Magnetic Resonance Imaging
Findings in Finnish Spitz Dogs with Focal Epilepsy

R. Viitmaa, S. Cizinauskas, L-A. Bergamasco, E. Kuusela, P. Pascoe, A-M. Teppo, T.S. Jokinen, L. Kivisaari, and M. Snellman

Eleven Finnish Spitz dogs with focal seizures and 3 healthy controls were evaluated. General clinical and neurological examinations, blood examination, urinalysis, cerebrospinal fluid examination, electroencephalography (EEG), and magnetic resonance imaging (MRI) of the brain were performed on all dogs. On EEG examination, focal epileptic activity was found in 7 of 11 dogs (64%), and generalized epileptic activity was observed in 4 of 11 dogs (36%). MRI (performed with 1.5 T equipment) detected changes in 1 epileptic dog. Mild contrast enhancement after gadolinium injection was identified in this dog's right parietal cortex. However, no such changes were observed in repeated magnetic resonance images. Special emphasis was given to seizure history to determine any correlations between seizure intervals and MRI findings. Our results indicate that Finnish Spitz dogs with focal seizures suffer from focal idiopathic epilepsy and have nondetectable findings on MRI or pathology. MRI showed poor sensitivity in detecting epileptogenic areas in our patients with focal seizures. Reversible MRI changes in 1 dog could have been caused by seizures.

Key words: Canine; Idiopathic epilepsy; Partial seizures; Reversible brain changes; Symptomatic epilepsy.

A diagnosis of idiopathic (primary) epilepsy in dogs typically is made after exclusion of other conditions and is based on a history of >2 seizures in the absence of other medical problems and normal physical findings, neurologic examinations, and clinicopathologic data.[1–3] Unfortunately, no universally accepted diagnostic criteria for dogs with idiopathic epilepsy exist in veterinary medicine, and electroencephalography (EEG) and magnetic resonance imaging (MRI) are not routinely included in confirming this diagnosis.[2,4]

The Neuroimaging Commission of the International League Against Epilepsy has recommended that an MRI examination be performed on every human patient with epilepsy.[5] MRI is considered the most valuable diagnostic tool for investigating the etiology of epilepsy because the presence of lesions is an important factor in planning epilepsy management and in predicting the prognosis of individual human patients.[6]

MRI findings in dogs with seizures usually pertain to patients with symptomatic (secondary) epilepsy. These dogs typically have seizures as a complication of brain tumors,[7–11] malformations,[12,13] metabolic diseases,[14] or brain inflammation.[15–17] MRI findings in dogs with focal idiopathic epilepsy seldom have been reported in the veterinary literature.[18,19] The use of advanced neuroimaging techniques in veterinary medicine is restricted mainly because of the high costs involved.[11]

Some authors have claimed that focal seizures or seizures with focal onset and secondary generalization should be classified as symptomatic or cryptogenic seizures.[1,20] No evidence, however, has emerged to support such a notion. The purpose of this study, therefore, was to describe MRI changes in a group of epileptic Finnish Spitz dogs with focal seizures, to define the contribution of the MRI examination in diagnosing idiopathic and symptomatic epilepsy. A further aim was to compare our findings with results in human medicine.

Materials and Methods

Two groups of dogs were studied: 3 healthy Finnish Spitz dogs that served as controls and 11 known epileptic Finnish Spitz dogs. All dogs underwent identical diagnostic evaluation.

