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Benign Familial Juvenile Epilepsy in Lagotto Romagnolo Dogs

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Background: Idiopathic childhood epilepsies with benign outcomes are well recognized in human medicine, but are not reported in veterinary literature. We recognized such a neurologic syndrome in Lagotto Romagnolo dogs.

Animals: Twenty-five Lagotto Romagnolo puppies from 9 different litters examined because of simple or complex focal seizures and 3 adult Lagotto Romagnolo dogs exhibiting similar clinical signs were used.

Methods: Clinical and diagnostic evaluations of affected dogs were conducted, including electromyography, electroencephalography, and other testing.

Results: Seizures in puppies began at 5 to 9 weeks of age and usually resolved spontaneously by 8 to 13 weeks. Those with the most severe seizures also had signs of neurologic disease between these seizures, including generalized ataxia and hypermetria. There were no abnormalities in routine laboratory screenings of blood, urine, and cerebrospinal fluid. Electromyography, brainstem auditory-evoked potentials, and magnetic resonance imaging revealed no specific and consistent abnormalities. Fourteen of 16 (87.5%) affected puppies and 2 of 3 (67%) adult dogs revealed epileptiform activity in the electroencephalogram. Histopathologic examination in 1 puppy and 1 adult dog revealed lesions of Purkinje cell inclusions and vacuolation of their axons restricted to the cerebellum. Pedigree analysis suggests an autosomal recessive mode of inheritance.

Conclusions and Clinical Importance: This disorder, with simple or complex focal seizures and cerebellar lesions, represents a newly recognized epileptic syndrome in dogs.

Key words: Cerebellar pathology; Focal seizure; Idiopathic epilepsy; Inheritance.

Epileptic seizures are a manifestation of excessive, hypersynchronous activity of neurons in the brain.[1] Idiopathic epilepsy syndrome in humans is defined as an epilepsy-only syndrome with no underlying structural brain lesion or other neurologic or clinical signs and is presumed to be genetic and usually age dependent.[2]

The purpose of this study was to describe clinical, electrodiagnostic, diagnostic imaging, and histopathologic findings in Lagotto Romagnolo (LR) dogs with a unique neurologic syndrome and to define the possible mode of inheritance of this syndrome.

Materials and Methods

The first recognized affected LR litter was presented to the Helsinki University Small Animal Hospital in April 2004 because of episodic tremor in 6 of 7 puppies. During 2004, 2 more affected litters with similar complaints were detected. The examination of these animals indicated a focal seizure disorder. At that point, a prospective study was planned in collaboration with Finnish LR breeders. During the years 2004 and 2005, 58 LR puppies from 9 different litters (34 females, 23 males, and 1 hermaphrodite) were studied. Inclusion criteria included breed (LR) and seizure episodes. Littermates of the affected puppies were also included in the study. Nine litters came from 6 breeders in different geographic areas of Finland. Litters were presented to the Helsinki University Small Animal Hospital or to the Referral Neurology Clinic Aisti because of neurologic signs, primarily of an episodic nature. The number of puppies, the number of affected puppies, and the examined puppies in each litter as well as the age at examination appear in Table 1. In addition to the puppies, 3 adult LR dogs were included in the study because of focal seizures and similar clinical findings; they were examined at the age of 1 year 8 months, 2 years 1 month, and 6 years, respectively. The Ethics Committee on Animal Trials approved the study protocol.

Signalments, history, and pedigrees of all affected litters were reviewed. The historic assessment included age at onset, course of the disease, character and frequency of seizures, interictal signs, possible exposure to toxins, and vaccination history. The 31 dogs from the 9 litters were presented to clinic and underwent a complete physical and neurologic examination performed by a board certified neurologist or neurology resident (SC, TJ, RV, JJ) (21 sick puppies and 10 healthy littermates). The neurologic examination was video recorded for all but 3 of the puppies. An additional 27 puppies (4 affected and 23 healthy littermates) from the same litters were considered for historic assessment, which included telephone interviews with the breeders or owners. In addition, the signalments and histories of the 3 adult dogs was evaluated, and a physical and neurologic examination of the dogs was completed. Pedigrees were available for 2 of these adult dogs. The owners of all affected dogs were encouraged to videotape the seizures.

A CBC and serum biochemistry analysis (sodium, potassium, calcium, magnesium, glucose, total protein, albumin, cholesterol, creatinine, urea, creatine kinase, alanine aminotransferase, alkaline phosphatase, and aspartate aminotransferase) was performed in 22 (17 sick and 5 healthy) puppies and urinalysis in 18 puppies (15 sick and 3 healthy). Cerebrospinal fluid (CSF), collected by cisternal puncture, was analyzed for total cell count, cytology, and protein content in 19 puppies (16 sick and 3 healthy). CBC, serum biochemistry, urinalysis, and CSF examination were also performed in 3 adult dogs.

Electroencephalography (EEG) was performed in 21 puppies (16 sick and 5 healthy) and electromyography (EMG) in 20 puppies

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Table 1. Number of Lagotto Romagnolo puppies in total and number of puppies with episodic tremor in each litter with the number of examined puppies.

