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A feline model of spontaneously occurring autoimmune limbic encephalitis

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ABSTRACT

Autoimmune encephalitis (AE) is an important cause of encephalitis in humans and occurs at a similar rate to infectious encephalitis. It is frequently associated with antibodies against the extracellular domain of neuronal proteins. Among human AE, that with antibodies against leucine-rich glioma-inactivated 1 (LGI1) is one of the most prevalent forms, and was recently described in cats with limbic encephalitis (LE). In this study, we describe a large cohort ($n = 32$) of cats with AE, tested positive for voltage gated potassium channel (VGKC)-antibodies, of which 26 (81%) harboured LGI1-antibodies. We delineate their clinical and paraclinical features as well as long-term outcomes up to 5 years.

Similar to human cases, most cats with LGI1-antibodies had a history of focal seizures (83%), clustering in the majority (88%), with interictal behavioural changes (73%). Among feline AE patients, there was no seizure type or other clinical characteristic that could distinguish LGI1-antibody positive from negative cats, unlike the pathognomic faciobrachial dystonic seizures seen in humans. Although six cats were euthanased in the first year for epilepsy-associated reasons, those attaining at least 1-year survival had good seizure control and quality of life with appropriate veterinary care and medication. Acute-phase immunotherapy (prednisolone) was given to the most severely unwell cases and its effect is retrospectively evaluated in 10 cats. Our data show LGI1-antibodies are an important cause of feline encephalitis, sharing many features with human AE. Further research should examine optimal therapeutic management strategies and the cause of LE in seronegative cats, building on paradigms established in the counterpart human disease.

Introduction

Autoimmune encephalitis (AE) is increasingly recognised as an important cause of encephalitis in humans with, at minimum, a prevalence comparable to infectious encephalitis (Dubey et al., 2017). Many forms are associated with autoantibodies against surface neuronal or synaptic proteins. These antibodies can gain access to their targets in vivo and, hence are likely pathogenic. Modulation of the normal functioning of these antigenic targets is believed to induce neurological manifestations such as seizures, psychiatric symptoms, memory loss, personality and behavior change (Prüss 2021; Uy et al., 2021).

One form of human autoimmune limbic encephalitis (LE) is associated with the voltage gated potassium channel complex (VGKC; Vincent et al., 2004). Formerly, the VGKC itself was thought to be the antigenic target (Kleopa et al., 2006), but it is now demonstrated that antibodies against leucine-rich glioma-inactivated 1 (LGI1) and contactin-associated protein-like 2 (CASPR2) are the true pathogenic mediators, and each autoantibody associates with distinctive clinical presentations (Irani et al., 2010; Lai et al., 2010). By contrast, VGKC-antibodies bind intracellular epitopes which are not physiologically relevant, lack a clear phenotype, and commonly occur without encephalitis syndromes (van Sonderen et al., 2016; Lang et al., 2017). Also, these groups show distinctive major histocompatibility complex (MHC) associations – confirming their fundamentally different aetiological basis (Binks et al., 2018). 'Faciobrachial dystonic seizures' (FBDS), consisting of a brief jerk of the arm, face, and/or leg, are seen

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only in LGI1-antibody encephalitis (LGI1-Ab-E) and are pathognomic (Irani et al., 2011). They form a paradigm for the other very frequent and varied focal seizure semiologies, including piloerection, dyscognitive, and autonomic seizures observed in patients with LGI1-antibodies (Rocamora et al., 2014; Steriade et al., 2016; Aurangzeb et al., 2017).

LGI1, a secreted protein, (Senechal et al., 2005) is known as an epilepsy-associated entity and genetic mutations in humans cause temporal lobe epilepsy, principally Autosomal Dominant Temporal Lobe Epilepsy (ADTLE), in which seizures can be provoked by audiogenic stimuli such as telephone bells (Kalachikov et al., 2002; Morante-Redolat et al., 2002; Michelucci et al., 2007). Most described mutations (>30) are exonic and prevent LGI1 secretion (Ho et al., 2012). LGI1 polymorphisms were not found in a familial form of feline epilepsy (Yu et al., 2017), although mutations in the related proteins LGI2 and ADAM23 (ADAM Metallopeptidase Domain 23), a pre-synaptic binding partner of LGI1 (Ohkawa et al., 2013), are recognised in genetic epilepsy in dogs (Seppälä et al., 2011; Seppälä et al., 2012; Koskinen et al., 2015).

Recently, AE was suspected in domestic cats. The onset is usually acute or subacute with altered behaviour (fear and aggression), and cluster complex partial seizures with orofacial automatisms, similar to those in human LE (Pakozdy et al., 2011, 2013a, 2014). As in human medicine, the first cases were identified through measurement of VGKC-antibodies, but more recently, LGI1-autoantibodies were confirmed in 4/14 (29%) seizuring cats (Pakozdy et al., 2013a). These serological findings were supported by histopathological examination of deceased cats showing marked deposition of IgG and complement C9neo, and neuronal loss (Klang et al., 2014).

The aim of this study was to describe the clinical, laboratory, radiological and pathological findings in a larger cohort of VGKC-positive client-owned cats and evaluate these cats for LGI1-antibodies. We compared the features of LGI1-antibody negative (seronegative) and -positive (seropositive) cats and aimed to identify prognostic factors which assess the chance of remission in cats with suspected LE.

