Original Article

Associations between neutering and idiopathic epilepsy in Labrador retrievers and Border collies under primary veterinary care in the UK.

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Abstract

There are sparse published scientific data on associations between neutering and the severity and survival of dogs with idiopathic epilepsy. This study aimed to explore the timing of neutering with respect to onset of seizures in dogs with idiopathic epilepsy. Associations between neutering and both age of onset of seizures and the occurrence of cluster seizures or status epilepticus were examined. Survival analysis investigated the effects of sex-neuter categories. The median survival time of Border collies was compared with data previously reported in literature.

The study included veterinary primary-care clinical data on 117 Labrador retrievers and 57 Border collies diagnosed with idiopathic epilepsy from the VetCompass™ project in the UK. The majority (74.2%; $P \leq 0.001$) of neutered cases were neutered before the onset of seizures. Age (years) at onset of seizures did not differ between dogs intact at time of onset and dogs neutered before onset of seizures (males 3.6 versus 3.7; $P = 0.468$ and females 3.4 versus 4.1; $P = 0.154$). Neuter status was not associated with the occurrence of cluster seizures (males $P = 0.947$ and females $P = 0.844$). Dogs intact at onset of seizures had longer median survival times than dogs neutered before onset of seizures (males 1436 days vs 1234 days; $P = 0.019$ and females 1778.5 days vs 1261 days; $P = 0.027$). Median survival time of 1393 days for Border collies was longer than previously reported ($P \leq 0.001$). These results do not support recommendations to neuter dogs with idiopathic epilepsy within an evidence-based treatment plan.

Keywords: Canine; Castration; Dog; Seizure; Spay

Introduction

Idiopathic epilepsy is the most commonly diagnosed chronic neurological disorder in dogs, with a prevalence of 0.62% estimated in primary veterinary practices in the UK (Kearsley-Fleet et al., 2013). A male predisposition has been reported within many breeds (Van Meervenne et al., 2014). Furthermore, seizure occurrence has been reported as associated with the oestrous cycle in bitches with idiopathic epilepsy, suggesting a beneficial effect of neutering (Shell, 1993; Knowles, 1998; Thomas, 2000; Van Meervenne et al., 2015). However, published data on the impact of neutering on the incidence and prevalence of canine epilepsy is scarce and often contradictory. No association between neuter status and prevalence of canine epilepsy was reported in an epidemiological study with 539 cases collected from the VetCompass Animal Surveillance project in the UK (Kearsley-Fleet et al., 2013). Significantly more neutered dogs were reported in an epileptic cohort of 1260 cases compared to a control population using data from a UK-based diagnostic company (Short et al., 2011). In addition, neutering was associated with increased risk of epilepsy diagnosis for both males and females in a US study that explored effects of neutering cross a range of diseases (Belanger et al., 2017). Unfortunately, inference from most of these studies was limited because they did not report whether these dogs were neutered before or after onset of seizures (Short et al., 2011; Kearsley-Fleet et al., 2013).

The published literature also offers limited information on associations between neutering and the clinical course of epilepsy in dogs. Sex and neuter status were not significant risk factors for survival in 172 referral cases in Japan (Hamamoto et al., 2016). Similarly, neither sex or neuter status were identified as risk factors in a study of 17 epileptic Danish Labrador retrievers but the analysis was limited by inclusion of only one neutered dog (Berendt et al., 2002). Neutered males had shorter survival and more cluster seizures compared to intact male dogs in a more recent study of 78 referral dogs with idiopathic epilepsy in Denmark. However, data on time of neutering in relation to onset of seizures was not provided (Fredso et al., 2014). No associations between either sex or neuter status and cluster seizures were identified in a multi-breed study of 384 dogs treated at a UK canine referral epilepsy clinic (Packer et al., 2016), whereas another UK multi-breed study evaluating 407 referral epileptic cases reported a significant association between both neuter status and sex with the occurrence of cluster seizures (Monteiro et al., 2012). Furthermore, neither sex or neuter status were identified as risk factors for the occurrence of status epilepticus in 32 referred dogs with idiopathic epilepsy in the US (Saito et al., 2001). Information on timing of neutering in relation to the onset of seizures has been reported in some breed-specific studies but no beneficial effect of neutering on the type, frequency, severity or duration of seizures has been reported (Heynold et al., 1997; Hülsmeyer et al., 2010; Weissl et al., 2012).

This study aimed to describe the timing of neutering, if it occurred, in a cohort of Labrador retrievers and Border collies with idiopathic epilepsy under primary veterinary care in the UK. Associations were explored between neutering and both age of onset of seizures and the occurrence of cluster seizures or status epilepticus as measures of the severity of epilepsy. We also aimed to report survival analysis separately for males and females and to compare the median survival time of the Border collies in the current study against data previously reported in literature.

