and diarrhoea were the most frequently observed adverse effects. Nephro- and hepatotoxicity only occurred in association with extremely high blood levels (>3000 ng/ml) (Plumb, 1999). We observed severe adverse gastrointestinal effects with life-threatening anaemia in one dog only (case 8) after 5 months of CY therapy and full remission. Cyclosporine therapy was stopped in this patient; no more clinical signs were shown by this patient over the following 1-year period. We believe, in agreement with earlier reports, that cimetidine treatment should be considered in patients with CY therapy and gastrointestinal signs (Daigle, 2002). The other six patients generally tolerated cyclosporine quite well. Mild episodic gastrointestinal signs were only present in two patients. 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). Phenobarbital can reduce levels of cyclosporine in the blood and this effect should be considered in patients on anticonvulsant treatment (Plumb, 1999). We used 3mg/kg doses of

CY in the dogs (cases 8 and 9) on phenobarbital therapy, but we did not routinely control the CY or phenobarbital blood levels.

Gingival hyperplasia was not observed in the present study, although it was reported as another adverse effect in cyclosporine-treated dogs (Seibel et al., 1989; Allenspach et al., 2006; Adamo et al., 2007).

The lack of his to pathological 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. The selection was based on similar criteria, including focal/multifocal clinical signs, CSF pleocytosis, CT/MRI changes and the histopathological diagnosis. Since 2004 we have used additional cyclosporine therapy in dogs with a tentative diagnosis of GME without any form of pre-selection.

The second limitation in our study was the restricted number of repeated imaging and CSF analyses, which were only performed in 2 cases (cases 9 and 14). The results suggested inflammatory changes due to the treatment. The third limitation of our study was the low number of cases.

Cyclosporine is a lipophilic peptide with poor blood-brain barrier permeability, but it canbe present in the CNS because GME is a perivascular disease (Bagley et al., 1990). A previous pharmacokinetic study showed the lack of a correlation between cyclosporine blood concentrations and clinical responses in atopic dermatitis, which suggested that individual treatment is more reasonable than the routine monitoring of blood concentrations (Steffan et al., 2004). Cyclosporine treatment has advantages compared to procarbazine 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. Randomized, double-blind studies with higher case numbers should be performed to compare the efficacy of this therapy with other treatment modalities.

6.4. Gabapentin therapy in dogs with cluster seizures

6.4.1. 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. IE was considered when the results of interictal neurological examinations and routine serum biochemistry and haematology were normal. Cerebrospinal fluid analysis, computed tomography (CT, Type CT Pace High Speed, Fa. General Electric, Vienna, Austria) and magnetic resonance imaging (MRI, MR unit 0.23 Tesla, Outlook, Gold Performance®, Philips Medizinische Systeme, Vienna, Austria) had to have shown no underlying cause of the seizures or more than one year had to have passed since the onset of seizures, with no interictal neurological signs. The first seizure had to have occurred between 1to 6years of age. A further criterion was that the dogs had to have experienced at least one CS with and one without the administration of gabapentin.

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.

6.4.2. Results

Out of 54 possible patients with CS only 15 dogs fulfilled all of the criteria. Seven females and eight males were included. The mean age of cluster onset was 7 years old (SD: 3.14). The mean body weight was 23.93 kg (SD: 8.71kg). The breed distribution is shown in *Table 8* below.

Table 8. **Breed distribution in dogs with cluster seizures and gabapentin therapy**

Breed	n	Percentage %
Mixed breed	6	40.0
Irish Setter	2	13.3
Beagle	2	13,3
Border Collie	1	6.7
Cocker Spaniel	1	6.7
Golden Retriever	1	6.7
Podenco Canario	1	6.7
Weimaranian	1	6.7
Total	15	100

Outcome

At the time of completing the manuscript only seven dogs (46.7%) were still alive. The other eight dogs were euthanized due to therapy-resistent seizures.

Long-term therapy

The most frequently used antiepileptic drug in our study for long-term treatment was phenobarbital. Other drugs were also used: potassium bromide (6), levetiracetam (4), clonazepam (2), and zonisamid (1). Four dogs received monotherapy, ten dogs received two drugs, and one dog received three drugs.

Age of seizure onset

The mean age of seizure onset was 2.9 years old. The mean age at the first cluster seizure was 3.6 years; however, six dogs showed cluster seizures from the beginning. The age of onset did not differ between the living and euthanized dogs (P=0.34)

Effect of gabapentin therapy on the number of seizures, the type of seizure, seizure duration, seizure severity, and the general interictal condition during cluster seizures

The overall mean number of seizures prior to the start of the study was estimated by the owners as being 95 (SD: 64). The range was considerably high from 30 to 200 seizures.

The mean number of cluster seizures prior to the study was 22.75 (range: 4–100). Gabapentin treatment was used in different numbers of cluster seizures: mean 8.29 (SD: 7.05). 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. Urination and defecation was not significantly influenced by the use of gabapentin. The patient's quality of life and the owner's quality of life did not significantly differ (P=0.28/P=0.053) between ultimately euthanized and living dogs.

Adverse effect

Lethargy, ataxia, polyphagia, polydipsia and irritation were the most frequently reported adverseeffects(*Table 9*).

Table 9.**Adverse effects**

Adverse effects	N/Responders
Lethargy	13/14
Ataxia	9/13
Irritation	9/14
Polyphagia	9/14
Polyuria	8/13
Vomitus, Anorexia, Pruritus	2/13
Diarrhoea	1/13

6.4.3. Discussion

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%. On the other hand, almost the same number of dogs deteriorated following the use of gabapentin. 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.

