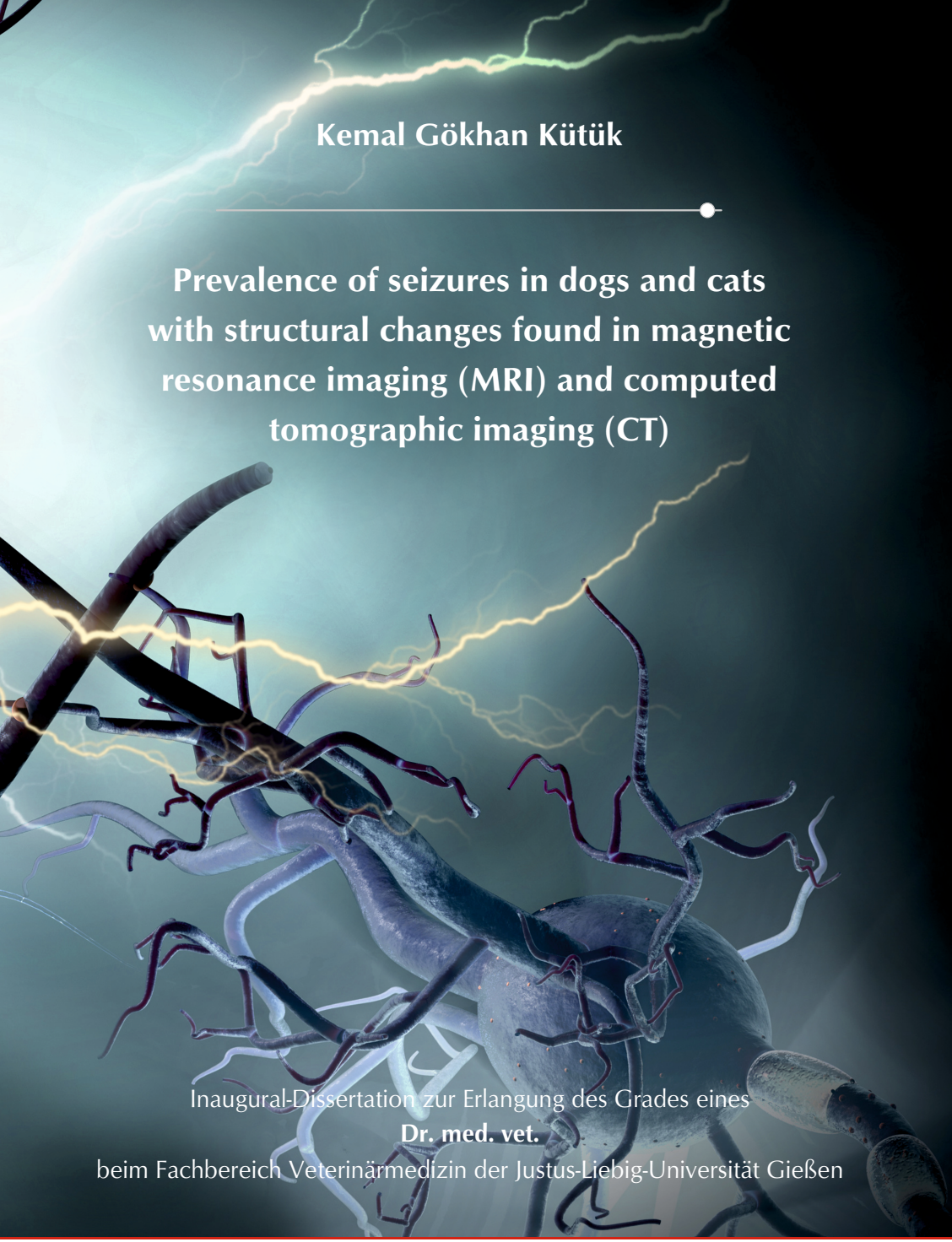
Kemal Gökhan Kütük

Prevalence of seizures in dogs and cats with structural changes found in magnetic resonance imaging (MRI) and computed tomographic imaging (CT)



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von

Kemal Gökhan Kütük
Tierarzt aus Istanbul

Gießen 2018

Mit Genehmigung des Fachbereichs Veterinärmedizin

der Justus-Liebig-Universität Gießen

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Abbreviations

ADC	Apparent diffusion coefficient
CDV	Canine distemper virus
CNS	Central nervous system
CSF	Cerebrospinal fluid
CT	Computed tomography
CVD	Cerebrovascular disease
DSH	Domestic Shorthair
DWI	Diffusion weighted imaging
DWM	Dandy-Walker malformation
DWV	Dandy–Walker variant
EEG	Electroencephalography
EPSP	Excitatory post synaptic potential
FCoV	Feline Coronavirus
FIP	Feline infectious peritonitis
FLAIR	Fluid attenuated inversion recovery
GABA	Gamma-aminobutyric acid
GME	Granulomatous meningoencephalitis
ICH	Intracranial hemorrhage
ILAE	International league against epilepsy
IPSP	Inhibitory post synaptic potential
MGCS	Modified Glasgow Coma Scale
MRI	Magnetic resonance imaging
MRT	Magnetresonanstomographie
NLE	Necrotizing leukoencephalitis
NME	Necrotizing meningoencephalitis
PDS	Paroxysmal depolarization shift
PDW	Proton density weighted
PTS	Posttraumatic seizure
T1-W	T1 weighted
T2-W	T2 weighted
TBI	Traumatic brain injury
VPS	Venticulo-peritoneal shunt
ZNS	Zentralnervensystem

1. Introduction

Although it is known since ancient times, epilepsy and epileptic seizures are not yet completely understood. Epilepsy refers to a complex clinical condition that consists of recurrent epileptic seizures, which are clinical manifestation of transient, abnormal, excessive electrical activity of the brain (LECOUTEUR, 1995). Epilepsy accounts for a considerably high proportion of neurologic disorders in both human and veterinary medicine. Approximately 3% of people experience at least one epileptic seizure at any time during life-time. Estimated incidence of epileptic seizures in small animals is varying from 0.5 to 5.7% of all dogs, and from 0.5 to 1% of all cats (LECOUTEUR, 1995; KNOWLES, 1998; CHANG & LOWENSTEIN, 2003; BERENDT, 2005; COATES & BERGMAN, 2005; CHANDLER, 2006).

The certain underlying mechanisms of developing an epileptic seizure are poorly defined. However, any intracranial pathology can potentially give rise to recurrent epileptic seizures. The intracranial pathologies that can cause epileptic seizures can be classified as neoplasia (primary or secondary), cerebrovascular diseases (ischemic or hemorrhagic stroke), inflammatory and infectious diseases, metabolic-toxic insults, developmental malformations, degenerative disorders and brain trauma. Whereas all these insults would cause severe clinical symptoms in human patients, neurological deficits in a dog or a cat can be minor or only transient. Furthermore, examination of cognitive abilities is very limited in a clinical setting.

The great difficulty in this respect is the occurrence of primary epilepsy that can be present without, or next to structural alterations without being functionally associated to it. On the other hand, development of seizures (epileptogenesis) after a given brain insult (brain trauma, malformation, inflammation) can take years, and a present structural lesion can create seizures at a later time. Studies regarding the occurrence, association and the rate of seizures with certain brain diseases are lacking. Therefore, the purpose of this study was to determine a present association between diagnostic imaging findings and the occurrence of seizures in dogs and cats.

2. Review of the literature

2.1 Epilepsy and epileptic seizures

Epilepsy and epileptic seizures are one of the most common and widespread neurologic problems in both veterinary and human medicine. Epilepsy does not characterize itself always with convulsive attacks; however, a broad spectrum of clinical manifestations might be outcome of epileptic seizure activity (BERENDT, 2004; PODELL et al., 1995; CHANDLER, 2006).

2.2 History

The word ”Epilepsy” originates from the Greek word “*epílēpsis*” or from Latin word “epilepsia” in the meaning of to be taken, to be seized or attacked. The Greek physicians and philosophers Hippokrates (460-377 B.C.) and Galèn (130-210 B.C.) described the epileptic seizures as a symptom of intracranial dysfunction or a systemic disease contrary to the common beliefs based on religion or supernatural powers. In 1824, the physician Calmeil classified epileptic seizures according to their symptomatology, and the neurologist John Hughlings Jackson proposed a classification of epilepsy that based upon anatomical localization, physiological imbalance, and the pathological process (JACKSON, 1931; BERENDT, 2004).

The early studies about epileptic seizures in small animals include also comparison of clinical symptoms between the human and animal type of epilepsy. In the scientific journals “Archiv für Wissenschaftliche und Praktische Heilkunde” and “Die Nervenkrankheiten unserer Hunde” studies can be found in which the authors compare the symptomatology of epileptic seizures in man and dog, and in which also the terms genuine, essential or idiopathic epilepsy exist, as they were used in human epilepsy terminology at that time (HOERLEIN, 1987; BERENDT, 2004).

2.3 Definition of epilepsy and epileptic seizures

The word *seizure* originates from the Greek that means *to take hold*. In the modern terminology, the word “seizure” is used for any sudden and severe event. In both human and veterinary medicine, it is needed to define the terms epileptic seizure and epilepsy to simplify the determination of basic clinical conditions (FISHER et al., 2005). For this purpose, the clinical and electroencephalographic classification of epileptic seizures published by Commission on Classification and Terminology of International League against Epilepsy (ILAE) in 1981 and the classification of epilepsies and epileptic syndromes published by Commission on Classification and Terminology of ILAE in 1989 are used to establish standardization in human medicine (ENGEL, 2006).

A seizure can be defined as nonspecific, paroxysmal and abnormal events of the body (PODELL, 2004). An epileptic seizure is the clinical manifestation of abnormal, excessive, hypersynchronous activity of a set of neurons that are located in the prosencephalon (LECOUTEUR, 1995; PODELL, 2004; DELAHUNTA, 2009). In the proposal of ILAE, an epileptic seizure is also described as a transient occurrence of signs and/or symptoms caused by abnormal excessive or synchronous neuronal activity in the brain. It is also proposed that transient demarcated occurrence in time with a clear start and finish, numerous characteristic features, such as altered consciousness, cognition and behavior, and abnormal enhanced synchrony of neurons may be considered as elements of epileptic seizure (FISHER et al., 2005). The terms *fit*, *ictus* and *convulsion* are also synonymous terms that are similarly used to describe clinical manifestations of an epileptic seizure (KORNEGAY & LANE, 1989; LECOUTEUR, 1995).

Epilepsy is not a disease, or a single syndrome, but is more a clinical symptom complex caused by any number of impaired brain functions in which two or more unprovoked epileptic seizures over a longer period involved (BERENDT, 2004; PAKOZDY et al., 2008). In the new proposal on definitions of ILAE, epilepsy is defined as a disorder of brain characterized by an enduring predisposition to generate epileptic seizures and by the neurologic, cognitive, psychological, and social consequences of this condition

(FISHER et al., 2005). Basically, epilepsy represents a disorder of the brain that is characterized by recurrent seizers of any type that occur as a result of transitory disturbance of brain functions. It has a sudden and spontaneous onset with tendency to recurrence. Transient cerebral overload can cause a single seizure; however, the neurologic condition is called epilepsy when the seizures become recurrent and unprovoked by any systemic disease (DELAHUNTA, 2009; OLIVER et al, 1997; LECOUTEUR, 1995; KORNEGAY & LANE, 1989; BERENDT, 2004).

Epileptic seizures indicate any kind of cerebral dysfunction. Loss of control in various degrees, sudden nature, and clinical similarity between each attack are among the clinical characteristics of epileptic seizures (BERENDT, 2004).

2.4 Epidemiology

Seizure disorders are one of the most common neurological disorders in domestic animals as well as in humans. In the general population, approximately 3 % of persons experience epilepsy at any time of their lives (PODELL et al., 1995; CHANG & LOWENSTEIN, 2003; BERENDT, 2004).

In veterinary medicine, studies those were on naturally occurred seizure disorders, and those were on experimental animal models of epileptic seizures and epilepsy have demonstrated that epilepsy and epileptic seizures occur in many species including rodents, cats, dogs, horses, cattle, goats and primates. Among these species, dogs and cats are the species that most commonly exhibit epileptic seizures (OLIVER, 1987; FISHER, 1989). Estimated incidence of epileptic seizures in small animals is varying from 0.5 % to 5.7 % of all dogs, and from 0.5 % to 1 % of all cats (LECOUTEUR, 1995; KNOWLES, 1998; CHANG & LOWENSTEIN, 2003; BERENDT, 2005; COATES & BERGMAN, 2005; CHANDLER, 2006).

2.5 Pathophysiology

The nature of epileptic seizures and epileptogenesis is in both human and veterinary medicine poorly understood. A neuron is described as “an excitable tissue constantly held in check” by Alexander DeLahunta (DELAHUNTA & GLASS, 2009). The membrane potential of neurons is maintained by energy-dependent sodium-potassium pump, membrane ionic channels, and by electrochemical gradients at a level of -70 millivolts in the resting phase. An external stimulation that is able to achieve the neuronal threshold potential causes an increase in the permeability of the cell to sodium and calcium, which subsequently results in an influx of positive charge to inside the cell membrane, and in a wave of depolarization along the neuron which is called action potential or excitatory post synaptic potential (EPSP). If the neuronal stimulation causes an increased permeability to chloride anion, through the influx of negative charge the neuron becomes hyperpolarized, therefore, the neuron becomes refractory to excitatory input and an inhibitory post synaptic potential (IPSP) has been generated. Communication of neurons with each other occurs via these EPSPs and IPSPs (KORNEGAY & LANE, 1989; MARCH, 1998; CHANDLER, 2006; DELAHUNTA, 2009).

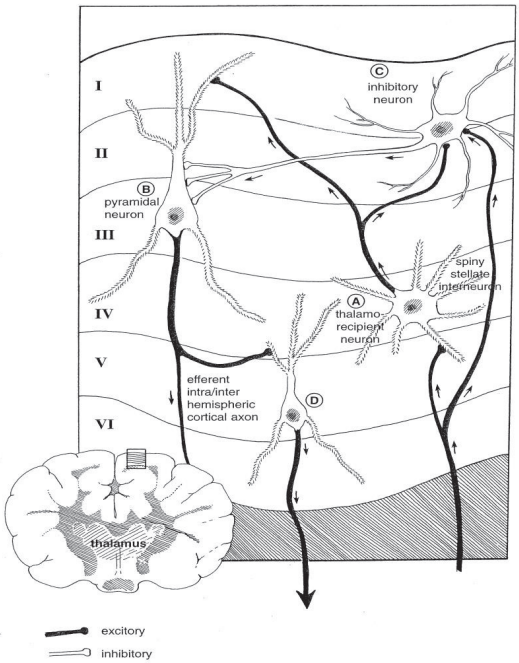

Figure 1: Inhibitory and excitatory connections of neurons in neocortex (From: March PA: Seizures: Classification, etiologies, and pathophysiology (Clin Tech Small Anim Pract 1998; 13: 119 – 131).

The basic cellular event at the time of a seizure is paroxysmal neuronal discharge and epileptic neurons are able to produce a prolonged period of discharge that is called paroxysmal depolarization shift (PDS), which allows them to be in a state of hyperexcitability in the certain time period. This may happen because of an excess of excitatory synaptic stimulation or because of the increased excitability of the neuron itself (OLIVER, 1987; KORNEGAY & LANE, 1989; MARCH, 1998). The excitatory and inhibitory influences represent a well-balanced activity in a seizure-free brain. It is commonly suggested that an imbalance between excitation and inhibition, such as an

augmentation in excitatory neurons activity or a lack of inhibition that subsequently leads to PDSs, may play a crucial role in epileptogenesis (MARCH, 1998; PODELL, 2004).

Gamma-aminobutyric acid (GABA) is the primary inhibitory neurotransmitter agent in the central nervous system (CNS), and glutamate is the primary excitatory neurotransmitter agent. A generalized imbalance between neurotransmitter agents because of an insufficient inhibition due to lack of synthesis or release of GABA, or excess of glutamate may be one of the fundamentals of epileptogenesis. Defective inhibition of GABA-$_B$ and GABA-$_A$ receptors, or defective activation of GABA neurons, and also defective intracellular buffering of calcium may lead to conditions favorable to epileptic seizures (MARCH, 1998; LORENZ & KORNEGAY, 2004; PODELL, 2004; BERENDT, 2004; CHANDLER, 2006).

Experimental studies on rats have shown that contact of cerebral cortex with blood, as in brain contusion after head trauma, may have a trigger factor in epileptogenesis. Intra-cortical injections of blood, haem compounds and iron ion derivatives produce epileptogenic foci that have pathologic and electrophysiological features (MORI et al., 1990; PAGNI & ZENGA, 2005).

Spread of abnormal paroxysmal discharge from a seizure focus is crucial to arise of an epileptic seizure. The spread of the discharge to adjacent neurons occurs either by means of synaptic connections or due to extracellular environmental alterations, and to ipsilateral and contralateral cortical areas it occurs by means of intra- and interhemispheric pathways. Repetitive exposure of normal neurons to spontaneous stimulations results in an inherent increased excitability and they also may involve to the seizure focus. This increased cortical excitability that occurs subsequent to constant stimulation of abnormal discharge or the seizure activity itself, which leads to expansion of epileptic focus is called “kindling phenomenon” (OLIVER, 1987; KORNEGAY & LANE, 1989; MARCH, 1998).

