Raimondi, F., Shihab, N., Gutierrez-Quintana, R., Smith, A., Trevail, R., Sanchez-Masian, D., & Smith, P. (2017). Magnetic resonance imaging findings in epileptic cats with a normal interictal neurological examination: 188 cases. Veterinary Record. DOI: 10.1136/vr.104142

Veterinary Record

Magnetic Resonance Imaging findings in epileptic cats with a normal interictal neurological examination: 188 cases

Journal:	*Veterinary Record*
Manuscript ID	vetrec-2016-104142.R2
Article Type:	Paper
Date Submitted by the Author:	06-Mar-2017
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Abstract:	Epilepsy is a common neurological condition in dogs and cats. Although an increased likelihood of significant brain lesions with age has been identified in neurologically normal dogs with epileptic seizures, the underlying aetiology of epileptic seizures in cats that present with normal physical and neurological examinations remains unknown. In this cross – sectional study, we examined magnetic resonance imaging (MRI) findings in a large population of cats with a normal interictal physical and neurological examination. We hypothesised that age would have an impact on the prevalence of detectable lesions. First, following the guidelines for dogs and in accordance with previous studies, we divided the cats into three age groups (aged 1 year or younger, between 1 and 6 and older than 6) and calculated the proportion of cats with a detectable lesion on MRI in these groups. In the first group, 3/32 cats (9.4%) had significant MRI abnormalities that were all consistent with congenital malformation; in the second group, only 5/92 (5.4%) MRI scans were abnormal and in the third group, 15/ 65 (23.1%) cats showed abnormal findings that were predominantly lesions of neoplastic origin. Second, to investigate the impact of age further, data were investigated as a continuous variable using receiver operating characteristic (ROC) analysis. This indicated an optimal cut off age of 5 years, above which MRI abnormalities were more likely, with an increase in the odds of a significant structural lesion increasing by 14% per year.

Magnetic resonance imaging findings in epileptic cats with a normal interictal neurological examination: 188 cases

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Keywords: Feline, epilepsy, brain, magnetic resonance imaging

Word count: 3925

Abstract:

Epilepsy is a common neurological condition in dogs and cats. Although an increased likelihood of significant brain lesions with age has been identified in neurologically normal dogs with epileptic seizures, the underlying aetiology of epileptic seizures in cats that present with normal physical and neurological examinations remains unknown. In this cross – sectional study, we examined magnetic resonance imaging (MRI) findings in a large population of cats with a normal interictal physical and neurological examination. We hypothesised that age would have an impact on the prevalence of detectable lesions.

First, following the guidelines for dogs and in accordance with previous studies, we divided the cats into three age groups (aged 1 year or younger, between 1 and 6 and older than 6) and calculated the proportion of cats with a detectable lesion on MRI in these groups. In the first group, 3/32 cats (9.4%) had significant MRI abnormalities that were all consistent with congenital malformation; in the second group, only 5/92 (5.4%) MRI scans were abnormal and in the third group, 15/ 65 (23.1%) cats showed abnormal findings that were predominantly lesions of neoplastic origin.

Second, to investigate the impact of age further, data were investigated as a continuous variable using receiver operating characteristic (ROC) analysis. This indicated an optimal cut off age of 5 years, above which MRI abnormalities were more likely, with an increase in the odds of a significant structural lesion increasing by 14% per year.

Introduction

Epileptic seizures are transient paroxysmal disturbances in brain function caused by an imbalance in excitatory and inhibitory neuronal transmission. They arise through disturbances in forebrain function and can be caused by metabolic derangements, by genetic or acquired abnormalities in neuronal function or by structural brain disease (Berendt and others 2015, Berg and others 2011, Finnerty and others 2014, Munana 2013, Pakodzy and others 2014, Wahle and others 2014). The diagnostic approach to cats with epileptic seizures includes complete physical and neurological examinations, analysis of various biochemical and haematological parameters, advanced imaging of the brain and analyses of cerebrospinal fluid when appropriate (Bailey and others 2009, De Risio and others 2015, Rusbridge 2005). Understanding the probability of a significant structural brain lesion in cats with epileptic seizures helps clinicians assess the need for advanced brain imaging. Although cats with neurological deficits have a high risk of structural brain disease, a significant lesion in a non-eloquent region of the brain might be undetectable on neurological examination (Schwartz and others 2011, Smith and others 2008). As a result, many animals that appear neurologically normal will have an identifiable lesion on magnetic resonance imaging (MRI). An increase likelihood of a significant brain lesion with age has been established in neurologically normal dogs with recurrent seizures, and studies have indicated a substantially higher risk in dogs older than six years of age, which is primarily related to the higher prevalence of neoplastic lesions in older animals (Armasu and others 2014, De Risio and others 2015, Schwartz and others 2013, Smith and others 2008).

Although applying the same patterns to cats may seem reasonable, such an assumption is questionable. First, idiopathic epilepsy is thought to be relatively rare in cats, which decreases the likelihood of diagnosing this form of epilepsy and increases the likelihood of young cats presenting with a significant brain lesion than similarly aged dogs. Second, cats

with meningioma, which is the most common brain neoplasm in cats, are less likely to have epileptic seizures than dogs with brain neoplasia (Bagley and others 1999; Cameron and others 2015, Schwartz and others 2011, Snyder and others 2006, Tomek and others 2006, Troxel and others 2003) which may decrease the prevalence of identifiable lesions in geriatric cats compared with that in dogs.

