Phenotype, inheritance characteristics, and risk factors for idiopathic epilepsy in Finnish Spitz dogs

Ranno Viitmaa, DVM; Sigitas Cizinauskas, DVM; Toomas Orro, DVM, PhD; Meri Niilo-Rämä, DVM; Emilia Gordin, DVM; Hannes Lohi, PhD; Eija H. Seppälä, PhD; Hanna Bragge; Marjatta Snellman, Dr Med Vet, PhD

Objective—To determine the phenotype, inheritance characteristics, and risk factors for idiopathic epilepsy (IE) in Finnish Spitz dogs (FSDs).

Design—Prospective epidemiological study.

Animals—2,141 FSDs.

Procedures—From 2003 to 2004, questionnaires (n = 5,960) were sent to all owners of 1- to 10-year-old FSDs in Finland. Phone interviews were performed 1 to 2 years later.

Results—Estimated prevalence of IE was 5.36% (111/2,069 of FSDs that were still alive). Males were predisposed to IE. The median age of onset was 3 years (range, 0.6 to 10 years). The median seizure frequency was 2 seizures/yr (range, 0.5 to 48 seizures/yr), and the median duration of the seizure episode was 11.75 minutes (range, 1.5 to 90 minutes). The majority (85%) of the seizures had a focal onset, and 54% were characterized as generalized secondary. A generalized seizure phase was determined to be a risk factor for development of progressive disease. Factors associated with the occurrence of a generalized phase were the age of onset, duration of the seizure, number of feeding times per day, and whether the dog was used for hunting. The seizures were not progressing in 67.8% of the dogs and were easily controlled by antiepileptic treatment in 78.9% of the dogs. The heritability estimate of IE in FSDs was 0.22; IE was best explained as a polygenic trait.

Conclusions and Clinical Relevance—In the present study conducted in Finland, complex focal seizures were the most common seizure type for FSDs with IE, and a generalized seizure phase was a risk factor for progression of the disease. Results suggested a benign course of epilepsy in FSDs. (J Am Vet Med Assoc 2013;243:1001–1009)

Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tr>
<td>CFS</td>
<td>Complex focal seizures</td>
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<tr>
<td>CI</td>
<td>Confidence interval</td>
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<td>FSD</td>
<td>Finnish Spitz dog</td>
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<td>IE</td>
<td>Idiopathic epilepsy</td>
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<td>SFS</td>
<td>Simple focal seizures</td>
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Idiopathic epilepsy in dogs has been defined as recurrent seizures for which no underlying abnormalities can be identified, although a genetic predisposition may be suspected. Risk factors for the occurrence and progression of epilepsy are poorly defined in veterinary medicine. One possible reason for this is the limited populations evaluated during epidemiological studies of IE in dogs. The FSD is a breed that is used traditionally as a barking hunting dog for game birds and also as a guard dog. The FSD is a relatively rare breed, with a mean of only 814 newly registered dogs/yr (2001 to 2011), as recorded by the Finnish Kennel Club. Currently, their database, which is used only by breeding advisors, includes 569 epileptic dogs (1980 to 2013).

The present prospective epidemiological investigation was performed by means of questionnaires and phone interviews and was designed to cover the largest possible FSD population in Finland. We hypothesized that homogenization of a study population through the selection of 1 breed might provide us with a more meaningful characterization of epilepsy in dogs for future use. The objective of the study reported here was to define the prevalence of IE within the FSD population in Finland and to define the clinical characteristics...
Materials and Methods

Study design—Information on the FSDs registered in Finland was collected from databases of the Finnish Spitz Breeder Club and the Finnish Kennel Club. The questionnaire was sent to all owners of 1- to 10-year-old FSDs during the period from June 2003 to July 2004. All dog owners were asked to complete the questionnaire and send it back in a prepaid addressed envelope. The owners could choose if their dogs’ clinical information would be public or for scientific use. The owners were asked to underline the most appropriate answers in the questionnaire. For some questions, the owners were asked to write a short description of an event. The first page of the questionnaire contained general information such as the name of the owner and breeder and the dog’s name, registration number, sex (sexually intact, spayed, or castrated), dominating personality trait (lively, nervous, depressed, or phlegmatic), and height and weight. Other questions sought information on the feeding (type of food and feeding times), environment (living indoors or outdoors), presence of other animals in the household, hunting or sports dog, and amount of time spent per day under the owners’ visual supervision. Owners whose dogs were known to have epileptic seizures were asked to answer additional questions. These questions included the age of onset, total number of observed seizures, frequency of the seizure at the beginning of disease onset and later in life (progression), and existence of clusters of seizure episodes or status epilepticus. Additional questions requested information about the time of seizure occurrence, (ie, during sleeping, exercise, or excitement) and about the timing of the seizure in relation to the diet (ie, shortly after feeding or after a period of fasting). The owners were also asked whether the seizures had any regularity (ie, at the same time of day or season) and if the weather conditions, sexual cycle (female dogs), concurrent disease, or any medication influenced the occurrence of seizures; these consisted of yes or no questions with the opportunity to specify. Owners were also asked whether they recognized any changes in the behavior of their dogs just before the actual seizure episode (minutes or hours). The duration of such initial signs was sought and recorded. The owners were asked to specify any clinical signs they had recognized during the main seizure episode from a defined list. They were also asked to evaluate the responsiveness (indicator of consciousness) of the dog twice: at the start of the seizure and during the seizure episode itself. Moreover, information regarding the presence of postictal signs and their durations was sought. The owners were asked to subjectively rate the seizure as mild, moderate, or severe and to describe whether they were able to influence the course of the seizure. Another set of questions covered the relevant medical information, evaluations performed, diagnosis, treatment (medication, dose, and side effects), and treatment efficacy for each affected dog. Contact information for the veterinarian and a description of the examinations or a copy of the examination results were also requested.

