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Behavioral Abnormalities in Lagotto Romagnolo Dogs with a History of Benign Familial Juvenile Epilepsy: A Long-Term Follow-Up Study

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**Background:** Lagotto Romagnolo (LR) dogs with benign juvenile epilepsy syndrome often experience spontaneous remission of seizures. The long-term outcome in these dogs currently is unknown. In humans, behavioral and psychiatric comorbidities have been reported in pediatric and adult-onset epilepsies.

**Hypothesis/Objectives:** The objectives of this study were to investigate possible neurobehavioral comorbidities in LR with a history of benign familial juvenile epilepsy (BFJE) and to assess the occurrence of seizures after the remission of seizures in puppyhood.

Animals: A total of 25 LR with a history of BFJE and 91 control dogs of the same breed.

**Methods:** Owners of the LR dogs in the BFJE and control groups completed an online questionnaire about each dog's activity, impulsivity, and inattention. Principal component analysis (PCA) served to extract behavioral factors from the data. We then compared the scores of these factors between the 2 groups in a retrospective case–control study. We also interviewed all dog owners in the BFJE group by telephone to inquire specifically about possible seizures or other neurological problems after remission of seizures as a puppy.

**Results:** Lagotto Romagnolo dogs with BFJE showed significantly higher scores on the factors *Inattention* and *Excitability/Impulsivity* than did the control group (P = .003; P = .021, respectively). Only 1 of the 25 BFJE LR exhibited seizures after remission of epilepsy in puppyhood.

**Conclusions and Clinical Importance:** Although the long-term seizure outcome in BFJE LR seems to be good, the dogs exhibit behavioral abnormalities resembling attention deficit hyperactivity disorder (ADHD) in humans, thus suggesting neurobehavioral comorbidities with epilepsy.

Key words: Comorbidity; Epilepsy; Excitability; Impulsivity.

**P**sychiatric, cognitive, and social neurobehavioral comorbidities have been identified in human patients with epilepsy. The etiology of these comorbidities is multifactorial.<sup>1,2</sup> The term comorbidity refers to a more than coincidental presence of 2 disorders in the same patient, but does not judge the causal relationship of the 2 conditions.<sup>3</sup> Childhood epilepsies are common in human medicine, and the majority of these patients will become seizure-free by adulthood.<sup>4</sup> However, reports have confirmed an increased incidence of behavioral disorders of various kinds in children with epilepsy.<sup>5</sup> Younger age at seizure onset is reportedly associated with a higher risk for comorbidities,<sup>2,3</sup> even

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#### Abbreviations:

ANOVA ADHD ADLTE BCECTS BFJE	analysis of variance attention deficit hyperactivity disorder autosomal dominant lateral temporal lobe epilepsy benign childhood epilepsy with centrotemporal spikes benign familial juvenile epilepsy
IE	idiopathic epilepsy
LR	Lagotto Romagnolo
PCA	principal component analysis

in benign childhood epilepsy syndromes.<sup>6–13</sup> The long-term outcome of these comorbidities, however, remains largely unknown.<sup>14–16</sup>

Psychiatric comorbidities that have a higher prevalence in patients with epilepsy include mood disorders, anxiety disorders, attention deficit hyperactivity disorder (ADHD), and other psychiatric disorders.<sup>3</sup> Attention deficit hyperactivity disorder is 1 of the most common comorbidities of epilepsy, and children with epilepsy are at much higher risk for ADHD, with a prevalence of 20–40% as opposed to 5% in the general pediatric population.<sup>5,16–21</sup>

Regardless of whether childhood epilepsies are common in children, only 1 well-defined juvenile epilepsy syndrome has been reported in dogs.<sup>22</sup> Benign familial juvenile epilepsy (BFJE) in Lagotto Romagnolo dogs is characterized by focal-onset seizures that start at the age of 5–9 weeks and spontaneously remit by the age of 13 weeks.<sup>22</sup> A recent study identified a nonsense mutation in the *LGI2* gene as a cause of BFJE.<sup>23</sup> The long-term outcome of seizures or other neurological problems in BFJE, however, remains unknown. Little is

