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A cohort study of epilepsy among 665,000 insured dogs: Incidence, mortality and survival after diagnosis

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ABSTRACT

The main objective of this study was to estimate the incidence and mortality rates of epilepsy in a large population of insured dogs and to evaluate the importance of a variety of risk factors. Survival time after a diagnosis of epilepsy was also investigated. The Swedish animal insurance database used in this study has previously been helpful in canine epidemiological investigations. More than 2,000,000 dog-years at-risk (DYAR) were available in the insurance database.

In total, 5013 dogs had at least one veterinary care claim for epilepsy, and 2327 dogs were euthanased or died because of epilepsy. Based on veterinary care claims the incidence rate of epilepsy (including both idiopathic and symptomatic cases) was estimated to be 18 per 10,000 DYAR. Dogs were followed up until they were 10 (for life insurance claims) or 12 years of age (veterinary care claims). Among the 35 most common breeds in Sweden, the Boxer was at the highest risk of epilepsy with 60.3 cases per 10,000 DYAR, and also had the highest mortality rate of 46.7 per 10,000 DYAR (based on life insurance claims). Overall, males were at a higher risk than females (1.4:1). Median survival time (including euthanasia and death) after diagnosis was 1.5 years. In general, breeds kept solely for companionship lived longer after diagnosis than those kept for dual-purposes, such as hunting and shepherd and working breeds. The study demonstrates marked breed differences in incidence and mortality rates, which are assumed to reflect genetic predisposition to epilepsy.

Introduction

Epilepsy is characterised by repeated seizures originating from the brain and categorised according to aetiology. Idiopathic epilepsy (IE) refers to seizures for which no morphological brain abnormalities can be identified, and is associated with a possible genetic aetiology, whereas symptomatic epilepsy (SE) refers to seizures caused by an identifiable structural lesion in the brain (Chandler, 2006).

The prevalence of epilepsy was estimated to be ~1–2% in a hospital-based population in Germany (Schwartz-Porsche, 1994), but was higher for breeds exhibiting breed-specific genetic epilepsy (Berendt et al., 2002, 2008; Casal et al., 2006; Gulløv et al., 2011). Breed-related IE has been described in a number of dog breeds, including the Labrador retriever, Belgian shepherd, Boxer, Hungarian Vizsla, English springer spaniel, Irish wolfhound and Border collie (Famula et al., 1997; Jaggy et al., 1998; Nielen et al., 2001; Patterson et al., 2003, 2005; Casal et al., 2006; Berendt et al., 2009; Hülsmeyer et al., 2010). Dogs with epilepsy are reported to have an increased risk of premature death, most commonly by euthanasia, if seizures cannot be controlled (Saito et al., 2001; Proschowsky et al., 2003; Berendt et al., 2007; Arrol et al., 2012; Monteiro et al., 2012).

Although it is a common neurological condition, no epidemiological studies of epilepsy have been conducted in large cohorts of different dog breeds, and the general incidence (and prevalence) of epilepsy is therefore unknown. Databases of insurance claims records allow for retrospective cohort studies and are commonly used in human and veterinary epidemiology (Egenvall et al., 1999; Christensen et al., 2007). The Swedish dog population is unique in that a large proportion of the animals is covered by an insurance plan. A current estimate shows that Agria[1] covers approximately 50% of the insured dogs, thereby representing 40% of the Swedish dog population (M. Berglin, personal communication, 2012).

It has previously been shown that the dog population insured by the main Swedish insurance company for companion animals, Agria, is similar to the general population of dogs in Sweden (Egenvall

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[1] See: www.agria.se.

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et al., 1999). Furthermore, the accuracy of the general diagnostic information in the Agria insurance database was considered adequate when validated against randomly selected medical records (Egenvall et al., 1998). A validation study regarding canine epilepsy was performed for a representative sample of the Agria insurance database; insurance claims for the diagnosis were compared to diagnostic information in practice records and showed a positive predictive value (the proportion of recorded cases that actually had epilepsy) of 71% (Heske et al., 2014). It was therefore concluded that this database could be used for epidemiological studies on epilepsy in dogs.

The aim of the present study was to estimate the incidence as cases per 10,000 dog-years at-risk (DYAR) and mortality rates (deaths/10,000 DYAR) of epilepsy in a large population of insured dogs, and to evaluate the importance of breed, sex, age and region as risk factors for the condition. The secondary objective was to estimate the expected survival time after a diagnosis of epilepsy among life-insured dogs, and to assess the same potential risk factors for euthanasia or death.

