Idiopathic epilepsy in dogs – part one: patient approach

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Dogs with recurrent epileptic seizures, and where no interictal neurological deficits or abnormalities on routine diagnostic tests are evident, have traditionally been defined as having “idiopathic epilepsy”.

Rather than being a specific, single diagnosis, it is probable idiopathic epilepsy represents a complex interplay between genetic predisposition and intrinsic and extrinsic environmental factors, and the term “presumed genetic” has also been suggested to define these patients.

A genetic basis for idiopathic epilepsy has been proposed in a number of breeds, including the golden retriever, Labrador retriever, Bernese mountain dog, Irish wolfhound, English springer spaniel, Keeshond, Hungarian vizsla, standard poodle, border collie and Finnish spitz (Viitmaa et al, 2013) and a possible susceptibility locus for epileptic seizures has been characterised in the Belgian shepherd dog (Seppälä et al, 2012).

Reflecting its importance in veterinary medicine, idiopathic epilepsy is reported as the most common chronic neurological disease in dogs, with a prevalence of around 0.6 per cent in first opinion practice. Generalised seizures (where there is impairment of consciousness) are the most common type of epileptic seizure in dogs, while partial seizures appear to be relatively more common in cats; this, in part, represents the tendency for dogs with idiopathic epilepsy to have generalised seizures, or focal seizures with rapid secondary generalisation.

The accurate description of generalised seizures in a patient with suspected idiopathic epilepsy is important, firstly to differentiate the episodes from other causes of collapse (for example, syncope) and secondly because the presence of generalised seizures is one of the criteria for making a diagnosis of idiopathic epilepsy.

Seizure classification by anatomical localisation of cause

Once we are confident the episodes do represent epileptic seizures, the next stage is to perform the neurological examination. Epileptic seizures imply a forebrain disorder and, as such, the neurological assessment concentrates on evaluation of forebrain function; however, it is important not to ignore the remainder of the neurological examination as some lesions may present with

clinical signs of multifocal or widespread neurological disease.

The cause of epileptic seizures may originate outside (extracranial, with symmetrical neurological deficits if present) or inside (intracranial) the brain. Intracranial causes may be further subdivided into functional disorders (no gross structural changes are evident in the brain and therefore usually no neurological deficits are evident in the interictal period) and structural disorders (where there is a gross structural cause for the seizures within the brain – for example, a brain tumour – and which often have asymmetrical neurological deficits). These functional intracranial disorders are defined by the term “idiopathic epilepsy” if there is no known genetic cause and represent the most common cause of epileptic seizures in the dog.

In addition to epileptic seizures, other clinical signs of forebrain lesions that may be apparent if there is an intracranial structural or extracranial lesion may include the following:

- Altered behaviour – for example, loss of litter training or house training.
- Decreased levels of consciousness – typically from a subtle decrease in awareness to the level of a stupor. The animal is less responsive to external stimuli rather than complete loss of consciousness.
- Contralateral conscious sensory deficits – including decreased facial sensory awareness and conscious proprioceptive deficits.
- Contralateral blindness – this usually represents loss of the contralateral conscious visual field with subcortical light reflexes (such as an intact pupillary light reflex and an intact dazzle reflex).
- Circling – usually towards the lesion, but the circling can be contralateral depending on the exact site of the lesion.
- Head turn (not a head tilt) – usually towards the side of the lesion and usually only evident in dogs that also demonstrate circling.

The presence of neurological deficits in the interictal period is an important indication for performing further investigation (Figure 1). If the neurological deficits are symmetrical then the further investigation should initially concentrate on extracranial causes, whereas asymmetrical neurological deficits are more suggestive of an intracranial cause.

Some intracranial causes may demonstrate symmetrical neurological deficits if the CNS lesion is symmetrical (for example, obstructive hydrocephalus).

In the dog with idiopathic epilepsy, a normal neurological examination is one of the important criterion for the diagnosis of idiopathic epilepsy.

However, when performing the neurological examination it is essential to recognise seizures may cause temporary, mild neurological deficits themselves, irrespective of the underlying cause – so-called “postictal depression”. These are usually temporary and resolve after a few hours.