Litter No.	Total No. of Puppies	Age at Examination (weeks)	No. of Affected Puppies	No. of Examined Puppies (affected/healthy)
1	7 (4♀, 3♂)	8	6 (3♀, 3♂)	7 (6/1)
2	9 (4♀, 4♂, 1⚥)	5, 7, 8	6 (2♀, 4♂)	9 (6/3)
3	1 (1♀)	12, 17	1 (1♀)	1 (1/–)
4	6 (5♀, 1♂)	6, 8,[a] 12[a]	1 (1♀)	6 (1/5)
5	6 (4♀, 2♂)	8, 10[a]	3 (3♀)	3 (2/1)
6	8 (4♀, 4♂)	13	2 (1♀, 1♂)	1 (1/–)
7	7 (5♀, 2♂)	14	3 (2♀, 1♂)	1 (1/–)
8	7 (3♀, 4♂)	8	2 (1♀, 1♂)	2 (2/–)
9	7 (4♀, 3♂)	10	1 (1♀)	1 (1/–)

♀, female; ♂, male; ⚥, hermaphrodite.
[a] Re-examination of affected puppy/puppies.

(15 sick and 5 healthy). A brain stem auditory-evoked response (BAER) was performed in 14 puppies (11 sick and 3 healthy). An EEG was performed under medetomidine[a] sedation (0.04 mg/kg IM). Dogs who resisted needle placement after 15 minutes of initial sedation received an additional dosage of medetomidine (0.02 mg/kg IM). Dogs were placed in sternal recumbency and subcutaneous needle electrodes were inserted over the calvaria. A 17-channel monopolar montage was used as described previously.[3] The total recording time was 20 minutes. Each EEG recording was visually examined (LB). In EMG, intramuscular potentials were recorded from one side of the body (1 front and 1 hind limb and paraspinal muscles) under sedation (medetomidine[a] and butorphanol[b]), and propofol[c] was administered intravenously (IV) as needed. The BAER was performed under the same sedation as EMG. Alternating click stimuli of 90 decibels sound pressure level (dB SPL) were delivered through earplugs; a masking noise of 50 dB SPL was applied to the contralateral ear. Between 500 and 2,000 clicks were averaged, and each recording was repeated twice. EEG, EMG, and BAER were also performed as described in all 3 adult dogs.

Magnetic resonance imaging (MRI) was performed in 24 puppies (18 sick and 6 healthy) and 3 adult dogs. The dogs were positioned in sternal recumbency under general anesthesia. Anesthesia was maintained with propofol[c] (0.5–1 mg/kg as needed based on the clinical assessment) when performing MRI with a 1.5 Tesla MRI machine and with 1.5–2.0% isoflurane[d] when performing MRI with a 0.2 Tesla MRI machine. MRI was performed with a 1.5 Tesla MRI machine[e] in 13 dogs (7 from litter 1, 5 from litter 2, 1 dog from litter 6) and with another 1.5 Tesla MRI machine[f] in 4 dogs (2 dogs from litter five and 2 adult dogs). T2-weighted images and multiplanar reconstructions (with reconstructions as T1-weighted images) before and after contrast (gadolinium[g]) application were obtained, and sagittal, transverse, and dorsal planes were examined with 3-mm slice thickness. MRI was performed with a 0.2 Tesla MRI machine[h] in 10 additional dogs (the only dog from litter 3, 4 dogs from litter 4, 1 dog from litter 7, 2 dogs from litter 8, 1 dog from litter 9, and 1 adult dog). T1-weighted images were examined in at least 2 planes (usually transverse and sagittal) before and after contrast (gadolinium[g]), and T2-weighted images were also examined in at least 2 planes (usually transverse and dorsal planes) (4-mm slice thickness).

Postmortem pathologic examination was performed in the most severely affected puppy from litter 2 and in 1 adult dog. The entire central nervous system, along with samples of peripheral nerves (*N. ischiadicus*, *Plexus brachialis*), liver, heart, lung, kidney, and spleen, were fixed in 10% neutral buffered formalin and processed for routine histologic examination using hematoxylin-eosin stain for all samples and an additional luxol fast blue-cresyl echt violet for the nerve samples. Immunohistochemistry (IHC) of the cerebellum for canine parvovirus antigen was performed using a monoclonal antibody against canine and feline parvovirus.[i] IHC of the cerebellum was also performed for canine distemper virus antigen.[j]

Long-term follow-up of puppies and adult dogs was performed by examination, telephone contact with the owner or breeder, or both. Also, the owners of the examined dogs were advised to report any additional seizures or other kinds of abnormal behavior.