Materials and methods

Insurance process

During the study period (1995–2006) Agria offered two main insurance plans for dogs. One was a veterinary care insurance plan, for which the cost of veterinary treatment exceeding the deductible was reimbursed in case of disease. The other was a life insurance plan where the owner would reimbursed the monetary value of the dog if it died or was euthanased because of disease or accident. Most dogs were insured as puppies, but dogs could enter the program up to the age of 6 years (Egenvall et al., 2000).

Study population and variables

Insurance claims files for the years 1995–2006 were selected and dogs covered for either veterinary care or life insurance during this period were included in the analysis. Dogs were followed up to 10 years of age for life insurance claims, and up to 12 years of age for veterinary care claims. Data regarding breed, sex, date of birth, date of death, date of entry into the database, date of exit, reason for exiting the database, dates of insurance claims for disease, diagnostic codes for each claim, postal code and type of insurance were retrieved from the claims files.

Breeds were classified according to the FCI (Fédération Cynologique Internationale) breed classification system and some breeds (e.g. miniature and medium-size poodles) were combined in the analysis (Bonnett et al., 1997). Diagnostic codes were assigned by the attending veterinarian, based on a standardised system including about 8000 diagnoses (Swedish Animal Hospital Association, 1993). In this system two codes are associated with epilepsy and were analysed together, namely, idiopathic epilepsy and epileptic convulsions (also including SE cases). Using dog-owners' postal codes, addresses within the three main cities were coded as urban and the remaining areas as rural. Sweden was divided into three regions, North, Central and South, resulting in five geographic regions, namely, South Urban, South Rural, Central Urban, Central Rural and North Rural (there are no large cities in the Northern region).

Survival analysis was performed in a subset of dogs <10 years of age with both veterinary care and life insurance, and with a veterinary care claim for epilepsy. The dogs were followed from the date of epilepsy diagnosis until the date of death or censoring either because of exit from the database or reaching the end of the study-period (31 December 2006). The endpoint of interest was death for any reason (including epilepsy). For each dog, the explanatory variables age at diagnosis, sex, breed, and region were obtained from the insurance database. Dogs that died or were euthanased the same day as their initial veterinary care claim for epilepsy were not included, because the aim was to provide an estimate of expected survival.

Statistical analysis

Data were handled and analysed in SAS (SAS Institute). An epilepsy-case was defined as a dog for which there had been at least one reimbursed veterinary care claim with a diagnosis of epilepsy (veterinary care case) or a life insurance claim with this diagnosis (life insurance case); only the first claim for epilepsy was counted for each dog in each analysis. The DYAR were counted from the first insurance date until exiting the database because of (1) terminating the insurance (e.g. death), (2) becoming a case, or (3) reaching the end of the study period. Age distributions of the respective case-types were calculated.

Rates were calculated separately for veterinary care (incidence rates [IRs]) and life insurance claims (mortality rates [MRs]). Rates were calculated for the entire study population, and stratified by breed, sex and geographical region. The rates were multiplied by 10,000 to obtain the number of cases of epilepsy per 10,000 DYAR. Table 1 shows the details of number of cases per dog-years at risk divided into categories of sex and regions for veterinary care claims and life insurance claims. Breed-specific rates were presented in Tables 2 and 3 for the 35 most common breeds (breeds accounting for most DYAR) in the veterinary care and life insurance databases, respectively. Models were built using backwards manual elimination of variables with $P > 0.05$.

The survival analysis was performed in STATA (StataCorp). Kaplan–Meier curves were produced by breed if the number of cases in the breed was ≥80. A Cox proportional hazards model with a shared frailty effect for breed was developed to evaluate the effect of the potential risk factors (age at diagnosis, sex, region and breed) on survival after a diagnosis of epilepsy. The assumption of proportional hazards was assessed using Schoenfeld residuals as described by Dohoo et al. (2009) and, if violated, an interaction with time was included in the model. The cut-off for statistical significance was set to $P \leq 0.05$.

Results

Study population and cases

The veterinary care study population included 665,249 dogs accounting for 2,792,352 DYAR. In total, 5013 (0.75%) dogs (2921 males

Table 1
Incidence/mortality rates for epilepsy per 10,000 dog-years at risk (DYAR) for veterinary care and life insurance in a population of Swedish dogs insured during 1995–2006. The age distribution of the cases is shown, and the population subdivided into categories of sex and Swedish geographical regions.