This study was performed at the Small Animal Clinic of the University of Helsinki in collaboration with the Finnish Spitz Breeding Committee. Dog owners who had previously informed the Finnish Spitz Breeding Committee about the presence of epileptic seizures in their dogs submitted these dogs for further evaluation of epilepsy. The study protocol was approved by the Ethics Committee on Animal Trials. Presence of at least 2 focal seizure episodes, complete seizure history and clinical data, absence of changes in general physical and neurologic examinations performed by a European College of Veterinary Neurology diplomate or resident, and normal blood examination and urinalysis were the minimum criteria for inclusion of dogs in the study. In addition, all dogs underwent EEG examinations. Blood examination included CBC and serum biochemistry (sodium, potassium, calcium, phosphorus, magnesium, glucose, total protein, albumin, globulin, cholesterol, blood urea nitrogen, creatinine, total bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and creatine kinase). Urinalysis consisted of specific gravity, chemistry, and sediment examinations. EEG was performed under medetomidine[a] sedation (0.04 mg/kg IM). An additional 0.02 mg/kg of medetomidine was given IM if the dog was not ready for examination 15 minutes after the initial injection. EEG examinations were performed in a quiet, darkened room. Dogs were placed in sternal recumbency and needle electrodes were inserted SC over the calvaria. A 14-channel monopolar montage was used, modified from a 17-channel

Table 1. Scanning protocols used for magnetic resonance imaging of Finnish Spitz dogs.

SE Sequences	Plane	TR (msec)	TE (msec)	FoV (mm)	Matrix Size	SL (mm)
T1WI	Sagittal	490.0	20.0	140 × 140	202 × 256	3
	Transverse	680.0			220 × 256	
	Dorsal	490.0			256 × 256	
T2WI	Sagittal	3,100.0–3,500.0	96.0	145 × 145 or 155 × 155	259 × 512	3
	Transverse	3,300.0–4,000.0			259 × 512	
	Dorsal	3,300.0–3,700.0			259 × 512	
MPR	All planes	11.1	4.3	126 × 202	170 × 256	1.1
FLAIR	Dorsal	8,500.0	105.0	120 × 160	140 × 256	3

SE sequences, spin echo sequences; TR, repetition time; TE, echo time; FoV, field of view; SL, slice thickness; T1WI, T1-weighted images; T2WI, T2-weighted images; MPR, multiplanar reconstruction; FLAIR, fluid-attenuated inversion recover.

monopolar montage, as described previously.[21] The total recording time was 20 minutes.

The following variables were evaluated: age, gender, age at 1st observed epileptic seizure, seizure type, frequency and duration, and therapy history.

Seizures were classified according to initial clinical signs, as described by Licht et al.[3] A generalized seizure involved both cerebral hemispheres with manifestation of bilaterally symmetrical signs. A focal seizure had asymmetrical signs or signs restricted to one part of the body. Focal seizures were divided into simple focal seizures (SFS) and complex focal seizures (CFS). The main distinction between these focal types was whether or not consciousness was preserved, with CFS being characterized by impaired consciousness and SFS by preserved consciousness. Impaired consciousness was characterized mainly by the lack of responsiveness of the dog during the epileptic episode. When focal seizures had progressed to generalized seizures, they were classified as secondary generalized focal seizures.

Idiopathic epilepsy was diagnosed when no etiopathologic correlation to demonstrable organ disorder was proven, and a possible hereditary predisposition was suspected for recurrent seizures. Symptomatic epilepsy was considered when seizures were a consequence of a known or suspected disorder of the central nervous system.[22]

