

SUMMARY

The doctoral thesis entitled „Research on the diagnosis and treatment of epilepsy in dog” is structured according to the rules in force and comprises two parts: the first part is entitled „The current state of knowledge” and comprises 34 pages (23,4%) and the second part entitled „Personal contributions” details the results of the doctoral research and contains 111 pages (76,6%). In addition to these two parts, the thesis also includes introduction, summary, list of bibliographic sources, list of abbreviations, list of figures and list of tables. The present paper includes 82 figures and 23 tables, 272 bibliographic sources being used.

The first part, „ The current state of knowledge”, is structured in two chapters and provides information on the diagnostic protocol and therapeutic management of canine epilepsy. The first chapter of the thesis describes succinctly, systematically, the etiopathogenesis and the main forms of epilepsy, useful in the etiological diagnosis of the disease, as well as clinical and paraclinical examinations included in the diagnostic algorithm of canine epilepsy according to the literature.

The second chapter approaches the therapeutic strategies addressed in case of diagnosing canine epilepsy. On the one hand, the neurological emergencies represented by cluster epilepticus and status epilepticus can occur both at home and in a hospital unit. The onset site of neurological emergencies influences the speed of therapeutic intervention and the route of administration of first-line medication, thus determining the rate of success in stopping convulsive activity. On the other hand, in most cases, it is necessary to initiate the treatment of chronic disease according to the individual characteristics of patients. The ultimate goal is to give both the patient and the owner a satisfying level of quality of life.

In chapter three is detailed the place of the research, namely the Internal Medicine Clinic and the Neurology Service of the Faculty of Veterinary Medicine, University for Life Sciences „Ion Ionescu from Brad” in Iași. The goal of the doctoral paper entitled „Research on the diagnosis and treatment of epilepsy in dog” is to investigate the degree of neuroinflammation found in canine epilepsy and subsequently to identify the correlation between clinical and paraclinical efficiency of phenobarbital in epileptic dogs, responsive to long-term treatment.

The first goal of the paper was to determine the incidence rate of the menace response in correlation with the etiology of the epileptiform syndrome as part of the clinical diagnosis.

The second objective of the research refers to identifying the concentration of C-reactive protein (CRP) and establishing the neutrophil-lymphocyte ratio (NLR) among epileptic patients as a complementary method of differential diagnosis of canine epilepsy.

The third objective was to determine the impact of phenobarbital, initially from a clinical point of view by investigating the control of the convulsive activity in relation to the incidence of adverse effects, and then from a paraclinical point of view reflected by the brain bioelectric activity and the balance of appetite hormones.

The originality of the doctoral thesis is given by:

- First data on the dynamics of the NLR in epileptic patients in accordance with the etiology of the epileptiform syndrome and the frequency of seizures;
- First reporting on the determination of serum levels of appetite hormones, namely ghrelin and leptin, in the context of polyphagia and weight gain of epileptic patients under long-term phenobarbital monotherapy.

Chapter 4 emphasizes the importance of neuroexamination of the patient with convulsive activity, as the first step in distinguishing post-ictal symptoms from a possible neurological emergency or the onset of an intracranial inflammatory process. The absence of the menace response involves altered pathways or cognitive integrity. Thus, neurological examinations were performed in 57 dogs of different breeds and ages, with focal and generalized seizures, diagnosed according to IVETF criteria with idiopathic, structural or reactive epilepsy. The group of patients with structural epilepsy was best represented (n=26), followed by idiopathic epileptic dogs (n=19) and reactive seizures (n=12). Following neuroexamination, the menace response was the most commonly identified neurological deficit in patients with structural epilepsy, compared to other neurological deficits or etiological causes. The results of the research can facilitate the interpretation of the menace response in clinical context. Thus, the detection of this deficiency favors the diagnosis of structural epilepsy and can be a tool to monitor the recovery of cortical physiological activity in patients with reactive seizures.

