Clinical characterization of epileptic seizures in Pomeranians with idiopathic epilepsy or epilepsy of unknown cause

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Abstract

Background: Focal epileptic motor seizures manifested by limb contraction have been recognized anecdotally in Pomeranians.

Objectives: To investigate clinical features of idiopathic epilepsy (IE) and epilepsy of unknown cause (EUC) in Pomeranians as well as the ADAM23 haplotype frequency previously reported as a common risk haplotype for epilepsy in several breeds of dogs.

Animals: Twenty-eight Pomeranians, including 15 with IE and 13 with EUC. Nine Pomeranians with epilepsy and 8 control Pomeranians were used for ADAM23 risk haplotype analysis.

Methods: Case series study including both retrospectively and prospectively collected cases. The ADAM23 haplotype was determined by direct sequencing of PCR amplicons. Data were analyzed descriptively.

Results: Focal epileptic seizures (FS) were the predominant type of seizure in 22 of 28 dogs (78.6%). Among these, 12 of the IE dogs (80.0%) and 10 of the EUC dogs (76.9%) showed FS. Notably, 21 of 22 Pomeranians with FS (95.5%) showed limb contraction during ictal periods. Some dogs with FS also showed immobility, generalized tremors, difficulty walking or moving, autonomic signs, orofacial automatisms or some combination during ictal events. Ten dogs with FS and limb contraction had electroencephalography (EEG) performed, and interictal epileptiform discharges were identified in 9 dogs. The haplotype frequency of ADAM23 in cases was lower (27.8%) than that of the controls (56.3%).

Conclusions and Clinical Importance: In our study, FS was the predominant type of seizure in Pomeranians, and almost all cases with FS showed limb contraction, regardless of whether having IE or EUC.

KEYWORDS

canine, electroencephalography, focal motor seizure, seizure phenomenology, seizure semiology

Abbreviations: ASM, antiseizure medication; CSF, cerebrospinal fluid; EEG, electroencephalography; EUC, epilepsy of unknown cause; FS, focal epileptic seizures; FMS, focal motor seizures; FSvGS, focal epileptic seizures evolving into generalized epileptic seizures; GS, generalized epileptic seizures; IE, idiopathic epilepsy; IVETF, International Veterinary Epilepsy Task Force; MRI, magnetic resonance imaging.

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1 | INTRODUCTION

Epilepsy is a common functional brain disorder in dogs, and clinically is defined as ≥2 unprovoked epileptic seizures >24 hours apart. According to the International Veterinary Epilepsy Task Force (IVETF) classification, epileptic seizures are classified into 3 types: focal epileptic seizures (FS), generalized epileptic seizures (GS), and focal epileptic seizures evolving into generalized epileptic seizures (FSvGS). In several breeds of dogs, FS is commonly recognized in idiopathic epilepsy (IE), which is characterized by a suspected genetic background or no indication of structural epilepsy with clinical onset between 6 months and 6 years of age. Focal epileptic seizures represent lateralized or regional signs or both such as motor, autonomic, or behavioral signs. Among these, FS characterized by elementary motor events such as stereotypical muscle contraction or automatisms is also referred to as focal motor seizures (FMS).

A few forms of unique stereotypical FS in specific breeds of dog have been reported with proven or suspected genetic backgrounds. Focal epileptic seizures with limb contraction in Pomeranians has been sporadically recognized in Japan. However, thus far, clinical features of epilepsy in Pomeranians have not been described. Furthermore, in epilepsy in dogs, many breeds are suspected of having susceptible genetic backgrounds; these are likely to be complex genetic traits for IE. An ADAM23 haplotype is reportedly a common risk haplotype for epilepsy in some breeds of dogs.

An acknowledged hypothesis is that FS with limb contraction (a unique FMS form) is a relatively common seizure semiology in a population of Pomeranians with presumed IE or epilepsy of unknown cause (EUC, dogs with an age of seizure onset <6 months or >6 years in which the underlying cause for epilepsy is unknown) in Japan and a wide age range for clinical onset is seen.