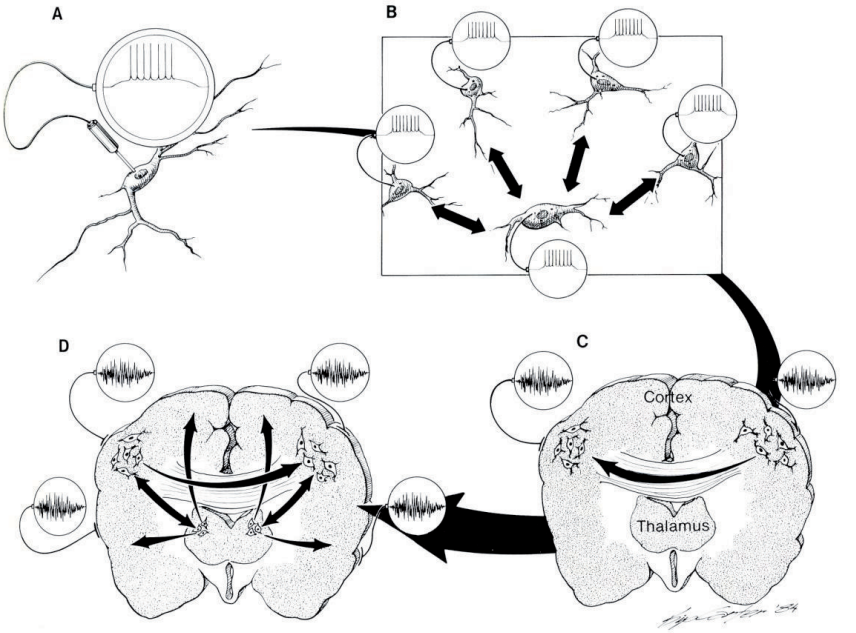

Figure 2: Spread of abnormal discharge from a focus through the cerebrum. A, Paroxysmal depolarization shift in a single neuron. B, Spread of abnormal discharge to adjacent neurons. C, Propagation of seizure activity to contralateral cortical areas along axonal pathways. D, Generalization of seizure activity to the entire diencephalon. (From: Oliver JE, Jr. Seizure disorders and narcolepsy. In: Oliver JE, Hoerlein BF, Mayhew IG, editors. Veterinary Neurology. Philadelphia: WB Sounders Co; 1987: 285-302.

2.6 Classifications

To identify and characterize specific diseases and symptoms classifications have been needed since ancient times. Historical records have shown that seizure classification in human also has been employed. In veterinary medicine a standardized terminology and classification that is universally accepted has not existed yet, while epilepsy nomenclature

has been transferred mainly from human medicine. In humans, epilepsy and epileptic seizure classification was established by the Commission on Classification and Terminology of ILAE with proposals published in 1981 and 1989. The classification bases on localization of the seizure focus, the degree of alteration on consciousness, and possible abnormalities recorded by Electroencephalography. However, direct use of human classification of epileptic seizures in veterinary medicine is restricted (COMMISSION ON CLASSIFICATION AND TERMINOLOGY OF THE ILAE, 1981 and 1989; BERENDT, 2004; DELAHUNTA, 2009). Although in veterinary medicine numerous attempts have been made to classify epilepsy and epileptic seizures by modifying classifications which were made for humans, those based on etiology and seizure type were mainly accepted (BERENDT, 2004; PODELL, 2004; LORENZ & KORNEGAY, 2004).

2.6.1 Classification of epilepsy in veterinary medicine

Classification of epilepsy of dogs and cats are made basically on the basis of underlying etiology and consists of three categories; idiopathic/cryptogenic epilepsy, symptomatic epilepsy and reactive epilepsy (PODELL et al., 1995; MARCH, 1998; PODELL, 2004; BERENDT, 2004; SCHRIEFL et al., 2008; LORENZ et al., 2011).

2.6.1.1 Idiopathic epilepsy

The term idiopathic originates from the Greek word “idios” which means self, own or personal (COMMISION ON CLASSIFICATION AND TERMINOLOGY OF THE ILAE, 1989). Idiopathic epilepsy was described by the Commission on Classification and Terminology of ILAE in 1981 as epilepsy that consists of recurrent seizures those without any underlying pathology other than a possible genetic predisposition and those were not preceded by any other disease.

In veterinary medicine, idiopathic epilepsy was also named as primary epilepsy, true epilepsy or functional epilepsy by numerous authors and were used to define recurrent seizures with any demonstrable pathologic cause or underlying etiology those were presumed to arise from a hereditary origin that give rise to an imbalance between excitatory and inhibitory excitations (SCHWARZ-PORSCHE, 1998; LORENZ & KORNEGAY, 2004; PODELL, 2004; LORENZ et al., 2011). In the patients with idiopathic epilepsy, patient history, seizure description, clinical and neurological examination, laboratory analysis (e.g. complete blood count, fasting serum biochemistry or hormone levels), analysis of cerebrospinal fluid, electroencephalography and other diagnostic imaging techniques such as magnetic resonance imaging (MRI) reveal any possible cause of seizures (SCHWARZ-PORSCHE, 1998; BERENDT, 2004; CHANDLER, 2006).

Although all breeds of dogs including mix-breeds are affected, idiopathic epilepsy is diagnosed commonly in purebred dogs with the first onset of seizures between the ages of 1 and 5 years. However, seizures can occasionally be seen before 6 months of age or as late as 10 years. In the patients with an interval between seizures more than 4 weeks and normal inter-ictal neurologic examination idiopathic epilepsy is likely to be diagnosed (HOLLIDAY, 1980; PODELL, 2004; THOMAS, 2010). In dogs and cats idiopathic epilepsy usually begins with a single seizure and characteristically, following seizures are frequently observed after a period of rest or sleep, while they are observed rarely during activity. Frequency between seizures varies from days to months; however, as the disorder becomes chronic, the length between seizures decreases (LECOUTEUR, 1995; PAKOZDY et al., 2008).

In the literature, it is reported that idiopathic epilepsy is the most common diagnosed type of epilepsy. Of dogs with seizure disorders, approximately 45% of cases are suffering from idiopathic epilepsy (JAGGY & STEFFEN, 1995; BERENDT & GRAM, 1999; PAKOZDY et al., 2008). The rate of idiopathic epilepsy in cats with seizure disorders varies from 21.4% to 59% (SCHWARZ-PORSCHE & KAISER, 1989; RUSBRIDGE, 2005; CIZINAUSKAS et al., 2008; SCHRIEFL et al., 2008; PAKOZDY et al., 2010). A genetic basis for idiopathic epilepsy in cats has not been established (QUESNEL et al., 1997;

BARNES et al., 2004; SCHRIEFL et al., 2008). However, in many breeds of dogs heredity of idiopathic epilepsy has been confirmed or suspected (OLIVER & LORENZ, 1993; PATTERSON et al., 2003; PATTERSON et al., 2005; CASAL et al., 2006).

The term cryptogenic derives from the Greek word “cryptos” meaning hidden or occult and is used to refer to a disease with an unknown cause. The term was first introduced in 1989 by Commission on Classification and Terminology of ILAE to use for the classification of epilepsies with an undetermined etiology that are presumed to be symptomatic (COMMISSION ON CLASSIFICATION AND TERMINOLOGY OF THE ILAE, 1989; BERENDT & GRAM, 1999). Cryptogenic epilepsy which is also named by some authors as probable symptomatic epilepsy is diagnosed when any underlying cause can be disclosed by routine diagnostic testing; however, it is assumed to be symptomatic due to the seizure characteristic, signalement or age of onset (SCHWARZ-PORSCHE, 1998; BERENDT, 2004).

2.6.1.2 Symptomatic epilepsy

Symptomatic epilepsy, also named as secondary, acquired or structural epilepsy, implies an epilepsy syndrome that consists of recurrent seizures caused by an identifiable disorder of the central nervous system (BERENDT & GRAM, 1999; ENGEL, 2006). Symptomatic epileptic seizures might be the sole clinical manifestation of an intracranial pathology, as well as they might be accompanied by other neurological deficits depending on the lesion localization. However, course of the seizures is often not to be correlated with severity of the lesion (SCHWARZ-PORSCHE & KAISER, 1989; PODELL, 2004; GANDINI et al., 2010).

Associated central nervous system diseases have a broad spectrum including degenerative diseases (e.g. storage diseases, spongioform encephalopathy) congenital or developmental malformations (e.g. hydrocephalus, lissencephaly, intracranial arachnoid cyst) inflammatory or infectious diseases (e.g. bacterial or viral diseases,

granulomatous meningoencephalitis), vascular disorders, neoplasia and trauma (SCHWARZ-PORSCHE & KAISER, 1989; FENNER, 1981; PARENT & QUESNEL, 1996; BERENDT, 2004; KLINE, 2006).

In human medicine, micro-structural pathologies have been determined as a cause of epileptic seizures (BERENDT, 2005). Fatzer et al. (2000) described hippocampal and piriform lobe necrosis in cats as a subtle central nerve system pathology resulting in epileptic seizures. Neurologic examination of patients with symptomatic epilepsy may be unremarkable or epileptic seizures may be the only clinical sign without any abnormality within the inter-ictal phase (SCHWARZ-PORSCHE & KAISER, 1989; BERENDT, 2005).

2.6.1.3 Reactive epilepsy

In addition to determinable structural and idiopathic intracranial causes of epileptic seizures, extracranial causes of epileptic seizures have also been identified. Reactive epilepsy can be described as epilepsy that characterized with recurrent seizures, which occur as a result of reaction of normal brain to an extracranial metabolic/toxic insult or physiological stress (PODELL et al., 1995; MARCH, 1998). Extracranial disorders that arise as a consequence of failure or malfunction of other organ systems lead to seizures by means of affecting or altering the normal neuronal metabolism or electrophysiology of central nerve system (LECOUTEUR, 1995; DELAHUNTA & GLASS, 2009). Schriefl et al. (2008) reported the prevalence of recurrent seizures in cats as 22%. Patients with reactive epilepsy mainly exhibit symptoms of a systemic illness; however, inter-ictal physical examination may not reveal any systemic abnormality (PODELL, 2004; DELAHUNTA & GLASS, 2009). Most common causes of recurrent seizures associated with metabolic disorders in cats include hepatopathies, hypoglycaemia, hypocalcaemia, thiamine deficiency, renal disease, hyperlipoproteinaemia, hyperthyroidism and hypoxia. Organophosphate, carbamate, lead and strychnine poisoning are the toxic causes that are commonly seen in cats associated with reactive seizures (LECOUTEUR, 1995;

PARENT & QUESNEL, 1996; KLINE, 1998; PODELL, 2004; SCHRIEFL et al., 2008; DELAHUNTA & GLASS, 2009; BRAUER et al., 2011; LORENZ et al., 2011).

Idiopathic

- Genetic Diseases
- Chanellopathies

Symptomatic

- Developmental/Anomalous
  - Hydrocephalus
  - Lissencephaly
  - Porencephaly, Hydranencephaly
  - Polymicrogyria
  - Agenesis of Corpus Callosum
  - Intracranial Cyst/diverticulum
- Degenerative
  - Storage Diseases
  - Neuronal Ceroid Lipofucinosis
  - Leukodystrophies
  - Mitochondrial Encephalpathy
  - Spongioform Encephalopathy
  - Multiple System Neuronal Degeneration
- Inflammatory
  - Granulomatous Meningoencephalitis
  - Necrotizing Encephlitides
  - Eosinophilic Meningoencephalitis
  - Other Corticosteroid-responsive Inflammatory Diseases
- Infectious
  - Bacterial
  - Viral
  - Protozoal
  - Fungal
  - Parasitic
  - Ricketsial
- Neoplastic
  - Extra-axial
  - Intra-axial
  - Intraventicular
- Traumatic
- Vascular
  - Hemorrhagic
  - Ischaemic

Reactive
○ Metabolic • Liver or Renal Disease • Hypoglycemia • Electrolyte Imbalance • Endocrine • Thiamine Deficiency ○ Intoxication

Table-1: Classification of epilepsy according to underlying etiology (Modified from Podell, 2004 and Lorenz et al., 2011).

2.7 Phenomenology of epileptic seizures

Epileptic seizures are clinical manifestations of paroxysmal discharge of neurons in a certain location or in the entire brain and they represent themselves with numerous clinical signs depending on the location that they arise from (SCHWARZ-PORSCHE, 1998; DELAHUNTA & GLASS, 2009). These clinical signs may be seen as motor activity, sensational alterations, psychogenic abnormalities (behavior) or autonomic disturbances (OLIVER et al., 1997; BERENDT, 2004). In the classification of epileptic seizures, it may be of benefit to define the term consciousness, responsiveness and awareness. In the proposal for the classification of epileptic seizures of the Commission on Classification and Terminology of ILAE, they were defined as that consciousness is “the degree of awareness and/or responsiveness of the patient to the externally applied stimuli”, responsiveness is “the ability of the patient to carry out simple commands or willed movement and awareness is “the patient’s contact with events during the period in question and its recall” (COMMISSION ON CLASSIFICATION AND TERMINOLOGY OF ILAE, 1981).

Epileptic seizures can be classified according to their clinical course under three main categories. These are self-limiting (isolated), clustered, or continuous (status epilepticus) seizures. Clustered seizures imply two or more isolated seizures within twentyfour hours

while continuous seizures are defined as a state of seizure activity that lasts more than thirty minutes or a seizure activity with a high frequency without full recovery between the seizure episodes. Each of these categories can be divided into two subcategories according to their clinical manifestations and EEG findings as being primary generalized or partial (i.e. focal, local) seizures. Partial seizures can also be classified as simple partial seizures, complex partial seizures and partial seizures with secondary generalization. To refer to seizures, terms as grand mal and petit mal are also in use by veterinary clinicians, although this terminology is no longer recommended. The term grand mal is used to describe generalized tonic-clonic seizures, while the term petit mal used by veterinarians incorrectly to refer to focal seizures. The fact is that the term petit mal refers to generalized, non-convulsive seizures which are also called as absence seizures (LECOUTEUR, 1995; MARCH, 1998; SCHWARZ-PORSCHE, 1998; PODELL, 2004; BERENDT, 2004). Most of the dogs with epileptic seizures mainly suffer from primary generalized seizures and infrequently from complex partial seizures, whereas the rate of complex partial seizures in cats with epileptic seizures is relatively higher (PARENT & QUESNEL, 1996).

2.7.1 Primary generalized seizures

Primary generalized seizures are the most commonly observed seizure type in domestic animals. Based on the clinical manifestations and EEG findings, it is determined that seizure activity involves both brain hemispheres. This bilateral widespread activity is seen in the ictal EEG with a sudden loss of normal electroencephalographic rhythm followed by paroxysmal burst discharges throughout the cerebral cortex, which are hyper-synchronous and symmetric in both hemispheres. Impaired consciousness and bilateral motor manifestations may also be associated with initial involvement of both hemispheres. Spread of a seizure activity with a focus in one hemisphere immediately to the thalamus and subsequent activation of entire cerebrum throughout its neurons that are functioning in the diffuse cortical projection system or direct existence of seizure focus in the thalamic system may also cause both hemispheres being involved in seizure

activity simultaneously (HOLLIDAY, 1980; COMISSION ON CLASSIFICATION AND TERMINOLOGY OF ILAE, 1981; DELAHUNTA, 2009).

Primary generalized seizures may or may not be accompanied by loss of consciousness and/ or convulsions. Based on these features, generalized seizures can be named as tonic–clonic, tonic, clonic, myoclonic, atonic, or absence seizures (LECOUTEUR, 1995; SCHWARZ-PORSCHE, 1998; BERENDT, 2004).

Generalized tonic–clonic seizures are the form that is most commonly seen at a rate of approximately 60% in cats and 80% in dogs with epileptic seizures (SCHWARZ-PORSCHE, 1998). A generalized epileptic seizure may clinically consist of four components.

The so called prodromal phase is a long-lasting phase that patients experience prior to the seizure activity. It may last from hours to days and behavioral changings such as seek for attention, anxiety, restlessness may be observed in this period (LECOUTEUR, 1995; SCHWARZ-PORSCHE, 1998). Berendt and Gram (1999) reported a rate of 11% in dogs with epileptic seizures suffering from prodromes varying from thirty minutes to twenty-four hours.

Aura is the period that may last from seconds to several minutes. Patients exhibit motor activity such as licking or pacing or autonomic disturbances such as salivating or vomiting. Cats often exhibit hectically running around in this phase (MARCH, 1998; PODELL, 2004).

Ictus is the phase where actual seizure occurs. In most cases, primary generalized seizures are accompanied by complete loss of consciousness at any point of ictal phase. However, in animals it is difficult to determine whether consciousness is altered; hence, it is usually evaluated by means of patients' responsiveness and/or awareness. Ictal phase may start suddenly and generalize without any initial sign or may occur following a prodromal phase or aura. Animals usually exhibit a tonic phase at the beginning of seizure activity with extensor rigidity of all limbs and opistotonus causing the patient to fall, which lasts usually 10 to 30 seconds. Subsequent to the tonic phase, clonic phase

begins with uncoordinated, jerking and running-like movements of the limbs. During the clonic phase, involuntary orofacial muscle movements, hypersalivation, staring with dilated pupils, urination, defecation, piloerection can usually be seen. This actual ictal phase consisted of tonic–clonic manifestations may last a few seconds to several minutes (LECOUTEUR, 1995; DELAHUNTA, 2009).

Postictal phase is the period that follows the cessation of seizure activity and lasts from minutes to days. In the postictal phase, physiologic recovery of the brain and the body takes place. Due to the cerebral exhaustion, patients may exhibit behavioral abnormalities, disorientation and ataxia. Depending on the severity of the epileptic seizure, patients may suffer from severe weakness, sensory and/or motor disturbances and blindness which are in common named as Todd's paralysis (LECOUTEUR, 1995; MARCH, 1998; SCHWARZ-PORSCHE, 1998; PODELL, 2004).

Generalized tonic seizures are generally observed in dogs and patients exhibit a tonic extension of the head and extremities caused by generalized increased muscle tone of all limb and trunk muscles. Alterations of consciousness may also be seen during the severe phases of tonic seizure activity. Generalized clonic seizures consist of rhythmic muscle contractions and running or paddling-like movements of limbs and they appear without tonic phase or components. Cats experience clonic seizures frequently, while it is rare to be seen in dogs. Myoclonic seizures are characterized by repetitive, brief contractions of one or more muscle groups that are subsequently causing to myoclonic twitching of head, neck and extremities, which are usually strong and frequent enough to make the patient not able to stand and cause to fall to side or into sitting position. Myoclonic seizures may appear spontaneously or following a visual stimulation or light and sound, and are associated with "Lafora disease" or "Lafora epilepsy" caused by a storage disease (LECOUTEUR, 1995; LORENZ et al., 2011). Absence seizures occur with a sudden onset and loss of consciousness for a brief time period and recognized by interruption of ongoing activity and blank staring. It may be easy to recognize in people on the basis of specific clinical manifestations, whereas it is either very uncommon or difficult to determine in dogs and cats, although similar conditions have been noted

(COMISSION ON CLASSIFICATION AND TERMINOLOGY OF ILAE, 1981; LECOUTEUR, 1995; LORENZ et al., 2011). Atonic seizures are characterized by sudden loss of muscle tone and are well recognized in people, whereas they are either extremely rare or not described in domestic animals (SCHWARZ-PORSCHE, 1998; LORENZ et al., 2011).

