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*.
<https://doi.org/10.1136/vr.104142>

Peer reviewed version

Link to published version (if available):
[10.1136/vr.104142](https://doi.org/10.1136/vr.104142)

[Link to publication record in Explore Bristol Research](#)
PDF-document

This is the author accepted manuscript (AAM). The final published version (version of record) is available online via British Veterinary Association at <http://veterinaryrecord.bmj.com/content/early/2017/04/06/vr.104142> . Please refer to any applicable terms of use of the publisher.

University of Bristol - Explore Bristol Research

General rights

This document is made available in accordance with publisher policies. Please cite only the published version using the reference above. Full terms of use are available:
<http://www.bristol.ac.uk/red/research-policy/pure/user-guides/ebr-terms/>

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

Journal:	<i>Veterinary Record</i>
Manuscript ID	vetrec-2016-104142.R2
Article Type:	Paper
Date Submitted by the Author:	06-Mar-2017
Complete List of Authors:	Raimondi, Francesca; Southern Counties Veterinary Specialists LLP, Neurology Shihab, Nadia; Southern Counties Veterinary Specialists, Nadia is an ECVN Diplomate Gutierrez-Quintana, Rodrigo; University of Glasgow, School of Veterinary Medicine Smith, Alexander; Langford Veterinary Services, small animal hospital Trevail, Raquel; Southern Counties Veterinary Specialists LLP, Neurology Sanchez-Masian, Daniel; Small Animal Teaching Hospital, University of Liverpool, Neurology/Neurosurgery Smith, Pete; Davies Veterinary Specialists,
Abstract:	<p>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.</p> <p>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.</p> <p>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.</p>

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

SCHOLARONE™
Manuscripts

Confidential: For Review Only

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

3 Authors:

4 Corresponding author:

5 Francesca Raimondi, DVM MRCVS

6 Southern Counties Veterinary Specialists (SCVS)

7 6 Forest Corner Farm

8 Ringwood, Hampshire, BH24 3JW, UK

9 francy.raimondi@gmail.com

10 tel. +44 1425 485615

11 fax. +44 1425 480849

12

13 Nadia Shihab, MAVetMB Dip ECVN MRCVS

14 Southern Counties Veterinary Specialists (SCVS)

15 6, Forest Corner Farm,

16 Ringwood, Hampshire, BH24 3JW, UK.

17

18 Rodrigo Gutierrez-Quintana, MVZ MVM Dip ECVN MRCVS

19 School of Veterinary Medicine,

20 Bearsden Rd, Bearsden, Glasgow, G61 1QH, UK

21

22 Alexander Smith, BVetMed, MRCVS

23 Langford Small Animal Referral Hospital,

24 Langford Road, Bristol, BS40 5DU, UK

25

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

26 Raquel Tremain, DVM Dip ECVN MRCVS

27 Southern Counties Veterinary Specialists (SCVS)

28 6 Forest Corner Farm,

29 Ringwood, Hampshire, BH24 3JW, UK.

30

31 Daniel Sanchez-Masian, Lic Vet Dip ECVN MRCVS.

32 Small Animal Teaching Hospital,

33 Chester High Rd, Neston, CH64 7TE, UK

34

35 Peter M. Smith, BSc, BVM&S, PhD, Dip ECVN, MRCVS.

36 Davies Veterinary Specialists

37 Manor Farm Business Park

38 Higham Gobion, Hitchin, SG5 3HR, UK

39

40 Keywords: Feline, epilepsy, brain, magnetic resonance imaging

41

42 Word count: 3925

43

44

45

46

47

48

49

50

51

52

53

54

55

56

57

58

59

60

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.