Chapter 5 consists of two subchapters, initially being analyzed the CRP concentration in epileptic patients compared to other neurological pathologies, respectively neuromuscular junction, spinal or intracranial localization in the absence of seizures. In total, the study included 184 patients with neurological disorders for whom 237 doses of CRP were performed. Following the comparative analysis, the highest incidence rates of CRP abnormalities were identified in idiopathic epileptic dogs with cluster epilepticus (33%) and patients with intracranial disorders without seizures (26%) or with epileptic activity (20%). A low incidence was detected for dogs with neuromuscular pathologies (18%), spinal disorders (17%) and reactive seizures (14%). Patients with idiopathic epilepsy and isolated attacks did not experience abnormal CRP. As a result, increased CRP was associated with the identification of a structural change at intracranial level, independent of the clinical features, and with cluster epileptic activity. Subsequently, a similar result was also identified in the NLR, so patients diagnosed with idiopathic (medium \pm error standard: 6.49 ± 0.69) and structural (medium \pm error standard: 8.19 ± 0.86) epilepsy obtained the highest NLR values ($p = 0,001$; $p = 0,012$). Interestingly, an NLR above the control group was identified for all epileptic patients (mean \pm standard error: 3.84 ± 0.36 ; $p = 0,005$). This research reinforces the hypothesis issued in the current literature, according to which neuroinflammation is a constant process in canine epilepsy, regardless of its etiology, and it is expressed paraclinically by detecting abnormal CRP and NLR values. The study of neuroinflammation in the context of canine idiopathic epilepsy is a topic of major interest, as confirmation of the existence of this process within epileptogenesis could provide new directions of multimodal therapeutic management.

The sixth chapter describes a number of clinical and paraclinical challenges encountered in epileptic patients on long-term phenobarbital therapy. Phenobarbital is the most widely used anticonvulsant in veterinary medicine, with increased efficacy as monotherapy, although its administration is associated with a set of side effects. Polyphagia and weight gain are among the most common side effects of chronic administration of this anticonvulsant, in addition to the occurrence of sedentary, polydipsia and polyuria. The cause of the occurrence of these disorders is not elucidated until now, the hypotheses taken into account are the occurrence of obsessive-compulsive behavior or the change in the metabolic rate and implicitly the imbalance of appetite-regulating hormones represented by ghrelin and leptin. The underlying changes in hunger are represented by the increase in ghrelin while lowering leptin levels. In addition, according to the literature from human

medicine, the identification of a low level of ghrelin simultaneously with an increased leptin value is associated with an unsatisfactory control of convulsive activity. Through the anamnesis and clinical examination, the therapeutic efficiency of the medication was discovered, respectively the decrease by 50% of the frequency and/or intensity of the convulsive attacks. Adverse effects of antiepileptic therapy associated with increased body mass score were also quantified. Subsequently, through electroencephalography, periodic interictal discharges (DPI) were investigated and the main frequency bands were calculated. Thus, for all epileptic patients, during the recordings of brain bioelectric activity, we identified a small number of sharp wave, spikes or spike-wave complex. The beta frequency band showed the highest relative power (50.43%), followed by alpha (37.09%) and theta (11.58), while the lowest value was attributed to delta frequency bands (0.90%). The simple morphology of these graphoelements correlated with a physiological background activity was associated with a reduced degree of cortical hyperexcitation. Finally, serum levels of ghrelin and leptin in epileptic patients were detected and compared to those obtained in a control group and a geriatric patient group. The motivation for dosing these biochemical parameters in healthy or older dogs is given by the absence of information on the physiological serum levels of these two neuropeptides in pet carnivores. Thus, the serum level of ghrelin in epileptic patients was higher than the value obtained in the control group, but without statistical significance ($p=0,263$). Regarding serum leptin levels, by benchmarking the same groups, epileptic patients had lower values than those obtained in statistically confirmed healthy dogs ($p= 0,006$; $p=0,005$). The data obtained underline the antiepileptic effect of phenobarbital and disprove the hypothesis that the appetite hormone imbalance is at the origin of the increase in body mass score observed in epileptic patients under chronic phenobarbital monotherapy.

The last chapter summarizes the conclusions of the research carried out, reflecting the most important results in the context of diagnosis and therapeutic management of canine epilepsy.