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Seizure Investigation and Management in the Cat

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Feline seizures differ from canine seizures in a number of ways. The manifestation of the seizures is different with most cats presenting with atypical seizures (often representing focal seizure episodes, with a high incidence of vocalisation, aggression and salivation). At the onset the seizure frequency may be high, often with multiple short seizure episodes per day. This high frequency of onset does not necessarily equate to difficulty in controlling the seizures or a poor prognosis. Although idiopathic epilepsy in cats is an important cause of seizures, other systemic and/or neurological findings are common - it is therefore important to assess for the presence of underlying causes in cats.

Classification of seizure disorders by anatomical localisation of the underlying cause

The most important clinical determinant in any patient with seizures is whether the cause of the seizures is located within brain (intra-cranial) or outside the brain (extra-cranial). Intra-cranial causes can be further differentiated between those causing structural changes to the brain (e.g. a brain tumour) and those with no abnormalities on investigation (so-called functional abnormalities, e.g. idiopathic epilepsy). Idiopathic epilepsy usually has no other neurological deficits in the inter-ictal period. Extra-cranial causes of seizures (e.g. metabolic and toxic causes) often present with diffuse and symmetrical forebrain signs. Structural intra-cranial causes often present with asymmetrical forebrain signs.

Important extra-cranial causes of epileptic seizures

Extracranial causes of epileptic seizures (also known as reactive seizures) represent a reaction of the normal brain to a systemic insult or metabolic or physiological stress. Reactive seizures differ from intra-cranial causes of epileptic seizures, as no primary chronic brain disorder (functional or structural) underlies the seizures. Extra-cranial causes of seizures may originate from outside the body (toxic disorders) or within the body (metabolic disorders). In both instances, the neurological examination may be either normal or abnormal in the inter-ictal period. If neurological deficits are present in the inter-ictal period, then they are typically bilaterally symmetrical, often associated with a reduced level of awareness (stuporous or obtunded), and are non-localising in terms of the anatomic diagnosis.

Hepatic encephalopathy

Hepatic encephalopathy secondary to a porto-systemic shunt (PSS) is the most common extra-cranial cause of seizures in young cats. Seizures secondary to hepatic encephalopathy are often associated with an altered mental status and/or behaviour in the inter-ictal period and frequently the cats demonstrate ptysmalism. This evidence of altered mental status and behaviour usually waxes and wanes in severity over time. Other signs of asymmetrical forebrain involvement can be observed.

PSS most commonly occur in mixed breed cats, Persians and Himalayans. Control of seizures in the short term is based on reducing the production and absorption of the seizure-inducing substances from the gastro-intestinal tract, including ammonia, aromatic amino acids, short chain fatty acids and false neurotransmitters. Medical management comprises a combination of antibiotics to reduce GIT bacterial load (e.g. ampicillin), colon acidifiers to decrease ammonia production and convert ammonia into ammonium which is non-absorbable (in particular lactulose, which also acts as a laxative) and a low-protein diet. In kittens with severe seizures then lactulose enemas can be used to obtain a more rapid result (10 ml/kg of a mixture of 1 part lactulose to 2 parts saline).

Thiamine deficiency

Thiamine (as thiamine pyrophosphate) is important in carbohydrate and amino acid metabolism, forming an essential component of 2-oxoacid dehydrogenases (including pyruvate dehydrogenase and branched chain oxoacid dehydrogenase) and transketolase. Thiamine deficiency causes a progressive encephalopathy in cats, other animals and in human patients. Thiamine deficiency may cause seizures in cats exclusively fed on fresh fish diets (with high dietary levels of thiaminase), fed exclusively on diets where the thiamine has been destroyed (cooked food) or in cats that are anorexic/polyuric. Thiamine has also been reported in dogs in association with severe seizures. Other clinical signs are invariably present in association with thiamine deficiency in both cats and dogs: most commonly vestibular signs, but also including ataxia, dilated and unresponsive pupils, mentation changes and decreased gag reflex.