A total of 5,960 questionnaires were sent, and answers were received regarding 2,299 (38.6%) dogs. The questionnaires were evaluated and classified, and the owners of epileptic dogs, owners of dogs with 1 seizure episode, owners of dogs with unclear status, and owners that submitted incomplete information were invited for an interview (297 FSD owners in total). Phone calls were made by the authors (RV, MNR, and EG) 1 to 2 years after the questionnaires were received and were reviewed by the first author (RV). During the interviews, the owners were provided with detailed descriptions and a list of categorical answers. Specific questions were asked about the very beginning of the seizure episode to confirm the seizure type classification. The owners were asked to report whether any changes in treatment or the course of the disease, such as the shortening or lengthening of the interictal period or the presence of seizure clusters or status epilepticus, had occurred in the meantime. The course of epilepsy was defined as stable (where the frequency and duration of the seizure episodes remained the same), progressing (where the frequency or duration of the seizure episodes was increasing or cluster episodes of status epilepticus had appeared), or diminishing (where the frequency or duration of the seizure episodes was decreasing over time). The time period used to define the course of epilepsy in every affected dog started at the moment of the first seizure and ended either at the time of the owner’s interview (if medication had not been initiated) or at the initiation of epilepsy medication. In addition, the owners were asked about the appearance of seizures that clearly differed from those previously described to detect the presence of multiple seizure types in individual dogs. Detailed descriptions of such episodes were recorded, and the seizures were classified.

Only those dogs with at least 2 seizure episodes and without interictal neurologic abnormalities or evidence of clinical signs of epilepsy were included in the epileptic group. All dogs with insufficient information (n = 117), dogs whose owners could not be contacted by phone (10), dogs with only 1 seizure episode at the time of the phone call (24), and dogs younger than 1 year at the time of answering the questionnaire (5) were excluded from the study (156). Idiopathic epilepsy was diagnosed by a veterinarian in 73 of the 141 (51.8%) cases. In all examined dogs, a diagnosis was made on the basis of the history of the seizures and the absence of abnormalities in the general clinical and neurologic examinations. The most frequent additional workup included blood hematology and serum biochemical examinations (35 [27.8%] dogs). At a later time, blood samples collected from 113 epileptic FSDs in the course of another study were examined. Idiopathic epilepsy was diagnosed in 18 selected dogs by electroencephalography, MRI, and positron emission tomography.

We used a modified version of the classification system of Licht et al for the classification of seizure type. Seizures were classified as generalized or focal according to the initial clinical signs. Focal seizures were divided into SFS and CFS. The main distinction be-
between these was whether consciousness was preserved, with CFS having impaired consciousness and SFS having preserved consciousness. Impaired consciousness was characterized mainly by the lack of responsiveness of the dog during the epileptic episode. The seizure was also classified as CFS (even with preserved consciousness) when there was a combination of at least 2 of the following signs: motor, autonomic, behavioral signs, or automatism. The possible episode progression was recorded. When the simple focal onset was not clearly distinguishable from the complex focal signs, we classified these episodes as CFS. When the focal episode was secondarily generalized, it was classified as an SFS or CFS with secondary generalization. When the owners had never been present at the time of the initial signs, but just recognized a generalized phase of seizure, the episode was classified as a generalized seizure with an unknown onset. Seizures remained unclassified when the owners were not able to describe the dog's responsiveness during the seizure episode. Initial signs lasting for 1 hour or more were classified as prodrome. When these signs lasted for < 1 hour, they were considered to be the local beginning of an ictal event. Prodrome and postictal signs were not counted as a part of ictus. Finally, the seizures were classified as simple focal, complex focal, local with secondary generalization, secondary generalized with unknown onset, or primary generalized.