We aimed to characterize clinical features of IE/EUC in Pomeranian dogs including seizure semiology and electroencephalography (EEG) findings, and to investigate the frequency of the common risk haplotype in the ADAM23 gene reported previously for epilepsy in dogs.

2 | MATERIALS AND METHODS

Ours was a descriptive, case series study of both retrospectively and prospectively collected cases. Some cases also were included in a genetic investigation of the ADAM23 risk haplotype frequency in Pomeranians, which previously has been reported in IE in some breeds of dogs.

2.1 Study population, inclusion criteria, and exclusion criteria

Medical records from the Neurology and Neurosurgery Service of Nippon Veterinary and Life Science University (Tokyo, Japan) from April 1999 to December 2019 and those from the Neurology and Neurosurgery Service of Azabu University (Kanagawa, Japan) from June 2006 to December 2019 were searched to identify dogs that were diagnosed as “IE,” “suspected IE,” or “EUC.” Furthermore, additional cases diagnosed as “IE,” “suspected IE,” or “EUC” by a veterinarian from August 2019 to May 2020 were recruited prospectively in collaboration with veterinary neurologists in several referral practices in Japan, and clinical data were collected using a standardized questionnaire from August 2019 to May 2020.

Because most of the cases obtained retrospectively had been diagnosed before publication of IVETF consensus proposal, the diagnostic scheme and epilepsy-specific magnetic resonance imaging (MRI) protocol proposed by IVETF in 2015 were not completely adopted.

We used the following inclusion criteria: history of recurrent epileptic seizures (≥2 seizures occurring >24 hours apart), normal laboratory findings (CBC and serum biochemistry with or without urinalysis), normal interictal neurologic examination, and no indication of structural epilepsy on MRI for dogs with age at clinical seizure onset <6 months or >6 years. Magnetic resonance imaging findings such as Chiari-like malformation or relatively mild to moderate ventricular enlargement (without relevant neurological deficits other than epilepsy) were accepted, and they were not used as exclusion criteria because they have been reported to have no association with epilepsy in other breeds. Some cases in our study had been diagnosed with mild hydrocephalus in addition to IE. Diagnosis of hydrocephalus is more complex than simply MRI findings of enlarged ventricles, and standardized criteria for the diagnosis of hydrocephalus have not been used in the previous diagnoses for the current cases. Based on only 1 of the findings, such as narrowing of the subarachnoid space, some cases had been recorded as mild hydrocephalus in the medical records. Therefore, in our study, cases diagnosed with mild hydrocephalus together with IE on MRI were reevaluated using the recently proposed criteria, which were derived from those described previously. Namely, clinically relevant hydrocephalus was based on a ventricle/brain ratio > 0.62 and presence of ≥2 of the following morphological criteria: flattening of gyri and sulci, deformation of the interthalamic adhesion, disruption of the internal capsule, dilatation of the olfactory recess, and presence of periventricular edema. Based on the criteria, cases classified as clinically silent ventriculomegaly rather than clinically relevant hydrocephalus were included in our study.

The exclusion criteria were as follows: history suggesting other intracranial diseases, indication of structural epilepsy by MRI or cerebrospinal fluid (CSF) analysis or both, and seizure semiology that did not correspond to epileptic seizures and indicated other causes such as syncope, vestibular disease, paroxysmal dyskinesia, narcolepsy, idiopathic head tremor, or compulsive disorder.

Finally, cases that met the criteria were assigned to IE or EUC: IE included dogs with age of onset between 6 months and 6 years old whereas EUC included dogs with age of onset ≤6 months or ≥6 years old and with MRI that showed no indication of structural epilepsy, in
accompany with the age range proposed by IVETF. Dogs were not required to have CSF analysis to be diagnosed with EUC for our study. With regard to the terminology mentioned above, the IVETF proposal classifies IE into 3 subclasses: IE (genetic), IE (suspected genetic), and IE (unknown cause). Because no reports about confirmed or suspected genetic background for IE in Pomeranian dogs have been published to date, IE in Pomeranians was classified as IE (unknown cause) and was simply referred to as IE in our study. Based on the terminology proposed by IVETF, unknown cause (not either IE or structural epilepsy) was referred to as EUC in our study, as mentioned earlier.

