Clinical commentary

EEG-confirmed epileptic activity in a cat with VGKC-complex/LGI1 antibody-associated limbic encephalitis

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ABSTRACT – A 5-year-old, female client-owned cat presented with acute onset of focal epileptic seizures with orofacial twitching and behavioural changes. Magnetic resonance imaging showed bilateral temporal lobe hyperintensities and the EEG was consistent with ictal epileptic seizure activity. After antiepileptic and additional corticosteroid treatment, the cat recovered and by 10 months of follow-up was seizure-free without any problem. Retrospectively, antibodies to LGI1, a component of the voltage-gated potassium channel-complex, were identified. Feline focal seizures with orofacial involvement have been increasingly recognised in client-owned cats, and autoimmune limbic encephalitis was recently suggested as a possible aetiology. This is the first report of EEG, MRI and long-term follow-up of this condition in cats which is similar to human limbic encephalitis.

Key words: feline, epilepsy, limbic encephalitis, EEG, seizure

Feline temporal lobe epilepsy (FTLE) is well-known from experimental research (Wada et al., 1974). The characteristic ictal signs are orofacial automatisms such as salivation, facial twitching, head nodding, and head turning, and these may progress to generalised convulsive motor seizures. Very similar naturally-occurring focal seizures with behavioural changes have been reported worldwide in cats (Pakozdy et al., 2011). The presence of antibodies against leucine-rich glioma inactivating factor 1 (LGI1), a component of the voltage-gated potassium channel (VGKC) complex, were first identified in five cases (Pakozdy et al., 2013). Here, we describe a cat with temporal lobe seizures, high seropositivity against (VGKC)/LGI1, bilateral temporal lobe MRI

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hyperintensities, and EEG-confirmed electrical epileptic seizure activity. To the best of our knowledge, this is the first comprehensive description of limbic encephalitis (LE) associated with VGKC-complex/LGI1 antibodies in a cat.

**Case study**

A 5-year-old female neutered indoor European Shorthair cat was brought to our clinic with a three-day history of behavioural changes. The first signs were episodic hypersalivation, staring, and tremor for about one minute, followed by disorientation, panting, and unusual vocalisation. The episodes were progressive in duration and intensity, and occurred every 1-2 hours. Clinical examination was unremarkable, except for mild constipation. The neurological examination revealed decreased menace responses and anxious behaviour. Mild chewing movements and bilateral orofacial twitching were witnessed several times, lasting about 30 seconds, and between episodes the cat appeared progressively confused and tetraparetic. Status epilepticus was suspected and midazolam (0.2 mg/kg iv, followed by 0.4 mg/kg/hour constant rate infusion [CRI] therapy) was started. Routine haematology and blood chemistry revealed no important changes. Tests for feline leukaemia virus (FeLV) and feline immunodeficiency virus (FIV) were negative. Abdominal sonography and thorax radiography were unremarkable. MRI (Siemens Magnetom Espree 1.5-T) showed bilateral hyperintensities in the temporal lobes (figure 1) but the CSF analysis was normal. EEG was performed according to Redding and Knecht (1984) and showed an episode with synchronous discharges for about two minutes (figure 2). During the electrographic epileptic activity, the cat was clinically in sleep and no motor or autonomic signs could be recognised. Over the following days, phenobarbital, gabapentin, and levetiracetam were administered orally and midazolam was gradually tapered. The cat recovered uneventfully and was discharged after eight days of hospitalisation with phenobarbital (3 mg/kg BID), gabapentin (10 mg/kg TID), and levetiracetam (12 mg/kg TID) therapy. However, some days later, the cat presented again with growling, disorientation, insomnia, stranguria, and periuria. Fever (41.8°C), haematuria, and leukocyturia were identified. Cystitis was suspected and marbofloxacin (2 mg/kg SID) was started, but urine bacteriological cultures were negative. LE with feline interstitial cystitis (fIC) was suspected and prednisolone (1 mg/kg BID) was initiated. During the following eight weeks, prednisolone and gabapentin were gradually tapered and six months after the initial presentation, the cat is now seizure-free, with good general condition, no urination problem, and only mild paraparesis. The current medication is phenobarbital (3 mg/kg BID) and levetiracetam (12 mg/kg TID). Retrospectively, raised voltage-gated potassium channel-complex

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**Figure 1.** Transverse FLAIR (A) and T1WI (B) after paramagnetic contrast injection. There is a bilateral symmetrical hyperintensity in the dorsal and ventral aspect of the hippocampus (arrows) in the FLAIR sequence and marked heterogeneous contrast enhancement (arrows) on T1WI. Bar: 1 cm (extremity coil, 3-mm slice thickness with 0.6-mm interslice distance, transverse T1WI SE 501/12, and transverse FLAIR TIRM 8500/82).
Figure 2. Subclinical partial epileptic seizure which started on the left occipital (O1) region and spread to the left side, towards the frontal and right occipital (O2) regions. Rhythmic positive spike activity with growing amplitude appeared first at lead 4 (Fp1/O1, left side). Positive spike activity together with the O1-O2 negative activity indicated O1 origin. The rhythmic discharges with mildly lower amplitude almost immediately appeared from all leads connected with the occipital fields (O1, O2) showing O1-O2 propagation. The negative activity of discharges at the O1-O2 lead clearly showed again left-sided origin (O1). The seizure discharges propagated towards the anterior leads (Fp1 electrode). The amplitude was greatest at lead 4 (Fp1/O1). The frequency was about 8 Hz.