Results

Of the 58 dogs studied, 25 (15 females and 10 males) exhibited signs of neurologic disease, primarily of an episodic nature, as puppies (Table 1). The affected puppies began to exhibit abnormal signs at a mean age of 6.3 weeks (range 5 to 9 weeks). Signs included seizures characterized by generalized tremor, ataxia, and stiffness. Seizures were independent of the time of the day; some seizures occurred during sleep, others during exercise such as playing with other puppies. The frequency of seizure episodes varied among puppies from multiple episodes per day to 1 episode per week. One puppy experienced only 1 seizure. Seizures lasted from 10 seconds to a few minutes and consisted of whole body tremor (all limbs, body, and head were tremoring). Some puppies were sitting or lay laterally during the seizure, but some dogs were able to eat or walk during seizure episodes (for example, when the owner was calling the puppy). The amplitude of the tremor seemed to increase with exercise in cases where the dog was able to move during the episode. During these seizures, most of the puppies appeared conscious (responded to speaking; interpreted as simple focal seizure), but those who were in lateral recumbency during episodes especially failed to respond normally and appeared to have impaired or even lost consciousness (interpreted as complex focal seizure or secondarily generalized seizure). Clinical signs varied among puppies and in litters where multiple puppies were affected; some exhibited more severe signs. Also, the severity of seizures varied among individuals during the course of the disease. Although most of the puppies were normal between seizures, some breeders or owners reported falling or ataxia in some puppies between seizures. Otherwise, puppies were bright and healthy. The last seizures were

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noticed at a mean age of 10 weeks (range 7.5 to 13 weeks) in all litters. Two parts of 1 seizure in 1 affected puppy appear in the supplementary video clip that can be viewed at jvet.intmed.org

One dog from litter 6 that came to its present owner at the age of 12 weeks and began to exhibit focal seizures characterized by tremor restricted to the head (movement of the head in the horizontal plane) at the age of 1 year 7 months represents an exception to this clinical course. The breeder of this puppy reported that the puppy was normal until the age of 12 weeks. This dog exhibited seizures for several days followed by 1–2 months between the subsequent seizures. The last seizures occurred 6 months after the 1st episode. Another adult dog came to its present owner at the age of 6 months and as an adult began to exhibit focal seizures comparable to those described in the above puppies (the exact time of onset was unknown). Seizures were sometimes more frequent (3 times per week), and sometimes several months passed without seizures. The dog was imported, and its pedigree was unavailable. The 3rd adult dog came from a litter with no history of seizures during puppyhood. This dog experienced 3 focal seizure episodes characterized by head tremor during 2 days at the age of 2 years 1 month. After the 3rd episode, phenobarbital[k] medication (2 mg/kg q12h) was administered, and the seizures became milder and less frequent. Its last seizure occurred 1 month after the first seizure, and the dog's head tremored in the horizontal plane.

One dog from litter 2 received phenobarbital[k] (2 mg/kg q12h) from the age of 7 weeks because of focal seizures and remained symptom-free during this medication period. The medicine was discontinued at the age of 11 weeks because of the disappearance of seizures. The dog went to a new owner at the age of 12 weeks, and 1 week after the move experienced 2 seizures 1 week apart. The medication was readministered at the age of 13 weeks, and afterward the puppy experienced only 1 small seizure. The medication was gradually discontinued after 1 month. Since then, the dog has appeared normal (now 1 year 10 months). Other affected puppies or adult dogs (beside these 2 animals mentioned previously) received no antiepileptic medication. None of the puppies received vaccinations before the onset of signs.

Owners had managed to videorecord seizures in 2 puppies and 1 adult dog. An additional 2 puppies and 1 adult dog experienced a seizure episode during the examinations, and the authors were able to see and videorecord them. Upon re-examination of these videos, a lateralization during the seizures was visible such that the one side of the body was more severely affected.

The breeders reported the parents of all 9 litters were phenotypically normal. Physical examination revealed no abnormalities in the affected or control puppies. Abnormal findings were, however, present in the neurologic examination between seizures in 10 affected puppies, including generalized ataxia (7 dogs) and hypermetria (5 dogs), intention tremor (3 dogs), tremor (3 dogs), decreased postural reactions in all 4 limbs or in hind limbs only (8 dogs; both the proprioceptive positioning and hopping reactions were decreased), and bilaterally decreased menace reaction in all dogs (considered normal for puppies). The severity of neurologic signs varied among puppies from mild changes to more severe ataxia with falling. Puppies with the most severe seizures also revealed the most remarkable findings in neurologic examination. Based on the deficits in the neurologic examination, a multifocal intracranial problem mainly involving the cerebellum was suspected. Of the 10 puppies with changes in the neurologic examination, 9 were re-examined until no changes were found in the neurologic examination. Interictal neurologic deficits usually disappeared earlier as seizures. Mental status appeared normal in all puppies. In addition to the affected puppies, abnormalities in the neurologic examination were also found in 2 control puppies that exhibited no seizures (mild intention tremor and proprioception decreased in all 4 limbs, respectively). All 3 adult dogs studied had a normal physical and neurologic examination.

Hematologic and biochemical analyses and urinalysis revealed no significant changes that could explain the clinical signs. The results of the CSF examination were within reference range in all dogs.

Interictal EEG analysis in 14 affected puppies indicated epileptiform activity, including sharp waves and spikes (focal activity in 13 puppies and generalized activity in 1 puppy). Typical focal EEG changes are visible in Figure 1. Only 2 affected puppies revealed normal EEG recordings. EEG was performed in 12 puppies while they were still experiencing seizures (including 1 affected puppy with a normal EEG pattern). In 4 puppies, EEG was performed 1 to 4 weeks (mean 2.1) after the last seizure. Of the 5 healthy littermates studied, 4 had normal and 1 had abnormal EEG recordings with sharp waves. Epileptiform activity was revealed in the EEG of 2 of the 3 adult dogs. EMG and BAER recordings appeared normal in all examined dogs.