75 Introduction

76 Epileptic seizures are transient paroxysmal disturbances in brain function caused by an
77 imbalance in excitatory and inhibitory neuronal transmission. They arise through
78 disturbances in forebrain function and can be caused by metabolic derangements, by genetic
79 or acquired abnormalities in neuronal function or by structural brain disease (Berendt and
80 others 2015, Berg and others 2011, Finnerty and others 2014, Munana 2013, Pakodzy and
81 others 2014, Wahle and others 2014). The diagnostic approach to cats with epileptic seizures
82 includes complete physical and neurological examinations, analysis of various biochemical
83 and haematological parameters, advanced imaging of the brain and analyses of cerebrospinal
84 fluid when appropriate (Bailey and others 2009, De Risio and others 2015, Rusbridge 2005).
85 Understanding the probability of a significant structural brain lesion in cats with epileptic
86 seizures helps clinicians assess the need for advanced brain imaging. Although cats with
87 neurological deficits have a high risk of structural brain disease, a significant lesion in a non-
88 eloquent region of the brain might be undetectable on neurological examination (Schwartz
89 and others 2011, Smith and others 2008). As a result, many animals that appear
90 neurologically normal will have an identifiable lesion on magnetic resonance imaging (MRI).
91 An increase likelihood of a significant brain lesion with age has been established in
92 neurologically normal dogs with recurrent seizures, and studies have indicated a substantially
93 higher risk in dogs older than six years of age, which is primarily related to the higher
94 prevalence of neoplastic lesions in older animals (Armasu and others 2014, De Risio and
95 others 2015, Schwartz and others 2013, Smith and others 2008).
96 Although applying the same patterns to cats may seem reasonable, such an assumption is
97 questionable. First, idiopathic epilepsy is thought to be relatively rare in cats, which
98 decreases the likelihood of diagnosing this form of epilepsy and increases the likelihood of
99 young cats presenting with a significant brain lesion than similarly aged dogs. Second, cats

1
2
3 100 with meningioma, which is the most common brain neoplasm in cats, are less likely to have
4
5 101 epileptic seizures than dogs with brain neoplasia (Bagley and others 1999; Cameron and
6
7 102 others 2015, Schwartz and others 2011, Snyder and others 2006, Tomek and others 2006,
8
9 103 Troxel and others 2003) which may decrease the prevalence of identifiable lesions in geriatric
10
11 104 cats compared with that in dogs.
12

13
14 105 To investigate the prevalence of structural brain disease in cats of varying ages suffering
15
16 106 from epileptic seizures we examined the MRI findings of a large population of cats with
17
18 107 normal interictal physical and neurological examinations and without significant
19
20 108 abnormalities on haematology or serum biochemistry analysis (including fasting bile acids
21
22 109 and electrolytes).
23

24
25 110 In accordance with the international veterinary epilepsy task force (IVETF) guide lines for
26
27 111 dogs (De Risio and others 2015), we divided the cats into three age groups (aged or younger
28
29 112 than one year, between one and six years and older than 6 years) and we compared the
30
31 113 proportion of cats with a detectable lesion on MRI in these different groups. We also
32
33 114 analysed whether there was an optimal cut off age at which structural epilepsy was more
34
35 115 prevalent than idiopathic epilepsy and we assessed the association of age with the likelihood
36
37 116 of suffering from structural epilepsy.
38

39 117 Materials and methods

40
41
42
43
44 118 Electronic and hardcopy records of five United Kingdom (UK) referral hospitals (Southern
45
46 119 Counties Veterinary Specialists, Hampshire (2009 to 2016); Davies Veterinary Specialists,
47
48 120 Hertfordshire (2007 to 2016); Langford Small Animal Veterinary Referral Hospital, North
49
50 121 Somerset (2009 to 2016), Small Animal Hospital, University of Glasgow (2008 to 2016);
51
52 122 and Small Animal Teaching Hospital, Liverpool, Merseyside (2009 to 2016)) were searched
53
54 123 to identify the records of cats presenting with epileptic seizures that were either focal,
55
56 124 generalized or focal epileptic seizures evolving into generalized seizures.
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

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

131 Epilepsy was classified as either structural epilepsy or idiopathic epilepsy of unknown origin.

132 Epileptic seizures were classified in three different groups: focal epileptic seizures,
133 generalized epileptic seizures and focal epileptic seizures evolving into generalized epileptic
134 seizures (secondary generalization) (Berendt and others 2015).

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

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

144 All cats underwent screening tests, including haematology, serum biochemistry analysis,
145 electrolytes and fasting bile acids and those with significant abnormalities were excluded.

