Idiopathic epilepsy in the Italian Spinone in the United Kingdom: Prevalence, Clinical Characteristics, and Predictors of Survival and Seizure Remission

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Background: There is lack of data on idiopathic epilepsy (IE) in the Italian Spinone (IS).

Objectives: To estimate the prevalence of IE in the IS in the United Kingdom (UK) and to investigate predictors of survival and seizure remission.

Animals: The target population consisted of 3331 IS born between 2000 and 2011 and registered with the UK Kennel Club (KC). The owners of 1192 dogs returned phase I questionnaire. Sixty-three IS had IE.

Methods: Population survey. The owners of all UK KC-registered IS were invited to complete the phase I questionnaire. Information from the phase I questionnaire and veterinary medical records was used to identify IS with IE and obtain data on treatment and survival. Additional information was obtained from owners of epileptic IS who completed the phase II questionnaire.

Results: The prevalence of IE in the IS in the UK was estimated as 5.3% (95% CI, 4.03–6.57%). Survival time was significantly shorter in IS euthanized because of poorly controlled IE compared with epileptic IS that died of unrelated disorders (P = 0.001). Survival was significantly longer in IS with no cluster seizures (CS) (P = 0.040) and in IS in which antiepileptic medication was initiated after the second seizure rather than after ≥3 seizures (P = 0.044). Seizure remission occurred only in 3 IS.

Conclusions and Clinical Importance: The prevalence of IE in IS (5.3%) is higher than in dogs (0.6%) in the UK. Idiopathic epilepsy in IS has a severe phenotype. Antiepileptic medication initiation after the second seizure and aggressive treatment of CS may improve survival.

Key words: Canine; Mortality; Seizures; Semiology.

Idiopathic epilepsy (IE) refers to recurrent seizures with no underlying cause other than a possible hereditary predisposition. In this context, the term “idiopathic” refers to a disorder “by itself” rather than “of unknown cause”. The underlying cause of IE is episodic hyperexcitability of cortical neurons, resulting from largely unknown cellular and molecular mechanisms. The genetic risk for IE is likely to be complex, including interaction among multiple genes and environmental factors.

Idiopathic epilepsy is the most common chronic neurologic disorder in dogs, reported at a prevalence of between 0.5 and 5% in a nonreferral population and of 1–2.6% in a referral hospital population. Breed- and country-specific prevalence of IE ranges from 1.3 to 18.3%. The proportion of epileptic dogs suffering cluster seizures (CS) and status epilepticus (SE) varies among studies and canine breeds. Survival time of dogs with IE has been reported to be significantly shorter in dogs euthanized because of IE than in dogs euthanized because of other disorders. Survival of dogs with IE can be affected by sex, age at IE onset, and occurrence of CS and SE. Remission (defined as being seizure-free with or without treatment for ≥1 year) can occur in some dogs with IE. The likelihood of remission can be affected by various factors including sex, age at IE onset, presence of CS, as well as seizure frequency and number before initiation of antiepileptic medication (AEM).

Although IE has been reported in the Italian Spinone (IS), no scientific study on IE has been conducted in this breed to date. The purpose of this study was to estimate the prevalence of IE in the IS in the United Kingdom. The study was performed at the Animal Health Trust and was supported by the Italian Spinone club of Great Britain.

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Abbreviations:
UK United Kingdom
KC Kennel Club
IE idiopathic epilepsy
IS Italian spinoni
AEM antiepileptic medication
CS cluster seizures
SE status epilepticus
MRI magnetic resonance imaging
CFSE cerebrospinal fluid

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Kingdom (UK). In addition, clinical characteristics of IE and predictors of survival and remission were investigated.

Materials and Methods

The study was designed as a population survey of owners of IS in the UK with follow-up questionnaires for IS diagnosed with IE.