If you perform the neurological examination shortly after an epileptic seizure and find evidence of neurological deficits, then repeat the assessment a day later to confirm whether these neurological deficits are genuine before assuming these represent interictal neurological deficits (Figure 2).

The longer or more severe the seizures, the longer the postictal depression may last – particularly after severe cluster seizures or status epilepticus. Following epileptic seizures there may also be reversible changes within the brain, evident on MRI (Figure 3), or even mild elevations in the cerebrospinal fluid cell count.

Confirmation of diagnosis

Although idiopathic epilepsy is a diagnosis of exclusion, certain clinical characteristics exist in dogs that make it more likely.

Most affected dogs have their first seizure between one and three years of age, but the accepted age range with a high likelihood of idiopathic epilepsy is between six months to six years of age (although the precise definition of this age range varies between different publications). Dogs out of this age range can still have a diagnosis of idiopathic epilepsy, but structural intracranial causes and extracranial causes become more likely (Arrol et al, 2012). If an animal fits all the other criteria for idiopathic epilepsy, but is out of the normal age range, some authors have referred to these cases as “cryptogenic epilepsy”.

The seizures tend to be generalised tonic-clonic seizures or partial seizures with rapid secondary generalisation (and additionally, are usually characterised by autonomic signs, with the most common being hypersalivation and urination).

The seizures tend to occur while the dog is relaxed – usually in the house or from sleep. In some individual cases they may be excitement-related – for example, when getting excited at the prospect of going for a walk – but will still tend to be in the house rather than during exercise itself.

There are no abnormalities in the interictal period, including the physical and neurological examination.

There is no evidence of alterations in the complete blood count or biochemical tests. Blood samples collected shortly following an epileptic seizure (particularly following a severe or prolonged seizure) may demonstrate some mild abnormalities – most commonly elevation of the creatine kinase (or creatine phosphokinase) due to the muscular exertion associated with the epileptic seizure.

Certain breeds are over-represented (in particular, but not limited to, border collies, Labrador retrievers, golden retrievers, Irish setters and German shepherd dogs).

The aforementioned clinical criteria allow a high predictive value for the presence of idiopathic epilepsy, with just the combination of a seizure onset between six months and six years of age, a normal physical and neurological examination, normal blood work and generalised seizures, equating to a 95 per cent probability of a diagnosis of idiopathic epilepsy (Smith et al, 2008).

In this case it would not be unreasonable to make a presumptive diagnosis of idiopathic epilepsy without the need for further advanced diagnostic imaging or invasive diagnostic tests. If there was a subsequent poor response to antiepileptic medication, or further clinical signs or neurological deficits developed, then the presumptive diagnosis of idiopathic epilepsy could be revisited, and repeated assessment and possible further investigation would be indicated.

Extracranial disease as a differential diagnosis

The two major categories of extracranial disease that may present with epileptic seizures are metabolic diseases and toxic causes.

The most important metabolic diseases as a cause of epileptic seizures are hepatic insufficiency (in particular, portosystemic shunts in young animals and acquired hepatic disease in older dogs), electrolyte disturbances and hypoglycaemia (usually secondary to insulinoma and evident in older dogs).

It is essential, therefore, the blood tests performed as part of the routine evaluation of a dog with epileptic seizures includes a fasting blood glucose and hepatic function testing (ideally a pre and postprandial bile acid assay).

Toxic causes of epileptic seizures are harder to identify on the basis of diagnostic tests and a detailed history to establish any potential toxin exposure is required. Most toxic causes of epileptic seizures usually present as an acute onset of epileptic seizures (which may be partial or generalised) in a dog that otherwise does not have a history of epileptic seizures, with a high frequency of epileptic seizures at the onset and that rapidly resolve.

Toxic causes are also more common in younger dogs or dogs that have a tendency to scavenge for food. Multiple animals may also be simultaneously affected.

Intracranial disease as a differential diagnosis

A large variety of structural intracranial diseases may present with epileptic seizures and these frequently have asymmetrical neurological deficits. It is useful to subdivide them on the basis of age of onset. In younger dogs congenital anomalies (with the most important being congenital hydrocephalus), and infectious and inflammatory (in particular granulomatous meningoencephalitis) CNS diseases are more common. In older dogs, intracranial neoplasia (primary or metastatic) is the most common structural intracranial cause of seizures.