There were no abnormalities detected in the MR images of most puppies. The only change observed in some puppies (3 affected puppies from litter 1, 1 affected puppy from litter 4, and 1 healthy puppy from litter 4) was caudal enlargement of the 3rd ventricle, which was interpreted as incidental finding (Fig 2). MRIs did not reveal abnormalities in the 3 adult dogs examined.

The gross pathologic examination revealed a small cerebellum, which weighed only 7% of the total brain weight (4 g of 56 g, normal >10%), and petechiae in the mucosa of the stomach and intestines in the worst affected puppy. The gross examination of the adult dog was unremarkable. The histopathologic examination of the puppy revealed changes limited to the cerebellum consisting of small (1–2 μm in diameter), smooth, homogenous, pale, eosinophilic, intracytoplasmic inclusions in Purkinje cells and mild scattered Purkinje cell loss. The cellularity of the granule cell layer appeared normal, but occasionally large (>80 μm in diameter) swollen axons, interpreted as Purkinje cell axons and

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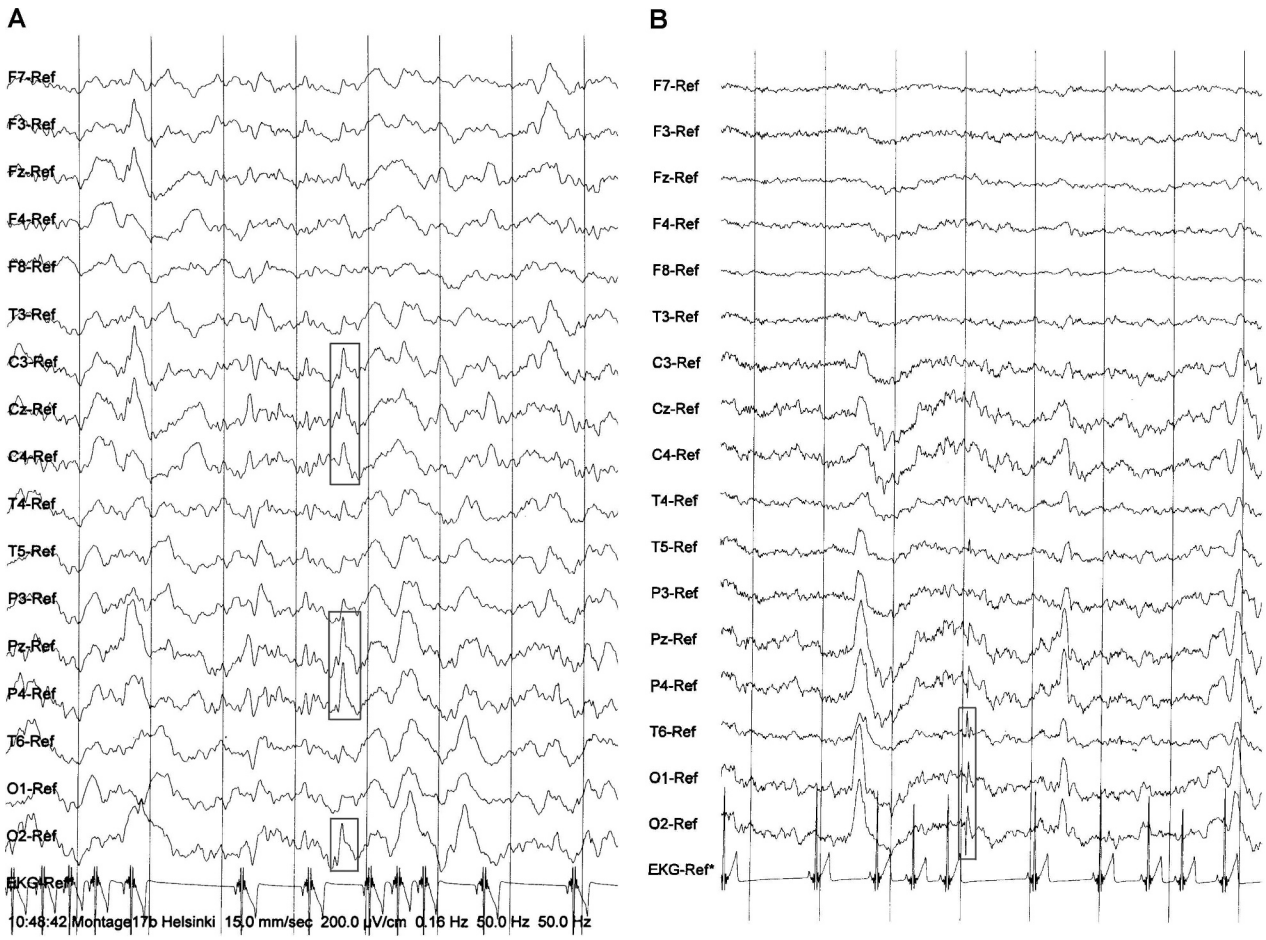