Data Collection

The owners of all UK Kennel Club (KCC)-registered IS born between 1st January 2000 and 31st December 2011 were sent a letter inviting them to participate in the study. The IS club of Great Britain promoted the importance of this study for the breed. Italian Spinoni (IS) owners were asked by the UK KC to complete an initial questionnaire (phase I) to investigate if their IS had ever had a seizure, if ≥2 seizures had occurred at least 24 hours apart, date of birth, sex, age at seizure onset, interictal clinical status, information on seizure etiology based on the diagnosis of a veterinarian, and date and cause of death (for deceased dogs). The standardized questionnaire could be completed online or on paper depending on the IS owner’s preference. Written consent was sought to enable the investigators to contact the IS owners, the primary veterinarian, and the veterinary neurologist (when referral had occurred) for additional information. Participants were made aware of the importance of updating the investigators on seizure occurrence in IS that at the time of the phase I questionnaire had no seizure or only 1 seizure.

Phase I questionnaires, the primary veterinarian’s, and, when available, the veterinary neurologist’s medical records (including results of diagnostic investigations) were reviewed by the investigators. All owners of IS diagnosed with IE based on results of phase I investigation were invited to complete a phase II questionnaire containing 110 questions on various aspects of epilepsy (see “Supporting information”) including: occurrence of behavioral abnormalities at IE onset (before AEM initiation), seizure phenomenology (based on the owner’s open-ended description and several individual questions), dates on which seizures occurred (based on the owner’s seizure diary), occurrence of CS and SE, date of AEM initiation, AEMs administered, AEM-related adverse effects, and seizure remission. The part of the questionnaire investigating behavioral abnormalities and AEM-related adverse effects was developed based on previously published studies in epileptic dogs. Information on survival was updated until the time data collection ended.

Definition

Idiopathic epilepsy was defined as recurrent seizures (≥2 seizures occurring >24 hour apart) with an onset between 6 months and 6 years of age in dogs with normal interictal physical and neurologic examinations and results of a CBC and biochemistry profile within the normal reference range. Structural epilepsy was defined as recurrent seizures (≥2 seizures occurring >24 hour apart) provoked by cerebral pathology including vascular, inflammatory, infectious, traumatic, anomalous, developmental, neoplastic and degenerative diseases identified by clinical examination, diagnostic imaging, cerebrospinal fluid (CSF) analysis, or postmortem examination. Reactive seizures were defined as the reaction of a normal individual to a systemic metabolic or exogenous toxic disorder identified by clinical and diagnostic investigations. Epilepsy etiology was considered unclassified when available information was inadequate. Seizures with bilateral motor signs from their onset with or without autonomic signs and impairment or loss of consciousness were classified as generalized seizures. Lateralized or regional (eg, 1 body part) motor signs were classified as focal motor seizures. Focal motor seizures that transitioned from initial lateralized or regional involvement to bilateral involvement were defined as focal motor seizures with secondary generalization. Cluster seizures were defined as ≥1 seizure within 24 hour with full recovery of consciousness between seizures. Status epilepticus (SE) was defined as continuous seizure activity lasting ≥5 minutes or ≥2 discrete seizures within 24 hour without full recovery of consciousness in between seizures. Seizure frequency was assessed by counting seizure number per month as well as seizure days per month. Survival time was defined as the time from seizure onset until death or the end of the follow-up period. Remission was defined as seizure absence for ≥12 months before time of completion of phase II questionnaire or the IS’s death. Remission with treatment was defined as remission on current AEM and remission without treatment as remission after discontinuation of AEM.

