J Vet Intern Med 2014;28:182–188

Clinical Characterization of Epilepsy of Unknown Cause in Cats

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Background: The diagnosis of feline epilepsy of unknown cause (EUC) requires a thorough diagnostic evaluation, otherwise the prevalence of EUC could be overestimated.

Hypothesis: Feline EUC is a clinically defined disease entity, which differs from feline hippocampal necrosis by the absence of magnetic resonance imaging (MRI) signal alteration of the hippocampus. The objectives of this study were (1) to evaluate the prevalence of EUC in a hospital population of cats by applying well-defined inclusion criteria, and (2) to describe the clinical course of EUC.

Animals: Eighty-one cats with recurrent seizures.

Methods: Retrospective study—medical records were reviewed for cats presented for evaluation of recurrent seizures (2005–2010). Inclusion criteria were a defined diagnosis based on laboratory data, and either MRI or histopathology. Final outcome was confirmed by telephone interview with the owner. Magnetic resonance images were reviewed to evaluate hippocampal morphology and signal alterations.

Results: Epilepsy of unknown cause was diagnosed in 22% of cats with epilepsy. Physical, neurologic, and laboratory examinations, and either 1.5 T MRI and cerebrospinal fluid analysis or postmortem examination failed to identify an underlying cause. Cats with EUC had a higher survival rate ($P < .05$) and seizure remission occurred frequently (44.4%).

Conclusion and Clinical Importance: A detailed clinical evaluation and diagnostic imaging with MRI is recommended in any cat with recurrent seizures. The prognosis of cats with normal MRI findings and a clinical diagnosis of EUC are good. Standardized imaging guidelines should be established to assess the hippocampus in cats.

Key words: Feline; Hippocampus; Outcome; Seizure.

Several terms such as "idiopathic" or "primary" epilepsy have been used to classify seizures of unknown cause in cats.[1–3] In the past, the term "idiopathic" has been reserved for canine and human epilepsy of presumed genetic etiology.[4–8] Confusion in terminology arose when this term was applied to describe seizures in cats because genetic epilepsy has never been recognized in client-owned cats. Description of presumed genetic epilepsy in this species so far has been limited to 1 report in an experimental breeding colony.[9] Consequently, the present article follows the recent suggestions of the Commission on Classification and Terminology of the International League Against Epilepsy (ILAE), which differentiates between genetic epilepsy and epilepsy of unknown cause.[10,11] Similar guidelines recently have been established in veterinary medicine.[12]

The reported prevalence of epilepsy of unknown cause (EUC) in cats with seizures ranges from 25 to 54%.[1,3,13] There is ongoing discussion as to whether the prevalence of EUC has been overestimated because of the inconsistent application of magnetic resonance imaging (MRI) and postmortem examination (PME), or use of low-field MRI.[1,3,14] Thus, some cases that previously were included as idiopathic possibly were caused by structural brain disease that had been missed. It was recently postulated that complex partial seizures (CPS) with orofacial involvement in cats might be associated with feline hippocampal necrosis (FHN) and immune-mediated limbic encephalitis with voltage-gated potassium channel (VGKC) complex antibodies.[15,16] There are few reports describing these entities in cats, applied MRI diagnostic criteria varied, and histologic correlates of altered hippocampal MR signal intensity were rarely assessed.[15–18] In cases without PME to support the diagnosis of feline limbic encephalitis-hippocampal necrosis complex, it is controversial whether borderline T2 hyperintensity of the hippocampus and parahippocampal structures represent the cause or consequence of seizures.

Therefore, the aims of this study were to define feline EUC as a disease entity different from FHN, to evaluate the prevalence of EUC in a hospital

Abbreviations:

AED	antiepileptic drug
ASS	acute symptomatic seizures
CPS	complex partial seizures
CSF	cerebrospinal fluid
EUC	epilepsy of unknown cause
FHN	feline hippocampal necrosis
FLAIR	fluid-attenuated inversion recovery
MRI	magnetic resonance imaging
PME	postmortem examination
VGKC	voltage-gated potassium channel

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Submitted June 27, 2013; Revised September 15, 2013; Accepted October 8, 2013.

