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Myoclonus Epilepsy in Geriatric Dogs

Diplomarbeit

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vorgelegt von

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Content

Myoclonus epilepsy in geriatric dogs

1. Introduction

Myoclonus is a skeletal muscle twitch that cannot be controlled at will (Meinck 2007). Berendt et al. (2015) describe myoclonus as a sudden brief (< 100 msec) involuntary single or multiple contraction(s) of muscle(s) or muscle groups of variable topography (axial, proximal limb, distal). Limbs and facial muscles are particularly affected (Nelson 2010). There is a subdivision into physiological, and pathological myoclonus (Lowrie und Garosi 2017). A physiological myoclonus is twitching when falling asleep or hiccup (Lowrie und Garosi 2017). The pathophysiological manifestations and clinical symptoms are similar in myoclonus and epilepsy. Lowrie und Garosi (2017) define a myoclonus as idiopathic or hereditary if no pathophysiological cause can be found. If the etiology is epilepsy, the patient suffers from an epileptic myoclonus (Lowrie und Garosi 2017). Further potential etiologies are intoxication and paraneoplastic event (Bauer J. 2001).

1.1. Myoclonus in humans

Myoclonus occurs in different forms of epilepsy in humans. Progressive myoclonus epilepsy (PMEs) is an example for a hereditary myoclonus (Orsini et al. 2019). Clinically as well as genetically, PMEs constitute an extraordinary group of heterogeneous diseases. They are due to different neurological worsening. These include generalized epilepsy, dementia, ataxia and myoclonus (Orsini et al. 2019). This can develop at any age but is developed most often in late childhood. PME often first occurs between 10 and 13 years (Platen 2020). “A combination of positive and negative myoclonus is typical of PMEs” (Orsini et al. 2019). A negative myoclonus is defined as a temporarily interrupted muscle tone and a positive myoclonus presents as short lasting muscle contractions (Haubenberger, Pirker 2014. During a seizure typically a negative myoclonus is followed by a positive myoclonus (Meinck 2007). Lafora Disease (LD) is an inherited, severe form of progressive myoclonus epilepsy. In Lafora Disease congenital deposits of Lafora bodies occur in the nerve tissue of the brain (Roger J. 1991). This is caused by a mutation of the genes EPM2A, which code for Laforin and EPM2B, which code for Malin (Turnbull et al. 2016). Laforin and Malin are responsible for the glycogen structure (Turnbull et al. 2016). The mutations results in deposits of polyglucosans, which are also known as Lafora-Bodies (Turnbull et al. 2016). Lafora-Bodies are mainly found in the brain, but also in liver cells, muscle cells of the skeleton and heart, and in cells of apocrine and exocrine glands (Turnbull

et al. 2016). In the beginning of the LD myoclonic seizures are observed. As the disease is progressing other neurological signs also appear (Turnbull et al. 2016). Lafora disease is progressive and within 10 years leads to the death of the person concerned (Parihar et al. 2018).

1.2. Myoclonus epilepsy in cats

A form of myoclonus epilepsy also has been demonstrated in cats. It is called Feline audiogenic reflex seizures (FARS) and occurs in old cats and with a breed predisposition in Burmese cats (Lowrie et al. 2016).

Lowrie et al. (2016) conducted an extensive FARS study, for which an online questionnaire was established and provided to cat owners and their veterinarians. In total 128 filled questionnaires were returned and evaluated. Inclusion criteria were three or more generalized tonic-clonic seizure (GTCS), that were triggered by acoustic stimuli. A total of 96 cats met the criteria. 47 female cats, of which 30 were neutered and 49 male cats, of which 35 were neutered (Lowrie et al. 2016). The mean age of the cats at the onset of the symptoms was 15 years. After analyzing the video recording of the cats, it seems, that the most cats showed myoclonic seizures, sometimes progressing into GTCS. Lowrie et al (2016) found out that the clinical course of FARS was usually not progressive, however as the cats were rather older the general condition of the cats deteriorated over time. This was noticeable among other clinical signs through uncoordinated, weak pelvic limbs, failure to jump and strong weight loss (Lowrie et al. 2016). Interestingly Lowrie et al. (2016) found out that about 50% of the cats included in the study had impaired hearing or were deaf.

In a follow up study Lowrie et al. (2017) compared the efficacy of treatment with levetiracetam or phenobarbital. The included 57 cats were randomly divided into two groups, which were given either levetiracetam or phenobarbital (Lowrie et al. 2017). 29 cats in the phenobarbital group and 28 cats in the levetiracetam group completed the study. It was demonstrated that levetiracetam had a significantly better effects than phenobarbital and could reduce the number of days when myoclonic seizures occurred in all 28 cats in the group by about 50 %. In the phenobarbital group seizures decreased by only in 1 of cats by 50 % (Lowrie et al. 2017).