(VGKC) antibodies were identified, both at first and second presentation (330 and 467 pmol/L, respectively) (control human and feline sera: <100 pmol/L; [Pakozdy et al., 2013]), and found to bind to LGI1.

Discussion

A recent study supported the notion that an immune-mediated process may cause LE in cats, with secondary hippocampal neuronal loss (Pakozdy et al., 2013). Five of 14 cats with complex partial seizures (CPS) with orofacial automatisms were reported to have raised levels of VGKC-complex antibodies. Follow-up sera were available for 5 cats after remission and all antibody concentrations had fallen to within the control range. These results strongly suggested that immune-mediated LE exists in cats and is frequently associated with temporal lobe seizures, however, the lack of MRI and histopathological data limited the conclusions. The case presented here demonstrates for the first time that EEG and MRI data of a cat with LE associated with VGKC-complex/LGI1 antibodies are consistent with the human disease first described in 2001 (Buckley et al., 2001).

The presented case is interesting with regards to a number of different aspects: first, EEG was recorded during epileptic seizures; secondly, antibodies against the VGKC-complex/LGI1 were present; thirdly, the MRI showed temporal lobe changes; and fourthly, a problem with urination was also observed. There is growing evidence that spontaneous temporal lobe epilepsy (TLE) occurs worldwide in cats. Epileptic seizures associated with neuronal cell loss of the hippocampus and piriform lobe was first described in client-owned cats in Switzerland, and since then it has been reported worldwide (Fatzer et al., 2000). The neuronal loss in the hippocampus of epileptic cats was reported to be similar to that associated with human hippocampal sclerosis, with most severe neuronal loss in the CA1 segment, which is also known as the “vulnerable” or Sommer’s sector. Clinically, the studied cats showed CPS with orofacial automatisms, such as salivation, facial twitching, lip smacking, chewing, licking, and swallowing. Likewise, vegetative and emotional signs occurred. The cat described here exhibited similar semiology with orofacial automatisms, although initially only behavioural changes were observed.

A major weakness of the previously published papers on feline epilepsy is the lack of EEG confirmation
of epileptic seizures. EEG is not easy to apply in veterinary medicine as there is lack of agreement among veterinary neurologists regarding appropriate techniques and interpretation, and the data obtained are inconsistent. There are limited EEG results in healthy cats, but even less data for cats with recurrent seizures. The consequence of these limitations is that the “abnormal excessive or synchronous neuronal activity in the brain” which defines epileptic seizures has not systematically been confirmed in cats. Thus, the seizure event can only be suspected to be epileptic based on clinical, laboratory, and neuroimaging findings. Indeed, we found little evidence of epileptiform discharges in cats in the clinical veterinary literature for comparison. Brauer et al. (2012), however, found interictal spike activity in six of 13 epileptic and none of the six healthy cats, suggesting that interictal EEG can be diagnostic. Nevertheless, the recorded EEG (figure 2) likely represents epileptic discharges since many features are similar to experimental electroclinical findings in cats with hippocampal seizures. The EEG recordings in the present case are similar (figure 2) to those reported by Creutzfeldt (1956), following direct stimulation of the cornu ammonis in cats. Creutzfeldt described characteristic phases of the epileptic discharges, which start at 7 Hz with increasing frequency. Later, spike-wave or wave-spike potentials appear and termination is usually abrupt, similar to the cat described here. Creutzfeldt (1956) observed experimentally that, in sleep, epileptic discharges of the temporal lobe frequently do not cause clinical signs, as was seen in our cat.

It is possible that more information on feline EEG may be available in the future based on further studies of cats with autoimmune encephalitis and clusters of seizures. EEG montage for cats, recommended by Redding and Knecht (1984), may not be the most appropriate in these animals, because it concentrates on recording from the dorsal part of the brain rather than the temporal lobe. In our case, recording of epileptic activity was possible even though the electrode placement was not ideal, suggesting that better electrode placement could be diagnostic for a considerable portion of cats.

Immune-mediated medial TLE is a newly recognised epilepsy in human beings and the most frequent immunoreactive target is LGI1 (Vincent et al., 2004; Wieser et al., 2005; Irani et al., 2010; Lai et al., 2010). LGI1 is the main known component of the VGKC complex and is strongly expressed in the hippocampal neuropil where it appears to modulate VGKC activity. The antibodies are thought to interfere with this modulation leading to reduced VGKC function and neuronal hyperexcitability. Of particularly note, characteristic faciobrachial dystonic seizures have been recognised in patients with LGI1-antibody associated LE (Irani et al., 2011) and the semiology in our cat had some similarities, although forelimb involvement was not reported.

Although, feline interstitial cystitis (FIC) is frequent in cats, the aetiology is unknown, and affected cats may represent a naturally occurring model of human interstitial cystitis (HIC) (Buffington, 2011). We speculate that several possible links between FIC and hippocampal disorders may exist. First, the temporal lobe and the limbic system are responsible for gastrointestinal, vegetative, and emotional functions, thus, it is logical that dysfunction of these regions may cause complications of urination and defecation (Kaada, 1951). Secondly, chronic stress may cause hippocampal change and FIC, concomitantly. Thirdly, stress caused by the disorder itself, or by the hospitalisation, may cause FIC alone. Furthermore, autonomic peripheral dysfunction may be present due to the auto-antibodies and may cause complications of urination, in addition to limbic dysfunction, as is the case in Morvans’ syndrome (Irani et al., 2010).

LE and TLE are newly recognised clinical conditions in cats, and further studies are needed to characterise these problems. Such investigations may be beneficial to understand epileptic disorders in this species and determine whether such cats are a potential model for human TLE or LE.

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References


