

## STANDARD ARTICLE

# Seizure-precipitating factors in dogs with idiopathic epilepsy

Johanna A. Forsgård<sup>1</sup>  | Liisa Metsähonkala<sup>2</sup> | Anna-Mariam Kiviranta<sup>1</sup>  |Sigita Cizinauskas<sup>3</sup> | Jouni J.T. Junnila<sup>4</sup> | Outi Laitinen-Vapaavuori<sup>1</sup> | Tarja S. Jokinen<sup>1</sup><sup>1</sup>Department of Equine and Small Animal Medicine, Faculty of Veterinary Medicine, University of Helsinki, Helsinki, Finland<sup>2</sup>Pediatric Neurologist, Hospital of Children and Adolescents, Helsinki University Central Hospital, Helsinki, Finland<sup>3</sup>Referral Animal Hospital Aisti, Vantaa, Finland<sup>4</sup>4Pharma Ltd, Helsinki, Finland**Correspondence**Johanna A. Forsgård, Department of Equine and Small Animal Medicine, Faculty of Veterinary Medicine, University of Helsinki, P.O. Box 57, 00014 Helsinki, Finland.  
Email: johanna.hippi@helsinki.fi**Funding information**

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**Background:** Stress, sleep deprivation, and infectious diseases are important seizure-precipitating factors in human epilepsy patients. However, these factors have not been thoroughly studied in epileptic dogs.**Objective:** Seizure-precipitating factors are common in dogs with idiopathic epilepsy and the occurrence of these factors associate with the dogs' signalment, personality, and epilepsy-related factors.**Animals:** Fifty dogs with diagnosed idiopathic epilepsy from the hospital populations of University Veterinary Teaching Hospital of University of Helsinki and Referral Animal Hospital Aisti.**Methods:** In a retrospective cross-sectional observational study, owners were interviewed about their dogs' possible seizure-precipitating factors according to a predefined questionnaire. The dogs were identified and selected by searching the medical records of the participating animal hospitals.**Results:** The prevalence of seizure-precipitating factors in the study population was 74% (37/50). The most frequently reported factors included stress-related situations, sleep deprivation, weather, and hormonal factors. In dogs with focal onset seizures, the number of precipitating factors was 1.9 (95% CI 1.1-3.4) times higher compared to dogs with generalized seizures.**Conclusions and Clinical Importance:** Seizure-precipitating factors are common in dogs with idiopathic epilepsy, and the nature of these factors is consistent with those of human patients. Aside from antiepileptic medication, acknowledging and avoiding seizure-precipitating factors could help veterinarians achieve better treatment outcomes.**KEYWORDS**

canine epilepsy, reflex seizures, seizure-precipitating factors, triggering factors

## 1 | INTRODUCTION

Many human epilepsy patients report precipitating factors associated with their seizures.<sup>1-4</sup> These seizure-precipitating factors include, for instance, sleep deprivation, emotional stress, infectious diseases, menstrual cycle, and alcohol consumption.<sup>1-3</sup> Patients usually experience both unprecipitated and precipitated seizures.<sup>2</sup> In particular, seizure-precipitating factors often seem to accompany genetic epilepsies. In

the new ILAE etiological classification of human epilepsies, the term genetic epilepsies includes the previously classified idiopathic epilepsy.<sup>5</sup> Although, patients with other types of epilepsies frequently report precipitants as well.<sup>3,6</sup> In addition, the prevalence and nature of precipitating factors in human epilepsy patients correlate with age, sex, and seizure type.<sup>3,4,6-9</sup> Precipitating factors do not necessarily initiate the seizure immediately, but the seizure follows, for example, within 24 hours.<sup>10</sup> Some precipitating factors, such as sleep deprivation, are common, affecting many epilepsy patients, whereas other precipitants are more specific, such as photostimulation.<sup>2,3,11</sup> The mechanisms by which precipitating factors lower the seizure threshold are most likely quite diverse.<sup>12</sup>

**Abbreviations:** EEG, electroencephalogram; IVETF, International Veterinary Epilepsy Task Force; MRI, magnetic resonance imaging; RAHA, Referral Animal Hospital Aisti; UVTH, University Veterinary Teaching Hospital of University of Helsinki.