In our dogs the rectal application of diazepam by the owner had no satisfactory effects, although no severe side effects occurred either. A further indication was the prophylactic application in the pre-ictal phase. Since a considerable number of owners can recognize predictors of ongoing seizures (Raw u. Gaskell, 1985; Jaggy u. Bernardini, 1998), the findings of our study clearly indicate that gabapentin, if administered before the first seizure occurs, has the most positive effect. Animal models and human studies have shown that gabapentin is effective against partial seizures (Sivenius et al., 1991; McLean et al., 1993; Anhut et al., 1994; Taylor, 1995; Hosford et al., 1997; Mares et al., 1997; Baulac et al., 1998; Chadwick et al., 1998; Taylor et al., 1998). Since it is difficult or even impossible to distinguish exactly between seizure types in animals, we cannot rule out the possibility that our responders were suffering from partial seizures with secondary generalization. Among the non-responders were patients for which the seizures worsened after treatment. In human literature the fact that antiepileptic drugs (AED) can exacerbate seizures (Loiseau, 1998) is well documented. As almost all AEDs reduce the level of alertness, they can thus enhance susceptibility to seizures. This mechanism could be important as our patients were under multiple AED treatments. Furthermore, gabapentin in particular has been reported to exacerbate specific types of seizures, such as absence and myoclonic seizures (Ojemann et al., 1992; Vossler, 1996; Wong et al., 1996; Kocki et al., 2006). Although these seizure types were not considered to play a role in our patients, we cannot rule out that gabapentin will have a negative effect on CS in some dogs. The observed worsening of seizures in four patients may have been a consequence of gabapentin; however, spontaneous fluctuations of the disease also occur.

Both seizure intensity and seizure duration act as important indicators for the owners' evaluation of the effectiveness of antiepileptic therapy. 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).

Twenty-nine percent of owners were of the opinion that their dogs' general interictal condition had considerably improved during a CS when gabapentin was administered. 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. Forty percent of owners reported a considerable cost reduction due to the initiation of gabapentin because of the reduced requirement for hospitalization. To our mind, these findings are positive since most of the dogs included were refractory epileptics. The owners of such severely affected dogs are often very critical judges, although we cannot rule out the possibility that a placebo effect may have played a role in this very subjective evaluation.

Most of the dogs in this study received more than one AED; additional AEDs might have increased not only the treatment costs but also the adverse effects and impairments on the quality of life. This is why the unnecessary use of second therapy (bitherapy) should be avoided. Bitherapy should only be considered if monotherapy does not lead to the required effect; such patients are therapy-resistant epileptic dogs. In such patients, despite adequate first AED serum concentrations, the occurrence of CS and status epilepticus cannot be avoided. A previous study on dogs suffering from either status epilepticus or CS measured phenobarbital (the first AED) concentrations at 6 to 12-month intervals and no owner reportedany alteration in AED application prior to this emergency situation (Saito et al., 2001).

In 40% of the dogs included in our study the disease had started with the occurrence of CS. In the literature, only a few breeds – German shepherds, Border collies and Dalmatians (Taylor, 2006) – are known to show CS from the outset. In our study, affected dogs were either other breeds or mixed-breed dogs. It is possible that dogs in which the disease starts with CS are more likely to be difficult to treat.

Since almost all dogs were receiving phenobarbital as a long-term medication it is possible that the side effects observed after the application of gabapentin could, at least to a certain extent, be due to a summation effect. Most of the side effects reported in this study also occur during treatment with phenobarbital alone. However, it should be noted that it is almost

impossible to differentiate between post-ictal signs and side effects in CS since lethargy, ataxia, polyphagia, polydipsia and agitation are the usual post-ictal phenomena. Agitation as an adverse effect was reported in seven dogs after the application of gabapentin. Since this side effect cannot definitively be attributed to phenobarbital, it might represent a gabapentin-specific side effect or a summative effect.

The potential need to give the drug TID can make it difficult for some owners to reliably administer gabapentin. Although a recently tested sustained-release formulation of gabapentin in beagles showed excellent in vitro results (gabapentin was released for 12 h), it showed similar in vitro pharmacokinetic parameters to the immediate-release tablet (Rhee et al., 2008). In contrast, an extended-release formulation of gabapentin has been found to be effective in human patients with painful diabetic peripheral neuropathy (Sandercock et al., 2009).

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. A recent study that investigated the placebo effect in canine epilepsy found that owners reported a reduction in seizure frequency in approximately 80% of dogs in the placebo group. Furthermore, almost two thirds of dogs would have been classified as responders (Munana et al., 2010). The assessment of antiepileptic treatment efficacy is not easy, even in human medicine, since the effects are mainly based on patient reports and natural fluctuations in disease also have to be considered. In order to overcome this inherent problem, The International League Against Epilepsy (ILAE) developed evidence-based guidelines and the quality of evidence was classified into four classes (ILAE Commission on Antiepileptic Drugs, 1998). Class I, II, and III studies only include randomized trials that were not carried out on pet animals. Only expert opinions, case reports and short-term open-label studies have been published on treatment of canine epilepsy, which belong – according to human evaluation – to the weakest class (IV) of evidence.

Considering these aforementioned limitations, it seems that add-on at-home gabapentin is useful in the treatment of CS after the identification of responders. We found a statistically non-significant tendency for dogs that had experienced more seizures per CS prior to the use of gabapentin to be more likely to be classified as responders (P=0.43); furthermore, two

thirds of dogs in which seizures had mostly occurred during the day showed a reduction in the number of seizures in a CS. 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.

7. 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.

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9. The candidate's publications related to the present dissertation

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

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11. Acknowledgement