10.1111/jvim.12250

population of cats by applying rigid inclusion criteria, and to describe the clinical course of EUC.

Materials and Methods

Data Collection

The medical records of cats with seizures were reviewed retrospectively (2005–2010). The inclusion criteria were documentation of ≥2 seizures occurring on different days (≥2 seizure days), laboratory investigations, and, for cats that were still alive, an observation period of ≥1 year after seizure onset, and performance of either MRI or PME. To ensure the diagnosis of epilepsy, cats with only 1 seizure day were excluded from the study. Cases in which a metabolic or toxic aberration was identified as the cause of seizures were classified as having acute symptomatic seizures (ASS), and were included in the study but did not require MRI or PME.[19] Seizure history, and any additional diagnostic tests, were reviewed. The following clinical variables were extracted from the medical records: breed, sex, age at seizure onset, date of most recent seizure, seizure type, information regarding initial antiepileptic drug (AED) treatment, most recent serum concentrations of AEDs, date and cause of death, and final clinical diagnosis.

Classification of Epilepsy

The definition and classification of epilepsy and epileptic seizures corresponded to recent ILAE recommendations.[10,11,19,20] The diagnostic criteria for EUC were normal interictal neurologic examination, normal laboratory test results, normal CSF analysis, and no abnormalities on either MRI or PME. Structural epilepsy was defined as epilepsy caused by any cortical, subcortical, or thalamic structural lesion evident on MRI or histopathology. FHN was included in this group if confirmed by conclusive MRI criteria (T1 hypo-isointensity, T2- and T2-weighted fluid-attenuated inversion recovery [T2-weighted FLAIR] hyperintensity compared to grey matter, and various degrees of contrast enhancement on postcontrast T1) or PME.[17,18] ASS were diagnosed if a severe metabolic or toxic aberration known to cause seizures was clearly identified.[19,21–23]

Classification of Seizures

Seizures were classified as focal or generalized based on observations at the clinic and description of the owners at the initial presentation and during subsequent phone conversations. Focal seizures were defined as paroxysmal occurrence of abnormal movements of 1 part of the body, such as contractions of 1 limb or facial muscles, with or without impairment of consciousness or autonomic signs, or as focal seizures evolving to generalized seizures.[10] Generalized seizures were characterized by involvement of both sides of the body or the whole body with the animal presenting mostly in a lateral recumbency, with loss of consciousness, tonic-clonic limb movements, and salivation, urination, and defecation. Status epilepticus was defined as a generalized seizure lasting >5 minutes, cluster seizures without regaining full consciousness between seizures, or focal seizures lasting >30 minutes.

Review of Imaging and Histopathologic Data

Diagnostic imaging was routinely performed using a 1.5 Tesla unit.[a] The following pulse sequences were used: T1-weighted pre- and postcontrast (gadodiamide 0.15 mmol/kg IV), T2-weighted and T2-weighted FLAIR with slice thickness of 2.5 mm. Images were obtained in transverse, dorsal, and sagittal planes, with the cats positioned sternally. Diffusion-weighted and gradient-echo T2* images were acquired in some cases. All MRI scans of cats classified as EUC were reviewed by a board-certified radiologist (AB). Additionally, transverse and dorsal images of MRI scans with presumed T2 signal hyperintensity in 1 or both hippocampi were compared in a nonblinded fashion to brain images of cats presented for reasons other than seizures. Review focused on signal alteration (T1 hypo-isointensity, T2, T2-weighted FLAIR hyperintensity) and contrast enhancement of the hippocampus and piriform lobe. Cerebrospinal fluid was routinely obtained from the atlantooccipital site and assessed for protein concentration, total cell count, and differential count within 30 minutes. All records of PME of cats classified as EUC were reviewed and neurohistologic specimens were reviewed (KM, EW).