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To our knowledge, only 2 studies exist on seizure-precipitating factors in dogs with epilepsy. In intact female dogs with idiopathic epilepsy seizures tend to cluster during estrus and for the subsequent 1-3 months.<sup>13</sup> Various stimuli, such as visits to a veterinary clinic, a grooming facility, or a boarding facility, frequently trigger seizures in dogs.<sup>14</sup> In humans, controlling the patient's possible seizure-precipitating factors is part of the treatment plan. Thus, identification of these factors could have practical implications in canine epilepsy treatment as well.

In our questionnaire-based study, we aimed to determine the prevalence and the nature of possible seizure-precipitating factors in dogs with idiopathic epilepsy. Our main hypothesis was that, similar to human epilepsy patients, seizure-precipitating factors are common in dogs with idiopathic epilepsy. In addition, we sought to define the possible associations between the existence of seizure-precipitating factors and canine signalment and epilepsy-related factors. We hypothesized that the occurrence of precipitating factors correlates with canine signalments and epilepsy-related factors.

## 2 | MATERIALS AND METHODS

### 2.1 | Participants

In this cross-sectional observational study, we aimed to recruit 50 client-owned dogs diagnosed with idiopathic epilepsy. The dogs were collected during 2016 and 2017 among the hospital population of the University Veterinary Teaching Hospital (UVTH) of the University of Helsinki, and during 2017 among the hospital population of the privately owned Referral Animal Hospital Aisti (RAHA), in Vantaa, Finland. The number of dogs was estimated based on studies on the effect of estrus in seizure frequency and reflex seizures in dogs.<sup>13,14</sup> We selected dogs until reaching the goal of 50 dogs.

In addition to a diagnosis of idiopathic epilepsy, dogs included had to have at least 2 seizures more than 24 hours apart during the previous 6 months and seizure onset occurred at least 6 months before enrollment to the study. We applied the following criteria to confirm an idiopathic epilepsy diagnosis based on International Veterinary Epilepsy Task Force (IVETF) criteria and the Tier I confidence level:<sup>15</sup> (1) onset of seizures between the age of 6 months and 6 years, (2) abnormalities were not detected in clinical and neurological examination, and (3) abnormalities were not detected in routine blood samples (CBC and basic serum biochemistry). If the dog did not meet the age category, magnetic resonance imaging (MRI) of the head was mandatory to exclude possible structural changes in the brain. Participation in the study was voluntary for the owners. We excluded dogs if the owners were not willing to complete the questionnaire or if the epileptic nature of the paroxysmal events was unclear based on the owner's description.

### 2.2 | Data collection

To collect the data, 1 of the authors (Johanna A. Forsgård) interviewed all dog owners face-to-face or by telephone using a predefined questionnaire. Our study group developed the questionnaire based on the

literature regarding precipitating factors in humans with epilepsy.<sup>1,2,6,8</sup> To keep the questionnaire simple and approachable for the owners and to ensure a high compliance, we selected only questions we considered to be the most relevant for the aims of our study. In addition, we tested the questionnaire with 10 pilot dogs. According to this pilot study and feedback from the participating owners, we adjusted the questionnaire for the main study. All the interviews were conducted by 1 neutral researcher, who was not involved in the treatment of the dogs.

We selected the possible precipitating factors according to those identified most frequently in human studies and which were also applicable to dogs. The questionnaire consisted of 18 questions including signalments of the dog, a description of the canine personality, epilepsy-related factors, a diagnostic workup, and questions about possible seizure-precipitating factors. Questions regarding personality were modified from the Monash Canine Personality Questionnaire<sup>16</sup> and included activity, persistence, aggression, fearfulness, and trainability. Questions about epilepsy-related factors included the onset of seizures, the duration of epilepsy, seizure type, seizure description, the manifestation of possible cluster seizures or status epilepticus, seizure duration, seizure frequency, and any prescribed antiepileptic medication.