Hypoglycaemia

Hypoglycaemia secondary to insulin overdose in diabetic cats or due to an insulinoma frequently present with seizures. Hypoglycaemia may cause weakness, syncope or seizures depending on the degree of hypoglycaemia, but more importantly the rate at which the hypoglycaemia
fluctuates. Less commonly hypoglycaemia may also be associated with (among others) severe sepsis and hepatic insufficiency.

**Toxic causes**

There is a large list of toxins that may potentially cause seizures, including carbamates, organophosphates, lead poisoning, ethylene glycol toxicity, methadecaldehyde (slug bait), strychnine, etc.

**Ionic imbalance**

Examples of ionic imbalances that may cause seizures include hypocalcaemia, hyponatraemia, etc.

**Important structural intra-cranial causes of epileptic seizures**

Most animals demonstrate neurological deficits in the inter-ictal period which are often asymmetrical. However, in some cases the lesion causing the seizures lies in an otherwise ‘silent’ region of the brain (causing only seizures but no other localising neurological deficits). The most common structural intra-cranial causes of epileptic seizures include:

- Brain tumours, in particular meningiomas as the most common feline brain tumour
- Inflammatory (immune-mediated) CNS disease: immune-mediated encephalitis is less common in the cat than it is in the dog (in which granulomatous meningoencephalitis or GME is one of the more common structural brain diseases), but should still be considered
- Infectious CNS diseases: including FIP, Toxoplasmosis, FeLV, Cryptococcus and FIV
- Other less common causes include head trauma and congenital causes: e.g. congenital hydrocephalus

**Seizures due to functional intra-cranial causes**

The term primary or idiopathic epilepsy implies a functional forebrain disorder causing recurrent epileptic seizures with a normal interictal period and no identifiable toxic, metabolic or structural intracranial cause. Idiopathic epilepsy is an important cause of seizures in cats. The diagnosis of idiopathic epilepsy is a diagnosis of exclusion. Unlike in the dog where there are certain clinical characteristics (e.g. age of onset, seizure type, seizures from rest, etc.) which are useful in predicting idiopathic epilepsy, in the cat the presentation can be very variable. However, an important criterion is the absence of neurological deficits in the interictal period.

**Investigation of seizure disorders**

When deciding on appropriate tests to investigate the causes of seizures, consideration should be taken of the animal’s age, the suspected anatomical localisation of the underlying cause and presence or absence of inter-ictal neurological deficits in formulating the diagnostic plan. Routine haematology and biochemistry (including a glucose determination) should be performed in all cases. In cats less than a year of age a pre- and post-prandial bile acid assay should also be performed. If finances are limited then at this stage it would not be unreasonable to make a diagnosis of idiopathic epilepsy if:

- There is a normal haematological and biochemical evaluation
- There are no abnormalities in the inter-ictal period
- If these cases later developed further clinical signs to suggest an alternative diagnosis, or if the seizure control was poor, then further investigation would be indicated. However, because underlying causes for seizures are so common in cats a full investigation should be performed wherever possible:

**First investigate for possible extra-cranial causes**

- Complete haematology
- Comprehensive biochemistry including pre- and post-prandial bile acid assay
- Urinalysis
- Total T4 in adult cat suspected of hyperthyroidism
- FeLV, FIV and FIP tests
- Toxoplasma serology

**Then consider investigation of intra-cranial causes**

- Thoracic radiographs
- MRI or CT of the brain
- CSF analysis (protein quantification, complete and differential cell count)
- CSF PCR for coronavirus, Toxoplasmosis, FeLV, FIV and Borna virus

**Maintenance therapy for feline seizures**

The aim of any anti-epileptic treatment is to ‘control’ the seizures by reducing their frequency, intensity and severity with minimum side effects - treatment is unlikely to totally abolish the seizures. Where possible the underlying cause of the seizures should be treated. In some metabolic and toxic disorders (in particular porto-systemic shunts, hypoglycaemia and some intoxications) standard treatment regimes would be contraindicated.