Material and methods

This retrospective cohort study used clinical data from the VetCompass™ Animal Surveillance project. VetCompass™ collates de-identified electronic patient record

(EPR) data from primary-care veterinary practices in the UK for epidemiological research (O'Neill et al., 2014).

Ethical approval of the project was granted by the Royal Veterinary College Ethics and Welfare Committee (reference number 2015-1369; 18 August, 2015).

The study included all dogs under veterinary care from January 1st 2013 to December 31st 2013 in the VetCompass™ database. Case-finding for candidate idiopathic epilepsy cases involved initial screening of all EPRs using a range of search terms [clinical note search terms: seiz*/ epile*/ convuls*/ anti-epil*/ anti-convuls*/ fenob*/ felbam*/ pheno*/ bromid*/ levet*/ zonisam*/ pexion/ KBr/ "had a fit"/ "had 1 fit"/ "had fits"/ "2 fits"/ epiphen~1/ epilease~1/ potassium bromid~1/ keppra~1/ zonegran~1/ phenoleptil~1/ pexion~1 and treatment search terms: epiphen~1/ pheno*/ epilease~1/ bromid*/ KBr/ Libromide/ levetiracetam/ keppra~1/ pexion/ zonegran/ anti-epil*]. Candidate cases were randomly ordered using the *RAND* function in Microsoft Excel (Microsoft Office Excel 2007, Microsoft Corp.). The clinical records of dogs recorded as Labrador retriever or Border collie breeds were manually assessed against the idiopathic epilepsy case definition until 200 confirmed cases were included. Inclusion criteria for an idiopathic epilepsy case required evidence in the clinical records of at least two generalised seizures > 24 hours apart. Exclusion criteria included: 1. evidence that seizures were caused by structural epilepsy or were reactive seizures; 2. first seizure occurred at < 6 months or > 6 years of age without normal magnetic resonance imaging (MRI) of the brain and cerebrospinal fluid (CSF) results or < 1 year follow up without the development of other neurological symptoms than seizures.

Additional information extracted on confirmed idiopathic epilepsy cases included: date of birth, sex, date of first seizure, neuter status at time of first seizure, date of neutering, whether seizure activity was recorded as contributing to the neutering decision, other reasons for neutering, point in oestrous cycle when first seizure was recorded, did the owner report a perceived association between seizure and oestrous cycle, count of cluster seizures, count of status epilepticus events, final date recorded as alive, date of death and cause of death. Cases lacking information on date of first seizure and neuter status at time of first seizure were excluded from the analysis. Six sex-neuter groups were defined that described the status at the onset of seizures: males intact, males neutered before the onset of seizures, males neutered after the onset of seizures, females intact, females neutered before the onset of seizures and females neutered after the onset of seizures.

After data checking and cleaning in Microsoft Excel, age (days) at onset of seizure was calculated based on birth date and date of first recorded seizure. Survival time in days was calculated based on date of first reported seizure and date of death. Survival time was censored at the date of the final available record for dogs that did not die during the available study period. This means, that if the dogs were still alive at the final available record, survival time was calculated based on date of first reported seizure and date of final record alive. Thus, the data were right censored (Urfer, 2008).

Statistical analyses were conducted using SPSS 24 (IBM Corp., Released 2012). Statistical significance was set at $P < 0.05$. Descriptive statistics were reported relative to the neutering time point. Sex-neuter groups were compared using chi^2 tests. Association between neuter status and the age of onset of seizures was analysed using an independent-samples Mann-Whitney U test. Associations between sex-neuter groups and the occurrence of cluster seizures were assessed using the chi^2 tests test of homogeneity or Fisher´s exact test (when < 5 expected counts in groups). Survival times were compared between males and females using an independent t-test. Survival data are displayed as Kaplan-Meier curves and analyses between sex-neuter groups was performed separately for males and females using the Log Rank test with a chi^2 distribution. Median survival time was chosen to compare groups with a small sample size as described by Chen and Zhang (2016). Median survival time of Border collies was compared to data reported in literature (Hülsmeyer et al., 2010) using a univariate Wilcoxon Signed-Rank Test.

Results

Descriptive statistics at the point of neutering

Eight hundred candidate cases were initially reviewed to confirm 200 idiopathic epilepsy cases. From these, 26 cases were later excluded from analysis because information was not available on the date of first seizure or on neuter status at first seizure. The final analysis included 174 idiopathic epilepsy cases: 117 Labrador retrievers and 57 Border collies.