The possible seizure-precipitating factors were initially investigated through an open-ended question followed by a check list. This check list consisted of flickering lights, attending a dog show, attending a competition, visitors at home, playing with other dogs, a change in daily routine, unfamiliar places, getting scared, altered sleep patterns, extensive physical exercise, illness, pain, vaccination, a change in feeding, forgetting medication, a change in the life situation, weather (hot or cold temperature or humidity), and presence of females in estrus (for male dogs only). The effect of the estrous cycle on seizure frequency in bitches was investigated separately. In addition, owners were asked to evaluate how often their dogs experienced precipitated seizures (always; in more than 50% of seizures; in about 50% of seizures; in less than 50% of seizures, or at sporadic times) and how quickly after the possible precipitating factor does the seizure occur (during or immediately after; within 24 hours; within 48 hours; after more than 48 hours, or it only affects seizure frequency). Finally, the owners were also asked if their dog's seizures occurred during sleep, rest, when waking up, when active, or anytime.

### 2.3 | Statistical analysis

All statistical analyses were completed at 4Pharma Ltd using SAS System for Windows, version 9.3 (SAS Institute Inc., Cary, North Carolina). To analyze the possible association between precipitating factors and canine signalment, personality, and epilepsy-related factors, we used logistic regression analysis and Poisson regression analysis. The canine signalment, personality, and epilepsy-related factors were used as explanatory factors in all of the statistical analyses. These variables included age, sex, personality variables (activity, persistence, aggression, fearfulness, and trainability), age at seizure onset, seizure frequency, seizure type, occurrence of cluster seizures and status epilepticus, number of antiepileptic drugs, and if seizures occurred during rest or activity.

The existence of precipitated seizures was analyzed using univariate logistic regression analyses with each explanatory factor modeled

separately. Similar logistic regression models were also fit to investigate the possible association between the 2 most common seizure-precipitating factors separately and the explanatory factors. The number of seizure-precipitating factors was analyzed using Poisson regression analysis. First, the univariate Poisson regression models were fit and, second, variables that reached statistical significance in the univariate analyses were included in a multivariate Poisson regression model as fixed factors. We considered  $P < .05$  as statistically significant.

### 3 | RESULTS

#### 3.1 | Participants

The 50 dogs recruited to the study (37 from UVTH and 13 from RAHA) belonged to 29 different breeds. The most frequently occurring breeds were mixed breed (9/50), Lagotto Romagnolo (4/50), Spanish water dog (4/50), and Cairn Terrier (3/50). The mean age of the dogs was 6.5 years (range 1.1-12.2 years). Table 1 summarizes the basic clinical aspects and epilepsy-related factors of the dogs. A total of 34 dogs (34/50, 68%) had an MRI of the head. In the subgroup of dogs without an MRI of the head (16/50, 32%), the mean duration of epilepsy was 3.8 years (range 0.5-10.2 years). Only 2 of these dogs had an epilepsy duration of <1 year. Neither of these dogs had cluster seizures or status epilepticus at seizure onset and otherwise fulfilled

**TABLE 1** Signalments and epilepsy-related factors of the dogs

Mean age (range), y	6.5 (1.1-12.2)
Sex (%)	
Male	12 (24)
Female	12 (24)
Neutered male	15 (30)
Neutered female	11 (22)
Mean age at seizure onset (range), y	3.7 (0.7-7.8)
Mean duration of epilepsy (range), y	2.8 (0.5-10.2)
Seizure type	
Focal seizures	18
FOSEBG	14
Generalized seizures	22
OU	1
Cluster seizures (%)	35 (70)
Status epilepticus (%)	11 (22)
Mean seizure frequency/month (range)	1.2 (0.2-10.0)
Number of medications (%)	
0	4 (8.0)
1	23 (46)
2	16 (32)
3	7 (14)
Manifestation of seizures (%)	
Rest (sleep, rest, waking up)	39 (78)
Activity	4 (8.0)
Anytime	7 (14)