1.3. Myoclonus epilepsy in dogs

Some cases of myoclonus epilepsy or Lafora Disease have also been described in dogs, with a special breed predisposition to Beagles (Alisauskaite et al. 2020 and Gredal et al. 2003) as well as wirehaired Dachshund, Corgi, miniature Poodles, Poodles, Pointer and Bassets

(Alisauskaite et al. 2020; Berendt et al. 2015; Lowrie und Garosi 2017). The dogs affected started to show symptoms between 6 and 13 years of age and the seizures could be triggered by visual stimuli (Aubrey A. Webbe et al. 2009; Schoeman et al. 2002; Lowrie und Garosi 2017) The course of the disease was described as progressive (Lowrie und Garosi 2017).

As in humans, studies in dogs have also shown that the EPM2A gene leads to an incorrect synthesis of Laforin. Lafora-Bodies can also be found in nerval tissues of affected dogs (Minassian et al. 2000). However, the exact function of Laforin is not fully understood (Minassian et al. 2000). The gene defect, which leads to a double expression of the EPM2B gene, could also be found in wirehaired Dachshunds (Aubrey A. Webbe et al. 2009). It is inherited recessively (Chambers et al. 2018; Lowrie und Garosi 2017). As in humans, Lafora-Bodies can be detected in many types of tissue (Alisauskaite et al. 2020). The exact diagnosis can only be established with the help of a postmortem biopsy and histopathological examinations (Gómez-Garre et al. 2000). In histopathological sections Lafora-Bodies can be stained using the periodic acid-Schiff (PAS) method (Minassian et al. 2000).

In 2003 a case study about a female Beagle was published. The dog was presented because of progressive myoclonic twitching (Gredal et al. 2003). During the clinical examination seizure-like twitching of the head and forelimbs were observed. The twitching was triggered by changes in movement directly in front of the face, changes in sounds or light, and by touching the nose (Gredal et al. 2003). An electrocephalogram (EEG) was conducted. The findings suggested a myoclonus epilepsy (Gredal et al. 2003). Treatment was started with a daily dose of 8 mg/kg of phenobarbital. However, this treatment did not improve the dog`s condition.

Furthermore, Chambers et al (2018) demonstrated that myoclonic seizures can be triggered in Dachshunds by certain, usually visual stimuli.

Whereas in Rhodesian Ridgebacks Wielaender et al (2017a) described another idiopathic form of myoclonus epilepsy, which is initiated by a mutation of DIRAS gene, other than in Lafora Disease.

In the course of the study twenty-four Rhodesian Ridgebacks with an average age of six months were examined. Further diagnostic was performed: Twelve Rhodesian Ridgebacks had a MRI and seven a CT (Wielaender et al. 2017a).In addition, 17 a portable EEG (Wielaender et al. 2017b).The EEG revealed up to 50 myoclonic seizures per hour, which could develop into a GTCS. In 8 Rhodesian Ridgebacks the seizures were triggered by a specific stimulus. Moreover, a full genome sequencing was conducted, and a defective DIRAS1 gene

was identified. The DIRAS gene is suspected of controlling the release of acetylcholine and is probably important in the formation of neurons (Wielaender et al. 2017a).

A variety of anti-epileptic drugs had been used in the treatment of myoclonic seizures of the Rhodesian Ridgebacks, such as, phenobarbital, potassium bromide and levetiracetam. potassium bromide and levetiracetam, both showed good effectiveness (Wielaender et al. 2017a).

It is known that myoclonus can occur without any relation to epilepsy, too. Myoclonus can be a symptom of various forms of encephalomyelitis, for example because of a distemper infection. (Lowrie und Garosi 2017). However, distemper can be recognized by focal lesions of the spinal cord (Lowrie und Garosi 2017).

Myoclonus epilepsy in geriatric dogs is not a well-known phenomenon. Goldston (1989) defined geriatric in small dogs with an age of 11.5 years and in giant breeds with an age of 7.5 years. Nevertheless, myoclonus epilepsy was observed occasionally at the Veterinary University Vienna, Department for Small Animals, Neurology Section.

1.4 Aims and Hypothesis

The aim of this study was to investigate myoclonus epilepsy in geriatric dogs systematically, analyses the university database and summarize findings. Here we expect that idiopathic myoclonus epilepsy is occurring in geriatric dogs, laboratory diagnostic examinations including MRI imaging are inconclusive and treatment response to levetiracetam is good. Main focus is whether myoclonus epilepsy is occurring in elderly dogs and if it is a progressive disease or not.