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known about other comorbidities of epilepsy in dogs. Only 1 previous study has investigated behavioral comorbidities in epileptic dogs, suggesting that such dogs exhibit neurobehavioral comorbidities with the development of epilepsy.<sup>24</sup>

Owner-completed questionnaires previously have proved to be reliable for studying the behavior of privately owned dogs.<sup>25–27</sup> Online questionnaires have the advantage of reaching larger populations in a more cost-effective manner, and questionnaires gather information on the dog's overall behavioral history, whereas potentially more objective behavioral tests capture only a brief moment of the present behavior.

The first objective of this study was to use an ownercompleted questionnaire survey to identify possible behavioral differences in dogs with a history of BFJE compared to dogs with no history of epilepsy, with a special focus on ADHD-like signs including inattention, impulsivity and hyperactivity. Second, our aim was to determine the occurrence of seizures or other neurological problems in dogs with a history of BFJE.

#### **Materials and Methods**

## Animals

Two groups of client-owned Lagotto Romagnolo (LR) dogs were enrolled in the study. We recruited dogs with a history of juvenile epilepsy from among dogs that had participated in a previous clinical or genetic study of BFJE<sup>22,23</sup> by contacting the dogs' owners by email or phone and asking them to complete an online questionnaire. Those dogs the owners of which answered the online questionnaire were included in the BFJE group. One of the dogs in the BFJE group had received antiepileptic medication (phenobarbital) as a puppy. To determine the current status of the dog and especially the presence of possible neurological signs or behavioral problems after the remission of seizures, BFJE dog owners who completed the questionnaire also participated in a telephone interview within a month after completing the online questionnaire. The duration of the follow-up period for the BFJE dogs was defined as the time between the last seizure episode in puppyhood and the time of the telephone interview.

Control dogs of the same breed with no history of BFJE were contacted to participate in the questionnaire study by email or through individual breeders and the Lagotto Romagnolo breed club. The inclusion criteria for the control dog group were LR dogs with no history of BFJE or adult-onset epilepsy. The information in our database on the carrier status for the *LGI2* c.1552A>T (p.K518X) mutation responsible for BFJE was checked for both BFJE dogs and control dogs.

#### Questionnaire

We developed an online questionnaire to compare the dogs' activity, impulsivity and inattention levels. The questionnaire included 77 questions, of which 46 inquired about details of the dog's background and daily routines, and 31 were related to the dogs' activity, impulsivity, and inattention behavior. Questions concerning the dog's activity, impulsivity and inattention behavior were drawn from 2 previously published studies on impulsivity and activity levels in dogs. These 2 sets of questions named K<sup>28</sup> and Q<sup>29</sup> in our study previously have been validated; questionnaire Q has been shown to correlate with impulsive behavior and physiological correlates, thus showing good external validity.<sup>26</sup>

## Statistical Analysis

We manually checked the data related to the online questionnaire survey for errors (eg, double entries). For the statistical analysis, we used commercially available software.<sup>a</sup> We used the *t*-test for independent samples to compare the distribution of age and sex between the BFJE and the control group.

Principal component analysis (PCA) with varimax rotation and Kaiser normalization was conducted to explore the factorial structure of the questionnaire. The coding scales for the K and Q questions differed slightly: the scale for the K questions ranged from 1 to 4 and for the Q questions from 1 to 5. Therefore, the scores received from the K questions were divided by 4 and the scores from the Q questions were divided by 5 before the PCA to unify the scales from the 2 sets of questions. All 31 questionnaire items were grouped into 9 factors based on an eigenvalue >1. These 9 factors accounted for 66.1% of the common variance in item scores. Variables with loadings <0.40 were excluded from the factors. We also considered the biological interpretation of the factors. This analysis left us with 7 factors (Table 1) to use as a measure of activity, impulsivity, and inattention in the subsequent analysis.

