

Canine Epilepsy and Lafora disease

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Introduction

Epileptic seizures are one of the most common chronic neurological diseases in the canine species. Estimated prevalence of canine epilepsy is 0.5-5%. An epileptic seizure is an event that originates in the brain however its cause can be found anywhere else in the body or in the environment. The management of epileptic seizures changes dramatically depending on the underlying cause, on the frequency, on the severity and on the life style of the owner and pet. Epilepsy is one of the most often misdiagnosed, mistreated or undertreated conditions.

Definitions

An **epileptic seizure** is the clinical manifestation of a paroxysmal disturbance of the brain function. Also it can be defined as the manifestation of hypersynchronous abnormal neuronal activity in the cerebral cortex.

Epilepsy is referred as a chronic neurological condition characterized by recurrent epileptic seizures. Epilepsy is often considered when two or more seizures occur at least one month apart.

Type of Seizures

In veterinary medicine a modified version of the International League Against Epilepsy (ILAE) guidelines for seizures classification has been advocated.

This is the recent proposed epileptic **seizure types** classification:

Self-limiting

- Focal
 - Sensory
 - Motor
 - Elementary
 - Automatism (automotor)
- Generalized
 - Tonic-clonic
 - Clonic
 - Myoclonic
 - Atonic

Clustered or continuous (status epilepticus)

- Focal
 - Motor (epilepsia partialis continua)
 - Sensory (aura continua)
- Generalized

Reflexive (known precipitating stimuli)

A **self-limiting seizure** is an isolated event that occurs once in 24 hours, appears suddenly out of a background of normality and then disappears with similar abruptness. **Cluster seizures**, on the other side, indicate the reoccurrence of seizures two or more times within 24 hours with return of normal consciousness in between events. The definition of **status epilepticus** (SE) is more than 5 minutes of continuous seizures or two or more discrete seizures between which there is incomplete recovery of consciousness. SE requires prompt treatment to limit the potentially fatal consequences of the severe neuronal injury due to continuous seizuring.

No matter if a seizure is self-limiting, a cluster or status epilepticus, it can present either in a **focal** form or in a **generalized** form. Focal seizures are the manifestation of a discrete epileptogenic event in the cerebral cortex. An example of focal motor seizures is the facial twitching or limb twitching, without any behavioral changes. When we assist at a behavioural change then we refer to a focal seizure with automatism (automotor seizure). Typical example of this seizure is the fly-catching in dogs. Generalised seizures originate from both cerebral hemispheres at once and from the start. Occasionally a focal seizure can progress to a generalised one, this is referred to as **focal seizure with secondary generalization**.

Ictal phenomenology

Based on its clinical manifestation an epileptic seizure can be divided in four stages, the prodrome, the aura, the ictal period and the post ictal period.

The prodrome: is the period of time that precedes the onset of a seizure. Owners often report that they “can predict” when their pet is going to have a seizure. This is because in this phase we may see changes in behavior of the dog, such as increase nervousness, attention-seeking, restlessness.

The aura: is the initial manifestation of a seizure. This can last minutes to hours and is usually characterised by a stereotypical sensory or motor behaviour (i.e. sniffing, liking, pacing), autonomic patterns (i.e. hypersalivation) and psychic events (i.e. frantic barking). Electroencephalography (EEG) can at this stage identify abnormalities.

The ictal period: is the actual paroxysmal event.

The post ictal period: is the time that starts immediately after a seizure and can continue for minutes, hours or days. It is often characterized by unusual behaviour (i.e. inappropriate urination/defecation, increased thirst or appetite), disorientation, ataxia, paresis, and blindness.

Seizures aetiology

The causes of seizures are by all means too many to list them all, we will then try to keep it schematic and short.

Idiopathic/Primary epilepsy implies that no underline structural brain lesions can be identified and that a **genetic origin** is presumed. This condition is typically diagnosed in young animals (6 months to 5 years of age) that are neurologically completely normal in between seizures.