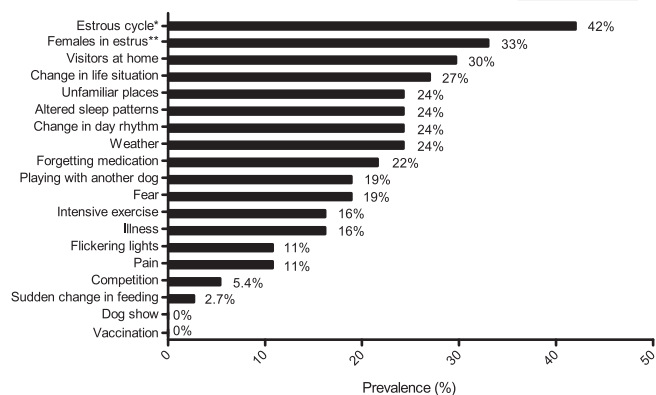
Abbreviations: FOSEBG, focal onset seizure evolving to become generalized; OU, onset unknown seizures.

the criteria for idiopathic epilepsy diagnosis determined by IVETF (Tier I confidence level). In comparison, 2 dogs without an MRI had cluster seizures at seizure onset, but their epilepsy duration was 1.0 and 1.3 years, respectively. Among the remaining dogs without an MRI, the epilepsy duration was at least 2.5 years. Thus, idiopathic epilepsy was considered the most likely diagnosis in all of the dogs included in this study. The majority of the dogs did not have any long-term sickness or medications. Those who did reported glaucoma (1) and hypothyroidism (2). Three dogs had undiagnosed signs of gastrointestinal disease, which were controlled with a special diet.

#### 3.2 | Seizure-precipitating factors

When asked through an open-ended question, 29 of the 50 owners (58%) reported that their dog had some precipitating factors for seizures. Almost all these owners recognized only 1 (18/29, 62%) or 2 (10/29, 34%) precipitating factors. By contrast, when choosing from the checklist, 37 of the dog owners (37/50, 74%) recognized at least 1 seizure-precipitating factor. Out of 37 owners who reported precipitating factors, 8 (22%) reported 1 precipitating factor, 8 (22%) reported 2, 10 (27%) reported 3, 4 (11%) reported 4, and 7 (19%) reported 5 or more precipitating factors. The highest number of precipitating factors reported in a single dog was 9. From the open-ended question, the most frequently reported precipitating factors were stress (6/29, 21%), excitement (6/29, 21%), and hot weather (5/29, 17%). In comparison, the most frequently reported factors from the check list were having visitors at home (11/37, 30%), a change in the life situation (10/37, 27%), a change in the daily routine (9/37, 24%), altered sleep patterns (9/37, 24%), unfamiliar places (9/37, 24%), and weather (9/37, 24%), further specified as hot weather for 8 dogs (8/37, 22%) and cold weather for 1 dog (1/37, 2.7%). Out of 12 intact males, 4 (33%) owners reported exposure to females in estrus acted as a precipitating factor. In addition, in 1 neutered male, seizures were precipitated by exposure to females in estrus. Out of the 12 intact females, 5 (42%) owners identified the estrous cycle as a precipitating factor. Three dogs had seizures during estrus, 1 dog approximately 1 week before estrus, and 1 dog during the subsequent 2 months. None of the owners reported dog shows or vaccinations as precipitating factors. The prevalence of individual precipitating factors is presented in Figure 1.