Closely connected families with multiple epileptic dogs over several generations were selected for further pedigree analysis. The exact pedigree data obtained from the Finnish Spitz Breeder Club and the Finnish Kennel Club databases were recorded for these dogs. The clinical status of the dogs (healthy or affected) was confirmed by a repeated phone call with each dog's owner.

The epilepsy prevalence was calculated for the FSDs that were living when their owners answered the questionnaire (111 epileptics/2,069 total dogs). The epilepsy phenotype description was based on information obtained for 141 epileptic dogs (111 alive and 30 dead epileptic dogs at the time of the investigation). The epidemiological evaluation of epilepsy in FSDs was based on the widest available population of 2,141 dogs, which included 143 epileptic dogs. Any inconsistencies in the number of dogs included in the estimation of the various answers were caused by incomplete questionnaires and cases in which owners were not confident about the correct answer. Our database included some dogs that were up to 15 years of age, as some owners still had living FSDs older than 10 years and submitted questionnaires about these animals.

Statistical analysis—Statistical analyses were performed with a commercial software package. A mixed logistic regression model was used to analyze the factors associated with epilepsy. Moreover, a stepwise backward elimination procedure was used to fit the final model. For the description of the dogs' dominating personality trait, a binary factor was used (lively or not) because most dogs were characterized as lively. The age of the dogs was adjusted for the probability of having epilepsy, which increases with age; the age and the quadratic term of the age were included in the model. The dogs' sires were used as a random factor to account for the clustering effect. Univariate analysis was used to evaluate the different factors and epilepsy phenotype characteristics associated with disease progression (progressing or stable) or with generalized forms of seizures in diseased dogs. For pairwise comparisons in multicategorical factors, the Bonferroni adjustment was used. The results from logistic regression analyses are presented as an OR with 95% CI. The level of significance was set at 5% (P < 0.05).

The heritability of epilepsy was evaluated by variance component estimation with the restricted maximum likelihood estimation method and modeling software. The linear model used included epilepsy status as the dependent variable and sex, hunting (used or not), personality trait (lively or not), living conditions (only outdoors or both indoors and outdoors), age, and quadratic term of age as fixed factors. The random factors were the additive genetic effect (determined with information on the dam, sire, and sire's sire) and the error term. The heritability was calculated by dividing the additive genetic variance by the sum of the additive genetic variance and residual variance.

Results

The prevalence of IE in the Finnish population of FSDs was 5.36% (111 epileptics/2,069 total dogs). Epilepsy was more prevalent among males than females (OR, 1.7; 95% CI, 1.2 to 2.5; P = 0.006). Other personality traits (phlegmatic, depressed, and nervous) were more associated with IE than was the characteristic of lively (OR, 5.9; 95% CI, 2.9 to 11.7; P < 0.001). Being used in hunting and living exclusively outdoors were negatively associated with epilepsy (OR, 0.5; 95% CI, 0.3 to 0.9; P = 0.01 and OR, 0.6; 95% CI, 0.4 to 0.9; P = 0.01, respectively). The median age, height, and weight (25% and 75% quartiles) of healthy and epileptic dogs, respectively, was 62 (38 and 87) and 76 (58 and 111) months, 46 (43 and 48) and 45.5 (43 and 48) cm, and 12 kg (26.4 lb; 10 and 14 kg [22 and 30.8 lb]) and 13 kg (28.6 lb; 12 and 15 kg [26.4 and 33 lb]). The sex distribution for the healthy FSDs was as follows: 915 (45.8%) sexually intact males, 37 (1.9%) castrated males, 966 (49.8%) sexually intact females, and 50 (2.5%) spayed. The sex distribution for the epileptic FSDs was as follows: 81 (56.6%) sexually intact males, 5 (3.3%) castrated males, 57 (37.8%) sexually intact females, and 3 (2.1%) spayed. The number of feeding times per day for healthy and epileptic FSDs, respectively, was once daily for 792 (40.1%) and 44 (40.0%) dogs, twice daily for 958 (48.5%) and 67 (47.2%) dogs, and 3 times daily for 224 (11.4%) and 31 (21.8%) dogs. The predominant personality trait in healthy and epileptic FSDs, respectively, was described as lively for 1,941 (97.8%) and 122 (87.8%) dogs, phlegmatic for 5 (0.3%) and 2 (1.4%) dogs, depressed for 10 (0.5%) and 4 (2.9%) dogs, and nervous for 28 (1.4%) and 11 (7.9%) dogs. Of 1,983 healthy FSDs, 1,784 (90.0%) were used for hunting; of 142 epileptic FSDs, 110 (77.5%) were used for hunting. Of 1,980 healthy FSDs, 1,446 (73.0%) lived only outdoors and 534 (27.0%) lived both indoors and outdoors; of 133 epileptic FSDs, 80 (60.1%) lived only outdoors and 53 (39.9%) lived both indoors and outdoors.
The heritability of IE in FSDs was estimated from the linear variance component model as 0.22 (standard error = 0.07). The median inbreeding coefficient in epileptic dogs was 9 (25% and 75% quartiles, 8 and 11; range, 7 to 24) and that of healthy dogs was 9 (25% and 75% quartiles, 7 and 11; range, 3 to 57). Therefore, the inbreeding coefficient was not associated with epilepsy. The segregation of IE in the sample of FSDs pedigrees is presented (Figure 1).

