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Original Scientific Paper**SEIZURES IN DOGS AND CATS****Nenad ANDRIĆ***

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Summary

When dogs or cats get seizures, epileptic seizures and epilepsy are usually thought of. However, it is important to take into account the existence of seizures that are similar to epileptic seizures but do not belong to epileptic seizures (non-epileptic seizures). Non-epileptic seizures occur suddenly, are short-term, disappear as quickly as they occur, recur and have no epileptic etiology and can be of non-neurological and neurological origin. Unlike non-epileptic seizures, epileptic seizures have a specific neural origin and represent excessive, synchronous, usually self-limiting epileptic activity of brain neurons. Epileptic seizures should be distinguished from reactive seizures because reactive seizures occur as a natural response of a healthy brain to transient disorders (metabolic or toxic in nature) and they disappear after the cause ceases to act. Absolute confirmation that it is an epileptic seizure can be difficult because it requires both visualization of the seizure and registration of changes on the EEG. In practice, the suspicion that epileptic seizures occurs is based on information from the medical history and videos. In making a differential diagnosis when an seizure occurs, it is necessary to take into account the age of infected animals, the presence of clinical signs other than the seizure, the presence or absence of disease progression, video recording, blood counts and blood biochemical parameters results, CST test results, and X-ray, MRI or CT findings. The first step in a diagnosis is to determine whether the lesion that leads to the onset of the seizure is localized extracranially or intracranially. If the lesion is localized extracranially, it should be determined whether the problem originates outside the body (poisoning with xylitol, organophosphates, chocolate) or from the body (hypothyroidism, hypocalcemia, kidney disease, etc.). If the process is localized intracranially, it should be determined whether the process is progressive (tumor, inflammation, hydrocephalus, etc.) or not.

Keywords: seizures, dogs, cats**INTRODUCTION**

In the clinical practice of small animals, seizures are one of the most common neurological problems. The term seizure was not clearly defined until year 2015, when the International Veterinary Working Group on Epilepsy, by consensus, made recommendations for the definition of seizure-related terms, the definition of epilepsy and the classification of epilepsy in dogs and cats (Berendt, 2015). The term seizure was previously mostly used when epileptic seizures were suspected, with epileptic seizures

often not differing from reactive seizures, which led veterinarians to be skeptical when it came to a diagnosis. Based on the recommendation of this working group, the term seizure can be used for any sudden, short-term and transient event. Therefore, this does not mean that the event is epileptic. An epileptic seizure is a manifestation of excessive synchronous, usually self-limiting epileptic activity of brain neurons. Epileptic seizures can be manifested by the appearance of short episodes with convulsions or focal motor, autonomic signs or signs of behavioral disorders.

Reactive seizures, unlike epileptic seizures, represent the natural response of a healthy brain to transient dysfunctions (metabolic or toxic in nature) and they can stop (they are reversible in nature) if the cause or disorder that led to them is eliminated.

The normal brain responds with an seizure in response to various stimuli originating from the central nervous system (CNS), but also to many stimuli outside the CNS (Figure 1).