2.7.2 Partial seizures

Partial (focal, local) seizures are the clinical manifestations of abnormal paroxysmal discharge of a limited number of neurons that are localized in the cortex of one cerebral hemisphere (epileptic focus). They exhibit numerous clinical signs depending on the area that they originate, which involves motor, sensory, or behavioral disturbances. Partial seizures are characterized by regional spikes, spike–waves or sharp–waves in EEG recordings during inter-ictal periods. Partial seizures are generally associated with a focal structural intracranial pathology subsequent to an acquired disease of the brain such as congenital anomalies, postnatal trauma, neonatal hypoxia, and encephalitis (HOLLIDAY, 1980; COMISSION ON CLASSIFICATION AND TERMINOLGY OF ILAE, 1981; PODELL et al., 1995; BERENDT, 2004).

Partial seizures are divided into two categories depending on the alterations in consciousness; Simple partial seizures and complex partial seizures. A partial seizure activity may be limited to surrounding area, but also may become more massive and spread thorough the subcortical areas involving the entire cerebrum and therefore, evolve into a generalized seizure, which is called “focal seizure with secondary generalization” (HOLLIDAY, 1980; BERENDT, 1999; LORENZ et al., 2011).

2.7.2.1 Simple partial seizures

Simple partial seizures occur without alterations in state of consciousness of the patient and characterized by focal unilateral motor disturbances involving a part of the body such

as the face or one limb (PARENT & QUESNEL, 1996). Simple partial seizures are mainly recognized by focal motor signs that usually include unilateral facial muscle twitching, episodic tremors, head turning, abnormal rhythmic blinking or twitching of an extremity and, characteristically in cats, twitching of the whiskers. These motor signs that occur at the onset of seizure activity are the key features in the identification of partial seizures (BERENDT, 2004; DELAHUNTA, 2009). In addition to motor signs, typical autonomic signs such as mydriasis and salivation may also be observed (DELAHUNTA, 2009; LORENZ et al., 2011).

A partial seizure with progressive involvement of motor signs followed by clonic contractions of head, neck and/or shoulder and limb muscles is also called as “Jacksonian march” (PODELL, 2004; DELAHUNTA, 2009).

2.7.2.2 Complex partial seizures

Complex partial seizures are a clinical form of simple partial seizures accompanied by altered consciousness and behavioral abnormalities. Sensory, autonomic, psychogenic, and paroxysmal behavioral signs may also be seen. Psychogenic disturbances include fly biting, attacking to imaginary objects or startling without a reason. Involuntary licking and chewing movements and behavioral alterations such as anxiousness, aimless wandering, attention seeking or aggression are well known clinical manifestations of complex partial seizures. Cats may exhibit other typical behavioral disturbances such as inappropriate hissing, growling or excessive vocalization. Because of these behavioral alterations are complex partial seizures also known as psychomotor seizures (LECOUTEUR, 1995; BERENDT, 2004). Cats usually suffer from complex partial seizures of which episodes may last more than one hour with a tendency to evolve into status epilepticus (SCHWARZ-PORSCHE & KAISER, 1989; PARENT & QUESNEL, 1996; DELAHUNTA, 2009).

2.7.2.3 Partial seizures with secondary generalization

Partial seizures may generalize when paroxysmal activity spreads rapidly through thalamus and its diffuse cortical projections or other subcortical structures in the entire brain, rather than staying limited to epileptic focus. Secondary generalization can occur either subsequent to simple partial seizures or complex partial seizures. Therefore, clinical signs at the onset of seizure activity reflect the anatomical localization of seizures focus lasting seconds to minutes before the rapid secondary generalization takes place with loss of consciousness and generalized convulsions. Given the rapid evolving to generalized seizure, in most cases, a careful observation is crucial to recognize the signs of aura, and therefore, to identify a partial seizure. Several studies have revealed that partial seizures with secondary generalization are the most commonly observed form in dogs (HOLLIDAY, 1980; PODELL et al., 1995; BERENDT & GRAM, 1999; BERENDT et al., 2002; LORENZ et al., 2011).

Partial (focal, local) Seizures

◦ Simple partial seizures
  • With motor signs
  • With somatosensory or special-sensory symptoms
  • With autonomic symptoms or signs
  • With psychic symptoms
◦ Complex partial seizures
  • Simple partial onset followed by impairment of consciousness
  • With impairment of consciousness at onset
◦ Partial seizures evolving to secondarily generalized seizures

Generalized Seizures (Convulsive or Non-convulsive)
◦ Absence seizures ◦ Myoclonic seizures ◦ Clonic seizures ◦ Tonic seizures ◦ Tonic – clonic seizures ◦ Atonic seizures
Unclassified Seizures

Table-2: International classification of epileptic seizures in people (From Commission on Classification and Terminology of ILAE, 1981).

2.8 Seizure–like episodes

Seizure–like episodes, or nonepileptic seizures, are paroxysmal events of which clinical manifestations resemble to that of epileptic seizures, however, do not arise from an abnormal neuronal discharge in the brain. They occur with a sudden onset and short

duration and disappear without postictal phase (SCHWARZ-PORSCHE, 1998; PENNING et al., 2009).

Syncope refers to a paroxysmal, self-limiting partial or complete loss of consciousness accompanied by loss of muscle tone and motor activity. It occurs suddenly, taking place in a short time period with total recovery and without postictal signs. They are usually associated with a sudden reduction or transient cessation of cerebral blood supply due to cardiac or respiratory diseases (THOMAS & DEWEY, 2008; PENNING et al., 2009).

Cataplexy is defined as sudden partial or generalized loss of muscle tone without alteration in consciousness following to a stimulation which is usually excessive excitement or emotions. It is associated with narcolepsy and is observed as the characteristic clinical sign in animals with narcoleptic syndrome (THOMAS & DEWEY, 2008; DELAHUNTA & GLASS, 2009).

Narcolepsy is a disorder of sleep/awake state control mechanism characterized by excessive sleepiness in the daytime including sudden attacks of falling asleep and cataplexy occurring several times a day with a duration ranging from a few seconds to more than 30 minutes. The attacks are typically triggered by excitement because of food, seeing a loved person or play, but they might occur spontaneously as well. The episodes can be interrupted by making loud noise, stirring or a similar stimulation (THOMAS & DEWEY, 2008; GANDINI et al., 2010; LORENZ et al., 2011). Some other diseases characterized by paroxysmal events of which clinical manifestation may resemble to those of epileptic seizures are episodic weakness, Scotty cramp, episodic falling of Cavalier King Charles Spaniels and familial reflex myoclonus of Labrador Retrievers (BRAUND, 2003).

Non-epileptic Seizures

◦ Syncope
  • Cardiac arrhythmias
  • Congenital heart disease
  • Cardiomyopathies
◦ Episodic weakness
  • Metabolic in origin (Hypoglycemia, Addisonian crisis, etc.)
  • Myasthenia gravis
  • Polymyopathy, polyneuropathy
◦ Narcoleptic seizures
◦ Cataplectic seizures
◦ Attacks of vertigo
  • Vestibular symptoms
◦ Recurring attacks of pain

Table-3: Classification of non-epileptic seizures (from Schwarz-Porsche, 1998).

3. Aim of the study

MRI is the most important diagnostic procedure in the workup of dogs and cats with seizures. Unfortunately, the experience about the relation between certain structural lesions and the occurrence of seizures is quite limited in veterinary medicine. This is important with respect to the fact that idiopathic epilepsy is a rule-out diagnosis based on the absence of structural (as well as toxic and other) lesions of the brain. The same holds for a high number of infectious and inflammatory diseases in dogs and cats (LAMB et al, 2005) that do not create visible structural lesions in MRI. The possible presence of more than one (visible) lesion in an epileptic animal causes the necessity to be sure about the relation between an imaging finding and epileptic seizures. This knowledge has an importance for treatment planning and prognosis in each individual animal.

In this study, we therefore wanted to retrospectively evaluate the prevalence of seizures in dogs and cats with vascular, inflammatory, infectious, traumatic, anomalous, neoplastic and degenerative lesions of the brain in the course of disease or rehabilitation.

4. Materials and methods

4.1 Data acquisition

Medical records of the Small Animal Surgery Clinics of the Department of Veterinary Clinical Sciences, Justus-Liebig University, Giessen, Germany between 2006 and 2012 were retrospectively evaluated. Patient data was automatically filtered for the key word “Epilepsie”, “epileptische Anfälle”, “generalisierte Anfälle”, and “partielle Anfälle”. This filter process includes the classical primary generalized seizure with loss of consciousness and generalized motor activity involving the whole body. Furthermore, animals with seizures without alterations in the state of consciousness, motor activity limited to a specific part of the body or only with autonomic signs were recorded (simple partial seizures). Identification of seizures on time of introduction were made on the basis of the description of the patient owners or direct observation by the examining clinician (video analysis). In order to exclude reactive seizures dogs and cats underwent a complete blood count, a biochemistry panel, electrolytes, as well as in house serum ammonia and bile acids. In patients with status epilepticus a toxicology screening was initiated. Only non-reactive epilepsy cases were included.

Groups were built according to general lesion types according to VITAMIN D scheme. For each group patient data including breed, age at the onset of seizures or at the time of referral, neurologic examination and diagnostic imaging findings, the clinical and, if available, histopathological diagnosis were collected. To estimate the seizure prevalence for a given disease group all patients with the same diagnosis, but without clinical signs of seizure activity were collected from the database.

Questionnaire of Interview
• How did your animal recover from the injuries after the accident?
• Were there any behavior problems after the time of discharge (loss of learned behavior, a change in behavior towards family members, loss of house training?)
• Have you ever seen any new muscle movements of the face, such as twitching of the face, ears or whiskers?
• Has your animal ever shown unusual behavior, such as abnormal head movements, remarkable periods of licking, or catching flies?
• Abnormal vocalization?
• Have you ever noticed altered mental status such as depression, absence or excitement?
• Has your pet experienced an epileptic seizure?
• If yes, with or without loss of consciousness, with or without defecation and urination
• When were the first changes detectable?
• Is your animal currently under any medical therapy? If yes, with success?

Table-4: Questions of interview of patient owners.

4.1.1 Data acquisition in head trauma patients

A second filter run was performed using the key words “Schädel-Trauma”, “Schädel-Hirn Trauma”, “Schädel-Trauma”, “Hirn-Trauma”, and “Gehirn-Trauma”. Thereby dogs and cats were identified that were affected by head traumas of all kinds and underwent MRI or CT examination at JLU. The time of the accident was searched. Animals were included in this study, if the trauma was at least two years before the data acquisition for the study. To obtain information about the occurrence of post traumatic seizures, patient owners were interviewed via telephone. The interviews were performed by asking questions,

which were defined to obtain required information and therefore were standardized. The questionnaire included the questions listed in the Table-4.

4.2 Clinical evaluation of head trauma patients

Traumatic brain disease can be diagnosed from the medical history. Assessment of neurologic condition of patients with head trauma was made by means of the Modified Glasgow Coma Scale (MGCS) proposed by Shores (SHORES, 1983) based on the neurologic examination findings. MGCS consists of three main parts; Motor activity, brainstem reflexes and level of consciousness with each part scored from 1 to 6. According to the scoring system, a patient can be assigned with a minimum score of 3 and a maximum of 18. Evaluation of the patients based on the MGCS score was made as following; a score of 3-8 was indicating a severe head trauma with grave prognosis, 9-14 indicating a moderate head trauma with poor to guarded prognosis and 15-18 indicating a mild head trauma with a good prognosis

4.3 Classification of lesion types

In the following chapter, the lesions will be shortly characterized and the imaging findings that lead to the diagnosis of a particular brain lesion will be described.

4.3.1 Vascular diseases

4.3.1.1 Brain infarction

Ischemic brain diseases have been diagnosed on the basis of MRI findings alone. MRI has been proven to be sensitive and specific in detecting changes that occur after strokes in both human and veterinary medicine (AUGUSTIN et al., 2000). In the acute stage a

hypointense signal on T1-weighted (T1-W) and hyperintense signal on proton density on T2-weighted (T2-W) images can be seen. The lesion follows vascular distribution. A parenchymal enhancement with paramagnetic contrast agent is not seen in the acute stage. In subacute (1 week or older) revascularization and blood-brain barrier breakdown may cause parenchymal enhancement with contrast agents.

The mainstay of diagnosis, however, is diffusion-weighted-imaging (DWI), which is very sensitive in detection of brain infarcts. Ischemia in brain parenchyma results in diminished diffusion of water molecules within the affected territory due to disruption of normal cellular metabolism and energy depletion and failure of Na+/K+ ATPase, which leads to a shift of water from the extracellular towards the intracellular compartment. Whereas the total water content does not change, the distribution within the extra- vs. intracellular compartments change, which results in the restricted diffusion of intracellular protons. This phenomenon of restricted diffusion associated with ischemic damage persists at least for a week in human patients. Increased DWI signal in ischemic brain tissue is observed and a concurrent reduction of the apparent diffusion coefficient (ADC), which can also be seen in dogs and cats (GAROSI, 2006; SCHMIDT & KRAMER, 2015).

Lesions were classified according to location within the brain (telencephalon, thalamic/midbrain, pons/medulla, cerebellum, multifocal) and infarct type (territorial vs lacunar). Territorial infarcts were defined as lesions occurring in the vascular territory of the main cerebral arteries (rostral cerebral, middle cerebral, caudal cerebral) or cerebellar arteries (rostral cerebellar, caudal cerebellar).

Lacunar infarcts were described as lesions in the vascular territory of small intra-parenchymal and deep perforating artery. The striate artery, proximal and distal perforantin artery, caudal perorating arteries, and paramedian branches arising from the proximal portion of the caudal cerebral artery are involved in this type of infarction.

Follow-up on each patient was obtained from the hospital records or telephone consultation with the owners, referring veterinarian, or both. We recorded length of time since the diagnosis of brain infarction, clinical outcome (defined as alive, deceased, or

euthanized) and recurrence of neurologic signs due to suspected or confirmed subsequent infarcts.

4.3.1.2 Brain hemorrhage

Intracranial hemorrhage (ICH) occurs after rupture of a blood vessel within the brain, allowing blood to leak inside the parenchyma. The sudden increase in pressure within the brain can cause damage to the brain cells surrounding the blood. Seizures are a common complication after brain hemorrhage in humans (SUNG & CHU; 1989).

Hemorrhage is also diagnosed by MRI. The appearance of intracranial hemorrhage on MRI is depending on the age of the hematoma and on the imaging sequence used (T1 weighting, T2 weighting). Hemoglobin changes through several forms such as oxyhemoglobin, deoxyhemoglobin, and methemoglobin. In the last stage, the erythrocytes are broken down leaving ferritin and hemosiderin in the brain tissue. The diagnosis is based on T2*-weighted sequences. This imaging sequence is sensitive to magnetic field inhomogeneities created by the magnetic blood iron. The disturbance of the local magnetic field results in a focal signal void by which the hemorrhage can be unambiguously diagnosed.

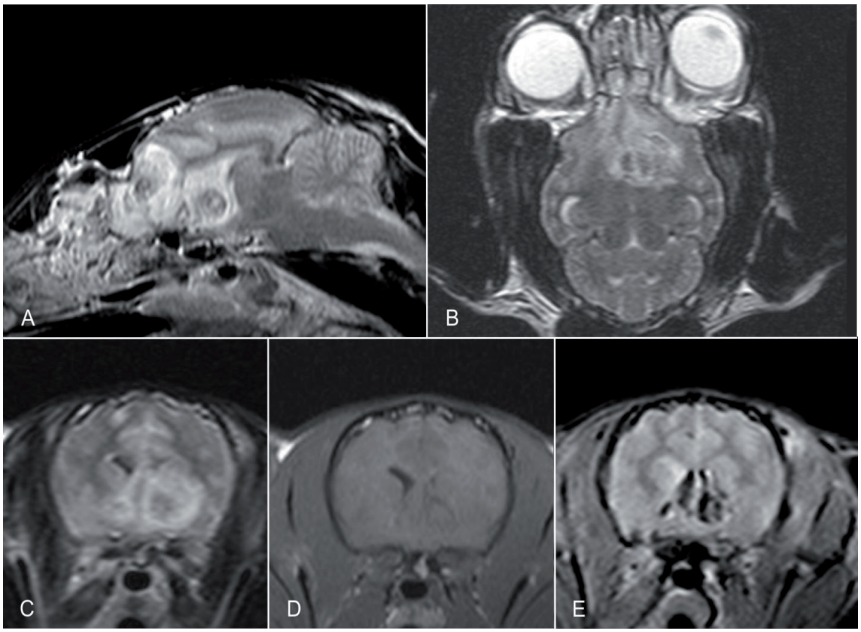

Figure-3: Sagittal, dorsal and transversal T2-W and T1-W images of a cat with intracranial hemorrhage. The gradient echo sequence (T2*) shows a signal void indicative for blood iron that disturbs the magnetic field in this area.

4.3.2 Inflammatory/ Infectious

4.3.2.1 Feline infectious peritonitis

Feline infectious peritonitis (FIP) is a common progressive immune-mediated disease of cats, caused by mutated enteric feline Coronavirus (FCoV). There are two main forms of the infection commonly seen: “dry or non-effusive” from and “effusive” form. The effusive form is typically characterized by peritonitis, pleuritis or the combination of both with protein rich fluid accumulation, accompanied by fever, weight loss and elevated serum

globulin levels. Dry form is rather characterized by multifocal granulomatous inflammation and necrotizing vasculitis in various organs, especially in mesenteric lymph nodes, kidneys, eyes and CNS. Multifocal pyogranulomatous meningoencephalitis and myelitis are frequently seen in dry form. Inflammation is seen usually in meningeal and epidermal layers and is often perivascular. FIP is the most common cause of inflammatory CNS lesions in cats causing neurological symptoms including seizures in up to 25% of cases (BRADSHAW et al, 2004; SHERDING, 2006; TIMMANN et al, 2008; PEDERSEN, 2009).

