

Association between Estrus and Onset of Seizures in Dogs with Idiopathic Epilepsy

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Background: Catamenial epilepsy in humans is defined as changes in seizure frequency over the course of the menstrual cycle. Three hormonally based patterns of seizure exacerbation have been determined.

Objectives: The aim of this study was to evaluate whether there is an association between onset of seizures and the estrous cycle in intact bitches with presumptive idiopathic epilepsy and whether a pattern to the onset of seizures could be recognized.

Animals: Forty-five intact female dogs from a hospital population with a presumptive diagnosis of idiopathic epilepsy.

Methods: In a retrospective study, the database of a small animal hospital in Sweden was searched for medical records of intact female dogs diagnosed with epilepsy or seizures. The stage of the estrous cycle as reported either by the owner or the veterinarian at the time of the first seizure was noted.

Results: Of the 45 dogs with idiopathic epilepsy, 17 (38%) had their first seizure when in heat and six dogs (13%) had their first seizure 1–3 months after heat. Nine dogs (20%) had seizures reoccurring in relation to their estrous cycle.

Conclusions and Clinical Importance: These findings suggest an association between estrus and onset of seizures in intact bitches with presumptive idiopathic epilepsy. Two hormonally based patterns could be recognized: one during heat and one during a specific time point at the end of diestrus. This could be explained by the proconvulsive effects of estrogen or loss of protective effect against seizures of progesterone, respectively.

Key words: Catamenial epilepsy; Diestrus; Heat; Neurology.

Epilepsy is the most common chronic neurological disorder in the dog.¹ The prevalence of suspected idiopathic epilepsy in dogs is 0.6% in first opinion practice in the United Kingdom² and has been reported to be up to 33% in certain families of genetically predisposed breeds.³ Little is known on the effect of sex hormones on seizures in female dogs, although some studies have proposed a correlation.^{4–10}

The effect of sex hormones on seizures is well documented in humans. The first reports of the successful use of potassium bromide as an anti-epileptic drug in humans describe the cure of ‘hysterical’ epilepsy in women with seizures in relation to their menstrual cycle.^{11,12} Catamenial epilepsy is nowadays defined as changes in seizure frequency over the course of the menstrual cycle. Three hormonally based patterns have been recognized in humans: perimenstrual and periovulatory during a normal cycle and throughout the second half of the menstrual cycle in anovulatory cycles.^{13,14}

The purpose of this retrospective study was to determine whether there was a relationship between the estrous cycle and onset of seizures in intact female dogs with presumptive idiopathic epilepsy. The second aim of the study was to determine whether certain patterns to onset of seizures could be recognized.

Materials and Methods

Clinical records of intact female dogs with a diagnosis of seizures or idiopathic epilepsy were collected from October 1, 2008 till the December 31, 2012 at the small animal hospital Läckeby Djursjukhus, Läckeby, Sweden. The following inclusion criteria were applied for a presumptive diagnosis of idiopathic epilepsy:

- Recurrent seizures, defined as two or more seizures being at least 4 weeks apart
- Onset of seizures between 6 months and 6 years of age, with an unremarkable interictal general clinical and neurological examination and an unremarkable neurological follow-up examination after at least 3 months.
- Dogs with onset of seizures when older than 6 years had to survive more than 1 year after the onset of seizures without developing additional neurological deficits.
- Unremarkable laboratory blood results including complete blood cell count and routine biochemical profile (including electrolytes, glucose, urea, creatinine, albumin, total protein, aspartate aminotransferase, and ammonia).

Magnetic resonance imaging (MRI) of the brain to exclude symptomatic epilepsy was desired but not required as an inclusion criterion. All dogs were presented to the clinic at the onset of seizures. The stage of the estrous cycle as reported either by the owner or the veterinarian at the time of the first seizure was retrospectively retrieved from the medical records. In this study, heat was defined as the stage of the estrous cycle where serosanguinous vulvar discharge was seen. If available, information on the recurrence of seizures in association with the estrous cycle was retrospectively collected from regular follow-up visits in the medical records of all dogs.

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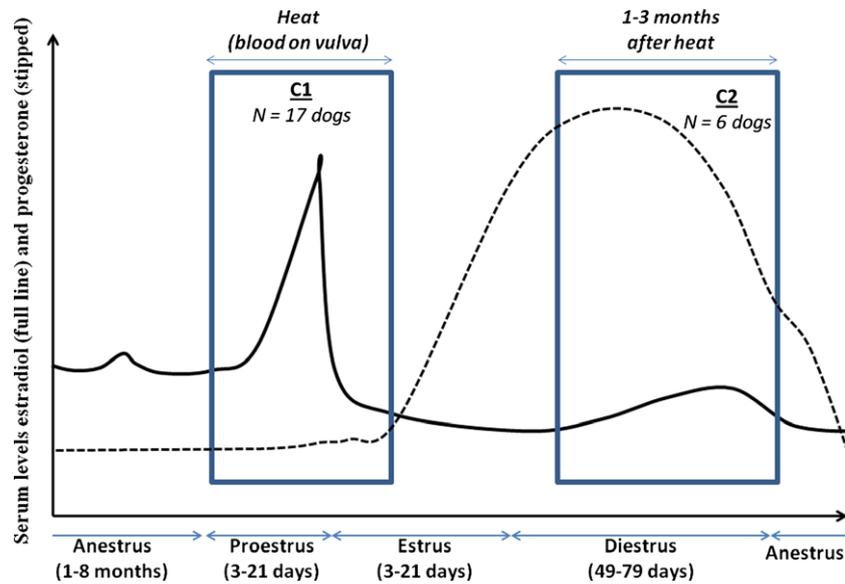


Fig 1. Schematic presentation of the changes in serum hormone levels in dogs during the estrous cycle.²¹ Two patterns of start of seizures could be recognized in dogs: one during heat (C1) and one during diestrus (C2). *N*, number of dogs.