In 7 of 37 (19%) dogs with precipitating factors, a seizure occurred during or immediately after the precipitating factor. Among 13 dogs (35%), a seizure occurred within 24 hours after exposure to a precipitating factor. Among 4 dogs (11%), a seizure occurred within 48 hours, in 1 dog (2.7%) a seizure occurred 48 hours after exposure, and among 4 dogs (11%), the factors only affected the seizure frequency. In 8 dogs (22%), the time span from the precipitating factor to seizure occurrence varied across different precipitating factors. In these 8 dogs, some precipitating factors produced a seizure within at least 48 hours (either during or immediately, within 24 hours, or within 48 hours) and after longer periods of time in others (either after 48 hours or only affected the seizure frequency). When assessing the distribution of precipitated seizures, 29 of 37 (78%) owners reported that only sporadic seizures had some precipitating factor influencing the seizure occurrence. In 3 patients, seizures were



**FIGURE 1** The prevalence of single seizure-precipitating factors included in a checklist. \*Only intact female dogs. \*\*Only intact male dogs

precipitated less than half the time but more than sporadically. In 5 dogs (5/37, 14%), seizures were precipitated less than half the time. In only 1 of these dogs did all seizures have some precipitating factor in the background.

### 3.3 | Associations between precipitating factors and signalment, personality, and epilepsy-related factors

No statistically significant effects were found in the logistic regression analyses for the existence of precipitated seizures and the previously defined signalments, personality, and epilepsy-related factors. In addition, no significant effects were found in the analyses of the 2 most frequently reported precipitating factors (visitors at home and a change in the life situation) nor for any of the explanatory factors.

In the univariate Poisson regression analysis of the number of occurring precipitating factors, 2 statistically significant factors were detected: sex and seizure type, whereby females and dogs with focal onset seizures had more precipitating factors. When these factors were tested using a multivariate Poisson regression analysis, only seizure type remained statistically significant. Thus, in our study population, among dogs who had focal onset seizures, the number of precipitating factors was 1.9 (95% CI 1.1-3.4) times higher compared to dogs with generalized seizures.

## 4 | DISCUSSION

Our study shows that most owners of dogs with diagnosed idiopathic epilepsy think that their dog has at least 1 factor precipitating seizures. Yet, in most cases, the dogs had both precipitated and unprecipitated seizures. The most frequently reported seizure-precipitating factors in our study included having visitors at home, a change in the life situation, a change in the daily routine, altered sleep patterns, unfamiliar places, and weather as well as hormonal factors. In more than half of the dogs, the seizure occurred within 24 hours of exposure to the precipitating factor.

The prevalence of seizure-precipitating factors in our study population reached 74%. This corresponds well to human questionnaire-based

studies, in which the prevalence varies between 27.5% and 98%.<sup>1-4,8,17,18</sup> Furthermore, our study showed that almost all of the dogs had both precipitated and unprecipitated seizures, a finding also similar to human studies.<sup>2</sup> However, in only 14% of the dogs, at least half of the seizures were precipitated, whereas in 78% of the dogs, only sporadic seizures had a precipitating factor. In human studies, most patients reported that at least half of their seizures were precipitated.<sup>2</sup> Furthermore, the dogs in our study population generally had more than 1 factor precipitating their seizures. The highest number of precipitating factors for a single dog was 9. A recent case series reported similar findings among epileptic dogs.<sup>14</sup> Likewise, researchers have shown that many human patients often have more than 1 precipitating factor for seizures.<sup>3,6-8</sup> For example, according to 1 human study, the highest number of precipitating factors reported in a single patient reached up to 26;<sup>9</sup> more commonly, human epilepsy patients have at most 10 different precipitating factors.<sup>4,19,20</sup>

In our study, having visitors at home, a change in the life situation, a change in the daily routine, and unfamiliar places were among the 6 most common precipitating factors. Because all these factors represent changes in the dog's life, it is safe to assume that they also cause the dog some degree of stress. Stress was also the most frequently reported precipitating factor in the open-ended question. Similarly, a recent case series reported that the 3 most common triggering factors for seizures in epileptic dogs were a visit to the veterinarian, grooming facility, or boarding facility.<sup>14</sup> In that study, researchers speculated that these events could be regarded as stressful situations.<sup>14</sup> In most human studies, patients report stress as the most frequent precipitating factor for seizures, whereby up to 83% of patients identified it as a precipitant.<sup>2,3,6-8,11,19-22</sup> Studies show that in laboratory animal models, most stress hormones affect the brain in an excitatory manner and, therefore, may have proconvulsant effects.<sup>23</sup> In diary studies among human epilepsy patients, stress has also been associated with seizure occurrence.<sup>10,24</sup> For instance, 1 study found that after a less stressful day, the probability of seizures was significantly lower for 2 consecutive days.<sup>24</sup> In addition, another study showed that moderate and severe stress significantly increased the likelihood of seizures the next day.<sup>10</sup> Because stress mechanisms are fairly similar among all mammals, we might assume that stress acts as a precipitating factor in dogs as well.