The median age of the dogs at the onset of seizures was 3 years, and 78% of the dogs had their first seizure when they were < 4 years old (25% and 75% quartiles, 24 and 48 months; range, 7 to 120 months). The median age at the onset of seizures in the dogs with and without veterinary examinations was 3 years (range, 6 to 120 months) and 3 years (range, 6 to 96 months), respectively. The median frequency of seizures was 2 seizures/y (25% and 75% quartiles, 1.5 and 4 seizures/y; range, 0.5 to 48 seizures/y). The median frequency of seizures for the dogs with veterinary examinations was 3 seizures/y (range, 0.5 to 48 seizures/y), and that for the dogs without examinations was 2 seizures/y (range, 0.5 to 18 seizures/y). The median duration of ictus, including initial signs, was 11.75 minutes (25% and 75% quartiles, 7 and 22.5 minutes; range, 1.5 to 90 minutes; n = 138). The median duration of ictus for the dogs with veterinary examinations (n = 72) was 12.3 minutes (range, 2 to 90 minutes), and that for the dogs without examinations (66) was 10.8 minutes (range, 1.5 to 80 minutes). Initial clinical signs of ictus with a median duration of 3 minutes (25% and 75% quartiles, 1.5 and 5.5 minutes; range, 0.5 to 60 minutes) were recognized in 87 of 127 (68.9%) dogs. These signs were recognized as behavioral (ie, hiding without reason; n = 79), automatism (ie, repeated changing of position or licking movements; 10), motor (ie, weakness or tremors; 17), and autonomic (ie, vomiting; 3). The consciousness level at the time of the initial signs was classified as normal in 20 dogs and impaired in 66 dogs. The median duration of the ictal signs (not including the initial signs) was 10 minutes (25% and 75% quartiles, 5.5 and 20 minutes; range, 1 to 80 minutes). The most important ictal signs were motor (n = 123 dogs), which were recognized as tremors (17), weakness (49), tonic-clonic (40), tonic (16), and clonic (1). The motor signs were localized to the limbs in 59 dogs, localized to the face in 3 dogs, and involved the whole body of 61 dogs. Behavioral signs were recognized in 20 of the 119 (16.8%) dogs. Autonomic signs (n = 105 dogs) included salivation (87), vomiting or regurgitation (38), and urination or defecation (29). Automatisms were observed in 49 of 120 (40.8%) dogs, and they mainly involved coordinated paddling of all 4 limbs at the time of the generalized phase. The level of consciousness was classified in the final stage of ictus as normal in 3 dogs, impaired in 56, and lost in 67 of 126 dogs. Postictal signs...
including restlessness, impaired responsiveness, thirst, and hunger were found in 117 of 136 (86.0%) dogs. The median duration of postictal signs was 21.3 minutes (25% and 75% quartiles, 5 and 75 minutes). Cluster episodes were present in 22 of 136 (16.2%) dogs.

Of 141 dogs, 120 (85.1%) had focal onset seizures. Seizure episodes were classified as SFS in 3 dogs and as SFS with secondary generalization in 18 of 141 (12.9%) dogs. The seizures of 41 of the 141 (29%) dogs were CFS, and the seizures were CFS with secondary generalization in 38 (41.1%) dogs. The seizures of 1 dog were primary generalized, and the seizures of 10 dogs were generalized but with unknown onset. We were not able to classify the seizures in 10 dogs. Additionally, 24 of 128 (18.8%) dogs experienced seizure episodes of multiple seizure types. These episodes usually had similar onsets with or without generalization. Differently classified episodes were SFS in 3 dogs, CFS in 13 dogs, and CFS with secondary generalization in 8 dogs. The distribution of SFS for dogs with and without veterinary examinations was 11 of 72 (15.3%) dogs and 10 of 66 (15.2%) dogs, respectively, and that for CFS was 31 of 72 (70.8%) dogs and 48 of 66 (72.7%) dogs, respectively. The distribution of seizures with generalized phase for the dogs with veterinary examinations was 54 of 72 (75%) dogs and for those without veterinary examinations was 33 of 66 (50%) dogs.

A typical epileptic seizure in FSDs could be described as follows: after a stressful situation, the dog began to be restless and regurgitated some foam. The dog was not responsive when called by the owner. Thereafter, the dog’s movements started to be uncoordinated and the dog’s hind limbs became progressively weaker, although it tried to remain standing. At that stage, the owner would not be able to get any response from the dog. The episode lasted for approximately 11 minutes. Subsequently, the dog would recover gradually but was tired and behaved abnormally for approximately 20 minutes.