Statistical Analysis

Survival periods measured in days from the date of the first seizure were used in survival analyses with failure defined as euthanasia directly related to IE. Italian Spinoni that were alive at the end of the follow-up period or that died as a result of disorders other than IE were censored. Kaplan-Meier survival plots and corresponding nonparametric log-rank tests for equality of survivor functions were examined initially, followed by univariable Cox’s proportional hazard regression analysis after checking that the assumption of proportional hazard across categories of each variable was not violated. In Cox’s proportional hazard regression, the risk (hazard ratio, HR) of nonsurvival for each category of binary and categorical variables relative to a baseline reference category, was estimated with corresponding 95% confidence limits. Binary and categorical variables examined included sex (male versus female), reproductive status (neutered versus intact), age at seizure onset (<3 versus ≥3 years), time from IE onset to treatment initiation (≤2 versus >2 months), number of seizures before treatment onset (≤2 versus >2), seizure frequency before treatment onset (≤2 versus >2 seizures/mo, and ≤2 versus >2 seizures/day/ mo), occurrence (yes/no) of CS and SE before AEM initiation and anytime in life, and cause of death (IE-related versus other cause). Association between the above variables (except cause of death) and seizure occurrence (yes/no) in the ≥12 months before completion of phase II questionnaire or death also was evaluated by the same methods. Optimal cut-off values for age at seizure onset, time from IE onset to treatment initiation, total number of seizures before treatment onset, and seizure frequency before treatment onset were determined based on generating ordered categories of the data and examining the relationship between these ordered exposure categories and outcome. Statistical significance was defined at \( P ≤ 0.05 \) and all data analyses were performed using Stata12.0.4

Results

Invitation to participate in the study was sent to the owners of 3331 IS in the UK. Of these, 1192 returned the phase I questionnaire (response rate, 36%). Questionnaires were returned online for 1116 (94%) IS and mailed for the remaining 76 (6%) IS. After review of the phase I questionnaires, the primary veterinarian’s, and, when available, the veterinary neurologist’s medical records, 6,455 IS; 95% CI, 4,035–6,575 IS were identified with IE (Fig 1). Of these 63 IS, 23 (37%) were examined by a veterinarian specialist in neurology, 19 (30%) underwent magnetic resonance imaging
Results of these investigations were unremarkable. Mean ± SD age at first seizure was 38 ± 17 months (median, 35 months; range, 11–72 months). Age distribution is illustrated in Figure 2. Twenty-one IS were females (15 spayed) and 42 were males (19 neutered). Median follow-up time from first seizure to study end or death was 35 months (range, 5–124 months).

The phase II questionnaire was returned for 47 (75%) IS (Fig 1). Of these, 26 (55%) were reported to develop behavioral abnormalities (most commonly associated with abnormal perception and anxiety) at epilepsy onset before initiation of AEM. The remainder of the IS were not reported to have behavioral abnormalities at epilepsy onset.

Seizure Phenomenology

Data on seizure phenomenology was available for the 47 IS whose owners completed the phase II questionnaire. All 47 IS had generalized tonic-clonic seizures with impaired consciousness and autonomic manifestations (eg, increased salivation, urination, defecation) as the most common seizure type. Rhythmic running movements of all 4 limbs (when the IS was laterally recumbent) were reported in 42 (89%) IS. Focal motor onset with secondary generalization was consistently recognized by the owners of 24 IS (51%). The owners of 11 (23%) IS did not report focal motor onset and the owners of 12 (26%) IS were not sure if the seizure had focal onset.

Preictal signs (eg, anxiety, restlessness, increased affection, contact-seeking behavior, withdrawal, hiding, aggressiveness, vocalization) were reported in 27 (57%) IS and were not observed in the remainder. The preictal phase was reported to last <30 minute in 8 IS, 30 minute to 24 hour in 11 IS and >24 hour in 6 IS. The preictal phase duration was unknown in the remaining 2 IS.

Postictal signs (eg, disorientation, aggressive behavior, restlessness, pacing, lethargy, deep sleep, hunger, thirst, ataxia, proprioceptive deficits, blindness) were reported in all 47 (100%) IS. The postictal phase commonly lasted <30 minute in 13 IS, 30 minute to 24 hour in 28 IS and >24 hour in 4 IS. The postictal phase duration was unknown in 2 IS.