Materials and methods

Research was approved by the local research ethics committee (University of Veterinary Medicine, Vienna (Project PP 13011230; 20 April 2012) and written informed consent obtained. Client-owned cats with focal and/or generalised seizures were enrolled if they met the inclusion criteria of: (1) minimum of one seizure; (2) VGKC-antibody titre on at least one serum sample > 100 pmol/L; and (3) magnetic resonance imaging (MRI) or histopathological study of the brain. Abnormal MRI and/or cerebrospinal fluid (CSF) findings were not mandatory for recruitment, as it is recognised that these can be unremarkable in human LGI1-Ab-E. (Graus et al., 2016). Demographic and clinical parameters were recorded. All cats underwent at least one full general clinical and neurological examination. The standard diagnostic work-up usually included haematology, biochemistry, screening for feline immunodeficiency virus (FIV) and feline leukemia virus (FeLV), CSF analysis, and brain MRI. Auxiliary tests could include thiamine and/or thyroid hormone levels, thoracic x-ray, and abdominal ultrasound. Testing for VGKC-antibodies by radioimmunoprecipitation assay and LGI1- and CASPR2-antibodies by live cell-based assay was performed in Oxford on stored sera (Irani et al., 2010).

MRI was performed with a high-field machine (Magnetom Espree, 1.5 Tesla, Siemens Healthcare). Hippocampal abnormalities were evaluated using a modified multiparametric visual scoring system (Claßen et al., 2016). Briefly, a score of 1 was assigned if the hippocampus was unremarkable; 2 if changes were questionable; and 3 if obvious hippocampal pathology was visible.

Acutely, a count was made of the total number of seizures and daily seizures prior to therapeutic intervention, and daily seizures at month one. Seizures were categorised as focal or generalised (if possible, primary vs secondary generalized) according to owner description and clinical observations. Additionally, staging was performed, if possible, by a classification system for temporal lobe seizures in cats (Sato, 1975). Follow-up data were collected, including survival time, number of seizures/year, and quality of life (QoL).

Two methods were used to capture long-term seizure control. Firstly, the number of seizures/year were placed into five groups: excellent control (1; seizure-free), good control (2; 1–5 seizures), moderate control (3; 6–10 seizures), poor control (4; >10 seizures) and very poor (5; >25 seizures; Pakozdy et al., 2013b). A second categorisation described cats as: seizure free (1), seizures continuing with (2), or without (3) partial therapeutic success (Potschka et al., 2015). QoL was assessed by owner interview and clinical assessment, based on general clinical condition and medication side-effects. It was only assessed cats surviving the first year of treatment and was defined as good (no impairment, 1), acceptable (minor impairment, 2) and poor (severe impairment, 3).

Statistical analysis was performed in R (version 4.0.3) using standard statistical methods (Fisher's exact test for categorical data due to small sample size of VGKC group, Mann-Whitney U test for continuous non-parametric data, and paired t-test for matched samples).

Results

Clinical and paraclinical features at presentation

For the VGKC-assay, cats were considered positive if greater than 100 pmol/L (Pakozdy et al., 2013a). Thirty-two cats were identified with VGKC-antibodies > 100 pmol/L on at least one serum sample (79 samples from 32 cats, of which 54/79 [68.4%] were VGKC-positive; range, 105.3–2075.2 pmol/L; mean, 349.1 pmol/L; standard deviation, 335.1). Twenty-six of 32 cats (81%) had LGI1-autoantibodies (Fig. 1). In 10/32 (31.2%) cats, at least one sample exceeded the VGKC mean of positive sera of 349.1 pmol/L and these cats were defined as high titre. All were in the LGI1-antibody group (n = 10/26; 38.5%), compared to none of the six cats without LGI1-reactivities. No cats were positive for CASPR2 -antibodies. A summary of demographic information and neurological presentation by antibody status is provided in Table 1. Of 18 features compared between the groups, no clinical or paraclinical characteristic could distinguish LGI1-antibody positive from LGI1-antibody negative cats.

Almost all cats were Domestic Shorthair (n = 31/32; 93%), 19/32 (59%) were female and the median age of onset was 3.42 years (age in days was converted to age in years; range, 1–16 years). Serum sodium was normal in 27/32 cats tested and there were no clinically relevant abnormalities on blood or infection screening (Supplementary Table S1), except one case of thrombocytopaenia in a LGI1-autoantibody positive cat and one case of hyperthyroidism in a LGI1-autoantibody negative cat. CSF analysis was available for 24/32 and included cell count, cytology, protein concentration and glucose. All parameters were unremarkable, except for one cat with mildly elevated protein concentration (19 LGI1-autoantibody positive, five LGI1-autoantibody negative). MRI was normal in 80% (n = 24/30), including equal proportions of LGI1-antibody positive (n = 20/25; 80%) and negative (n = 4/5; 80%) cats.

Most cats had focal (temporal lobe seizures, n = 21/27; 78%) or generalised (n = 27/32; 84%) seizures, and many had both seizure types (n = 17/27; 63%), with comparable proportions in both groups (Table 1). Cluster seizures (two or more seizures within 24 h; Berendt et al., 2015) were common (n = 27/32; 84%). Similar to human LE, in which behavioural and personality change – including irritability - are frequent accompaniments, 22/32 (69%) cats had interictal behavioural change and 12/32 (38%) had a history of unprovoked aggression.