General data regarding the factors associated with focal versus generalized seizures are summarized (Table 1). The generalized data included dogs with both primarily generalized and secondary generalized seizures. The only factor associated with a progressive course of epilepsy was the presence of a generalized phase of seizure (OR, 2.6; 95% CI, 1.0 to 6.3; P = 0.039). The age at seizure onset was significantly (P = 0.009) associated with the seizure generalization, and a generalized phase of seizure occurred more frequently when the first seizure occurred during the first 3 years of life (OR, 2.7; 95% CI, 1.3 to 5.8). The correlation between the generalized phase of seizure and the age at seizure onset is presented (Figure 2).

When generalized seizures (primarily or secondarily) were compared with focal seizures, they were more prevalent in dogs with a shorter ictal episode. Longer seizures (up to 20 minutes) tended to be focal seizures rather than generalized ictal events. Seizures longer than 20 minutes tended to be generalized (Figure 3). This tendency was statistically significant because generalization was more common with seizures lasting 1 to 10 minutes (OR, 4.7; 95% CI, 1.7 to 13.0; P = 0.006) or seizures longer than 20 minutes (OR, 3.4; 95% CI, 1.4 to 8.3; P = 0.012), compared with seizures lasting 11 to 20 minutes.

Another factor correlated with seizure generalization was the number of feeding times per day. Epilepsy generalization was more frequent among dogs that received food once per day than among dogs that ate 3 times/day (OR, 3.4; 95% CI, 1.2 to 9.5; P = 0.034). Similarly, dogs fed once per day had a higher risk of generalized seizures than dogs that ate twice per day. However, this was not significant (OR, 2.1; 95% CI, 0.9 to 5.1; P = 0.196). In addition, hunting was associated with seizure generalization (P = 0.036) because dogs used for hunting received food once per day, whereas the dogs that were not used for hunting had more feeding times per day.

### Table 1—Factors associated with focal versus generalized seizures in FSDs (n = 131) on the basis of data collected during a prospective epidemiological study in Finland from June 2003 to July 2004.

<table>
<thead>
<tr>
<th>Factors</th>
<th>Focal seizures (n = 44)</th>
<th>Seizures with generalization (n = 87)</th>
<th>P value</th>
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<tr>
<td><strong>Disease progression</strong></td>
<td></td>
<td></td>
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<tr>
<td>Progressing</td>
<td>8 (19.1%)</td>
<td>29 (37.7%)</td>
<td>0.039</td>
</tr>
<tr>
<td>Stable</td>
<td>34 (81.0%)</td>
<td>48 (62.3%)</td>
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<tr>
<td><strong>Median (IQR) age at seizure onset (mo)</strong></td>
<td>40.5 (27–57.5)</td>
<td>30 (19–48)</td>
<td>0.032</td>
</tr>
<tr>
<td><strong>Age of dog at seizure onset</strong></td>
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<td></td>
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<tr>
<td>≤ 36 months</td>
<td>21 (47.7%)</td>
<td>62 (71.2%)</td>
<td>0.009</td>
</tr>
<tr>
<td>&gt; 36 months</td>
<td>23 (52.3%)</td>
<td>25 (28.7%)</td>
<td></td>
</tr>
<tr>
<td><strong>Duration of seizure episode</strong></td>
<td></td>
<td></td>
<td>0.004*</td>
</tr>
<tr>
<td>1–10 min</td>
<td>15 (34.9%)</td>
<td>41 (47.1%)</td>
<td></td>
</tr>
<tr>
<td>10–20 min</td>
<td>20 (46.5%)</td>
<td>16 (18.4%)</td>
<td>0.012†</td>
</tr>
<tr>
<td>&gt; 20 min</td>
<td>8 (18.8%)</td>
<td>30 (34.5%)</td>
<td>0.052*</td>
</tr>
<tr>
<td><strong>Feeding times per day</strong></td>
<td></td>
<td></td>
<td>0.196†</td>
</tr>
<tr>
<td>1</td>
<td>9 (20.5%)</td>
<td>31 (35.6%)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>19 (43.2%)</td>
<td>40 (46.0%)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>16 (36.4%)</td>
<td>16 (18.4%)</td>
<td>0.034†</td>
</tr>
<tr>
<td><strong>Used for hunting</strong></td>
<td></td>
<td></td>
<td>0.038</td>
</tr>
<tr>
<td>Yes</td>
<td>29 (65.9%)</td>
<td>71 (82.6%)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>15 (34.1%)</td>
<td>15 (17.4%)</td>
<td></td>
</tr>
</tbody>
</table>

5,860 questionnaires were sent, and responses were received regarding 2,299 (38.6%) dogs. The questionnaires were evaluated and classified, and the owners of epileptic dogs, owners of dogs with 1 seizure episode, owners of dogs with unclear status, and owners that submitted incomplete information were invited for an interview (297 FSD owners in total). Phone calls were made 1 to 2 years after the questionnaires were received. During the phone interviews (RV), the owners were provided with detailed descriptions and a list of categorical answers. Specific questions were asked about the very beginning of the seizure episode to confirm the seizure type classification. The owners were asked to report any changes in treatment or the course of the disease.

