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Survival in 76 cats with epilepsy of unknown cause: a retrospective study

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Abstract

Survival of cats with epilepsy of unknown cause (EUC) has not been reported. Seizure semiology and its relationship to treatment outcome and survival was studied in a population of 76 cats. A questionnaire for seizure semiology was developed based upon experimental data. Seizure semiology was characterized by owner interviews at least one year after discharge. Seizures were classified as: (1) primary generalized and (2) focal without and (3) with secondary generalization. Median age at seizure onset was four (range 0.3 to 18) years. One third of cats with EUC presented with primary generalized seizures and 78% of those with initially focal seizures progressed to secondary generalized seizures. Clinical signs of generalized seizures included sudden onset of loss of consciousness and tonic-clonic seizures, while cats with focal seizures had unilateral signs. Antiepileptic drug (AED) therapy was initiated in 62 cats. Complete remission rate was 42% and median survival time was 3.2 (range 1 to 11) years with or without AED, and 91% were still alive at the time of interview. Neither semiology nor seizure type predicted survival, response to treatment, and outcome in cats with EUC. A seizure-free status of >12 months was observed in 79% of cats without AED.

Epilepsy in dogs and people is associated with an increased risk of death and the disorder may associated with reduced survival rates (Berendt and others, 2007; Hauser and others,

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1980). In contrast, no such studies on survival have been published on cats with epilepsy. The original classification scheme for epilepsy in humans from the International League Against Epilepsy (ILAE) in 1989 divided the seizure aetiologies into idiopathic, symptomatic, and cryptogenic epilepsies (Commission of ILAE, 1981, and 1989). Idiopathic epilepsy was defined as chronic recurring seizures without any underlying structural brain lesions and other neurological signs and is presumed to be genetic in origin. Symptomatic epilepsy was due to identifiable cerebral lesions. The term cryptogenic is used, when a specific cause cannot be identified, but is suspected due to persistent neurological signs.

More recently, the term Epilepsy of Unknown Cause (EUC) has been adopted to classify seizure disorders where no underlying cause can be identified. Based upon a recent classification system by the International Veterinary Epilepsy Task Force Consensus Report in 2015, EUC replaces former terms such as idiopathic epilepsy and primary epilepsy and embraces categories such as cryptogenic epilepsy and presumed idiopathic epilepsy (Berendt and others 2015). Reported prevalence of feline EUC range between 22 and 54% (Rusbridge 2005, Schriefl and others 2008, Wahle and others 2014). The main diagnostic criteria in cats with EUC include absence of pathological findings by diagnostic imaging and cerebrospinal fluid (CSF) analysis and/or a history of seizures with no abnormalities detected on neurologic examination during interictal periods. The median age at onset of seizures in EUC is generally <7 years, but the range varies considerably between 0.4 and 14.4 years, and no breed or sex predilections have been identified (Moore 2013, Schriefl and others 2008, Pakozdy and others 2010, Wahle and others 2014).

In one study, 30% of cats with EUC were poorly controlled but in contrast, seizure free intervals of several months and years have been reported (Pakozdy and others 2013). EUC includes a variety of yet to be determined aetiologies, which may respond differently to antiepileptic drug (AED) therapy, and they may also have different outcomes (Wahle and others 2014).

There is a need to introduce new tools that improve characterization and prognosis of cats with EUC. Recent technological advances such as ictal video monitoring, interictal non-invasive or invasive electro-encephalography, magnet-encephalography, structural and functional magnet resonance imaging (MRI) or nuclear imaging can be helpful in the better characterization of seizure disorders of unknown aetiology, but are hardly available for animals to date (Hasegawa 2016). In contrast to these high-end technologies informant-described seizure onset characterization and ictal behaviour (semiology) are still required to define seizure type and assess response to antiepileptic treatment. This information is available from most cat owners and may represent the only source of information along with a clinical neurological examination because of limited ability to pursue diagnostic testing in clinical practice and infrequent seizure episodes restricting direct observation during a clinic visit. The value of analysing and describing seizure semiology has previously been demonstrated in cats with experimentally induced epilepsy. Following the induction of seizures by various systemically and intra-cerebrally applied pharmacological agents, detailed observations and descriptions of seizure phenotypes have been made in cats. With each experimental setting uniform and specific patterns were described suggesting that certain triggers produced characteristic seizure phenotypes (Mutani 1967, Reimer and others