We calculated the individual factor scores for each dog as the sum of the scores from individual items included in that factor. Comparisons between the scores for behavioral factors of the BFJE and the control groups were examined using an independent samples *t*-test; all tests were used 2-sided, and a *P*-value < .05 was considered significant. For further analysis, we divided the BFJE group into 2 subgroups: those with mild BFJE (defined as a history of  $\leq$  5 focal seizures) and those with severe BFJE (>5 seizures). We used an independent samples *t*-test to compare the factor scores between these subgroups.

#### Results

Altogether, 185 LR dog owners completed the questionnaire, yielding 25 dogs with a history of BFJE (89% or 25 of the 28 BFJE dogs the owners of which we contacted) and 160 control dogs. Because all BFJE dogs were >4 years old, we excluded from the study 67 control dogs that were <4 years old. We excluded an additional 2 dogs from the control group because of adult-onset epilepsy. The remaining 91 control dogs were included in the analyses.

Twenty BFJE dogs were homozygous for the LGI2 mutation, and 3 of the phenotypically affected dogs were heterozygote carriers based on the gene test; 2 affected dogs were not genetically tested. The 3 heterozygote carriers of the LGI2 mutation had had seizures similar to those in the BFJE (ie, focal-onset seizures characterized by whole-body tremor, ataxia, and stiffness). Clinical examinations performed on all 3 dogs excluded other seizure-causing diseases<sup>22</sup>, thus the dogs were also included in the BFJE group. In addition, a recent study has indicated that, in a minority of cases, the LGI2 mutation can cause epilepsy in the heterozygous state.<sup>23</sup> Of the 91 control dogs, 56 were genetically tested for the LGI2 mutation, and 36 were homozygous wild type, 20 carried the LGI2 nonsense mutation, and none were homozygous for the mutation; 35 control dogs were not genetically tested.

The mean age was 7.4 years (range, 4.6-10.7) and 6.4 years (range, 4.0-12.6) in the BFJE and control groups, respectively, at the time of questionnaire

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Table 1.	Results	01	principal	compo	onent analysis.

Item	Loading
Factor 1: Low Self-control	
(K11) It is likely to react hastily, and that's	0.708
why it is failing tasks	
(K12) It's attention can be easily distracted	0.696
(K6) It fidgets all the time	0.694
(K13) It cannot wait, as it has no self-control	0.574
(K5) It cannot be quiet; it	0.561
cannot be easily calmed	
Factor 2: Impulsivity (Q7) My dog does not think before	0.709
it acts (eg, it would steal food without	0.709
first looking to see if someone is watching).	
-(Q14) My dog appears to have a	-0.675
lot of control over how it responds.	
(Q17) My dog is not very patient.	0.653
(Q8) My dog can be very persistent	0.635
(eg, it will continue to do something	
even if it knows it will get	
punished or told off).	
-(Q10) My dog is easy to train.	-0.449
Factor 3: Inattention	
(K1) Your dog has a difficult time	0.725
learning, because it is careless or other	
things can easily attract it's attention	
(K3) It's difficult for it to concentrate	0.646
on a task or play	
(K4) It leaves from its place when	0.613
it should stay	
(K7) It seems that it doesn't listen	0.526
even if it knows that someone is speaking to it	
Factor 4: Excitability/Impulsivity	0.504
(Q1) My dog shows extreme	0.784
physical signs when excited	
(eg, drooling, panting, raising	
hackles, urination, licking lips, widening of eyes).	
(Q2) When my dog gets	0.631
very excited, it can lead to fixed	0.031
repetitive behavior (ie, an action	
that is repeated in the same way	
over and over again), such as tail	
chasing or spinning around in circles.	
-(Q13) My dog calms down very quickly	-0.499
after being excited.	
(Q3) I would consider my dog to be	0.480
very impulsive (ie, it has sudden, strong	
urges to act; it acts without forethought;	
acts without considering the effects of its actions)	
(Q18) My dog seems to get excited for no reason.	0.438
Factor 5: Reactivity	
(Q15) My dog is very interested in new	0.774
things and new places.	
(Q16) My dog reacts very quickly.	0.766
Factor 6: Short attention	
(K2) It's easy to attract its attention,	0.786
but it loses its interest soon	
-(Q12) My dog takes a long time to lose	-0.751
interest in new things.	
Factor 7: Aggressiveness	
Factor 7: Aggressiveness (Q5) My dog becomes aggressive (eg, growls, snarls, snaps, bites) when excited.	0.788