Veterinary care insurance			Incidence			Age of cases		Percentiles	
Category	DYAR	Cases	Rate	95% CI		Mean	SD	5	95
All	2,780,690	5013	18	18	19	5.5	3.1	0.9	10.9
Male	1,367,875	2921	21	21	22	5.3	3.1	0.9	10.8
Female	1,412,815	2092	15	14	15	5.7	3.1	1.0	11.0
Middle rural	889,764	1494	17	16	18	5.4	3.1	0.9	10.7
Middle urban	375,956	963	26	24	27	5.9	3.2	1.1	11.2
North rural	306,536	288	9	8	10	5.0	3.1	0.7	10.4
South urban	318,906	713	22	21	24	5.6	3.1	1.0	10.9
South rural	889,528	1555	17	17	18	5.3	3.1	0.9	10.9
Life insurance			**Mortality**			**Age of cases**		**Percentiles**	
Category	**DYAR**	**Cases**	**Rate**	**95% CI**		**Mean**	**SD**	**5**	**95**
All	2,045,650	2327	11	11	12	5.2	2.8	1.0	9.5
Male	1,016,307	1368	13	13	14	5.0	2.7	1.0	9.4
Female	1,029,343	959	9	9	10	5.5	2.8	1.0	9.6
Middle rural	662,527	760	11	11	12	5.3	2.7	1.1	9.5
Middle urban	259,685	254	9	9	11	5.5	2.8	1.1	9.7
North rural	252,204	345	12	12	15	4.8	2.7	0.6	9.4
South urban	216,451	218	9	9	11	5.4	2.8	1.0	9.6
South rural	654,784	750	11	11	12	5.2	2.8	0.9	9.4

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Table 2
Incidence rate for epilepsy per 10,000 dog-years at risk (DYAR) for veterinary care by breed, in a population of dogs insured during 1995–2006. The 35 breeds with most dog-years at risk (DYAR) in veterinary care during the study period are shown and ranking is by the incidence rate.

Breed	Cases	DYAR	Incidence rate		
			Rate	95% CI	
Boxer	115	19,070	60.3	49.3	71.3
Border terrier	107	28,798	37.2	30.1	44.2
Cavalier King Charles spaniel	173	55,637	31.1	26.5	35.7
Labrador retriever	399	136,189	29.3	26.4	32.2
Poodle, medium and miniature	161	58,558	27.5	23.3	31.7
Yorkshire terrier	54	21,280	25.4	18.6	32.1
Rottweiler	98	40,321	24.3	19.5	29.1
Papillon	66	28,203	23.4	17.8	29.0
Miniature schnauzer	63	28,064	22.5	16.9	28.0
Beagle	47	20,791	22.6	16.1	29.1
Bernese mountain dog	39	18,636	20.9	14.4	27.5
Standard poodle	52	24,909	20.9	15.2	26.6
Border collie	116	58,098	20.0	16.3	23.6
Shetland sheepdog	75	38,246	19.6	15.2	24.0
Flat-coated retriever	65	33,823	19.2	14.6	23.9
Golden retriever	279	156,149	17.9	15.8	20.0
German pointer, smooth- and wirehaired	50	28,183	17.7	12.8	22.7
English springer spaniel	104	60,013	17.3	14.0	20.7
Collie longhaired	70	41,045	17.1	13.1	21.0
Swedish elkhound	79	48,036	16.5	12.8	20.1
Mongrel	557	346,732	16.1	14.7	17.4
Hamilton hound	54	35,968	15.0	11.0	19.0
Bichon frisé	38	26,697	14.2	9.7	18.8
Jack Russell terrier	59	43,502	13.6	10.1	17.0
Cairn terrier	45	35,965	12.5	8.9	16.2
English cocker spaniel	51	42,546	12.0	8.7	15.3
Dachshund, normal size, not longhaired	186	161,321	11.5	9.9	13.2
German shepherd dog	212	189,540	11.2	9.7	12.7
West Highland white terrier	26	24,079	10.8	6.7	14.9
Soft-coated wheaten terrier	22	24,386	9.0	5.3	12.8
Drever	50	55,654	9.0	6.5	11.5
Shih Tzu	16	19,170	8.4	4.3	12.4
Bearded collie	20	24,005	8.3	4.7	12.0
Finnish hound	15	19,192	7.8	3.9	11.8
Norwegian elkhound, grey	17	40,839	4.2	2.2	6.1

and 2092 females; 1.4:1) had at least one veterinary care claim for epilepsy. The life insurance study population included 549,197 dogs accounting for 2,046,650 DYAR. In total, 2327 dogs (0.42%) (1368 males and 959 females; 1.4:1) were euthanased or died because of epilepsy.