MRI examinations were performed with 1.5 T Siemens Magnetom[b] and 1.5 T Picker Edge[c] equipment with standard human knee coils. Animals were under general anesthesia throughout the procedure. An over-the-needle catheter was placed in one of the cephalic veins. Dogs were premedicated with butorphanol,[d] 0.2 mg/kg IM, and atropine,[e] 0.02 mg/kg IM, 30 to 60 minutes before induction. Induction was performed with propofol,[f] 3–5 mg/kg IV, and diazepam,[g] 0.25–0.5 mg/kg IV to effect. Dogs were intubated and received oxygen through a non-rebreathing system at a rate of 2 L/min. Anesthesia was maintained with constant propofol infusion of 0.3–0.6 mg/kg/min diluted in 0.9% saline solution. Pulse rate, respiratory rate, and end-tidal carbon dioxide were monitored during the procedure. Dogs were placed in sternal recumbency. Routine T1-weighted (T1W) and T2-weighted (T2W) images in all 3 standard planes (ie, sagittal, transverse, and dorsal) were recorded. Multiplanar reconstructions (MPR) were used instead of T1W images in 4 epileptic dogs and all control dogs. Reconstruction later was performed in all 3 planes as T1W images. Fluid-attenuated inversion recovery (FLAIR) sequence was performed in these 4 dogs in the dorsal plane. T1W images or MPR were repeated immediately after bolus IV injection of gadolinium-diethylenetriaminepenta-acetate (-DTPA) dimeglumine,[h] at 0.2 mL/kg (0.1 mmol/kg). Scanning protocols used for MRI of Finnish Spitz dogs are presented in Table 1.

Scans were reviewed independently by 2 radiologists (MS and LK). The scans of healthy Finnish Spitz dogs were examined 1st to identify any breed-specific differences. Reviewers were informed about scans belonging to healthy control or epileptic Finnish Spitz dogs. The scans were examined for (1) asymmetry and dilatation of fluid spaces, (2) developmental anomalies, (3) hippocampal abnormalities (size or structure), (4) proportions and localization of gray and white matter, (5) focal identifiable changes, (6) presence of inflammation, and (7) other (eg, posttraumatic) changes.

Cerebrospinal fluid (CSF) samples were collected from the cerebellomedullary cistern after MRI examination. Total cell count, cytology and protein concentration were evaluated.

Results

Nine intact males, 1 castrated male (dog 6), and 1 intact female (dog 9) Finnish Spitz dogs were included. The age of the dogs ranged from 2.5 to 8.6 years (mean, 5.3 years), and body weight was from 10.4 to 17.0 kg (mean, 13.5 kg). All examined dogs were used as hunting dogs. The dogs were, on average, under the supervision of the owner or a family member 25 to 50% of the time.

Focal motor signs were noted as the 1st sign of a seizure episode in 8 dogs; tonic-clonic movements were recorded for 5 (dogs 2, 5, 6, 7, and 11) and tonic movements for 3 (dogs 3, 8, and 9) of them. Tonic-clonic motor signs tended to start in the face (dogs 5, 6, and 7), in both limbs on the left side (dog 2), or in the right hindlimb (dog 11). Seizures of these 5 dogs were allocated to the CFS group because of altered responsiveness. In addition to tonic-clonic motor signs, behavior changes (fear and restlessness in dog 2; hiding and disorientation in dogs 5, 6, 7, and 11), or autonomic signs (vomiting and salivation in dog 11) were present. Dog 11 also had 1 simple focal episode that lasted 1 minute and was characterized by short jerking movements of the right hindlimb in the standing position with normal responsiveness during the seizure. Focal tonic-clonic motor signs generalized after 1 to 3 minutes in all 5 dogs, except in the aforementioned simple focal episode of dog 11. Seizures with tonic motor signs in 3 dogs (dogs 3, 8, and 9) were characterized by the dogs suddenly assuming a "saw bench" position, with extension of the neck while remaining in the standing position. Owners reported that the dogs' eyes were fixed in dorsal (dogs 8 and 9) or ventral (dog 3) strabismus. All dogs had impaired consciousness during these episodes. The episodes typically lasted 1 to 2 minutes in dogs 8 and 9 and up to 2 hours in dog 3.