Vascular disease, although it can occur in dogs of all ages, uncommonly demonstrates epileptic seizures as part of the clinical presentation. Head trauma may result in epileptic seizures, either shortly after the trauma or as a delayed effect. The probability of seizures following head trauma increases with the presence of skull fractures and is highest where there are concurrent neurological deficits.

Head trauma is more common in younger dogs due to their increased risk of being involved in road traffic accidents. In addition to the baseline routine physical and neurological examinations, complete blood count and routine biochemical tests performed to exclude extracranial disease, the exclusion of intracranial disease may additionally include urine analysis, survey thoracic and abdominal radiographs (to investigate underlying disease – in particular, neoplasia), abdominal ultrasound (in particular for neoplasia and vascular disease) and advanced diagnostic imaging of the brain.

Management

The guidelines for treatment of idiopathic epilepsy are individual to the requirements of each case and demands placed on the owner. There is increasing evidence to suggest early instigation of antiepileptic therapy is beneficial to the long-term quality of life of a patient (Shihab et al, 2011; Weissl et al, 2012). It is important to recognise the treatment is aimed at managing the epileptic seizures and is not addressing the underlying cause. Once started, the treatment is likely to be continued indefinitely and is therefore referred to as “chronic therapy”.

There may be situations where short-term antiepileptic therapy is warranted – mainly in situations where the underlying cause of the seizure episodes is reversible (for example, in toxic causes or in cases of treatable CNS disease, such as some inflammatory diseases); however, this does not apply in most cases with idiopathic epilepsy.

When to start chronic therapy

While any guide to treatment is a matter of opinion, increasing evidence suggests early instigation of treatment in canine epilepsy is beneficial for patient and owner quality of life.

However, there is a need to balance the demands any treatment regime places on owners, as well as the adverse effects on the animal, with the benefits of the treatment itself (Chang et al, 2006).

We are more likely to tolerate a low seizure frequency in our canine patients than in human patients. This is because of differences in life expectancy between human patients and dogs (with the shorter canine life expectancy equating to less time for progression of seizures) and the advantages of complete seizure freedom in human patients, which are not relevant in dogs (for example, being able to drive and the ability to work in certain professions). However, in certain clinical scenarios treatment is likely to be highly beneficial, even when the epileptic seizures occur

at a relatively low frequency – particularly those associated with severe seizures or seizure- related adverse effects.

Treatment should ideally be initiated once the dog meets one or more of the following criteria:

- the dog experiences status epilepticus
- the dog has cluster seizures
- the seizures are characterised by severe postictal effects
- there is an identifiable structural lesion present, or prior history of brain disease or injury (although this precludes the diagnosis of idiopathic epilepsy in most cases)
- there is an increasing seizure frequency or severity
- two or more isolated seizure events occur within a six-month period

Choice of initial therapy

Two veterinary licensed therapeutic agents exist for the management of epileptic seizures in dogs – phenobarbital and imepitoin. The decision regarding which to use is guided by the requirements of the patient.

Both medications have been shown to be effective for the management of idiopathic epilepsy; however, differences are apparent in time to onset of effect and monitoring requirements. There are also likely to be differences in the spectrum of adverse effects and clinical efficacy in individual animals, allowing us the opportunity to individually tailor the treatment to our patient to optimise quality of life.

Phenobarbital

The advantages of phenobarbital for management of idiopathic epilepsy are it is a highly effective antiepileptic medication (estimated to be efficacious in around 82 per cent of dogs with idiopathic epilepsy) with a longer serum half-life and is, in general, of relatively low cost. Phenobarbital does have a delay in time to steady state onset (a steady state is only achieved after around seven to 10 days).

In animals with severe seizures, where a more rapid onset is required and phenobarbital has been selected as the antiepileptic medication, then a loading dose should be used, which is usually associated with more severe adverse effects in the short-term and the owner should be warned about these. The individual doses of phenobarbital are also determined by serum concentration and not the oral dose – the aim is to keep the blood levels within the “therapeutic range”.

Phenobarbital may also have adverse effects on the liver and, less commonly, the bone marrow. The monitoring of serum concentrations of phenobarbital and monitoring of hepatic function requires initial and subsequent blood samples, which, to some degree, negates the lower cost of

the medication and means phenobarbital may be less suitable in dogs that are hard to blood-sample. Phenobarbital is not suitable for use in dogs with hepatic impairment.