Treatment and outcome

These are summarised in Table 2. Phenobarbital was initiated in most cats (n = 26/28; 93%), and in all the LGI1-antibody positive cats (n = 24/24, 100%) compared to half (n = 2/4; 50%) of LGI1-antibody

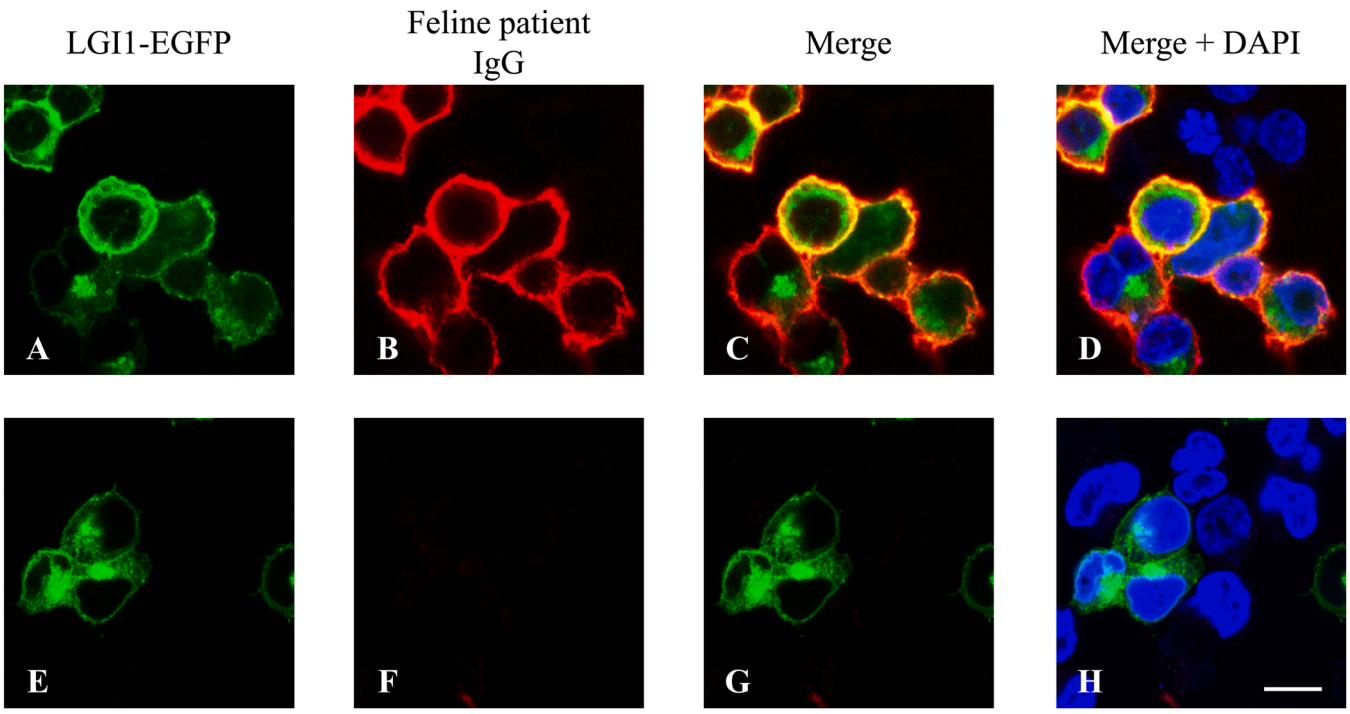

Fig. 1. Representative picture of a cell-based assay of a LGI1-antibody positive cat from this study, a 3.7-year-old spayed female treated with phenobarbital and levetiracetam. Cells expressing LGI1 (A) are bound by red-fluorescent tagged cat IgG molecules (B), with antibody and antigenic target co-localisation (C). Nuclei of non-transfected cells are stained with DAPI, and lack feline IgG binding (D). Panels E-H show a negative result in a control cat. Scale bar on panel H represents 10 μm. DAPI, 4′,6-diamidino-2-phenylindole; LGI1, leucine-rich glioma-inactivated 1. EGFP, enhanced green fluorescent protein. With thanks to Dr Antonio Berretta for help with microscopy and figure preparation.

negative cats ($P = 0.016$). There were no other significant differences in treatment between the groups. An additional anti-epileptic drug (AED) was added in around half ($n = 13/28$; 46%).

Ten cats received prednisolone in the first month, of which 9/24 (37.5%) in the LGI1-antibody positive and 1/4 (25%) in the seronegative group. Of cats with available data, 6/23 (33%; five LGI1-antibody positive, one LGI1-antibody negative) were euthanased due to epilepsy complications (Table 3). The overall 1-year survival rate was approximately 70–80%, and seizure frequency at 1 month fell from a mean of 3.6–0.17 daily ($P = 0.001$; paired *t*-test). At last data collection point, for cats not lost to follow up, 12/22 (55%) were still alive, including five with 4 years of follow-up and one with 5 years of follow-up.

Long term seizure control and QoL

Next, long-term outcomes were explored. A subset ($n = 11$ at 1 year to $n = 1$ at year 5) of cats had assessment of seizure control (Pakozdy and Potschka scores) and QoL (Pakozdy score) at yearly intervals. Most cats had no or few seizures/year, with a mean seizure score between 1 to approximately 2 on both scales at all time points. Similarly, mean QoL score indicated good to acceptable status (between 1 and 2) at each assessment. There were no statistically significant differences in any of the scores between the two serological groups (Table 4).

Effect of steroid treatment and other prognostic factors

In humans, LGI1-Ab-E is frequently rapidly - and seizures markedly - responsive to steroids. We explored the effect of steroid treatment in our feline cohort. Ten cats received steroids in the first month, of which nine harboured LGI1-antibodies (outcomes summarised in Table 5; details of corticosteroid treatment in the first month in Table 3).

