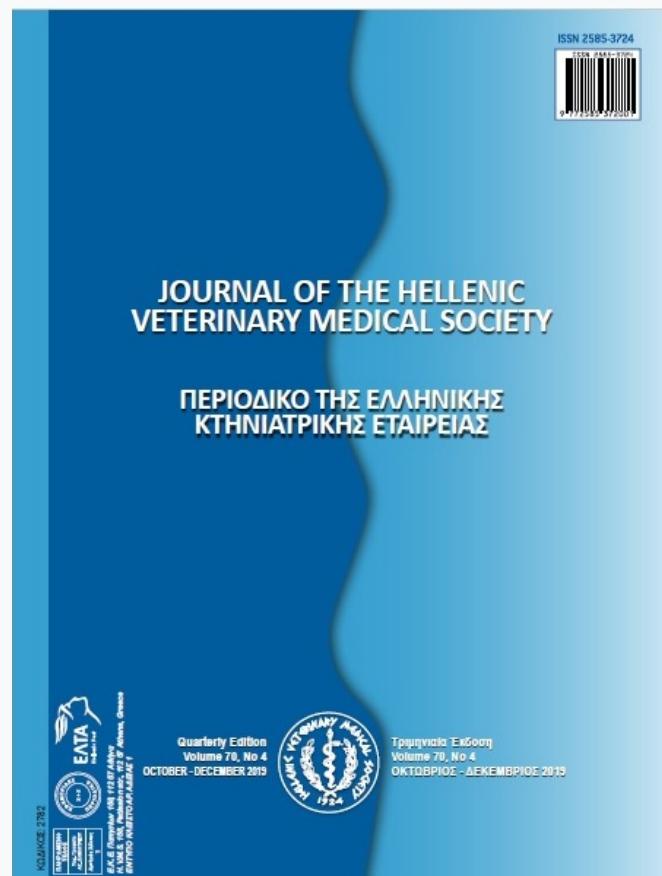


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Feline Epilepsy: An update

RD BAKA, ZS POLIZOPOULOU

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Feline Epilepsy: An update

R.D. Baka¹, Z.S. Polizopoulou¹

¹*Diagnostic Laboratory, School of Veterinary Medicine, Faculty of Health Sciences, Aristotle University of Thessaloniki, Thessaloniki, Greece*

ABSTRACT: Epileptic seizures are the most common neurological disorder in the clinical setting. Their etiology is multifactorial and is mainly divided into structural, reactive and idiopathic epilepsy. Structural epilepsy can be caused by vascular events, inflammatory conditions (encephalitis), traumatic injuries, neoplasia, congenital and inherited (degenerative) disorders. Reactive epilepsy is caused by exposure in toxins or metabolic derangements. Although idiopathic epilepsy was thought to be rare in cats, it is now established as a common cause. Epileptic seizures in cats appear with various clinical presentations including generalized, focal with or without secondary generalization epileptic seizures. Diagnostic investigation is crucial in order to establish final diagnosis and to determine the therapeutic plan. Diagnostics include physical and neurological examination with detailed history (drug or toxin exposure), routine hematology (CBC, biochemistry, urinalysis), specific laboratory tests if concurrent or metabolic disease are suspected, advanced diagnostic imaging (CT/MRI) whether intracranial disease is suspected and cerebrospinal fluid (CSF) analysis. Most commonly used antiepileptic drugs (AED) in cats are phenobarbital and levetiracetam. Bromide is contraindicated in cats due to severe respiratory disease caused as an adverse life-threatening reaction. Diazepam is an emergency AED used to eliminate cluster seizures or status epilepticus but it should be avoided as a long-term medication because it has been associated with fatal hepatotoxicity. Gabapentin is another potential antiepileptic drug however its long-term efficacy has to be evaluated. Prognosis depends on the underlying etiology and treatment response. In most cats quality of life is improved and (>50% reduction of epileptic seizures) regardless of etiology. The complete remission of epileptic seizures in cats is rare and most cats should be maintained on anti-epileptic therapy.