146 Additional tests for extracranial disorders were performed when clinically appropriate and
147 included post prandial bile acid and ammonia concentrations, thoracic radiography,
148 abdominal ultrasonography, echo- and electrocardiography, serial blood pressure
149 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 were located in areas of the brain inconsistent with the clinical

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

1
2
3 197 A total of 188 cats with epileptic seizures and without interictal neurological deficits
4
5 198 suggestive of primary forebrain disease were included in this study.
6
7 199 Of these, 131/188 (69.7%) presented with a history of generalised tonic-clonic epileptic
8
9 200 seizures and 14 of these had episodes of cluster seizures. A further 9/188 (4.8%) suffered
10
11 201 from focal epileptic seizures that evolved into generalised epileptic seizures (i.e. secondary
12
13 202 generalization). 36/188 (19.2%) cats presented with focal epileptic seizures, 12 of which were
14
15 203 focal epileptic seizures characterised by psychomotor activity (running around the house,
16
17 204 glazed eyes, dilated pupils and aggression). Another 8/188 (4.3%) cats suffered from cluster
18
19 205 of focal epileptic seizures, with oro-facial involvement characterized by salivation, facial
20
21 206 twitching, lip smacking, chewing, licking or swallowing, motor arrest (motionless starring)
22
23 207 and behavioural changes (mainly aggression). Finally, 4/188 (2.1%) cats presented with
24
25 208 feline audiogenic reflex seizures (FARS) characterized by myoclonic jerks that were
26
27 209 triggered by sound, and these epileptic seizures were frequently followed by secondary
28
29 210 generalization.
30
31
32
33 211 Neurological deficits in 19 cats were considered representative of post-ictal deficits and had
34
35 212 resolved by a subsequent examination. Post-ictal abnormalities included minor delays in
36
37 213 postural reactions, decreased menace responses, obtunded mentation and behavioural
38
39 214 changes.
40
41
42 215 Classifying the cats according to the age of onset of seizures, 32 (17%) cats were aged or
43
44 216 younger than one year, 91 (48.7%) cats were aged between one and six years and the
45
46 217 remaining 65 (35.6%) cats were older than six years old.
47
48
49 218 The most represented breed was the domestic short hair cat (77.65 % of the population),
50
51 219 followed by Bengal (3.72%) and Maine Coon (3.2%) breeds. The distribution between males
52
53 220 (55.85%) and females (44.15%) was approximately equal.
54
55
56 221 Magnetic resonance imaging abnormalities were detected in 35/188 cases (18.6%).
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

231 Six further MRI abnormalities were classified as post-ictal. In those cases, deemed to have a
232 significant finding, the majority of the lesions were located at the level of the piriform lobe (5
233 cases - 22%), hippocampus (5 cases - 22%) and frontal cortex (5 cases - 22%). A diffuse
234 cortical distribution was seen in three cases (13%), two had lesions in the olfactory bulb
235 (8.6%), and there was one example (4.3%) in each of the parietal cortex, temporal cortex and
236 in the lateral and medial geniculate nuclei.

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

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

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

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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

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

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

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

1
2
3 297 The logistic regression analysis showed that age is significantly associated with the
4
5 298 possibility of suffering from structural epilepsy ($p<0.01$) with the likelihood of suffering
6
7 299 from a structural brain disease increasing 14% per year. (table 3)
8
9
10 300 Discussion
11
12 301 The present study describes the diagnostic findings in a population of cats presenting with
13
14 302 seizures but with no evidence of forebrain dysfunction on neurological examination.
15
16 303 The findings of this study show that MRI is useful to detect lesions in clinically silent regions
17
18 304 of the brain in both young and old cats and indicate that lesions are more prevalent in cats
19
20 305 greater than six years of age. This is similar to findings in dogs and appears to reflect an
21
22 306 increased risk of brain neoplasia with age. By undertaking ROC analysis, we were further
23
24 307 able to show that five years appears a more suitable cut off age at which prevalence of
25
26 308 structural epilepsy surpassed the prevalence of idiopathic epilepsy.
27
28
29 309 Although our data are inconsistent with the traditional anecdotal impression that the
30
31 310 prevalence of epilepsy of unknown origin in cats has been overestimated because of the
32
33 311 inconsistent application of MRI (Barnes 2004, Pakozdy and others 2010, Schriefl and others
34
35 312 2008), our findings fits well with the assumption that animals with congenital structural brain
36
37 313 anomalies usually develop problems within the first year (Bagley 2005), because 9.4% of cats
38
39 314 aged or younger than 1 year old diagnosed with structural epilepsy showed MRI changes
40
41 315 suggestive of congenital malformation.
42
43
44 316 Cats without identifiable lesions are usually diagnosed with probable structural epilepsy
45
46 317 (Barnes and others 2004, Platt 2001, Quesnel and others 1997, Thomas 2010). However, the
47
48 318 alternative hypothesis is that some of these individuals have idiopathic epilepsy.
49
50
51
52 319 The prevalence of structural epilepsy in this study is 12.2% (23/188 cases). This prevalence is
53
54 320 low when compared to other previous published studies (Barnes and others 2004, Pakoszy
55
56 321 and others 2010, Schrief and others 2008, Whale and others 2014) in which structural
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