The distribution of cases across the sex-neuter groups is shown in table 1. Of the 128 neutered dogs, the majority were neutered before the onset of seizures (95/128; 74.2%; $P \leq 0.001$). This was also shown for each sex independently (males 63/82; 76.8%; $P \leq 0.001$ and females 32/46; 69.6%; $P = 0.008$). Of the male cases that were intact at the onset of seizures, the majority remained intact after the onset of seizures (38/57; 66.7%; $P = 0.012$). None of the 19 neuter procedures in males following the onset of seizures had recorded evidence that the procedure was part of a clinical plan for seizure management. Fourteen of 22 female cases that were intact at the onset of seizures were neutered following the onset of seizures, but this difference was not statistically significant (14/22; 63.6%; P =0.201). A perceived association between seizures and oestrous was recorded in the clinical notes for 4/11 (36.4%) Labrador retrievers that were neutered following onset of seizures and the neuter procedure was recorded as part of the seizure management plan for 3/4 (75%) of these. None of the three female Border collies that were neutered following the onset of seizures showed a recorded perceived association between seizures and oestrous but the neuter procedure formed part of seizure therapy for 1/3 (33.3%) of these dogs.

Age of onset of seizures

Median ages at onset of seizures for the sex-neuter groups are shown in table 2. Age at onset of seizures did not differ between dogs that were intact at time of onset and those that were neutered before onset of seizures for either males (P =0.468) or females (P =0.154). For both male and female cases, animals neutered after onset of seizures were younger at seizure onset than animals neutered before onset (males P =0.024 and females P =0.048).

Association sex-neuter group and cluster seizures or status epilepticus

The occurrence of cluster seizures or status epilepticus for each sex-neuter group is shown in table 3. The number of cluster seizures (males P =0.947 and females P =0.844) did not differ across the sex-neuter groups within either sex. There were only 3 status epilepticus events reported in these 174 dogs with idiopathic epilepsy.

Survival

During the data period available to the study, 19/117 (16.2%) Labrador retrievers and 19/57 (33.3%) Border collies died. In 13 of the 38 deceased dogs, epilepsy was reported as the main reason for euthanasia. Nineteen cases were euthanised for conditions that were unrelated to epilepsy including only one death related to the reproductive system (pyometra). The cause of death was not reported in the medical record for six dogs. The median survival time of all 174 cases was 1259 days (interquartile range (IQR) 1251). Median survival time for Labrador retrievers was 1245 days (range 15-4357 and 95% confidence interval 1148-1420) and for Border collies was 1393 days (range 31-4514 and 95% confidence interval 1058-1729). The median survival of Border collies in the current study was longer than the 755 days previously reported in literature (Hülsmeyer et al., 2010) ($P \leq 0.001$). The mean survival time for females (1564 days) did not differ to the mean survival time for males (1427 days) ($P = 0.405$).

Kaplan-Meier survival curves are displayed in figures 1-4. Males intact at the onset of seizures had longer median survival times compared to dogs neutered before onset of seizures (1436 days vs 1234 days respectively; $P = 0.019$). Survival did not differ between the three male sex-neuter groups ($P = 0.055$). Females intact at time of onset of seizures had longer survival times than females neutered before the onset of seizures (1778.5 days vs 1261 days respectively; $P = 0.027$). The three sex-neuter groups of females did not differ in survival ($P = 0.078$).

Discussion

The primary aim of the current study was to explore associations between neutering and idiopathic epilepsy in dogs. To reduce confounding from breed-related factors, the study included only Labrador retrievers and Border collies. Both breeds reportedly have a high prevalence of idiopathic epilepsy (Heynold et al., 1997; Jaggy et al., 1998; Berendt et al., 2002; Hülsmeyer et al., 2010; Short et al., 2011; Kearsley-Fleet et al., 2013; Heske et al., 2014) .

Of the 174 dogs included in the final analyses, 128 dogs (73.6%) were neutered and 46 dogs were intact at the end of data collection. For both breeds and both sexes, the majority of neutered cases were neutered before the onset of seizures. This reflects the high prevalence of neutering in dogs in general in the UK that might have promoted the associations between neuter status and prevalence of epilepsy previously identified by Short et al. (2011) and Belanger et al. (2017). Both of these studies reported neuter status as a risk factor for the prevalence of idiopathic epilepsy. However, in contrast, an epidemiological study based on similar primary-care veterinary data to the present study, identified no association between neuter status recorded at time of final record and prevalence of epilepsy (Kearsley-Fleet et al., 2013).