Assessment of Clinical Course

The final outcome for all patients discharged from the hospital was assessed by telephone interviews with the owners. Owners were consulted regarding current AED treatment, seizure frequency, most recent seizure (date), and (if applicable) cause of death. Seizure period was defined as the time (days) from the onset of epilepsy (first observed seizure) to the last observed seizure of the cat's life. Active epilepsy was defined as ≥1 epileptic seizure event during the last year or in the year preceding death. Seizure remission was assumed if ≥1 year had passed without any seizures. Seizure remission time was defined as the number of years from the last observed seizure until the date of contact.

Statistical Analysis

Statistical analyses were performed using Prism 5.[b] The D'Agostino and Pearson omnibus test was used to test for normal distribution of data. Age at seizure onset was compared by the Mann–Whitney *U*-test and Kruskal–Wallis test. Fisher's exact test was used to compare seizure types and sex. Survival times (calculated from seizure onset) were displayed graphically using Kaplan–Meier curves (evaluated by log-rank test). Epilepsy-related death was considered an event. Cats still alive at the end of the study or lost to follow-up were censored. The level of significance was $P \leq .05$.

Results

Eighty-one cats fulfilled the inclusion criteria. Of these, structural brain lesions were detected by MRI or PME in 38 cats (47%) and unequivocal metabolic or toxic abnormalities were evident in 25 cats (31%; ASS). In 18 cats (22%), the cause of epilepsy remained undefined, despite extensive diagnostic investigations suggesting a diagnosis of EUC (Table 1). Neither age of seizure onset nor sex differed between the groups ($P > .05$; Table 2). Initial histopathologic PME indicated the presence of FHN in 1 cat.

Detailed Description of Feline EUC

Signalment and Seizure History. Epilepsy of unknown cause was diagnosed in 18 cats and subsequently confirmed by PME in 2 cats (Table 1). Fifteen cats (83%) were domestic shorthair and 3 were purebred cats (Turkish Angora, Bengal, Russian White).

Table 1. Summary of diagnostic evaluation of cats with seizures.

	Etiology		
	EUC	Structural Epilepsy	ASS
Variable	n	n	n
MRI, CSF,[a] PME, LAB	1	2	1
MRI, CSF,[a] LAB	15	6	2
MRI, PME, LAB	0	4	0
MRI, LAB	1	14	1
PME, LAB	1	12	7
LAB	0	0	14
Study group size	18	38	25
Percentage[b]	22%	47%	31%

EUC, epilepsy of unknown cause; ASS, acute symptomatic seizures; MRI, magnetic resonance imaging (1.5 T); CSF, cerebrospinal fluid analysis; PME, postmortem examination; LAB, detailed laboratory investigation.

[a]Analysis reference values: total nucleated cell count, ≤5/μL; protein concentration, ≤0.3 g/L; differential count; 2 samples blood contaminated.

[b]Scale basis: all affected cats (n = 81).

Table 2. Comparison of age at seizure onset and sex.

	Etiology			
Variable	EUC	Structural Epilepsy	ASS	*P*-value
Age at seizure onset (years)				
Median	3.8	7.8	7.4	.259[a]
Range	0.4–14.4	0.3–19.0	0.4–22.0	

	EUC	not EUC	*P*-value
Sex			
Male	7	29	.788[b]
Female	11	34	

EUC, epilepsy of unknown cause; ASS, acute symptomatic seizures.

[a]Kruskal–Wallis test was used to compare age at seizure onset between cats with EUC, structural epilepsy or ASS.

[b]Fisher's exact test was used to compare sex between cats with EUC and not EUC (structural epilepsy and ASS).

The median age at seizure onset was 3.8 years (range, 0.4–14.4). Most cats were kept exclusively indoors (78%); only 4 cats (22%) lived partially outdoors. None of the owners referred to trauma or contact to potential poisons as possible predisposing events for seizures.