2. Material and Method

The electronic database at the Veterinary University Vienna; Department for Small Animals, Neurology Section was searched for non-beagle dogs that were diagnosed with myoclonus epilepsy. Due to genetic diseases resulting in myoclonus epilepsy such as Lafora disease beagles were excluded from the study. It was searched in a period from 2015 to 2020. Signalment, clinical and laboratory parameters were analyzed. The cases were checked for disease characteristics like: age, triggers for myoclonic seizure and comorbidities, therapy and outcome. For summery, see table 1.

3. Case Reports

3.1. Case 1

A 17 years old, female-neutered, 11 kg weighted Jack Russel Terrier was presented, because of progressive myoclonus attacks about two months. In addition, heart failure, a cataract on both eyes and a geriatric vestibular disease was reported as preexisting conditions. The clinical and neurological examinations were age-appropriate, and no abnormalities were found. The myoclonic seizures occurred spontaneously or sunshine related. Using sunglasses improved the condition only slightly. Levetiracetam 11 mg/kg TID was started in tablet form. For this patient no long-term follow-up is available, as the dog was euthanized soon due to unrelated causes.

3.2. Case 2

A 17 years old mixed breed, female- neutered, 7 kg weighted dog was presented because of myoclonic and convulsive generalized seizure. The myoclonic seizures could be triggered by sunlight. Slight evidence for canine cognitive dysfunction was reported such as doors fail to find. The clinical examination showed a holosystolic heart murmur 2/6. Neurologically a mild tetraparesis was found, and the conscious proprioception and the menace response were also reduced. The dog showed a cataract on both eyes. Levetiracetam 20 mg/kg BID was started in tablet form. After further seizures levetiracetam was increased to TID. A follow up after two months was done and revealed that no more seizures have occurred.

3.3. Case 3

A 14 years-old female-neutered, 18 kg weighted Cocker Spaniel was presented because of myoclonic seizures. The twitching started three months before the presentation and usually occurred during a relaxed state and lasted only a few seconds. However, in the cause of the three months the seizures were progressive. The clinical examination was inconclusive, and the neurological examination showed only a slightly reduced menace response. Levetiracetam was started with 14 mg/kg BID in tablet form. A follow up after three months was conducted and the owner reported that no more seizures have occurred and that the dog was generally in a better condition than before the treatment started.

3.4. Case 4

A 14-year-old Stafford/Golden Retriever mixed breed female dog was presented because of myoclonic seizures. She weighs 22 kgs. The first symptoms appeared at around 12 years of age. The seizures occurred when the dog entered the apartment after a walk and after

getting up. Upon first presentation the neurological and clinical examination showed no abnormal finding. No abnormalities were found during an MRI examination of the brain. A splenectomy was performed four months before the first seizure due to a hematoma and an adenocarcinoma was found in the lungs and removed. A full-body CT performed thereafter showed no further pathological changes. A previous blood test showed mild regenerative anemia. To treat the seizures, 23 mg/kg levetiracetam BID was given in tablet form. In ten months follow up the owner reported that the dog has not had any seizures since the therapy with levetiracetam was started.

4. Table 1: Summary of age, breed, body weight, major complaint, comorbidities, laboratory test and parameters, therapy and outcome

age at the onset of myoclonus (years)	breed	weight (kg)	major complaint	comorbidities	laboratory tests	laboratory parameters	therapy	outcome
17	Jack Russell Terrier	11	Myoclonic seizures caused by sunlight or spontaneous	Cataracts on both eyes, vestibular syndrome, heart insufficiency	ACTH stimulation test	Cortisol basal worth: 1,31 µg/dl Cortisol after 90 min: 20,40 µg/dl Potassium: 3,9 mmol/L	Sunglasses Levetiracetam 11 mg/kg BID to TID	Euthanasia due to myoclonus unrelated cause
17	mixed breed	7	Myoclonic and convulsive seizures caused by sunlight	Cataracts on both eyes, slight dementia, Vitum cordis, increase in volume Mamma, holosystolic heart murmur 3/6, PU/PD, hypertension	Hematology, Blood chemistry	Erythrocytes 4,45 10^6/µl, Hemoglobin 9,8 g/dl, MCHC 34,2 g/dl, Monocytes 865,52/µl Glucose 99mg/dl, Urea 43,6, Cholinesterase 811 U/L, Phosphor 0,8 mmol/L, All other values in the reference range	Levetiracetam 20 mg/kg BID to TID	Myoclonic seizures have decreased within two months, dementia is not progressing
17	Cocker Spaniel	18	spontaneous, at no time exact cause be determined; but according to the owners	Cataracts on both eyes, renal insufficiency, mamma tumor, PU/PD, vestibular syndrome,	Hematology, Blood chemistry	Glucose, Creatinine, Urea, Bun/Crea Ratio, Phopsphor, CA, TP, ALB,	Levetiracetam 14 mg/kg BID	No myoclonic seizures after 6 months