Incidence and age, breed, sex and region

Table 1 shows IRs and MRs for all dogs, by sex and region, including the age distribution of the cases. The mean age at the first veterinary care insurance claim was 5.5 (SD 3.1) years, whereas the mean age for life insurance claims was 5.2 (SD 2.8) years. The IR and MR of epilepsy were estimated to be 18 and 11 per 10,000 DYAR, respectively. Among the 35 most common breeds for a veterinary care-claim, the Boxer had the highest rate, with 60.3 cases per 10,000 DYAR. The Boxer was also found to have the highest MR associated with epilepsy among the 35 most common dog breeds, with a MR of 46.7 per 10,000 DYAR (Table 3). Incidence and mortality rates for all breeds in the dataset are presented in the breed table (see Appendix: Supplementary data).

Survival after diagnosis

The subset of dogs with both veterinary care and life insurance, and with a veterinary care claim for epilepsy between 1995 and 2006, included 3655 dogs. Of these, 1543 dogs died or were euthanased. During the study period, 978 (63.4%) died of epilepsy (i.e. had a life insurance claim for this diagnosis), and 565 (36.6%) died for other reasons.

In the survival analysis, 110 dogs were excluded because they had a life insurance claim for epilepsy on the same day as the first veterinary care claim, and hence the survival time after diagnosis was 0. The dataset for analysis therefore comprised 3545 dogs, of which 1436 died during the study-period. The median survival time after diagnosis was 1.5 years (range, 1 day to 9.2 years). Overall, 197 different breeds were represented in the dataset.

Fig. 1 shows the Kaplan–Meier plot of the probability of survival after an epilepsy diagnosis by breed for the 11 breeds represented by ≥80 cases. The final Cox proportional hazards model is presented in Table 4. Evaluation of the Schoenfeld residuals revealed that the assumption of proportional hazards was violated for the variable of age at diagnosis. A statistically significant interaction term between age at diagnosis and time was therefore included in the model. The final model also included a highly significant shared frailty effect for breed (likelihood ratio test: $P < 0.001$), as well as a significant effect of sex on the survival after a diagnosis of epilepsy (HR = 0.87; $P = 0.02$) indicating that females lived longer than males after an epilepsy diagnosis. Dogs living in the North region had a 22% higher hazard of death after an epilepsy diagnosis. For each year after the time of diagnosis, the hazard of dying increased by 6%. However, the higher the age at the time of diagnosis,

Table 3
Mortality rate for epilepsy per 10,000 dog-years at risk (DYAR) by breed, in a population of life-insured dogs insured during 1995–2006. The 35 breeds with most dog-years at risk (DYAR) in life insurance during the study period are shown and ranking is by the mortality rate.

Breed	Deaths	DYAR	Mortality rate		
			Rate	95% CI	
Boxer	70	14,979	46.7	35.8	57.7
Hamilton hound	79	31,679	24.9	19.4	30.4
Swedish elkhound	98	44,085	22.2	17.8	26.6
Rottweiler	71	32,962	21.5	16.5	26.6
Border collie	96	44,682	21.5	17.2	25.8
Beagle	30	17,220	17.4	11.2	23.7
Finnish hound	30	17,943	16.7	10.7	22.7
German pointer, smooth- and wirehaired	35	22,931	15.3	10.2	20.3
Papillon	27	19,118	14.1	8.8	19.5
English springer spaniel	61	46,668	13.1	9.8	16.4
Cavalier King Charles spaniel	56	44,352	12.6	9.3	15.9
Golden retriever	137	116,194	11.8	9.8	13.8
Bernese mountain dog	19	16,241	11.7	6.4	17.0
Drever	57	51,137	11.1	8.3	14.0
Shetland sheepdog	31	28,012	11.1	7.2	15.0
Wachtelhund (German spaniel)	16	15,168	10.5	5.4	15.7
Border terrier	23	22,620	10.2	6.0	14.3
Flat-coated retriever	27	27,342	9.9	6.2	13.6
English cocker spaniel	29	30,604	9.5	6.0	12.9
Mongrel	143	157,404	9.1	7.6	10.6
Collie longhaired	27	29,789	9.1	5.6	12.5
Labrador retriever	89	102,994	8.6	6.8	10.4
German shepherd dog	123	147,354	8.3	6.9	9.8
Yorkshire terrier	12	14,600	8.2	3.6	12.9
Miniature schnauzer	16	20,312	7.9	4.0	11.7
Poodle, medium and miniature	28	41,039	6.8	4.3	9.4
West Highland white terrier	11	17,830	6.2	2.5	9.8
Standard poodle	10	18,944	5.3	2.0	8.6
Cairn terrier	13	261,120	5.0	2.3	7.7
Jack Russell terrier	14	29,420	4.8	2.3	7.3
Bearded collie	7	17,546	4.0	1.0	6.9
Norwegian elkhound, grey	13	35,885	3.6	1.7	5.6
Bichon frisé	7	20,204	3.5	0.9	6.0
Dachshund, normal size, not longhaired	40	124,713	3.2	2.2	4.2
Soft-coated wheaten terrier	6	19,848	3.0	0.6	5.4