Keywords: antiepileptic treatment, epilepsy, feline, seizures

Corresponding Author:

Rania D. Baka, Stavrou Voutyra str. 11, 54627, Thessaloniki, Greece
E-mail address: raniadbaka@gmail.com

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ETIOLOGY OF SEIZURES IN CATS

Epileptic seizures are the most common neurological condition encountered in companion animal practice with an estimated prevalence (in a referral hospital population) of 0.5% to 3.5% in cats (Pakozdy et al., 2010).

Structural epilepsy appears when an underlying structural lesion or disease is identified (Bailey and Dewey, 2009). The major categories of structural epilepsy in cats include vascular events, inflammatory conditions/ encephalitis, infectious etiologies, traumatic injuries, neoplasia, congenital malformations and degenerative conditions (Bailey and Dewey, 2009).

Reactive seizures may result from a wide variety of extracranial causes, including toxins, drugs and metabolic disease (O' Brien, 1998). Similar findings are reported by Rusbridge (2005) and Barnes (2004), where hepatic encephalopathy was the predominant diagnosis in the metabolic group of diseases. However, Schriefl (2008) reports that the percentage of reactive seizures is higher. Kline (1998) indicated that reactive seizures due to hepatic encephalopathy occurred infrequently in cats. Thus, in cats presented with epileptic seizures history should focus on previous drug administration and potential exposure to toxins (O' Brien, 1998).

Hypertension occurs more frequently as a sequel of chronic kidney disease, hyperthyroidism or hypertrophic cardiomyopathy (Kline, 1998). Hypertensive cats more commonly present with retinopathy and blindness, but vascular changes in the brain may lead to arteriosclerosis, focal hemorrhage, epileptic seizures, ataxia, nystagmus, sudden collapse and paraparesis (O' Brien, 1998). Polycythemia can cause epileptic seizures, blindness, abnormal behavior aggression, ataxia, pupillary dilatation and ptalism (Kline, 1998). Most cats with clinical signs will have a hematocrit of 63% or greater (Khanna and Bienzle, 1994; Watson et al., 1994). Uremia is a relatively uncommon cause of reactive seizures and is usually quite severe before inducing either focal or generalized seizures (Kline, 1998).

While reactive seizures present a serious clinical manifestation for many of these conditions, they can be controlled or eliminated if the underlying cause is detected and treated (O' Brien, 1998).

Inflammatory diseases have been reported to ac-

count for 32-44% of histologically confirmed central nervous system diseases in cats (Bradshaw et al., 2004; Rand et al., 1994). The most common cause of meningoencephalitis in cats is feline coronavirus, the etiological agent of feline infectious peritonitis (De Risio et al., 2012). Other known etiologies of feline meningoencephalitis are uncommon and include viruses such as feline immunodeficiency virus (FIV), feline leukemia virus (FeLV), feline parvovirus, pseudorabies virus/ porcine herpesvirus 1, rabies virus, Borna disease virus, West Nile virus, encephalomyocarditis virus, and protozoal, bacterial, rickettsial, fungal and parasitic agents (Gunn Moore, 2005; Schwab et al., 2007). In a large number of feline cases with central nervous disease, histopathological changes consistent with lymphohistiocytic (non-suppurative) meningoencephalitis are found (Schwab et al., 2007). Although, lymphohistiocytic meningoencephalitis is usually suggestive of viral infection, the causative agent is often not identified (De Risio et al., 2012). In lymphohistiocytic meningoencephalitis of unknown origin the clinical signs appear at a young age (2 years or less), and the progression is no longer than a couple of weeks (Gunn Moore, 2005; Rand et al., 1994). De Risio (2012) presented different evidence regarding the disease. More specifically, cats with lymphohistiocytic meningoencephalitis appeared with peculiar clinical signs (spastic gait, stiff tail), the onset of the disease was late (mean 9 years) and the progression of signs was very slow (mean 11 months). A causative agent could not be identified. Thus, the cats in this study had been affected by a unique, previously unreported condition (De Risio et al., 2012). MRI images of the brain must be evaluated carefully as many mass lesions regarded as tumors can be fungal or protozoal granulomas (Foster et al., 2001; Pfohl and Dewey, 2005). Brain abscesses due to bite wound were also identified in cats (Costanzo et al., 2011).