Overall, cats that received prednisolone within the first month had a significantly higher number of daily seizures (mean/day, 6.75; range, 1.43–20) compared to those that did not (mean/day, 1.98; range, <1–10; $P = 0.015$, Mann-Whitney U test) and were also more likely to present in status epilepticus ($n = 5/10$; 50% in the steroid group vs. $n = 1/18$, 5.6% in the non-steroid group; $P = 0.013$, Fisher's exact test). Although there was no similar relationship between likelihood of cluster seizures and prednisolone therapy, all 10 cats that received steroids did experience cluster attacks. Among cats administered steroids, 55.6% ($n = 5/9$ with available data) were euthanased for reasons related to their epilepsy after a mean of 114.33 days (range, 53–214 days; median, 76 days) compared to no cats in the no-prednisolone group ($n = 0/13$; $P = 0.005$; Fisher's exact test). Similar results were obtained when considering only LGI1-antibody positive cats. In the steroid group, 4/9 cats survived with a mean survival time of 3.75 years and a reduction of the mean seizure frequency from 2.7 seizures/day before presentation to 0.14 seizures/day in the first year of therapy (data available in $n = 3/4$ cats).

Two disease factors were identified which linked to prognosis. One was the number of seizures at presentation. In the six cats that were euthanased due to epilepsy-related factors, mean number of seizures was higher at presentation (mean, 15; range, 10–20) compared to cats not euthanased (mean seizures/day, 2.4; range, <1–10; $P = 0.04$; Wilcoxon-Mann-Whitney U test). Hippocampal pathology also was relevant to prognosis as measured by MRI score: 75% ($n = 3/4$) cats with an MRI score 4 were euthanised, compared to 11% ($n = 2/18$) of those with a lower MRI score ($P = 0.024$; Fisher's exact test; outcome not available for one cat with MRI score 3).

Histopathology

Necropsy and histopathological examination of the brain were performed in four cats. In three LGI1-antibody positive cats euthanased between 2 and 6 months after the start of treatment, histology revealed bilateral hippocampal sclerosis, characterised by neuronal loss and gliosis (Fig. 2). In one LGI1-antibody negative cat, euthanased 2 days

Table 1
Summary of 32 cats included in this study. Percentages are given as a proportion of the number of cats with available data.

Feature	LGI1-antibody-positive (*n*, %)	LGI1-antibody-negative (*n*, %)	All cats (*n*, %)	LGI1 positive vs. LGI1 negative *P*
Number of cats	26 (81%)	6 (19%)	32 (100%)	ND
Breed	DSH (26/26, 100%)	DSH (5/6, 83%), Siamese (1/6, 17%)	ESH (31/32; 93%), Siamese (1/32; 7%)	ND
Female (%)[b]	16/26 (62%)	3/6 (50%)	19/32 (59%)	ns
Median age in years converted from age in days (range)	3 (1–6)	7 (1–16)	3.42 (1–16)	ns
Median weight in kg (range)	4.3 (2.8–7.4)	4.6 (3.4–7.1)	4.3 (2.8–7.4)	ns
Presentation				
Temporal lobe seizures (Sato 3–4)[c]	19/23 (83%)	2/4 (50%)	21/27 (78%)	ns
Generalized seizures (Sato 6)[d]	23/26 (88%)	4/6 (66%)	27/32 (84%)	ns
Focal and generalized seizures	16/23 (70%)	1/4 (25%)	17/27 (63%)	ns
Cluster seizures	23/26 (88%)	4/6 (66%)	27/32 (84%)	ns
Status epilepticus	6/26 (23%)	1/6 (17%)	7/32 (22%)	ns
ICU care needed	12/26 (46%)	1/6 (17%)	13/32 (41%)	ns
Elevated inner body temperature	5/26 (19%)	1/4 (25%)	6/32 (19%)	ns
Interictal behavioural abnormality[e]	19/26 (73%)	3/6 (50%)	22/32 (69%)	ns
Unprovoked aggression	12/26 (46%)	0/6 (0%)	12/32 (38%)	ns
Seizure frequency				
1–5 total prior to treatment	8/26 (31%)	4/5 (80%)	12/31 (39%)	ns
6–10 total prior to treatment	5/26 (19%)	0/5 (0%)	5/31 (16%)	ns
> 10 total prior to treatment	13/26 (50%)	1/5(20%)	14/31 (45%)	ns
Mean daily pre-treatment[f] (range)	4 (<1–20)	1.6 (<1–5)	3.6 (<1–20)	ns
Mean total pre-treatment[f] (range)	9.63 (1–20)	3.25 (1–5)	8.5 (1–20)	ns
Paraclinical feature				
VGKC titre > 349.1 pmol/L	10/26 (38.5%)	0/6 (0%)	13/32 (41%)	ns
MRI:	20/25 (80%)	4/5 (80%)	24/30 (80%)	ns
-Normal (Score 1)	1/25 (4%)	0/5 (0%)	1/30 (3%)	ns
-Mild abnormalities (Score 2)	4/25 (16%)	1/5 (20%)	5/30 (17%)	ns
-Marked abnormalities (Score 3)	1/26 (4%)		2/31 (6.5%)	
-Plus extrahippocampal change[g]				

DSH, Domestic Shorthair; LGI1, leucine-rich glioma-inactivated 1; ND, not done; ns, not significant (P > 0/05); VGKC, voltage-gated potassium channel
[a]Fisher's exact test for categorical, Mann-Whitney U test for continuous data
[b]All spayed except one female entire in LGI1 group
[c]Salivation, licking, pupillary dilatation, facial twitching, masticatory movements. No data available for 5 cats 3 LGI1, 2 VGKC)
[d]Primary generalised or secondary generalised
[e]Aggression, restlessness with or without compulsive walking, increased appetite, altered reaction to the owner
[f]Data not available in nine cats; $n = 7$ LGI1; $n = 2$ VGKC
[g]Additional minor extrahippocampal changes: one cat with mild cerebral atrophy, one cat with small fluid accumulation in the right parietal lobe and caudal cerebellum

Table 2
Treatment and outcomes in 32 cats. Percentages are given as a proportion of the number of cats with available data.

