ANALYSIS AND EVALUATION OF CEREBRAL BIOELECTRIC BEHAVIOR IN DOGS WITH EPILEPSY THROUGH ELECTROENCEPHALOGRAM

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Abstract
The goal of the current study was to evaluate electrophysiological status of primary (EP) and secondary epilepsy (ES) regarding clinical and neurological findings. Other purpose was to analyze the interictal, intraictal and postictal parameters that could help to differentiate between the two types of epilepsy and a description of interictal epileptiform discharges (EDs) for a better understanding of canine epilepsy.

Methods - 93 dogs with histories of seizures were referred to the Clinic for Internal Medicine from Faculty of Veterinary Medicine, Iași, during the study period. Electrical potentials acquisition was performed using the electroencephalograph Neurofax S, MEB 9400K Nihon Kohden. Before the test, all dogs underwent general anesthesia with medetomidine hydrochloride (Domitor, Pfizer) 30 µg/kg inj. i.m. Stainless steel needle electrodes were subcutaneously placed, in an 8 channel bipolar montage, according to the model Redding and Knecht (1984).

Results – In the present study, the neurological examination was suggestive of ES in 70% of cases in ES group, but in EP group clinical and neurological examination were typically unremarkable and postictal behavioural changes were occasionally observed. Interictal electroencephalographic examination of dogs with epilepsy often showed EDs. We found EEG changes that could be considered EDs in 88.88% from dogs with primary epilepsy and 100% in those with secondary epilepsy. The EEG abnormalities identified were polispikes, spikes, sharp waves and spikes-waves complexes. As the EDs in our epileptic dogs, were often detected, the diagnostic value of the EEG in the work-up appeared to be very high.

Conclusion – The clinical and neurological findings are important indicators, but not enough to distinguish between ES and EP. EEG in epileptic dogs seems to have a high sensitivity for detecting EDs in this clinical setting.

Key words: electroencephalogram, electrophysiology, epilepsy, dog.

INTRODUCTION

Epilepsy is a chronic brain disease, of varied etiology, defined by the presence of the seizures of definite epileptic nature and by evolutionary criterion, made of their tendencies to repeat in absence of triggering factors, known at variable intervals. We must mention that epilepsy is not synonymous to epileptic seizures that can represent the symptom of a general metabolic neurological local condition.

Electroencephalography is the most specific method in order to define the epileptogenic cortex. It supports the clinic diagnosis of epilepsy, having a sensitivity of approximately 80-90% in serial records and a specificity with false positive rates of 0.2-3.5% in healthy subjects (Walcyak and Jazakar, 1998), although they depend on varied factors like: age, recording mode, activation procedures (sleep, intermittent light stimulation, hyperventilation), etc.

Epilepsy is the field in which, as Jasper presented at the Electroencephalography Congress in Paris (1949), electroencephalographic method found the most important practical and theoretical application. Introduced by Berger a clinical study of epilepsy, it serves to the scientific foundation of the modern concepts on epilepsy as a disease or a syndrome. The data proved by electroencephalography mostly lead to the elucidation of the multiple aspects linked to etiology, physiopathology,
classification and treatment of epilepsy (Foldvary et al., 2001). The researches regarding the epileptic disease led to the conclusion that, no matter of etiology, epilepsy is a cerebropathy that clinically exteriorizes by a very wide range of manifestations, mostly paroxysmal (Aminoff, 2005).

The study objectives consisted in analyzing the electroencephalographic expression of the nervous system activity in dogs with epilepsy:
- by assessing the electrical neurophysiological status of the patients with idiopathic epilepsy compared to those with symptomatic/reactive epilepsy regarding age, gender, breed, clinical and neurological signs;
- analysis of the ictal, intraictal and postictal electroencephalographic parameters, with a significant role in differentiating the two types of epilepsy;
- description of epileptiform discharges.