**Aims of treatment**

- Reduce the frequency and severity of seizures.
- It is important to explain to the owner that it is very likely that the animal will still seizure despite the therapy
- Minimise potential side effects
- Minimise the demands made on the owner

**Initial anticonvulsant therapy**

Treatment of seizures in cats relies on phenobarbitone or diazepam as maintenance drugs of choice. Phenobarbitone does not usually result in clinically
significant enzyme induction in cats and the elimination half-life therefore remains stable. Potassium bromide is not appropriate as a maintenance therapy in most cats due to unacceptable side effects.

Phenobarbitone
The half life of phenobarbitone in cats is 34 to 43 hours, but auto-enzyme induction is negligible and therefore drug concentrations of phenobarbitone are not expected to decrease in cats receiving long-term phenobarbitone therapy. Frequent monitoring of blood levels is therefore less important in cats. The time to reach steady state is approximately five times the elimination half-life (10 to 12 days in cats).

The drug acts by facilitating GABA-mediated synaptic inhibition by binding to barbiturate receptors on the chloride channel complex. Phenobarbitone binding results in higher intracellular concentrations of chloride and hyper-polarization of the resting membrane potential.

- The initial dose is 2 to 3 mg/kg BID (i.e. total daily dose of 4 to 6 mg/kg)
- Individual dosages are determined by the serum concentration (once the serum concentration has stabilised), not the actual oral dose

Diazepam
Diazepam is also effective as a maintenance treatment in cats. In dogs it is not effective as a maintenance therapy due to its short half-life. Functional tolerance does not appear to develop in cats on diazepam. The starting dose is 2 to 5 mg/kg BID or TID. The effective serum concentration is 500 to 700 nmol/l. There are minimal side effects in cats on diazepam, although acute hepatic necrosis as an idiosyncratic reaction has been reported.

Potassium bromide
The use of potassium bromide is contraindicated in most cats due to the development of severe respiratory signs, secondary to eosinophilic bronchoalveolitis. In those cases where use in unavoidable: potassium bromide has a long half life in cats of around 10 days and the starting dose is 1.5 mg/kg SID.

Treatment of refractory epilepsy in cats (adjunctive therapy)
Refractory epilepsy is where the animal’s quality of life is compromised by frequent or severe seizures episodes, despite appropriate therapy with phenobarbitone and/or diazepam.

Because the clinical effect of phenobarbitone is related to the serum concentration the first step in any cat apparently refractory to phenobarbitone therapy is to assess the serum levels. It is also important to exclude other factors that may be contributing to poor seizure control:

- Poor owner compliance (dosages missed)
- Dosage too low (determine serum concentration of phenobarbitone)
- Incorrect diagnosis (repeat investigation)
- Interference with absorption (malabsorption)
- Drug interaction affecting phenobarbitone metabolism
- Another new disease causing seizures

Poor owner compliance can be difficult to prove but can be a particular problem in cats. If you are strongly suspicious then hospitalise the animal to ensure they receive all the doses for a few days, before repeating the blood level determination. If the low blood levels were due to poor owner compliance then increased blood levels should already be evident after only a few days. It is also important to recognise that any treatment is unlikely to totally resolve the seizures and to ensure that the owners are being realistic about what they term ‘adequately controlled’.

Combination treatment with phenobarbitone and diazepam is the first management choice in refractory feline epilepsy. If this combination therapy is not effective and there are adequate serum concentrations then treatment with Keppra (levetiracetam) can be assessed as an add-on maintenance treatment or on its own. Levetiracetam is not veterinary licensed and the owners need to be made aware of this.

Levetiracetam (Keppra®)
Levetiracetam is associated with few side effects and has minimal hepatic toxicity. Although it is of benefit in some cases, it has an extremely short elimination half-life in the cat which would normal preclude its use as a routine maintenance anticonvulsant therapy. Recommended dosages in cats are 5 to 30 mg/kg BID to TID.