2.2 Clinical data collection

The data of Pomeranian dogs with IE or EUC that met the criteria were further analyzed. Based on the medical records, seizure types were re-classified based on the IVETF proposal. Collected data included the following: signalment (i.e., age, sex, and neuter status), body weight, diagnostic interventions, details of seizure information such as age at onset, seizure type classification, detailed seizure description, monthly seizure day frequency (i.e., number of days in a month that a dog has at least 1 seizure), seizure duration, preictal or postictal events, history of cluster seizures or status epilepticus at the time of diagnosis, and clinical response to antiseizure medications (ASMs). Clinical response to ASM was re-evaluated based on the IVETF proposal. Follow-up was performed to categorize outcome as seizure-free (3 times the longest pretreatment interictal interval and at least 3 months), partial therapeutic success (decrease in seizure frequency or clusters and status epilepticus), no response, and undetermined. Furthermore, videos of ictal events (when available) provided by dog owners were used to confirm seizure semiology. The EEG findings were used as supportive data for the characterization when available.

2.3 Diagnostic intervention method

Magnetic resonance imaging acquisition was performed using a 1.5 or 3.0-Tesla MRI scanner except for 3 dogs that underwent MRI using a 0.3, 0.4, or 1.5-Tesla MRI scanner at other institutes.

Scalp EEG examinations were carried out using a digital electroencephalogram device in either of the channel montages derived from previous literature for 15 to 40 minutes. In short, the average potential reference (6 dogs) and the referential derivation (4 dogs) were used for EEG monitoring. Sedation was performed using medetomidine (6 dogs) or dexmedetomidine (2 dogs) administration or sevoflurane inhalation (2 dogs). Detailed information of EEG examinations is summarized in Appendix S1.

Cerebrospinal fluid analysis, including at least cell count and total protein concentration, was evaluated when available. When a sufficient amount of CSF was collected, cytology also was performed. Fasting and postprandial serum bile acid concentrations also were retrieved from the medical records when available.

2.4 ADAM23 haplotype analysis

Ethylendiaminetetraacetic acid blood samples from Pomeranians diagnosed with IE, EUC, or other diseases, were archived or buccal swabs were collected and submitted by owners in accordance with an approved Institutional Animal Care and Use Committee protocol of Nippon Veterinary and Life Science University (accession number: H30-3) or an approved Biobank protocol of Azabu University. Genomic DNA was extracted from whole blood using commercially available column-based DNA extraction kits.

Six variants on the risk haplotype in ADAM23 previously reported were amplified by PCR and determined by direct sequencing, as previously described. Primer sequences and PCR condition are summarized in Table S1.

2.5 Data analysis

Data are presented descriptively. Categorical data are presented with frequencies and percentages when relevant. Descriptive statistics presented as median and range were used. Data analyses and visualizations were performed using R (version 4.1.2) software.

3 RESULTS

3.1 Study Population

Data from 37 Pomeranians with a history of seizures and that were previously diagnosed with IE, suspected IE, or EUC were retrospectively collected. Furthermore, 3 Pomeranians with a history of seizures that were diagnosed with IE, suspected IE, or EUC by a veterinarian also were prospectively recruited for data collection. Therefore, data from 40 Pomeranians were obtained. Five dogs with epileptic seizures, which were diagnosed with ventriculomegaly or mild hydrocephalus, were considered clinically silent ventriculomegaly as described above and included in the study. Twelve dogs that did not meet the criteria were excluded (Figure 1).