Sudden behavior changes, such as fear or trying to make contact with the owner, were the initial signs of seizures in 3 dogs (dogs 1, 4, and 10). In all 3, behavior changes alone, with no motor signs, were observed. Dogs showed signs of restlessness or repeated meaningless movements (eg, constant wandering from 1 corner of the room to the other), which were interpreted as automatism[3] or disorientation. These signs were considered to represent focal seizure activity. The duration of these signs was 1 to 5 minutes. Impaired consciousness was observed in 2 animals (dogs 4 and 10) and normal consciousness in 1 (dog 1). In dogs 8 and 9, 2 variations of seizure onset were noted. In some seizure episodes, tonic motor signs were observed 1st (as described previously), and in the other episodes, behavioral changes preceded motor activity. Progression of the seizures also was not uniform in these 2 dogs. Some ictal events generalized after the initial behavior changes. In other seizure episodes, progression was partial, with mild tonic-clonic motor signs localized to the limbs on one side of the body. This motor activity never involved whole body. The limbs on the contralateral side remained normal; the dogs remained in standing position and tried to find support from the walls. Furthermore, the motor activity during some ictal events was observed on the left side and, in others, on the right side of the body.

Seizure episodes generalized secondarily in 10 dogs. Nevertheless, some of these 10 dogs also had ictal events without generalization (as previously described in dogs 8, 9, and 11). Dog 3 was different from the other 10 dogs in that it had CFS without generalization or primarily generalized episodes. Generalization was characterized by tonic-clonic motor signs that were symmetrical and involved the whole body. The dogs were in lateral (most frequent) or sternal (seldom) recumbency. Consciousness was lost during the generalized phase in 5 animals (dogs 4, 6, 8, 9, and 10) and impaired in another 5 (dogs 1, 2, 5, 7, and 11). Autonomic signs were observed in 9 dogs, occurring mainly at the end of the generalized phase and characterized by salivation, urination, and defecation. The postictal phase consistently occurred in all episodes, except in the SFS in 1 dog (dog 11). This phase was characterized by fear, fatigue, disorientation, and thirst. The duration of postictal signs ranged from 2 minutes to 2 hours (usually one-half to 1 hour).

All dogs were found to be normal on general physical and neurologic examinations. No clinically relevant changes were present on laboratory evaluations. CSF analyses were within reference range (<5 cells/μL; <25 mg/dL protein) in all dogs. Interictal epileptogenic activity in EEG recordings was generalized in 4 dogs and focal in 7 dogs. Focal activity tended to generalize or spread contralaterally in 7 dogs. The epileptic activity occurred in the anterior right hemisphere (dog 1), the central posterior right hemisphere (dogs 2 and 4), the posterior areas (dogs 5 and 6), the left temporal area (dog 10), or the posterior temporal derivation and the entire posterior derivation (dog 11).

Three dogs (dogs 3, 4, and 7) were being treated with phenobarbital (2–3 mg/kg PO q12h in 2 dogs and 2–3 mg/kg PO q24h in 1 dog). Serum phenobarbital concentrations were measured in all treated dogs (dog 3, 8 μg/mL; dog 4, 20 μg/mL; dog 7, 8 μg/mL; therapeutic range, 15–45 μg/mL). Eight dogs had never received antiepileptic therapy.

No MRI changes were noted, except in dog 3. Mild contrast enhancement after gadolinium injection was observed in the right parietal cortex of this dog. The size of the lesion was 5.5 mm, and it was visible in 2 transverse slices (Figure 1). Non-contrast images of this dog were normal. No changes were present in a repeated MRI examination of this patient (Figure 2).

Dog 2 was euthanized after examination, and dog 7 was euthanized 6 months later. The reasons for euthanasia were the inability of the owner to take care of an epileptic dog and aggressive behavior. A postmortem examination was performed on dog 2. Samples from the right half of the brain (where epileptic activity had been noted on EEG) were formalin-fixed, paraffin-embedded, and stained for routine histopathologic examination (hematoxylin-eosin). No changes in gray and white matter, meninges, or ependyma were found. The left half of the brain was frozen and saved for possible additional examinations. No histologic changes were seen in the spinal cord or the peripheral nerves. No other relevant changes were observed in general pathology. All examinations performed on healthy control dogs yielded normal results.