Ischemic cerebrovascular accidents rarely appear in cats and they are usually associated with concurrent disease (Whittaker et al., 2018). The prognosis is guarded, although this will be dependent on the severity and type of the relevant concurrent disease (Whittaker et al., 2018).

Head trauma is common in dogs and cats and typically results from kicks, bites, motor vehicle or missile object injuries (Braund, 2003). A relevant previous study indicated that brain injuries in cats were typically caused by crash accidents (Syring et al., 2001). Traumatic brain injury reportedly causes structural

epilepsy in companion animals (Bailey and Dewey, 2009; Braund, 2003; Parent and Quesnel, 1996). Although epileptic seizures that appear as a result of traumatic brain injury are often refractory to antiepileptic treatment in humans (Herman, 2002), cats with medical history of mild to moderate head trauma had $\leq 5.6\%$ probability of developing post-traumatic epileptic seizures (Grohmann et al., 2012). However, clinicians are advised to monitor cats with history of head trauma for development of structural epilepsy (Grohmann et al., 2012).

The most common central nervous system neoplasm in cats is meningioma (Kline, 1998; Mattoon and Wisner, 2004; Pakozdy et al., 2010). It can occur singly or in multiple sites (Kline 1998). Meningiomas typically affect the older feline patient (>8 years old), males are disproportionately affected over females (Gorden et al., 1996; Kornegay, 1991). Another neoplastic cause of primary or secondary central nervous system neoplasm is lymphoma (Kline, 1998). The signalment of cats with lymphoma differs from than with meningioma, in that these cats tend to be young to middle-aged (between 7-10 years old) (Kline, 1998).

Cats may develop obstructive hydrocephalus secondary to infectious diseases such as feline infectious peritonitis (FIP) (Lavelle, 2014). Hydrocephalus can result from autosomal recessive inheritance in Siamese cats (Hoskins, 1990).

Structural epilepsy was more frequent than idiopathic epilepsy in cats (Pakozdy et al., 2010). Idiopathic epilepsy reflects conditions that have no underlying cause (Bailey and Dewey, 2009) and genetic mechanisms are the presumed etiology (Cunningham and Farnbach, 1987). Cats determined as having a seizure disorder with unidentified etiology are referred as idiopathic epileptics (Bailey and Dewey, 2009).

Idiopathic epilepsy is recognized in cats; however, cats are generally older at the onset of seizures than are dogs with idiopathic epilepsy (Bailey et al., 2008). Although idiopathic epilepsy was thought to be rare in cats (Bailey and Dewey, 2009; Berg and Scheffer, 2011; Kline, 1998; Pakozdy et al., 2010; Schriefel et al., 2008), new evidence suggest that between 21% and 59% of cases are idiopathic (Cizinauskas et al., 2011; Quesnel et al., 1997b; Schriefel et al., 2008), another study indicate a 25% of cats with seizures as having idiopathic epilepsy (Schriefel et al., 2008). Other authors have defined idiopathic epilepsy as inherited epilepsy (Parent and Quesnel, 1996; Quesnel et al.,

1997b; Shell, 2000).

In contrast to idiopathic epilepsy in dogs, whose diagnosis was based on age and normal clinicopathological testing, this should not be applied in cats (Schriefel et al., 2008). Additionally, idiopathic epilepsy in dogs is assumed to be genetic in origin but no information support such an assumption in cats (Pakozdy et al., 2010).

In many cases of feline epilepsy, an underlying cause of epileptic seizures was suspected but never proven ante-mortem (Kline, 1998). These include previous post-traumatic, post-inflammatory and post-ischemic lesions that were quiescent and non-progressive (Kline, 1998). This form of idiopathic epilepsy was probably more common than true idiopathic epilepsy in the cat (Parent and Quesnel, 1996).