1967, Marcus and others 1968, Gloor and Testa 1974, Gutnick and Prince 1975, Rapport and others 1975, Griffith and others 1987, Louis and others 1990, Fenney and others 1998). The association of seizure type based upon semiological features and outcome as well as survival has to date not yet been examined in a larger population of cats categorized as EUC.

The purpose of this retrospective study was to examine survival and treatment outcome in cats with EUC in relation to semiology and seizure type.

Materials and methods

Medical records of cats with a primary complaint of seizures, presented between 1997 and 2012 to the Section of Neurology, Vetsuisse Faculty of the University of Zürich, Switzerland, were reviewed. Information on signalment, age at onset of seizures, and number of seizures before presentation was retrieved. At the time of admission, all cats had to have experienced more than three seizure episodes that were clearly separated from each other by at least one day. Cats with reactive seizures – which occur as a natural response of the normal brain to a transient (traumatic, metabolic, or toxic) disturbance in function – were excluded (Berendt and others 2015). Furthermore, results of clinical and neurological examinations, haematology and serum chemistry tests and infectious disease screening were evaluated. If available, results of CSF analysis, computed tomography (CT) and/or MRI were used for analysis. Owners of cats with EUC were contacted by phone at least one year and maximally 15 years after their cat's first presentation for seizures at the clinic. If an owner of a cat could not be reached, the cat was excluded from further study. All owners were interviewed by one of the authors (AS), and responses were also reviewed by one neurophysiologist (IM) and boarded veterinary neurologists (FS, LG).

Seizure aetiologies were determined based on the International Veterinary Epilepsy Task Force Consensus Report (Berendt and others 2015). To be included in the study cats were required to have a normal interictal neurological examination, normal hematology and serum chemistry and a normal CSF analysis. Normal crosssectional imaging of the brain was an optional inclusion criterium.

Seizure type was classified based upon semiology into (1) primary generalized tonic-clonic seizures, (2) seizures with focal onset, and (3) focal seizures with secondary generalization. Primary generalized seizures were characterized by acute onset of lateral recumbency and tonic-clonic limb movements accompanied by autonomic signs and loss of responsiveness. Focal seizures were defined as paroxysmal occurrences of abnormal movements of one part of the body, such as contractions of one limb or facial muscle group, with or without impaired consciousness or autonomic signs, such as salivation and involuntary urination and defecation (Wahle and others 2014).

Interviews regarding semiology were performed using a detailed questionnaire specifically designed for the purpose of this study (Table 1). Specific questions regarding semiology were created based upon a review of the literature for clinical signs observed in experimental epilepsy studies reported in cats. Data from 9 experimental studies describing the semiology and the localization of the affected brain regions were selected (Mutani 1967, Reimer and

others 1967, Marcus and others 1968, Gloor and Testa 1974, Gutnick and Prince 1975, Rapport and others 1975, Griffith and others 1987, Louis and others 1990, Fenney and others 1998). The questionnaire contained specific and open-ended questions about semiology and were used by the first author to collect information during phone interviews.

Outcome questions included recording of survival from time of discharge, initial and subsequent clinical features of seizures, owner-perceived general health status of the cat at time of follow-up, frequency of seizures, and if medical treatment was required to control seizures. Partial remission was defined as reduction of seizure frequency by >50% with AED therapy at the time of follow-up. Complete remission was defined by a seizure-free period of at least one year with or without AED therapy. Epilepsy-related cause of death was defined as euthanasia motivated by circumstances directly associated with seizures. If the cat died or was euthanized for reasons unrelated to seizures, death was registered as due to other causes. Cats that were lost to follow up were censored at the time that they were last known to be alive.