323 This difference is most likely due to the inclusion criteria of our study. These were restricted

324 to cats with a normal interictal physical and neurological examination whereas in the

325 previous studies inclusion criteria included cats presenting with reactive seizures and/or

326 neurological deficits and therefore more susceptible to structural brain lesions.

327 The MRI scanners used in this study included 1 and 1.5 T superconducting electromagnets

328 (used in around 50% of cases) and a 0.4 T permanent magnet and although the images

329 obtained using high field (>1T) magnets are excellent for identifying both large and subtle

330 structural lesions, it remains possible that the group of cats undergoing low field MRI had

331 subtle structural lesions that were not detected. However, in the 99 cats that underwent high

332 field MRI, subtle lesions identified that would have been missed with low field MRI were not

333 identified. Therefore, the proportion of cats in which a subtle lesion might have been missed

334 by a low field MRI was likely negligible.

335 The conclusions of this study are similar to those in previous studies in dogs (Armasu and

336 others 2014, De Risio and others 2015, Schwartz and others 2013, Smith and others 2008)

337 which demonstrated that the age at seizure onset and neurological examination findings were

338 both significantly associated with the type of brain disease, with our results indicating, the

339 odds ratio of structural disease increasing of 14% per year of life.

340 Another interesting finding in this study that is similar to the finding of studies previously

341 conducted in dogs (Schwartz and others 2011, Smith and others 2008) was that most of the

342 lesions (73.91%) were located in the olfactory, frontal and pyriform lobes, and the

343 hippocampus. Although dysfunction in these areas is less likely to cause neurological

344 deficits, lesions located in these area could act as strong epileptogenic foci because of the

345 widespread connections to the limbic system.

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

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

357 The classification of MRI changes as post-ictal is also open to question. We based our
358 interpretation of such changes on previous studies that demonstrate hyperintensity on T2WI
359 and FLAIR imaging following seizures, particularly in the hippocampus and pyriform lobe
360 (Kim and others 2001, Marioni-Henry and others 2012, Mellema and others 1999, Viitmaa
361 and others 2006). It was recently postulated that such MRI changes in the hippocampus and
362 associated extra-hippocampal regions could represent necrosis secondary to immune-
363 mediated limbic encephalitis with voltage-gated potassium channel (VGKC) complex
364 antibodies (Fatzer and others 2000, Pakozdy and others 2013, Pakozdy and others 2011,
365 Schmied and others 2008). Although we found no CSF abnormalities in cases defined as
366 having post-ictal changes, it is difficult to be certain whether borderline T2 hyperintensity of
367 the hippocampus and parahippocampal structures represents the cause (Fatzer and others
368 2000, Pakozdy and others 2013, Pakozdy and others 2011, Schmied and others 2008) or
369 consequence of the epileptic seizures (Marioni-Henry and others 2012). To avoid incorrect
370 classification of these cases, the criteria suggested by Wahle (Wahle and others 2014) were

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

371 followed, whereby cats were considered to have hippocampal necrosis only if confirmed by
372 conclusive MRI criteria and the occurrence of treatment-resistant complex partial seizures
373 with orofacial involvement (Wahle and others 2014). Cats classified as having post-ictal
374 changes did not meet these criteria.
375 In addition to the cases mentioned above, four cats older than six years had a history of
376 myoclonic jerks that typically progressed to generalised epileptic seizures and were triggered
377 by high frequency sounds. Although MRI and CSF analysis of these animals were within
378 normal limits and seizures were well controlled on medical treatment, these cats may be
379 suffering from a syndrome known as feline audiogenic reflex seizures (FARS), which has a
380 geriatric onset and suspected degenerative aetiology (Lowrie and others 2016). In the absence
381 of MRI changes, we classified the animals belonging to this group as having epilepsy of
382 unknown origin.