To investigate the prevalence of structural brain disease in cats of varying ages suffering from epileptic seizures we examined the MRI findings of a large population of cats with normal interictal physical and neurological examinations and without significant abnormalities on haematology or serum biochemistry analysis (including fasting bile acids and electrolytes).

In accordance with the international veterinary epilepsy task force (IVETF) guide lines for dogs (De Risio and others 2015), we divided the cats into three age groups (aged or younger than one year, between one and six years and older than 6 years) and we compared the proportion of cats with a detectable lesion on MRI in these different groups. We also analysed whether there was an optimal cut off age at which structural epilepsy was more prevalent than idiopathic epilepsy and we assessed the association of age with the likelihood of suffering from structural epilepsy.

Materials and methods

Electronic and hardcopy records of five United Kingdom (UK) referral hospitals (Southern Counties Veterinary Specialists, Hampshire (2009 to 2016); Davies Veterinary Specialists, Hertfordshire (2007 to 2016); Langford Small Animal Veterinary Referral Hospital, North Somerset (2009 to 2016), Small Animal Hospital, University of Glasgow (2008 to 2016); and Small Animal Teaching Hospital, Liverpool, Merseyside (2009 to 2016)) were searched to identify the records of cats presenting with epileptic seizures that were either focal, generalized or focal epileptic seizures evolving into generalized seizures.

The following information was obtained from the medical record: breed, sex, age of onset of epileptic seizures, results of neurologic and physical examinations, and clinicopathological tests performed, diagnostic imaging results and cerebrospinal fluid (CSF) analysis when performed.

The definition and classification of the epilepsy and seizure types were based on the IVETF recommendations (Berendt and others 2015).

Epilepsy was classified as either structural epilepsy or idiopathic epilepsy of unknown origin. Epileptic seizures were classified in three different groups: focal epileptic seizures, generalized epileptic seizures and focal epileptic seizures evolving into generalized epileptic seizures (secondary generalization) (Berendt and others 2015).

Cats were included in the study if they had suffered at least two unprovoked epileptic seizures in a time frame of at least 24 hours (Berendt and others 2015) but were excluded if they were known or suspected to have reactive seizures resulting from toxin exposure, a metabolic syndrome, or an anaesthesia-related incident.

All cats included in the study were required to have a normal physical and interictal neurological examination, designated by a recognised specialist in veterinary neurology, and an MRI scan analysed by a recognised imaging specialist. In cats that presented in status epilepticus, neurological evaluation was postponed until complete recovery from the seizure to avoid temporary post-ictal deficits.

All cats underwent screening tests, including haematology, serum biochemistry analysis, electrolytes and fasting bile acids and those with significant abnormalities were excluded. Additional tests for extracranial disorders were performed when clinically appropriate and included post prandial bile acid and ammonia concentrations, thoracic radiography, abdominal ultrasonography, echo- and electrocardiography, serial blood pressure measurements, thyroxine (T4) concentration and serological tests for certain infectious agents

(feline leukemia virus (FELV), feline immunodeficiency virus (FIV), Toxoplasma *gondii* and Feline Coronavirus). These were performed at the discretion of the clinician and only cats with normal findings on these additional tests were included in the study.

A CSF analysis at a reference laboratory was required for inclusion in this study unless the MRI findings indicated increased intracranial pressure and an increased risk of injury to the patient. All cats included underwent brain MRI under general anaesthesia using one of the following MR scanners depending on the institution: 0.4 Tesla (T) MRI (Aperto MRI Hitachi, Wellingborough, UK); 1 T (Panorama Philips, Guildford, UK); 1.5 T (Petvet Hallmarq, Surrey, UK) and 1.5T (Philips Gyroscan, Guildford, UK) and 1.5 T (Magnetom Essenza and Symphony, Siemens, Camberley, UK)

Magnetic resonance protocols varied between institutions. In all cases, these included at least two orientations (transverse and sagittal) for T2 weighted images (T2WI), one or two orientations (transverse or dorsal) for T2WI fluid attenuated inversion recovery (FLAIR) sequences and one or two orientations (transverse and sagittal or dorsal) for T1 weighted images (T1WI) before and after administration of paramagnetic (gadolinium-based) contrast medium. In most cases, a transverse-orientation images of gradient echo (GE) T2 * was obtained.

Certain MRI abnormalities were classified as incidental findings. These included minor anatomical variations that were considered as an implausible cause of epileptic seizures. These variations included abnormality linked to normal breed variations such as crowding of the caudal cranial fossa associated to a brachycephalic skull conformation, asymmetry of the cerebral lateral ventricle (Pivetta and others 2013), arachnoid cysts that were not causing occipital lobe and cerebellar compression of more than 10% and with associated normal CSF analysis (Duque and others 2005, MacKillop 2011, Matiasek and others 2007) and finally MRI abnormalities that where located in areas of the brain inconsistent with the clinical

signs (e.g., neuroanatomical localisation) (Vite and Cross 2011).