Ultimately, 28 cases met the criteria, comprising 15 IEs and 13 EUCs, with demographic data summarized in Table 1. Distribution of age at the onset of IE and EUC dogs is shown in Figure 2.

In total, 22 (78.6%) of 28 dogs including 9 IEs (60.0%) and 13 EUCs (100%) underwent MRI.

Cerebrospinal fluid analysis, including cytology, was performed in 2 dogs (7.1%; 1 IE and 1 EUC), with no clinically relevant findings in both dogs. Bile acid stimulation testing was performed in 2 dogs (7.1%; 1 IE and 1 EUC), and results were normal.

3.2 Seizure semiology

Clinical data of all 28 dogs with IE and EUC are summarized in Table 1. Focal onset seizure (ie, FS and FSvGS) accounted for 82.1%
Of all cases. Of note, in 22 dogs (78.6%) with FS, 21 dogs (95.5%) showed FS with limb contraction. Focal epileptic seizures with limb contraction were characterized by unilateral limb contraction (typically thoracic limb, Figure 3), and other limb(s) followed the initial limb's involvement in some dogs (Video S1). In 21 dogs showing FS with limb contraction, it was reported that only 1 limb was affected in 10 dogs, ≥2 limbs were involved in 9 dogs, and 2 dogs had incomplete information about affected limbs; 1 or 2 forelimbs were affected with no record of the affected side(s).

Focal epileptic seizures with limb contraction in Pomeranians included tonic or clonic movement with abnormal limb posture (i.e., sustained or intermittent involuntary limb muscle contractions). Some dogs also reportedly showed immobility, generalized tremors, and difficulty walking or moving during the ictal event (Video S1). Furthermore, autonomic signs or automatisms such as urination (6 dogs), vomiting (5 dogs), defecation (3 dogs), mydriasis (2 dogs), salivation (2 dogs), or licking (2 dogs) were reported in 14 dogs (Video S1: Cases 1 and 3). Seizure semiology also was confirmed by videos of

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**TABLE 1** Comparison of clinical data between idiopathic epilepsy (IE) cases and epilepsy of unknown cause (EUC) cases

| Variables                              | Overall (n = 28) | IE (n = 15) | EUC (n = 13) |
|----------------------------------------|-----------------|------------|-------------|
| Sex                                    |                 |            |             |
| Male (neutered)                        | 12 (4)          | 5 (2)      | 7 (2)       |
| Female (neutered)                      | 16 (9)          | 10 (6)     | 6 (3)       |
| Body weight (kg), median (range)       | 2.6 (0.7-8.2)   | 3.5 (1.9-8.2) | 2.4 (0.7-4.4) |
| Age at onset (months)                  | 40.5 (2-120)    | 43.0 (9-67) | Seizure onset <6 months old: 4.0 (2–5) |
|                                        |                 |             | Seizure onset >6 years (74 months) old: 92.5 (77-120) |
| Seizure type                           |                 |            |             |
| FS                                     | 22 (78.6%)      | 12 (80.0%) | 10 (76.9%)  |
| FSvGS                                  | 1 (3.6%)        | 0          | 1 (7.7%)    |
| GS                                     | 4 (14.3%)       | 2 (13.3%)  | 2 (15.4%)   |
| GS with unknown onset                  | 1 (3.6%)        | 1 (6.7%)   | 0           |
| The presence of limb contraction among FS | 21 (95.5%)      | 11 (91.7%) | 10 (100%)   |
| History of cluster seizures            | 13 (46.4%)      | 9 (60.0%)  | 4 (30.8%)   |
| History of status epilepticus          | 2 (7.1%)        | 1 (6.7%)   | 1 (7.7%)    |

Note: Data were presented as count (percentage) of cases unless otherwise indicated.
Abbreviations: EUC, epilepsy of unknown cause; FS, focal epileptic seizures; FSvGS, focal epileptic seizures that evolved into generalized epileptic seizures; GS, generalized epileptic seizures; IE, idiopathic epilepsy.
ictal events that owners provided in 10 cases, including 6 IEs and 4 EUCs. Information about consciousness was available in 23 dogs, and 16 dogs appeared to be aware of their surroundings during the FS period. However, the presence of autonomic signs or consciousness were not always specified in the medical records in the retrospective cases.