Fig 1. Electroencephalographies (EEGs) obtained from 2 Lagotto Romagnolo puppies. Both puppies exhibited focal seizures and focal epileptiform activity in interictal EEG (paper speed 15 mm/s, 1 s/division). **(A)** Sharp waves (amplitude: 200 µV/cm) and **(B)** spikes (amplitude: 100 µV/cm) are visible in these EEG recordings.

revealing severe vacuolar and vesicular degeneration, also appeared. Similar changes occurred in the histopathology of the cerebellum in the adult dog, but the intracytoplasmic inclusions were larger (up to 5 µm in diameter) and sometimes multiple or elongated. The axonal changes in the granular cell layer of the adult dog were mild, consisting mainly of occasional conventional swollen axons (spheroids) and fewer vacuolated axons. The parvoviral and distemper immunohistochemistry was negative in both dogs. Histopathologic changes appear in Figure 3.

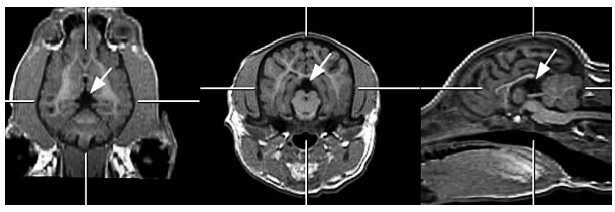


Fig 2. Magnetic resonance images of 1 puppy from litter 1. Multiplanar reconstructions in all 3 planes (dorsal, transverse, and sagittal) are presented as T1-weighted images. Enlargement of the 3rd ventricle is visible in all 3 planes.

The pedigree structure and the relatedness of the puppies studied appear in Figure 4. This multigenerational pedigree includes 115 dogs, of which 25 (21.7%) were reportedly affected with observed segregation frequency of 0.43 (25/58). All affected puppies were related, but had no single common ancestor. Male and female dogs seemed equally affected—43.5% (10/23) and 44.1% (15/34), respectively.

In puppies, the mean long-term follow-up period was 18 months (range from 7 to 23 months) after the last seizure (at a mean age of 20 months; range from 9 months to 26 months). In the long-term follow-up, 1 of the affected puppies experienced 1 seizure at the age of 8 months. Other affected puppies were normal at the time of follow-up. In 2 adult dogs, the follow-up period was 3 months after the last seizure in both dogs (the other dog remained under phenobarbital medication).

Discussion

This study describes an apparently novel syndrome in LR puppies characterized by focal seizures, epileptiform activity in interictal EEG, and pathologic changes

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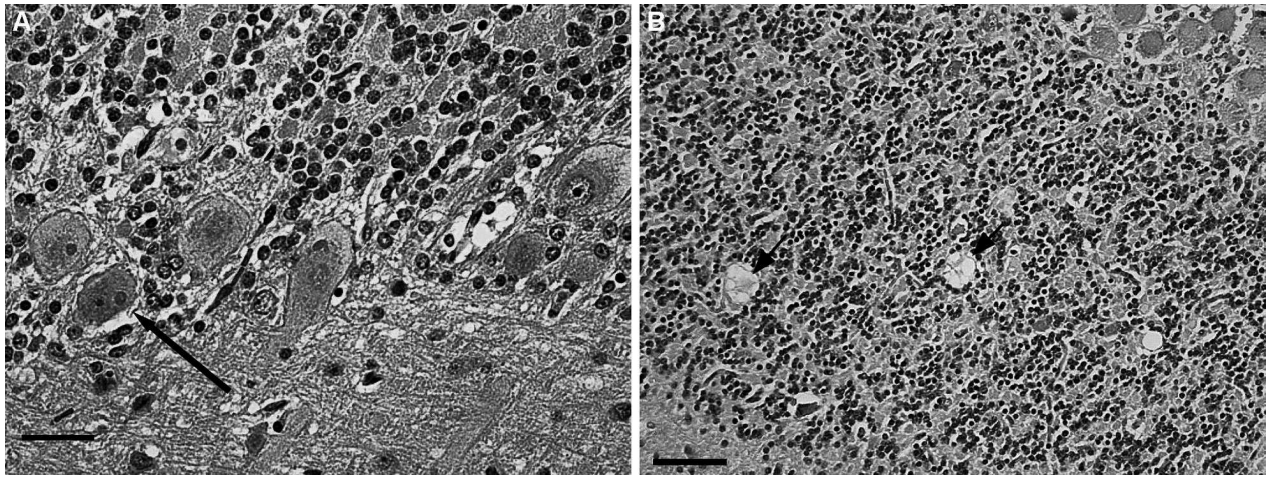


Fig 3. Two sections of the cerebellum of 1 affected Lagotto Romagnolo adult dog and puppy, respectively. **(A)** Histopathology revealed eosinophilic inclusions in the Purkinje cells. Scale bar = 50 μm. **(B)** In the granular cell layer there were swollen axons, interpreted as Purkinje cell axons revealing vacuolar and vesicular degeneration. Scale bar = 100 μm. Hematoxylin-eosin stain.

confined to the cerebellum suggestive of a juvenile epilepsy syndrome. In most of the animals, the outcome is benign, but 3 adult dogs were affected.