In the present study, males and females differed in their proportions neutered after onset of seizures (33.3% vs 63.6% respectively). One explanation might be that female dogs are generally more likely to be neutered than males in the UK where this study took place and perhaps also in some other countries (Hoffman et al., 2018; McGreevy et al., 2018). Veterinarians may additionally perceive neutering as having greater benefits in female dogs with epilepsy than in male dogs. Owners and veterinarians might find it easier to link seizure occurrence to hormonal fluctuations during the oestrous cycle in female dogs, whereas, hormonal fluctuations may be less apparent in male dogs. Veterinarians documented an association between seizures and oestrous cycle in four of 14 female dogs and recorded a recommendation of neutering as part of their therapeutic plan for the epilepsy in four dogs in the present study. Conversely, none of the 19 neuter procedures in male dogs were recorded as part of the seizure management. It is possible that information on the clinical rationale for neutering was not fully documented in the clinical records and therefore the current study may have under-estimated the perceived associations.

The current study did not identify a difference in age at onset of seizures between dogs that were intact and dogs that were neutered before onset of seizures. However, male and female dogs neutered after onset of seizures were significantly younger at time of onset of seizures compared to dogs that were neutered before onset of seizures. This suggests that owners may be more willing to neuter at a younger age once epilepsy is diagnosed.

The median survival time of 1393 days from first recorded seizure in the Border collies was significantly longer than the median survival time of 755 days reported in a study of 49 Border collies with idiopathic epilepsy in Germany (Hülsmeyer et al., 2010). This might reflect differences in study populations: primary-care cases in the current study compared to teaching hospital cases in the German study. Referral caseloads are biased towards more complex cases which may negatively impact survival (Bartlett et al., 2010). Additionally, differences in experience, confidence and competence between primary-care and ´canine epilepsy specialty clinics´ may affect diagnostic certainty and outcomes for epilepsy cases. Other studies have shown that referral data heavily underestimate survival and longevity compared to primary-care data (Patronek et al., 1997; O'Neill et al., 2013). It might be concluded that Border collies with idiopathic epilepsy presented in primary-care practices have a better prognosis than has been generalised from previously published studies and that caution should be taken when generalising and interpreting survival results from referral populations to primary-care populations. Breed-specific survival studies for Labrador retrievers were not available in the literature for similar comparison.

In the current study, Kaplan-Meier analyses identified the longest survival times for dogs that were intact (both male and female) at onset of seizures whereas dogs neutered before onset had the shortest survival times. This agrees with a recent referral practice study in Denmark, where neutered male dogs with idiopathic epilepsy had shorter survival times than intact males although information on time of neutering was lacking (Fredso et al., 2014). A cohort study of 49 Border collies that were referral epilepsy cases in Germany did not identify an association between neuter status and survival time (Hülsmeyer et al., 2010). Although the German study did report the time of neutering with respect to the onset of seizures, this information was unfortunately not incorporated into the analyses. A referral study of idiopathic epilepsy cases in Japan similarly did not identify neuter status as a risk factor for survival (Hamamoto et al., 2016). Breed-specific studies on Labrador retrievers, Border collies and Australian shepherd dogs, where information on the time of neutering was available, concluded that there was no beneficial effect of neutering following onset of seizures on the type, frequency, severity or duration of seizures (Heynold et al., 1997; Hülsmeyer et al., 2010; Weissl et al., 2012). It is worth noting that analyses of associations between neutering and survival time in cohorts of dogs with epilepsy generally apply a core assumption that there is no difference in the survival time between neutered and intact dogs in the wider general population. However, the available evidence is unclear on the validity of this assumption. A longevity analysis based on a UK primary-care population that was similar to the current study reported that female neutered and male intact or male neutered dogs had longer life spans compared to female intact dogs (O'Neill et al., 2013). Another study which questioned whether female dogs age differently than male dogs reported that overall neutered dogs lived longer, with neutered females being the longest-lived group (Hoffman et al., 2018). In the UK, neutered Labrador retrievers were reported with greater longevity than intact Labrador retrievers (McGreevy et al., 2018). However, the inference from all of these studies is limited because neutering was simplistically modelled as a time-independent binary variable (single value at the final record), whereas neutering is truly a time-dependent variable with the probability of a positive neuter status increasing with age (O'Neill et al., 2013; Hoffman et al., 2018; McGreevy et al., 2018). To overcome this limitation, and one of the strengths of the present study, we included data into the analysis on the time of neutering with respect to the onset of seizures.