Statistics

All the statistical analysis was under taken in R (R Core Team 2016) Survival analysis using a cox proportional hazard regression models was undertaken using the coxph function in the survival package. A parametric survival curve was also fitted to the data using the survred command from the same package (Therneau 2015, Therneau and Grambsch 2000). As a comparison, we also undertook a relative survival analysis using a life table for Japanese cats (Hayashidani and others, 1989). This was the only life table available for cats. For this analysis we used the relsurv package. Kaplan Meier curves were also calculated to illustrate the survival curves of this group of cats suffering from epilepsy and any differences in survival of cats with and without remission. Fisher test was used to analyse differences in proportions of cats receiving treatment and undergoing remission

Results

Study population

During a 15-year period between 1997 and 2012 a total of 226 cats were presented with seizures to the Vetsuisse Clinic Zürich. Adequate medical records were available from 197 cats for further analysis. However, 35 cats were euthanized or died due to presence of intracranial pathology or request from the owners during initial hospitalization and twelve cats were found to have reactive seizures due to metabolic-toxic aetiologies and were therefore excluded. Another 70 cats were excluded, because owners could not be reached. For 80 cats, i.e. 36% of all cats with seizures, the owners were available for follow-up information after hospitalization. Based upon additional medical record and follow-up information four cats were found to have structural epilepsy (space occupying mass in frontal lobe, hydrocephalus, traumatic brain injury, post-anaesthesia complications) and were therefore excluded. Thus, the remaining 76 cats were considered to have EUC and were included in this retrospective study.

While Domestic short hair (63 cats; 83%) were by far most commonly represented among the 76 cats with EUC, there were nine purebred cats, including three Maine Coon and two Persian cats and one Siamese, Norwegian Forest, Bengal and Bombay cat; in addition, there were four cats of unknown breed. This breed distribution reflected the typical feline patient population at the authors' institution. Gender distribution was equal with three intact and 35 castrated males and six intact and 32 spayed females. The median age at seizure onset was four years (range of 0.3 to 18 years).

Seizure type classification based on semiology

Of the 70 cats with EUC and available semiology information, 23 cats (33%) had primary generalized seizures (Table 2 and 3). Clinical signs included sudden onset of loss of consciousness, primary generalized tonic-clonic seizures, salivation, urination, and/or defecation. Owners were not aware of any pre-ictal signs such as changes in behaviour. Owners of four animals reported that seizures occurred first during sleep.

Focal seizures were observed in 47 cats (67%). Pre-ictal abnormal behaviour signs were noted in nine cats minutes to hours before ictal signs occurred. The cats appeared to be awake but confused and not properly reacting to external stimuli and to the owner. Clinical signs of focal seizure activity included rapid conscious running, clonic movements of one body part such as tail or one limb, twitching of unilateral facial muscles, and circling in one direction. Progression from focal (motor, autonomic and/or behavioural signs) to secondary generalized seizures was observed in 78% (37 of 47) of cats with focal seizure onset. There was no statistical difference in the median age between cats with focal seizures and cats with primary (and secondary) generalized seizures at onset of seizures.

Outcome and survival

Overall, the median time of follow-up of surviving cats with EUC (52; 68%) was 3.2 years (range 1 to 11 years). Twenty-four (32%) cats died during the study period; the median survival time was one year (range 0.1 to 12 years). Death appeared epilepsy-related in 16 (21%) cats, and eight patients (11%) died due to other causes. Age at time of seizure onset and remission were significant independent predictors of survival. The hazard ratio for age at onset was 1.12 ($p=0.015$). This means that there was a 12% increase in the risk of death per time period for each increase of one year from the onset of seizures. For the 76 cats, the median survival time was 4.9 years (Fig 1). The hazard ratio of remission was 10.4 ($p=0.002$). Thus, the risk of death was 10 times higher in cats without remission compared to those that showed remission per unit time period.