			rather from a relaxed state	lameness (especially after getting up), synovial sarcoma, hypertension		Globulin, ALB/Glob, ALT, ALKP, GGT, TBIL, Cholesterol in the reference range		
14	Stafford/Golden Retriever mixed breed	22	When entering the house, after getting up	Hematoma on the spleen, adenocarcinoma in the lungs	Hematology, Blood chemistry	Erythrocytes 4,34x10^6/µl, Hemoglobin 11,5 g/dl, Hematocrit 33,4%, RDW 14,6%, Monocytes 534,48/µl White Blood Cells: 18,47 K/µl Neutrophils 15,51 K/µl Eosinophils 0 K/µl, All other values in the reference range	Levetiracetam 23 mg/kg BID	No myoclonic seizures after 10 months only if the dose is forgotten by the owner

5. Results

Four cases were found at the electronic database of the University of Veterinary Medicine Vienna. All presented dogs were female and neutered. The median of age of the first myoclonic seizure was 15,5 years and ranged from 14 to 17 years. The median of weight was 14.5 kg and ranged from 7-22 kg.

One of the main predisposed factors triggering seizures were light stimuli such as sunlight or the alternation between bright and dark. Three patients could be triggered into myoclonic seizures by light stimuli. In two of them, the seizures occurred also spontaneously. One dog had myoclonic seizures, when she was relaxed.

A variety of comorbidities occurred in the dogs. Three of four dogs had cataracts in both eyes. Heart insufficiency due to mitral valve disease was present in two of the dogs. Hypothyroidism occurred in one patient. In addition, one dog suffered from mild dementia. Furthermore, two cases showed azotemia and one dog was presented with severe hypertension (table 1)

The general clinical examination and neurological examination did either show no abnormalities or only very mild abnormalities in all dogs. Vital parameters of all 4 dogs were in normal ranges. Hematology and blood chemistry were conducted in three dogs (table 1). And in all dogs an ACTH stimulation test was performed and ruled out hypercorticism.

Therapy and outcome

All dogs were treated with levetiracetam. The dose for each dog was adjusted individually. In our study, the dosage was between 11 and 23 mg/kg two or three times a day, depending on the dog. They responded very well. Within the six-month follow-up period the myoclonic seizures were clearly reduced approximately 100 %. One dog was euthanized shortly after the presentation int the clinic due to comorbidity.

6. Discussion

Myoclonus epilepsy is known in Beagle dogs but seems to appear in old dogs of other breeds as well. In our study Beagle dogs have been excluded due to genetic defects and the four dogs included in this study were geriatric dogs. The myoclonic seizures were triggered by light stimuli in the majority of the patients. The condition was not progressing rapidly and levetiracetam helped to abolish seizure episodes. The etiology of the myoclonus, however, could not have been identified.

Myoclonus epilepsy is known since decades in Beagle dogs (Montgomery und Lee 1983). Similar to the Lafora Disease in humans Lafora bodies were also found in Beagle dogs. These are then distributed throughout the neuronal systems, however, they are more common in the cerebellum and thalamus (DAVIS et al. 1990). Symptoms can be myoclonic twitching of the head and forelimb (Gredal et al. 2003). Similar symptoms have also been found in the wirehaired Dachshund (Gredal et al. 2003). However, these were not as clear as with Beagles (Gredal et al. 2003).

Wielaender et al. (2017a) studied another idiopathic form of myoclonus epilepsy which is initiated by a mutation of the DIRAS gene. Malfunction of the DIRAS gene was not further reviewed in our study. Nevertheless, as presented by this study as well as Wielaender et al. (2017a) levetiracetam as treatment of myoclonus epilepsy showed good effectiveness irrespective of the etiological cause.

In the past decade there have been studies on old cats suffering from myoclonus epilepsy. High-frequency sounds can cause cats to have a myoclonic seizure (Lowrie et al. 2016). If the stimulus persists, the myoclonic seizure can evolve into a generalized seizure (Lowrie et al. 2016). Lowrie et al. (2016) did not conduct any further diagnostic examinations but based their study on a questionnaire that was sent to owners and their veterinarians. Deafness was noted in approximately 50% of the cats. Otherwise no neurological peculiarities were found (Lowrie et al. 2016). Two of the dogs included in our study showed similar comorbidities as previously described in cats such as hypertension and PU/PD. Both symptoms were most likely due to renal failure.