*Overall P value for multivariate factor significance by the Wald test. P value of pairwise comparison with factor category without P value and corrected with the Bonferroni adjustment coefficient.
hunting had a higher risk of seizure generalization than nonhunting dogs (OR, 2.4; 95% CI 1.1 to 5.6).

Furthermore, 42 of 137 (30.7%) epileptic dogs received epilepsy medication, and phenobarbital was the predominant drug. Treatment was considered to be effective in 30 of 38 (78.9%) dogs, independently of whether the seizures were focal or secondarily generalized. Most of the treated dogs had a generalized phase of seizure.

Fatigue, increased drinking and eating, nervousness, and aggressiveness were the possible side effects of the treatment and were reported for 16 of 39 (41%) dogs by their owners. Treatment was believed to have a negative influence on the dogs’ hunting ability, although their dogs had never received any antiepileptic medication. This reflects the general opinion among the hunting community in Finland. Treatment with diazepam at the time of seizure was used in only 13 of 141 (9.2%) dogs.

Discussion

In the present study that evaluated the prevalence, clinical characteristics, and potential risk factors within the FSD population in Finland over a 1-year period (2003 to 2004), complex focal seizures were the most common seizure type for IE in FSDs, and a generalized phase of seizure was a risk factor for the progression of the disease. Results suggested a benign course of epilepsy in FSDs. To the best of our knowledge, the present study provides the first clinical description of the phenotype, risk factors, and mode of inheritance of IE in FSDs. However, as the majority of information was based on evaluations provided by the dog owners, it should be noted that some subjective measures were present in this study.

Older classifications and terminology in the field of epilepsy have been questioned in the last several decades. Epileptic seizures are considered to be a response of the brain to a large variety of stimuli. Genetic factors that play an important role in the development of IE may influence the individual basic level of epileptogenicity. These factors may also be causative or influence the moderation of the disease development. Although the causative genes of IE in dogs have not published, the genetic predisposition of IE has been documented for several dog breeds. Postulated modes of inheritance include a polygenic recessive allele in the Golden Retriever, Labrador Retriever, Bernese Mountain Dog, Belgian Tervuren, and Belgian Sheepdog. A partially penetrant autosomal recessive allele has also been suggested in the Irish Wolfhound and English Springer Spaniel. Similarly, an autosomal recessive allele has been suggested in the Keeshond, Vizsla, Standard Poodle, and Border Collie. In human medicine, an obvious extraneous cause is absent in approximately 70% of all epileptic patients, and these cases are presumed to have a predominantly genetic basis. Epilepsy is thought to have a complex genetic basis with an unknown number of susceptibility genes in 40% of human patients. Some dominant and autosomal recessive epilepsy genes are already known. A more complex pattern of inheritance such as polygenic recessive or autosomal recessive with incomplete penetrance seems to fit best with the heritability estimate of 0.22 in FSDs obtained in our study. Even if the first pedigree analysis supported the hypothesis of an autosomal recessive mode of inheritance, the high incidence of IE in many litters could also be explained by a high homozygosity level in this dog breed. We believe that the use of pedigree drawing or segregation analysis of the general non–preselected breed population can introduce bias into inheritance estimates. When we more closely evaluated the litters of epileptic FSDs, we found not only several epileptic littermates but also some bloodlines completely without epileptic dogs. Therefore, an IE
prevalence of 5.36% in the Finnish population of FSDs serves as a general estimate and can differ considerably depending on the bloodline. We believe that the design of our study could underestimate the IE prevalence. For practical considerations, questionnaires were not sent to the owners of FSDs > 10 years of age. As there is evidence that seizures appear most often in dogs within this age group, discounting this population may lead to an underestimation of the degree prevalence. However, our database included some dogs up to 13 years of age. Therefore, the population curve followed a normal distribution. Although the owners of all dogs were encouraged to complete a questionnaire regardless of the clinical disease status of the dogs, the owners of epileptic dogs were less likely to respond. During the last decade, much work has been done within the Finnish Spitz Breeder Club to encourage people to talk openly about epilepsy. Although the published estimates of IE prevalence in different dog breeds range from 0.5% to 18.3%, the mean for all dog breeds is believed to be between 1% and 5%.\textsuperscript{13,22-24} With the use of that estimate, there appears to be a slightly higher incidence of IE in FSDs in the Finnish population than in the general dog population. However, there is no consistency in the study populations or in the methods of the veterinary studies that cover the topic. Therefore, caution should be used when interpreting published studies.