Seizure Type. Focal or focal onset seizures were identified in 9 cats and generalized seizures were identified in the remaining 9 cats. Cats with EUC were more likely to experience focal or focal onset seizures ($P = .0029$) compared to cats with structural epilepsy or ASS. Cats with focal seizures presented with salivation (n = 8), orofacial motor signs (n = 7), vocalization (n = 3), urination or defecation (n = 2), mydriatic pupils (n = 1) and secondary generalization was evident in 6 cats. None of the cats with EUC experienced status epilepticus as the first seizure event, but 4 cats developed generalized status epilepticus during the course of the disease.

Clinical Evaluation. The neurologic examination was normal in all but 3 cats; these were examined postictally and displayed decreased menace response (n = 3) and abnormal postural reactions (n = 2). In 2 other cats, neurologic examination was limited because of severely aggressive behavior.

Laboratory abnormalities were present in 11 cats. These changes (lactate acidosis [n = 8], increased creatine kinase activity [n = 5], hyperglycemia [n = 2], and increased alanine aminotransferase activity [n = 2]) were considered mild and, consequently, not a cause of the seizures. One cat was presented with a single high systolic blood pressure measurement (210 mmHg). Sequential systolic blood pressure measurements were normal (110 mmHg) and a cerebrovascular accident was considered unlikely because of MRI that included T2* and diffusion-weighted sequences. Another cat had marked neutrophilia (22.55×10^9/L segmented neutrophils; range, 3–11 $\times 10^9$/L), and a single large abdominal lymph node abscess was removed surgically 3.5 months after seizure onset. Histopathologic examination showed severe reactive hyperplasia, lymphadenitis, and necrosis with infiltration of neutrophils, macrophages, and plasma cells. Immunohistochemistry failed to detect coronaviruses in macrophages, and the cat remained in good condition until follow-up evaluation 12.5 months after its first seizure.

No evidence of structural thalamocortical brain disease was identified on MRI. Review of MRI scans and comparison to brain images of cats without seizures failed to identify any unequivocal evidence of T2 or T2-weighted FLAIR hyperintense signal change in the region of the hippocampus and piriform lobe or contrast enhancement on postcontrast T1-images.

Cerebrospinal fluid was evaluated in 16 cats and was normal with regard to cytology, total nucleated cell count (median, 2 cells/μL; range, 0–5 cells/μL; reference range, ≤5 white blood cells/μL), protein concentration (median, 0.1 g/L; range, 0.06–0.3 g/L; reference range, ≤0.3 g/L), and negative Pandy test results in 14 cats with EUC. Cerebrospinal fluid analysis was either not performed or contaminated by blood in 2 cats each (Table 1).

Clinical Course of EUC

The 1-year survival rate was 73% (13/18 cats) in cats with EUC, which was significantly higher than the survival rate of cats with structural epilepsy or ASS (35%; 22/63 cats; $P < .05$; Fig 1). At the conclusion of the study, 13/18 cats with EUC still were alive, compared to 12/63 cats with structural epilepsy or ASS. For those 13 EUC cats, median follow-up time was 1.6 years (range, 1.0–6.3 years). Eight of 18 cats (44%) with EUC experienced seizure remission. Median seizure remission time was 1.4 years (range, 1.0–5.4 years). Seizure remission was maintained with (n = 5) or without AED (n = 3). Five of 10 cats with