CLINICAL SIGNS

Epileptic seizures can have a wide range of clinical signs and are not necessarily typical in all cases (Pakozdy et al., 2014). Seizure episodes can be generalized, with tonic-clonic movements as observed in dogs, focal, or focal evolving to generalized epileptic seizure (Bailey and Dewey, 2009; Berendt et al., 2015; Kline, 1998). Cats with focal seizures will twitch the eyelids, whiskers and/or ears either in combination or separately. Head shaking may occur as well as jerking of the body. They may salivate, urinate and their pupils may transiently dilate. Simultaneously, they may vocalize continuously and they may experience a temperature increase caused by hyperthermia (Kline, 1998). Focal episodes are frequently isolated or have a secondary generalization (Bailey and Dewey, 2009; Berendt et al., 2015). Focal continuous epileptic seizures occur more often as a presentation of status epilepticus in cats than in dogs (Kline, 1998).

Etiology was not associated with the type of seizure (Schriefel et al., 2008; Tokem et al., 2006). Idiopathic, generalized seizures are uncommonly observed in feline patients while partial and complex partial seizures prevail (Parent and Quesnel, 1996). Historically, focal epileptic seizures have been associated with structural lesion of the forebrain (Parent and Quesnel, 1996; Quesnel et al., 1997b), although the presence of focal lesions does not rule out a diagnosis of idiopathic epilepsy (Bailey and Dewey, 2009; Quesnel et al., 1997b; Schriefel et al., 2008). Tokem (2006) found that generalized epileptic seizures are the most common

seizure pattern in cats with intracranial neoplasia. In feline idiopathic epilepsy, focal and generalized epileptic seizures occur with relatively equal frequency (Schriefl et al., 2008). Focal epileptic seizures occur with near equal frequency in cats with idiopathic and cats with structural epilepsy (Pakozdy et al., 2010; Quesnel et al., 1997b; Schriefl et al., 2008). The frequency of intracranial disease as the most common underlying cause of epileptic seizures in cats is controversial (Barnes et al., 2004; Finnerty et al., 2014; Quesnel et al., 1997a; Schriefl et al., 2008).

Furthermore, a new type of seizure in cats (auditory reflex seizures) have been described (Lawrie et al., 2016). This type of seizure was precipitated by sensory stimuli and especially by loud sounds (Lawrie et al., 2016). Clinically, they can appear as generalized tonic-clonic seizures, myoclonic jerks, clinical absences or presumed absence seizures (Lawrie et al., 2016).

Timmann (2008) found that the occurrence of epileptic seizures in FIP cats indicated extensive brain damage and can, therefore, be considered to be an unfavorable prognostic sign.

It was presumed that lunar cycle can affect the frequency of epileptic seizures however Browand-Stainback (2011) reported no difference in seizure occurrence in the different phases of lunar cycle in both dogs and cats.

DIAGNOSIS

The diagnostic work-up for an epileptic cat include a thorough history, clinical and neurological examination, clinicopathological evaluation and advanced imaging (Bailey and Dewey, 2009). The baseline laboratory investigation includes a complete blood count (CBC), serum biochemistry profile, thyroid profile, blood pressure monitoring, measurement of serum bile acids concentration and urinalysis (Bailey and Dewey, 2009). These non-invasive tests may help to diagnose reactive seizures and are useful in planning anesthesia for any advanced imaging (Bailey and Dewey, 2009).