Discussion

A widely held opinion in the veterinary literature has been that epileptic seizures in canine idiopathic (primary) epilepsy are generalized, whereas symptomatic (secondary) epilepsy usually is characterized by partial seizures.[1,23–25] More recently, detailed observation of all stages of epileptic episodes in dogs has increased the number of focal seizures identified in various canine breeds.[3,19,20] Furthermore, adaptation of knowledge from human epileptology has encouraged veterinary specialists to diagnose idiopathic epilepsy in dogs with focal seizures.[19] Licht et al[3] pointed out that the lack of universally approved terminology in canine epileptology adds to confusion about whether seizures should be considered focal or generalized, and about which epilepsies are symptomatic and which are idiopathic. Seizures that were regarded as having generalized in the past are now more frequently recognized to have focal onset. All epileptic Finnish Spitz dogs included in our study had partial onset episodes that usually became generalized secondarily. In all but 1 dog, the high-field MRI examination failed to identify brain lesions. Presence of epilepsy was confirmed in these dogs by positive EEG examination and the animals' history. The genetic background of disease in Finnish Spitz dogs previously has been elucidated,[26] and an extensive epidemiological investigation currently is underway. A logical interpretation of our findings would be that the dogs suffered from focal idiopathic epilepsy, which is likely to be an inherited condition. Surprisingly, little has been published in veterinary medicine about MRI
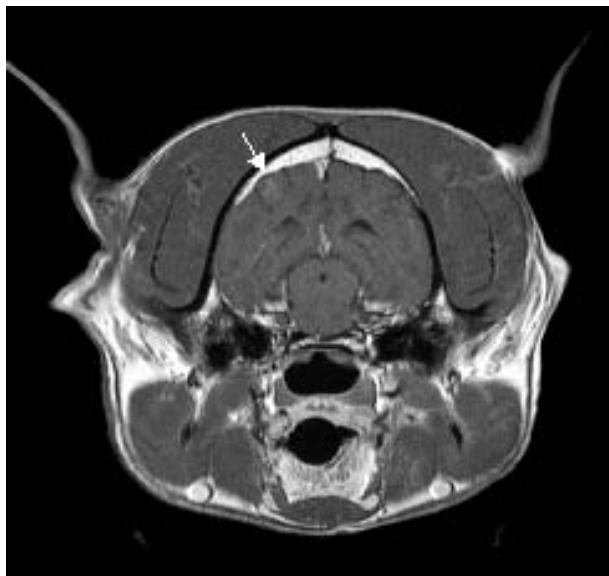
Fig 1. First magnetic resonance imaging (MRI) examination of dog 3. T1-weighted images (T1WI) after IV gadolinium administration in transverse plane repetition time [TR]/echo time [TE] 680/20.0). A 5.5 mm hyperintense area is present in the right parietal cortex (arrow).

findings in dogs with focal epilepsy. Therefore, the notion that focal epileptic seizures are caused by a focal structural brain lesion most probably is based on a pathophysiologic understanding of epilepsy. Focal idiopathic inherited epilepsies are well defined in human epileptology.[27–29] Over 80% of humans with epilepsy have focal epilepsy, and only 43% have a cerebral lesion.[6]
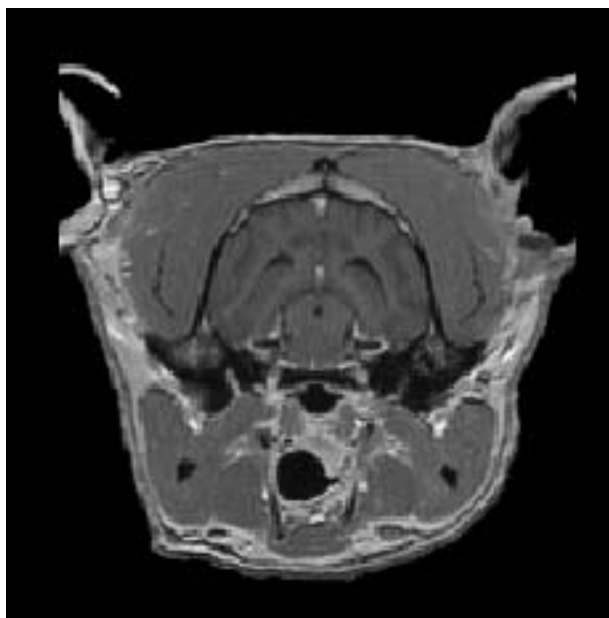