Additional information on seizure phenomenology can be found as “Supporting information.”

Seizure Number, Frequency, and Occurrence of Cluster Seizures and Status Epilepticus

Data on seizure number and frequency before AEM initiation were available in 44 IS. Mean ± SD total number of seizures was 4.9 ± 2.9 (median, 4; range, 2–14 seizures). Mean ± SD number of seizures per month was 3.4 ± 3.2 (median, 1.8; range, <1–11). Mean ± SD seizure day per month was 2.6 ± 2.4 (median, 1.3; range, <1–8).

Information on occurrence of CS and SE was available for all 63 IS by combining data obtained from the phase I and II questionnaires and the veterinary medical records. Cluster seizures and SE occurred before AEM initiation in 15 (24%) and 1 (2%) IS, respectively. Cluster seizures and SE occurred anytime in life in 46 (73%) and 13 (21%) IS, respectively.

Treatment

Data on treatment were available for all 63 IS based on information extrapolated from the primary veterinarian’s medical records. Fifty-seven (90%) IS were treated with ≥1 AEM (1 AEM = 22 IS, 2 AEMs = 18 IS, 3 AEMs = 12 IS, 4 AEMs = 3 IS, 5 AEMs = 2 IS) and 6 (10%) IS did not receive AEM. Median time from IE onset to treatment initiation was 2 months (mean, 10 ± 23; range, 0.2–122). The numbers of IS administered phenobarbitone, potassium bromide, levetiracetam, imepitoin, gabapentin, topiramate, and zonisamide were 51, 39, 17, 5, 3, 2, and 1, respectively. Of the 22 IS that received monotherapy, 19, 2, and 1 were treated with phenobarbitone, potassium bromide, and imepitoin, respectively.

Antiepileptic medication-related adverse effects

Data on AEM adverse effects were obtained from the 47 IS owners who responded to the phase II questionnaire.
AEM-related adverse effects were reported in 36 (82%) of 44 IS on AEM and were noted to persist to some degree after the first 3 wks or 3 months (for potassium bromide) from AEM initiation or dose increase in 30 (83%) of 36 IS with adverse effects. The AEM-related adverse effects most commonly reported were polyphagia, polydipsia, weight gain, sedation, and ataxia. When asked if overall AEM-related adverse effects were acceptable during the 3-month preceding phase II questionnaire completion or death, 28 (64%) IS owners answered yes, 8 (18%) answered no, and 8 (18%) were not sure or did not answer.

**Survival**

Information on date and cause of death initially was obtained from the phase I questionnaire and the primary veterinarian’s medical records. In addition, to obtain the most up-to-date information on dead/alive status, the primary veterinarians were contacted at the end of data collection (ie, when review of phase II questionnaires had been completed). At this time, 28 (44%) of 63 IS with IE were dead. Of these 28 IS, 8 (29%) had died of causes unrelated to epilepsy (mean survival time, 62 ± 38 months) and 20 (71%) had been euthanized because of poorly controlled IE (mean survival time, 22 ± 17 months). Overall, IE-related mortality rate was 32% (20/63).

**Remission**

Remission was considered to have been achieved with treatment in 3 (6%) of the 47 IS whose owners returned the phase II questionnaire. Of these 3 dogs, 2 had no seizures for 1 year and had been treated with phenobarbitone only or phenobarbitone, potassium bromide, and levetiracetam, respectively. The third dog had been seizure-free for 6 years on phenobarbitone and potassium bromide. Data on seizure occurrence in the months before questionnaire completion or death in all IS are summarized in Table S1.