Imepitoin

The advantages of imepitoin for managing idiopathic epilepsy are it is also a highly efficacious medication that has a very rapid time to onset of action (most often within two hours, but definitely within two days) and does not require monitoring of serum concentrations, avoiding the requirements for periodic blood sampling.

Imepitoin appears to have less adverse hepatic effects and it has also been suggested it has a less severe spectrum of adverse effects, but the relatively recent introduction of this medication means we are not yet in the position to objectively and impartially judge the severity of adverse effects.

In dogs with hepatic impairment, imepitoin (or as an alternative, potassium bromide) may be used as sole maintenance therapy. Imepitoin metabolism does involve the liver, therefore in severe hepatic disease levetiracetam – a non-veterinary licensed antiepileptic medication – may be more suitable, since its metabolism does not involve the liver.

Changing between phenobarbital and imepitoin

If there is a poor clinical response or adverse effects of a sufficient severity occur on treatment with either phenobarbital or imepitoin, it would be entirely appropriate to assess the response and adverse effect profile of the other medication to ascertain whether that would improve the animal's quality of life. If a dog is effectively controlled on one medication and there are no major adverse effects then the medication should not be changed.

Where the decision is made to switch from one medication to the other, consideration should be given to an appropriate withdrawal period, in particular with phenobarbital. The development of physical dependence is a recognised feature when using phenobarbital and other barbiturates (Tanaka et al, 1991; Bidlack and Morris, 2009).

While there will always be situations where this switch has to be made quickly – particularly in dogs with severe and life-threatening adverse effects – if the phenobarbital therapy has to be stopped then, wherever possible, it should be gradually tapered off over a period of weeks to months.

The clinical manifestations of an abrupt termination of phenobarbital therapy (also referred to as "abstinence syndrome") are characterised by CNS hyperexcitability and include motor, autonomic and behavioural changes, and, in some cases, may even include withdrawal seizures (Gay et al, 1983; Bidlack and Morris, 2008).

These withdrawal effects may appear as early as 12 to 24 hours after cessation of phenobarbital

therapy and can continue for up to 12 days. Longer-term therapy (of more than one month) has also been shown to result in more severe withdrawal effects.

Should a change of treatment be required then gradual weaning off the phenobarbital dose is important to avoid withdrawal effects. Our suggested protocol for weaning the phenobarbital dose would be to reduce it by 25% of the original dose each month (month one – 75% of the original phenobarbital dose; month two: 50% of the original phenobarbital dose; month three: 25% of the original phenobarbital dose).

We do not know whether any withdrawal effects might occur following sudden termination of imepitoin treatment and it would therefore be prudent to also gradually taper the imepitoin therapy.

Prior to withdrawing one medication it is important to first ensure effective serum concentrations of the other medication. In the case of imepitoin this means being on therapy for at least two days prior to starting to reduce the phenobarbital therapy.

In the case of phenobarbital this means demonstrating serum concentrations of phenobarbital within the therapeutic range once a steady state has been reached (usually after at least 14 days following the last change in phenobarbital dose).

Conclusion

Idiopathic epilepsy represents a common and important chronic neurological disease in dogs that has a significant quality of life impact on affected dogs and their owners.

The diagnosis in most cases does not require advanced diagnostic imaging. It can be predicted with a 95 per cent probability in dogs with a normal physical and neurological examination, routine blood tests that are within normal limits (including a CBC and serum biochemical tests) and an age of onset of the seizures between six months and six years of age.

We are now in the fortunate position of having a choice of two medications licensed for the management of idiopathic epilepsy in dogs – namely, phenobarbital and imepitoin. Both have been shown to be effective in dogs with idiopathic epilepsy and afford us the possibility to tailor our antiepileptic therapy specifically to the individual needs of a patient, thereby minimising the impact of the disease and our treatment on our patients.