MATERIALS AND METHODS

93 dogs with history of epileptic seizures were examined, presented in Internal Medicine Clinic of the Faculty of Veterinary Medicine during the study period. In 31 cases, the lack of a thorough examination or incomplete information led to their exclusion. Every studied patient (62) followed a clinical assessment. The standard neurological examination was performed to all patients, in conditions of thermal and mental comfort, after a period of accommodation with the examiner. Medical and family history were assessed. The neurological exam, in all patients, was preceded by hematological and biochemical blood analyze (AST, ALT, PAL, GGT, urea, creatinine, Ca, FT4, TSH, bile acids). The neurological examination consisted of assessing the gait, the posture reactions, the spinal and cranial nerves reflexes. In some patients, the neurological examination could not be performed due to the fact that they were in epilepticus status or under the influence of stabilizing antiepileptic medication. The examination was classified as being normal, symmetrical abnormal (the anomalies were located on both sides of the patient’s body) or asymmetrical abnormal (the anomalies were located on one side of the body only). Also, changes of the neurological examination were noticed, determined by anticonvulsant drugs. It has been demonstrated that these can imprint, in the first 10-15 days of use, transitory changes of the neurological exam, such as tables or sedation (Chang et al., 2006).

In some patients, the diagnosis included the abdominal ultrasound scanning (n = 41), transfontanelar ultrasound scanning (n = 7), chest X-ray (n = 35). The anamnestic data were obtained from the owners. From the ultrasound scanned patients, 27 were diagnosed with primary epilepsy (idiopathic) and 35 with secondary epilepsy (symptomatic/reactive).

The idiopathic epilepsy (IE) diagnosis was established when the results of hematological and biochemical analyses were in physiological limits, and subsequent to MRI/CT and LCR examinations, no changes were detected. IE prevalence is estimated as being between 0.5-5 % (Berendt, 2004) in dogs and approximately 0.5 % in cats (Schwartz-Porsche, 1994).

Symptomatic epilepsy is diagnosed when the seizures are determined by lesions in the brain structures (March, 1998). The intracranial causes of the epileptic seizures can be given by: congenital structural cerebral, central nervous system, infectious, inflammatory or degenerative diseases, tumors and traumatisms (Podell, 2004).

Reactive epilepsy can be caused by different toxic substances, by almost any metabolism perturbation (Brauer et al., 2011), such as hypoglycemia, hypoxia, hypersmolarity, disorders of the electrolytic balance, hepatic or renal disorders (O Brien, 1998).

The epileptic patients in our study belonged to the following breeds: Pekingese, German Sheppard, Poodle, Bichon, Tosa Inu, Basset Hound, Saint Bernard, common breed, Akita Innu, Yorkshire Terrier, Cocker, Labrador, Dalmatian, Pug, Chihuahua, Boxer and Beagle.

In 56 of the 62 patients, epilepsy manifested as generalized form. An epileptic attack was considered generalized, when the motor activity included the whole body. The partial epileptic attack was met in 3 patients only.
This is the clinical expression of a well localized brain site, which does not have the capacity to generalize itself. In a study on 70 dogs, regarding the characteristics and the symptomatology of the partial epilepsy in dogs, Berendt (2004) showed that the motor phenomena (localized in an area of the body) manifested in 69% of the patients are followed by those with paroxysmal and behavioral symptomatology (vocalizations, aggressiveness and fear attacks). The epileptic status outbreaks were met in 2 German Sheppard’s (male, 4 months and female, 6 years) and a common breed dog (female, 2.5 years). The epileptic status does not correspond to a unique homogeneous epileptic pattern, but to any of the seizure types, when they last for a long period of time, or appear at very short intervals.

From the patients with idiopathic epilepsy, 18 were males (non-castrated) and 9 females. The age of the dogs with idiopathic epilepsy varied between 3 months - 12 years, and their weight was between 1.5 - 47 kg.

From the patients diagnosed with secondary epilepsy, 11 were males and 24 females. The age of the dogs with secondary epilepsy varied between 3 weeks - 14 years, and their weight was between 1-32 kg.

In order to uniform the batches regarding the subjects’ fatigue degree, the tests were performed at the same moment of the day and in identical environmental conditions. The electroencephalogram was performed under general anesthesia, using medetomidine (Domitor, Pfizer) in a dosage of 0.03 mg/kg administered intramuscularly, in order to eliminate the artifacts triggered by the muscular contractions. After the anesthesia is installed, that is when the animal is no longer able to perform voluntary moves (in about 10-20 minutes after administration), the patients were put in sternal-abdominal decubitus.