**Statistical Analysis**

Survival time was significantly shorter in IS that were euthanized because of IE compared with IS that died of unrelated disorders (P = 0.001; Fig 3). Survival was significantly longer in IS in which AEM was initiated after the second seizure compared with IS treated ≥3 seizures (P = 0.044; Fig 4). Survival was significantly longer in IS with no CS compared with IS that had CS anytime in life (P = 0.040; Fig 5). Although nonsignificant at P < 0.05 compared with IS with no CS or no SE anytime in life, the risk of death increased more than 4-fold in IS with CS anytime in life (HR, 4.125; 95% CI, 0.95–17.89; P = 0.058) and more than 2-fold in IS with SE anytime in life (HR, 2.302; 95% CI, 0.90–5.88; P = 0.081).

Females had longer survival than males (P = 0.041) and neutered IS survived longer than intact IS (P = 0.049). However, there was confounding between sex and neuter status because a greater proportion of females were neutered compared with males. When these variables were evaluated in a multivariable Cox regression model they were no longer associated with survival.

No significant associations were identified between survival and age at seizure onset (<3 versus ≥3 year; P = 0.450), time from IE onset to treatment initiation (≤2 versus >2 mos; P = 0.648), seizure frequency before treatment onset (≤2 versus >2 seizures/mo; P = 0.448); and ≤2 versus >2 seizure/d/mo (P = 0.930), and occurrence (yes/no) of CS before AEM (P = 0.266) and SE anytime in life (P = 0.073). Association between survival and SE before AEM was not investigated because only 1 IS had SE before AEM.

No significant association was identified between total number of seizures before treatment initiation and seizure frequency before treatment initiation. However, a
significant relationship was identified between total number of seizures before treatment initiation and time from IE onset to treatment initiation in that those animals with only 1 or 2 seizures before treatment initiation had significantly shorter time from IE onset to treatment initiation. No significant associations were identified between seizure remission (for ≥12 months) and any of the examined binary or categorical variables (0.20 < P < 1.0).

Discussion

Study Design and Idiopathic Epilepsy Prevalence Estimate

The estimated prevalence of IE in the IS (5.3%) is higher that the prevalence of probable IE in dogs (0.6%) in first opinion practice in the UK. Prevalence of IE in other canine breeds in various countries ranges from 1.3 to 18.3%. In addition, in 1 extended Bel- gian Shepherd family, the prevalence of IE has been reported to be as high as 33%. The prevalence estimate in our study could have been affected by various factors. The response rate was 36%, therefore information is based only on a proportion of the entire population. Response rates in some of the previous studies have been higher (39–57%). The KC sent 2 reminders after the initial invitation letter, and the IS club of Great Britain was very proactive in promoting participation in the study through their annual newsletter, web site, and social media. Owners were encouraged to complete the phase I questionnaire regardless of the clinical disease status of their IS. Although the invitation letter stated that information on individual dogs was confidential to the investigators only, some IS owners or breeders might not have returned the questionnaire because of unwillingness to disclose the presence of epilepsy in their dog and breeding line (ie, responder bias). People also might not have responded because of the inconvenience of filling out a questionnaire. Conversely, owners of epileptic IS might have been more inclined to participate in a study of this condition than IS owners who have no knowledge or experience with this disease.

Italian Spinoni owners were given the option to complete the questionnaire online or on paper (a prepaid addressed envelope was provided). The majority (94%) preferred the online option. Online questionnaire-based surveys are time- and cost-effective ways of conducting epidemiologic studies. Prevalence estimation was not affected by mode of response (online or by mail) in a previous survey on IE in petit basset griffon vendeen.

The estimated prevalence of IE in IS in this study also might have been affected by the lack of investigations for structural brain disease (MRI and CSF analysis) in all IS included in the IE group. This may have resulted in IS with structural epilepsy being incorrectly diagnosed with IE. However, including only IS with brain MRI and CSF analysis results would have affected prevalence estimate too by excluding IS with IE whose owners were unable to afford these investigations. Our definition of IE was consistent with that of previous studies, and median follow-up time from first seizure to study end or death was 35 months (range, 5–124 months). Follow-up was <12 months in only 6 IS (with the following follow-ups in month each: 5.4, 6.2, 6.6, 8.1, 8.4 and 9.9). Two of these 6 IS were examined by a veterinary neurology specialist and 1 of these 2 IS also underwent MRI and CSF analysis. Therefore, the possibility of misdiagnosed IE in the 63 IS in this study is likely to be low.