Other MRI abnormalities were attributed to recently reported epileptic seizures. Such post-ictal changes have been previously described and consist of diffuse, poorly defined intra-axial hyperintensity on T2WI and FLAIR images, mainly located in the piriform lobes and hippocampus with no mass effect and with none or only very mild hyperintensity on T1WI following contrast administration. These changes were considered to represent a mixture of cytotoxic oedema and gliosis resulting from epileptic seizures (Kim and others 2001, Marioni-Henry and others 2012, Mellema and others 1999, Rusbridge and others 2015, Viitmaa and others 2006). The CSF analysis in these animals were within normal limits.

Statistical analysis was performed using a commercially available computer software (SPSS Statistic, Version 24, IBM, Armonk, New York).

The Fisher's exact test was performed to compare the prevalence of structural lesions between the three groups of cats (i.e. those aged 1 year old or younger, aged between 1 and 6 years old and older than 6 years). Statistical significance was set at $P < 0.01$, power test analysis was used to assess whether the groupings used were appropriate to retain statistically significant findings.

In addition, a receiver operating characteristic (ROC) analysis was performed on the entire group of cats to study the optimal cut off age at which prevalence of structural epilepsy surpassed the prevalence of idiopathic epilepsy.

Finally, a logistic regression analysis was performed to assess whether age is significantly associated with the likelihood of suffering from structural epilepsy.

Results

A total of 188 cats with epileptic seizures and without interictal neurological deficits suggestive of primary forebrain disease were included in this study.

Of these, 131/188 (69.7%) presented with a history of generalised tonic-clonic epileptic seizures and 14 of these had episodes of cluster seizures. A further 9/188 (4.8%) suffered from focal epileptic seizures that evolved into generalised epileptic seizures (i.e. secondary generalization). 36/188 (19.2%) cats presented with focal epileptic seizures, 12 of which were focal epileptic seizures characterised by psychomotor activity (running around the house, glazed eyes, dilated pupils and aggression). Another 8/188 (4.3%) cats suffered from cluster of focal epileptic seizures, with oro-facial involvement characterized by salivation, facial twitching, lip smacking, chewing, licking or swallowing, motor arrest (motionless starring) and behavioural changes (mainly aggression). Finally, 4/188 (2.1%) cats presented with feline audiogenic reflex seizures (FARS) characterized by myoclonic jerks that were triggered by sound, and these epileptic seizures were frequently followed by secondary generalization.

Neurological deficits in 19 cats were considered representative of post-ictal deficits and had resolved by a subsequent examination. Post-ictal abnormalities included minor delays in postural reactions, decreased menace responses, obtunded mentation and behavioural changes.

Classifying the cats according to the age of onset of seizures, 32 (17%) cats were aged or younger than one year, 91 (48.7%) cats were aged between one and six years and the remaining 65 (35.6%) cats were older than six years old.

The most represented breed was the domestic short hair cat (77.65 % of the population), followed by Bengal (3.72%) and Maine Coon (3.2%) breeds. The distribution between males (55.85%) and females (44.15%) was approximately equal.

Magnetic resonance imaging abnormalities were detected in 35/188 cases (18.6%).

Six MRI abnormalities were classified as "incidental findings"; thus, they were not considered in the study. These abnormalities included mild crowding of the caudal fossa and mild lateral ventricle enlargement found in a Persian cat, which may have been caused by normal breed variations associated with brachycephalic skull conformation; a focal fluid-filled dilatation within the third ventricle that appeared to be a small arachnoid cyst (Duque and others 2005, MacKillop 2011, Matiasek and others 2007); a small pituitary mass in a cat without hypercortisolaemia, insulin–resistant diabetes mellitus, acromegaly or compression of the surrounding tissue (Sellon and others 2009); and mild dilatation of the left olfactory recess, without amass effect on the surrounding parenchyma.

Six further MRI abnormalities were classified as post-ictal. In those cases, deemed to have a significant finding, the majority of the lesions were located at the level of the piriform lobe (5 cases - 22%), hippocampus (5 cases - 22%) and frontal cortex (5 cases - 22%). A diffuse cortical distribution was seen in three cases (13%), two had lesions in the olfactory bulb (8.6%), and there was one example (4.3%) in each of the parietal cortex, temporal cortex and in the lateral and medial geniculate nuclei.

Subdividing the animals according to age (figure 1), structural MRI abnormalities were found in 3/32 (9.4%) cats aged or younger than one year old. In one case, an abnormal sulcal pattern was observed at the level of the left temporal lobe and resulted in blurring of the white-grey matter junction and T2WI hyperintensity within the white and grey matter. The CSF analysis was within normal limits, and the lesion was suspected likely caused by a disorder of the temporal cortex formation (cortical dysplasia). In the other two cases, two small lesions CSF-filled cavities were observed within the brain; these had the imaging characteristics of CSF. In one case, the lesion was located at the level of the interventricular foramen and in direct contact with the ventricular system and in the second case the lesion was located at the level of the right frontal lobe, within the brain parenchyma and in direct

contact with the subarachnoid space. In both cases, the CSF analysis was within normal limits.

In the cats aged between 1 and 6 years, 5/91 (5.5%) had significant lesions on MRI (figure 2). Two cases presented with MRI changes that consisted of bilateral hippocampal T1WI hypointensity and T2WI hyperintensity with mild heterogeneous post-contrast hyperintensity on T1WI. In these cases, feline hippocampal necrosis was suspected. In each of the three other cases, there was a single small lesion with the imaging characteristics of CSF and no mass effect. In one, this was a small, well defined, wedge shaped lesion in the left occipital lobe, at the white-grey matter junction. This was suspected to be an ischemic lesion. In another, the lesion was at the rostral aspect of the calvarium and was suspected to be a congenital malformation. In the final case, there was a single well defined lesion in the right temporal lobe: this cat has a history of trauma a few months previously and this was felt to be the result of a brain injury.