Treatment with AED therapy was started in 62 (82%) cats during and/or after hospitalization. Reasons for not starting or discontinuing treatment were not specifically investigated but generally included inability to pill the cat, recommendation of referring veterinarian or spontaneous decision of the owner. Phenobarbital was given to all treated cats either alone or in combination with diazepam (6) or levetiracetam (12). Median survival time of treated cats was 2.3 years (range 0.1 to 11 years), and 65% were still alive at the time of follow-up. Treatment appeared effective in 44 (71%) cats (total number of improved seizure status including cats with complete and partial remission). Complete remission with AED

therapy was achieved in 21 (34%) cats with a median time of follow-up of 4.3 years (range 1 to 11 years). These cats were still alive at the time of follow-up except for one cat, who died after five years due to an epilepsy unrelated cause. Partial remission was observed in 23 (37%) cats with AED therapy, and 15 were still alive at the time of follow-up (median time of 2.5 years; range 1 to 11 years); eight cats died after a median survival time of 1.5 years (range 1 to 8 years). Death appeared epilepsy-related in four cats, and another four died due to other causes. The remaining 18 (29%) cats showed no remission with AED therapy, and 13 had died at the time of follow-up with a median survival time of only 0.3 years (range 0.2 to 4 years). In twelve of 13 cats death or euthanasia was epilepsy related.

In 14 cats without AED therapy, the median time of follow-up was 2.6 years (range 1 to 12 years). Complete remission without AED therapy occurred in eleven of 14 (79%) cats with a median time of follow-up of 3.2 years (range 1 to 12 years). At follow-up, twelve of 14 (86%) cats with EUC were alive, while two cats died for other reasons.

A total of 32 of 76 (42%) cats became seizure-free with or without AED including 14 animals with primary generalized tonic-clonic seizures, five with isolated focal seizures and ten with focal seizures and secondary generalization (Fig 2, Table 3). In three of 32 (9%) cats with complete remission death was not epilepsy-related (median survival time five years, range 5 to 12 years). The 29 (91%) cats with complete remission still alive had a median survival time of 3.2 years (range 1 to 11 years). There was a significant difference in the hazard ratio (ie survival) of cats achieving remission. Thus, cats that went into remission had a longer survival time. This was true both with the cox survival model (hazard ratio 10.4, $p= 0.0017$) and the relative survival model using normal Japanese cats as the control group (hazard ratio = 10.1, $p=0.0019$) Cats that were treated were more likely to be in the group that did not undergo remission ($p<0.01$), but treatment had no independent effect on survival times. No significant differences between, seizure type, and outcome were observed, and thus seizure type did not predict outcome in cats with EUC ($p>0.05$).

Discussion

In this study, 68% of cats with EUC survived for a mean follow-up time period of 3.2 years (range 1 to 11 years), and seizures were successfully controlled in 71% of the cats. Similarly, previous studies reported high survival rates and good outcomes in cats with EUC (Schriefl and others 2008; Pàkodzy and others 2010; Pàkozdy and others 2013; Finnerty and others 2014; Wahle and others 2014). In contrast, in 29% of the cats in the present study seizure control was not successful and in 21% death was related to seizures. Thus, identification of prognostic predictors is important for the motivation of clients to pursue treatment of cats diagnosed with EUC. The objective of this retrospective study was therefore to look for easily accessible information from clinical examination and owner interviews that allow more valid statements on outcome in affected cats.

Neither semiology nor seizure type were associated with outcome in terms of survival in the present survey. Moreover, seizure type based upon semiological classification was not predictive of seizure aetiology which is similar to what has been previously reported (Barnes and others 2004; Schriefl and others 2008; Pàkozdy and others 2010). Despite this, careful

recording of semiology and seizure type remains important when evaluating seizuring cats. Specific seizure disorders in cats have been reported including complex partial seizures with orofacial involvement in cats with limbic encephalitis and myoclonic seizures prior to generalized tonic-clonic seizures in cats with audiogenic reflex seizures (Pàkodzy and others 2011, Lowrie and others 2016). A very recent study found that ictal salivation is likely to be associated with EUC (Stanciu and others, 2017). Salivation was also one of the most common signs in cats with EUC in the present investigation. Recording of the initial signs of seizure events are required for determination of the so-called ‘symptomatogenic zone’ defined as the area of cortex which, when activated by an epileptiform discharge, produces the ictal signs. These indicate laterality and their sequential disturbance during the ictus relate to the propagation of seizure activity. This information may be useful in conjunction with electroencephalography and functional MRI, when surgical removal of seizure foci in epileptic cats will become a practical treatment option (Hasegawa 2016).