4.3.2.1.1 Diagnosis

Since the clinical signs are complex and may be atypical in most cases, CSF analysis and CT and/or MRI are commonly used as further diagnostic tools. Although MRI has proven to be useful in detecting intracranial disorders, its sensitivity in detecting the neural form of FIP is low, thus, in cats with an unremarkable MRI, CSF analysis results may refer to FIP. Lesions appear typically hyperintense on T2-W, and hypointense on T1-W. Fluid attenuated inversion recovery (FLAIR) has higher sensitivity in detecting milder lesions. Inflammation of meninges may not be visible on T2-W, and may be visible following contrast medium enhancement, but can be detected on FLAIR-sequencing. Sings of chorioditis, ependymitis and meningitis are common MRI findings of FIP (HECHT & ADAMS, 2010; SCHMIDT, 2015).

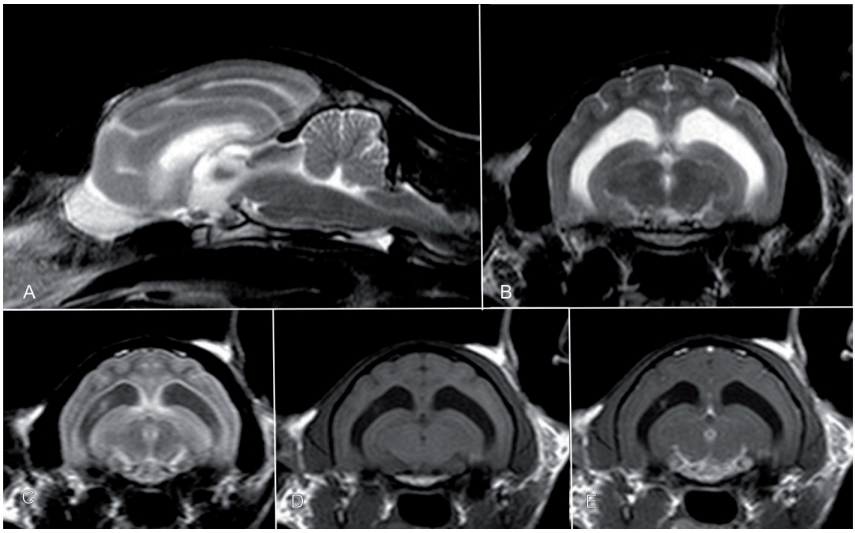

Figure-4: Sagittal and transversal T2-W (A and B), FLAIR (C) and T1-W (D and E) images of a cat with FIP.

4.3.2.2 Toxoplasmosis

Toxoplasmosis is a disease caused by an obligate intracellular protozoal parasite, Toxoplasma gondii. After oral uptake of Toxoplasma oocytes and parasitemia, proliferation of tachyzoites can occur in various organs during the acute stage. Symptomatic CNS toxoplasmosis rarely develops during primary infection in normal hosts. In the brain the parasite forms cysts preferentially establishing a chronic infection. Most infections with T. gondii are asymptomatic but can progress to a symptomatic disease after immune-compromise. Neurological signs of toxoplasmosis depend on the site of infection within the brain and can include seizures, tremors, depression, lethargy, muscle weakness, loss of coordination, and paralysis.

4.3.2.2.1 Diagnosis

Serology has been used to make a tentative diagnosis. A positive IgM titer in blood and CSF indicated an active infection with Toxoplasmosis. MRI findings are unspecific for the disease. In both cats T2-hyperintense masses were found consistent with Toxoplasma granulomas surrounded by severe edema. Moderate contrast enhancement was seen after gadolinium injection in T1-weighted sequences. Definitive diagnosis was performed postmortem using immunohistochemistry for *T. gondii* on formalin-fixed, paraffin-embedded tissues.

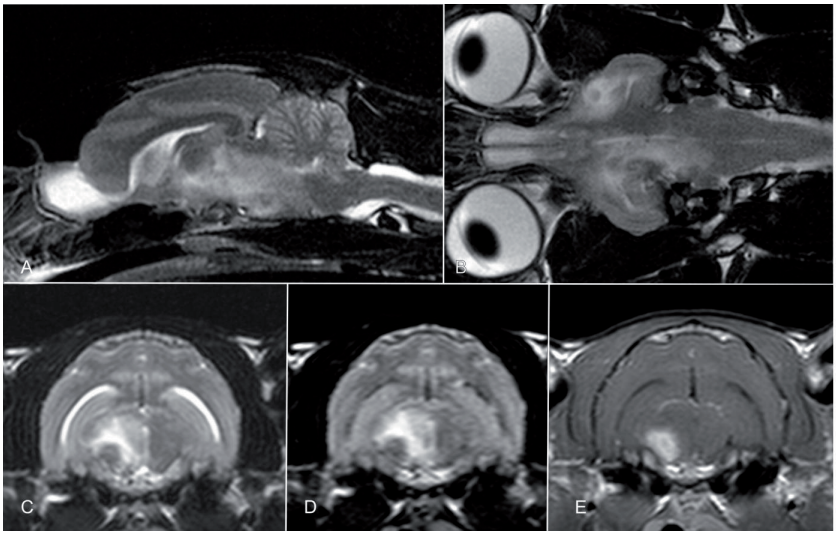

Figure-5: Sagittal, dorsal and transversal T2-W images of a cat with Toxoplasmosis.

4.3.2.3 Idiopathic encephalitis (meningoencephalitis of unknown origin)

Noninfectious idiopathic inflammatory diseases of the CNS are among often diagnosed underlying etiology of canine seizures. Granulomatous meningoencephalitis (GME), necrotizing meningoencephalitis (NME) and necrotizing leukoencephalitis (NLE) are the most common inflammatory CNS diseases. Each condition is characterized by its unique features, however, an aberrant immune response targeting the CNS seems to be a common cause of these disorders. GME is histologically characterized by perivascular infiltration of mononuclear cells in CNS and spinal cord parenchyma, with lesions predominantly occurring in the white matter, thus causing the neurological symptoms. Disseminated, focal and ocular forms have been described (ADAMO et al. 2007; SCHATZBERG, 2010; LORENZ et al, 2011).

NME and NLE account for two histologically distinct disorders among noninfectious inflammatory encephalitis. Both are considered as autoimmune disorders, yet the pathogenesis of both diseases is not understood. In NME, lesions are typically restricted to the cerebrum, affecting both hemispheres and leptomeningeal involvement is consistent. A demarcation between gray and white matter with extensive cavitations are also typical MRI and histopathology findings. In NLE main lesions occur with less meningeal involvement and predominantly in deep cerebral white matter and brain stem. Typical lesions found in MRI in NME include asymmetric lesions in prosencephalon affecting both grey and white matter, and show variable contrast medium enhancement in T1-W images. NLE associated lesions are multiple, asymmetric mainly in the subcortical white matter (HECHT & ADAMS, 2010; SCHATZBERG, 2010).

4.3.3 Traumatic brain disease

4.3.3.1 Imaging evaluation of head trauma patients

In the evaluation of head trauma patients use of radiography followed by CT and/or MRI is crucial for the patient management and for the prognosis. CT scan is considered as a better and faster option to detect any depressing fracture that needs to be taken care of as soon as possible, while MRI is more sensitive in the detection of intracranial alterations such as bleeding, infarct or brain edema. After the initial stabilization, along with the routine radiographic examination additional x-ray images of the skull were taken in the patients with a history of head. Evidences of skull fracture as well as other bone pathologies in the radiographs were noted. Houndfield-units were measured, if there were signs of attenuation change in the brain parenchyma. In MRI increased intracranial pressure was diagnosed if sulci were effaced, visible ventricular parts were obliterated or herniations were present. Intraparenchymal hyperintensities were consistent with edema, or hemorrhage, if signal void in gradient echo-sequences was noted.

4.3.4 Anomalous/ Congenital

4.3.4.1 Internal hydrocephalus

Hydrocephalus describes the abnormal accumulation of cerebrospinal fluid (CSF) within the cerebral ventricles. Depending on the etiology, hydrocephalus can be divided into congenital or acquired forms. Congenital hydrocephalus is most common in toy-breed dogs (VULLO et al. 1997; THOMAS, 1999; ESTEVE-RATSCH et al., 2001; OHLERTH & SCHARF, 2007; WOO et al., 2010). The exact causes are unknown but may include genetic factors, developmental anomalies, intrauterine viral infections or hemorrhage in the brain (THOMAS, 1999). It can also occur in association with a wide range of CNS anomalies, including meningomyelocele, Chiari malformation, Dandy-Walker syndrome

and other rostrotentorial malformations (THOMAS, 1999; THOMAS, 2010). According to the pathogenesis hydrocephalus can be graded into a communicating and non-communicating form. The latter can be caused by a blockage of CSF flow at the outflow through the lateral apertures, within the subarachnoid space at the level of the arachnoid or to congenital stenosis of mesencephalic aqueducts or lateral apertures (HECHT & ADAMS, 2010). In communicating hydrocephalus all parts of the ventricular system are patent, allowing unimpaired flow of the CSF.

Findings of conventional x-ray of the head such as dome-shaped head, thin structured bones or open fontanelle are suggestive for a hydrocephalus in very young dogs, as well as ventriculomegaly in ultrasound of the brain through the persistent fontanelle (Thomas, 2010). In this study diagnosis of hydrocephalus internus was based on CT and MRI findings. Primary CT findings of hydrocephalus internus include enlargement of one or more ventricles and subarachnoid space. Other findings may be related to the underlying etiology such as congenital anomalies, intraparenchymal masses or traumatic lesions. On the other hand, CT may fail to detect inflammatory periventricular changes and due to the low detail, it may fail to differentiate congenital malformations such as hydranencephaly or porencephaly (HECHT, 2011; LAUBNER & SCHMIDT, 2014). MRI findings include further detailed information related to internal hydrocephalus, such as signs of an increased intraventricular pressure including ventral deviation of fornix, dorsally shifted corpus callosum caused by enlargement of the third ventricle, CSF filled recessus of the bulbus olfactorius. Periventricular interstitial edema (Capping) was diagnosed based on T2W and FLAIR hyperintense areas in the periventricular white matter usually at frontal and occipital horns of lateral ventricles. Due to the high intraventricular pressure it comes to a signal loss on T2W images at the level of mesencephalic aquaeduct called Signal-Void-Sign (KARTAL & ALGIN, 2014; SCHMIDT, 2015).

4.3.4.2 Dandy Walker malformation

The Dandy–Walker malformation (DWM) is a continuum of aberrant development of the cerebellar vermis and the caudal cranial fossa, which can be associated with rostro-tentorial anomalies, such as hydrocephalus, agenesis of the corpus callosum and hypomyelination. This malformation has been described as a spontaneous anomaly in dogs, cats and other domestic species. A deletion in the VLDLR gene has been found in Eurasian dogs, which predisposes this breed to a Dandy Walker like malformation (Dandy–Walker variant, DWV), which is a unique entity believed to represent a milder form of the complex. The anatomical hallmarks of DWM are hypoplasia/aplasia of the cerebellar vermis, enlargement of the caudal fossa with upward displacement of the osseous tentorium, and cystic dilatation of the fourth ventricle. In DWV there is no cystic enlargement, but only cerebellar malformations. These characteristics can be clearly demonstrated in MRI as shown in Figure 6. VLDLR gene contains the code of very low density lipoprotein receptor which is involved in Reelin signaling pathway. Reelin signaling regulates the migration of the neurons in the cerebral cortex and cerebellum. An inherited gene deletion or mutation causing absence of receptors leads to maldevelopment or underdevelopment of CNS (FORSTER et al., 2010). In experimental studies, clinical symptoms in mice with lacking functional Reelin pathway were more severe than in VLDLR deficient mice (GERBER et al., 2015).

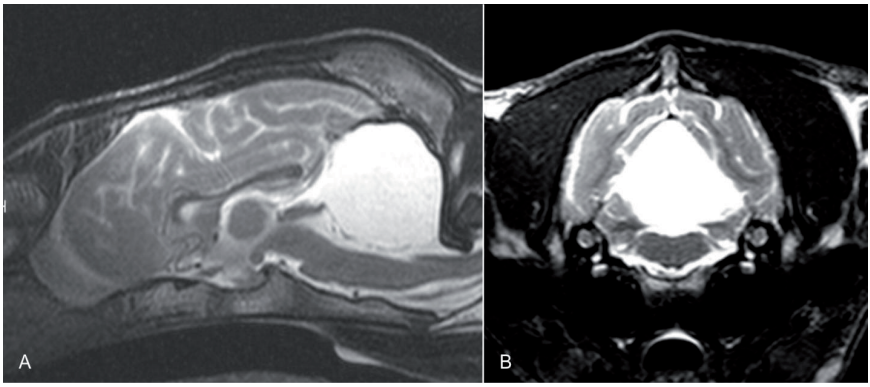

Figure-6: Sagittal and transversal T2-weighted image of a Crossbreed with Dandy Walker malformation. Note the missing vermis, the small remnants of the cerebellar hemispheres and the severely enlarged caudal fossa with elevation of the osseous tentorium cerebelli.

4.3.4.3 Porencephaly

A porencephaly is an encephaloclastic disorder of the central nervous system characterized by cavities within the cerebral hemisphere. The lesion connects the ventricular system with the subarachnoid space but it is widely used to describe any fluid-filled cavity in the fetal or neonatal brain (MACKILLOP, 2011). The origin of these cavities can be caused by damage during brain development, but may also be genetic. Ischemic brain damage, most often due to impaired blood flow in the middle cerebral artery, can cause porencephaly and in most extreme cases, almost the entire cerebral hemisphere may be replaced by fluid, which is called hydranencephaly. There can be variable preservation of the frontal, temporal, and occipital lobes, and of the basal ganglia and diencephalon. The brainstem and cerebellum are always preserved (MACKILLOP, 2011; HORI et al, 2015).

The pathogenesis of these encephaloclastic lesions is no different from necrotic lesions that arise in gestation. The main difference is that lesions arising early in gestation heal

without gliosis, but lead to liquefaction of brain parenchyma (VERBEEK et al., 2012; SCHMIDT et al, 2012).

Porencephaly in CT images is usually seen as a cavitation in the cerebral parenchyma with or without a connection to the ventricle or subarachnoid spaces (HECHT, 2011). Diagnosis of porencephaly in this study was made based on MRI images, showing CSF filled lesions within the cerebral parenchyma extending between subarachnoid space and ventricle wall, with any changes related to increased pressure. In unilateral lesions, contralateral ventricles and midline structures (e.g. corpus callosum, septum pellucidum) may remain within normal. Post contrast medium images are mainly without any sign of contrast enhancement (MACKILLOP, 2011; SCHMIDT et al, 2012; HORI et al, 2015; SCHMIDT, 2015).

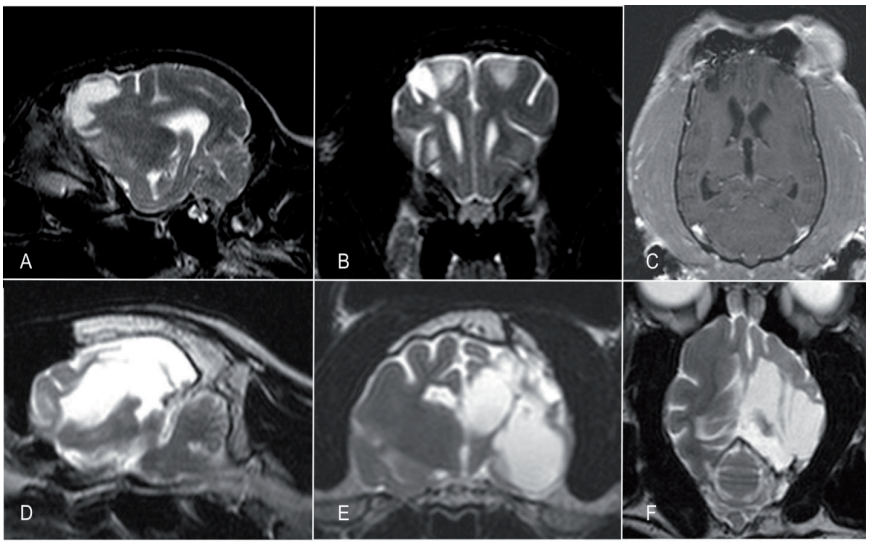

Figure-7: Sagittal transversal and dorsal T2-weighted images of a crossbreed with frontal lobe porencephaly (A-C) and a cat with a profound defect including almost the entire hemisphere.

In humans, familial porencephaly can be due to a mutation in the COL4A1-gene leading. This gene encodes a type IV collagen protein that is a component of basement membranes. The defect leads to a spectrum of signs and symptoms that involve fragile blood vessels (VERBEEK et al., 2012).

4.3.5 Brain neoplasia

Sensitivity of MRI in detecting intracranial tumors in humans reaches up to 99%. In animal patients, the sensitivity of MRI in detecting neoplastic brain disorders was reported around 90%. Assessment of intracranial lesions for neoplasia is based on described MRI characteristics of different tumor types such as topographic location, axial origin, tumor borders, mass effect, signal intensity and contrast enhancement (THOMAS et al, 1996; SNYDER et al, 2006; RODENAS et al, 2011). In dogs, most common diagnosed types of primary intracranial tumors are meningioma, glioma, choroid plexus and pituitary tumors. Meningiomas are the most common extra-axial tumors while astrocytomas are the most common type of intra-axial primary CNS tumors (TROXEL et al, 2004; RODENAS et al, 2011; WISNER et al, 2011; MOTTA et al, 2012). Meningiomas usually locate in forebrain, olfactory bulb and brainstem. MRI imaging characteristics of meningiomas include well-defined tumor margins and peritumoral edema. In T1W images they are usually iso- or hypointense, and mostly hyperintense in T2W images. They show moderate to marked contrast enhancement (THOMAS et al, 1996; WISNER et al, 2011; RODENAS et al, 2011; MOTTA et al, 2012). Gliomas are the tumors originating from neuroepithelial tissue. Astrocytomas are the most common type of gliomas and oligodendrogliomas and glioblastomas other commonly seen types of gliomas. Gliomas are typically intra-axial, heterogeneous, hypo- to isointense in T1W, iso- to hyperintense in proton density weighted (PDW) and T2W images. Contrast enhancement is associated with tumor grade and tends to increase with the grade in astrocytomas, which is highly variable in oligodendrogliomas. Choroid plexus tumors arise from the choroid plexus epithelium within the ventricles. In T1- and T2W images tumors may be hypo-, iso-, or hyperintense,

and typically marked homogenous contrast enhancement due to high papillary vasculature (YOUNG et al, 2011; BENTLEY et al, 2013).