Of the cats older than six years at seizure onset, 15/ 65 (23.1%) had a significant structural MRI abnormality (figure 3). These abnormalities included suspected neoplastic lesions (seven cases), of which five were intra-axial. These were well defined lesions in the piriform lobe, which were hyperintense in T2WI and FLAIR and isointense in T1WI with mild or no enhancement following contrast administration. These lesions were suspected to be gliomas. The remaining two neoplastic lesions were extra-axial with a wide meningeal base, homogeneous contrast enhancement and dural tail signs, moderate perilesional oedema, a mass effect on the surrounding brain parenchyma and secondary bone hyperostosis. These lesions were suspected to be meningiomas. In three cases, there was bilateral enlargement of the CSF spaces, most noticeable at the level of the sulci of the fronto-parietal lobes. These lesions were suspected to be related to cortical brain degeneration and age. Hippocampal necrosis, as defined previously, was suspected in two cases. In one case, intra-axial bilateral

and symmetrical lesions were noted in the lateral and medial geniculate nuclei; these were hyperintense on T2WI and hypointense on T1WI. These lesions did not cause any perilesional oedema or mass effect and they were felt likely to be the result of a metabolic encephalopathy. A case of acquired meningoencephalocele at the level of the parietal lobe and above calvaria was seen in a cat with a history of trauma. Finally, one cat had two small circular intra-axial lesions; these were hypointense on T1WI, T2WI and GET2* and were felt to be consistent with cerebral haemorrhages.

Statistical comparison of the number of clinically significant lesions on MRI in the different age groups showed that the proportion of idiopathic / structural epilepsy is not the same among the groups (Fisher's exact test, $p<0.01$) with the only significant difference in the proportion of idiopathic / structural epilepsy seen between group 2 (cats aged between 1-6 years) and group 3 (cats older than 6 years) (table1 $p= 0.005$). There is no difference in prevalence between the other groups, although the number of cases in these groups make any comparison underpowered to detect a significant difference (power 5% when comparing group 1 with group 2; power 14% when comparing group 1 with group 3).

Therefore, to investigate if the likelihood of cats suffering from structural epilepsy is correlated with their age, the cats belonging to group 1 and 2 were combined and the Fisher's exact test was applied between these newly formed groups (group 1 those 6 years old or younger and group 2 those older than 6 years old). Results indicated that the prevalence of structural epilepsy is significantly higher (Fisher's exact test, $p<0.01$) in the group 2 (cat older than 6 years) with a sample size sufficient to achieve 86% power and with a significance of type-1 error $\alpha= 0.05$ (table 2 $p= 0.002$).

The ROC analysis indicated that age is a moderately good discriminator between statuses. The area under the ROC curve (AUC) was 0.66 indicating an optimal cut-off at 5 years old (accuracy 74%, specificity 75%, sensitivity 65%). (figure 4)

The logistic regression analysis showed that age is significantly associated with the possibility of suffering from structural epilepsy ($p<0.01$) with the likelihood of suffering from a structural brain disease increasing 14% per year. (table 3)

Discussion

The present study describes the diagnostic findings in a population of cats presenting with seizures but with no evidence of forebrain dysfunction on neurological examination. The findings of this study show that MRI is useful to detect lesions in clinically silent regions of the brain in both young and old cats and indicate that lesions are more prevalent in cats greater than six years of age. This is similar to findings in dogs and appears to reflect an increased risk of brain neoplasia with age. By undertaking ROC analysis, we were further able to show that five years appears a more suitable cut off age at which prevalence of structural epilepsy surpassed the prevalence of idiopathic epilepsy.

Although our data are inconsistent with the traditional anecdotal impression that the prevalence of epilepsy of unknown origin in cats has been overestimated because of the inconsistent application of MRI (Barnes 2004, Pakozdy and others 2010, Schriefl and others 2008), our findings fits well with the assumption that animals with congenital structural brain anomalies usually develop problems within the first year (Bagley 2005), because 9.4% of cats aged or younger than 1 year old diagnosed with structural epilepsy showed MRI changes suggestive of congenital malformation.

Cats without identifiable lesions are usually diagnosed with probable structural epilepsy (Barnes and others 2004, Platt 2001, Quesnel and others 1997, Thomas 2010). However, the alternative hypothesis is that some of these individuals have idiopathic epilepsy.

The prevalence of structural epilepsy in this study is 12.2% (23/188 cases). This prevalence is low when compared to other previous published studies (Barnes and others 2004, Pakoszy and others 2010, Schrief and others 2008, Whale and others 2014) in which structural

epilepsy was observed in 41% to 62% of cats.

This difference is most likely due to the inclusion criteria of our study. These were restricted to cats with a normal interictal physical and neurological examination whereas in the previous studies inclusion criteria included cats presenting with reactive seizures and/or neurological deficits and therefore more susceptible to structural brain lesions.