Seizure types of 15 IE and 13 EUC cases are summarized and compared in Table 1. Eleven of 12 IE dogs with FS (91.7%) and all 10 EUC dogs with FS showed FS with limb contraction. One IE dog with FS, that did not show FS with the limb contraction, showed difficulty walking, difficulty standing up, and tremor as its seizure semiology. One dog with EUC showing FSvGS had generalized tremors as a part of its seizure semiology, but limb contraction was not reported. Furthermore, clinical data of EUC cases with age at clinical seizure onset <6 months or >6 years are summarized and compared in Table S2.

In 6 IE or EUC dogs showing FS with limb contraction, seizure semiology could be confirmed again at the time of our study using videos provided by the owners. Reviewing those videos of 6 dogs indicated that limb contraction itself did not last for the entire seizure duration. Limb contraction and abnormal limb posturing lasted from a few seconds to approximately 15 seconds and occurred repeatedly during an ictal event. Limb contraction was characterized by sustained or repetitive, tonic or flexed, limb posturing (Figure 3; Video S1).

In our study, monthly seizure day frequency only was determined for dogs that were observed for a minimum of 1 month before initiating ASM. There were 23 dogs, including 12 IEs and 11 EUCs, that had an observation period ≥1 month for increased seizure day frequency before initiating ASM (median, 2 months; range, 1-6 months). The other dogs had insufficient durations of observation to determine monthly seizure day frequency. The median monthly seizure day frequency (range) before initiating ASM was 1.3 (range, 0.3-7.0) for the entire study population, 1.0 (range, 0.3-7.0) for IE dogs and 1.5 (range, 0.3-4.0) for EUC dogs.

Preictal information was available for 9 dogs and postictal information was available for 12 dogs. Two dogs showed signs of anxiety such as attention seeking or clinging to the owner and 1 dog also showed restless wandering as a preictal phenomenon. One dog had a pelvic limb limp on the affected side and 1 experienced vomiting as a postictal phenomenon.

Cluster seizures were seen in 46.4% of Pomeranians with IE and EUC. However, status epilepticus was not a common finding (only 2 cases) in our study (Table 1).

3.3 EEG analysis

Electroencephalographic data was available for 10 (35.7%) of 28 dogs, including 4 IEs and 6 EUCs. All 10 dogs had FS with limb contraction. In 9 of 10 dogs, EEG showed interictal epileptiform discharges (IEDs) in the form of spikes, sharp waves, polyspikes or some combination of these (Figure 4). These were detected in a single or some combination of the following regions: frontal (5 dogs), central/parietal (3 dogs), temporal (1 dog), or occipital region (2 dogs). In 3 of 9 dogs with EEG
abnormalities, the IEDs were contralateral to the side where FS with initial limb contraction occurred. One dog showed partial contralaterality between IEDs site and FMS because FMS started on the contralateral side and progressed to the ipsilateral side. Two dogs had IEDs on both cerebral hemispheres whereas the FMS was observed unilaterally. Another dog showed partial contralaterality between IEDs site and FMS because FMS started on the same side and progressed to the contralateral side. Two dogs had IEDs ipsilateral to the side on which FS started. Detailed seizure characteristics and EEG findings for each dog are compared in Table S3 for 10 dogs that underwent EEG.

3.4 | ASM outcome

Antiseizure medication responsiveness could be evaluated in 12 dogs, including 5 IEs and 7 EUCs. Nine of 12 dogs (3 IEs and 6 EUCs) had monotherapy (zonisamide [7 dogs], phenobarbital [2 dogs]), and 3 dogs (2 IEs and 1 EUC) had dual therapy (combinations of phenobarbital and potassium bromide, zonisamide and potassium bromide, or levetiracetam and potassium bromide, respectively).