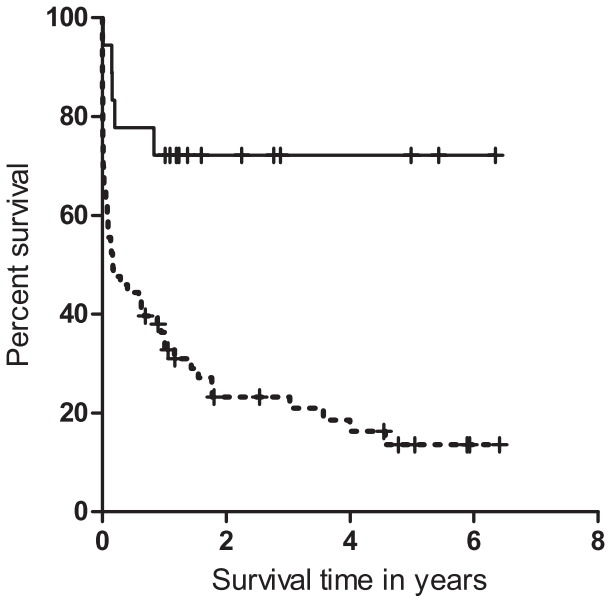

Fig 1. Kaplan–Meier curve depicting significant differences in survival rate of cats with EUC compared to cats suffering structural epilepsy or ASS ($P = .001$). Black line, cats with EUC; broken line, cats with structural epilepsy or ASS; censored cats, cats still alive or lost to follow-up at the time of analysis. EUC, epilepsy of unknown cause; ASS, acute symptomatic seizures.

active epilepsy died (n = 2) or were euthanized (n = 3) 5, 55, 58, 74, and 305 days after onset because of their seizures. The other 5 cats with active epilepsy were still alive at study conclusion. One cat was seizure-free for 6 months and thereafter experienced 4 seizures in 1 week after the owner had discontinued AED treatment. Another cat developed generalized seizures (>1 seizure/month) after 2 years of seizure remission. A third cat was seizure-free for 0.9 years at the conclusion of the study despite frequent seizures in the first month after diagnosis of epilepsy. The other 2 cats experienced frequent seizures. Median seizure period, defined as the time (days) from the onset of epilepsy (first observed seizure) to the last observed seizure of the cat's life, was 9 days (range, 3–1,070 days) for cats in seizure remission (n = 8) and 276 days (range 5–1,050 days) for cats with active epilepsy (n = 10).

Antiepileptic Drug Treatment

All cats with EUC initially were treated with phenobarbital. Cats in seizure remission with or without AED treatment initially were started on AED treatment a median of 2 days (range, 0–366 days) after the first seizure. At the conclusion of the study, cats that underwent seizure remission with AED treatment (n = 5) were treated with phenobarbital at a median dose of 1.6 mg/kg (range, 1.3–2.6 mg/kg) PO q12h. Serum phenobarbital concentration was monitored in 3 of these cats (median, 20.5 μg/mL; range, 15.5–28.3 μg/mL). In the active epilepsy group (n = 10), 9 cats were treated with phenobarbital at a median dose of 2.9 mg/kg PO q12h (range, 1.5–4.4 mg/kg). Cats in this group were started on treatment a median of 29 days (range, 0–322 days) after their first seizure. Serum phenobarbital concentrations were monitored in 6 of these cats (median, 29.3 μg/L; range, 12.7–45.4 μg/L). Four of them received levetiracetam adjunctive treatment at a median dose of 24.8 mg/kg PO q8h (range, 20–29 mg/kg). In 1 cat initially treated with phenobarbital (2.4 mg/kg PO q12h), potassium bromide (22.6 mg/kg PO q24h) was chosen as additional treatment because seizures were refractory and the owner refused to treat more than twice daily. After 3 months of treatment, potassium bromide was discontinued because of adverse respiratory effects. In addition, after a period of 1.5 years, phenobarbital gradually was decreased and then discontinued because of neutropenia (1.91×10^9/L; range, 3–11×10^9/L). At the time of writing, the seizures in this cat were controlled with levetiracetam 27 mg/kg PO q8h and zonisamide 6 mg/kg PO q24h.