A complete funduscopic examination is imperative in all cases (Gunn-Moore and Reed, 2011). Advanced diagnostics include magnetic resonance imaging (MRI) or computed tomography (CT) and potentially cerebrospinal fluid (CSF) analysis (Bailey and Dewey, 2009). However even in high-field MRI, small cerebrovascular or inflammatory lesions may

not be visible and thus whether the etiology cannot be identified by the diagnostic work-up it does not necessary mean that epilepsy is idiopathic (Pakozdy et al., 2010). A CSF tap is indicated if the imaging is normal or suggestive of intracranial disease and the cat is believed to have normal intracranial pressure (Bailey and Dewey, 2009). If there is a space-occupying mass suspected or there is evidence of brain herniation, a CSF tap is contraindicated (Bailey and Dewey, 2009). Normal CSF is clear and colorless with fewer than 5 cells/ μ l and less than 27mg/ dl protein (for a cisterna magna tap) (Bailey and Dewey, 2009). Abnormalities in CSF are very sensitive indicators of intracranial disease but they are not specific (Bailey and Dewey, 2009). However, when evaluated with CT/MRI, CSF analysis can be a helpful diagnostic tool (Bailey and Dewey, 2009). Bacterial cultures and infectious diseases titers (*Cryptococcus*, *toxoplasmosis* and *FIP*) may also be useful tests to perform on CSF (Dewey, 2006; Foster et al., 2001; Pfohl and Dewey, 2005; Timmann et al., 2008).

INDICATIONS TO START ANTI-EPILEPTIC THERAPY

There is no consensus among veterinary neurologists about when antiepileptic treatment should be started (Pakozdy et al., 2014). It was suggested not to start antiepileptic treatment after a single epileptic seizure, but the occurrence of frequent epileptic seizures over a short period of time warrants treatment commencement (Platt, 2001). Others recommended aggressive treatment for cats after a few seizure episodes (Quesnel et al., 1997a). An aggressive early start of treatment can be beneficial as the cat could avoid cluster seizures and refractory epilepsy (Pakozdy et al., 2014). The decision to start the treatment should be taken on a case-by-case basis after considering the severity of epileptic seizure, ictal signs, risk of treatment, owner compliance, serum monitoring possibilities, and the difficulties with long-term oral application (Pakozdy et al., 2014). Maintenance therapy is specifically recommended when a cat presents with more than one seizure within 6 months (either generalized or focal), has more than one cluster event (defined as more than one seizure in a 24 h period), or experiences status epilepticus (ie, continuous seizure activity that lasts more than 5 minutes or the presence of multiple seizures without returning to normal in between the seizures) (Bailey and Dewey, 2009). Early AED administration in cats with suspected idiopathic epilepsy has been shown to lower the seizure

frequency within the first year of therapy (Pakozdy et al., 2012).

Therapy with antiepileptic drugs is recommended when epileptic seizures occur post-trauma (Bailey and Dewey, 2009). Grohmann (2012) found that cats with medical history of mild to moderate head trauma had $\leq 5.6\%$ probability of developing post-traumatic seizures. In another study, it was mentioned that the seizure could appear immediate after head trauma or delayed and thus the owners should be informed about the potential need for antiepileptic drug either at the time of the trauma or in the future (Kline, 1998).

It is strongly advised to treat cats with antiepileptic drugs when there is evidence of structural forebrain disease (obtained via MRI/CT, CSF analysis) such as neoplasia, infectious or non-infectious encephalitis, or congenital disease. Additional therapy is also warranted to treat the primary cause of the seizures; however, even after appropriate management (ie, surgery to remove a meningioma), AED administration is often necessary and is typically lifelong (Bailey and Dewey, 2009).

ANTIEPILEPTIC TREATMENT

Phenobarbital (PB) is the current drug of choice in cats with multiple seizure episodes (Berg et al., 2006; Dewey, 2006; Finnerty et al., 2014; Thomas and Dewey, 2008). It is available in both oral and intravenous formulations (Bailey and Dewey, 2009). Phenobarbital is relatively affordable and historically has a low incidence of adverse effects, thus PB is an excellent AED choice for cats (Parent and Quesnel, 1996; Platt, 2001; Schwartz-Porsche and Kaiser, 1989). There is one report in which adverse effect of PB in a cat is mentioned; it included depression, anorexia, cutaneous eruptions and severe generalized lymphadenopathy, the signs appeared 21 days after PB administration and resolved 7-14 days after PB discontinuation (Ducote et al., 1999). There are several studies supporting the efficacy of PB of seizure control in epileptic cats (Finnerty et al., 2014). Seizure control was achieved in most cats with serum PB concentrations between 15-45 $\mu\text{g}/\text{ml}$, regardless of the cause of the seizures (Finnerty et al., 2014).