The MRI scanners used in this study included 1 and 1.5 T superconducting electromagnets (used in around 50% of cases) and a 0.4 T permanent magnet and although the images obtained using high field (>1T) magnets are excellent for identifying both large and subtle structural lesions, it remains possible that the group of cats undergoing low field MRI had subtle structural lesions that were not detected. However, in the 99 cats that underwent high field MRI, subtle lesions identified that would have been missed with low field MRI were not identified. Therefore, the proportion of cats in which a subtle lesion might have been missed by a low field MRI was likely negligible.

The conclusions of this study are similar to those in previous studies in dogs (Armasu and others 2014, De Risio and others 2015, Schwartz and others 2013, Smith and others 2008) which demonstrated that the age at seizure onset and neurological examination findings were both significantly associated with the type of brain disease, with our results indicating, the odds ratio of structural disease increasing of 14% per year of life.

Another interesting finding in this study that is similar to the finding of studies previously conducted in dogs (Schwartz and others 2011, Smith and others 2008) was that most of the lesions (73.91%) were located in the olfactory, frontal and pyriform lobes, and the hippocampus. Although dysfunction in these areas is less likely to cause neurological deficits, lesions located in these area could act as strong epileptogenic foci because of the widespread connections to the limbic system.

The cases analysed in this study involved a large population of cats widely distributed throughout the United Kingdom (UK). It is therefore expected to be a good representation of the cats with epileptic seizures and normal interictal examinations in the UK. Extrapolation of these results to cats outside of the UK will have to take into consideration any geographical differences in common feline seizure aetiology, in particular variations in prevalence of infectious diseases and their ability to result in seizures without interictal changes.

Sources of potential controversy associated with this study include the definition of an abnormal neurological examination and the definition of clinically significant lesions on MRI. These decisions were made with clinical practice in mind and neurological deficits were always deemed important if they were indicative of forebrain dysfunction.

The classification of MRI changes as post-ictal is also open to question. We based our interpretation of such changes on previous studies that demonstrate hyperintensity on T2WI and FLAIR imaging following seizures, particularly in the hippocampus and pyriform lobe (Kim and others 2001, Marioni-Henry and others 2012, Mellema and others 1999, Viitmaa and others 2006). It was recently postulated that such MRI changes in the hippocampus and associated extra-hippocampal regions could represent necrosis secondary to immune-mediated limbic encephalitis with voltage-gated potassium channel (VGKC) complex antibodies (Fatzer and others 2000, Pakozdy and others 2013, Pakozdy and others 2011, Schmied and others 2008). Although we found no CSF abnormalities in cases defined as having post-ictal changes, it is difficult to be certain whether borderline T2 hyperintensity of the hippocampus and parahippocampal structures represents the cause (Fatzer and others 2000, Pakozdy and others 2013, Pakozdy and others 2011, Schmied and others 2008) or consequence of the epileptic seizures (Marioni-Henry and others 2012). To avoid incorrect classification of these cases, the criteria suggested by Wahle (Wahle and others 2014) were

followed, whereby cats were considered to have hippocampal necrosis only if confirmed by conclusive MRI criteria and the occurrence of treatment-resistant complex partial seizures with orofacial involvement (Wahle and others 2014). Cats classified as having post-ictal changes did not meet these criteria.

In addition to the cases mentioned above, four cats older than six years had a history of myoclonic jerks that typically progressed to generalised epileptic seizures and were triggered by high frequency sounds. Although MRI and CSF analysis of these animals were within normal limits and seizures were well controlled on medical treatment, these cats may be suffering from a syndrome known as feline audiogenic reflex seizures (FARS), which has a geriatric onset and suspected degenerative aetiology (Lowrie and others 2016). In the absence of MRI changes, we classified the animals belonging to this group as having epilepsy of unknown origin.

Conclusion

In the absence of systemic disease that might trigger seizures, epileptic cats that are neurologically normal in the interictal period present a significantly increased likelihood of having an identifiable abnormality on MRI if they are older than 5 years old. Although histopathological confirmation was not possible in most cases in the current study, a large number of these lesions were considered to represent neoplasia. Identifying such lesions is crucial for determining the optimal treatment, and owners of cats in this age group should be strongly encouraged to pursue further investigation.

REFERENCES

BERENDT, M., FARQUHAR, R. G., MANDIGERS, P. J. J., PAKOZDY, A., BHATTI, S. F. M., DE RISIO, L. & OTHERS (2015) International veterinary epilepsy task force consensus report on epilepsy definition, classification and terminology in companion animals. *Vet Res* 11, 182.

BERG AT & SCHEFFER IE. (2011) New concepts in classification of the epilepsies: entering the 21st century. *Epilepsia* 52, 1058-1062.

FINNERTY EK, BARNES HELLER HL, MERCIER MN. GIOVANELLA CJ, VIVIAN WL & RYLANDER H (2014) Evaluation of therapeutic phenobarbital concentrations and application of a classification system for seizures in cats: 30 cases (2004–2013). *J Am Vet Med Assoc* 244, 195-199.

MUNANA KR (2013) Update: Seizure Management in Small Animal Practice. *Vet Clin North Am Small Anim Pract* 43, 1127-1147.

PAKOZDY A, HALASZ P & KLANG A (2014) Epilepsy in cats: Theory and Practice. *J Vet Intern Med* 28, 255-263.

WAHLE AM, BRUHSCHWEIN A, MATIASEK K, PUTSCHBACH K, WAGNER E, MUELLER RS & OTHERS (2014) Clinical characterization of Epilepsy of Unknown Cause in cats. *J Vet Intern Med* 28, 182-188.