The current study did not identify an association between the three sex-neuter groups and the occurrence of cluster seizures. These findings concur with a study of 384 dogs treated at a multi-breed canine specific epilepsy clinic in the UK that also failed to identify associations between either sex or neuter status and cluster seizures (Packer et al., 2016). However, a study of 407 dogs with idiopathic epilepsy reported that neuter status and sex were significantly associated with the occurrence of cluster seizure. Intact dogs were 1.4 times more likely than neutered dogs to show cluster seizures suggesting possible benefits to neutering in dogs with idiopathic epilepsy (Monteiro et al., 2012). Neutered male dogs had significantly more cluster seizures compared to intact male dogs in a study of 78 referral dogs in Denmark (Fredso et al., 2014). Unfortunately, data on the time of neutering is lacking in each of these studies, which makes comparison with the current study difficult. Additionally, there were only three status epilepticus events reported from the 174 idiopathic epilepsy cases in the current study; this low count did not lend itself to statistical analysis.

The current study had some limitations. Disease surveillance systems from primary-care clinics often record initial presenting complaints rather than the final veterinary diagnosis (Bartlett et al., 2010). To minimise this limitation, the medical records were manually assessed and the inclusion and exclusion criteria were designed to ensure that the extracted diagnosis of idiopathic epilepsy was as reliable as possible. The count of dogs that died was small. The year of the study (2013) was selected to offer up to four years of possible follow-up before the analysis was performed during 2017-2018. It is possible that death data were not captured for some cases that died at home or at clinics outside the VetCompass™ project. A possible option was to contact the owners for follow-up but the VetCompass™ project has been designed to capture anonymised data, so this precluded contacting owners. Even if this option was available, the resultant data could be subject to recall bias. Counts of seizures before and after neutering would have been a valuable proxy measure of disease severity. Unfortunately, during a pilot study, we noticed that the quality of the information recorded in the medical records on the number of seizures was unreliable. However, we did include the count of cluster events as a parameter for severity of disease, because these events appeared to be more reliably recorded. A longer follow up study that includes the count of seizure events as a proxy measure of clinical severity could offer more conclusive interpretations.

Conclusions

Most idiopathic epilepsy cases in the present study were neutered before the onset of seizures. This factor should be considered when interpreting the results from previously reported studies that generally do not account for the timing of neutering during analyses of associations between neuter status and idiopathic epilepsy. No association between neuter status and the occurrence of cluster seizures was found. Intact dogs had the longest survival times. These results do not support a recommendation to neuter dogs with idiopathic epilepsy as a part of an evidence-based treatment plan for idiopathic epilepsy.

Conflict of interest statement

None of the authors has any financial or personal relationships that could inappropriately influence or bias the content of the paper.

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Table 1

Sex and neuter status of 174 dogs with idiopathic epilepsy under primary veterinary care in the UK in 2013.

Sex-neuter status	Labrador retriever	Border collie
Intact male	27 (33.3%)	11 (28.2%)
Male neutered before onset of seizures	38 (46.9%)	25 (64.1%)
Male neutered after onset of seizures	16 (19.8%)	3 (7.7%)
Total male	81 (100.0%)	39 (100.0%)
Intact female	6 (16.7%)	2 (11.1%)
Female neutered before onset of seizures	19 (52.8%)	13 (72.2%)
Female neutered after onset of seizures	11 (30.6%)	3 (16.7%)
Total Female	36 (100.0%)	18 (100.0%)
Total	117	57

Table 2

Median age in days (years) at onset of seizures of 174 dogs with idiopathic epilepsy under primary veterinary care in the UK in 2013.

Sex-neuter status	*n*	Median age at onset in days (years)	IQR[a]
Intact male	38	1270.5 (3.5y)	836
Male neutered before onset	63	1328 (3.6y)	997
Male neutered after onset	19	845 (2.3y)	759
Male intact at seizure onset	57	1123 (3.1y)	942
Intact female	8	1348 (3.7y)	1188
Female neutered before onset	32	1516.5 (4.2y)	1179
Female neutered after onset	14	1093 (3.0y)	875
Female intact at seizure onset	22	1227.5 (3.4y)	874

[a] Interquartile range.

Table 3

Occurrence of cluster seizures or status epilepticus events recorded in the clinical records of 174 dogs with idiopathic epilepsy under primary veterinary care in the UK in 2013.