Discussion

Epilepsy of unknown cause was diagnosed in 22% of cats with recurrent seizures. This frequency is less than previously reported (25,[1] 38,[3] 41,[14] and 54,[13] 66%[24]) by other authors, who had called this entity idiopathic or presumed idiopathic seizures,[1] suspected idiopathic epilepsy,[2,24,25] probable symptomatic epilepsy,[14] or primary epilepsy.[3] However, in this study, all cats with epilepsy of unknown cause and structural epilepsy were examined by 1.5 T MRI or underwent PME. The remainder had ASS, which were attributed to severe metabolic disturbances or poisoning. Epilepsy of unknown cause must be diagnosed by exclusion of intracranial lesions and other causes. The application of advanced diagnostic imaging appears to be crucial for this diagnosis, and its use was limited in previous studies.[1,3]

The term "feline epilepsy of unknown cause" has been used in this investigation in accordance with the recent report of the ILAE Commission on Classification and Terminology.[10,11] Epilepsy of unknown cause was supported by the fact that none of the cats had a family history of epilepsy. However, cats, especially domestic shorthaired cats, often are acquired from shelters or farms and therefore pedigree data are less commonly available for cats than for dogs. Yet, only 1 report describes presumed genetic epilepsy in an experimental breeding colony.[9] Craniocerebral trauma was an unlikely cause because of a lack of supportive history. Furthermore, none of the owners reported exposure to potential toxins. Recently, head trauma has been reported to be associated with a substantial risk of developing epilepsy in dogs.[26] In contrast, recent studies failed to demonstrate a link between previous mild to moderate head trauma and the development of epilepsy in cats.[27]

A high proportion of the cats with EUC in this study showed CPS with orofacial involvement and a good outcome, similar to what has been described

recently in correlation with FHN.[15] FHN previously has been described as a frequent etiology for seizures in cats[3,17,25] whereas others only observed it infrequently.[1,28] When reviewing and comparing the MRI scans from cats with EUC and cats without seizures, we were unable to confirm hippocampal signal alterations in any of the cats in the study. This observation may imply that EUC either is a distinct disease entity in cats or that imaging of the feline hippocampus is severely limited using current imaging protocols.[18,29] Recently, FHN has been suspected based on T2-weighted hyperintensitiy only and concurrent contrast enhancement was not a requested feature.[15] In contrast, bilateral T2 hyperintensity in the hippocampus and piriform lobe has been interpreted as focal edema by others.[30] Hence, there is ongoing discussion whether reported hippocampal changes represent the cause or consequence of seizures. In human medicine, hippocampal sclerosis is the most common pathology underlying drug-resistant mesial temporal lobe epilepsy. In order to make a diagnosis of hippocampal sclerosis, a standard MRI protocol is used. Common MRI features are decreased hippocampal volume, increased signal intensity on T2-weighted imaging as well as disturbed internal architecture of the hippocampus.[31] Attempts have been made to evaluate the use of volumetry and to define an MRI protocol for assessment of the canine hippocampus.[32,33] Nothing comparable has been published for FHN. Consequently, the diagnosis or exclusion of FHN must be based on postmortem histopathologic findings in the absence of unequivocal MRI features. Future investigations of MRI and histopathologic correlates in the same patients are needed, but may introduce bias because they focus on nonsurviving cats. Alternatively, 3T MRI may be warranted.

The median age at seizure onset was 3.8 years in cats with EUC, as described previously.[1,3] A median age of onset of <5 years appears to mirror canine idiopathic epilepsy, but onset varied widely from 5 months to 15 years and we were unable to document a familial history of seizures in any of the cats with EUC. Furthermore, we cannot conclusively state that EUC in the cats of this study represents a single disease entity, and EUC may have a variety of causes.