4.3.6 Degenerative Disorders

Primary degenerative diseases of the CNS are generally inherited or congenital affecting therefore mainly young animals, such as storage diseases or leukodystrophic/ spongyform encephalopathies. Lysosomal storage diseases are characterized by accumulation of one or more products of interrupted intracellular metabolic activities caused by the lack of a specific enzyme that leads to cellular dysfunction due to toxic effects or cellular swelling. Abnormal maintenance and/or synthesis of neuronal myelin sheet is thought to be the cause of leukodystrophy. Degenerative diseases of the CNS cause cellular damage in the brain parenchyma without gross anatomical alterations leading to neurological dysfunction. Therefore, CT and MRI scans of patients are often without significant findings. However, symmetrical chances in signal intensity with concurrent significant structural alterations such as hydrocephalus, ventriculomegaly or cerebral atrophy may suggest an underlying degenerative encephalopathy (DEWEY, 2008; HECHT & ADAMS, 2010).

4.4 Statistical evaluation

According to the lesion groups mentioned above the prevalence of seizures related to each lesion type was determined using the formula: prevalence = number of animals with epilepsy/ number of animals per group.

Logistic regression analysis was used to asses for a possible correlation of the severity of head trauma with the occurrence of seizures.

5. Results

The retrospective search of the database has revealed a total of 209 dogs and 86 cats that met the inclusion criteria. Prevalence of seizures according to lesion types are presented below.

5.1 Vascular

Signalement, clinical signs, survival time and outcome of these patients are summarized in Table 6. There was a total of 21 dogs, in which MRI findings were showing characteristics of a vascular lesion. In 11 dogs, findings were consistent with hemorrhage and in 10 with infarction. 8 dogs were presented with seizures and 2 of them were with status epilepticus (both with infarction). There were 13 dogs with vascular CNS diseases without any seizure activity. Seizure prevalence was 0.38 (8/21) in dogs with cerebrovascular accident whereas the part of cerebrovascular diseases in dogs with seizures was 0.10 (8/77).

In 3 (8.8%) cats MRI results were consistent with vascular disease. Of those, 2 were thought to be hemorrhage, while in 1 cat with apathy and nystagmus a rostral cerebellar infarct was presumed. None of these cats had a history of seizure activity.

Age (years)	Breed	Clinical Signs	Diagnosis / localization	Outcome
2	Pug	Unilateral Ataxia, Nystagmus	Caudal cerebellar infarct	Alive, no seizure
5	Dachshund	Stupor, absent brainstem reflexes	Hemorrhage in the fourth ventricle, Cumarin intoxication	4 days no seizure, euthanized
11	Golden Retriever	Vestibular Syndrome	Brain stem hemorrhage	8 days, dead
3	German Shepherd dog	Obtundation	Hemorrhage	6 days no seizures, euthanasia
9	Chihuahua	Generalized Tremor, Pleurothotonus, Hypermetria, Nystagmus	Hemorrhage	Alive, no seizure
3	Vizsla	Hemiparesis, head tilt, disorientation	Thalamic Infarct	Alive, no seizure
4	Labrador	Obtundation, coma	Hemorrhage	Dead
6	Mixed breed dog	Obtundation, sudden coma	Hemorrhage, Cumarine intoxication	5 days no seizure, euthanized
8	Mixed breed dog	Hemiparesis	Striatocapsular Infarct	Alive, no seizure
4	Mixed breed dog	Obtundation	Hemorrhage of Unknown cause	5 years alive, no seizure
10	West Highland White terrier	Obtundation	Infarct, A. cerebri medialis	Lost to follow up
11	Dalmatian	Ataxia, discomfort	Infarct caudodorsal thalamus	Lost to follow up
4	Maltese	Opistothonus, tetraparesis Nystagmus	Rostral cerebrallar Infarct	4 days, euthanized

Table-6: Signalement, clinical signs, survival time and outcome of dogs with intracranial vascular disease without seizures.

Age (years)	Breed	History/ Primary complain	Diagnosis	Survival/ Outcome
2	West Highland White Terrier	Status epilepticus	Infarct, A. cerebri media	Euthanized
3	Münsterländer dog	Seizure	Hemorrhage	Dead
10	Mixed breed dog	Seizures	Hemorrhage	Dead
9	Mixed breed dog	Status epilepticus	Infarct, Thalamus	2 days, Euthanized
3	Australian Shepherd dog	Seizures	Hemorrhage	Lost to follow up
4	Mixed breed dog	Seizures	Hemorrhage	4 years alive no seizure
1	Mixed breed dog	Altered behavior, seizures	Infarct	Lost to follow up
5	Maltese	Seizures, opistothonus, Nystagmus	Infarct	Lost to follow up

Table-7: Signalment, clinical signs and outcome of dogs with seizures and intracranial vascular disease.

5.2 Inflammatory

5.2.1 Dogs

5.2.1.1 Infectious

Only in 5 dogs findings of MRI and CFS analysis were consistent with an inflammatory CNS disease caused by an infectious agent including neosporosis, toxoplasmosis, distemper virus and bacterial origin. Only 2 of these dogs were with seizures. Clinical symptoms of the remaining 3 dogs were other than general ataxia unspecific. The prevalence of seizures in dogs with infectious CNS inflammation was 0.4 (2/5).

5.2.1.2 Meningoencephalitis of unknown origin

In 56 dogs MRI findings and CSF analysis were consistent with inflammatory CNS disease in which diagnostic tests for infectious agents were negative. Granulomatous meningoencephalitis was the most common nature of the inflammation. Of these, 14 dogs were having seizures. In most of the remaining 42 dogs neurologic symptoms included ataxia, blindness, circling and vestibular signs as well as altered behavior and generalized tremors. The prevalence of epileptic seizures was 0.25 (14/56) in dogs with meningoencephalitis of unknown origin. Prevalence of inflammatory CNS diseases in dogs with seizures was 0.21 (16/77).

5.2.2 Cats

There were 5 cats diagnosed with infectious meningoencephalitis suffering from epileptic seizures. In 3 cats, neuronal form of FIP and in other 2 cats Toxoplasmosis was diagnosed. Seizures were the first clinical manifestation in all cats. Tonic-clonic and simple focal seizures were observed. There were 5 cats without seizures at an age between 10 months and 10 years in which infectious meningoencephalitis was suspected. Of those 2 were positive for Coronavirus, one for feline Immunodeficiency virus, and one for Toxoplasmosis. Weakness, obtundation, ataxia, head tilt, nystagmus, visual impairment, proprioceptive deficits and tetraparesis were among the clinical manifestations. The prevalence of epileptic seizures was 0.5 in cats with infectious CNS inflammation and prevalence of inflammatory CNS diseases in cats with seizures was 0.56.

5.3 Head Trauma

There were records of 110 cats that were hospitalized and treated in the Small Animal Clinics due to trauma. Those cats were suffering from head wounds and fractures of unknown origin and injuries assumed to be due to vehicle accidents. Fifty-two of 110 cats

were with records of neurologic examination performed by a veterinary neurology specialist and those were included in the study. Age at the time of hospitalization was ranging between 4 months and 15 years (mean: 4 years, median 3 years).

Nine of the 52 cats (17.3%) had mGCS between 9 and 14 suffering from moderate head trauma. The remaining 43 cats (82.7%) had mGCS between 15 and 18 which were suffering from mild head trauma. Head radiographs in 37 cats were with evident findings including facial bone fractures (n=37), separated mandibular symphysis (n=30), fractured maxillar (n=8) and mandibular bones (n=3). Only 6 of the 37 cats underwent CT of the head and in all those cats, results were without any evidence for a pressure fracture or intracranial hemorrhage.
Patient owners were interviewed via telephone 2 to 9 years after cats were discharged from the clinics. Owners of all of the 52 cats reported that cats showed full recovery after treatment, without having any clinical and neurological sign attributable to head trauma. Owners also did not report any behavior or mental change or activity that could be an outcome of a seizure activity of any type.

An Australian shepherd and Yorkshire terrier with an age of 2.5 years and 3 months, respectively, were suffering from epileptic seizures. Both dogs were referred after a recent head trauma with no seizure history**.** Both two dogs were suffering from primary generalized tonic-clonic seizures.

Findings	No. of Cats
MGCS 3-8	none
MGCS 9 - 14	9
MGCS 15 - 18	43
Fracture of viscerocranium	37
Fracture of neurocranium	none
Early onset seizures	none
Late onset seizures	none

Table-8: Cats with head trauma. (MGCS: Modified Glasgow Coma Score)

Regression analysis was not possible due to absence of seizures in the cats.

5.4 Congenital/ Anomaly

A total of 69 dogs were diagnosed with CNS anomaly and 15 (22%) dogs were suffering from seizures. Age at the time of referral was between 4 months and 4 years (mean: 2.1 years, median: 2 years). Internal hydrocephalus was diagnosed in 53 dogs and of those, 10 (18.9%) dogs were with seizures. Signalement, clinical signs and outcome have been summarized in table 9. Two of the dogs had tonic-clonic seizures. The clinical status in these dogs was severe and the owners decided for euthanasia. There were 54 (78.3%) dogs without seizures suffering from congenital diseases or anomalies. Age at the time of referral was between 1 week and 11 years (mean: 1.9 years, median: 1 year).

There were in total 5 cats in which CNS anomaly was diagnosed. In one cat with primary generalized tonic-clonic seizures, MRI findings were consistent with porencephaly. Age at seizure onset was 9 months. Other neurologic symptoms were aggression, ataxia and head tilt. There were 4 cats without seizures diagnosed with congenital

malformation/anomaly. In 3 of them, MRI findings were consistent with hydrocephalus. In the remaining one cat porencephaly was presumed based on CT findings. Age at the time of referral was between 3 months and 10 months (mean: 5 months). Three of those cats had hydrocephalus and one was with porencephaly. Main complains of these cats were generalized ataxia and progressive visual loss.

Breed distribution

Breeds of seizuring dogs included Australian shepherd, Beagle, Bull terrier, Chihuahua, English and French bulldog, Golden Retriever, Small Münsterlander, Poodel and Pug dog.

Seizure Type

Ten dogs (66.7%) diagnosed with hydrocephalus were suffering from tonic-clonic, simple partial and complex partial seizures. Porencephaly was diagnosed in 2 (13.3%) dogs that were suffering from tonic-clonic seizures. In one (6.7%) dog agenesis of the Corpus Callosum was diagnosed. In other 2 (13.3%) dogs with tonic-clonic seizures Dandy-Walker Malformation was the imaging diagnosis.

Lesion localization

Of those seizure free dogs, mild to severe hydrocephalus was seen in 43 (79.6%), in 4 of those dogs with an accompanying mild to severe Chiari-Like Malformation. Microgyria was diagnosed in a 1.5 years old Australian Shepherd. Quadrigeminal Cyst was detected in 2 dogs with an accompanying Chiari-Like malformation. Porencephaly with periventricular leukodystrophy was suspected based on the MRI findings in one Golden Retriever. Dandy-Walker Malformation was the imaging diagnosis in 7 dogs. Ataxia and/or visual loss were primary symptoms in all dogs of this group. Signalament, clinical signs, diagnosis and outcome of these patients are summarized in Table 10.

Results

The prevalence of seizures in cats with congenital anomaly was 0.2 (1/5). The prevalence in dogs was 0.22 (15/69). Prevalence of congenital malformation in cats with seizures was 0.11 (1/9) and 0.19 (15/77) in dogs.

Age	Breed	Clinical Signs	Outcome
4 Mo.	Munsterlander	Complex partial seizure, disorientation	Euthanized
2 Y	French Bulldog	Simple partial seizures	Lost to follow up
10 M	Pug	Tonic seizures	Lost to follow up
2,5 Y	English Bulldog	Tonic-clonic seizure	Lost to follow up
3 Y	Bull Terrier	Seizure	Lost to follow up
2 Y	Chihuahua	Seizure	2 years post VPS no seizure
4 Y	Beagle	Seizure	Lost to follow Up
9 M	Chihuahua	Seizure, ventrolateral strabismus, hypermetria	Euthanized
3 Y	Chihuahua	Seizure, visual imparement, head tilt	5 years post VPS, normal
6 M	English Bulldog	Seizure, visual impairment	Euthanized 2 months post VPS

Table-9: Signalement, clinical signs and outcome of dogs with seizures associated with Hydrocephalus. VPS: Ventriculo-peritoneal shunt

In the two dogs that were euthanized histopathological examination revealed granulomatous meningoencephalitis, that were not diagnosed at the time of initial diagnosis, or was falsely diagnosed as periventricular edema. In the Beagle porencephaly was seen in MRI in addition to the ventricular distension. It is unclear in these dogs, as to whether the seizures are due to the hydrocephalus or to the other diseases. Therefore, these three dogs were not included into the prevalence estimation. This leaves the prevalence to 13.2%.

Results

Age	Breed	Clinical Signs	Diagnosis	Outcome
7	Chihuahua	Non spesific	Hydrocephalus	Lost to follow up
2	Pug	Non spesific	Hydrocephalus	Lost to follow up
1,5	Australian Shepherd	Behaviour	Microgyria	Lost to follow up
10	Pug	Non spesific	Hydrocephalus	Lost to follow up
8	Yorkshire Terrier	Non spesific	Hydrocephalus	Lost to follow up
3	Chihuahua	Ataxia	Quadrigeminal Cyst	Lost to follow up
0,16	Labrador Retriever	Blindness	Hydrocephalus	Lost to follow up
2	Mix	Blindness	Hydrocephalus	Lost to follow up
0,5	Chihuahua	Non spesific	Hydrocephalus	Lost to follow up
0,75	Dachshund	Head tilt, Tetraparesis	Hydrocephalus	Lost to follow up
0,32	JRT	Ataxia	Hydrocephalus	Lost to follow up
3,9	Yorkshire Terrier	Ataxia	Hydrocephalus	Lost to follow up
4	Chihuahua	Head tilt, Positional Nystagmus	Hydrocephalus	Lost to follow up
7	Papillon	Non spesific	Hydrocephalus	Lost to follow up
0,16	Yorkshire Terrier	Blindness	Hydrocephalus	Lost to follow up
0,16	Mixed breed dog	Blindness	Hydrocephalus	Lost to follow up
1,5	Chihuahua	Blindness	Hydrocephalus	Lost to follow up
9	Englisch Bulldog	Non spesific	Hydrocephalus	Lost to follow up
3	Bolonka Zwetna	Blindness, Deafness	Hydrocephalus	Lost to follow up
11	Pug	Ataxia, Hypermetria	Quadrigeminal Cyst	Lost to follow up
?	Austrian Hound	Circling, Head Tremor, Obtundation	Hydrocephalus	VPS, 12 months post OP, euthanasia

0,3	Australian Shepherd	Visual alteration, Vestibular signs	Hydrocephalus	Lost to follow up
2	Mixed breed dog	Visual alteration	Hydrocephalus	Lost to follow up
2,3	Chihuahua	Opistothonus	Hydrocephalus	Lost to follow up
2	Bull Terrier	Non spesific	Hydrocephalus	Lost to follow up
1	Golden Retriever	Ataxia, Vocalization	Porencephalie	Lost to follow up
2	French Bulldog	Ataxia	Hydrocephalus	Lost to follow up
2m	Mixed breed dog	Tremor, Nystagmus, proprioceptive Deficit	DWM	Euthanized
3m	Eurasian	Nystagmus, Hypermetria	DWM	Alive, no seizure
3w	Golden Retriever	Screaming, Tetraparesis	DWM	Euthanized
6m	Eurasian	Hypermetria	DWM	Alive, 2 years after diagnosis,
6m	Eurasian	Hypermetria	DWM	Alive, 2 years after diagnosis,
3	Labrador	Stupor, Ataxia, Vebtrolateral strabism	Hydrocephalus	VPS, dead 3 years post OP
3	English Bulldog	Obtundation, Ataxia,	Hydrocephalus	VPS, alive 2 years post OP, no seizures
3	French Bulldog	Head tilt, Bbtundation	Hydrocephalus	VPS, alive 1,5 years post OP, no seizures
3m	Chihuahua	Circling, Blindness, Vestibular signs	Hydrocephalus	VPS, no improvement, no seizures, euthanasia
2	German Shepherd	Obtundation, Ataxia, Vestibular signs	Hydrocephalus	VPS, 3 month post OP, euthanasia
4m	JRT	Posttectal Blindness, Ataxia	Hydrocephalus	VPS, no improvement, euthanasia
3m	Australian Shepherd	Blind, Deafness, Obtunddation	Hydrocephalus	Euthanized
1	Pug	Ataxia	Hydrocephalus	VPS, 2 years post OP alive
3m	Chihuahua	Reduced menace response, ataxia	Hydrocephalus	VPS, 3 years post OP alive
3m	Eurasian	Nystagmus, hypermetria, absent menace resp.	DWM	Alive, no seizures
?	English Bulldog	Obtunddation, ataxia	Hydrocephalus	VPS, 2 years post OP alive

?	Peruvian hairless Dog	Obtunddation, ataxia, vestibular Signs	Hydrocephalus	VPS, 2 years post OP alive
6m	Maltese Mix	Circling, blindness	Hydrocephalus	VPS, 14 months post OP alive
1w	Golden Retriever	Vestibular signs, tetraparesis	Hydrocephalus	Euthanized
1,4	Boxer	Nystagmus, tetraparesis	Hydrocephalus	VPS, 8 months post OP alive
3	French Bulldog	Tremor, obtundation	Hydrocephalus	VPS, 8 months post OP euthanasia
5	Rotweiler	Agression, servical pain	Hydrocephalus	VPS, 8 month post OP euthanasia
4m	Austrian Hound	Ataxia, visual Impairment	Hydrocephalus	VPS, 6 month post OP euthanasia
4w	German Pinscher	Blindness, barking	Hydrocephalus	Lost to follow up
3m	West Highland White Terrier	Ataxia, screaming	Hydrocephalus	VPS, 1 week post OP slit ventricle syndrome, euthanasia
7m	Chihuahua	Non spesific	Hydrocephalus	lost to follow up
5m	Husky mix	Vestibular signs	DWM	alive, no seizure

Table-10: Signalement, clinical signs, diagnosis and outcome of dogs with congenital disorders.

