ABSTRACT

The Doctorate thesis named ***"Clinical and therapeutic research in epileptic syndromes of dogs"*** , was motivated first, by the little research regarding this condition in Romania, it's practical purpose being to establish the incidence of epileptic syndromes in dogs, in relation to different variation factors (breed, age, sex), to investigate the clinical and imaging characteristics of the epileptic syndrome of dogs, to establish the diagnostic value of the cerebrospinal fluid examination in dogs with epileptic syndrome and to quantify the impact of long term therapy with classic anticonvulsants (Phenobarbital) as a single drug and to identify the rate of diagnostic success and side effects of a combination of anticonvulsants (Phenobarbital + Gabapentin) in the therapy of epilepsy that didn't respond to single drug medication.

The thesis has 249 pages and is composed, according to legislation, of two main parts: the first, named **"The actual state of knowledge"** has 61 pages, 12 tables and 1 figures, and the second part, **"Personal contributions**" is 166 pages long , and has 38 tables, 29 diagrams and 46 figure for a better illustration of the content.

The first part is made up of five chapters that briefly show information from literature regarding the subject of the thesis which have been used for interpreting and comparing the data gathered in the second part.

The first chapter, named **"The etiology of canine epileptic syndrome"** shows data regarding the factors involved in starting an epileptic seizure. Genetic, viral, bacterial, parasitic, metabolic and endocrine factors that have been incriminated as the most common causes of epileptic syndromes in dogs are briefly presented.

The 5 sub-chapters of chapter 2 named **"Pathophysiological aspects of epilepsy in dogs"** show data from literature about the existent theories regarding the genesis of epileptic seizures. At the same time, it presents the biophysical-electrographic changes of epileptic neural aggregates, the pathophysiologic mechanisms of each type of epileptic seizure and molecular, neuro-chemical aspects and their implication in the genesis of epilepsy. At last, it describes the pathophysiological substrate of post ictal deficits.

Chapter 3 named **"Classification of epilepsy in dogs"** describes the premises of clinical grouping of epileptic syndromes according to their semiologic characteristics. All through the chapter, the 5 steps that must be taken in order to define the clinical type of epileptic seizures are briefly presented.

Chapter 4 describes the procedures and logic succession of steps to be taken for the **"Neurodiagnosis of epilepsy".**

Chapter 5 named "**The therapy of epileptic syndromes in dogs**" shows in its 5 sub-chapters the therapeutic strategies in the epileptic syndrome of dogs.

Part II, "Personal contributions", has 9 chapters that present and discuss the results of the investigations.

Chapter 6 named **"Research regarding the incidence of the epileptic syndrome in dogs"** aimed to establish the incidence of the epileptic syndrome (idiopathic and secondary, symptomatic) within the canine population taken into consideration. At the same time, by analyzing the data of the different groups of individuals (grouped according to age, sex) we aimed to establish the risk factors involved in the development of epileptic syndromes.

Researches were made over a period of 4 years, beginning on January 1 2004 until December 31, 2007 and included 3210 dogs of different age, breed and sex presented to consultation to the Internal Diseases Clinic of the Faculty of Veterinary Medicine in Iaşi. Only those dogs that showed convulsive fits of the epileptic type were selected for the study.

After the investigations we noticed that: in relation to the total number of dogs examined, the prevalence of the canine epileptic syndrome is 4,92% with a number of 158 patients. From the total of patients diagnosed with epilepsy, 62 (39,24%) had idiopathic epilepsy and 96 (60,76%), symptomatic epilepsy.

The symptomatic epilepsies diagnosed included 41,77% (66 patients) with inflammatory infectious epilepsy, 15,82 % (25 patients) with metabolic epilepsy and 3,16 % (5 patients) with traumatic epilepsy.

Regarding the age of the first paroxysmal events of the patients taken into account, we concluded that most patients with idiopathic epilepsy were aged between 1-4 years, represented by 42 dogs, that 67,75% of the patients with idiopathic epilepsy diagnosed in the four years. They were followed by the group of under 1 year olds, represented by 12 patients (that is 19,35% of all idiopathic epileptics). For a smaller number of cases, idiopathic epilepsy was diagnosed in patients aged between 4-7 years (6 patients representing 9,68%) and in those older than 7 years (2 dogs, respectively 3,22%).