There are few anecdotal reports on levetiracetam as an antiepileptic drug in the clinical setting (Bailey and Dewey, 2009). Levetiracetam was used as an adjunctive anticonvulsant therapy in cats with idiopathic epilepsy (Bailey et al., 2008). There was a marked

reduction in seizure frequency ($>50\%$ reduction) and in some cases there were no seizures after levetiracetam initiation (Bailey et al., 2008). Levetiracetam is well tolerated in cats and may be useful as an adjunct to phenobarbital in cats with idiopathic epilepsy (Bailey et al., 2008). Levetiracetam proved to be a promising option as a sole antiepileptic treatment in cats with seizure disorders. Despite its association with the honeymoon period in dogs and people (brief decrease in the number of seizures, then return to a frequency similar to what occurred prior to levetiracetam initiation), it did not seem to desensitize cats for over a year after its first administration. (Bailey et al., 2008; Kinirons et al., 2006; Volk et al., 2007).

Although, oral diazepam has a longer elimination time in cats (15-20h) than in dogs (3-4h), and the cats do not appear to develop a functional tolerance to the drug, it has been associated with a potentially fatal idiosyncratic hepatotoxicosis (Center et al., 1996; Hughes et al., 1996).

Bromide has been associated with life-threatening idiosyncratic allergic pneumonitis, reported in 35-42% of cats (Boothe et al., 2002; Wagner, 2001). Further studies report that 40% of cats receiving potassium bromide developed moderate to severe bronchoalveolitis/ pulmonary fibrosis and some of those cats were euthanized due to severity of clinical signs (Folger, 2009).

Gabapentin is another potential AED (Thomas and Dewey, 2008) however, there are no published data regarding chronic gabapentin therapy in feline epilepsy (Pakozdy et al., 2012).

Most cats can improve their quality of life and reduce aggression through a successful control ($>50\%$ reduction of seizures) regardless of etiology. Although there are reports showing a long term survival time in epileptic cats (range 3-21 months) (Quesnel et al., 1997a), some others disagree (Barnes et al., 2004; Schriefl et al., 2008). Survival time was shorter in cats with structural epilepsy; however in the same study survival time was longer in cats with probable structural epilepsy (epilepsy without any extracranial or identified intracranial disease that is not suspected to be genetic in origin) (Barnes et al., 2004), indicating that the cause and the degree of the brain damage in structural epilepsy can influence survival time. Euthanasia was elected soon after a diagnosis was established due to poor prognosis (Barnes et al., 2004) in cats. Poor seizure control, despite appropriate AED

administration was characterized as refractory epilepsy (Munana, 2013). Refractory epilepsy occurs in cats, less frequently than in dogs (Munana, 2013).

PROGNOSIS

Status epilepticus is a poor prognostic indicator in canine and feline epilepsy (Bateman and Parent, 1999; Schriefl et al., 2008). On the contrary, in epileptic dogs, the type of seizures was not associated with the survival time (Berendt et al., 2007).

Not only the number but also the severity of epileptic seizures is crucial (Pakozdy et al., 2012). It is possible that even a single epileptic seizure per year is harmful for patients because of its severity (status epilepticus, cluster seizures, prolonged post-ictal period); while other patients may not be affected by experiencing one epileptic seizure a week (Berg and Scheffer, 2011). For this reason it is important that not only the number of epileptic seizures, but also the adverse effects and the patient's quality of life are taken into account when evaluating control of epileptic seizures and effects of treatment, although naturally

quality of life is a highly subjective variable (Pakozdy et al., 2012). The complete remission of epileptic seizures in cats is rare (Pakozdy et al., 2012) and most cats should be maintained on anti-epileptic therapy (Platt, 2001).

CONFLICT OF INTEREST

None declared.

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