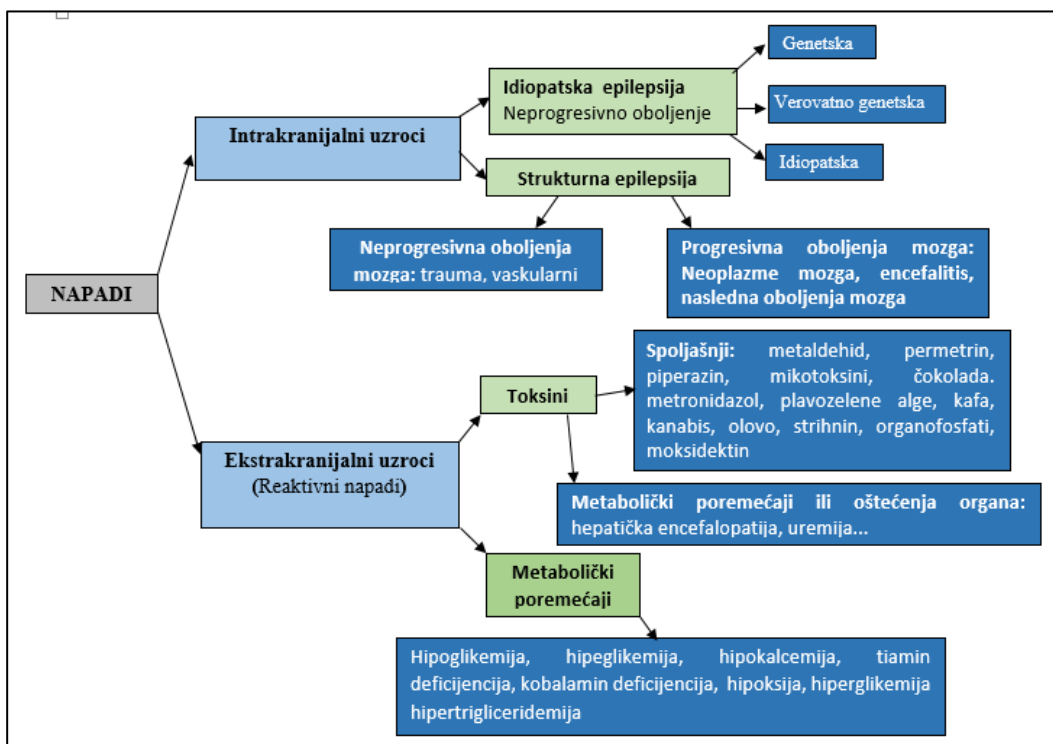


Figure 1 Causes of seizures in dogs and cats

Taking this fact into account, the first task of the clinician is to determine whether the causes of the seizures are extracranial or intracranial in nature. If the causes of the seizures are extracranial, they can originate from the body (but outside the nervous system) or outside the body (like intoxication). Intracranial causes of seizures can be progressive and non-progressive diseases. Progressive causes of seizures include diseases that over time can affect the increasing extent of brain tissue damage, which not only

provokes seizures but also leads to other neurological clinical signs. Idiopathic epilepsy is the most common cause of intracranial non-progressive seizures, but also some diseases that lead to development of structural epilepsy may also have the character of a non-progressive disease.

Given the large number of pathophysiological conditions that can lead to seizures, patient information (age category, species, breed), detailed information collected from medical history, clinical and neurological examinations and minimum data obtained by examination of hematological and biochemical parameters of serum, should allow setting differential diagnoses.

Patient information

Data on the age category in dogs with seizures is the first step on the basis of which a differential diagnosis is made (Table 1). The importance of breed predisposition (genetic basis) when it comes to seizures has been proven in some breeds of dogs with IE (Hülsmeier et al., 2015; Ekenstedt and Oberbauer, 2013; Seppälä et al., 2012). Unlike dogs in which idiopathic epilepsy is usually of genetic origin, there is little data to support such an assumption in cats.

Table 1 Differential diagnosis of seizures depending on age category

Diseases	Young up to 9 months	Adults 9 months - 5 years	Old more than 5 years
Lizencephaly	x		
Lysosomal enzyme storage disorder	x		
Trauma	x	x	x
Infection and other inflammatory diseases	x	x	x
Hypoglycaemia	x	x	x
Poisoning - Organophosphates, strychnine	x	x	x
Hepatic encephalopathy	x	x	x
Other acquired metabolic disorders	x	x	x
Juvenile epilepsy	x		
Idiopathic epilepsy	rare	x	rare
Structural epilepsy	x	x	x
Thiamine deficiency	rare	rare	
Brain tumor		rare	x
Paroxysmal dyskinesia	x	x	x

One study found that European shorthair cats may be predisposed to IE (Pakozdy et al., 2010), but this finding cannot be considered evidence of genetic origin (Pakozdy et al., 2014). The effect of sex hormones on seizures has been well documented in human medicine, where women have been diagnosed with catamenial epilepsy characterized by an increase in the frequency and severity of seizures during certain periods of the menstrual cycle (Verrotti et al., 2012).

A similar phenomenon has not been found in dogs and cats, so no reliable conclusions can be made about the effect of sterilization on the occurrence of seizures (lack of focused research and strong scientific evidence). In general, dogs with idiopathic epilepsy appear to be mostly male, but the role of androgens is controversial and there is a lack of research to focus on androgens and epilepsy (Van Meervenne, 2014).

Medical history

From medical histories it is necessary to collect information related to immunization, application of ectoparasites, diet, previous illness or injury, description of the seizures (video recording), circumstances under which the seizures occur, possible occurrence of some other clinical signs before the seizures and how the animal behaves between seizures (LeCouteur, 2005).

The use of antiektoparasites and their influence on the occurrence of seizures can be observed from two aspects. One involves overdose and the other hypersensitivity in dogs with a predisposition to IE. When it comes to hypersensitivity, the American Veterinary Medical Association (AVMA) and The European Medicines Agency have announced on their website that Bravecto® (isoxazoline) used as an antiektoparasitic in dogs and cats can lead to seizures, tremor and loss of coordination. In reports of side effects, some animals developed seizures without a known history of seizures (AVMA, 2018). AVMA reports that similar side effects can be caused by Nexgard® and Simparica®. Although relatively often in clinical practice intestinal parasite infestation is considered as the cause of the seizures, intestinal parasites can be considered as the cause of the seizures only in puppies/kittens with strong invasion and inadequate diet (poorly fed individuals, inadequate feeding frequency).

Dietary pattern is an important information in the medical history in patients with seizures. The reasons for the occurrence of diet-related seizures can be explained by certain food ingredients, lack of certain nutrients or due to the food preparation that destroy nutrients in commercial food, the lack of which has been proven to lead to seizures. Thus, it was found that in some puppies fed granules of Nutritional Balance Lamb & Rice all breeds GROWTH products (Bento-Kronen), the occurrence of seizures was caused by the source of plant proteins used in this food (WEBCANINE, 2011). Thiamine deficiency (vitamin B₁), among other clinical signs in dogs and cats, leads to seizures. Causes of thiamine deficiency include consumption of raw fish products that often contain thiaminase, cooked foods in which thiamine is destroyed by heating or by the use of meat preserved with thiamine-inactivating sulfites (Chang et al., 2016; Penderis et al., 2007; Singh et al., 2005; Steel, 1997).