(continued)

Table 1. (Continued)

Item	Loading
(Q9) My dog may	0.732
become aggressive	
(eg, growl, snarl, snap, bite)	
if frustrated	
with something.	
(Q4) My dog doesn't like to	0.514
be approached or hugged.	

Factor loadings of questionnaire items; 31 items from 2 questionnaires grouped into 7 factors with an eigenvalue >1 and of biological importance. Two sets of questions, labeled  $K^{28}$  and  $Q^{29}$ , have been validated previously.

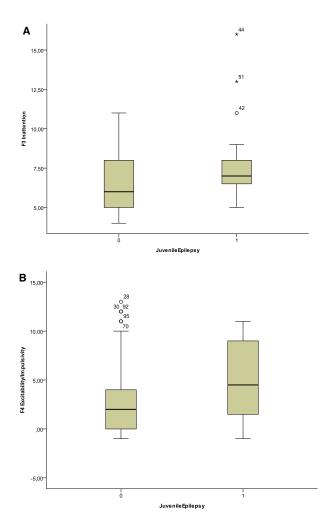
completion. There was a significant difference in the age of the groups (P = .033): the control dogs were younger than the dogs in the BFJE group. The BFJE group consisted of 11 male and 14 female dogs, and the control group consisted of 41 male and 50 female dogs. The distribution of sexes did not differ significantly between the groups (P = .926).

#### **Behavioral Factors**

Principal component analysis of the 31 questionnaire items identified 7 factors (Table 1). These 31 questions originated from the 2 different questionnaires, and mostly formed factors grouping with the questions from the same questionnaire. Four of the 7 factors found in our study closely resembled factors found in 2 previous studies. In 1 of them, investigators found 2 major fac-tors: inattention and activity-impulsivity.<sup>28</sup> Three of the 4 questions in 1 of our factors (inattention) were the same as in their inattention factor. Similarly, 4 of the 5 questions in our low self-control factor were the same as in the activity-impulsivity factor in the aforementioned questionnaire. The other study identified 3 major factors: behavioral regulation, aggression, and response to novelty.<sup>29</sup> Our *excitability/impulsivity* factor corresponds to the behavioral regulation factor in that study, because all of the questions loading significantly to our excitability/impulsivity factor also are included in the behavioral regulation factor. Similarly, our aggressiveness factor closely resembles their aggression factor.

#### **Behavioral Differences**

Analysis comparing the factor scores between the BJFE and control groups identified differences in 2 factors. The BFJE dogs had significantly higher scores for factors 3: *inattention* (P = .003) and 4: *excitability/impulsivity* (P = .021) than did the control group (Fig 1). Differences for the 2 factors remained significant even after excluding the 3 heterozygous dogs from the BFJE group (P = .002; P = .016, respectively). Because the dogs in the control group were younger than those in the BFJE group, we also compared the behavior of dogs with BFJE (n = 25) to that of the control dogs >5 years of age (n = 58), because in this case,



**Fig 1.** Box plots for behavioral factors *inattention* and *excitability/impulsivity*. Figures illustrate differences in behavioral factor scores for *inattention* (**A**) and *excitability/impulsivity* (**B**) between control dogs (0) and dogs with a history of benign familial juvenile epilepsy (1).

the ages of the groups did not differ significantly. Nevertheless, we found similar results: factors 3 (P = .003) and 4 (P = .015) had significantly higher scores in the BFJE group than in the control group. Behavior of the mildly and severely affected dogs of the BFJE group showed no differences.