The prevalence may have been underestimated if the IS classified as unaffected by IE at the time of this study developed the condition later in life. The mean age at first seizure was 38 ± 17 months. Of the IS that did not experience any seizures before response to the phase I questionnaire 275 were younger than 38 months. Therefore, some of these 275 IS might have been too young to have expressed the disease at the time of investigation. To optimize the prevalence estimate, participants were asked to update the investigators on seizure occurrence in IS that at the time of phase I questionnaire had no seizure or only 1 seizure, but the period of time during which this was possible was limited to 6 months.

Clinical Characteristics

The mean age at onset of IE in the IS (3.2 years) is similar to the mean age reported in Groenendael and Tervueren Belgian shepherds (3.3 years) and in Dalmatians (3.2 years). A younger age at IE onset has been reported in several other breeds. The relatively late onset of IE in IS makes determining its prevalence challenging because IS may be bred before developing IE.

Consistent with the majority of studies on IE in dogs, males were over-represented. No explanation for this difference in IE prevalence between sexes has been identified and further research is needed to investigate the effects of sex hormones on seizures in dogs.
Behavioral abnormalities consistent with fear or anxiety, defensive aggression, and abnormal perception have been reported in AEM-naive dogs at the onset of IE.16 Part of the phase II questionnaire was designed to investigate occurrence of these neurobehavioral comorbidities in IS. Fifty-five percent of IS developed behavioral abnormalities (most commonly associated with abnormal perception and anxiety) at IE onset before initiation of AEM. This finding further demonstrates that neurobehavioral comorbidities can occur in dogs with IE, similar to what is described in humans.34 Neurobehavioral comorbidities can have an adverse effect on the course and quality of life and therefore should be recognized and if possible treated or at least mitigated.

Similar to what has been reported in other canine breeds,3,11,12,14,15,31 focal motor onset seizures with secondary generalization were the most common seizure type in IS.

Preictal signs were reported by the owners of 57% IS and lasted >30 minute in 63% of IS with preictal signs. Recognition of the clinical manifestations that consistently precede a seizure represents a therapeutic opportunity for intermittent pulsed treatment with short-acting AEM such as levitiracetam or benzodiazepines. This approach may prevent seizure occurrence, or at least decrease seizure severity and duration.

Cluster seizures and SE occurred in a higher proportion of IS than in dogs of various breeds in recent UK studies.20,22 Of the breed-specific studies, only Border Collies have been reported to have a higher prevalence of CS (94%) and SE (53%),18 and Australian Shepherds a higher prevalence of SE (60%).21

Survival

Idiopathic epilepsy-related mortality rate in the IS in this study was 32%, higher than previously reported in numerous canine breeds (13–28%).12,14,19,21,23 Only in the Border Collie (35%) and Irish Wolfhound (52%) was IE-related mortality rate higher than in the IS.13,18 However, care should be taken when comparing these studies given differences in study design. Only our study and the studies by Berendt12 and Gulllov19 were population surveys with the target population being all dogs of a specific breed registered with the national KC over a period of several years. Similarly to previous studies in other canine breeds,12,18,23 survival time was significantly shorter in IS with IE euthanized because of IE rather than because of other disorders.

Of the numerous variables examined as predictors of survival, only AEM initiation after ≥3 seizures and occurrence of CS anytime in life were associated with poorer survival in IS. A statistically significant association between occurrence of CS and poorer survival has been identified in other canine breeds with IE.20,24 Although a significant relationship was identified between total number of seizures before treatment initiation and time from IE onset to treatment initiation, this latter variable was not associated with survival.