For the dogs with infectious inflammatory epilepsy the distribution of cases shows a maximum for patients aged less than a year old (35 dogs - 53,03%) followed by the age group 1-4 years represented by 23 dogs (34,85%).

A discreet predisposition of sex (up to 70% for the males) in the development of idiopathic epilepsy in dogs was shown by certain studies (PODELL M. et al. 1995; BERENDT M., 1999). In the group of patients we studied, the sex predisposition was of 83,87%. Idiopathic epilepsy was diagnosed in 10 females (16,13%).

By analyzing the distribution of cases with idiopathic epilepsy according to breed we noticed a higher frequency in Labradors (19,35%), German Shepherds and Golden Retrievers with a frequency of 14,51% each, our results being similar to those in literature (PODELL M, 2004; GHERGARIU S., 2000). We signal the diagnosis of idiopathic epilepsy in a Mioritic Shepherd Dog that showed severe cerebral atrophy on imaging exams.

Chapter 7 named **"Clinical aspects in epileptic syndromes of dogs"** has 2 sub-chapters that show the clinical manifestations of idiopathic as well as symptomatic epilepsy.

For idiopathic epilepsy, special care was given to the semiology of preictal phenomena. The prodrome and the aura were analyzed in an attempt to classify epileptic seizures ant to establish a therapy personalized for each individual.

The frequency of convulsive seizures type grand mal was of 93,54% (58 dogs). Generalized seizures type grand mal were characterized by the presence of all stages: tonic seizures followed by clonic contractions and ended by the stertor phase.

Post ictal phenomena persisted for minutes up to days and were characterized by a decrease of the reaction time for the photo-motor and defense reflexes and different degrees of proprioceptive deficit (both in the front and back legs) associated to central motor neuron symptoms (cortical origin ataxia).

Following the clinical aspects of the "grand mal" type epilepsy observations are described regarding the "petit mal" type epilepsy and partial epileptic seizures. The next sub-chapter presents clinical observations and para clinical aspects seen in patients with symptomatic epilepsy caused by inflammatory infectious encephalopathies, hepatic cerebral syndrome, renal failure and hypocalcaemia.

Chapter 8 named **"The cerebrospinal fluid examination in the epileptic syndrome of dogs"** aims to establish a normal profile of the characteristics of cerebrospinal fluid (in what concerns its biochemistry and cytology), to be a base for further investigations.

Next, we present the data obtained for post- traumatic and inflammatory infectious epilepsy.

The data we obtained for post traumatic epilepsy showed higher values for lactate (22,93 mg/dl), phosphorus (8,714 mg/dl), a moderate increase of protein concentration (45 mg/dl) and a value of aspartate amino transferase (ASAT) of 150 UI/l.

In inflammatory – infectious diseases, the protein concentration is clearly higher than the normal upper limit (25-40 mg/dl) reaching extreme values of over 1 g/dl. The quantity of albumins and globulins can give clues as for the origin of the increase in protein concentration: a clear increase in the concentration of albumins, with a relation albumin/globulin >1 suggests a pathologic process that has altered the blood-brain barrier, while a relation albumin/globulin <1 shows an increase production of globulins by intrathecal synthesis.

Chapter 9 named **"Study regarding the relevance of computer tomography (CT) in the diagnosis of epilepsy"** describes the results obtained after computer tomography examination of 14 patients diagnosed previously with idiopathic epilepsy. The results were normal for 9 dogs: the cerebral parenchyma showed no changes as to symmetry and cerebral topography, having a radio –attenuation between 25 and 42 HU, with a symmetric ventricular system containing liquid with a radio- attenuation of 6-8 HU.

In the case of the other 5 patients examined we identified morphological changes with an uncertain implication in epileptic seizures. Two patients showed internal hydrocephalus and 3 others showed different degrees of cerebral atrophy.