Sex-neuter status	*n*	Cluster	Status epilepticus
Intact male	38	17	0
Male castrated before onset	63	28	2
Male castrated after onset	19	8	0
Intact female	8	3	0
Female spayed before	32	12	1
Female spayed after	14	4	0

Figure legends

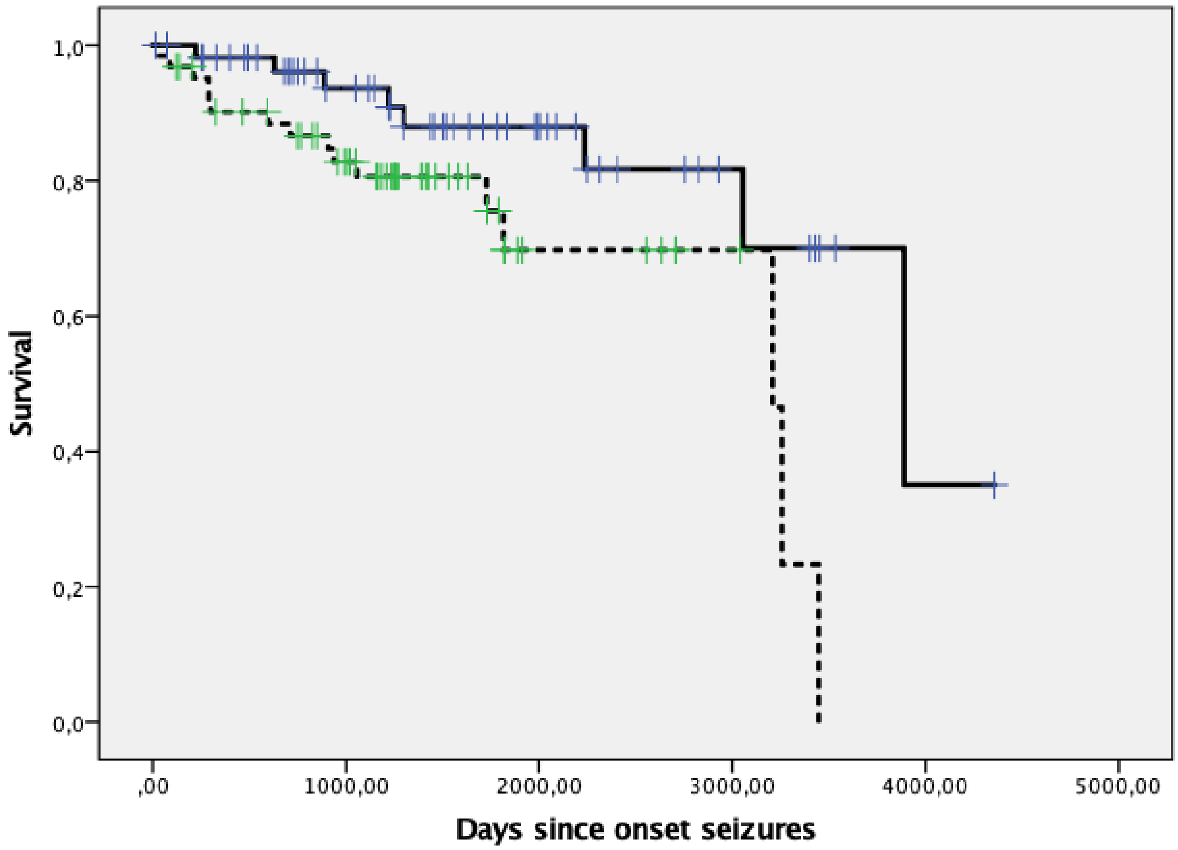

Fig. 1. Kaplan-Meier curve of 120 male dogs with idiopathic epilepsy under primary veterinary care in the UK in 2013. Solid line, group 1, intact at onset of seizures; Dotted line, group 2, neutered before onset of seizures.