BAILEY KS & DEWEY CW (2009) The seizuring cat Diagnostic work-up and therapy. *J Feline Med Surg* 11, 385-394.

DE RISIO L, BHATTI S, MUNANA K, PENDERIS J, STEIN V, TIPOLD A & OTHERS (2015) International veterinary epilepsy task force consensus proposal: diagnostic approach

to epilepsy in dogs. *Vet Res* 11, 148.

RUSBRIDGE C (2005) Diagnosis and control of epilepsy in the cat. *In Practice* 27, 208–214.

SCHWARTZ M, LAMB CR, BRODBELT DC & VOLK HA (2011) Canine intracranial neoplasia: clinical risk factors for development of epileptic seizures. *J Small Anim Pract* 52, 623- 627.

SMITH PM, TALBOT CE & JEFFERY ND (2008) Findings on low-field cranial MR images in epileptic dogs that lack interictal neurological deficits. *Vet J* 176, 320–325.

ARMASU M, PACKER RM, COOK S, SOLCAN G & VOLK HA (2014) An exploratory study using statistical approach as a platform for clinical reasoning in canine epilepsy. *Vet J* 202, 292-296.

SCHWARTZ M, MUNANA KR & NETTIFEE-OSBORNE J (2013) Assessment of the prevalence and clinical features of cryptogenic epilepsy in dogs: 45 cases (2003-2011) *J Am Vet Med Assoc* 42, 651-657.

BAGLEY RS, GAVIN PR, MOORE MP, SILVER GM & HARRINGTON ML (1999) Clinical signs associated with brain tumors in dogs: 97 cases (1992-1997) *J Am Vet Med Assoc* 215, 818-819.

CAMERON S, RISHNIW M, MILLER AD, STURGES B & DEWEY CW (2015) Characteristics and Survival of 121 Cats Undergoing Excision of Intracranial Meningiomas (1994-2011) *Vet Surg* 44, 772-776.

SNYDER JM, SHOFER FS, VAN WINKLE TJ & MASSICOTTE C. (2006) Canine intracranial primary neoplasia: 173 cases (1986-2003). *J Vet Intern Med* 12, 669-675.

TOMEK A, CIZINAUSKAS S, DOHER M, GANDINI G & JAGGY A. (2006) Intracranial

neoplasia in 61 cats: localisation, tumour types and seizure patterns. *J Feline Med Surg* 8, 243-253.

TROXEL MT, VITE CH, VAN WINKLE TJ, NEWTON AL, TICHES D, DAYRELL-HART B & OTHERS (2003) Feline intracranial neoplasia: retrospective review of 160 cases (1985-2001). *J Vet Intern Med* 17, 850-859.

PIVETTA M, DE RISIO L, NEWTON R & DENNIS R (2013) Prevalence of lateral ventricle asymmetry in brain MRI studies of neurologically normal dogs and dogs with idiopathic epilepsy. *Vet Radiol Ultrasound* 54, 516-521.

DUQUE C, PARENT J, BRISSON B, DA COSTA R & POMA R (2005) Intracranial arachnoid cysts: are they clinically significant? *J Vet Inter Med* 19,772-774.

MACKILLOP E (2011) Magnetic Resonance Imaging of intracranial malformation in dogs and cats. *Vet Radiol Ultrasound* 52, Supp.1 S42-S51.

MATIASEK LA, PLATT SR, SHAW S & DENNIS R (2007) Clinical and magnetic resonance imaging characteristics of quadrigeminal cysts in dogs. *J Vet Intern Med* 21, 1021-1026.

VITE CH & CROSS JR (2011) Correlating magnetic resonance findings with neuropathology and clinical signs in dogs and cats. *Vet Radiol Ultrasound*, 52 Supp. 1, S23-S31.

KIM, JA, CHUNG, JI, YOON, PH, KIM DI, CHUNG TS, KIM EJ & OTHERS (2001) Transient MR signal changes in patients with generalized tonicoclonic seizure or status epilepticus: periictal diffusion- weighted imaging. *AJNR* 22, 1149–1160.

MARIONI-HENRY K, MONTEIRO R &BEHR S (2012) Complex partial orofacial seizures

in English cats. Vet Rec 170, 471.

MELLEMA LM, KOBLIK PD, KORTZ GD, LECOUTEUR RA, CHECHOWITZ MA & DICKINSON PJ (1999) Reversible magnetic resonance imaging abnormalities in dogs following seizures. *Vet Radiol Ultrasound* 40, 588–595.

RUSBRIDGE C, LONG S, JOVANOVIK J, MILNE M, BERENDT M, BHATTI SFM & OTHERS (2015) International Veterinary Epilepsy Task Force recommendations for a veterinary epilepsy-specific MRI protocol. *Vet Res* 11, 194.

VIITMAA R, CIZINAUSKAS S, BERGAMASCO LA, KUUSELA E, PASCOE P, TEPPO AM & OTHERS (2006) Magnetic resonance imaging findings in Finnish Spitz dogs with focal epilepsy. *J Vet Inter Med* 20, 305– 310.

SELLON RK, FIDEL J, HOUSTON R & GAVIN PR (2009) Linear- Accelerator –Based Modified Radiosurgical Treatment of Pituitary Tumors in Cats: 11 cases (1997-2008) *J Vet Intern Med* 23, 1038-104.