We found a statistically significant predisposition for epilepsy in male FSDs, in that the incidence of epilepsy in males was 1.7 times as high as that of females. The predisposition of males for IE has also been documented for Golden Retrievers, Bernese Mountain Dogs, and Irish Wolfhounds.\textsuperscript{5,11,13} Nonetheless, according to our pedigree data, IE in FSDs does not appear to be sex-linked, as was assumed for Beagles, in which autosomal recessive and sex-linked suppressors were reported.\textsuperscript{25}

Results of an epidemiological study\textsuperscript{26} of human epilepsy indicate a slightly higher incidence of epilepsy in males overall. Importantly, the sex susceptibility may vary for specific epilepsy subtypes.\textsuperscript{27}

Factors found in the epilepsy risk analysis were the use of the dogs for hunting (OR, 0.3) and the housing of dogs exclusively outdoors (OR, 0.6). A likely explanation for the fact that healthy dogs were used more often for hunting is that dogs that started to have seizures were not subsequently taken on hunts. Interestingly, a large portion of epileptic dogs were still being used for hunting. Historically, it has been recognized that some of the epileptic FSDs may have extremely good hunting skills (very good senses and a high level of alertness). Therefore, it seems that epilepsy was systematically ignored for many years when breeding decisions were made. The majority of FSDs still live outdoors in the Northern parts of Finland. Living only in outdoor conditions was associated with a decreased risk of epilepsy. The suggestion that outdoor dogs are healthier because they live in conditions that are natural for FSDs is somewhat naive. Since the mean seizure frequency reported for FSDs living outdoors was very low (2 seizures/y), it could be argued that the owners may not always witness seizures in dogs living entirely outdoors and may therefore falsely classify them as healthy. On the basis of our experience, we suggest that the most common reason is that after the owners realize a dog is prone to seizures, they keep the animal under observation as much as possible. However, despite reaching the level of statistical significance, we were unable to provide biological justification for any of the factors found to be associated with the occurrence of IE in our study, except for the genetic predisposition.

Numerous predictors of seizure outcome, such as sex, seizures in relatives, prior neonatal seizures, prior febrile convulsions, age at seizure onset, abnormal neurological status, seizure frequency at onset of seizures, seizure etiology, type and number of seizure types, type of epilepsy syndrome, time prior to the onset of drug treatment, number of seizures prior to the onset of drug therapy, age at the onset of drug therapy, the early effect of drug therapy, and number of seizures during early drug therapy, have been suggested in research studies of epilepsy in humans.\textsuperscript{28} Nonetheless, the results from different studies are often controversial. Despite several publications that describe IE in a variety of dog breeds, publications are seldom able to demonstrate the predictors of epilepsy outcome. The only factors that predicted epilepsy outcome in these studies were the early initiation of treatment, advanced age at seizure onset, and high body weight.\textsuperscript{19,20-32} Our study included 143 epileptic dogs and 2,141 control dogs, and to the best of our knowledge, this is the most extensive epidemiological study of IE evaluating 1 dog breed in the veterinary literature. Importantly, unlike previous studies, we made an estimate for the native disease course. We found that the generalized phase of seizure was the only significant risk factor for the progression of epilepsy. A weakness of studying such a disease course is the relative subjectivity because the study was based on the owners’ judgment. We used a cutoff point at the time of the phone interviews for non-treated dogs or before starting treatment with antiepileptics for medicated dogs to minimize the influence of antiepileptic medication on the course of the disease. Although this time interval showed no statistical influence for any factor, some owners described the disease course as progressive at the beginning but self-limiting later, even without treatment. Despite carefully looking for initial clinical signs, we were not able to identify any detailed sign able to predict the course of the disease. Historically, veterinary researchers ignored the initial signs of a seizure episode and classified the majority of seizures as generalized. This point of view has changed in the last decade. We classified 85.1% of FSDs as suffering from focal onset seizures, but 53.9% had secondarily generalized seizures. Although initial signs of the seizure episode influence the seizure classification, we paradoxically seem to be back at the beginning looking for the presence of a generalized phase. A clear benefit of such a disease progression predictor is that a generalized phase of seizure can be easily recognized by the owners. In our analysis, the generalized phase was associated with a progressive course of epilepsy in every context in which it was observed: as a phase of secondary generalized (91.6%), primary generalized (0.8%), or generalized seizures with unknown onset (7.6%). We have to be aware of the disadvantages of such an untraditional approach, specifically ignoring the con-
text of the generalized phase. Categorizing all seizures this way makes it harder to find a generally meaningful and adaptable pathophysiologic explanation. Evidence provided mainly by experimental models such as kindling studies suggests that neuronal death depends on seizure spread and that propagated generalized seizures may be more harmful than partial seizures. The presence of secondary generalized seizures has been reported to be one of the factors associated with a poor outcome in human epileptic patients. Drawing direct comparisons with our data is difficult because of the different preselection of patients. Studies of human patients either concentrate on some particular epilepsy syndrome, focus on general nonpreselected epileptic populations that include all possible etiologic causes for seizures, or compare different treatment protocols. Our population represents patients presumably with IE, a genetic predisposition, no detectable brain lesions, and different seizure types. However, we found that secondary generalization, used as the pathophysiologic hallmark of seizure spread within the brain, could be used to predict disease progression. This result seems to be biologically meaningful and is in accordance with the literature. As most representative seizure types in our study were CFS and focal onset seizures with secondary generalization, our results could be applied most reliably to dogs with IE and to those with similar seizure types.