Idiopathic epilepsy in dogs is defined as recurrent seizures for which no underlying brain abnormality can be identified.[4] Idiopathic epilepsy is presumed to have a genetic cause both in dogs and in humans.[2,5] These puppies and adult dogs experienced simple or complex focal seizures with tremor as a major motor sign and had EEGs revealing epileptiform activity with no remarkable changes in blood, urine, EMG, BAER, MRI, or CSF examinations. On the other hand, tremor is an atypical manifestation of motor activity in idiopathic epilepsy.

Generalized tremors have been reported in diffuse central nervous system disorders and may result from structural abnormalities or the problem may be a functional defect in neurotransmission.[6] Generalized tremors have been reported in congenital disorders such as myelin abnormalities and storage diseases, intoxications, secondary to drug therapies, and encephalitis (also known as white shakers).[7] In these cases of generalized tremors, the tremor is seldom episodic, consciousness is preserved, and no epileptic activity in the EEG is reported. Toxic insult is unlikely here because the 9 litters studied were raised in 6 different kennels located in different towns across Finland, and the breeders reported no toxic insult. Tremors may also occur in a number of metabolic conditions such as hypocalcemia, hypoglycaemia, and hyperammonemia.[6] Laboratory examinations did not reveal metabolic abnormalities in these dogs. Also, the episodic nature of the disease and its benign outcome suggest the absence of structural brain disease.

Clinically, it may be difficult to distinguish paroxysmal movement disorders from seizure activity.[8–10] Movement disorders, or dyskinesias, are neurologic conditions characterized by abnormalities in movement and posture.[11] In humans, they are usually attributable to disorders of the basal ganglia or extrapyramidal system.[11] In paroxysmal movement disorders, interictal EEG should be normal and subjects should be conscious during the episode.[8] Episodic involuntary skeletal muscle activity with preserved consciousness during episodes has been reported in Boxer puppies and in an adult Bichon Frise.[9,10] Hyperkinetic conditions can also be regarded as dyskinesias and include ''Scottie cramp,'' hyperkinetic episodes in Dalmatian dogs, episodic falling in cavalier King Charles Spaniels, and hyperkinetic involuntary movements in the Shetland Sheepdog.[12–15] Consciousness is also fully preserved during these hyperkinetic episodes. EEG was performed on these reported paroxysmal movement disorders of dogs in 1 Dalmatian and 1 Shetland Sheepdog[13,15]; neither exhibited epileptiform activity interictally. These LR dogs exhibited changes in interictal EEG, and some of the dogs revealed decreased responsiveness during the seizure episodes. Accordingly, episodes were interpreted as focal seizures instead of paroxysmal movement disorders.

Researchers in human medicine have described benign childhood epilepsy syndromes. Benign familial neonatal seizures (BFNS) exhibit tonic or clonic seizures which, in most cases, appear during the 1st week of life.[16] Benign familial infantile seizures (BFIS) occur between 3 and 10 months of age with clusters of tonic or clonic, partial or generalized seizures that usually resolve in 1 year.[17] Both conditions appear as a benign course with no underlying disorder or neurologic abnormalities.[16,17] Benign childhood epilepsies with focal origin include benign childhood epilepsy with centrotemporal spikes (benign Rolandic epilepsy) and childhood epilepsy with occipital paroxysms (early onset Panayiotopoulos and late onset Gastaut type forms).[18–20]

EEG was performed in 16 affected puppies; in 14 puppies EEG revealed epileptiform activity. Also, 2 of the 3 adult dogs examined exhibited epileptiform activity in EEG. Epileptic animals exhibit EEG abnormalities during seizures, but interictally EEG can be normal.[21–23] EEG was also performed in 5 healthy littermates, 4 of which had normal recordings, but 1 revealed epileptic