Treatment	LGI1-antibody (*n*, %)	VGKC-only (*n*, %)	All cats (*n* %)	LGI1 positive vs. LGI1 negative *P*[a]
AED treatment in first month:	24/24 (100%)	2/4 (50%)	26/28 (93%)	0.016
-Phenobarbital	3/24 (12.5%)	2/4 (50%)	6/28 (21%)	ns
-Phenobarbital only	13/24 (53%)	0/4 (0%)	13/28 (46%)	ns
-Phenobarbital and levetiracetam or gabapentin	8/24 (33%)	1/4 (25%)	8/28 (29%)	ns
-Phenobarbital and levetiracetam and gabapentin	0/24 (0%)		1/28 (4%)	
-Levetiracetam only				
Prednisolone in first month	9/24 (37.5%)	1/4 (25%)	10/28 (36%)	ns
Prednisolone at any time	14/26 (54%)	2/6 (33%)	16/32 (50%)	ns
Outcome				
Mean daily seizures 1 month (range)[b]	0.19 (0–1)	0.01 (0–0.03)	0.173 (0–1)	ns
Euthanased in or at first year - epilepsy	5/18 (27%)	1/5 (20%)	6/23 (26%)	ns
Survival at 1 year[c]	13/18 (72%)	4/5 (80%)	17/23 (74%)	ns
Survival at 2 years	12/18 (66%)	4/5 (80%)	16/23 (70%)	ns
Survival at 3 years	11/17 (65%)	4/5 (80%)	15/22 (68%)	ns
Alive at last follow-up	9/17 (53%)[d]	3/5 (60%)[e]	12/22 (55%)	ns

LGI1, leucine-rich glioma-inactivated 1; ns, not significant (P > 0/05); VGKC, voltage-gated potassium channel
[a] Fisher's exact test for categorical, Mann-Whitney U test for continuous data
[b] Data not available for 5 cats, 2 LGI1, 3 VGKC
[c] Includes in survival group one cat euthanased at 1 year due to epilepsy
[d] Five cats with 4 years of follow-up, and two cats with 5 years of follow-up
[e] Two cats with 4 years of follow-up

after the first seizure, numerous necrosis of pyramidal cells within the cornu ammonis corresponding to hippocampal necrosis (Fig. 3) and moderate signs of oedema were observed. In three cases, mononuclear, parenchymal and perivascular inflammatory infiltrates were present within the hippocampus region (Fig. 2). These histopathological findings recall appearances in human LGI1-Ab-E, in which post-mortem cases (Dunstan and Winer, 2006; Park et al., 2007; Khan et al., 2009; Schultze-Amberger et al., 2012) depict hippocampal-predominant neuronal loss and perivascular cellular infiltrates, whereas IgG and complement deposition have been depicted in other human (Bien et al., 2012) and feline (Klang et al., 2014) cohorts. The three LGI1-antibody positive cats had received steroids. All four cats had experienced cluster seizures and status epilepticus, 3/4 had > 10 seizures before the presentation, one between six and 10 seizures.

Discussion

We describe 32 cats with LE or acute-onset seizures with VGKC antibodies, 26 also harbouring LGI1-autoantibodies. This is an important cohort which represents the largest published series of such cats to date. Although the prevalence of LGI1-antibodies in seizuring cats is not known, the acute epilepsy phenotype in consistent association with LGI1-antibodies suggests LGI1-antibodies are a significant aetiology of feline LE. This is in keeping with investigations in new-onset resistant status epilepticus in humans, which revealed a proportion to be associated with an antibody cause (Gaspard et al., 2015). Although 5/18 (27%) of cats with LGI1-antibodies were euthanased due to resistant disease, the remainder had a good outcome, demonstrating that despite

Table 3
Details of cats receiving prednisolone in first month.