A description of the seizures, the frequency and duration, and behavior of the animal between seizures (inter-ictal period), the circumstances under which the seizures occur

and a video recording of the seizures are necessary to assume what could be the causes of the seizures. First, it is important to determine if a seizure has occurred and then distinguish between epileptic seizures, syncope (the result of heart and/or lung disease), narcolepsy or cataplexy, or episodic weakness (myasthenia gravis, polymyopathy, polyneuropathy, or metabolic abnormalities). Tonic, clonic, or tonic-clonic muscle movements, with or without loss of consciousness, accompanied by signs of autonomic disturbance such as urination, defecation, or salivation generally indicate the presence of epileptic seizures. However, absolute confirmation of the epileptic nature of the seizure can only be obtained by simultaneously observing the characteristic changes in the EEG and the physical manifestations of the seizure, which is practically very difficult to perform in veterinary medicine (De Risio, 2015). The problem is, besides the low likelihood that epileptic seizure will occur during examination, the fact that there is currently no reliable, standard protocol for recording EEG in dogs.

The type of seizures in dogs or cats can be helpful in determining the nature of the underlying cause. Generalized seizures are characteristic of most metabolic and toxic causes of seizures, as well as idiopathic epilepsy. Focal seizures usually occur in animals with acquired focal or multifocal cerebral abnormalities that may be progressive or non-progressive (e.g., congenital cerebral abnormalities, neoplasms, encephalitis, or previous episodes of cerebral hypoxia, ischemia, trauma, or infection). However, focal seizures may also be registered in animals with metabolic encephalopathy that would be expected to cause generalized reactive seizures, and focal seizures with or without secondary generalization may be seen in animals with hereditary epilepsy, as well as animals with idiopathic epilepsy which have no pathological evidence of concomitant or previous intracranial disease. Psychomotor seizures can be seen in animals with lead poisoning, but also in structural or idiopathic epilepsies. Loss of consciousness accompanied by muscle atony is more often associated with episodes of narcolepsy or syncope. Muscle collapse and muscle flaccidity without loss of consciousness are most likely related to episodic weakness resulting from metabolic dysfunction.

Clinical and neurological examination

After collecting data that include patient information and medical history (it would be good to have a video of the seizures), a clinical examination should be performed to detect or rule out the existence of disease that originate outside the CNS, and which could be responsible for the seizures. In this assessment, haematological examination, routine serum biochemistry and urine analysis should rule out most causes of reactive seizures. The neurological examination should reveal whether there are other neurological signs besides the seizures, if the previous examination did not establish the existence of changes in other organ systems. If there are other neurological signs, special examination

methods should be used to determine the pathophysiological mechanism of the disease. For this purpose, the collection and examination of cerebrospinal fluid and examination of the head are performed by computed tomography (CT) and/or magnetic resonance imaging. If there is a suspicion that it is an intracranial disorder, regardless of the fact that there are no other neurological signs other than the seizures, it is also indicated to perform these specialist examinations, especially when it comes to older individuals. It is known, for example, that in the case of a brain tumor, the only clinical sign in the beginning may be seizures. However, if the dogs are between one and five years old and belong to breeds that have a proven genetic predisposition to epilepsy, have no other clinical signs of the disease and seizures usually occur during rest or sleep, the most likely diagnosis is idiopathic epilepsy. This is important from the aspect of the decision of the owner to agree or reject all the above mentioned specialist examinations, depending of his financial ability. Genetic, DNA testing can be applied to determine the existence of an inherited underlying disease, which is very important when it comes to valuable breeding individuals. Electroencephalography plays an important role in the diagnosis and treatment of epilepsy in humans, however it is less useful in dogs (and especially in cats) for the reasons already mentioned.

This diagnostic approach should help the clinician to determine the cause of the seizures, which will then enable the selection of the most appropriate therapy and increase the probability of therapeutic success. However, it should be explained to the owners that despite the adequately diagnosed and applied therapy, treatment failure can occur even in cases when it is not a progressive disease (idiopathic epilepsy that are refractory to therapy).

CONCLUSION

This diagnostic approach should help the clinician to determine the cause of the seizures, which will then enable the selection of the most appropriate therapy and increase the probability of therapeutic success. However, it should be explained to the owners that despite the adequately diagnosed and applied therapy, treatment failure can occur, even in cases of non-progressive diseases. For example, in dogs with idiopathic epilepsy, as well as in people with the same disease, in 25-30% of cases there is no satisfactory response to antiepileptic drug therapy (idiopathic epilepsy that are refractory to therapy).

Conflict of interest statement: The authors declare that there is no conflict of interest.

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