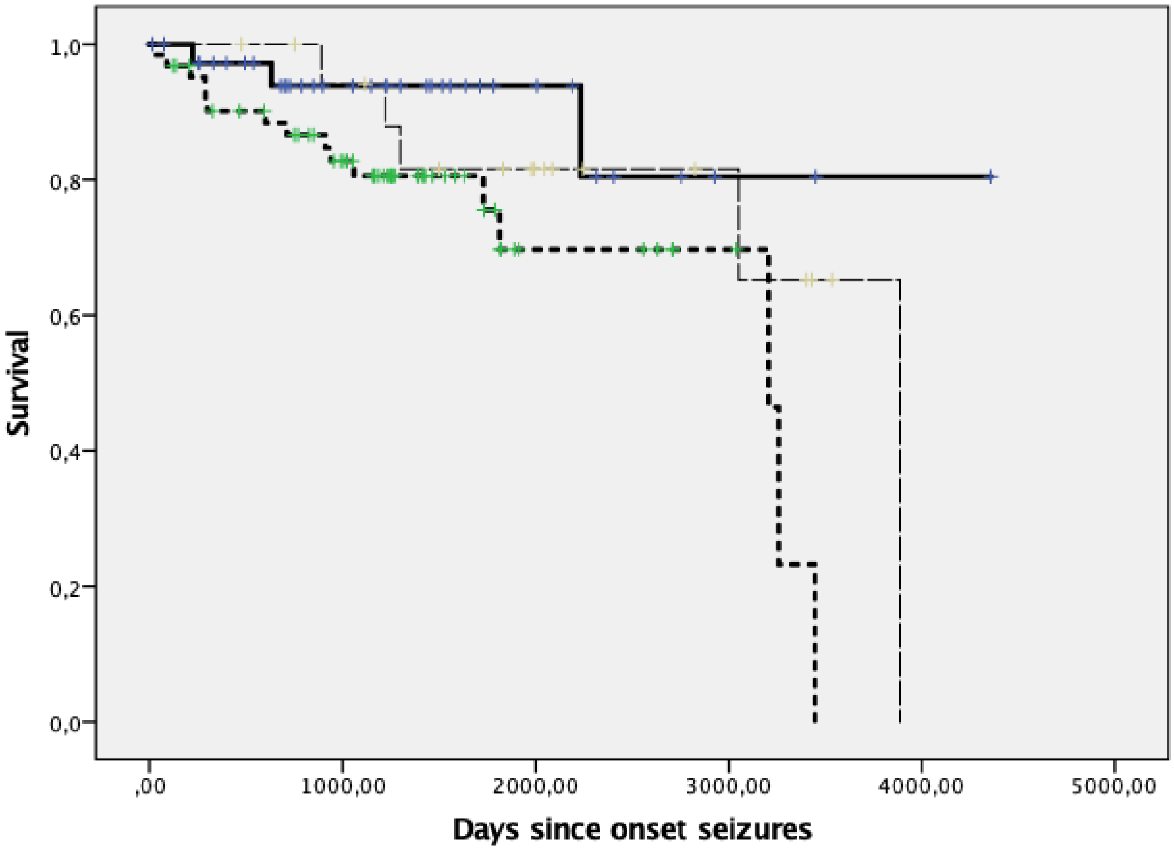

Fig. 2. Kaplan-Meier curve of 120 male dogs with idiopathic epilepsy under primary veterinary care in the UK in 2013. Solid line, group 1, intact at final record; Dotted line, group 2, neutered before onset of seizures; Dashed line, group 3, neutered after onset of seizures.

