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

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

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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 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 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 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.

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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.


See: www.agria.se.
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, 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 reimburse 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 puddles) were combined in the analysis (Bonnett et al., 1997). Diagnostiic 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 [IR]) 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 numbers 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 (breds 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 (StatCorp). 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. (2000) and, if violated, an interaction with time was included in the model. The cut-off for statistical significance was set to P ≤ 0.05.

Results

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.

<table>
<thead>
<tr>
<th>Category</th>
<th>DYAR</th>
<th>Cases</th>
<th>Incidence</th>
<th>95% CI</th>
<th>Age of cases</th>
<th>Percentiles</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Veterinary care</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>2,780,650</td>
<td>5013</td>
<td>18</td>
<td>18</td>
<td>19</td>
<td>5.5</td>
<td>3.1</td>
</tr>
<tr>
<td>Male</td>
<td>1,367,875</td>
<td>2921</td>
<td>21</td>
<td>21</td>
<td>22</td>
<td>5.3</td>
<td>3.1</td>
</tr>
<tr>
<td>Female</td>
<td>1,412,815</td>
<td>2092</td>
<td>15</td>
<td>14</td>
<td>15</td>
<td>5.7</td>
<td>3.1</td>
</tr>
<tr>
<td>Middle rural</td>
<td>889,764</td>
<td>1494</td>
<td>17</td>
<td>16</td>
<td>18</td>
<td>5.4</td>
<td>3.1</td>
</tr>
<tr>
<td>Middle urban</td>
<td>375,956</td>
<td>963</td>
<td>26</td>
<td>24</td>
<td>27</td>
<td>5.9</td>
<td>3.2</td>
</tr>
<tr>
<td>North rural</td>
<td>306,536</td>
<td>288</td>
<td>9</td>
<td>8</td>
<td>10</td>
<td>5.0</td>
<td>3.1</td>
</tr>
<tr>
<td>South urban</td>
<td>318,906</td>
<td>713</td>
<td>22</td>
<td>21</td>
<td>24</td>
<td>5.6</td>
<td>3.1</td>
</tr>
<tr>
<td>South rural</td>
<td>889,528</td>
<td>1555</td>
<td>17</td>
<td>16</td>
<td>18</td>
<td>5.3</td>
<td>3.1</td>
</tr>
<tr>
<td>Life insurance</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>2,045,650</td>
<td>2327</td>
<td>11</td>
<td>11</td>
<td>12</td>
<td>5.2</td>
<td>2.8</td>
</tr>
<tr>
<td>Male</td>
<td>1,016,307</td>
<td>1368</td>
<td>13</td>
<td>13</td>
<td>14</td>
<td>5.0</td>
<td>2.7</td>
</tr>
<tr>
<td>Female</td>
<td>1,029,343</td>
<td>959</td>
<td>9</td>
<td>9</td>
<td>10</td>
<td>5.5</td>
<td>2.8</td>
</tr>
<tr>
<td>Middle rural</td>
<td>662,527</td>
<td>760</td>
<td>11</td>
<td>11</td>
<td>12</td>
<td>5.3</td>
<td>2.7</td>
</tr>
<tr>
<td>Middle urban</td>
<td>259,685</td>
<td>254</td>
<td>9</td>
<td>9</td>
<td>11</td>
<td>5.5</td>
<td>2.8</td>
</tr>
<tr>
<td>North rural</td>
<td>252,204</td>
<td>345</td>
<td>12</td>
<td>12</td>
<td>15</td>
<td>4.8</td>
<td>2.7</td>
</tr>
<tr>
<td>South urban</td>
<td>216,451</td>
<td>218</td>
<td>9</td>
<td>9</td>
<td>11</td>
<td>5.4</td>
<td>2.8</td>
</tr>
<tr>
<td>South rural</td>
<td>654,784</td>
<td>750</td>
<td>11</td>
<td>11</td>
<td>12</td>
<td>5.2</td>
<td>2.8</td>
</tr>
</tbody>
</table>

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 3 shows IRRs and MRRs 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 at the time of diagnosis, each year after the time of diagnosis, the hazard of dying increased by 6%. However, the higher the age at the time of diagnosis, the higher the survival after diagnosis.

### 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.
higher breed-specific prevalence estimates are thought to reflect significant male predisposition for IE (study, which is in agreement with previous reports showing a 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 Tervuren) 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, 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 euthanised. 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

![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.](Image)
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 for hereditary epilepsy (Heske et al., 2014).

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