In the present study, we found that age at time of seizure onset was significantly associated with survival. Specifically, the risk of death in a cat with EUC increases 12% for each year after time of onset of seizures. This information should be of interest when discussing prognosis with cat owners. Furthermore, there was a significant association of survival with remission, i.e. cats with remission survived longer than those without. Death was directly associated with seizures in 21% of cats, and as a consequence, remission is likely to go along with prolonged survival. An important factor to consider is that older cats will have a decreased survival time simply because they are older. Hence it was important to include age of onset as a variable in the analysis to control for this factor. In survival analysis in humans when analysisn survival time for chronic diseases affecting mainly older patients, relative survival analysis is a standard practice using the life table of the population as controls to estimate any excess mortality or decreased survival caused by the disease in question. For example the survival times of potentially fatal human alveolar echinococcosis, where the mean age of diagnosis is 54 years, has been analysed in Switzerland and compared to the normal population (Torgerson and others, 2008). Unfortunately, there is very little published data on the life tables of normal cats. However, we were able to find a life table published for Japanese cats (Hayashidani and others, 1989) and we used this in a relative survival analysis to try and control for the natural increased death rates in older cats. This additional analysis did not change our main result that remission was associated with increased survival time. However, contemporaneous normal life expectancies of Swiss cats could be different.

The overall rate of complete remission of 42% in this study was in accordance with the results of previous surveys. Thus, feline EUC is manageable and may have a favourable outcome (Wahle and others 2014). Our finding that the rate of complete remission was significantly higher in cats without AED therapy compared to those treated (79% vs. 34%) was unexpected, albeit there have been no large surveys evaluating outcome and response to treatment in cats with EUC. In a previous small case study, phenobarbital treatment was regarded to be required to maintain a seizure-free status, because seizures recurred in six of eight (86%) of cats in which AED therapy was discontinued or the dosage reduced (Pàkozdy and others 2013). However, our findings are in accordance with another recent small case series in which seizure remission was achieved in three of five (60%) cats without treatment (Wahle and others 2014). It is possible that there are different subtypes of EUC and/or

seizure phenotypes of different severity neither requiring any nor continuous AED treatment. The fact that some of the cats categorized as being seizure-free without treatment received AED of variable duration at the time of seizure onset before it was discontinued while others never received AED does not allow to draw conclusions and represents a limitation. Until methods are available to identify cats with less severe form of disease before discontinuation of treatment, AED should be recommended for all cats with frequent seizures in order to minimize the risks associated with uncontrolled seizure activity.

Despite the wide availability of devices to document seizure events on video, detailed interviews with owners remain an important source of information for clinical signs of true seizure onset (De Risio and others 2015). In the present study, interviews were required to categorize the seizure type into primary generalized seizures and focal onset seizures with or without secondary generalization. While helpful, many “homemade” video tapes fail to document the entire epileptic event, which may lead to erroneous classification of the seizure type (Packer and others 2015, 2016). Compared to videos, owner-derived observations about seizure, however, appear less reliable, because of recall bias, and, therefore, one might question their use for diagnostic purposes. In human epileptology, the dilemma is identical, because epileptic patients may not be able to describe their symptoms and information about semiology has to be obtained from individuals who have witnessed the seizures. In one semiology investigation of human patients with EUC, seizure types based on observer description were correctly classified in 85% of patients when compared with the findings from video tapes (Heo and others 2008). The accuracy of the description was associated with the educational level of the observers. In a recent human study, there was excellent agreement between neurologists and caregivers for seizure identification when using a questionnaire based description of video-taped seizures (Benbir and others 2013). Description of seizure events is certainly a function of memory and time. However, individuals are remembering these highly emotional events better than non-emotional ones. Neuroimaging studies demonstrated that the amygdala plays a fundamental role during the encoding of emotional information (Kensinger & Schacter 2008). Individuals who show the greatest amygdala activity during the viewing of emotional items are those with the strongest emotional memory enhancement (Cahill and others 2000, Kensinger & Schacter 2008). Also, there is evidence that seizures in dogs induce physiological arousal due to psychological stress which may also hold true for their owners, thereby enhancing their memory function (Packer and others, 2017). In the present study of cats with EUC, most owners (92%) were able to recall seizure semiology even after many years. Because seizures in animals are also emotional events for owners, we propose that reliability of pet owner-derived descriptions of seizures are similarly valid as in humans. However, specific studies are necessary to confirm that this holds true for veterinary patients and their proximates.