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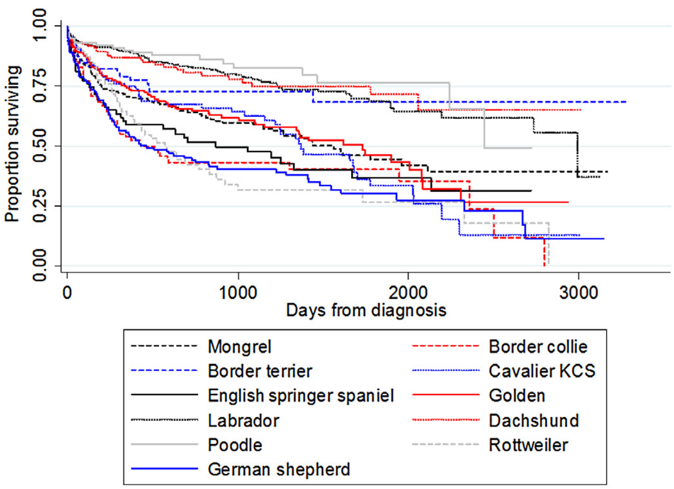

Fig. 1. The Kaplan–Meier plot of the probability of survival after a diagnosis of epilepsy by breed, for the 11 breeds represented with 80 or more cases.

the more the hazard of dying increased with time, because of the significant interaction between age at diagnosis and time.

Discussion

In this study on data from Sweden, the estimated incidence rate of epilepsy (including both idiopathic and symptomatic epilepsy cases) among the insured dogs was 18 cases per 10,000 DYAR, indicating that if 10,000 dogs were followed for 1 year, 18 would have at least one veterinary care claim for epilepsy. The proportion of insured dogs with a recorded claim for epilepsy (prevalence estimate) was 0.75%. This estimate is low compared to the commonly cited publication by Schwartz-Porsche (1994), in which the prevalence of epilepsy was calculated to be 1–2%. The reason for this discrepancy might be that Schwartz-Porsche (1994) studied a hospital-based referral population. Epidemiological studies conducted in Denmark in specific breeds have also reported higher prevalence estimates than those in the general population of dogs we report on here, with 8.9% (Petit Basset Griffon Vendeen), 9.5% (Belgian shepherds; Groenendael and Tervueren) and 3.1% (Labrador retriever) (Berendt et al., 2002, 2008; Gulløv et al., 2011). These higher breed-specific prevalence estimates are thought to reflect genetic influences within specific affected breeds.

An overall male predominance for epilepsy was found in our study, which is in agreement with previous reports showing a significant male predisposition for IE (Bielfelt et al., 1971; Falco et al., 1974; Wallace, 1975; Kathmann et al., 1999; Casal et al., 2006; Short et al., 2011).

IRs for different breeds varied extensively. Previous studies have suggested or reported inherited IE in many breeds such as the Labrador retriever, Belgian shepherd, Boxer, English springer spaniel, Irish wolfhound, Standard poodle, Border collie and Lagotto (Famula et al., 1997; Jaggy et al., 1998; Nielen et al., 2001; Patterson et al., 2005; Casal et al., 2006; Jokinen et al., 2007; Licht et al., 2007; Berendt et al., 2009; Hülsmeyer et al., 2010; Ekenstedt et al., 2012). Some of these breeds were also found to have an increased risk of epilepsy in our study, including the Boxer, the Labrador, and the Belgian shepherds which all had IRs significantly above the mean, based on non-overlapping 95% CI (mean IR 18, 95% CI 18–19) (see Appendix, supplementary data). Intra-breed differences in genotype between countries or continents are possible, and might explain differences in incidence between the Agria (Swedish) database and that in other countries.