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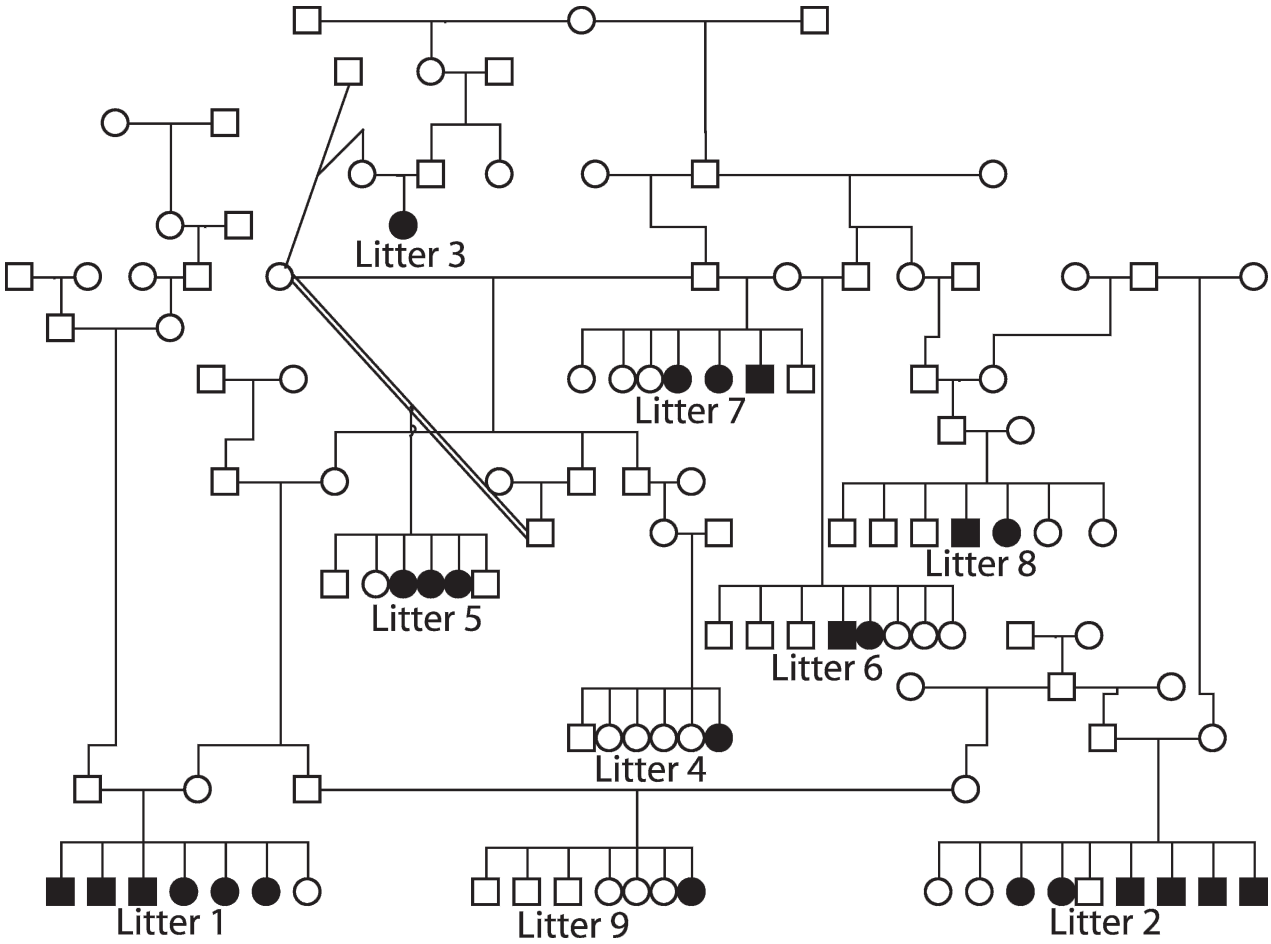


Fig 4. Pedigree of Lagotto Romagnolo puppies with juvenile epilepsy. All 25 affected puppies representing both sexes were born to unaffected parents, consistent with an autosomal recessive mode of inheritance. Square = male; circle = female; shaded symbol = affected dog. In litter 2, the only unaffected male dog is actually a hermaphrodite.

activity; 1 puppy may have experienced mild episodes that went unnoticed. On the other hand, the EEG may be abnormal in patients with no history of epileptic seizures. To the authors' knowledge, no recent reports describe EEG recordings in healthy puppies. The human juvenile brain appears more excitatory in nature, and in large studies of normal children, up to 9% exhibit epileptiform activity on the EEG.[18] Also, the siblings of children with benign Rolandic epilepsy in childhood may exhibit an abnormal EEG pattern similar to that of the affected child, but still never develop seizures.[18] The higher prevalence of epileptiform activity in affected puppies than in healthy littermates indicates that abnormal activity is connected to clinical seizures. One affected puppy with a normal EEG recording experienced a seizure (generalized tremor, lateral recumbency, unconsciousness) approximately 30 minutes before undergoing an EEG. Postictal phenomena in EEG have been studied in humans, and postictal attenuation in EEG has been noticed in 29% of patients,[24] which may explain the lack of epileptic signs in the EEG recording after the seizure episode.

Reports of BFNS cases have been reviewed, and interictal EEG was reported normal in 20 patients and abnormal in 22 patients. EEG was repeated in 10 of these 22 cases and appeared normal.[16] Interictal EEG has been reported normal in BFIS.[17] A normal EEG is exceptional in benign childhood epilepsies with a focal origin.[25] In Rolandic epilepsy, centrotemporal spikes occur in EEG, and interictal EEG is typically abnormal, with abnormalities exaggerated by sleep.[18,25] Spikes also seem to be activated by sleep in 90% of children with Panayiotopoulos syndrome.[26] Despite the remission of seizures, EEG abnormalities persisted in 75% of patients with Panayiotopoulos syndrome (mean follow-up 6 years).[26] In another study, occipital paroxysms persisted for several years after the clinical remission of benign childhood epilepsy. In the aforementioned study, EEG normalized consistently before the age of 16 years and most often before the age of 11 years.[19] Almost all of these dogs revealed abnormalities in EEG, and repeated EEG examinations are planned.