This survey was retrospective and relied heavily on owner recollection and observations. A limitation of the study was the assumption that each cat only suffered from one seizure type (ie the three seizure types were mutually exclusive) and it is known that in other species such as dogs or humans, more than one seizure type can occur concomitantly. From a clinical perspective this classification was made on the basis of the presenting semiology and thus we do not have the data to explore the hypothesis that survival may be linked to epileptic cats having more than one seizure type. Further, the lack of brain MRI of many cats in this

study represents a limitation as structural epilepsy could not be completely excluded. Indeed, lesions in the olfactory bulb or frontal lobe may not cause interictal neurological deficits. Focal seizures might have gone undetected in cats with complete remission (Packer and others 2016). Also, the lifestyle of some cats includes the risk that some seizures are not witnessed.

In conclusion, seizure semiology utilizing a structured questionnaire provides additional clinical information. Surprisingly, early onset of seizures in cats with EUC is associated with prolonged survival, and cats with EUC may become seizure free even in the absence of AED. Semiology and seizure type, however, do not predict survival. Further prospective investigations are warranted to confirm these findings.

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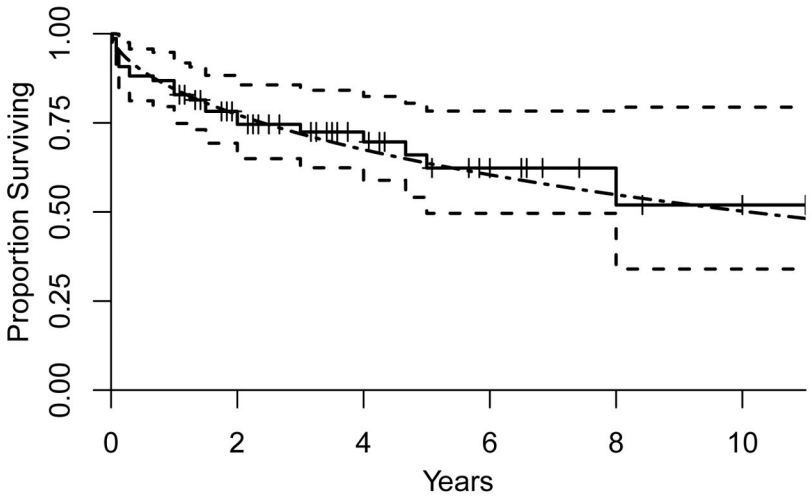

FIG 1. Kaplan-Meier curve of survival (—) and 95% confidence intervals (----) of 76 cats with epilepsy of unknown cause