5.5 Neoplasia

In 36 dogs with seizures the presumptive diagnosis was intracranial neoplasia. Age at the time of referral was varying between 5 years and 14 years (mean: 8.5 years, median: 8.2 years). In 17 dogs (47.2%) the lesion localization based on the diagnostic imaging was frontal lobe. The lesions were suspected to be of different types of neoplasia including meningioma (n=5), glioma/ glioblastoma (n=5), oligodendroglioma (n=2), astrocytoma (n=2), choroid plexus papilloma (n=1) and germinoma (n=1). There were 19 seizure free dogs with MRI findings that were suggestive for neoplasia. Age at the time of referral in those dogs was varying between 3.8 years and 15 years (mean: 8.6 years, median: 7.9 years). Signalment, clinical signs, presumptive diagnosis and outcome of these patients are summarized in table 12. Among these seizure free dogs, in 6 dogs (31.6%) lesion

was localized in thalamus or hypothalamus, and the differential diagnosis was including astrocytoma, choroid plexus papilloma, granulomatous meningoencephalitis as well as meningioma. The second common lesion localization was the frontal Lobe (n=5, 26.3%). Glioma/glioblastoma and basal meningioma were among differential diagnosis depending on the MRI findings

In 3 cats with seizures at ages of 6, 10 and 11 years (mean: 9 years) intracranial neoplasia was the presumptive diagnosis based on MRI findings (2 Meningioma and 1 Lymphoma). All 3 of them were suffering from primary generalized tonic-clonic seizures. In 13 cats without seizures MRI findings were suggestive of an intracranial neoplasia. Age at the time of referral was ranging from 2 months to 15 years (mean: 10.1 years, median: 11 years). The presumptive diagnosis was meningioma in 6 cats and 2 cats were with a histopathological diagnosis of lymphoma. In one cat a plexus cholesteatoma was associated with the meningioma. Ataxia, altered behavior, and disorientation were the most common neurological symptoms. The neurological examination was also remarkable with findings suggestive of an intracranial pathology (e.g. generalized ataxia, menace response and pupillary reflex deficits). Histopathological conformation was available in none of these cats.

Breed distribution

Among those seizuring dogs with neoplasia most frequently represented breeds included mix breed dogs (n=11, 30.5%), German shepherd (n=3, 8.3%), Labrador retriever (n=2, 5.5%) and french bulldog (n=2, 5.5%). Other breeds including american Staffordshire terrier, Beagle, Boston terrier, Boxer, Longhaired Collie, Dachshund, English bulldog, Small Münsterländer, Pincher, Tibet terrier, Vizsla and Yorkshire terrier were also represented.

Seizure type

Sixteen of 36 (44.4%) dogs with an intracranial neoplasia were suffering from primary generalized tonic-clonic seizures. In 13 of these (81.2%) dogs, the lesion was localized

in the frontal lobe, and in 8 (61.5%) the diagnosis was suspected to be glioma/ glioblastoma (n=2), neuroblastoma (n=4) and meningioma (n=2) of the olfactory bulb. Simple partial seizures were observed in 5 (13.8%) dogs. In two of them the lesion was localized in olfactory bulb, and in the remaining 3 dogs in different parts of the cerebrum. Three of 36 (8.3%) dogs were showing tonic seizures, and in 2 of these the lesion was in olfactory bulb suspected of neuroblastoma and glioma/ glioblastoma. Only one dog (2.7%) was experiencing complex partial seizures. In the remaining 11 (30.5%) dogs, a seizure classification based on the recordings was not possible.

The prevalence of seizures in dogs with neoplasia was 0.65 (36/55) and 0.46 (36/77) was the prevalence of brain neoplasia in dogs with seizures. The prevalence of seizures in cats with brain neoplasia was 0.19 (3/16). The prevalence of neoplasia in cats with seizures was 0.33 (3/9).

Age (Years)	Breed	Primary Clinical Signs	Localization/ Tumor Type	Outcome
5	Mix Breed	Complex partial seizure	not described	Euthanized
6	Labrador Retriever	Simple partial seizure	Astrocytoma	Euthanized
9,2	Beagle	Simple partial seizure, altered behaviour	Lymphoma	Euthanized
10	Mixed breed dog	Simple partial seizure	Rhinencephalon, Glioma/ Gliosarcoma	Euthanized
11	American Staffordshire Terrier	Simple partial seizure	Coronoid plexus papilloma	Euthanized
11	Longhaired Collie	Simple partial seizure	Frontal lobe	Euthanized
8	Bullmastiff	Tonic seizure	Parietal lobe, meningioma	Euthanized
9	Mixed breed dog	Tonic seizure	Frontal lobe- olf. Bulb, glioma/ glioblastoma	Euthanized
10,8	German Shepherd dog	Tonic seizure	Frontal lobe- olf. Bulb, glioma/ glioblastoma	Euthanized
5	Dachshund	Tonic-clonic seizure	Frontal lobe, astrocytoma	Euthanized
5	French Bulldog	Tonic-clonic seizure	Frontal Lobe-Bulbus olf. Glioma/ Glioblastoma	Euthanized
5	German Sherpherd dog	Tonic-clonic seizure	not described	Euthanized
5,5	Rhodesian Ridgeback	Tonic-clonic seizure	Frontal lobe- olf. Bulb, glioma/ glioblastoma	Euthanized
6	Viszla	Tonic-clonic seizure	Frontal lobe- olf. Bulb, glioma/ glioblastoma	Euthanized
7	Münsterländer dog	Tonic-clonic seizure	Interthalamic adhesion	Euthanized
7,9	Mixed breed dog	Tonic-clonic seizure	Frontal Lobe	Euthanized
8,3	Mixed breed dog	Tonic-clonic seizure	Frontal lobe- olf. Bulb, glioma/ glioblastoma	Euthanized
9,5	Mix Breed	Tonic-clonic seizure	Frontal lobe- olf. Bulb, glioma/ glioblastoma	Euthanized
10	Boxer	Tonic-clonic seizure	Adenocarcinoma	Euthanized
10,3	Boston Terrier	Tonic-clonic seizure	Frontal lobe- olf. Bulb, glioma/ glioblastoma	Euthanized

10,3	German Shepherd dog	Tonic-clonic seizure	Frontal lobe- olf. Bulb, glioma/ glioblastoma	Euthanized
11	Labrador Retriever	Tonic-clonic seizure	Frontal lobe-olfactory bulb, meningioma	Euthanized
11,4	Mixed breed dog	Tonic-clonic seizure	Frontal Lobe-olfactory bulb, cystic meningioma	Euthanized
12	Tibet Terrier	Tonic-clonic seizure	Frontal lobe, meningioma	Euthanized
14	Mixed breed dog	Tonic-clonic seizure	Occipital lobe, glioma	Euthanized
6	Mixed breed dog	Seizure	Thalamus	Euthanized
6	French Bulldog	Seizure, circling, ataxia	Oligodendroglioma	Euthanized
6	Yorkshire Terrier	Seizure	Pituitary macroadenoma	Euthanized
7	German Pinscher	Seizure, altered behaviour	Multicentric neoplasia	Euthanized
7,4	English Bulldog	Seizure, altered behaviour	Ventral hippocampus, Glioma/ glioblastoma	Euthanized
7,9	French Bulldog	Seizure, Ataxia	Oligodendroglioma	Euthanized
8	Mixed breed dog	Seizure	Temporal lobe	Euthanized
8	Mixed breed dog	Seizure, altered behaviour	Thalamus, germinoma	Euthanized
9	Rhodesian Ridgeback	Seizure	Glioma/ glioblastoma	Euthanized
11,3	Australian Shepherd	Seizure	Gliomatosis cerebri	Euthanized
13	Poodle	Seizure, weakness	Frontal lobe-bulbus olf. glioma/ glioblastoma	Euthanized

Table-11: Signalament, clinical signs, presumptive diagnosis and outcome of dogs with seizures and intracranial neoplasia.

Age (Years)	Breed	Primary Clinical Signs	Localization/ Tumor Type	Outcome
10	Boxer	Ataxia	Thalamus, astrocytoma	Euthanaized
8	Mixed breed dog	Ataxia	Fronta Frontal lobe- olf. Bulb, Glioma/ Glioblastoma	Euthanaized
6	Dobermann	Vestibular syndrome	Thalamus astrocytoma	Euthanaized
10	Bearded Collie	Blindness	Pituitary adenoma/carcinoma	Euthanaized
7	Mixed breed dog	Polyuria/ Polydipsia	Thalamus, basal meningioma	Euthanaized
13	Bull Terrier	Unknown	Frontal Lobe Bulbus Olf. Glioma/ Glioblastoma	Euthanaized
4,8	German hunting Terrier	Circling	not described	Euthanaized
15	Cocker Spaniel	Disorientation, tetraparesis	Multifocal	Euthanaized
9,5	Labrador Retriever	Unknown	Hypotalamus, Glioma	Euthanaized
13	American Staffordshire	Swelling on head	Pituitary adenoma/carcinoma	Euthanaized
7,5	Leonberger	Weakness, head pressing	Squamous-cell carcinoma metatsasis	Euthanaized
10,5	Cattledog	Aggression	Thalamus, coroid plexus papilloma	Euthanaized
5	Mixed breed dog	Blindness	Basal meningioma	Euthanaized
10,5	Boxer	Aggression	Frontal lobe	Euthanaized
6,8	Mixed breed dog	Blindness	Frantal lobe/olfactory bulb basal meningioma	Euthanaized
10,8	Maltese	Aggression, Ataxia	Thalamus	Euthanaized
6,3	German Shepherd	Tetraparesis	Temporal lobe	Euthanaized
3,8	Bordeaux Mastiff	Vestibular signs	Gliomatosis cerebri	Euthanaized
6,8	Afghan hound	Disorientation, visual alteration	Frontal lobe- olf. Bulb, Glioma/ Glioblastoma	Euthanaized

Table-12: Signalament, clinical signs, presumptive diagnosis and outcome of dogs with neoplasia.

Breed	Differential Diagnosis/ Localization	Symptoms
DSH	Pituitary adenoma	Aggression, ataxia
DSH	Meningioma / right hemisphere	Apathia, blindness, ataxia
DSH	Lymphoma/ left hemisphere	Altered behaviour, circling
DSH	Lymphoma	Blindness
DSH	right side hippocampus region	Circling
Main Coon	Meningioma, left ventricle	Disorientation
Main Coon	Meningioma, right hemisphere	Altered behaviour, vocalisation
DSH	Hypothalamus	Altered behaviour
DSH	Meningioma	Ataxia, opistothonus
DSH	Meningioma	Circling, altered behaviour
DSH	Thalamus, phlexus cholesteatoma	Ataxia, disorientation, altered mentation
DSH	Meningioma, midbrain	Disorientation
DSH	Cystic meningioma	Ataxia, disorientation
DSH	Falx meningioma	Seizures
DSH	Lymphoma	Ataxia, seizures
DSH	Meningioma in 3. ventricle	Ataxia, circling, seizures

Table-13: Symptoms and differential diagnosis in cats with suspected intracranial neoplasia.

5.6 Degenerative

There was only one Dachshund showing MRI changes relating to degenerative disorder of cerebrum which was presumed to be cerebral atrophy. At the time of referral the dog was at 8.5 years of age, and was referred to the clinics due to altered behavior.

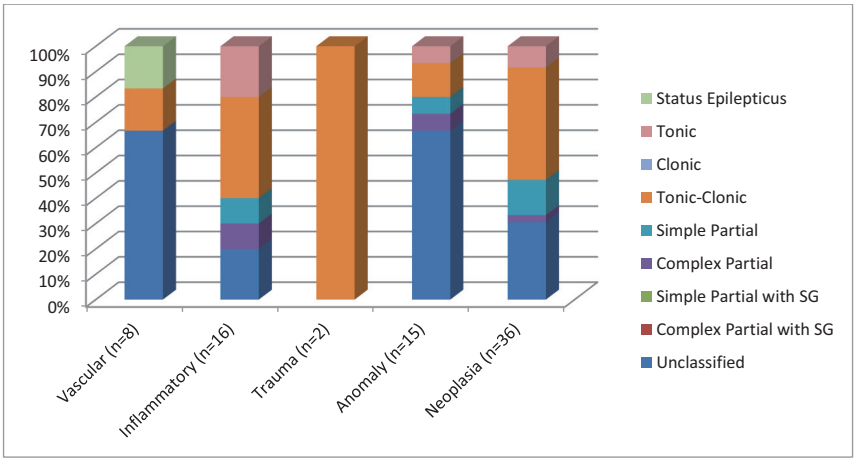

Figure-8: Types of epileptic seizures in dogs in association with underlying etiology. SG: Secondary generalization.

	with seizures	without seizures
Neoplasia	36 (17.2%)	19 (9.2%)
Congenital/ Anomaly	15 (7.2%)	54 (25.8%)
Inflammatory/ Infectious	16 (7.6%)	45 (21.5%)
Vascular	8 (3.9%)	13 (6.2%)
Trauma	2 (0.9%)	
Degenerative	-	1 (0.4%)
Total	77	132

Table-14: Number of dogs according to underlying etiology.

6. Discussion

The technical and scientific developments in medicine are in a constant growth, so as the scale of veterinary patients in practice. Among them, dogs and cats with neurologic disorders, especially those suffering from seizure disorders show an increased number with an estimated prevalence of 1% - 2% in dogs and 0.5%-5.7% in dogs in a referral hospital population (BERENDT, 2005; CHANDLER & VOLK, 2008). Currently, in general practice many of the veterinary patients with seizure disorders are still being treated with different therapy protocols regardless of the underlying cause, due to the lack of further diagnostic possibilities such as MRI or CT, or pure patient owner compliance. Although there are recently many studies published concerning the definition and classification, etiology, genetic background, therapy and outcome of epileptic seizures in dogs and cats, the need for information that can be directly applied by the non-specialist practitioners in order for a precise definition of epilepsy and to shorten the list of differential diagnosis, and thus, to find the best therapeutic approach, is still existing. Overall goal of this study was to be able to correlate neurological symptoms with a possible underlying cause, and therefore, to provide helpful information for decision making to the clinicians.

6.1 Structure of the Study

For the purposes of this study, records of a total of 184 cats and 359 dogs that were referred to the clinics were retrospectively examined. Main criteria were a complete diagnostic work-up including CT or MRI and a detailed documentation including a seizure description made by either the owner or the neurology specialists. The structure of the study was based on the acronym VITAMIN D, which stands for vascular, infectious/Inflammatory, traumatic, anomalous/congenital, metabolic, idiopathic, neoplastic and degenerative causes of neurologic diseases.

The presented study was designed to provide retrospective evaluation. Several patients had been insufficiently documented, and only the information documented precisely could be included.

6.2 Classification

In human medicine, definition and classification of epileptic seizures is still under debate. The lack of a standardized method causes confusion between the clinicians. This situation exists in veterinary medicine as well. The 2010 report of the ILAE proposed the terms genetic, structural- metabolic and unknown instead of idiopathic, symptomatic and cryptogenic, which has already been adopted in latest studies, while others suggested to modify the proposal for veterinary use (ILAE Commission on Classification and Terminology, 2010; MARIANI, 2013; WAHLE et al, 2014). In this study, there was no attempt to establish a new classification or use of a classification that was adopted from the latest proposal of ILAE. Instead, patients were recruited from the determined time period with the original diagnosis made after the work-up. The comparison of the classification of present study with other studies published in same time period reveals important differences due to authors' attempt for constitution of a better classification.

6.3 Vascular Diseases

Cerebrovascular disease occurs as a result of impaired blood supply. The incidence of ischemic stroke in humans is much greater than hemorrhages, accounting for 80% of cerebrovascular diseases. Hypertension is a frequent cause of hemorrhages, while emboli and atheromas caused by systemic or intracranial vascular diseases often gives often rise to an infarction. Several alterations in neurons and neuronal environment such as changes in membrane properties, neuronal loss, collateral sprouting, and in the late phase gliosis and meningocerebral cicatrix following cerebrovascular disease may cause seizures (KALIMO et al., 1997, CAMILO & GOLDSTEIN, 2004).

Overall occurrence of epileptic seizures in humans with ICH varies from 2% to 17%. In a study with large population, 67% of patients with ICH were having simple partial seizures, and status epilepticus occurred in 17%. 30% of patients had seizures as first manifestation of ICH (early seizures) (SUNG & CHU, 1989). In the present study, there

were a total of 21 dogs with suspected cerebrovascular encephalopathy and prevalence of epileptic seizures was 38.1% (n=8/21). Seizures were seen in 36.4% (n=4/11) of dogs with ICH. In a recent study in dogs with a clinical diagnosis of cerebral ischemic stroke, 56% of dogs were having seizures as acute clinical symptom (GRENDAL et al., 2013). Pakozdy et al (2010) and Schwarz et al (2013) reported the prevalence of cerebrovascular accident in dogs with seizures as 2.9% and 9.8%, respectively.

Estimated rates of early seizures range between 3% and 67%, and from 2% to 4% for late seizures in humans with stroke (CAMILO & GOLDSTEIN, 2004). Garosi et al (2005) reported only one dog with forebrain ischemic infarct with seizures as first manifestation out of 33 dogs with brain infarction. In this study, 40% (n=4/10) of dogs with ischemic infarct were with seizures. Two dogs were having primary generalized seizures and other 2 dogs developed status epilepticus.

Three dogs with ischemic infarct were euthanized due to the severe clinical symptoms. In other 3 dogs, no early or late seizures were reported. Concurrent diseases (e.g. cumarin intoxication, lungworm infection, thrombopenia and disseminated intravascular coagulation) complicated the long term follow up, because the dogs were either euthanized or died. Mean survival time for those dogs was 3 days. Follow-up information was obtained in 3 dogs, and in all 3 of them there was no evidence for late seizures noted, although one of them had developed early seizures.

Although cerebellar infarcts have been described in cats (CHERUBINI et al., 2007), there is lack of data on feline vascular encephalopathies. Hyperadrenocorticism, hyperthyroidism, hypertrophic cardiomyopathy, hepatic and renal diseases are among reported concurrent conditions in dogs and cats with intracranial vascular disease. In dogs also *Angiostrongylus vasorum* infection, primary and secondary brain tumors were reported (GAROSI et al., 2005; GAROSI, 2010; LOWRIE et al. 2012). Among clinical manifestations seizures have also been described. In a recent study in cats with histopathology- confirmed non-traumatic cerebrovascular disease (CVD), 7 out of 16 cats were having seizures (ALTAY et al., 2011). In this study, all of the cats with suspected vascular disease were seizure free.