Symptomatic epilepsy results from an identifiable structural abnormality in the brain (brain tumour, head trauma, inflammatory brain disease, haemorrhage, degenerative disease (Lafora disease)). These animals often demonstrate other neurological signs apart from the seizures.

Probable symptomatic epilepsy is referred to seizure for which an underlying cause is strongly suspected but cannot be identified and a genetic origin is not suspected (old dog with sudden onset of seizures)

Reactive seizures are due to exposure to a toxic/metabolic insult. Toxins that can cause seizures are several including ivermectine and derivates, organophosphates and carbamates, metaldehyde, lead. Common causes of metabolic reactive seizures are liver diseases (portosystemic shunts), hypoglycemia, hypocalcemia, hyperlipoproteinemia, and renal diseases.

Seizures work-up

Epileptic seizures are events that originate in the brain, however the cause of a seizure is not always found inside the cranial cavity.

The diagnostic investigations included laboratory evaluation (haematology, comprehensive biochemistry, endocrine test, serology for infectious diseases, urinalysis and genetic test if available). Ancillary diagnostic test: chest and abdominal radiographs in particular for old dogs, MRI (or CT) of the brain/head, cerebrospinal fluid (CSF) analysis, urine organic acid screening and electroencephalography (EEG).

Seizures treatment

The ways seizures are managed primarily depend on their underlying cause. Treatment for seizures requires a very good level of communication between the owner and the veterinarian. Finding the right medication and dosage can be a long and frustrating process for both parties. Also treatment for seizure is very dynamic and will need to be periodically readjusted for the rest of the dog's life. The owners of a seizing dog should also be informed from the start that despite all the commitment and expenses dedicated to their pet, it is very likely that he/she will continue to experience seizures (hopefully at a reduced frequency and severity). Treatment for epilepsy is in fact not a cure and it aims only at reducing the frequency and severity of the seizures. The side effects (immediate and long term) of the medication should be informed before the initiation of the treatment. Sedation, ataxia, lethargy, polydipsia, polyphagia are very commonly seen after the start of the medication. Medications that have a liver metabolism will cause liver enzyme induction. Only rarely impaired liver function may occur. For this reason regular blood tests to check

the medication level and liver function are always recommended. The most common used long term antiepileptic medications are: phenobarbitone, potassium bromide, levetiracetam, gabapentin and zonisamide.

At home therapy for cluster seizures

Some patients tend to suffer cluster seizures that require emergency treatment. The goal of this treatment at home is to prevent or reduce number of subsequent seizures and decreased severity.

Rectal diazepam has been the most often used (0.5mg/Kg). At higher dose (1-2mg/kg) is recommended for dogs on chronic phenobarbitone treatment due to increased metabolism of the drug. This treatment should be administered at the first sign of seizure and can be repeated up to three times within 24 hours. If seizure activity persists, the owner should seek urgent veterinary care.

Prognosis

The overall mortality is considered around 25% in dogs where 23% were euthanized and 2% died during SE.

Dogs with SE due to toxicosis have a more favourable prognosis than dogs with symptomatic epilepsy.

LAFORA DISEASE IN DOGS

Lafora disease is a hereditary disorder and is known to be transmitted as an autosomal recessive pattern. The condition is characterised by a late onset of epilepsy, myoclonus and dementia.

Myoclonus is a brief, involuntary twitching of a muscle or a group of muscles. It is important to know that myoclonus is a clinical sign and not a disease itself. Inherited conditions causing myoclonus in dogs include familial reflex myoclonus in Labrador Retrievers, and various cellular storage diseases, including Lafora disease and neuronal ceroid lipofuscinosis.

Most of the reports of Lafora disease in the veterinary literature involve Miniature Wire Haired Dachshunds, Beagles and Basset Hounds but Lafora disease can occur in any breed. Sporadically it has been reported in a Miniature Poodle, a Pointer, a Standard Poodle, Corgi and also in a Maine Coon cat.

In veterinary medicine, the genetic mutation causing the disease in Miniature Wire Haired Dachshunds and Basset hounds was discovered in 2005 (an expanded repeat mutation in the EPM2B gene).