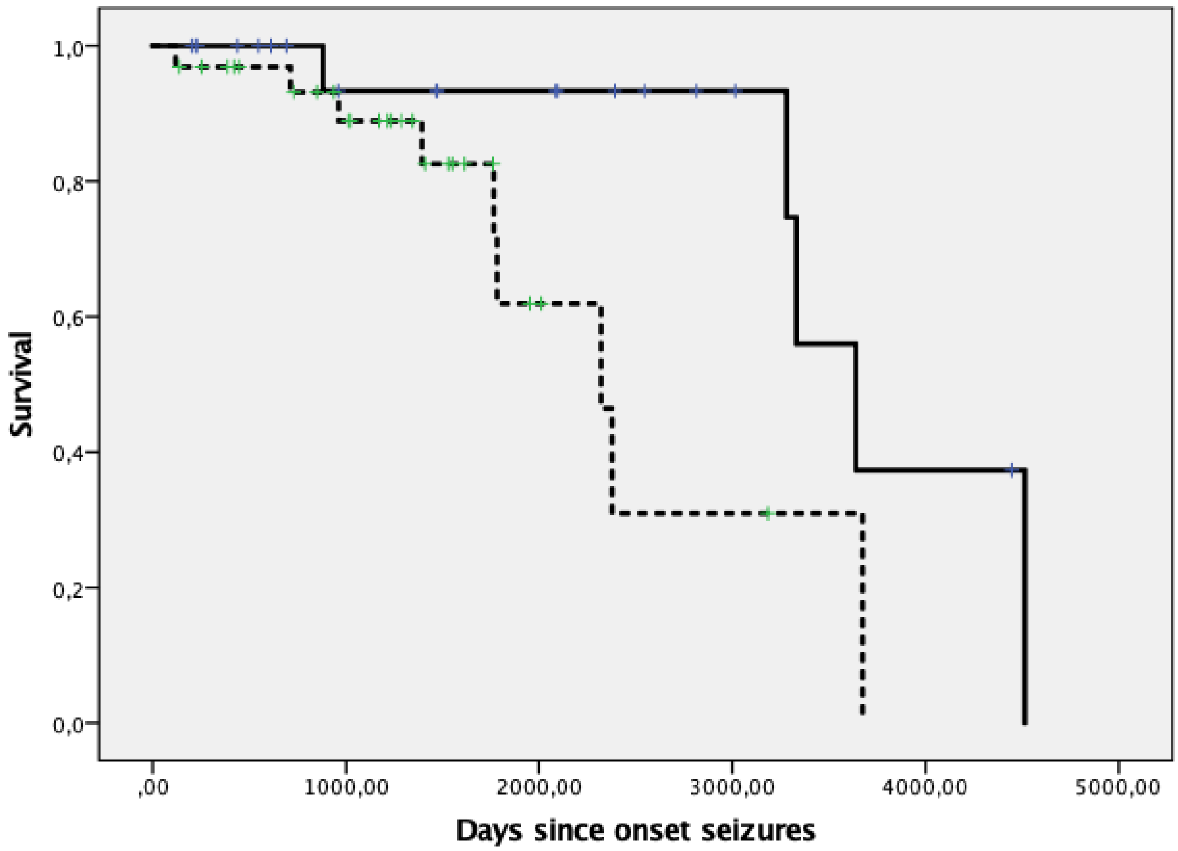

Fig. 3. Kaplan-Meier curve of 54 female dogs with idiopathic epilepsy under primary veterinary care in the UK in 2013. Solid line, group 4, intact at onset of seizures; Dotted Line, group 5, neutered before onset of seizures.

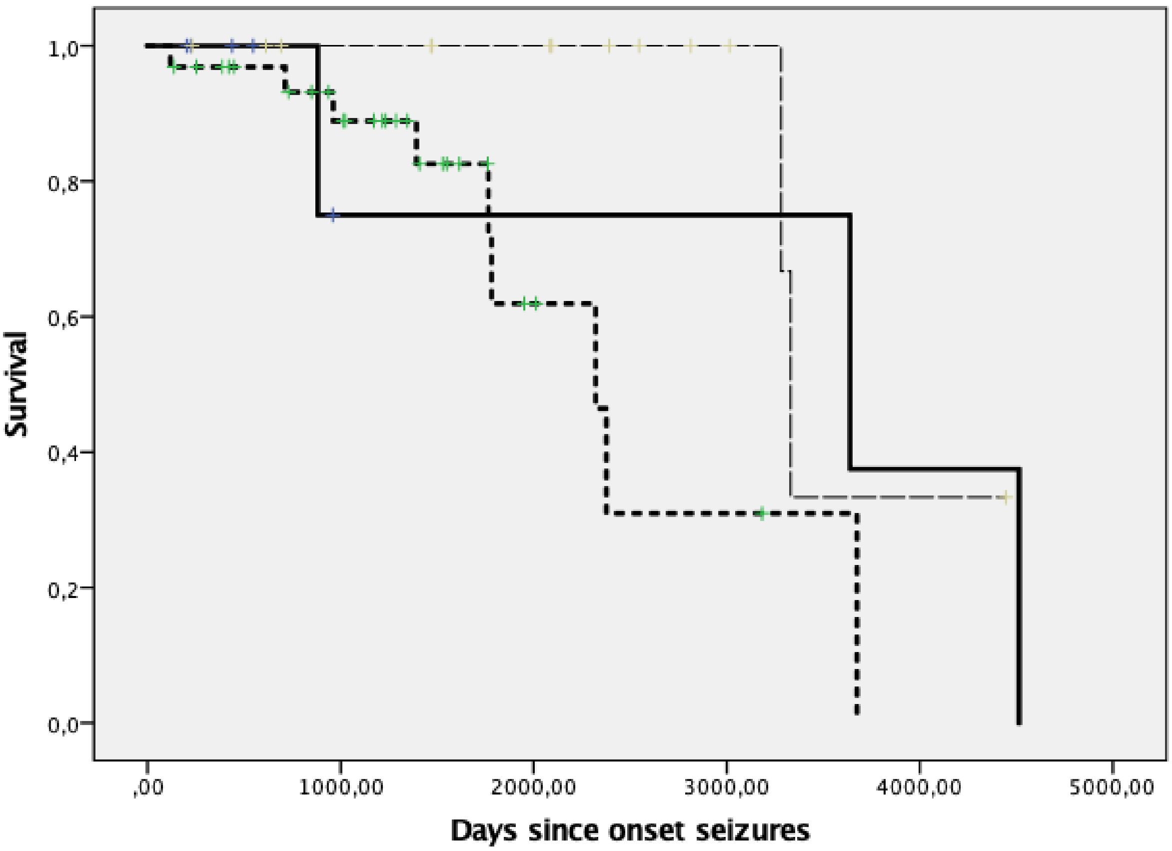

Fig. 4: Kaplan-Meier curve of 54 female dogs with idiopathic epilepsy under primary veterinary care in the UK in 2013. Solid line, group 1, intact at final record; Dotted line, group 2, neutered before onset of seizures; Dashed line, group 3, neutered after onset of seizures.