The acquisition of the biopotentials was made with Neurofax electroencephalograph (Nihon Kohden) for 30 minutes. Needle electrodes were introduced subcutaneously according to Redding and Knecht model (1984), using five electrodes: two frontals (F3, F4), one central (Cz) and two occipitals (O1, O2) used in bipolar montage, the reference electrode being placed on the nasal bone. Electrodes’ nomenclature is similar to the one described by 10-20 system in human medicine (Aminoff, 2005; Nordli et al., 2011).

The parameters used for each electroencephalographic recording were: sensitivity: 70 μV, time constant: 0.3 seconds, filter pass – down of 70Hz, filter pass – up 30 Hz and electrode impedance < 10Ω.

The visual analysis of the electroencephalographic tracks presumed the recording of the electroencephalographic pattern (any EEG characteristic activity), marking the background activity (any EEG activity that represents the frame where a normal or abnormal pattern appears), all the paroxysmal activities (spike, poly-spikes, sharp slow waves, wave-spike complexes, bursts of slow waves and spikes), as well as possible artifacts.

RESULTS AND DISCUSSIONS

In our study, 27 from the 62 dogs (43.54%), electroencephalographically investigated, were diagnosed with idiopathic epilepsy (IE). 35 (56.46 %) manifested epileptiform type seizures due to unknown causes. Croft (1965) recorded a balance higher than IE, 64 % - 167/260 of dogs; Jaggy and Bernardini (1998) referred only 53% (125/236) IE of the investigated population. Values close to our study were referred by Pakozdy (2012), when, from 240 investigated dogs, only 115 (48%) had IE. A cause of these variations in determining the percentage of IE is the continuous development and wide usage of the diagnostic imagistic patterns, especially CT and MRI.

From IE cases, the neurological examination was normal in 77.77 % of the patients (21 cases). Symmetrical changes were recorded in 18.51 % (5 cases), and asymmetrical ones in 3.70 %. In ES, 42.9 % of the cases, showed a normal neurological exam, the symmetrical neurological changes being recorded in 42.85% (15/35) of the dogs, and the asymmetrical ones in 14.28 % (5/35) only.

In this study, of the 27 dogs diagnosed with idiopathic epilepsy, 23 were pure breeds and only 4 were half-breed. Sheppard German and Bichon breeds were the most frequent suffering of IE, followed by patients from
Labrador, Golden Retriever, Pekinese and Cocker breeds, while Dalmatian, Akita Innu, Tosa Inu, Basset Hound, Saint Bernard, Golden Retriever and Yorkshire breeds were represented by one individual each. The results were similar to those in the specialty literature, obtained in time for pure breeds, by distinguishing familiar predispositions and other hereditary patterns on which the disease is based, described for Beagle, Belgian Tervueren and Sheepdog (Oberbauer et al., 2003), Keeshound (Hall and Wallace, 1996), Vizsla (Patterson et al., 2003), Labrador (Berendt et al., 2002), Golden Retriever (Srenk and Jaggy, 1996), Bernese Mountain Dog (Kathmann et al., 1999), English Springer Spaniel (Patterson et al., 2005), Irish Wolfhound (Casal et al., 2006) and for common breeds (Jaggy and Bernardini, 1998).

Unlike IE, the number of the half-breed patients grew to 11 in case of ES/ER, followed by dogs of Pekinese (n = 7), German Sheppard (n = 5), Bichon (n = 4) and Boxer (n = 2) breeds.

Regarding the sex of the patients, in our study, there were more males than females in the group of the dogs with IE (18M/9F) and more females than males in the group of the dogs with ES/ER (11M/24F), compared to previous studies, made by Jaggy and Bernardini (1998), which affirm that males and females were in approximately equal ratios. Similar results with those obtained by us were showed by Pakozdy (2012) when from 115 dogs with IE, 69 were males (69M/46F).