Results

A total of 90 intact female dogs were presented with a diagnosis of seizures or idiopathic epilepsy. Forty-five dogs fulfilled the inclusion criteria and were diagnosed with presumptive idiopathic epilepsy. Ten dogs of these 45 were older than 6 years and only one of them had MRI of the brain performed. Thirty-six dogs received anti-epileptic drugs. Eleven dogs had cluster seizures and two dogs experienced status epilepticus at onset of epilepsy, but the largest part of the group started with a single seizure.

Of the 45 dogs with presumptive idiopathic epilepsy, 17 (38%) had their first seizure when in heat (C1), and six (13%) had their first seizure at one specific time point between 1 and 3 months after heat (C2) (Fig 1). Furthermore, nine dogs (seven with onset of seizures during heat and two with onset of seizures 1–3 months after heat) of the 45 dogs (20%) had seizures reoccurring in association with their estrous cycle. Six of them had recurrence of seizures in association with heat or at a specific time point at the end of diestrus, therefore suffering both recognized hormonally based patterns. Three of the dogs with onset of seizures during heat were always in heat when an association was noted in the medical record during the further course of their epilepsy.

Discussion

These findings suggest an association between heat and onset of seizures in around a third of intact female dogs with presumptive idiopathic epilepsy. Adding the group of dogs which started having seizures at a specific time point 1–3 months after heat, 50% of intact female dogs with idiopathic epilepsy at this hospital

population started having seizures in relation to a certain period in their estrous cycle. Nine (20%) of these dogs showed an association of seizure activity during heat or 1–3 months after heat in the further course of their epilepsy. Ten to 70% of human epilepsy patients have an aggravation of their seizure disorder depending on their menstrual cycle¹⁵ and around one-third of women with intractable complex-focal seizures have catamenial epilepsy.¹³ In a human clinical setting, a 2-fold increase in seizure frequency for certain phases during the menstrual cycle is used to define catamenial epilepsy. The retrospective nature of this study, differences between estrous and menstrual cycles and the limitations of recording canine seizures, certainly partial seizures, made it impossible to verify this arbitrary definition in our canine patients.

Two patterns in relation to onset of seizures could be recognized in this study, one group of 17 dogs started to seizure during heat (C1) and another group of six dogs started to seizure at one specific point 1–3 months after heat, at the end of diestrus (C2) (Fig 1). Three hormonally based patterns are described in humans: perimenstrual and periovulatory during normal menstrual cycles and throughout the second half of the menstrual cycle in anovulatory cycles.^{13,14} These patterns are explained by differences in serum levels of estradiol or progesterone, and are positively correlated with the serum estradiol/progesterone ratio.^{13,14,16,17} Estradiol is believed to reduce the seizure threshold, to be proconvulsive, although recent literature is contradictory.^{18–20} Progesterone appears to have protective effects against seizures.^{15,19,20} The two patterns in dogs might also be explained by an increase in the ratio estradiol/progesterone during heat in the first group and by a decline of progesterone during an individually specific time

point at the end of diestrus (1–3 months after heat) in the second group.²¹ Heat was defined as the stage of the estrous cycle where serosanguinous vulvar discharge was seen, theoretically corresponding with proestrus and the beginning of estrus where the estradiol levels are increasing rapidly.²¹ The duration of the second pattern period, from 1 to 3 months after heat making up to 2 months makes it clearly more probable to find an association. However, we are only describing one seizure at one specific time point for each individual dog, presumably corresponding to the drop of progesterone at the end of diestrus. Anecdotally, veterinary surgeons have recommended ovariectomy of female dogs with idiopathic epilepsy to decrease seizure frequency and severity without any substantial evidence of beneficial effect. This might not be as beneficial as thought, as sterilization could also lead to a deprivation of the protective effect of progesterone. Nevertheless, ovariectomy can have other beneficial effects on the dogs' health and not the least in the prevention of breeding. Future studies are needed to correlate sex hormone blood levels and seizure frequency in dogs with idiopathic epilepsy. If an association can be found, then this could lead to a more targeted approach of hormonal treatment in addition to anti-epileptic medication in dogs with catamenial epilepsy.

As stated above, the retrospective nature of this study makes it impossible to make conclusions on a definition on catamenial epilepsy in this group of dogs. There might be an underestimation of associations as only data recorded in the medical records by the attending veterinarian is used. Additional data could have been collected during follow-up contact with the owner, although certain bias may arise there, as an owner is more likely to remember seizures during specific stages of the estrous cycle, certainly when they are asked to pay special attention to these periods. Another limitation in this study is the lack of advanced medical imaging to exclude symptomatic epilepsy. However, harder inclusion criteria such as a required neurological examination 3 months after onset of seizures and 1 year follow-up in dogs older than 6 years, made the inclusion of dogs with a structural brain lesion unlikely.

In conclusion, more than half of the intact female dogs with idiopathic epilepsy in this hospital population started having seizures during a specific period of the estrous cycle. Two specific periods are recognized, one during heat and one during a specific point at the end of diestrus.

Acknowledgment

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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