A comparison of veterinary care (Table 2) with life insurance (Table 3) claims reveals an interesting pattern. Typical dual-purpose breeds (having characteristics that serve two purposes, such as hunting and pet dog) have most life insurance claims, whereas some typical pet dog breeds have a high rate of veterinary care claims. This indicates that pet breeds are more likely to be treated for their epilepsy, while dual-purpose breeds are more likely to die or be euthanased. This discrepancy is likely to reflect the owners' requirements and acceptance for keeping a working dog with a chronic disease. It is also possible that some of the working, hunting and shepherd breeds are more at risk of developing refractory epilepsy as has been described in the Border collie (Hülsmeyer et al., 2010).

The median survival time after a diagnosis of epilepsy was 1.5 years. The possibility that the purpose of the dog might influence the survival-time can be observed in the Kaplan–Meier plot (Fig. 1). For the 11 breeds analysed in this way, survival after diagnosis varied extensively. In general, breeds simply kept as companions lived longer than those used for dual-purposes – such as hunting, shepherd and working breeds. The breed effect on survival was highly significant (as was seen by the shared frailty effect for breed) and could be useful information for clinicians. Females lived longer than males after a diagnosis of epilepsy. Older age at the time of diagnosis also influenced survival. Dogs diagnosed with epilepsy at a more advanced age had a shorter survival time after diagnosis than those diagnosed at a younger age.

When looking at the geographical distribution in Table 1, there are also noticeable differences. For the veterinary care claims, the majority of the cases were from the Middle Rural and the South Rural areas of Sweden, and cases were almost equally distributed between these areas. Claims from these regions were more than five times as common as those from the North Rural part of the country. For the life insurance, claims from the Middle Rural and the South Rural areas were only twice as common as that from the North Rural part of the country. Based on the survival analysis, there was an increased hazard of death after a diagnosis of epilepsy for dogs living in the North Rural area (HR = 1.22; $P = 0.055$). This might reflect the geographical distribution of the dog breeds, because breed distribution differs by regions, but also the large distances (200–300 km) between veterinary clinics in some parts of the country. Especially in the North Rural region of Sweden, there are few small animal clinics, and the availability of specialized veterinary services (such as small-animal specialists and advanced diagnostic imaging) is limited.

The Agria database used in this study provides a large number of cases from different clinics over several years, making the results less prone to referral bias. Because all animals were free from the disease when the study started and then followed through time, a cohort study design was appropriate and allowed for IR calculations.

No gold standard test exists to confirm the diagnosis of epilepsy. The physical and neurological examination and the routine diagnostic work-up are targeted towards excluding potential differential diagnoses that can mimic epilepsy. However, the diagnosis

Table 4
Cox proportional hazards model with a shared frailty effect for breed regarding survival after the diagnosis epilepsy, based on 3545 insured Swedish dogs between 1995 and 2006.

Factor	Hazard ratio	Standard error	*P*	95% confidence interval	
Sex	0.87	0.05	0.018	0.79	0.99
Living in the North	1.22	0.13	0.055	1.00	1.50
Age (in years) at diagnosis*	1.06	0.02	<0.001	1.03	1.09
Breed ($n = 197$)**	0.23	0.05			

* Significant interaction between 'Age at diagnosis' and time: $P < 0.001$.
** Likelihood ratio test of shared frailty effect for breed: $P < 0.001$.

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of 'epilepsy' is heavily dependent on the owners' observations of seizure activity and video documentation, through which certain characteristics associated with epilepsy such as short-lasting seizures and events involving focal and/or generalized seizure phenomenon and repetitive seizure event patterns, strongly indicates this diagnosis, minimising the uncertainty about the epilepsy diagnosis.

The two main diagnostic codes (idiopathic epilepsy and epileptic convulsions) used by practicing veterinarians diagnosing dogs with epileptic seizures or epilepsy were pooled for the present study. Dogs coded with epilepsy in the Agria database represent a mixture of dogs with IE and SE (Heske et al., 2014). It is possible that breeds with a high IR for epilepsy could have a genetic predisposition to idiopathic epilepsy as well as to underlying conditions resulting in symptomatic epilepsy, such as intracranial neoplasia or encephalitis. The Boxer, which has a high IR for epilepsy, has been reported to have a predisposition for brain tumours (Truvé, 2012) as well as for hereditary epilepsy (Nielen et al., 2001). Alternative diagnostic codes were available in the database for cases in which a specific alternative diagnosis, such as brain tumour or insulinoma, had been achieved. Nevertheless, this specificity of diagnosis may not have been attained in all such cases, implying that some cases of 'epilepsy' in this study may have had undiagnosed predisposing diseases.