The clinical and neurological examinations are important indicators that help us make the difference between IE and ES/ER. In our study, the clinical and neurological examination was suggestive for ES/ER in 70% of the cases in the group of patients with ES/ER, while in the group of patients with IE, the clinical and neurological examination was non-specific, and the changes of the postictal behavior were rarely noticed. Like Bagley (1999) and Pakozdy (2012), in many cases of ES/ER the clinical status was unclear when the patients presented for the first time, especially in those with intracranial disorders.

**Interictal electroencephalogram**

The visual analysis of the electroencephalographic tracks during the intercritical period showed a physiological background activity in 8/27 patients (29.62%) with IE. In human medicine, approximately 20% of the patients with clinically verified epileptic seizures do not present any electogenesis disorder, the anomalies appearing only in the moments the out breaks set off (Dumitru, 2002). Intercritical EEG tracts remained completely the same in the case of epilepsy with rare seizures only. In contrast with these were those where background EEG was disrupted 10/27 cases (37.03%), from the amplitude point of view or only of the basic frequency rhythms. There were also EEG tracks slightly modified, 6/27 (22.22%), by decrease or increase of the brain rhythms, permanently associated to the important increase of the amplitude. In serious cases of epilepsy – 3 cases (11.11%), EEG showed a profoundly changed and uneven bioelectrical activity; imitating the described classical aspect under the name of hypsarrhythmia (Nordli et al., 2011).

At the visual analysis of the tracks, in our study, the background activity was characterized by high amplitudes and low frequencies, probably as a consequence of using medetomidine, corresponding to the study developed by Short et al., (1992), which describe the inhibitor effect of the anesthetics from agonist alfa-2-adrenoeceptor group upon increased frequencies.

This background activity, in 95% of the study patients, was dominated by the presence of the theta and delta rhythms, while alpha and beta waves were less met. These results are similar with those described by Brauer et al. (2011) and Pakozdy (2012), using propofol as anesthetic protocol and de Jeserevics and col. (2007) who used medetomidine as anesthetic. The suppression of alpha and beta waves was also described after the anesthesia with medetomidine, being noticed after using other anesthetics like xilazine (Pellegrino and Sica, 2004) or a combination of propofol with medetomidine (Srenk and Jaggy, 1996).

The intercritical background showed a high instability and diversity from the electroencephalographic aspects, as there
were many discordances between the electric and clinical aspect of the epilepsy. In incipient cases and onset of epilepsy, the EEG alterations were discrete, resuming to a couple of overvaulted peaks and ample lent theta waves; appeared on a normal background track (figure 1).

When epilepsy had a longer evolution, the background activity showed an intersection of slow waves with abnormally frequent waves; rich in epileptiform interictal discharges (DIE) like: fast spike, slow waves, poly-spike, typical or atypical spike-wave complex.

Figure 1. Electroencephalogram of a dog, Bichon, of 2 years old and 5 month with IE. Normally dominant background activity with rapid peaks recorded on all derivations and ample rare slow theta waves

The spike-wave complexes (figure 2) were met in this study only in one patient. In human medicine, these occupy the largest share in interictal discharges, over 50 % in IE (Dumitru, 2002). These were hypervolted (values between 230-550 µV), bilateral symmetric and synchronic, during the entire encephalographic record, on a hypovolted background activity. Studies of Mendez (2006) showed the central and median line origin, probably in the thalamic intralaminar system of the peak-wave complexes. Dumitru (2002), in human medicine, showed that the spike-wave complex aspect is linked to a certain degree of immaturity of the brain, because this EEG aspect appears with a higher incidence before puberty. Hyper-synchronous slow waves (figure 3) of 1-2 cycles/second (c/s) and ample of 100-200 µV appeared in short or continuous bursts only in generalized form of epilepsy. They are the expression of the neuronal self-maintained hyper-synchronization processes, with different synaptic delays (Dumitru, 2002).
EEG tracks marked by typical hypsarrythmia (figure 4) were recorded in 3 cases (11.11 %), made of a chaotic succession of slow waves and peaks, of very high amplitude embedded by peaks and slow waves in abrupt decline, multi-focal, asynchronous. The basic rhythm was replaced by slow waves with a very varied aspect, with a theta and delta frequency of 1.5-2 c/s, up to polymorph elements with „jigsaw” and „abrupt walls” waves, the spikes combining with slow waves and producing more or less typical aspects, of spike-waves of very high amplitude (between 300-600 μV). The spikes varied from one moment to the other, from the localization and duration point of view. The high amplitude of the slow waves, spikes and wave-spikes represent the essential character of hypsarrythmia. In human medicine, from the electrical point of view, it would represent a severe and general suffering of an immature brain, but in these studies, it was met in adult patients with severe epilepsy → status epilepticus.