Another common precipitating factor in our study population was altered sleep patterns. Similarly, in human questionnaire studies, 1 frequently reported factor is sleep deprivation.<sup>2-4,6-9,19-21</sup> Electroencephalogram (EEG) studies have shown that sleep deprivation increases the number of interictal epileptiform discharges in patients with epilepsy.<sup>25,26</sup> However, findings from studies on sleep deprivation as a precipitating factor in humans with epilepsy remain inconsistent. Three diary studies found that sleep deprivation increased the likelihood of seizures for the following 2 days,<sup>10,27,28</sup> but researchers were unable to repeat these findings in an EEG-controlled study or in a sleep diary study.<sup>26,29</sup> Among dogs, evaluating possible sleep deprivation can be difficult for owners and, thus, they can easily overestimate or underestimate its importance. Hence, further prospective studies are needed to determine the importance of altered sleep patterns as a precipitating factor in epileptic dogs.

In our study, 9 owners (24%) reported that weather acted as a precipitating factor in their dog, for which 8 dogs reacted to hot weather and 1 to cold weather. Many studies have reported that weather may act as a precipitant in humans with epilepsy, particularly during hot or cold conditions.<sup>3,6-8,21</sup> A recent retrospective study showed that low atmospheric pressure and high air humidity increased the possibility of seizures for 1-2 days after exposure.<sup>30</sup> Yet, this same study found that temperature more than 20°C appears to act as a protective factor for seizures,<sup>30</sup> contradicting our results. However, in some epilepsy syndromes, seizures are especially easily provoked by high temperature, such as from a fever or during warm weather.<sup>31-33</sup> Dravet syndrome and generalized epilepsy with febrile seizures plus represent these kinds of epileptic syndromes.<sup>32,33</sup> Among others, mutations in the SCN1A gene appear to cause these syndromes.<sup>31,33</sup>

In our study population, the estrous cycle affected seizure occurrence in 42% of the intact females. This is consistent with a previous study, which reported that the estrous cycle affected the onset of epilepsy as well as seizure frequency among roughly one-third of intact females with idiopathic epilepsy.<sup>13</sup> However, owing to the nature of our study, it is impossible to confirm that seizures truly occurred because of the estrous cycle. However, among women, the hormonal cycle has also been frequently reported as acting as a precipitating factor.<sup>2,3,6,7,20,34</sup> Furthermore, among intact males, exposure to females in estrus was 1 important precipitating factor and even 1 neutered male had it as a precipitating factor. Somewhat related, the influence of male sex hormones on seizures is not well understood. Studies have shown that androgens have an anticonvulsant activity,<sup>35,36</sup> although some studies have reported conflicting results, whereby testosterone increased the frequency and severity of seizures.<sup>37,38</sup> Independent of sex hormones, exposure to females in estrus may cause stress in male dogs, which could also explain its ability to precipitate seizures.

In our study population, the time span between precipitating factor and seizure varied between dogs. However, more than half of the owners in our study reported that the seizure occurred within 24 hours after the precipitating factor. In humans, diary studies have shown that stress and sleep deprivation affects the likelihood of seizures for the subsequent 24-48 hours.<sup>10,24</sup> Oddly, the time span between the precipitating factors and seizure has not been otherwise studied in human epilepsy patients. In addition to precipitated seizures, a rare seizure type, so-called reflex seizures, is identified in human epileptology. Although in precipitated seizures the time span between precipitant and seizure may vary, in reflex seizures a specific factor triggers a seizure almost instantly, most likely by affecting neuronal activity in a specific brain area.<sup>39</sup> However, the difference between precipitated seizures and reflex seizures remains relatively unclear. Patients who only have reflex seizures are diagnosed with reflex epilepsy.<sup>39</sup> These epilepsies are exceedingly rare and include, for example, reading and writing epilepsy.<sup>40-42</sup> The definition of reflex seizures is not unambiguous in animal studies. A recent study described a generalized myoclonic epilepsy in juvenile dogs with photosensitivity.<sup>43</sup> In some of these dogs, visual stimuli, such as flickering or bright lights, triggered seizures, thus fulfilling the criteria for