Cat number, antibody status	Sex, onset age	Seizures pre-therapy	SE or cluster	Steroid treatment	AED treatment in first year	Euthanased[a]	Time to euthanasia (days)
4, LGI1	fs, 1.4 years	NA	Cluster, SE	0.65 – 3.33 mg/kg q12h, 74 days, start at day 2	Midazolam, Phenobarbital, Levetiracetam, Gabapentin	Yes	76
5, LGI1	fs, 5.16 years	20	Cluster	0.64 – 1 mg/kg q12h, 30 days, start at day 1	Midazolam, Phenobarbital, Levetiracetam, Gabapentin	Yes	na
8, LGI1	fs, 1.16 years	20	Cluster, SE	1.3 – 3.4 mg/kg q12h, 90 days, start at day 2	Midazolam, Phenobarbital, Levetiracetam, Gabapentin	No	na
12, LGI1	ms, 2 years	5	Cluster	0.25 mg/kg q12h, 90 days, start at day 12	Phenobarbital, Levetiracetam, Gabapentin	No	na
13, LGI1	ms, 3.83 years	17	Cluster, SE	3 mg/kg q8h, 10 days, start at day 6	Phenobarbital, Levetiracetam	No	na
15, LGI1	fs, 6 years	10	Cluster	2 – 3 mg/kg q12h, 14 days, start at day 4	Midazolam, Phenobarbital, Levetiracetam, Gabapentin	Yes	53
16, VGKC	ms, 11 years	5	Cluster	0,5 mg/kg q12h, 10 days, start at day 1	Phenobarbital	No	na
18, LGI1	fs, 1.5 years	NA	Cluster, SE	1.5 mg/kg, 10 days, start at day 1	Midazolam, Phenobarbital, Levetiracetam	Yes	na
27, LGI1	ms, 1 year	NA	Cluster, SE	2.5 mg/kg q12h, 150 days, start at day1	Midazolam, Phenobarbital, Levetiracetam	Yes	214
30, LGI1	ms, 2.5 years	7	Cluster	1 – 1.5 mg/kg q12h, 120 days, start at day 5	Midazolam, Phenobarbital, Levetiracetam	No	na

AED, anti-epileptic drug; fs, female spayed, LGI, leucine-rich glioma-inactivated 1; ms, male spayed; SE, status epilepticus; VGKC, voltage-gated potassium channel
[a] All cats were euthanased because of the ongoing seizures

Table 4
Seizure control and QoL scores for cats at years 1–5.

Survival time in years, (number of cats; group)	Mean seizure control – Pakozdy (median, range)	Mean seizure control – Potschka (median, range)	Mean QoL – Pakozdy (median, range)
1 ($n = 11$; nine LGI1-antibody positive)[a]	2.09 (1, 1–5)	1.42 (1, 1–2)	1.09 (1, 1–2)
2 ($n = 11$; nine LGI1-antibody positive)	1.34 (1, 1–4)	1.19 (1, 1–2)	1.09 (1, 1–2)
3 ($n = 10$; eight LGI1-antibody positive)	1.9 (1, 1–5)	1.4 (1, 1–2)	1.3 (1, 1–3)
4 ($n = 6$; four LGI1-antibody positive)	1.17 (1, 1–2)	1.17 (1, 1–2)	1 (1, 1–1)
5 ($n = 1$ LGI1-antibody positive)	1	1	1

LGI1, leucine-rich glioma-inactivated 1; QoL, Quality of Life
[a] Potschka score at 1 year available for one additional LGI1-antibody positive cat

Table 5
Steroid use and markers of severity in all cats with available data and LGI1 cats with available data.

Group	Outcome		P[a]
All cats with available data			
	Survived	Dead – epilepsy related	0.005
No prednisolone month 1	13	0	
Prednisolone month 1	4	5	
	No status epilepticus	Status epilepticus	0.013
No prednisolone month 1	17	1	
Prednisolone month 1	5	5	
	No cluster seizures	Cluster seizures	0.128
No prednisolone month 1	5	13	
Prednisolone month 1	0	10	
LGI1 cats with available data			
	Survived	Dead – epilepsy related	0.007
No prednisolone month 1	10	0	
Prednisolone month 1	3	5	
	No status epilepticus	Status epilepticus	0.015
No prednisolone month 1	14	1	
Prednisolone month 1	4	5	
	No cluster seizures	Cluster seizures	0.266
No prednisolone month 1	3	12	
Prednisolone month 1	0	9	

LGI1, leucine-rich glioma-inactivated 1
[a] Fisher's exact test

acute severe illness these cats can survive with good seizure control and QoL for many years (two cats with LGI1-antibodies survived for 5 years). However, further research is required to improve prognosis for the most severely unwell cats in which group, currently, euthanasia remains an option.

All cats were presented because of seizures. A large number ($n = 21/27$; 78%; Table 1) was diagnosed with feline partial cluster seizures with orofacial involvement (FEPSO), which is the clinical manifestation of temporal lobe seizures (Sato stage 3–4) in cats (Kitz et al., 2017). In 17/27 (63%) cats generalized seizures were noted in addition to focal episodes. Interictal behavioural change was common ($n = 22/32$; 69%). Unprovoked aggression was only seen in LGI1-antibody positive cats, but this was not statistically significant. It may be the study was not powered to detect significant differences given the modest number of LGI1-antibody negative cats included. Alternatively, in contrast to the situation in humans, it is possible feline LGI1-Ab-E is not easily able to be distinguished from other forms of feline LE on clinical grounds.

Clinical work-up and follow-up revealed no neoplastic disease, suggesting VGKC/LGI-antibody LE is non-paraneoplastic in most cat cases. A similar conclusion was reached in our previous cohort (Tröscher et al., 2017) and mirrors the low rate of malignancy in human LGI1-Ab-E (Graus et al., 2016; van Sonderen et al., 2016b).