Some factors were correlated with the generalized phase of seizure. Interestingly, the age at seizure onset was not directly correlated with disease progression but was correlated with a generalized phase of seizure. The age at seizure onset is an important factor in human epilepsy, and many age-specific epilepsy syndromes are recognized. The incidence of epilepsy is highest in children. Among the childhood epilepsies, IE has a strong negative correlation with focal seizures. The exact prognosis for outcome is usually syndrome-dependent. In veterinary medicine, there is a report about juvenile epilepsy in Lagotto Romagnolo dogs. These dogs had focal seizures with a benign outcome. In FSDs, the onset of seizures occurred considerably later than observed in the Lagotto Romagnolos. The majority of seizures were focal, but secondary generalization occurred more frequently when the first episode took place during the first 3 years of life.

Our study also demonstrated a bimodal relationship between the seizure duration and the generalized phase of seizure. Seizures that lasted up to 10 minutes were 4.7 times as likely to be generalized as seizures lasting for 11 to 20 minutes. However, seizures longer than 20 minutes were as likely (OR, 3.4) to be generalized as those lasting for 11 to 20 minutes. We have considered how that type of bimodal tendency can be explained. A study of seizure duration in human epileptic patients found that secondarily generalized tonic-clonic seizures had the longest duration, whereas primary generalized tonic-clonic and tonic seizures lasted for a shorter duration. From the partial-onset seizures, complex partial seizures had a longer duration than did simple partial seizures. However, variation within groups of the same seizure type can be caused by differences in the seizure locus. A study of CFS found that a mesial temporal lobe epilepsy group had significantly longer seizures than a neocortical extratemporal epilepsy group. We suggest that the same reasoning can be applied to our results. Nevertheless, it is impossible to confirm this because groups of all seizure types were not representative for statistical analysis and comparison. A different question related to seizure duration is at what point do seizures with a long duration become life-threatening? Although various criteria (seizure frequency, quality of life, and no need for medication) suggested a benign course of IE in FSDs, long-duration seizures are classically considered to be a sign of a non-benign course of epilepsy. It is remarkable that seizures lasting for up to 30 to 40 minutes were self-limiting in the FSDs and seldom needed special treatment at the time of the episode. In human patients, although the cutoff point for status epilepticus is 30 minutes, different patient groups may have seizures of different durations, which can be considered life-threatening. Morbidity and mortality rates vary for different age groups, especially in children, and for different epilepsy syndromes. Therefore, we instead suggest a syndrome approach (benign or not benign) for some canine epileptic patients, as a simple cutoff point for the inclusion of status epilepticus to estimate seizure outcome risks.

We found several factors, such as the number of meals per day and whether the dog was used for hunting, to be significantly correlated with the occurrence of a generalized phase of seizure. It is remarkable that the correlation between the number of meals per day was linear. This is consistent with a biological connection. More frequent eating should stabilize the blood glucose levels, and we thus speculate whether this is connected to the use of dogs for hunting or to excitement levels. Physiologic hypoglycemia due to exercise in hunting dogs has been suggested as a cause of seizures and neurogenic pulmonary edema. Hypoglycemia has not been proven as a factor but is a suggested etiology. We have analyzed blood samples from a larger number of FSDs in connection with an ongoing study and have found no abnormalities in the blood glucose levels except for 1 dog in which hyperglycemia was associated with a later onset of diabetes mellitus. Eating just once per day and excessive physical activity due to hunting may cause a reduction in glucose levels and may therefore serve as a metabolic trigger to induce seizures of greater magnitude. However, in addition to constituting excessive physical activity, hunting also causes high levels of excitement through the activation of the autonomic nervous system. Clinical studies should be undertaken to examine the levels of blood glucose, insulin, and stress hormones in FSDs during exercise or in connection with the frequency of meals to investigate the hypotheses suggested by our epidemiological study.

In the future, more extensive epidemiological studies should determine whether the findings described in this study are typical only for FSDs or can be generalized to the wider population of dogs with IE. We hope that the phenotypic characterization presented in this study, together with in-depth clinical examinations, could provide a useful basis for the meaningful characterization of epilepsy syndrome in FSDs.
References