Hydrocephalus was characterized by a clear asymmetry of lateral ventricles. At the same time, the second patient (male, German Dog) also showed a discrete dilation of the mesencephalic aqueduct. For both patients, the examination of radio-attenuation in the cerebral ventricles showed values between 0 and 9 HU, considered normal. Examining the density of cerebral parenchyma showed values between 22 and 42 HU. In this case, the presence of ventricular asymmetry can be considered "para-physiological" (situation also seen in human medicine) but can also be a sign of a previous process that determined the obstruction of the pathways for the elimination of CSF from the lateral ventricles.

In the case of the other 3 patients, the presence of cerebral atrophy was signaled by the presence of cerebrospinal fluid gaps within the cerebral cortex, with a radio-attenuation between 2 and 4 HU and size of up to 2-3 mm.

Interesting aspects were seen in 2 dogs. One 3 years old, male Maltese which had had epileptic seizures for 2 years previous to consultation, and receiving medication with Phenobarbital (4 mg/kg/12 h), showed, on computer tomography, a surprisingly high degree of cerebral atrophy compared to the age of the patient. In the brain stem and cerebellum, the CSF gaps were particularly evident.

The same situation was seen in a 1 year old Mioritic Shepherd dog which had epileptic seizures previous to consultation (during the last 2 months), with different degrees of loss of consciousness and attacks of aggressiveness. The CT examination showed evident spaces between gyruses in the frontal lobes. This suggests the presence of a clear atrophy of the frontal lobes. In literature this is the *first report* of cerebral atrophy in general and of the frontal lobe atrophy in a Romanian Sheep dog.

Chapter 10 named **"Results of the necropsy and histo-pathological exam of the encephalon in the epileptic syndrome of dogs"** describes the gross and histological lesions seen in canine epileptic syndrome and the correlation between them and clinical symptoms. The identified lesions consisted of cerebral edema, neural vacuolization, anisomorphic gliosis with satelitosis, subarachnoidian and intra cerebral hemorrhage as well as peri-vascular conjunctive proliferation.

Chapter 11 named **"Study regarding the efficacy of Phenobarbital in the treatment of idiopathic epilepsy of dogs"** aimed to investigate the efficiency of Phenobarbital in patients with idiopathic epilepsy. At the same time, it aimed to quantify side effects of Phenobarbital on liver and kidney metabolism.

The study made on a group of 15 dogs with idiopathic epilepsy showed that Phenobarbital has a special clinical efficacy (in 12 out of 15 dogs (80%) the administration had the desired effect, reducing epileptic seizures by 75 ± 13,17%).

In what concerns side effects, we noticed that after a short period of "accommodation" of the organism to the active substance, the blood status of liver transaminases and renal functional parameters (urea, creatinine) is not significantly modified.

At the same time, the administration of Phenobarbital was followed by a suppression of free serum thyroxin, without a correlation to the hypothyroidism described in literature for these situations.

Chapter 12 names **"The therapeutic efficiency of Gabapentin- Phenobarbital medication in drug-resistant idiopathic epilepsy of dogs"** investigates the impact of this double medication on clinical response and side effects.

The study was made on 11 dogs with single drug resistance and we noticed that 63,63% of the patients (7 dogs) showed a decrease in the number of seizures by at least 50% (an average of 67,26% $\pm$ 9,03) as the dose of Phenobarbital was also decreased by 62,71% $\pm$ 26,92.

Observing the influence of administering Gabapentin in association with Phenobarbital on liver function we noticed that blood variations of transaminases were not statistically significant ($p>0,05$). At the same time, although Gabapentin is mainly eliminated through the kidney, we

haven't noticed changes of the status of renal function. The results we obtained show that the administration of Gabapentin in doses of 40-50 mg/kg/12 hours is well tolerated by epileptic patients, with no alteration of the renal function, and it can reduce the frequency of seizures when it is used in combination with Phenobarbital

The chapter 13 named "General discussion of the results" presents the results compared to specialty literature, chapter from which resulted the general conclusions of the thesis specified in chapter 14 "General conclusion and recommendations".