The standard diagnostic work-up was unremarkable except for one LGI1-antibody negative cat with hyperthyroidism and one LGI1-antibody positive cat with thrombocytopaenia. While the aetiology of the thrombocytopaenia was not confirmed, idiopathic thrombocytopaenia may be immune-mediated, possibly representing an autoimmune co-morbidity in this case. Interestingly, hyponatremia, which is a common finding in human LGI1-Ab-E, was not detected in any examined cats. However, hyponatremia in human LGI1-Ab-E is caused by

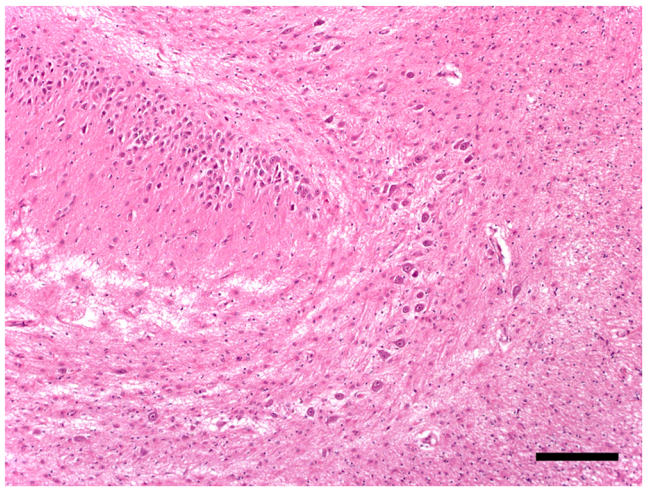

Fig. 2. Cat brain. Reduction of pyramidal neurons within the cornu ammonis together with gliosis and broadening of the dentate gyrus. Bar = 160 μm.

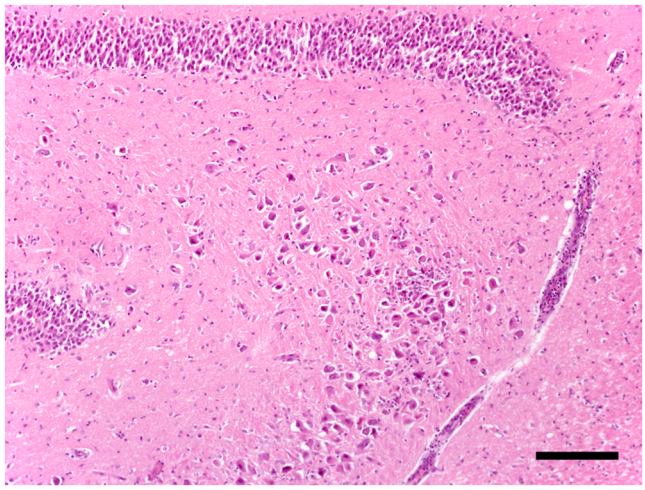

Fig. 3. Cat brain. Numerous, hypereosinophilic, shrunken, pyramidal neurons with pyknotic nuclei within the cornu ammonis. Note perivascular and parenchymal mononuclear inflammatory infiltrates. Hematoxylin-eosin.

hypothalamic dysfunction (Irani et al., 2012), which is not seen in cats. In a previous study, five LGI1-antibody positive cats did not show hypothalamic abnormality on histopathological evaluation (Tröscher et al., 2017).

In all seropositive cats, CSF analysis was unremarkable, similar to humans, although sometimes (approximately 25%) a mild lymphocytosis and/or elevated protein can occur (Irani et al., 2011). The bland CSF profile may be surprising for many veterinarians, as pleocytosis and inflammatory changes are expected in most veterinary encephalitides. We have previously shown the inflammation in feline LGI1-Ab-E preferentially activates the humoral arm of the immune system. T cell activation is seen in different regions of the feline brain, but is very mild and does not cause hypercellularity (Tröscher et al., 2017).

Brain MRI was unremarkable in most cats, another rather surprising finding. This could be linked to the mild cellular inflammatory changes, remaining below 1.5 Tesla sensitivity. Another factor is the much smaller brain size making diagnostic imaging for cats more challenging than for humans. MRI in humans may reveal unilateral or bilateral swelling/oedema of temporomesial structures in FLAIR and T2 weighted images (approximately 40%; Gadoth et al., 2017), followed by atrophy and mesial temporal lobe sclerosis (Urbach et al., 2006; Kotsenas et al., 2014). Similar acute changes could be detected only in 6/30 (20%) of our feline patients, and we did not have follow-up MRI to follow potential evolution to chronic degeneration.

In our cohort, the overall 1-year survival rate was approximately 75%, similar to cats with epilepsy of unknown cause (Pakozdy et al., 2013b; Wahle et al., 2014). The 1-year survival rate and the general outcome did not differ significantly between LGI1-antibody-positive and -negative cats. Although all high VGKC-titres were found in the LGI1-antibody group, this would still not identify > 60% LGI1-antibody positive cats. These findings mirror human investigations where VGKC antibodies at low titre are present in a range of conditions with unclear significance, including the healthy elderly, and do not denote a clear phenotype (Vincent et al., 2004; Rossi et al., 2015; van Sonderen et al., 2016; Lang et al., 2017). Therefore, current recommendations in human practice are to stop VGKC testing and, instead, evaluate sera for LGI1- and CASPR2-antibodies (van Sonderen et al., 2017).

The number of seizures before starting treatment influenced survival. Cats euthanased in the first year showed a significantly higher number of seizures than surviving cats. The connection between initial seizure severity and outcome is a known phenomenon, observed in cats with idiopathic epilepsy (Pakozdy et al., 2010), in dogs (Packer et al., 2014), and in humans. In a cohort of 103 patients with LGI1-antibodies and FBDS (Thompson et al., 2018) it was clearly demonstrated that, acutely, persistent seizures were linked to risk of developing sustained cognitive impairment. A smaller study of 16 patients (Aurangzeb et al., 2017) reported that in human LGI1-Ab-E, increased seizure frequency was prognostic of poorer long-term functional outcomes.