Fig 2. Repeated magnetic resonance imaging (MRI) examination of dog 3 at 13 months after the 1st examination. Multiplanar reconstruction in transverse plane in the same area as in Figure 1 after administration of gadolinium repetition time [TR]/echo time [TE] 11.1/96.0). No changes are visible.

MRI changes are more frequently detected in patients with temporal lobe epilepsy (76%) than in patients with extratemporal focal epilepsy (47%).[30] Hippocampal sclerosis (HS), the main cause of temporal lobe epilepsy in humans, is detected by MRI in approximately 55% of these patients.[31] The MRI features of HS are atrophy, disruption of internal structure, increased hippocampal signal on T2W images, and decreased T1W signal.[32] Visual analysis of transverse planes was used in the dogs in this study to detect hippocampal changes. No hippocampal structural changes were observed in any of these Finnish Spitz dogs with focal epilepsy, including the 2 dogs with EEG changes in the temporal area. However, the number of dogs was small, and pre-selection according to clinical signs and EEG pattern was not performed in this study. Therefore, it would not be valid to state that temporal lobe epilepsy in Finnish Spitz dogs is rare. Nevertheless, our findings do support a previous report that canine epilepsies may be mainly extra-temporal.[33] Lesions are visualized less frequently in humans with extra-temporal focal epilepsies than in humans with temporal lobe epilepsy.[30] Our results reveal that identification of epileptic lesions in dogs is even lower than in humans. The description of both focal temporal and focal extra-temporal epilepsies in humans with proven genetic backgrounds and no MRI changes also is relevant in veterinary epileptology.[31,34] Our findings indicate that in certain populations of dogs, focal idiopathic epilepsies without visible MRI changes can be detected. The pathogenesis of some focal idiopathic epilepsies in humans has been described recently. Various mechanisms, such as changes in the nicotinic acetylcholine receptor subunit or in leucine-rich glioma-inactivated factor 1 (epitempin), have been suggested.[29,35–37] However, the reason why changes, which are expressed ubiquitously in the central nervous system, are causing focal epilepsy, is unknown.[37] Described changes are not visible with imaging methods available at this time, but can be detected with immunohistochemistry.[35] No data on possible disease mechanisms of canine idiopathic epilepsies are available. Future research should concentrate on this area.

Reversible MRI abnormalities in the piriform lobe, temporal lobe, or both of 3 dogs after seizures have been reported previously.[10] These changes completely or partially resolved on re-evaluation. Of the dogs in this study, the only one in which MRI changes were detected (dog 3) had a 2-minute generalized seizure episode 3.5 hours before imaging, a seizure that was observed by the authors. Unfortunately, the very beginning of this seizure was not observed, and it is therefore impossible to say whether it was primarily or secondarily generalized. The previously recorded interictal EEG in this dog revealed generalized epileptic activity displayed as volleys of polyspikes and wave complexes, as well as synchronous and bilateral sharp waves. However, a contrast-enhanced area in the right parietal lobe was noted in this dog. These changes were not observed in an MRI repeated 13 months later. The time period between seizure occurrence and MRI imaging plays a critical

role. Lesion identification might improve if examinations were done on the same day as a seizure occurrence, as indicated by Mellema et al.[10] There was no evidence of brain changes in the other 10 dogs in this study, including dog 10, which had a 45-minute period of status epilepticus 21 days before MRI examination. Seizure frequency might be another important factor in induction of MRI changes. The overall seizure frequency in the dog population, approximately 1 seizure in 4 months, was relatively low. However, the fact that these Finnish Spitz dogs were living outside and spent only 25–50% of the time under the owners' supervision prompted us to assume that the actual seizure frequency was likely higher.