Complete seizure freedom for at least 1 year was observed in 5 dogs (41.7%; 1 IE and 4 EUCs) with monotherapy (4 dogs) or dual therapy (1 dog; median, 24 months; range, 12-72 months). Another IE dog had a decrease of seizure day frequency to 1 seizure day per year with monotherapy. This dog had presented with a seizure day frequency of 1 seizure day for approximately 10 days just before ASM initiation. In 2 dogs (1 IE and 1 EUC) receiving monotherapy, seizures were not observed after initiation of ASM for 4 or 8 months, respectively, but further follow-up information was not available. Two dogs (1 IE receiving dual therapy and 1 EUC receiving monotherapy) had partial therapeutic success in observation periods of 30 months and 6 months, respectively. The monthly seizure day frequency of the
former decreased from 1 to 0.5, and that of the latter decreased from 5.4 to 1.8. One EUC dog receiving monotherapy showed no seizures for 1 month, but this dog was considered undetermined because of a follow-up period <3 months. The remaining IE dog receiving dual therapy also was considered undetermined because a few seizures occurred and abnormal behavior episodes were witnessed after 1.5 years of freedom from seizures, and thus it was difficult to evaluate ASM responsiveness appropriately.

**3.5 ADAM23 haplotype analysis**

The DNA from 9 of the study dogs was available for ADAM23 haplotype analysis, including 4 dogs with IE that had FS, and 5 dogs with EUC, 4 that had FS, and 1 that had GS. Eight Pomeranian dogs diagnosed with neurological diseases other than IE or EUC were genotyped as controls. The frequency of the risk haplotype was 27.8% in 9 cases and 56.3% in 8 controls. Clinical information included for the ADAM23 haplotype analysis and results are summarized in Table S4.

**4 DISCUSSION**

A high proportion (78.6%) of Pomeranian dogs with IE or EUC had FS, although the sample size was small. In our study, FS was considered the predominant epileptic seizure type in Pomeranians. Focal onset seizures (i.e., FS and F5vGS) were found in 82.1% of all IE and EUC cases and it was a major seizure onset form, as reported in other cases and it was a major seizure onset form, as reported in other studies. 

Furthermore, generation of secondary epileptogenesis outside of the primary focus has been described in human patients, some of whom did not have an unequivocal lesion on MRI, as well as in experimental animal models of epilepsy. Therefore, a dog could have multiple irritative zones other than the seizure focus predicted by seizure semiology. To confirm accurate location of IEDs or the irritative zone associated with ictal signs, long term video-EEG monitoring is required.

In human medicine, dystonic posturing is defined as forced, unnatural posturing of an arm or leg on 1 side of the body. Some dogs showed sustained, unnatural posturing that resembled the dystonic posturing recognized in humans with epilepsy. In human medicine, dystonic posturing of an upper limb is a common clinical feature in temporal lobe epilepsy, and usually is considered to be contralateral to the epileptogenic focus. This unilateral dystonic posturing also is observed in frontal lobe epilepsy. Ictal dystonic posturing in temporal lobe epilepsy is considered to be caused by propagation of the ictal discharge into the basal ganglia, as well as in extratemporal lobe epilepsy such as frontal lobe epilepsy. Involvement of the basal ganglia in the generation of ictal dystonic posturing has been suggested by studies using single photon emission computed tomography (SPECT) and positron emission tomography (PET). These techniques may be useful in elucidating the underlying mechanisms of FS with limb contraction in Pomeranians.