Several mechanisms for the development of seizures due to cerebrovascular diseases both in humans and animals have been described (CAMILLO & GOLDSTEIN, 2004; HILLOCK et al, 2006). Cascades of chemical reactions leading to lowered depolarization threshold of neurons due to hypoxia is mainly suspected as underlying cause of seizures after ischemia. On the other hand, blood leakage into the brain parenchyma or subarachnoid spaces forming a space-occupying lesion and, therefore, causing a mass-effect to the surrounding brain tissue as well as formation of cytotoxic edema are among the mechanisms that are causing seizures following intracranial hemorrhagic strokes (HILLOCK et al, 2006; WESSMANN et al, 2009).

Literature regarding prognosis and outcome of cerebrovascular diseases is lacking in veterinary medicine. In a retrospective study with 33 dogs with ischemic brain infarction, no association between the size, region and the presence or absence of a concurrent disease was reported. Furthermore, there was no relation between outcome and size or localization of infarction. They reported 2 dogs that developed recurrent seizures at 10 and 31 weeks after diagnosis. Similar to this study, their study was also indicating that dogs with concurrent diseases precipitating intracranial infarction had significantly shorter survival times (GAROSI et al., 2005; HILLOCK et al., 2006). Due to the insufficient number of follow-up information and diagnostic reevaluation of seizure-free dogs in this study, rate of late seizures cannot be estimated properly.

In this study, all 3 cats were seizure free. Reported risk factors for post stroke seizures are cortical location, lesion severity and size. According to the literature, both in dogs and cats lesions involving the forebrain cortical area are mostly associated with seizures, while other neurologic signs are related to the location such as vestibular signs, ataxia, circling or hemiparesis. It is also reported that seizures are more common in dogs with cerebrovascular diseases than in cats (PLATT & GAROSI, 2003; ALTAY et al, 2011). Post-stroke seizures are one of the most important causes of late onset epilepsy in humans (SUNG & CHU, 1989; FUKUJIMA & CARDEAL, 1997; CAMILO & GOLDSTEIN, 2004).

The use of high-field MRI and DWI for the detection of CVD is very effective. However, it can be difficult to differentiate other intracranial diseases from CVD. Wolff et al (2012) determined the sensitivity and specificity of high-field MRI in the diagnosis of ICH as 33% and 89%, respectively, and in the diagnosis of ischemic infarcts as 67% and 100%, respectively.

6.4 Inflammatory/ Infectious

Infectious diseases of the CNS causing inflammatory changes, as well as the noninfectious inflammation of brain and meninges are common causes of seizures in dogs and cats. Seizures may appear along the course of disease and stop after rehabilitation, but they may persist or they may first appear in the post infectious period as a complication.

Canine distemper virus (CDV) encephalitis is probably the most common etiology in dogs with infectious inflammatory CNS disease. Among noninfectious inflammatory diseases, granulomatous meningoencephalitis (GME) and necrotizing encephalitis (NE) are the most common diagnosed diseases in dogs with seizures. Breed specific meningoencephalitis in dogs has also been described (TIPOLD, 1995; COATES & BERGMAN, 2005; LORENZ et al., 2011). In the study period, a total of 61 (29.2%) dogs were found with inflammatory CNS disease. Of those, 16 (26.2%) dogs were with seizures. According to recent studies, seizures appear in 5.1% - 13% of dogs with inflammatory CNS diseases (TIPOLD, 1995; ZIMMERMANN et al, 2009; SCHWARZ et al, 2013). Findings in most of the dogs were consistent with GME, while CDV encephalitis was diagnosed only in one dog with simple partial seizures. In dogs without seizures, GME was the most common diagnosis. Seizures in dogs with GME were rarely reported. In a study that reviewed 151 reported GME cases, only 11 dogs with seizures were found (O´NEILL et al., 2005). In the present study, Pugs with NME were over presented breeds among dogs with seizures. Levine et al. (2008) reported the incidence of NME in Pugs with neurological signs as 81%. All of the pugs with confirmed NME had seizure activity.

In another study, 94% of Pugs with NME had seizures (GRANGER et al., 2010). NME was also reported in other small breeds with seizure activity. Unfortunately, there are no studies designed to determine etiopathogenesis of seizures in dogs with necrotizing encephalopathies in certain breeds. Although NME and NLE were initially described as breed-specific necrotizing CNS diseases in Pug dogs and Yorkshire terriers, respectively, similar lesions were recently reported in other small breeds as well. The distinction in characteristics of lesions and whether they manifest seizures may depend on the variations in immunologic reaction (HIGGINS et al., 2008). Pathophysiology of infectious encephalitis related seizures is partially understood. Infectious agent-related differences in the mechanism of seizure activation have been described in human medicine (ENGELBORGHS et al, 2000; MISRA et al, 2008).

In cats, FIP, Toxoplasmosis and Cryptococcosis are the most common infectious diseases among others causing seizures. On the other hand, meningoencephalitis of unknown origin was also reported as the most common cause of seizures with inflammatory origin (SCHWARZ-PORSCHE & KAISER, 1989; PARENT & QUESNEL, 1996; KLINE, 1998). The prevalence of inflammatory CNS diseases in cats with seizures varies among studies between 5.6% and 47% (QUESNEL et al., 1997; SCHRIEFL et al., 2008; PAKOZDY et al., 2010).

In a retrospective study of 286 cases with neurological disorders, 32% of cats were diagnosed with inflammatory CNS disease. In our study, there were a total of 10 (29.4%) cats diagnosed with inflammatory CNS disease. Five of them were with seizures. Clinical and diagnostic investigation findings were associated with FIP in 3 cats and with Toxoplasmosis in 2 cats. Tonic clonic and simple focal seizures were noted. Among other localization-related signs, seizures were often reported in FIP. In a retrospective study with histopathology-confirmed cases of FIP, 25% of cats had seizures that were classified as generalized, partial complex and focal with and without generalization (TIMMANN et al, 2008).

The mechanisms of epileptogenesis following CNS infections are not well established in dogs and cats, probably vary considerably with the type of infection and are most likely

multifactorial. It has been suggested that an impaired balance between excitatory and inhibitory pathways towards excitation following secondary immunological, biochemical and physiological alterations within the neurons as well as in the neuronal environment due to the secretion of large amounts of inflammatory mediators plays a role in the activation of seizures rather than inflammation itself (ENGELBORGHS et al, 2000; CHEN et al, 2004; TIMMANN et al, 2008; VEZZANI et al, 2013).

However, structural damage in cortical areas after encephalitis, and meningitis and subsequent gliosis may constitute epileptogenic foci. The influence of proinflammatory signals may also lead to a residual pathological state. A damaged blood–brain barrier, neuronal death, and persistent neuronal hyperexcitability can potentially all contribute to epileptogenesis (CHOI & KOH, 2008). Furthermore, proinflammatory cytokines can decrease the seizure threshold via interaction with glutamate or gamma-aminobutyric acid-mediated neurotransmission. Inflammatory cytokines can activate microglial cells in general, which in turn increase the production of cytokines, which creates a vicious circle. It has been shown that IL-1, IL-3, IL-6, IL-8, interferon (IFN)-γ, and tumor necrosis factor (TNF)-α have proinflammatory roles, and epileptogenic effects (SINHA, 2008).

Viral infections stimulate interferon-gamma production of CD4+ and CD8+ T-cells. This may directly affect the neurotransmitter receptors on neurons and mainly glutamatergic transmission (KIM et al, 2008). In Canine Distemper Virus infection, epileptogenic factors also include direct virus-induced up-regulation of pro-inflammatory cytokines (IL-6, -8, -12 and TNF-alpha). Secondary cytokine expression after lymphocyte infiltration is rather minimal indicating direct stimulation of the cytokines by the virus (MARKUS, 2002).

Although CDV infection is traditionally associated with seizures it must not be the primary clinical sign of the nervous form of the disease (THOMAS et al, 1993). The occurrence of seizures may be age dependent. In adult dogs non-convulsive nervous disorders may be more prevalent (AMUDE, 2007). The individual nature and severity of the immune response mainly determines the fate of the infected organ. It has been postulated that an imbalance of proinflammatory and anti-inflammatory cytokines aggravates cell damage that contributes to neuronal hyperexcitability, which lowers the threshold for seizure

induction and triggers epileptogenesis. This maybe causes the presence of seizures in younger rather than in older dogs.

Toxoplasmosis was found to be a risk factor for epilepsy in humans (NGOUNGOU, 2015). Toxoplasma gondii also directly invades neurons. Astrocytes and microglia can protect themselves as a result of their ability to inhibit parasitic replication. Brain tissue cysts in the chronic stage of infection often remain silent, their wall may eventually rupture, liberating numerous bradyzoites. This bradyzoit spreading infects new cells and induces localized inflammation. The likelihood of seizures would depend on the location and numbers of cysts (HALONEN, 1996). Although not pathognomonic for toxoplasma infection the positive predictive value of MRI for the detection of the parasite was reported to be 100% when multiple cerebral lesions are associated with a mass effect or contrast uptake (NISSAPATORN, 2004). However, the parasite is also known for its ability to modify the levels of neurotransmitters such as serotonin, glutamate, and gamma aminobutyric acid (GABA) (WEBSTER, 2001). This effect alone may create seizures without any structural changes that would be identifiable in MRI.

Neurolopathological changes in FIP are usually massive consisting of meningitis, ependymitis, periventriculitis, and choroiditis. The virus itself does not seem to be the primary destructive agent, but the inflammatory cells that are recruited to the brain, which initiate the disease through secretion of proinflammatory cytokines. Increases in IL-10 (Dean et al 1997), IL-6 and IL-1 (GOITSUKA et al, 1990), and IL-1 (HASEGAWA & HASEGAWA, 1991), and reductions in IL-2, IL-4, IL-10, and IL-12 (GUNN-MOORE et al, 1998) have been described in both the systematic and neurological form of the disease (FOLEY, 2003). In a retrospective study of cats diagnosed histopathologically with FIP, 25% had seizures (TIMMANN, 2008). Structurally negative animals in MRI are hitherto not reported, but well known amongst specialists.

It has been reported that only 75% of infectious/inflammatory diseases of dogs and cats can be detected in MRI (NEGRIN et al, 2007). Neuronotropic effects and upregulation of glial cells are commonly not seen in MRI. Seizures are significantly more frequent in dogs and cats with localization of the inflammatory lesions to the forebrain. Changes of the

blood brain barrier with invasion of immune-cells, and the development of edema are very important for the generation of signal changes, but may not be present.

In summary, if structural changes are seen in MRI and infectious agents can be identified, seizures can be attributed to the infection. If no structural changes are found, further investigation is indicated to rule out other ethiologies.

6.5 Trauma

In dogs and cats brain injury following head trauma is usually associated with vehicle accidents and falls (GRIFFITHS, 1987; FRIEDENBERG et al., 2012). Brain injury may occur due to primary and secondary pathological alterations. Primary TBI includes direct damage to brain parenchyma (e.g. due to depressed cranial bone fractures) or cerebral blood vessels causing intracranial hemorrhage and brain edema. Secondary TBI is caused by a combination of activation of several interrelated inta- and extracranial biochemical pathways that lead to further brain damage, which may occur during minutes to days after trauma (AGRAWAL et al, 2006; LORENZ et al., 2011). Clinical signs include seizures that may occur hours to years following TBI. Post-traumatic seizures may be focal or generalized depending on the location and severity of brain injury (GRIFFITHS, 1987; LORENZ et al., 2011). The underlying mechanisms in development of PTSs are poorly understood. The pathogenesis of PTSs is thought to be partly due to increased intracranial pressure, change in neurotransmitter concentrations, calcium and sodium influx into brain cells leading to cytotoxic edema, increased release of excitatory amino acids and other cytotoxic mediators at the site of the lesion causing secondary neuronal damage (MCNAMARA, 1999; AGRAWAL at al., 2006; PITKÄNEN et al., 2009; LORENZ et al., 2011). It is known that the CNS is able to recover by means of neuronal plasticity which is defined as the ability to create structural and functional chances in neuronal circuits such as axonal sprouting and dendritic modifications. Disorganization in the course of this recovery process or a shift towards increased excitability also leads to epileptogenesis (SAHOO et al, 2007; LAMAR et al, 2014).

Traumatic brain injury is reportedly among the underlying etiologies of secondary epilepsy in small animals (PARENT & QUESNEL, 1996; PAKOZDY et al., 2008; BAILEY & DEWEY, 2009). In humans with mild and moderate injuries, within 5 years PTSs appear in 0.5% and 1.2% of cases, respectively (ANNEGERS et al., 1998).

There were two dogs with seizures evaluated in this study that were referred to the clinics due to recent head trauma, consisting 2.6% of dogs with seizures. In a retrospective study with 240 dogs with seizures, history of head trauma was reported in 1.2% (3/240) of dogs as underlying cause (PAKOZDY et al., 2008). In other studies in dogs with head trauma the prevalence of early PTSs has been reported between 3.5% and 28%. Prevalence of late seizures was reported between 6.6% and 8% (FRIEDENBERG et al., 2012; STEINMETZ et al., 2013; BELTRAN et al, 2014). It is known that prediction of outcome based on MGCS is very inaccurate. In a recent study in dogs, it was reported that severe findings in MRI in the early phase after traumatic brain injury were correlated with poor outcome, while seizures were mostly associated with intraprenchymal lesions (BELTRAN et al, 2014).

Cats of the present study were all seizure free two years following head trauma (late PTS). Therefore, based upon the results of this study it is not possible to prove the development of PTSs in cats, as well as the association between severity of posttraumatic clinical condition and probability of developing PTSs. In another study, a large population of cats with a history of trauma of any kind was retrospectively analyzed. It was reported that 3.1% of those cats had seizures after the trauma. Diagnostic evaluation with MRI was however done only in a small proportion of the patients. In the same study, it was also reported that in a population of cats diagnosed with idiopathic/ cryptogenic epilepsy 23.9% had history of trauma of any kind, and of those, 72.7% had head trauma. It was therefore assumed that traumatic brain injury in a portion of patients with recurrent seizures without any underlying cause detected may be the underlying cause (STEINMETZ et al, 2010). This difference in the frequency of developing PTSs between cats and humans might be associated with different biological reactions of the brain to trauma. However, data regarding such differences between species is lacking. The low number of cats with head trauma that can return to home and survive until brought to a

veterinary clinic for treatment should be taken into consideration in the evaluation of PTSs in cats, whereas humans with head trauma were examined and treated in a shorter time period. Cats that would have survived the severe head trauma might have developed PTSs. Anatomical differences of brain in size and shape between cats and humans could also influence the effects of head trauma.

The evaluation of whether cats develop PTSs was made based upon information obtained by owner interview. At the time of admission to the clinic, due to the increased risk of general anesthesia in the critical patients and high costs, use of further diagnostic work up with MRI or CT to determine any intracranial pathology following the impact was limited. Also the lack of reevaluation of patients by means of clinical examination and diagnostic imaging and the low number of patients are other limitations of this study.

Due to the nature of outdoor cats, subtle seizure activities, simple partial seizures in particular, might have been overseen or falsely interpreted. For determination of the frequency of PTSs in cats, further studies with larger populations with standardized protocols are needed.

To determine the history of head trauma as an underlying etiology in dogs diagnosed with idiopathic or cryptogenic epilepsy, as well as the rate of late posttraumatic seizures was not among the aims of this study. However, it can be concluded that dogs with head trauma or TBI has considerably high risk for developing seizures in early and late posttraumatic period than cats.

Summarized, it must be stated that seizures in cats with a history of moderate brain trauma and without structural changes in the brain should be further investigated for other underlying causes of seizures if MRI is normal. The association between structural changes of the parenchyma and the occurrence of seizures should be further investigated.

6.6 Anomaly

Disorders of the CNS in veterinary patients related to malformations causing seizures have been described. Brain malformations inducing seizures include hydrocephalus, porencephaly, lissencephaly, hydranencephaly, polymicrogyria, Chiari-like malformation and agenesis of the corpus callosum (DEWEY, 2003; LORENZ & KORNEGAY, 2004). Hydrocephalus is described as excessive accumulation of CSF within the ventricular system or subarachnoid space (MACKILLOP, 2011; LORENZ et al., 2011). In this study, there were 69 dogs and 5 cats diagnosed with a congenital disorder of the brain or an anomaly. Of those, 15 dogs and 1 cat were suffering from seizures. The prevalence of congenital malformation in dogs with seizures was 19.5%, and 11.1% in cats. Pakozdy et al (2008) reported cerebral anomalies in 4.16% of dogs with seizures. In the present study, hydrocephalus was the diagnosis in 53 dogs, and only 13.2% (n= 7/53) of them had epileptic seizures of various types. Similarly, in a study with hydrocephalic Maltese dogs less than 20% had seizures (SIMPSON, 1989). On the other hand, some authors have also reported the hydrocephalus as the most common cause of seizures among developmental CNS diseases of dogs, especially under 1 years of age (PODELL et at, 1995; LORENZ et al, 2011). Although hydrocephalus is a common congenital disorder of domestic animals, it is proportionally less seen in cats than in dogs. There were 3 cats in this study diagnosed with hydrocephalus in which ataxia was the common clinical sign, whereas seizures were not the case. Dewey et al. (2003) reported 2 cats with external hydrocephalus treated with VPS. Both cats had developed post-shunt seizures, while only one was initially presented due to epileptic seizures. Hydrocephalus affects approximately 1 in 1000 birth in humans (TULLY & DOBYNS, 2014). Prevalence of epileptic seizures in children is considerably lower prior to shunt placement than post-shunt. In a retrospective study of 802 children with hydrocephalus seizures were recorded in 32% and of those 28.6% had experienced a first seizure before shunting. Perinatal insult to the brain such as trauma, intraventricular hemorrhage, infection and anorexia were considered risk factors for the development of seizures (BOURGEOIS et al., 1999).

Elevated intracranial pressure and damage or loss of brain parenchyma following excessive CSF accumulation are also considered to predispose to seizure development (VULLO et al, 1997; DEWEY et al, 2003). However, the correlation between ventricle size and clinical signs or seizure development is reported to be low (VITE et al, 1997; THOMAS[1], 2010). In a study in Cavalier King Charles Spaniels with Chiari-like malformation, there was no significant association between ventriculomegaly or caudal fossa overcrowding and seizures (DRIVER et al, 2013). On the other hand, it has been reported that clinical signs in normal pressure hydrocephalus are less severe than in hypertensive hydrocephalus (VULLO et al, 1998; THOMAS, 2010). Underlying etiology such as tumor, inflammation or head trauma or co-existence of other changes in brain parenchyma such as periventricular encephalitis, hemorrhage, neovascularization, brain atrophy may play a role in the activation of epileptogenesis in patients with hydrocephalus (COATES et al, 2006). Since behavioral alterations or seizures may be the only clinical signs presented, a full work-up in all cases of young animals is essential to exclude congenital disorders (DELAHUNTA & GLASS, 2009).