The paroxysmal activity was recorded in 24 of 27 dogs with idiopathic epilepsy (88.88 %) and in all the patients with symptomatic/reactive epilepsy. This was made of: fast spikes and slow waves and spike-wave complexes. The most frequent paroxysms were represented by poly-spikes and bursts of slow waves and rapid spikes met in 17 from the 27 patients with IE, followed by sharp waves (16 cases). The results are similar with those obtained in time in other study literature (Pakozdy, 2012), which affirms that the peaks are the basic element of the epileptiform activity on the electroencephalogram.

The highest prevalence of the interictal discharges was recorded in patients under one year old and in those of 3-5 years, category. We consider that these results were based on IE affinity to manifest itself between 6 months and 5 years (Oliver et al., 1997, Armasu et al., 2013) or between 1-5 years (Thomas, 2003).

The presence of the DEI varies on a wide range in veterinary medicine compared to the human one. Thus, if in the case of human patients with epilepsy at approximately 20-50 % characteristic EEG discharges are recorded from the first electro-encephalographic test (Glick, 2002), the results of the EEG investigations regarding the DIE in epileptic dogs are between 12– 100 % (Pakozdy, 2012; Morita et al., 2002).
The high variability of the number of epileptic dogs that present specific EEG changes could be because of using different acquisition protocols for bioelectrical and anesthetic protocols and varied recording time. This variability regarding the DIE is based on using a different EEG wave acquisition protocol, as well as on the varied number of electrodes and the different recording time. It is known that using a higher number of electrodes that cover a wider brain area increases the chances to obtain an interictal activity, characteristic to epilepsy. Pellegrino and Sica (2004) describe a standardized protocol of the EEG examination in dogs, using 12 electrodes, 2 of them inserted in the temporal muscle, in direct contact with the cranium. In this study, 5 electrodes, or the Redding and Knecht (1984) model, was used. We chose this protocol to obtain the potentials, as the dimensions of the head varied between breeds (Chihuahua → Saint Bernard) and age (3 weeks – 14 years) and there was no prejudice upon the temporal muscle like in the case of using the previous model. In this study, a minimum recording time of 30 minutes was used, similar to those described by Pellegrino and Sica (2004), considered enough to detect the epileptic activity, if present.

Another cause that induces a variability of the DIE is determined by the fact that some anesthetic substances intensify the appearance of the epileptic activity, and others have anti-epileptic effects, inhibiting the events characteristic to epilepsy (Chandler, 2006).

In this study, medetomidina (as sole anesthetic) was used to insensibilize the dogs, an alfa-2-adrenoceptor agonist with sedative, analgesic and relaxing properties for the muscle, used on a large scale in veterinary medicine as tranquilizing or pre-anesthesia medicine (Clarke, 1997). Medetomidine, used in epileptic dogs for recording and quantitative EEG analysis (q EEG) was described by Itamoto et al. (2001) as sole anesthetic and by Short and col. (1992) in combination to halothane and ketamine. Jaggy and Bernardini (1998) describe a protocol where medetomidine is administered together with propofol. This, administered in a dose of 50 mg/kg, gave in all studied patients a good level of sedation in almost 15-20 minutes. Although, there were always divergences regarding the pro or anti convulsive properties of the medetomidine (Miyazaki et al., 1999), it is considered that administered as a sole anesthetic it has no proepileptic activity (Jeserevics et al., 2007). The anesthetic and relaxing properties, the easy administration, the existence of an antidote as well as the results obtained by a study in human patients demonstrating that medetomidine intensifies the detection of the paroxysmal epileptiform activity on EEG examination (Flink et al., 2002) , make medetomidine the election anesthetic for EEG recordings in dog.