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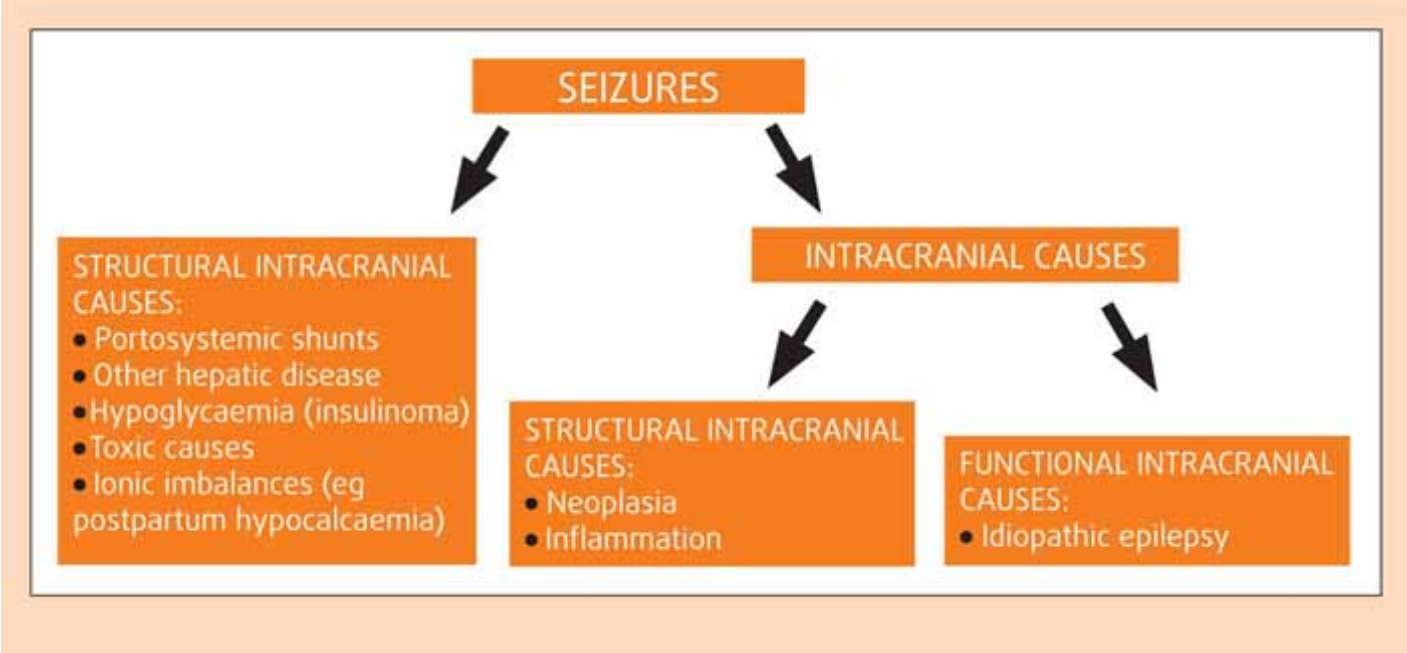

Figure 1. The importance of the neurological examination in decision making in idiopathic epilepsy. The demonstration of a normal neurological assessment in the interictal period is one of the criterium for making a diagnosis of idiopathic epilepsy and other functional causes of epileptic seizures (such as genetic causes). However, it is not just a normal neurological examination that is useful in defining the neuroanatomical localisation of the seizure cause. The finding of symmetrical neurological deficits implies extracranial causes of epileptic seizures should be considered first, before intracranial causes. Asymmetrical neurological deficits imply a structural intracranial lesion (such as neoplasia or inflammatory disease).

Figure 2. The neurological examination in the interictal period is useful for detecting whether epileptic seizures may be secondary to a systemic disease (reactive seizures) or secondary to a structural intracranial cause (symptomatic epilepsy). However, it is important to remember seizures may cause temporary, mild neurological deficits themselves, irrespective of the underlying cause – so called “postictal depression”. These are usually temporary and resolve after a few hours. If the dog is presented shortly after an epileptic seizure and deficits are evident on the neurological examination then the neurological examination should be repeated a few hours to a day later to confirm whether these neurological deficits are genuine.