Conclusions

The present study included both idiopathic and symptomatic epilepsy cases, and illustrated marked breed differences in the IR and MR of canine epilepsy. Males had higher rates of epilepsy than females. In general, dogs only lived 1.5 years after diagnosis. Breeds kept as family dogs generally had a better prognosis than breeds kept for dual-purposes, although it is not clear whether this reflects owner bias or different severities of disease.

Conflict of interest statement

Agria Insurance supplied data and financial support for this study. Agria Insurance Foundation for Research played no role in the study design or in the collection, analysis and interpretation of data, nor in the decision to submit the manuscript for publication. 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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Appendix: Supplementary material

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tvjl.2014.09.023.

References

Arrol, L., Penderis, J., Garosi, L., Cripps, P., Gutierrez-Quintana, R., Goncalves, R., 2012. Aetiology and long-term outcome of juvenile epilepsy in 136 dogs. Veterinary Record 170, 335.

Berendt, M., Gredal, H., Pedersen, L.G., Alban, L., Alving, J., 2002. A cross-sectional study of epilepsy in Danish Labrador Retrievers: Prevalence and selected risk factors. Journal of Veterinary Internal Medicine 16, 262–268.

Berendt, M., Gredal, H., Ersbøll, A.K., Alving, J., 2007. Premature death, risk factors, and life patterns in dogs with epilepsy. Journal of Veterinary Internal Medicine 21, 754–759.

Berendt, M., Gulløv, C.H., Christensen, S.L., Gudmundsdottir, H., Gredal, H., Fredholm, M., Alban, L., 2008. Prevalence and characteristics of epilepsy in the Belgian shepherd variants Groenendael and Tervueren born in Denmark 1995–2004. Acta Veterinaria Scandinavica 50, 51.

Berendt, M., Gulløv, C.H., Fredholm, M., 2009. Focal epilepsy in the Belgian shepherd: Evidence for simple Mendelian inheritance. Journal of Small Animal Practice 50, 655–661.

Bielfelt, S.W., Redman, H.C., McClellan, R.O., 1971. Sire- and sex-related differences in rates of epileptiform seizures in a purebred Beagle dog colony. American Journal of Veterinary Research 32, 2039–2048.

Bonnett, B.N., Egenvall, A., Olson, P., Hedhammar, Å., 1997. Mortality in insured Swedish dogs: Rates and causes of death in various breeds. Veterinary Record 141, 40–44.

Casal, M.L., Munuve, R.M., Janis, M.A., Werner, P., Henthorn, P.S., 2006. Epilepsy in Irish Wolfhounds. Journal of Veterinary Internal Medicine 20, 131–135.

Chandler, K., 2006. Canine epilepsy: What can we learn from human seizure disorders? The Veterinary Journal 172, 207–217.

Christensen, J., Vestergaard, M., Olsen, J., Sidenius, P., 2007. Validation of epilepsy diagnoses in the Danish National Hospital Register. Epilepsy Research 75, 162–170.

Dohoo, I., Martin, W., Stryhn, H., 2009. Veterinary Epidemiologic Research, Second Ed. Ver Inc., Charlottetown, Prince Edward Island, Canada.

Egenvall, A., Bonnett, B.N., Olson, P., Hedhammar, Å., 1998. Validation of computerized Swedish dog and cat insurance data against veterinary practice records. Preventive Veterinary Medicine 36, 51–65.

Egenvall, A., Hedhammar, Å., Bonnett, B.N., Olson, P., 1999. Survey of the Swedish dog population: Age, gender, breed, location and enrollment in animal insurance. Acta Veterinaria Scandinavica 40, 231–240.

Egenvall, A., Bonnett, B.N., Olson, P., Hedhammar, Å., 2000. Gender, age, breed and distribution of morbidity and mortality in insured dogs in Sweden during 1995 and 1996. Veterinary Record 146, 519–525.

Ekenstedt, K.J., Patterson, E.E., Mickelson, J.R., 2012. Canine epilepsy genetics. Mammalian Genome 23, 28–39.

Falco, M.J., Barker, J., Wallace, M.E., 1974. The genetics of epilepsy in the British Alsatian. Journal of Small Animal Practice 15, 685–692.

Famula, T.R., Oberbauer, A.M., Brown, K.N., 1997. Heritability of epileptic seizures in the Belgian tervueren. Journal of Small Animal Practice 38, 349–352.