reflex seizures.<sup>43</sup> In our study, we could not identify any clear cases of reflex epilepsy.

Our statistical analysis showed that dogs with focal onset seizures had more precipitating factors than dogs with generalized seizures. The mechanism for how precipitating factors facilitate seizures remains unknown. Researchers have suggested that the precipitating factors affect the general brain homeostasis, thereby lowering the seizure threshold.<sup>12</sup> The most typical precipitants differ between epilepsy types and epilepsy syndromes, suggesting the existence of different precipitating mechanisms and that epilepsy etiology may contribute to sensitivity to a precipitant.<sup>3,6,8,44</sup> Different dog breeds may be prone to different genetic epilepsy syndromes, which remain unclearly defined in veterinary medicine. The existence of different epileptic syndromes among the dogs studied here could partly explain the variations in our study regarding the nature and number of precipitating factors as well as the time span from the precipitating factor to seizure.

Similar questionnaire studies have been used to report seizure-precipitating factors in human epilepsy patients. Thus, we considered a questionnaire-based study sufficient to make an initial estimate regarding the prevalence and nature of precipitating factors in dogs, as well. However, we acknowledge that our study has limitations and results should be interpreted with caution. Firstly, an MRI of the brain was not performed for 32% of dogs participating in the present study. Thus, we cannot exclude the possibility that some of these dogs had structural epilepsy, although we consider this unlikely. This lies in our adherence to the guidelines provided by IVETF consensus regarding the diagnostic approach to epilepsy in dogs and given that the duration of the epileptic seizures was >1 year in most of these dogs. Secondly, although the entire study group was rather large, the high prevalence of seizure-precipitating factors led to a small control group with no precipitants, thereby reducing the power of the statistical analyses. Thirdly, the owners were aware that we were investigating precipitating factors, which might have influenced their answers. Fourth and the main limitation of our study was that owners' responses relied on their memory and perceptions. Thus, any recall bias may contradict the results. In addition, some precipitating factors are situations in which owners make assumptions about their dog or the surroundings. Finally, the use of checklist in the questionnaire can lead to higher probability to false-positive answers. However, we wanted to use both open-ended questions and tick list to achieve as comprehensive results as possible. More detailed and validated questionnaire may have minimized the bias caused by the nature of our study. However, the most reliable data could be achieved with a prospective diary for both the precipitating factors and for the seizures.

In conclusion, our study shows that seizure-precipitating factors are common in dogs with idiopathic epilepsy and that these dogs show both precipitated and unprecipitated seizures. The most frequently recognized seizure precipitants in our study consisted of stress-related situations, sleep deprivation, and hormonal factors, which are consistent with those reported in human epilepsy patients. In our study population, dogs with focal onset seizures were prone to have more precipitating factors than dogs with generalized seizures. Further prospective studies are needed for a more precise estimation of the prevalence of precipitating factors and to further verify if the



factors reported by the owners in our study population indeed facilitate seizures in epileptic dogs. Clinically, when a dog is diagnosed with epilepsy, seizure-precipitating factors should be taken into consideration to achieve better treatment outcomes.

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## CONFLICT OF INTEREST DECLARATION

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

Authors declare no IACUC or other approval was needed.

## HUMAN ETHICS APPROVAL DECLARATION

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

## ORCID

Johanna A. Forsgård  <https://orcid.org/0000-0002-4696-2163>

Anna-Mariam Kiviranta  <https://orcid.org/0000-0002-9542-7247>

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