Regarding the used anesthetic dose, its variations can lead to an accentuation or inhibition effort of the ictal activity seen on EEG. In human medicine, using small doses of propofol led to the increase of the ictal
activity, by intensifying the peaks on EEG (Leijten, 2001). In time, the studies show that propofol was the most used anesthetic for EEG recordings, alone (Bergamasco et al., 2003) or in combination with medetomidine (Jaggy and Bernardini, 1998). It was demonstrated that in intravenous perfusions, 0.5-0.9 mg/kg, it significantly increases the absolute prevalence, but not the relative one of the slow delta rhythm on canine EEG towards the end of the recording period of 20 minutes (Bergamasco et al., 2003). Hufnagel et al. (1990) showed that a dose of 70 mg of propofol changes the activity of the human brain towards a diffuse delta and theta activity or polyphase rhythms made of delta and alpha waves or superposed beta waves, together with the previous studies developed after its use in human medicine, with precaution on epileptic patients.

Jaggy and Bernardini (1998) reported that approximately 86 % of the dogs with idiopathic epilepsy develop paroxysmal discharges on EEG, under the anesthesia with medetomidine of 0.025 mg/kg and propofol 2 mg/kg. Using higher doses of propofol, 2-6mg/kg, Pákozdy (2012) noticed these manifestations in only 12.5% of the epileptic dogs. These results confirm that propofol, in man and dog, used in small doses, triggers the increase of the epileptical activity and, together with the increase of the dose, the attenuation effect of the epileptical activity appears, noticed on electroencephalography, but not an isoelectrical trace, not even at the maximum dose of 140 mg/kg (Hufnagel et al., 1990). Thus, we can conclude that the pro or anticonvulsive effects of the propofol depend on its concentration in the brain level. In the case of the anesthesia with medetomidine, there were no changes described in the EEG track, changes that depend on the administered dose up till present.

**Interparoxysmal electroencephalogram**

The electrical crisis suddenly appeared on all derivations, then intensified by neuronal recruiting phenomenon and in 2-3 seconds the EEG anomalies spread in all brain areas, as DIE became bilateral synchronous. This aspect corresponds to the moment in which the activity of the entire brain adapted to the rhythm developed by the epileptic site (Dumitru, 2002). The access was characterized by a succession of peaks with a frequency of 15-35 cycles/second, which increased progressively in amplitude, reaching values of up to 250-500 µV (figure 5).

![Figure 5. EEG during an epileptic seizure recorded in a German Sheppard of 7 years old](image)

After these ample and rapid anomalies, which correspond to the tonic phase of the seizure, the morphology of the electrical paroxysms changed. In a couple of seconds, the rhythm of epileptic discharges decreased to 3-5 cycles/second (postparoxysmal phase).

**Postictal electroencephalogram**

Immediately after seizure, the electroencephalogram was characterized by a
much flattened aspect of the tracks, almost isoelectric. Upon this aspect of electrical silence, sometimes, for intervals of 10-15 seconds, short bursts of peaks (figure 6) or degraded spike-wave complexes appeared, clinically followed each time by generalized twinges or synchronous myoclonic bursts in the extremities.

CONCLUSIONS

The idiopathic epilepsy represents the most frequent etiology of convulsions in dogs and is responsible for almost half of the investigated cases (43.56 %) in this study. Secondary and reactive epilepsy were mostly established by uremic encephalopathy (12.9 %) and hydrocephalus (11.29 %). Clinical status and neurological examination are not enough to differentiate the idiopathic epilepsy of the symptomatic or reactive one. Indications as epileptic status, cluster, partial seizures, vocalizations during a seizure and altering the interictal neurological status are more predictors of symptomatic epilepsy; whilst the apparition of the first seizures, between 1-5 years of age or during the pause period, leads to the diagnosis of idiopathic epilepsy.

Examining the cerebral behavior of the epileptic patients during the interictal period under general anesthesia with medetomidine showed epileptiform discharges of 88.88 % in patients with IE and of 100 % in those with ES/ER. The most frequent paroxysms were represented by the poly-spikes and the bursts of slow waves and fast spikes met in 17 of the 27 patients with IE, followed by sharp waves (16 cases).

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REFERENCES