Epilepsy in young animals may be outgrown, which is also suggested in repeated EEG.[22] In this present study, EEG was performed while 12 puppies were still experiencing seizures. EEG was performed 1 to 4 weeks after the last seizure in 4 puppies, but all of

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these recordings revealed epileptiform activity. Further measurements are required to follow possible changes in epileptiform activity with clinical improvement.

Approximately 10% of BFNS patients will develop epilepsy in adulthood, but the reason for this relapse is unclear.[16,27] The incidence of idiopathic epilepsy in adulthood does not differ from that of the general population in BFIS, but in untreated cases isolated or brief clusters of seizures may occur within 1 year of age.[17]

The neonatal brain appears more resistant to neuronal damage resulting from seizures than that of adults.[28] On the other hand, increasing evidence suggests that recurrent brief seizures during the neonatal period adversely affect brain development and may predispose one to cognitive, behavioral, or epileptic complications later in life.[29–31] To medicate at least the most affected puppies may be reasonable to prevent seizures from recurring later in life.

This present study also presents 3 adult dogs, only 1 of which was related to the puppies examined. The pedigree or information about the littermates of 1 of the dogs was unavailable. The 3rd examined adult dog came from a litter with no abnormal signs reported in puppyhood. The 1st puppies examined were born in January 2004; the 1st adult case involved a puppy from this litter. Only 1 additional dog that had experienced seizures as a puppy (and was also examined as a puppy) experienced a similar seizure at the age of 8 months. Perhaps more relapses will occur later as the other litters age. Further follow-up studies with current litters are necessary to answer this question.

A postmortem pathologic examination revealed eosinophilic inclusions in the cerebellar Purkinje cells. These inclusions were interpreted as pseudo-Negri bodies, which include cytoplasmic lamellar bodies in dogs. Studies have identified lamellar bodies both in normal animals and in animals with neurologic defects, especially in Purkinje cells.[32] Electron microscopy would be necessary to confirm the nature of these inclusions. The authors suggest that the connection between cortical excitability and cerebellar degenerative pathology in these puppies is most likely caused by a common etiological factor. Cerebellar pathologic changes may explain the interictal neurologic examination findings (such as hypermetria and ataxia) in the most affected puppies.

Studies have reported a syndrome of bovine familial convulsions and ataxia in purebred and crossbred Aberdeen Angus cattle, with pathologic changes confined to cerebellar Purkinje cells and their axons.[33–36] Newborn and young calves with this condition exhibit spastic seizures and residual ataxia. The remission of seizures in surviving animals may be followed by the remission of ataxia and clinical normality by the age of 2 years.[34,35] Although the pathogenesis remains unknown, researchers have suggested a metabolic disorder affecting Purkinje cells and their axons.[36] Others have suggested that the convulsive episodes may represent exacerbations of cerebellar signs rather than true cerebral seizures because of the lack of changes in EEG in a convulsive calf.[37] A metabolic disorder of the Purkinje cells cannot be excluded, but on the other hand, interictal EEG revealed epileptiform activity in the brains of these dogs.

There was no sex predilection in affected dogs, and all puppies were born to clinically normal parents. Although the disease status of many older dogs in the pedigree remains unconfirmed, the number of affected dogs and the overall structure of the pedigree suggest an autosomal recessive mode of inheritance. The observed segregation frequency was higher than the expected segregation frequency of 0.25 for autosomal recessive inheritance. The observed segregation frequency, however, does not take into account that 2 carrier parents may by chance produce a healthy litter. Also, the disease status of parents could not be confirmed although the breeders of affected litters reported no seizures in them. Further genetic studies are underway to map the disease locus and gene.

Although the clinical picture (frequency and severity of seizures) varied among individuals, the course of the disease was very similar in affected puppies with spontaneous recovery. In addition, 3 adults exhibited similar focal seizures, and 1 of these dogs was a littermate of an affected puppy. We suggest this to be a new benign familial juvenile epilepsy syndrome in LR dogs with possible relapse in adulthood and a recessive mode of inheritance.

Footnotes

[a] Medetomidine hydrochloride, Domitor 1 mg/mL, Orion Pharma, Espoo, Finland
[b] Butorphanol tartrate, Torbugesic Vet 10 mg/mL, Fort Dodge Veterinaria SA, Girona, Spain
[c] Propofol, Rapinovet vet 10 mg/mL, Shering-Plough Animal Health, Farum, Denmark
[d] IsoFlo, Abbott Laboratories, Kent, UK
[e] Siemens Magneton Symphony 1.5 T, Siemens AG, Medizinische Technik, Germany
[f] Philips Gyroscan Intera 1.5 T CV Nova Dual, Philips Medical Systems, Best, Netherlands
[g] Gadolinium, Magnevist 469 mg/mL injection, Schering AG, Berlin, Germany
[h] Vet-MR 0,2 T, Esaote, Genova, Italy
[i] MCA 2064, Serotec, Oxford, UK
[j] MCA 1893, Serotec, Oxford, UK
[k] Barbivet vet 30 mg tablets, Vetcare Oy, Salo, Finland

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