Similar to previous studies including both pure-breed and cross-breed dogs,23,26 no statistically significant association was identified between age at IE onset and survival in the IS. However, studies in the Border Collie and Australian Shepherd have shown significantly decreased survival time in dogs with onset of IE before the age of 2 years, which was nearly the median age at seizure onset in these breeds.18,21 The study in Australian Shepherds also showed as association between shorter survival and a high initial seizure frequency (≥10 seizure days in the first 6 months of IE).23

Remission

One important outcome variable of epilepsy studies is remission, both spontaneous or AEM-induced. Remission of epilepsy has been reported in several studies, ranging between 12 and 24% of the investigated first opinion or referral, single- or multiple-breed canine populations.11,18,19,21–24,27 In these studies, remission was defined as freedom from seizures, either or without treatment for ≥1 year.18,21 ≥2 years,11 or ≥3 years.23,24 In this study, only 3 (6%) IS were seizure-free for ≥1 year. The lower remission rate in IS compared with that of other breeds may be a consequence of a more severe IE phenotype and decreased AEM responsiveness in IS compared with other canine breeds. However, AEM response also may have been affected by suboptimal use of AEM.23 Due to the high proportion of IS included in our study had been referred to a veterinary neurology specialist, whereas all dogs included in some previous studies were treated at referral centers where AEMs were individualized and optimized based on therapeutic monitoring.18,21,22,24 Therefore, a higher proportion of IS might go into remission or at least have a better outcome than detected in this study if AEM is individualized and optimized by a veterinary neurology specialist.

In our study, as well as in a previous study in Australian Shepherds,21 no statistically significant predictors of remission could be identified, yet likely because of low statistical power. A recent study in a multiple-breed referral canine population showed that dogs that did not achieve remission were more likely to be male and to have previously experienced CS.22 In a study in Border Collies with IE, seizure frequency during the initial 6 months of IE was significantly lower in dogs in remission compared with dogs with ≥1 seizures in the year preceding death or study end.18 Similarly, a high seizure frequency and a higher number of seizures before AEM or in the first 6 months after AEM initiation have been associated with decreased likelihood of remission in people.35,36

In conclusion, this study shows that the prevalence of IE in the IS is higher than in the general canine population in the UK. Idiopathic epilepsy in IS frequently has a severe phenotype, high mortality rate and low remission rate. Initiation of AEM after the second seizure and prevention or aggressive treatment of CS may improve survival. Investigation of the genetic component of IE in IS currently is ongoing.
Footnote

* StataCorp, 4905 Lakeway Drive, College Station, TX.

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Conflict of Interest Declaration: Authors disclose no conflict of interest.

Off-label Antimicrobial Declaration: Authors declare no off-label use of antimicrobials.