Based on our results, it seems hippocampal MRI changes also influence outcome, however this parameter as a biomarker may be not completely independent from the number of prior seizures. Cats with more severe MRI changes were significantly more likely to be euthanised. In humans with LGI1-Ab-E, severity of hippocampal MRI changes has been identified as a negative prognostic factor for long-term neuropsychiatric morbidity (Finke et al., 2017; Miller et al., 2017).

In our study 10/28 (36%) cats received immunotherapy additionally to AEDs in the first month. Surprisingly, these cats had a worse outcome than those that did not receive early steroid treatment. However, LGI1-antibody testing is not available as standard diagnostic work-up in feline patients and a trial of immunotherapy was initiated on clinical grounds. Steroids were administered to the most severely affected cats, including those without confirmed LGI1-antibodies, where a definite autoimmune aetiology may be unconfirmed. Also, the presence and proportion of antibodies from the subclass IgG1 (complement-activating) versus IgG4 (non-complement activating) in feline LGI1-Ab-E is yet to be explored, although histopathological studies of deceased cats show complement deposition (Klang et al., 2014). Since IgG1 in human LGI1-Ab-E is associated with worse outcomes (Thompson et al., 2017), if feline LGI1-Ab-E is a predominant IgG1 disease, this may explain a poorer immunotherapy response in cats and call for consideration of therapies targeting the complement cascade in feline disease.

Another factor may be the varied time-to-immunotherapy and regimens, including immunomodulatory rather than immunosuppressive doses of corticosteroids (Table 3). Recommended anti-inflammatory doses of prednisolone in dogs and cats range from 0.55 to 1.1 mg/kg/day, while immunosuppressive doses of prednisolon recommended for the cat range from 2.2 to 8.8 mg/kg/day (Lowe et al., 2008). By comparison, in humans, current practice is to initiate immunosuppressive doses corticosteroids (50 – 60 mg) at disease onset (Abboud et al., 2021). Based on our results in cats, no clear conclusion can be given regarding the use and benefit of steroid therapy, as more severe cases were treated.

Considering our data there are several limitations. Cats are not under observation all day and mild focal seizures (Sato 1–2) can be missed. Therefore, we only counted seizures classified as Sato 3–6. Moreover, it is often not easy to differentiate between a generalized seizure and a focal seizure with generalisation (Sato 6) even for veterinarians (Sato,

1975). There is variability in feline MRI sequence availability and positioning, and interpretation for borderline changes is challenging (Claßen et al., 2016). We did not evaluate for CSF LGI1-antibodies, which would be of interest to assess in cats, although generally held to be less sensitive in human LGI1-Ab-E compared to serum testing (van Sonderen et al., 2016b; Gadoth et al., 2017).

Conclusions

Our findings show LGI1-antibodies are an important cause of LE in domestic cats. Despite this, surface neuronal antibodies were not identified in approximately 20% of our cohort, leaving the possibility of additional entities being present in seronegative cats. Among seizuring cats, some cases were resistant and others responded well to treatment and went into long-term remission. A low number of seizures and the absent MRI changes are possible positive prognostic factors. LGI1-antibodies may be a more prevalent aetiology in domestic cats than previously recognised, and further research is required to evaluate clinical presentation and optimal cat-specific management. Cats surviving the first year seem to have a manageable course of disease, attaining stable seizure control and a good QoL with antiseizure treatment.

Conflict of interest statement

UG received a grant from the University of Veterinary Medicine Vienna (Success Stipendium). BL is a named inventor on patents for antibody assays and has received royalties. PW is a named inventor on patents for antibody assays and has received royalties. He has received honoraria from Biogen Idec, Mereo Biopharma, Retrogenix, UBC, Euroimmun AG and Alexion; travel grants from the Guthy-Jackson Charitable Foundation; and research funding from Euroimmun AG. Work in the Autoimmune Neurology Diagnostic Laboratory is supported by the NHS Commissioning service for NMOSD. SRI is supported by Wellcome Trust (Grant number 104079/Z/14/Z), a Medical Research Council Fellowship (MR/V007173/1), the BMA Research Grants- Vera Down grant (2013) and Margaret Temple (2017), Epilepsy Research UK (P1201), the Fulbright UK-US commission (MS-Society research award) and by the NIHR Oxford Biomedical Research Centre. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health. For the purpose of Open Access, the author has applied a CC BY public copyright licence to any Author Accepted Manuscript version arising from this submission. SRI is a co-applicant and receives royalties on a licenced patent application WO/210/046716 (UK patent no., PCT/GB2009/051441) entitled 'Neurological Autoimmune Disorders' and 'Diagnostic Strategy to improve specificity of CASPR2 antibody detection. (PCT/G82019 /051257) SRI has received honoraria/research support from UCB, Immunovant, MedImmun, Roche, Cerebral therapeutics, ADC therapeutics, Brain, CSL Behring, UCB and ONO Pharma. SRI is a co-applicant on grants from PetSavers (03.20) and Petplan Charitable Trust (S20-924-963). SB is supported by the Wellcome Trust and has had salary support from the National Institute for Health Research (NIHR). SB holds grants from PetSavers (03.20) and Petplan Charitable Trust (S20-924-963). SB is a co-applicant on a patent application entitled 'Diagnostic Strategy to improve specificity of CASPR2 antibody detection' (TBA/BB Ref. JA94536P.GBA). AP is a co-applicant on grants from PetSavers (03.20) and Petplan Charitable Trust (S20-924-963). None of the authors has any other financial or personal relationships that could inappropriately influence or bias the content of the paper.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tvjl.2023.105974.

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