Furthermore, we used 2-way analysis of variance (ANOVA) to simultaneously analyze the effect of sex and neutering status on the behavioral factor scores. This analysis identified significant differences only based on the neutering status for factor 7: *aggressivity* (P = .047) so that both neutered female and male dogs showed higher scores for this factor.

#### **BFJE Follow-Up**

The mean follow-up period for dogs in the BFJE group was 7.1 years (range, 4.75–10.75 years). Of the 25 dogs with a history of BFJE, 24 experienced no additional seizures after remission of epilepsy by the

age of 4 months. Thus, the remission rate for BFJE was 96% (24/25). One dog with a history of juvenile epilepsy had had 1 seizure episode at the age of 8 months. Twenty-four dogs showed no other neurological signs after remission of epileptic seizures, whereas 1 dog, which tested genetically homozygous for the LGI2 p.K518X mutation, had slowly progressive generalized ataxia since puppyhood and was euthanized at the age of 11 years; pathological examination confirmed cerebellar cortical degeneration. The dog was euthanized after the owner of the dog had completed the questionnaire. During the telephone interview, the owners of 4 dogs with a history of BFJE reported behavioral abnormalities including hyperactivity (2 dogs), separation anxiety (1 dog), and aggressivity (1 dog). The owners of 21 dogs reported no changes in their dogs' behavior.

In addition to the dog with cerebellar cortical degeneration, 2 dogs with a history of BFJE were euthanized at the ages of 6 and 8.5 years because of cancer and a heart problem, and 3.5 and 2.5 years before the owners completed the questionnaire, respectively. Of the 25 dogs in the BFJE group, 22 were still alive at the time of this study.

### Discussion

Behavioral abnormalities in the factors *inattention* and *excitability/impulsivity* are apparent in dogs with a history of BFJE, even after a follow-up period of at least 4 years. These abnormalities are comparable to those observed in ADHD in humans. The long-term outcome regarding seizures was good, and only 1 dog experienced seizures after puppyhood. These findings highlight the importance of neurobehavioral comorbidities in canine epilepsy despite seizure remission.

Clinical signs of ADHD are more common in certain epilepsies, such as frontal lobe epilepsy, childhood absence epilepsy, and Rolandic epilepsy, and may even antedate seizure onset.5,17,21 Attention deficit hyperactivity disorder in humans is characterized by inattention, impulsivity, and hyperactivity.<sup>16</sup> In our study, the factors inattention and excitability/impulsivity measured the dog's ability to concentrate as well as excitability or impulsivity, which can be considered comparable to behavioral abnormalities seen in ADHD patients. These factors had higher scores in dogs with a history of BFJE than in controls. Younger dogs usually are more impulsive,<sup>29</sup> active and have higher inattention scores than do older dogs.<sup>28</sup> In our study, the dogs in the control group were younger than those in the BFJE group. Accordingly, we might expect to see higher average scores for inattention and impulsivity in the control group. However, we found exactly the opposite, which makes the observed difference more convincing.