Dystonia is characterized by sustained or intermittent involuntary muscle contractions that cause abnormal, often repetitive, movements, postures, or both. In the proposal of IVETF, the term dystonic was defined as: “Sustained contractions of both agonist and antagonist muscles producing athetoid or twisting movements which when prolonged may produce abnormal postures.” Dystonic seizure is included in the category of motor tonic seizure and is an adjunctive term used for epileptic seizures. On the other hand, in the consensus statement of the International Veterinary Canine Dyskinesia Task Force, dystonic movements also are mentioned, which indicates a wide variety of speed (from slow to shock-like) and duration (from a flash to hours). Some Pomeranians in our study showed dystonic seizures, that is, tonic seizures with abnormal postures (Video S1, Case 2); some showed clonic or myoclonic seizures of the limb(s) (i.e., dystonic spasms or myoclonic dystonia) and abnormal postures with the limb flexed (i.e., dystonic movements, Video S1, Cases 1 and 3). Therefore, the term dystonic seizure only was applicable to FS with tonic limb dystonia. Eventually, the term FS with limb
Paroxysmal dyskinesia is a group of involuntary movement disorders characterized by self-limiting episodes including dystonia and other abnormal involuntary, nonstereotypical movements. Importantly, sudden dystonia (i.e., sustained muscle contraction causing abnormal movements and postures of limbs, trunk, head or some combination of these) is a main phenomenon reported in paroxysmal dyskinesia in some breeds of dogs. A similar abnormal posture, limb dystonia, was also a common finding in the Pomeranians in our study. As for some episodes seen in veterinary clinical practice, it may be difficult to differentiate between epileptic and nonepileptic paroxysms. However, clinical characteristics of FS include decreased or absent conscious responses; autonomic signs such as urination, defecation, or salivation; orofacial movements (automatism) including mastication, lip smacking, licking, chewing, and yawning; and, pre- or postictal abnormalities or both, whereas paroxysmal dyskinesia does not include such clinical characteristics.

In our study, owner-reported information about consciousness during the ictal phase was available for 23 dogs. Sixteen dogs were reported to be aware during the ictal event, which may suggest that the majority of IE or EUC in Pomeranians with FS may represent focal aware motor seizures that sometimes may be confused with paroxysmal dyskinesia. Although information about consciousness and the presence of autonomic or orofacial signs was not always specified in the medical records of the retrospective cases, 14 dogs showed autonomic signs or orofacial automatism. Furthermore, 9 of 10 dogs that underwent EEG showed IEDs. Our study also emphasizes the importance of EEG when events are not easily distinguished between epileptic and nonepileptic paroxysms. Information regarding the clinical response to ASM was available in 12 dogs, and a good response overall was reported. Five of 12 dogs had a complete seizure-free outcome for at least 1 year (median, 24 months; range, 12-72 months). Although paroxysmal dyskinesias are commonly self-limiting and have a benign course, the higher rates of good ASM response also supports the diagnostic likelihood of epilepsy. The evidence (including EEG abnormalities, ASM response, and homogeneous and short seizure duration ≤5 minutes) reinforced the conclusion that the limb contraction episodes seen in these dogs were epileptic in nature rather than representing paroxysmal dyskinesia.

Our study included Pomeranian dogs with IE or EUC in Japan. Therefore, predisposition to this syndrome in Pomeranians might reflect a higher allele frequency of variant(s) associated with this syndrome in a population of Pomeranians in Japan. However, by reviewing several ictal videos posted by owners in countries other than Japan using the online video sharing platform YouTube with the search terms: “pomeranian” AND “seizure” OR “epilepsy,” Pomeranians exhibiting FS appeared to be found in other parts of the world. Idiopathic epilepsy cases among most breeds of dogs are considered to have a complex inheritance pattern, and underlying genetic variants remain to be elucidated. A risk haplotype in ADAM23 has been identified in epilepsy in some breeds. Unlike some breeds that have been reported to have a risk haplotype for IE in ADAM23, the frequency of the reported risk haplotype was lower in our cases than in controls. Because the number of cases and controls genotyped in our study was small (9 and 8 dogs, respectively), our results are preliminary. Further genomic investigation will be required to investigate the underlying genetics of IE and EUC in Pomeranian dogs.