(·-·-·) = Smoothed parametric survival curve

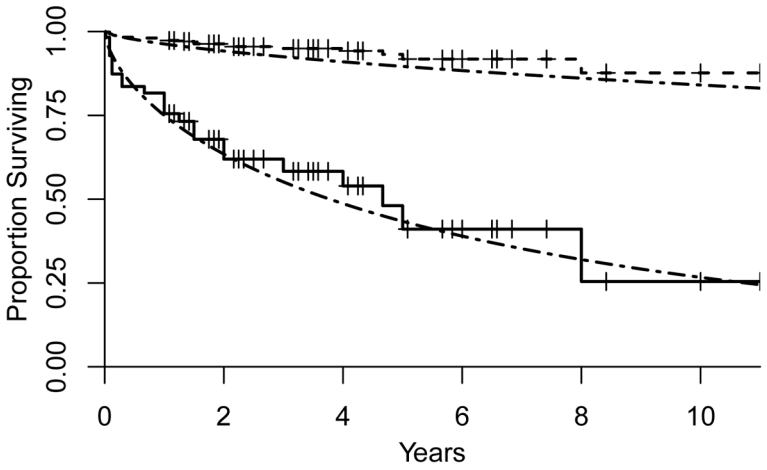

FIG 2. Kaplan-Meier curves of survival for 32 cats in remission (----) and 44 cats not in remission (—) of 76 cats with epilepsy of unknown cause

(·-·-·) = Smoothed parametric survival curves

TABLE 1

Results of owner interview for 70 cats with epilepsy of unknown cause: Semiology and classification of seizure type.

Clinical signs for semiology	Cats	Seizure type		
		Primary generalization	Focal without secondary generalization	Focal and secondary generalization
Generalized signs				
- Tonic - clonic generalized seizures in recumbence	53	23	0	30
- Loss of consciousness	53	21	0	32
- Urination	25	10	0	15
- Defaecation	3	1	0	2
Focal or part of generalized signs				
- Salivation	40	15	3	22
- Rapid running (psychomotor seizures)	26	0	5	21
- Isolated twitching of facial muscle	15	0	3	12
- Circling to one side	12	0	2	10
- Fearful or aggressive behaviour[1]	10	0	2	8
- Tonic movement in one limb	11	0	3	8
- Pupillary dilatation	10	1	1	8
- Pre-ictal unresponsiveness[2]	9	0	1	8
- Behavioural arrest (freezing)[3]	9	0	1	8
- Isolated twitching of the tail	5	0	3	2
Total	**70**	**23**	**10**	**37**

[1] Bite, strike, hissing, piloerection, and/or ear retraction;

[2] Arrest of movement, unresponsiveness to external stimuli, and/or change in behaviour (minutes to hours before seizure);

[3] Unresponsive blank staring and panting, followed by a return to normal.

TABLE 2

Long term survival of 76 cats with epilepsy of unknown cause

Seizure type	Cats #	Median time of follow-up[1] in years (range)	Status at end of study				Mean survival time in years[2]
			Dead		Alive		
			# (%)	Median in years (range)	# (%)	Median in years (range)	
Primary generalized	23	3.3 (0.02 to 10)	5 (22)	0.7 (0.02 to 8)	18 (78)	3.5 (1.1 to 10)	4.9
Focal	10	3.0 (1 to 11)	2 (20)	4 (3 to 5)	8 (80)	2.5 (1 to 11)	
Focal with secondary generalized	37	1.8 (0.08 to 12)	16 (43)	1 (0.08 to 12)	21 (57)	1.5 (1 to 8.4)	
No semiology information	6	5.1 (1.3 to 11)	1 (17)	1.5	5 (83)	6 (1.3 to 11)	

[1] Time from clinic admission to follow-up interview, at least one year after discharge from Vetsuisse Clinic Zürich

[2] Kaplan-Meyer analysis

TABLE 3

Semiology and remission rates in 76 cats with epilepsy of unknown cause with and without antiepileptic drug therapy (AED)

Seizure type	# of cats	Age of onset median in years	Complete remission [1]		Partial remission[3] <50% seizure frequency with AED[2]	No remission[4] with or without AED
			Total	With AED		
Primary generalized	23	3	14 (61%)	4	5	4 (17%)
Focal	10	5	5 (50%)	1	4	1(10%)
Focal with secondary generalized	37	4	10 (27%)	3	12	15 (41%)
No semiologic information	6	6	3 (50%)	1	2	1 (17%)

[1] No seizures in the last 12 months with or without AED

[2] No seizures in the last 12 months under AED

[3] <50% Seizure frequency with AED

[4] No remission with or without AED