Different epilepsy syndromes may pose different risks for cognitive and behavioral development problems, but variability within and across syndromes exists.<sup>3</sup> Genetic childhood focal seizures and related epileptic syndromes comprise 3 well-defined electroclinical syndromes recognized by the International League Against Epilepsy: benign childhood epilepsy with centrotemporal spikes

(BCECTS, Rolandic epilepsy), Panayiotopoulos syndrome, and idiopathic childhood occipital epilepsy of Gastaut.<sup>30–33</sup> The disorder BFJE in Lagotto Romagnolo dogs also represents focal idiopathic epilepsy in juvenile dogs.<sup>22</sup> Studies have reported mild cognitive deficits in patients with idiopathic childhood occipital epilepsy of Gastaut.<sup>6,11</sup> Several studies have investigated neurobehavioral comorbidities in BCECTS. Children with centrotemporal spikes, with or without clinical seizures, are at higher risk for cognitive and behavioral problems.<sup>7–10,12,13</sup> Although reports indicate cognitive deficits in BECTS, some studies have indicated that these deficits resolve with seizure remission and electroencephalographic normalization.<sup>14,15</sup> In addition, it remains an open question whether a reduction in epileptogenic activity is associated with improvements in behavioral disorders, such as ADHD.<sup>16</sup> Thus, the relationship between an altered course of brain development and changes in cognition, and whether these changes are persistent upon remission of epilepsy and cessation of treatment, thus remain largely unknown.<sup>3</sup> The results of our study suggest that, even after seizures have been in remission for several years, behavioral abnormalities are still evident.

Bidirectional relationships between epilepsy and various neurobehavioral comorbidities have been suggested in both pediatric and adult epilepsy, because these comorbidities might be present at diagnosis or even before epilepsy onset.3 A common biological mechanism exists in various comorbidities and epilepsy, such as abnormalities of the neurotransmitter pathways involving serotonin, norepinephrine, dopamine, glutamate, and γ-amino-butyric acid (GABA).<sup>2</sup> Studies have suggested several underlying mechanisms responsible for comorbidities in epilepsy, including the underlying etiology of the seizures (possible underlying brain pathology), adverse effects of antiepileptic drugs, seizure characteristics (eg, seizure type, frequency, severity, duration, and age at seizure onset), seizure-induced cerebral damage, abundant interictal epileptic activity, and psychosocial factors.<sup>1,2,17,34</sup> In our study, we avoided many confounding effects, because only 1 of the dogs was receiving antiepileptic medication, and for all of the dogs, the seizures had stopped already during puppyhood. In addition, psychosocial factors can be considered unimportant in dogs. Thus, our approach provides information about neurobehavioral comorbidities unrelated to ongoing seizures or seizure-related factors, medications or social effects. Consequently, BFJE serves as an effective model for investigating the specific impact of epileptic activity per se. Moreover, the homogeneity of the dogs in the BFJE group, all of which shared a similar seizure type, decreases the effect of differences in various kinds of epilepsies or seizure types on behavioral comorbidities.

Substantial evidence indicates that childhood-onset epilepsy is associated with an abnormal prospective pattern of brain development<sup>35–39</sup> and that these structural or microstructural abnormalities in cortical and subcortical structures are linked to neurobehavioral comorbidities.<sup>38–44</sup> This may well explain poorer psychosocial outcomes in adults and even in children whose childhood epilepsy was in remission and who had stopped medications.<sup>4</sup> Also, our study found differences in behavior during long-term follow-up, even though our dogs with a history of BFJE had been seizure free for several years. This may be because of a possibly negative effect of early onset seizures on the developing brain or the presence of an antecedent neurobiological effect.

The LGI protein family consists of 4 members: 1-4.45 Hyperactive behavior has been described in a family with autosomal dominant lateral temporal lobe epilepsy (ADLTE) resulting from a mutation in the LGII gene.<sup>46</sup> According to other studies, ADHD has even antedated the onset of epilepsy, indicating that both of these conditions may represent epiphenomena of underlying neurobiological abnormalities not identified to date.<sup>47</sup> Some have suggested that the LGII mutation could have an impact on other diseases of synaptic connectivity despite ADLTE.<sup>45</sup> The protein LGI2, which is mutated in BFJE, is important for initial synapse formation during development of the central nervous system<sup>45</sup> and also could have a similar impact. This could explain the ADHD-like behavioral abnormalities in dogs with a history of BFJE.