Gulløv, C.H., Toft, N., Baadsager, M.M., Berendt, M., 2011. Epilepsy in the Petit Basset Griffon Vendeen: Prevalence, semiology, and clinical phenotype. Journal of Veterinary Internal Medicine 25, 1372–1378.

Heske, L., Berendt, M., Jäderlund, K.H., Egenvall, A., Nødtvedt, A., 2014. Validation of the diagnosis canine epilepsy in a Swedish animal insurance database against practice records. Preventive Veterinary Medicine 114, 145–150.

Hülsmeyer, V., Zimmermann, R., Brauer, C., Sauter-Louis, C., Fischer, A., 2010. Epilepsy in Border Collies: Clinical manifestation, outcome, and mode of inheritance. Journal of Veterinary Internal Medicine 24, 171–178.

Jaggy, A., Faissler, D., Gaillard, C., Srenk, P., Graber, H., 1998. Genetic aspects of idiopathic epilepsy in Labrador retrievers. Journal of Small Animal Practice 39, 275–280.

Jokinen, T.S., Metsähonkala, L., Bergamasco, L., Viitmaa, R., Syrjä, P., Lohi, H., Snellman, M., Jeserevics, J., Cizinauskas, S., 2007. Benign familial juvenile epilepsy in Lagotto Romagnolo dogs. Journal of Veterinary Internal Medicine 21, 464–471.

Kathmann, I., Jaggy, A., Busato, A., Bärtschi, M., Gaillard, C., 1999. Clinical and genetic investigations of idiopathic epilepsy in the Bernese mountain dog. Journal of Small Animal Practice 40, 319–325.

Licht, B.G., Lin, S., Luo, Y., Hyson, L.L., Licht, M.H., Harper, K.M., Sullivan, S.A., Fernandez, S.A., Johnston, E.V., 2007. Clinical characteristics and mode of inheritance of familial focal seizures in Standard Poodles. Journal of the American Veterinary Medical Association 231, 1520–1528.

Monteiro, R., Adams, V., Keys, D., Platt, S.R., 2012. Canine idiopathic epilepsy: Prevalence, risk factors and outcome associated with cluster seizures and status epilepticus. Journal of Small Animal Practice 53, 526–530.

Nielen, A.L., Janss, L.L., Knol, B.W., 2001. Heritability estimations for diseases, coat color, body weight, and height in a birth cohort of Boxers. American Journal of Veterinary Research 62, 1198–1206.

Patterson, E.E., Mickelson, J.R., Da, Y., Roberts, M.C., McVey, A.S., O'Brien, D.P., Johnson, G.S., Armstrong, P.J., 2003. Clinical characteristics and inheritance of idiopathic epilepsy in Vizslas. Journal of Veterinary Internal Medicine 17, 319–325.

Patterson, E.E., Armstrong, P.J., O'Brien, D.P., Roberts, M.C., Johnson, G.S., Mickelson, J.R., 2005. Clinical description and mode of inheritance of idiopathic epilepsy in English springer spaniels. Journal of the American Veterinary Medical Association 226, 54–58.

Proschowsky, H.F., Rugbjerg, H., Ersbøll, A.K., 2003. Mortality of purebred and mixed-breed dogs in Denmark. Preventive Veterinary Medicine 58, 63–74.

Saito, M., Munana, K.R., Sharp, N.J., Olby, N.J., 2001. 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). Journal of the American Veterinary Medical Association 219, 618–623.

Schwartz-Porsche, D., 1994. Seizures. In: Braund, K.G. (Ed.), Clinical Syndromes in Veterinary Neurology, Second Ed. Mosby, St. Louis, MO, pp. 234–251.

Short, A.D., Dunne, A., Lohi, H., Boulton, S., Carter, S.D., Timofte, D., Ollier, W.E., 2011. Characteristics of epileptic episodes in UK dog breeds: An epidemiological approach. Veterinary Record 169, 48.

Swedish Animal Hospital Association. 1993. Diagnostic registry for the horse, the dog and the cat (Diagnosregister för häst, hund och katt) Tåberg, Tåbergs tryckeri, Sweden.

Truvé, K., 2012. Bioinformatics Mining for Disease Causing Mutations: Using the Dog Genome as a Model for Human Diseases (Doctorial thesis). Swedish University of Agricultural Sciences, Uppsala. Acta Universitatis Agriculturae Sueciae 64, 41–46.

Wallace, M.E., 1975. Keeshonds: A genetic study of epilepsy and EEG readings. Journal of Small Animal Practice 16, 1–10.

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