It must be summarized that a more specific classification system according to the underlying cause of hydrocephalus is needed to assess the association of seizures with high intraventricular pressure, periventricular inflammation, inflammatory changes in the CSF, hypoxia induced changes and many more. The prevalence of seizures in hydrocephalus seems to be highly overestimated.

The prevalence of seizures in porencephalic defects seem to be low and needs to be further elucidated.

In this study, there were 3 dogs and 2 cats with porencephaly. Two of the dogs and 1 cat have developed primary generalized seizure. Porencephaly is a rarely reported malformation. However, it seems to be commonly associated with epileptic seizures, although mostly vestibulo-cerebellar signs were reported (MACHADO et al, 2012; HORI et al, 2015). The association between porencephaly and seizures is poorly understood. Proposed underlying mechanisms included cystic hypertention, cortical dysplasia and hippocampal atrophy (DAVIES et al, 2012). In a case report, seizures were found to be

associated with porencephaly and cortical dysplasia in a dog (MACHADO et al, 2012). Recently, porencephaly and concurrent hippocampal atrophy was reported in 2 dogs and one cat with seizures (HORI et al, 2015).

In dogs and cats with Dandy-Walker Malformation clinical signs are typically associated with cerebellar dysfunction such as generalized ataxia, hypermetria, intention tremors as well as vestibular dysfunction. Clinical symptoms described in several reports are similar to the human disequilibrium syndrome, including generalized ataxia, dysmetria/ hypermetria, head tremors, nystagmus and seizures (KORNEGAY, 1986; THOMAS, 1999; SCHMIDT et al, 2008; BERNARDINO et al., 2015). Other concurrent developmental disorders reported in humans include agenesis of the corpus callosum, lissencephaly, hydrocephalus, enlargement of the caudal fossa and cerebellar cortical dysplasia. Hydrocephalus in dogs with cerebellar vermian hypoplasia or DWM was also reported (KORNEGAY, 1986; SCHMIDT et al., 2008). Seizures are not typical for malformations of the posterior fossa, however, up to 90% of humans with lissencephaly have seizures (BONKOWSKY et al., 2008). Similarly, seizures in dogs with dysplastic cerebellar vermis or cerebellum and concurrent lissencephaly have been described (DELAHUNTA & GLASS, 2008). In the study period, there were 9 dogs diagnosed with DWM and of those in only 2 (22.2%) dogs epileptic seizures were recorded. Similar results were also reported in a recent study with Eurasier dogs. Although presence of hydrocephalus and partial agenesis of the corpus callosum was in some dogs detected, a relation with development of seizures was not suspected (BERNARDINO et al, 2015).

Dandy-Walker-malformation without rostrotentorial changes should not be seen as an underlying cause for seizures.

6.7 Neoplasia

In this study, the prevalence of seizures in dogs with intracranial neoplasia is 65.5%. The reported prevalence of epileptic seizures in dogs with intracranial neoplasia is ranging from 45% to 73% (BAGLEY et al., 1999; SCHWARZ et al., 2011; ROSSMEISL et al.,

2013). We also found that unlike cats most of the dogs with an intracranial neoplasia develop epileptic seizures, while the frequency of tumor-related seizures was low in overall population of this study. In our study, the prevalence of neoplasia in dogs with seizures at ≥ 5 years of age is 78.3 %. This was 49.5% in a study in dogs with seizure onset at ≥ 5 years of age (GHORMLEY et al., 2015), while in another recent study in dogs at ≥ 7 years of age at seizure onset, neoplasia was suspected in 56.5% of cases (SCHWARTZ et al., 2013). The results of this study are very consistent with latest reports, showing that risk of developing tumor-associated seizures significantly increases with the age.

We found that the frontal lobe is the most common (47.2%, n=17/36) tumor localization in dogs. Furthermore, in 81.2% of dogs primary generalized tonic-clonic seizures were the clinical manifestation of the neoplasia in the frontal lobe. On the other hand, neoplasia located in the thalamus, midbrain or hindbrain was found in most of the dogs without seizures. Schwartz et al (2011) reported also very similar results. In our study, the most common suspected tumor type was Meningioma, followed by glioma/ glioblastoma, oligodendrioglioma and astrocytoma, which is very similar to the recent publications (SNYDER et al., 2006; DE RISIO, 2014).

The number of dogs with seizures affected by an intracranial neoplasia was higher. This study revealed the prevalence of neoplasia identified by MRI in dogs with seizures as 46.7% (36/77), of those, 47.2 % was localized in the frontal lobe. In other 19 dogs with a suspected intracranial neoplasia, epileptic seizures were not the case. In addition, thalamus/hypothalamus was the most common lesion localization (6/19, 31.6%), followed by frontal lobe (5/19, 26.3%), and the remaining were defined as multifocal.

The results of this investigation revealed the prevalence of neoplasia in cats with seizures as 33%. There were a total of 16 cats with an identified intracranial lesion which was suggestive for neoplasia. Only 3 of those cats were referred to the clinics due to epileptic seizures, while remaining 13 cats were referred for further evaluation of various neurological symptoms, including altered behavior and mentation, ataxia, circling and blindness. Therefore, in this study the prevalence of epileptic seizures in cats with

intracranial neoplasia was 19%. In all other than one cat, the neurological examination was remarkable, indicating an intracranial lesion. In one cat with epileptic seizures the neurological examination was unremarkable whereas MRI results were suggestive for meningioma. In 8 cats meningioma was diagnosed based on MRI findings, while in 3 cats histopathological diagnosis was lymphoma.

The results of this study show that intracranial neoplasia is the most common cause of symptomatic epilepsy in cats also. Similar to our results, in recent studies reported prevalence of seizures in cats with intracranial neoplasia is also nearly 23% (TROXEL et al., 2003; TOMEK et al., 2006). Schriefl et al. (2008) and Pakozdy et al. (2010) reported the prevalence of neoplasia in cats with seizures as 18.7% and 13%, respectively. These results are considerably similar with the results of our study. In some of these very similar studies, Troxel et al (2003) and Tomek et al (2006) also reported the percentage of cats with intracranial neoplasia without history of epileptic seizures as 77.5% and 77%, respectively, which are also very consistent with the results of the present study.

The pathophysiology of tumor-associated seizures is still under investigation. It has been reported that toward excitation shifted balance between intracortical inhibitory and excitatory mechanisms caused by different biochemical, anatomical and physiological changes lies on the basis of pathophysiology of seizures associated with brain tumors.

Breakdown of the blood-brain-barrier can contribute to the development of epileptic activity. A decreased expression of transmembrane junctional proteins and heightened release of vascular endothelial growth factor in the peritumoral tissue was found in rats with tumors and epileptic seizures (CHI et al., 2008). The spread of epileptic activity can be increased as a consequence of tumor induced upregulation of connexin 43 that mediates electrical and metabolic coupling between cells (ARONICA et al, 2001). Other proposed mechanisms of tumor-induced epileptogenesis include changes in peritumoral amino acid levels, metabolic imbalance, edema, pH alterations and morphological changes (BEAUMONT & WHITTLE, 2000; SCHALLER & RUEGG, 2003; SCHALLER, 2005). These include degradation or diminished maintenance of inhibitory synapses (McNamara, 1999). The capability to preserve homeostatic functions as the clearance of

neuronally released potassium and glutamate from the extracellular space can be impaired. High extracellular potassium levels can both, generate epileptiform activity and prevent repolarization (Seifert et al, 2010). All these factors can obviously differ tremendously between tumor types and histological subtypes and are beyond detection under clinical conditions.

The retrospective structure of this study prevents the standardization of diagnostic evaluations, which is an important limitation of this study. The patient classification was made on the basis of clinical diagnosis, which was made based upon clinical findings, CSF examination and MRI findings. Even though MRI has approximately 90% sensitivity for detecting neoplasia, dogs and cats might have been misdiagnosed as having neoplasia versus other intracranial diseases (WOLFF et al., 2012).

In summary, the occurrence of seizures is more likely in primary neuroectodermal tumors with forebrain location.

6.8 Degenerative Disorders

Several degenerative disorders of the CNS causing seizures have been identified in dogs and cats, including storage diseases (e.g. neuronal ceroid lipofucinosis), leukodystrophies, spongy degenerations and abiothrophies. Since the degenerative diseases are genetic in origin, clinical signs are typically chronic progressive and begin in the early ages (DEWEY, 2008; LORENZ et al., 2011). Genetic defects responsible for the diseases have been identified and degenerative disorders that are seen in specific breeds have been also reported. Tentative diagnosis can be made based upon clinical signs and CSF examination, urinalysis, and diagnostic imaging findings, while definitive diagnosis is made by genetic testing, tissue biopsy for detection of deficient enzymes or storage protocols for storage diseases or by histopathological examination (BRAUND, 2003; DEWEY, 2008; DELAHUNTA & GLASS, 2009; DE RISIO, 2014). There was only one wire-haired Dachshund with no seizure history included into this study with suspected cerebral atrophy. Considering the conventional diagnostic work-up in seizure patients,

the low number of patients diagnosed with suspected degenerative diseases may be explained by specific diagnostic modalities of degenerative CNS diseases which are not applicable in routine. On the other hand, as it was in the present study, studies in dogs and cats with seizures are widely based upon remarkable findings of diagnostic work-up, in which borderline findings, such as mild lateral ventricular asymmetry or widening, mild density changes or mildly elevated CSF protein levels, are considered irrelevant for epileptogenesis, so that the patients were diagnosed with idiopathic or cryptogenic epilepsy. MRI characteristics of several degenerative diseases in single cases have been defined (HECHT & ADAMS, 2010). However, use of MRI and CSF analysis combination as primary diagnostic tool for detection of degenerative diseases cannot be recommended. There is any report on prevalence of degenerative diseases in seizure patients, thus, further studies are undoubtedly needed.

7. Conclusion

Whereas limited case numbers may not allow to draw conclusions about vascular, neoplastic and degenerative brain disease and epileptic seizures, two main results can be taken from this epidemiological study. It has been stated that seizures are the typical clinical sign found in animals with internal hydrocephalus and in animals with head trauma. As we could not confirm this statement from our source population a reappraisal of these notions and further epidemiological, multicenter studies are necessary to further elucidate the association and underlying pathophysiology of seizures and internal hydrocephalus as well as brain trauma.

8. Summary

The purpose of this study was to determine a possible association between diagnostic imaging findings and the occurrence of seizures in dogs and cats. We, therefore, retrospectively evaluated the prevalence of seizures in dogs and cats with vascular, inflammatory, infectious, traumatic, anomalous, neoplastic and degenerative lesions of the brain in the course of disease or rehabilitation. Medical records of the Small Animal Surgery Clinics of the Department of Veterinary Clinical Sciences, Justus-Liebig University, Giessen, Germany, were evaluated retrospectively. Groups were built according to general lesion types and according to the VITAMIN D scheme. For each group, patient data including breed, age at the onset of seizures or at the time of referral, seizure type, neurologic examination and diagnostic imaging findings, the clinical and, if available, histo-pathological diagnosis were collected. Assessment of neurologic condition of patients with head trauma was made by means of the Modified Glasgow Coma Scale (MGCS). A time period of at least two years after the discharge of the patient was planned for the evaluation of long-term outcome in animals with head trauma. To obtain information for long-term evaluation, patient owners were interviewed via telephone. According to the lesion groups mentioned the prevalence of seizures related to each lesion type was determined using the formula: prevalence = number of animals with epilepsy/ number of animals per group.

The retrospective search of the database has revealed a total of 346 dogs and 143 cats that were referred either due to epileptic seizures or clinical neurological symptoms that underwent CT or MRI of the neurocranium. Of those, 209 dogs and 86 cats have fulfilled the inclusion criteria and enrolled into the study. In dogs with cerebrovascular accident seizure prevalence was 0.38. None of the cats in this study with suspected vascular cerebral disease had a seizure history. The prevalence of seizures in dogs with infectious CNS inflammation was 0.4 and with non-infectious inflammatory CNS diseases was 0.21. In cats, the prevalence of seizures due to inflammatory CNS diseases was 0.5. In the group of traumatic brain diseases none of the included patients showed epileptic seizure activity. A total of 69 dogs were diagnosed with CNS anomaly and of those 22% were

suffering from seizures. Internal hydrocephalus had a prevalence of 13.2 %. In this group were 5 cats were included and only one cat with porencephaly had seizures. The prevalence of seizures in dogs with brain neoplasia was 0.65 and 0.19 in cats. There was only one Dachshund showing MRI changes relating to degenerative disorder of the cerebrum, which was presumed to be cerebral atrophy.

Whereas limited case numbers may not allow to draw conclusions about vascular, neoplastic and degenerative brain disease and epileptic seizures, two main results can be taken from this epidemiological study. It has been stated that seizures are the typical clinical sign found in animals with internal hydrocephalus and in animals with head trauma. As we could not confirm this statement from our source population a reappraisal of these notions and further epidemiological, multicenter studies are necessary to further elucidate the association and underlying pathophysiology of seizures and internal hydrocephalus as well as brain trauma.

9. Zusammenfassung

Der Zweck dieser Studie war es, die Assoziation zwischen Befunden von diagnostischen Bildgebungsverfahren und dem Auftreten von Anfällen bei Hunden und Katzen zu bestimmen. Die Prävalenz von Krampfanfällen bei Hunden und Katzen mit vaskulären, entzündlichen, infektiösen, traumatischen, neoplastischen und degenerativen Läsionen sowie Missbildungen des Gehirns wurden im Verlauf der Erkrankung oder Rehabilitation retrospektiv dokumentiert. Die Aufzeichnungen von Hunden und Katzen, die einer Magnetresonanztomographie (MRT) oder Computertomographie (CT) des Kopfes unterzogen wurden, wurden untersucht. Die Gruppen wurden nach den allgemeinen Läsionstypen nach dem VITAMIN D-Schema gebildet. Für jede Gruppe wurden Patientendaten einschließlich Rasse, Alter bei Beginn der Anfälle oder zum Zeitpunkt der Überweisung, Anfallsart, Befunde der neurologischen Untersuchung und Bildgebungsverfahren sowie die klinische und, wenn vorhanden, histo-pathologische Diagnose dokumentiert. Die Beurteilung des neurologischen Zustands von Patienten mit Kopftrauma erfolgte mittels modifizierter Glasgow Coma Scale (MGCS). Besitzer von Tiere mit Schädelhirn-Trauma wurden mindestens zwei Jahren nach der Entlassung des Patienten per Telefon nach möglicher Anfallsaktivität befragt. Nach den angegebenen Läsionsgruppen wurde die Prävalenz von Anfällen, die mit jedem Läsionstyp in Verbindung stehen, nach folgender Formel bestimmt: Prävalenz = Anzahl der Tiere mit Epilepsie / Anzahl der Tiere pro Gruppe.

Die retrospektive Suche der Datenbank ergab insgesamt 346 Hunde und 143 Katzen, die entweder Aufgrund der epileptischen Anfällen oder neurologischen Symptome überwiesen und mittels MRT oder CT untersucht worden sind. Insgesamt 209 Hunde und 86 Katzen haben die Einschlusskriterien erfüllt. Bei Hunden mit zerebrovaskulärer Erkrankung wurde eine Prävalenz von epileptischen Anfällen von 0,38 bestimmt. Keine der Katzen in dieser Studie mit Verdacht auf vaskulärer Zerebralkrankheit hatte epileptische Anfälle. Die Prävalenz von Anfällen bei Hunden mit infektiöser ZNS-Entzündung betrug 0,4 und bei nicht-infektiösen entzündlichen ZNS-Erkrankungen 0,21. Bei Katzen betrug die Prävalenz von Anfällen durch entzündliche ZNS-Erkrankungen 0,5. In der Gruppe der Schädel-Hirn Trauma Patienten zeigte keiner der eingeschlossenen

Patienten epileptische Anfälle. Insgesamt wurden 69 Hunde mit ZNS-Anomalie diagnostiziert und von diesen 22% hatten Anfälle. Hunde mit einem Hydrozephalus zeigten eine Prävalenz von 13,2 %. In dieser Gruppe waren insgesamt 5 Katzen enthalten und nur eine Katze mit Porencephalie hatte Krampfanfälle.

Die Prävalenz von Krampfanfällen bei Hunden mit Neoplasien des Gehirns betrug 0,65 und 0,19 bei Katzen. Es gab nur einen Dackel mit MRT Befunden die degenerative Erkrankung des Großhirns zeigten, und daher wurde die zerebrale Atrophie diagnostiziert.

Während begrenzte Anzahl der Fälle nicht erlaubt, Schlussfolgerungen über vaskuläre, neoplastische und degenerative Hirnkrankheiten und epileptische Anfälle zu ziehen, ergeben sich aus dieser epidemiologischen Studie zwei Hauptergebnisse. Obwohl in der Literatur immer wieder angegeben ist, dass Krampfanfälle das typische klinische Zeichen bei Tieren mit Hydrozephalus und bei Tieren mit Kopftrauma sind, können wir diese angaben nicht bestätigen. Eine Neubewertung dieser Begriffe und weitere epidemiologische, multizentrische Studien sind notwendig, um die Assoziation und die zugrundeliegende Pathophysiologie von Krampfanfällen und innerem Hydrozephalus sowie Hirntrauma weiter zu erforschen.

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12. Erklärung

Ich erkläre: Ich habe die vorgelegte Dissertation selbständig und ohne unerlaubte fremde Hilfe und nur mit den Hilfen angefertigt, die ich in der Dissertation angegeben habe. Alle Textstellen, die wörtlich oder sinngemäß aus veröffentlichten oder nicht veröffentlichten Schriften entnommen sind, und alle Angaben, die auf mündlichen Auskünften beruhen, sind als solche kenntlich gemacht. Bei den von mir durchgeführten und in der Dissertation erwähnten Untersuchungen habe ich die Grundsätze guter wissenschaftlicher Praxis, wie sie in der "Satzung der Justus-Liebig-Universität Gießen zur Sicherung guter wissenschaftlicher Praxis" niedergelegt sind, eingehalten

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