BARNES HL, CHRISMAN CL, MARIANI CL, SIMS M & ALLEMAN AR (2004) Clinical signs, underlying cause, and outcome in cats with seizures: 17 cases (1997–2002). *J Am Vet Med Assoc* 225,1723–1726.

PAKOZDY A, LESCHNIK M, SARCHAHI AA, TICHY AG & THALHAMMER JG (2010) Clinical comparison of primary versus secondary epilepsy in 125 cats. *J Feline Med Surg* 12, 910-6.

SCHRIEFL S, STEINBERG TA, MATIASEK K, OSSIG A, FENSKE N & FISCHER A (2008) Etiologic classification of seizures, signalment, clinical signs, and outcome in cats with seizure disorders: 91 cases (2000–2004). *J Am Vet Med Assoc* 233, 1591–1597.

BAGLEY RS (2005). Clinical evaluation and management of animals with seizures. In: Bagley, R.S. (Ed.), Fundamentals of Veterinary Clinical Neurology. Blackwell Publishing, Ames, 363–376.

PLATT SR (2001) Pearls of Veterinary Practice. Feline Seizure Control. *J Am Anim Hosp Assoc* 37,515-517.

QUESNEL AD, PARENT JM, MCDONNELL W, PERCY D & LUMSDEN JH (1997) Diagnostic evaluation of cats with seizures disorders: 30 cases (1991-1993) *J Am Vet Med Assoc* 210, 65-71.

THOMAS WB (2010) Idiopathic Epilepsy in Dogs and Cats. *Vet. Clin. Small. Anim* 40, 161-179.

FATZER R, GANDINI G, JAGGY A, DOHERR M & VANDEVELDE M (1990) Necrosis of hippocampus and piriform lobe in 38 domestic cats with seizures: A retrospective study on clinical and pathologic findings. *J Vet Intern Med* 4:26-39.

PAKOZDY A, HALASZ P, KLANG A, BAUER J, LESCHNIK M, TICHY A & OTHERS (2013) Suspected limbic encephalitis and seizure in cats associated with voltage-gated potassium channel (VGKC) complex antibody. *J Vet Intern Med* 27, 212–214.

PAKOZDY A, GRUBER A, KNEISSL S, LESCHNIK M, HALASZ P & THALHAMMER JG (2011) Complex partial cluster seizures in cats with orofacial involvement. *J Feline Med Surg* 13, 687–693.

SCHMIED O, SCHARF G, HILBE M, MICHAL U, TOMSA K & STEFFEN F (2008) Magnetic resonance imaging of feline hippocampal necrosis. *Vet Radiol Ultrasound* 49,343-349

LOWRIE M, BESSANT C, HARVEY RJ, SPARKES A & GAROSI L (2016) Audiogenic reflex seizures in cats. *J Feline Med Surg* 18,328-33.

FIGURES

Figure 1. Graph showing the number of cats with normal (black) and structural (grey) MRI abnormalities in different age groups.

Figure 2. Graph showing the aetiology of structural epilepsy in cats aged between 1 to 6 years old.

Figure 3. Graph showing the aetiology of structural epilepsy in cats older than 6 years old.

Figure 4. Receiver Operating Characteristic (ROC) analysis: The area under the ROC curve (AUC) was 0.66 indicating that age is a moderately good discriminator between statuses). The optimal cut-off is 5 years old (accuracy 74%, specificity 75%, sensitivity 65%).

Table 1

Fisher's Exact test between the 3 groups of age: group 1 cats aged 1 years old or younger, group 2 cats older than 1 years old and aged 6 years old or younger, group 3 cats older than 6 years. The proportion of idiopathic / structural epilepsy is not the same among the groups (Fisher's exact test, $p<0.01$). Further analysis performed between different pairings of these 3 groups is represented by the letters in subscript. Each subscript letter (a, b) denoted a subset of 2 Groups whose proportion do not differ significantly from each other at 0.01 level (group 1 and group 3 (a) and group 1 and group 2 (b)). The only significant difference in the proportion idiopathic / structural epilepsy is between the group 2 (b) and group 3 (a). The proportion in group 1, instead do not differ significantly from the group 2 (b) and the group 3 (a)

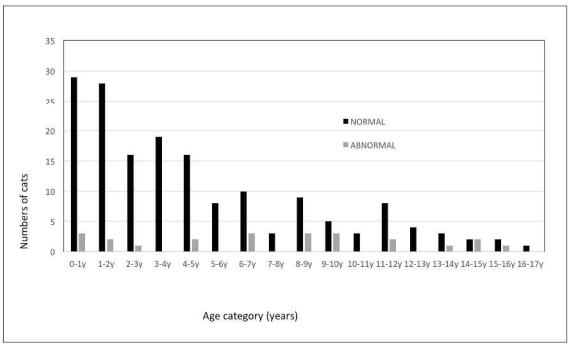
Table 2

Fisher's Exact test between 2 groups of age: group 1 cats aged 6 years old or younger, group 2 cats older than 6 years old. The prevalence of structural epilepsy is significantly higher (Fisher's exact test, $p<0.01$) in the group 2 (cat older than 6 years). The sample is sufficient to achieve 86% power with a significance of type-1 error $\alpha= 0.05$

Table 3.