The most recent investigation of primary epilepsy recruited higher numbers of cats over a longer period of time, but utilized different inclusion criteria than did the present study.[34] Differentiating features were inconsistent use of brain imaging (52% examined by MRI, CT, or PME versus 100% in the present investigation). This approach may have favored inclusion of cats with structural epilepsy caused by FHN or limbic encephalitis. Consequently, the prevalence of EUC was lower in the present (22%) than in previous investigations (38%).[3,34] Yet, both studies documented comparable age of onset, good outcomes and frequent seizure remission for long periods in association with early treatment. In this study, cats with EUC had a significantly higher 1-year survival rate, compared to cats with structural epilepsy or ASS. At the end of the 12-month follow-up period, 73% of the EUC cats were still alive, which coincides with previous descriptions.[1,34] Seizure remission also was a frequent feature in the first systematic investigation of epileptic cats, but the follow-up time was very variable (ie, 3–18 months) and only subtle structural brain lesions were found.[35] We confirmed that many cats with EUC had an excellent long-term prognosis and that the epilepsy tended to follow a self-remitting course in a proportion of cats. Cats with EUC exhibited a 44% seizure remission rate with phenobarbital treatment. This remission rate is higher than observed in dogs with idiopathic epilepsy with reported long-time seizure remission rates from 15 to 24%.[36–38] In this investigation, cats with seizure remission were treated earlier in their disease course. Research in human patients has shown that in addition to underlying cause (and possibly age), early seizure control also is an important indicator of outcome.[39–41] Our data indicate that an aggressive diagnostic and therapeutic approach may improve prognosis and may be associated with favorable outcome as suggested previously.[1,34,42] However, it is still possible that EUC follows a self-limiting course, which is either defined by complete seizure remission or low seizure frequency with interictal periods >1 year.

In this study, many cats in the seizure remission group had a short initial seizure period of <1 month. One could therefore consider other self-limiting conditions (eg, inflammatory or vascular disease, ASS) as possible underlying causes. The role of inflammation as a predisposing cause for seizures has been the focus of recent epilepsy research.[43–45] Hematology and CSF findings including cytology were not suggestive of inflammation, and other evidence for inflammation was only present in 1 cat, as indicated by neutrophilia and an enlarged mesenterial lymph node. However, 1 cat did not have CSF analysis or PME performed, and therefore inflammation might have been missed in this cat. Limbic encephalitis associated with antibodies against VGKC recently has been proposed in cats with CPS with orofacial involvement and suspected hippocampal pathology.[16] The clinical features and the outcome of cats in this study are very similar to those of cats with CPS and orofacial involvement. However, in our case series we were unable to confirm hippocampal signal intensity changes and thus were reluctant to use the terms hippocampal necrosis or limbic encephalitis. However, because VGKC antibodies were not measured in this study, limbic encephalitis cannot be excluded as a potential cause of seizures. Therefore, future studies of feline epilepsy should not only include detailed imaging investigations, but also measurement of VGKC antibodies.

Inherent limitations of this study include the small number of cats, the heterogeneity of the group, the retrospective nature of the study, lack of video documentation of the seizures, and the fact that outcome was partly based on owner treatment decisions. In addition, the consistent application of diffusion-weighted and postcontrast T2-weighted FLAIR in addition to

postcontrast T1 protocols as well as oblique views of the hippocampus might have enhanced detection of infarcts, inflammatory lesions as well as hippocampal and piriform lobe abnormalities.

Conclusions

Results of this study confirm that EUC exists in a proportion of cats with seizures. Extensive diagnostic evaluation is recommended for any cat with seizures to rule out structural epilepsy and ASS because EUC can be associated with a good prognosis. Well-defined imaging and histopathologic guidelines should be used for assessment of the feline hippocampus in order to provide a clinical and not only a postmortem diagnosis of FHN.

Footnotes

[a] SIEMENS Magnetom Symphony; Siemens AG, Erlangen, Germany
[b] Prism 5; GraphPad Software, La Jolla, CA

Acknowledgments

None of the authors was supported by a grant or has any financial or personal relationships that could inappropriately influence or bias the content of the article.

Conflict of Interest Declaration: The authors disclose no conflict of interest.

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