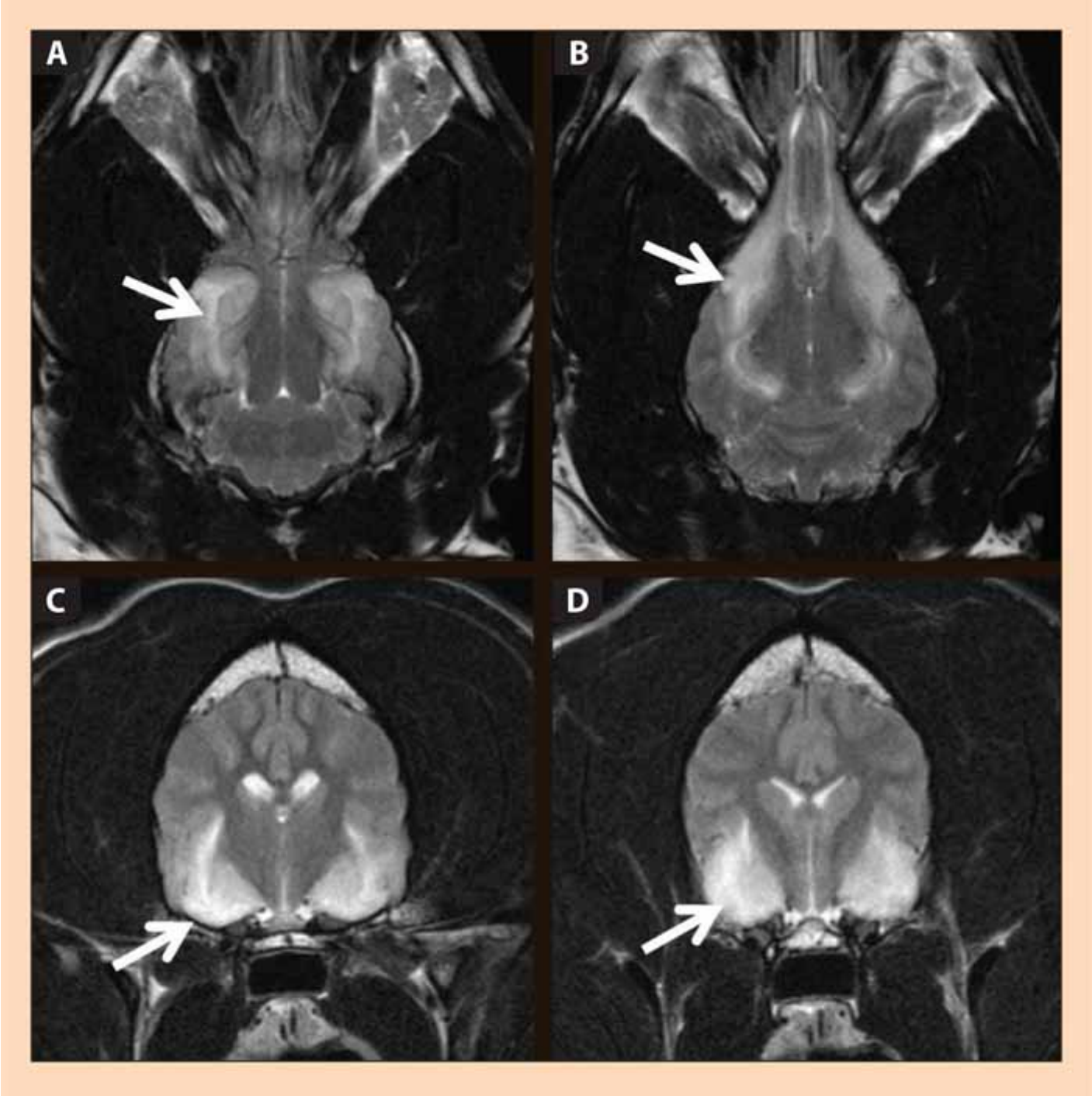

Figure 3. MRI is useful for the exclusion of structural intracranial causes of epileptic seizures; however, epileptic seizures may induce changes within the brain that may be evident on MRI investigation. It is important to recognise these changes as seizure-induced, rather than as the

cause of the seizures and, ideally, any MRI investigation should not be performed immediately after a severe seizure episode. One of the most common seizure-induced changes identified on MRI is bilaterally symmetrical hyperintensities on T2- weighted MR images – arrows in the dorsal plane (**A,B**) and transverse plane (**C,D**) images – particularly affecting the pyriform lobes of the brain.

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