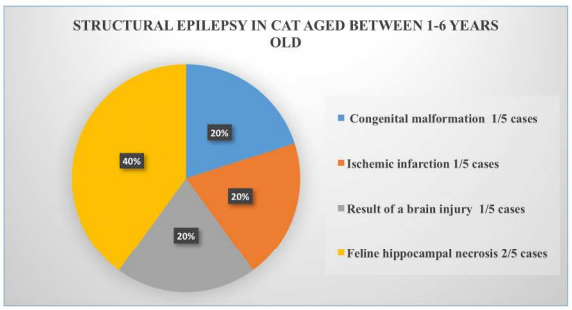
Logistic Regression Analysis indicating that age is significantly associated with the event of suffering from structural epilepsy ($p<0.01$). Odds ratio for age is 1.14 (confidence interval 1.04-1.26), this means that the likelihood of structural disease increases 14%/year.

AGE PREVALENCE	NORMAL	ABNORMAL
0-1y	29	3
1-2y	28	2
2-3y	16	1
3-4y	19	0
4-5y	16	2
5-6y	8	0
6-7y	10	3
7-8y	3	0
8-9y	9	3
9-10y	5	3
10-11y	3	0
11-12y	8	2
12-13y	4	0
13-14y	3	1
14-15y	2	2
15-16y	2	1
16-17y	1	0



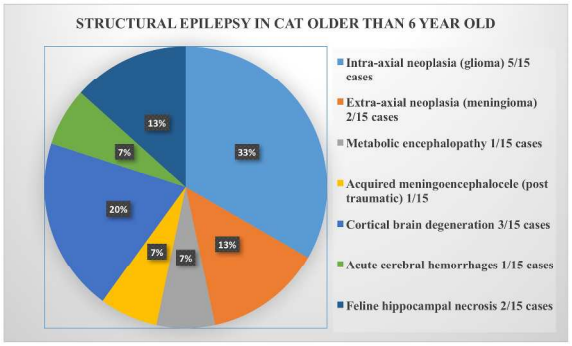
Graph showing the number of cats with normal (black) and structural (grey) MRI abnormalities in different age groups.

figure 1
541x304mm (225 x 225 DPI)



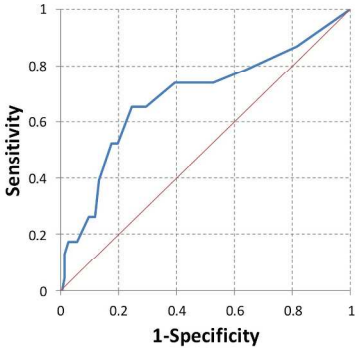
Graph showing the aetiology of structural epilepsy in cats aged between 1 to 6 years old.

figure 2
376x211mm (300 x 300 DPI)



Graph showing the aetiology of structural epilepsy in cats older than 6 years old.

541x304mm (225 x 225 DPI)



Receiver Operating Characteristic (ROC) analysis: The area under the ROC curve (AUC) was 0.66 indicating that age is a moderately good discriminator between statuses). The optimal cut-off is 5 years old (accuracy 74%, specificity 75%, sensitivity 65%).

figure 4
541x304mm (225 x 225 DPI)

Age	Idiopathic Epilepsy	Structural Epilepsy	Total
Group 1: age <= 1 y	29 a,b	3 a,b	32
Group 2: age between 1-6 y	86 b	5 b	91
Group 3: age >6 y	50 a	15 a	65
Total	165	23	188
Fisher's Exact Test 0.005			

Fisher's Exact test between the 3 groups of age: group 1 cats aged 1 years old or younger, group 2 cats older than 1 years old and aged 6 years old or younger, group 3 cats older than 6 years. The proportion of idiopathic / structural epilepsy is not the same among the groups (Fisher's exact test, $p<0.01$). Further analysis performed between different pairings of these 3 groups is represented by the letters in subscript. Each subscript letter (a, b) denoted a subset of 2 Groups whose proportion do not differ significantly from each other at 0.01 level (group 1 and group 3 (a) and group 1 and group 2 (b)). The only significant difference in the proportion idiopathic / structural epilepsy is between the group 2 (b) and group 3 (a). The proportion in group 1, instead do not differ significantly from the group 2 (b) and the group 3 (a)

table 1
1693x952mm (72 x 72 DPI)

Age	Idiopathic epilepsy	Structural epilepsy	Total
Group 1: <=6	115	8	123
Group 2: >6	50	15	65
Total	165	23	188
Fisher's exact Test 0.002			

Fisher's Exact test between 2 groups of age: group 1 cats aged 6 years old or younger, group 2 cats older than 6 years old. The prevalence of structural epilepsy is significantly higher (Fisher's exact test, $p<0.01$) in the group 2 (cat older than 6 years). The sample is sufficient to achieve 86% power with a significance of type-1 error $\alpha = 0.05$

table 2
1693x952mm (72 x 72 DPI)

	B	Sig.	Exp(B)	95% C.I.for EXP(B)	
				Lower	Upper
Age	.135	.006	1.144	1.040	1.259
Constant	-2.708	.000	.067		

Logistic Regression Analysis indicating that age is significantly associated with the event of suffering from structural epilepsy ($p<0.01$). Odds ratio for age is 1.14 (confidence interval 1.04-1.26), this means that the likelihood of structural disease increases 14%/year.

table 3
1693x952mm (72 x 72 DPI)