This fits well with the achievement acquired in human medicine where myoclonic seizures were related to kidney disease (Kiziltan et al. 2018).The main triggers for the myoclonic seizures in the cats were acoustic stimuli and not light stimuli, as in the four dogs presented in our study

(Lowrie et al. 2016). However, the seizures could occur spontaneously in both dogs and cats (Lowrie et al. 2016).

The ages of the cats and the 4 dogs in this study at the onset of myoclonic seizures were approximately the same with 15 years, ranging from 10 – 19 years. (Lowrie et al. 2016).

The cats in the follow up study from Lowrie et al (2017) study were treated with levetiracetam or phenobarbital. Levetiracetam worked better. All cats treated with levetiracetam showed a 50% reduction in seizures. In the phenobarbital group it was only one (Lowrie et al. 2017). Treatment with levetiracetam also showed good results in the four dogs included in this study.

A retrospective study was conducted in humans examining myoclonia at higher age. It turned out, that myoclonus is often associated with dementia (Kiziltan et al. 2018). Among the dogs in this study there was also one with mild dementia.

Unfortunately, only an incomplete work-up of the cases was performed. Although the clinical examination found several comorbidities, no clear connection to the myoclonic signs could be made. The blood-work had no relevant changes in relation to myoclonus epilepsy. Brain MRI showed no significant pathology; however, it was performed only in one patient. The incomplete work-up is likely to reflect real-life situation, as the owner desire for diagnostic work-up decreasing with the increasing age of old patients. It is additionally an animal welfare question and not a medical issue alone. The possible effective treatment is usually more important than the diagnosis. The therapy with levetiracetam seems to be beneficial, however further studies are necessary to investigate this question.

7. Conclusion

Myoclonic epilepsy occurs in geriatric dogs. Whereas the routine laboratory and brain MRI seems to be usually inconclusive, the treatment response to levetiracetam is good. Further research needs to be done to deepen the knowledge about myoclonus epilepsy in geriatric dogs to improve treatment and therefore long-term prognosis.

8. Summary

Four non-beagle dogs were presented in the years 2015 to 2020 because of myoclonic epileptic seizures. None of the dogs showed severe neurological deficits in between the episodes. All dogs were geriatric at presentation (12 years of age or older) and female. Several comorbidities were documented, but no clear etiology for the myoclonic seizures could be confirmed. Levetiracetam reduced or eliminated the myoclonus episodes in all patients. No further progression was reported in the first 6-month follow-up period. Our case series first reports, that myoclonus epilepsy occurs in geriatric dogs without rapid progression, similarly to cats. The etiology is unclear, but a degenerative Cephalopathy seems likely as it is assumed in cats. Levetiracetam seems to be an effective treatment in geriatric myoclonus epilepsy, however further investigations are necessary for a firm conclusion.

Vier Hunde wurden wegen myoklonischer epileptischer Anfälle vorgestellt. Es waren keine Beagle inkludiert. Keiner der vorgestellten Hunde zeigte zwischen den Episoden ein schweres neurologisches Defizit. Bei der Vorstellung waren alle Hunde geriatrisch (> 12 Jahre) und weiblich. Es wurden mehrere Komorbiditäten dokumentiert. Es konnte aber keine eindeutige Ätiologie für die myoklonischen Anfälle bestätigt werden. Levetiracetam reduzierte die myoklonsichen Episoden oder verhinderte diese komplett bei allen Patienten. Unsere Fallserie berichtet erstmals, dass Myoklonus Epilepsie bei geriatrischen Hunden ohne schnelles Fortschreiten auftritt, ähnlich wie bei Katzen. Die Ätiologie ist unklar, aber eine degenerative Gehirnveränderung scheint wahrscheinlich, wie sie auch bei Katzen angenommen wird. Levetiracetam ist eine wirksame Behandlung bei geriatrischer Myoklonus Epilepsie, jedoch sind weitere Untersuchungen erforderlich, um ein endgültiges Ergebnis zu erzielen.

9. List of abbreviations

PME - Progressive myoclonus epilepsy

LD - Lafora Disease

ILAE - International League Against Epilepsy

IVETF - International Veterinary Epilepsy Task Force

FARS - Feline audiogenic reflex seizures

GTCS Generalized tonic-clonic seizure

SID - semel in die (once a day)

10. List of figures

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