Only 1 study in the veterinary literature has investigated behavioral changes with the development of idiopathic epilepsy (IE) in dogs.<sup>24</sup> The investigators found that in 71% of all dogs with IE, at least 1 behavior changed with epilepsy, but the study included no control dogs. The study found that drug-naïve dogs with epilepsy began to act more anxious or fearful when approached by unfamiliar dogs or people, in unfamiliar surroundings, or when faced with unpredictable movements. The dogs also acted more aggressively when being handled or approached by other dogs or unfamiliar people. Researchers suggested that these changes in behavior may be comparable to anxiety disorders observed in people with epilepsy. Changes in behavior also were observed depending on medication status. Our study compared corresponding factors examining reactions to strange people, other dogs or unfamiliar items, as well as possible aggressiveness, in the BFJE dogs to those of the control group, but found no difference.

Researchers have reached no clear consensus about the effects of seizure frequency or the degree of seizure control and the severity or presence of neurobehavioral comorbidities.<sup>5,18,48,49</sup> We compared behavior scores in mildly or severely affected BFJE dogs, depending on their seizure history and found no significant differences in behavior scores between these 2 groups, possibly because of the small number of dogs in both subgroups. Nevertheless, the results of our study suggest that, in BFJE, the severity of any behavioral abnormalities seems to be independent of the frequency or severity of seizures.

The remission of seizures in our BFJE dogs was nearly complete; only 1 dog experienced seizures after puppyhood during long-term follow-up. Only 1 previous study has assessed the remission rates of juvenile epilepsy in dogs (defined by seizures occurring before the age of 1 year), and remission rates in that study were substantially lower than those reported in children.<sup>50</sup> The remission rate of 96% in our study population was comparable to that in studies of genetic childhood epilepsies.

The main limitation of this study was that the owners of the BFJE dogs might have been influenced by the fact that they knew their dogs had a history of juvenile epilepsy and that the investigators were looking for potential differences in behavior. On the other hand, the majority of the owners of the BFJE dogs reported no abnormalities in their dogs' behavior during telephone interviews although behavioral differences were identified in the questionnaire study. Furthermore, because behavioral comorbidities of epilepsy are not well understood in veterinary medicine, we might expect dog owners to be unaware of the kinds of abnormalities in behavior that could be possible with epilepsy. An additional limitation of the study was the low number of BFJE dogs; a higher number of sick dogs may have enabled us to detect differences in the behavior of mildly and severely affected dogs. In this study, all of the affected dogs were at least 4-year old. Although a long follow-up period was essential to ensure remission of seizures, the fact that all of the affected dogs were rather old may have decreased our ability to detect previous ADHD-like abnormalities in behavior. Furthermore, 3 affected dogs were dead at the time of this study, and the owners may have been unable to recall their dog's actual behavior, especially if the dog had died long before this study was performed. As a result, our study protocol with the questionnaire survey may have caused recollection bias, but this would have affected both the BFJE and control groups. In addition, because behavioral differences were evident only in the questionnaire study, we cannot define the age of onset of behavioral abnormalities in the BFJE dogs.

### Conclusions

Although the prognosis for seizure outcome in BFJE is good, the results of this study, based on a validated questionnaire about impulsivity and activity, suggest that the behavior of dogs with a history of BFJE differs from that of control dogs. These behavioral abnormalities resemble clinical signs of ADHD in humans. Behavioral differences seem to be independent of seizure characteristics, such as the frequency or severity of seizures. In addition, we detected behavioral abnormalities even after a long seizure-free period. Thus, the findings of our study support the hypothesis that a common neurobiological factor underlies seizures and neurobehavioral comorbidities.

### Footnotes

<sup>a</sup> IBM SPSS Statistics, version 21; IBM, Armonk, NY.

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

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

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