383 Conclusion

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

391

392

393

394 REFERENCES

- 395 BERENDT, M., FARQUHAR, R. G., MANDIGERS, P. J. J., PAKOZDY, A., BHATTI, S.
396 F. M., DE RISIO, L. & OTHERS (2015) International veterinary epilepsy task force
397 consensus report on epilepsy definition, classification and terminology in companion
398 animals. *Vet Res* 11, 182.
- 399 BERG AT & SCHEFFER IE. (2011) New concepts in classification of the epilepsies:
400 entering the 21st century. *Epilepsia* 52, 1058-1062.
- 401 FINNERTY EK, BARNES HELLER HL, MERCIER MN. GIOVANELLA CJ, VIVIAN
402 WL & RYLANDER H (2014) Evaluation of therapeutic phenobarbital concentrations and
403 application of a classification system for seizures in cats: 30 cases (2004–2013). *J Am Vet*
404 *Med Assoc* 244, 195-199.
- 405 MUNANA KR (2013) Update: Seizure Management in Small Animal Practice. *Vet Clin*
406 *North Am Small Anim Pract* 43, 1127-1147.
- 407 PAKOZDY A, HALASZ P & KLANG A (2014) Epilepsy in cats: Theory and Practice. *J*
408 *Vet Intern Med* 28, 255-263.
- 409 WAHLE AM, BRUHSCHWEIN A, MATIASEK K, PUTSCHBACH K, WAGNER E,
410 MUELLER RS & OTHERS (2014) Clinical characterization of Epilepsy of Unknown Cause
411 in cats. *J Vet Intern Med* 28, 182-188.
- 412 BAILEY KS & DEWEY CW (2009) The seizuring cat Diagnostic work-up and therapy. *J*
413 *Feline Med Surg* 11, 385-394.
- 414 DE RISIO L, BHATTI S, MUNANA K, PENDERIS J, STEIN V, TIPOLD A & OTHERS
415 (2015) International veterinary epilepsy task force consensus proposal: diagnostic approach

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

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

418 SCHWARTZ M, LAMB CR, BRODBELT DC & VOLK HA (2011) Canine intracranial
419 neoplasia: clinical risk factors for development of epileptic seizures. *J Small Anim Pract* 52,
420 623- 627.

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

423 ARMASU M, PACKER RM, COOK S, SOLCAN G & VOLK HA (2014) An exploratory
424 study using statistical approach as a platform for clinical reasoning in canine epilepsy. *Vet J*
425 202, 292-296.

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

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

432 CAMERON S, RISHNIW M, MILLER AD, STURGES B & DEWEY CW (2015)
433 Characteristics and Survival of 121 Cats Undergoing Excision of Intracranial Meningiomas
434 (1994-2011) *Vet Surg* 44, 772-776.

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

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

- 438 neoplasia in 61 cats: localisation, tumour types and seizure patterns. *J Feline Med Surg* 8,
439 243-253.
- 440 TROXEL MT, VITE CH, VAN WINKLE TJ, NEWTON AL, TICHES D, DAYRELL-
441 HART B & OTHERS (2003) Feline intracranial neoplasia: retrospective review of 160 cases
442 (1985-2001). *J Vet Intern Med* 17, 850-859.
- 443 PIVETTA M, DE RISIO L, NEWTON R & DENNIS R (2013) Prevalence of lateral
444 ventricle asymmetry in brain MRI studies of neurologically normal dogs and dogs with
445 idiopathic epilepsy. *Vet Radiol Ultrasound* 54, 516-521.
- 446 DUQUE C, PARENT J, BRISSON B, DA COSTA R & POMA R (2005) Intracranial
447 arachnoid cysts: are they clinically significant? *J Vet Inter Med* 19, 772-774.
- 448 MACKILLOP E (2011) Magnetic Resonance Imaging of intracranial malformation in dogs
449 and cats. *Vet Radiol Ultrasound* 52, Supp.1 S42-S51.
- 450 MATIASSEK LA, PLATT SR, SHAW S & DENNIS R (2007) Clinical and magnetic
451 resonance imaging characteristics of quadrigeminal cysts in dogs. *J Vet Intern Med* 21, 1021-
452 1026.
- 453 VITE CH & CROSS JR (2011) Correlating magnetic resonance findings with
454 neuropathology and clinical signs in dogs and cats. *Vet Radiol Ultrasound*, 52 Supp. 1, S23-
455 S31.
- 456 KIM, JA, CHUNG, JI, YOON, PH, KIM DI, CHUNG TS, KIM EJ & OTHERS (2001)
457 Transient MR signal changes in patients with generalized tonicoclonic seizure or status
458 epilepticus: periictal diffusion- weighted imaging. *AJNR* 22, 1149-1160.
- 459 MARIONI-HENRY K, MONTEIRO R & BEHR S (2012) Complex partial orofacial seizures