Clinical Features

In the early stage of the disease, myoclonic seizures are the most often reported clinical signs, and have been noted in affected dogs usually from 5 years to 7 years of age. Other clinical signs, which may appear as the disease progresses, include depression, somnolence, blindness, ataxia and dementia. Myoclonic seizures can be characterised by sudden muscular twitching, from jerky head movement to generalised muscle fasciculation

with severe myoclonic contractions of the head and the neck muscles. They can be precipitated by external stimuli (change in noise, flickering light), appear individually or in quick sequence, and may progress into tonic-clonic seizures.

Diagnosis

An appropriate history, physical examination and neurological examination should always be performed prior to suggesting Lafora disease as a differential diagnosis.

Seizures are the most common neurological problem in small animal medicine. A history of seizure activity suggests a forebrain dysfunction.

Laboratory evaluation (haematology, biochemistry, endocrine tests) is the first step to be taken as it is necessary to investigate for a potential metabolic disease that could cause seizures, or that could complicate the treatment of seizures, before more advanced diagnostic tests (that may require a general anesthetic) are performed. This entire test should be normal in a dog affected by Lafora disease.

Magnetic resonance imaging and cerebrospinal fluid analysis will help to rule out other potential underlying cause of seizure activity. Patients affected by Lafora disease do not have any structural lesion on MRI of the head. Electroencephalography can help lead to the early diagnosis of Lafora disease. This may reveal typical features of isolated polyspike bursts as well as identifying the presence of erratic myoclonus that is not correlated with EEG activity.

There is currently a genetic test for Lafora disease in the Miniature Wire Haired Dachshund, which is currently only available at The Hospital for Sick Children in Toronto. Unfortunately they can only distinguish between affected, carriers (animals that have one copy of the abnormal gene and will have no signs of the disease) and animals that are considered to be clear (they do not have the mutation) from blood samples. They are currently investigating the possibility to be able to distinguish between affected, carrier and clear patients also from saliva (cheek swabs).

It has been reported that Beagles have a different mutation, for which there is not any genetic test currently available.

Lafora disease may also be confirmed by identification of the Lafora bodies in biopsies of muscle, liver or nerve, but a negative result on the biopsy does not rule out the disease. On the other hand, Lafora disease in dogs cannot be based solely on the histological finding (biopsy results) of Lafora-like inclusion bodies as these inclusions have been reported to be incidental findings within neurons of aged dogs. Biopsy results need to be accompanied by the typical signs of progressive myoclonic seizures in order to make the diagnosis of Lafora disease.

Treatment

Therapy in Lafora disease is currently limited to symptomatic management of the seizures. While initially the response may be good, seizure control inevitably deteriorates with time. The agents used in the attempt to limit seizure activity include phenobarbitone and/or potassium bromide as the first choice therapy in veterinary medicine. If these antiepileptic drugs do not provide good seizure control, then unlicensed antiepileptic drugs are

considered (levetiracetam, zonisamide). In human literature it has been reported that gabapentin may aggravate myoclonus and so this should be avoided.

In human medicine low-carbohydrate diet failed to limit the progression of the disease. One study in dogs supported preliminary evidence that a diet high in anti-oxidants and with low glycaemic index slows the progression of the clinical signs, although large prospective studies should be performed to reach further conclusions.

The use of sunglasses in dogs (Doggles) may decrease the external stimuli (light), which could therefore decrease the myoclonic episodes.

Prognosis

Lafora disease is a progressive condition, where the seizures will worsen with time, becoming refractory to treatment. Further clinical signs such as depression, somnolence, blindness, ataxia and dementia may develop, leading owners to request euthanasia.

SEARCH FOR DNA TEST FOR EPILEPSY

Over the past few years investigations have been focus on idiopathic epilepsy and pedigree analysis and it has shown a genetic component in several breeds of dogs. Recently a mutation has been found as a cause of Juvenile Epilepsy in Lagotto Romagnolo Dogs. Idiopathic epilepsy appears to be genetically complex and current investigations are being carried to further investigate this disease in different breeds of dogs.

Suggested readings

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