Our study had some limitations. First, it included only a small number of cases, which may cause random error. For that reason, the prevalence of FS with limb contraction in Pomeranians could change when evaluated on a larger scale with more cases. Second, selection bias may have occurred if patients with atypical seizure types such as FS with limb contraction (as compared to GS) may have been selectively referred. Third, there is the possibility of bias in collection of data retrospectively from medical records. Because the data for many cases was collected from existing medical records, some data with respect to preictal or postictal events was missing. Conversely, because seizure semiology has been confirmed by veterinarians only in cases for which video was provided, there is a possibility that in other cases, the information described in the medical records was influenced by information bias. Fourth, it was not possible to apply the criteria for all cases included in our study because data for most cases were obtained retrospectively and a majority of the cases were diagnosed before the IVETF consensus guidelines were published. In particular, in our study, it is a shortcoming that the majority of the presumed EUC cases did not undergo CSF analysis. In a previous report, 24% of dogs with inflammatory CSF (6 of 25 dogs) showed normal MRI findings, but the clinical signs of dogs with normal MRI findings were not described. We acknowledge the possibility that presumptive IE or EUC cases without CSF analysis might have had inflammatory CSF findings although brain MRI findings obtained in all EUCs and in 9 of 15 IEs were considered normal. However, although the duration of the observation period varied, 7 of 13 EUCs and 5 of 15 IEs for which follow-up information was available did not develop any other neurological signs during the follow-up period. Furthermore, serum biochemistry showed no clinically relevant abnormalities in any of the dogs, and abnormal MRI or EEG findings suggestive hepatic encephalopathy were not detected, although bile acid stimulation testing was completed in very few dogs. Fifth, there still is a chance of epileptic seizure occurrence in dogs with clinically silent hydrocephalus because seizures have been long recognized in dogs with internal hydrocephalus. However, a recent study reported only 2 dogs having seizures in 98 dogs diagnosed with internal hydrocephalus. Furthermore, in another recent study, no dog developed epileptic seizures in 44 dogs with internal hydrocephalus that underwent ventriculoperitoneal shunting. Hydrocephalus itself was considered most unlikely to be epileptogenic. Sixth, although attention was given not to include cases that may have had paroxysmal dyskinesia in our study, a slight possibility of misdiagnosis remains. Finally, the number of samples used for the ADAM23 haplotype analysis was small and pedigree information was not available, leaving the genetic basis of remaining cases unknown.
5 | CONCLUSION

In conclusion, we described the clinical characterization including seizure semiology of IE, EUC, or both in Pomeranian dogs in Japan, although sample size was small. Of note, 78.6% of Pomeranian dogs with IE and EUC in our study showed FS, and FS with limb contraction accounted for 95.5% of FS. Therefore, FS with limb contraction (ie, FMS) may be a major epileptic seizure type in Pomeranian dogs. Additional studies would be necessary to elucidate the prevalence as well as mechanism of FS with limb contraction and to determine the underlying genetics of IE, EUC or both in Pomeranian dogs.

ACKNOWLEDGMENT

This study was partially supported by The Science Research Promotion Fund from Promotion and Mutual Aid Corporation for Private School of Japan (PMAC). The authors thank the gene bank (Biobank, Azabu University, Kanagawa, Japan), which was a MEXT-Supported Program for the Strategic Research Foundation at Private Universities (2011-2015), for providing the DNA samples of Pomeranians with or without epilepsy (ie, cases or controls) for the preliminary genetic analysis, some of which were also included and analyzed in the current descriptive study. The authors also thank Dr Naoaki Matsuki and other colleagues for their help in collecting clinical data as well as the dog owners for provided videos.

CONFLICT OF INTEREST

Authors declare no conflict of interest.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

The study was approved by the ethics committees of Nippon Veterinary and Life Science University (accession number: H30-3). Archiving of blood samples at Azabu University was undertaken in accordance with an approved Biobank protocol of Azabu University.

HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study.

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SUPPORTING INFORMATION
Additional supporting information can be found online in the Supporting Information section at the end of this article.