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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, TEPPONEN
AM & OTHERS (2006) Magnetic resonance imaging findings in Finnish Spitz dogs with
focal epilepsy. *J Vet Intern 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.

- 1
2
3 482 BAGLEY RS (2005). Clinical evaluation and management of animals with seizures. In:
4
5 483 Bagley, R.S. (Ed.), *Fundamentals of Veterinary Clinical Neurology*. Blackwell Publishing,
6
7 484 Ames, 363–376.
8
9
10 485 PLATT SR (2001) Pearls of Veterinary Practice. Feline Seizure Control. *J Am Anim Hosp*
11
12 486 *Assoc* 37,515-517.
13
14
15 487 QUESNEL AD, PARENT JM, MCDONNELL W, PERCY D & LUMSDEN JH (1997)
16
17 488 Diagnostic evaluation of cats with seizures disorders: 30 cases (1991-1993) *J Am Vet Med*
18
19 489 *Assoc* 210, 65-71.
20
21
22
23 490 THOMAS WB (2010) Idiopathic Epilepsy in Dogs and Cats. *Vet. Clin. Small. Anim* 40, 161-
24
25 491 179.
26
27
28 492 FATZER R, GANDINI G, JAGGY A, DOHERR M & VANDEVELDE M (1990) Necrosis
29
30 493 of hippocampus and piriform lobe in 38 domestic cats with seizures: A retrospective study on
31
32 494 clinical and pathologic findings. *J Vet Intern Med* 4:26-39.
33
34
35
36 495 PAKOZDY A, HALASZ P, KLANG A, BAUER J, LESCHNIK M, TICHY A & OTHERS
37
38 496 (2013) Suspected limbic encephalitis and seizure in cats associated with voltage-gated
39
40 497 potassium channel (VGKC) complex antibody. *J Vet Intern Med* 27, 212–214.
41
42
43 498 PAKOZDY A, GRUBER A, KNEISSL S, LESCHNIK M, HALASZ P & THALHAMMER
44
45 499 JG (2011) Complex partial cluster seizures in cats with orofacial involvement. *J Feline Med*
46
47 500 *Surg* 13, 687–693.
48
49
50
51 501 SCHMIED O, SCHARF G, HILBE M, MICHAL U, TOMSA K & STEFFEN F (2008)
52
53 502 Magnetic resonance imaging of feline hippocampal necrosis. *Vet Radiol Ultrasound* 49,343-
54
55 503 349
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

506

507

508

509

510

511

512

513

514

515

516

517

518

519

520

521

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)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

545 Table 2

546 Fisher’s Exact test between 2 groups of age: group 1 cats aged 6 years old or younger, group

547 2 cats older than 6 years old. The prevalence of structural epilepsy is significantly higher

548 (Fisher’s exact test, $p<0.01$) in the group 2 (cat older than 6 years). The sample is sufficient

549 to achieve 86% power with a significance of type-1 error $\alpha= 0.05$

550

551 Table 3.

552 Logistic Regression Analysis indicating that age is significantly associated with the event of

553 suffering from structural epilepsy ($p<0.01$). Odds ratio for age is 1.14 (confidence interval

554 1.04-1.26), this means that the likelihood of structural disease increases 14%/year.

555

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 $\leq$ 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)