References

1. Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised classification of epilepsies and epileptic syndromes. Epilepsia 1989;30:389–399.
2. Jeffery ND. Canine epilepsy: in search of a fitting end. Vet J 2014;199:311–312.
3. Ekenstedt KJ, Oberbauer AM. Inherited epilepsy in dogs. Top Companion Anim Med 2013;28:51–58.
4. Schwartz-Porsche D. Epidemiological, clinical and pharmacokinetic studies in spontaneously epileptic dogs and cats. ACVIM 1986;4(II):1161–1163.
5. Podell M, Fenner WR, Powers JD. Seizure classification in dogs from a nonreferral-based population. J Am Vet Med Assoc 1995;206:1721–1728.
6. Fuchmann G, Doerr MG, Jaggy A. Canine neurological diseases in a referral hospital population between 1989 and 2000 in Switzerland. J Small Anim Pract 2006;47:582–587.
7. Bellumori TP, Famula TR, Bannasch DL, et al. Prevalence of inherited disorders among mixed-breed and purebred dogs: 27,254 cases (1995–2012). J Vet Intern Med 2014;28:1782–1789.
8. Hallum TR, Famula TR, Bannasch DL, et al. Prevalence and characteristics of epilepsy in the Belgian Shepherd variants: prevalence, semiology, and selected risk factors. J Vet Intern Med 2012;26:1115–1120.
9. Monteiro R, Adams V, Keys D, Platt SR. Canine idiopathic epilepsy: prevalence, risk factors and outcome associated with cluster seizures and status epilepticus. J Small Anim Pract 2012;53:526–530.
10. Weisz J, Hulsmeier V, Brauer C, et al. Disease progression and treatment response of idiopathic epilepsy in Australian Shepherd dogs. J Vet Intern Med 2012;26:116–125.
11. Packer RM, Shihab NK, Torres BB, Volk HA. Clinical risk factors associated with anti-epileptic drug responsiveness in canine epilepsy. PLoS ONE 2014;9:e106026.
12. Berendt M, Gredal H, Erbsoll AK, Alving J. Premature death, risk factors, and life patterns in dogs with epilepsy. J Vet Intern Med 2007;21:754–759.
13. Fredso N, Koch BC, Toft N, Berendt M. Risk factors for survival in a university hospital population of dogs with epilepsy. J Vet Intern Med 2014;28:1782–1788.
14. Saito M, Muhana KR, Sharp NJ, Olby NJ. Risk factors for development of status epilepticus in dogs with idiopathic epilepsy and effects of status epilepticus on outcome and survival time: 32 cases (1990–1996). J Am Vet Med Assoc 2001;219:618–623.
15. Arrol L, Penderis J, Garosi L, et al. Aetiology and long term outcome of juvenile epilepsy in 136 dogs. Vet Rec 2012;170:335.
16. Proschowsky HF, Rugbjerg H, Erbsoll AK. Mortality of purebred and mixed-breed dogs in Denmark. Prev Vet Med 2003;58:63–74.
17. Short AD, Dunne A, Lohi H, et al. Characteristics of epileptic episodes in UK dog breeds: an epidemiological approach. Vet Rec 2011;169:48.
18. Wessmann A, Volk HA, Parkin T, et al. Evaluation of quality of life in dogs with idiopathic epilepsy. J Vet Intern Med 2012;28:510–514.
19. Berendt M, Gullov CH, Fredholm M. Focal epilepsy in the Belgian shepherd: evidence for simple Mendelian inheritance. J Small Anim Pract 2009;50:655–661.
20. Licht BG, Licht MH, Harper KM, et al. Clinical presentations of naturally occurring canine seizures: similarities to human seizures. Epilepsy Behav 2002;3:460–470.
21. Heynold Y, Faisdler S, Steffen F, Jaggy A. Clinical, epidemiological and treatment results of idiopathic epilepsy in 54 Labrador Retrievers: a long-term study. J Small Anim Pract 1997;38:7–14.
22. Van Meerenva SA, Volk HA, Matiasek K, Van Ham LM. The influence of sex hormones on seizures in dogs and humans. Vet J 2014;201:15–20.
23. Lin JJ, Mula M, Hermann BP. Uncovering the neurobehavioural comorbidities of epilepsy over the lifespan. Lancet 2012;380:1180–1192.
24. Mohanraj R, Brodie MJ. Early predictors of outcome in newly diagnosed epilepsy. Seizure 2013;22:333–344.
25. Abimbola S, Martinuk AL, Hackett ML, et al. Early predictors of remission in newly diagnosed epilepsy: a systematic approach to reviewing prognostic factor studies. J Neurol Res 2014;36:1–12.
Supporting Information

Additional Supporting Information may be found online in Supporting Information:

Data S1. Additional information on seizure phenomenology and etiology in the Italian Spinoni included in this study and the Phase II questionnaire.

Table S1. Seizure occurrence in 47 Italian Spinoni with idiopathic epilepsy (phase II responders) before questionnaire completion or death.