Seizure pseudolocalization (ie, seizures originating in one brain area although a structural abnormality is visualized in another brain region) must be taken into account in MRI studies of epileptic patients.[5] HS, for example, is known often to be a secondary pathology in humans and dogs because hippocampal neurons are vulnerable to excitotoxic damage by intense and prolonged seizure activity.[32,33,38] Secondary hippocampal changes in the brains of dogs with suspected idiopathic epilepsy have been reported.[39,40] Whether hippocampal changes in these dogs would have been visualized on MRI is unknown because MRI examination was not performed. Results in this study reveal that visualization of an epileptic focus is difficult. To enhance epileptogenic focus detection, an EEG was performed on all dogs in this study. Unfortunately, little is known about EEG correlations with clinical presentation of seizure episodes in veterinary medicine.[2,4,40] Practically no publications have compared clinical seizure presentation, EEG, and MRI findings in dogs. Focal onset seizures were present in 11 of 11 dogs (100%), focal epileptic activity on EEG in 7 of 11 dogs (64%), and MRI changes in 1 of 11 dogs (9%). Generalized interictal activity on EEG was noted in 4 dogs, including the dog with MRI changes (dog 3). The MRI changes in this dog were more likely the result of the seizure, and not the permanent seizure focus, because no changes were detected during repeated examination despite the dog continuing to have seizures. No focal EEG activity being present in the lesion area supports this notion. EEG provided a higher sensitivity in detecting epileptic activity than did MRI in Finnish Spitz dogs with focal idiopathic epilepsy. Correlations among clinical diagnosis and EEG and MRI findings in human epileptic patients have been investigated.[6] In humans with lobar epilepsy, MRI lesions were found in 38% of patients with negative, and in 48% of patients with positive, interictal epileptic discharges. Both EEG and MRI results were negative in 31% and positive in 24% of patients. However, had the number of dogs included in this study been larger, more positive MRI findings might have resulted.

MRI is seldom applied in the diagnosis of idiopathic epilepsy in dogs in routine small animal practice. Nevertheless, the situation is rapidly changing, and MRI likely will be used more frequently in the future. MRI currently is indicated in animals in which symptomatic epilepsy is suspected.[24] A high correlation among the results of neurologic examination, CSF analysis, and MRI findings have been identified in dogs with seizures when reactive epilepsy was excluded by negative blood examination results. MRI was abnormal in 97% of dogs with abnormal results in both CSF analysis and neurologic examination. By contrast, MRI detected changes in only 6% of dogs with normal results of neurologic examination and CSF analysis.[11] We revealed a similar correlation, because all dogs included here had normal neurologic, blood, and urine examinations, as well as normal CSF analysis results. MRI examination identified no permanent changes in the brains of any of these dogs. These findings combined with those of Bush et al[11] clearly indicate that neurologic examination is a sensitive indicator of secondary epilepsy when neurologic deficits are detected. On the other hand, dogs most likely suffer from idiopathic epilepsy when the interictal neurologic examination is normal. These results further indicate that classification of patients into idiopathic and symptomatic categories should be based on the patient's diagnostic evaluation rather than on the seizure pattern (ie, frequency and type) alone. Both focal and generalized seizures can be idiopathic in origin.

More advanced neuroimaging techniques may increase detection of primary and secondary lesions in dogs with idiopathic epilepsy in the future. Progress in diagnostic imaging techniques in human medicine[5,30] suggests that the epileptogenic foci of what we now consider to be idiopathic epilepsy may someday become visible. Lesion detection might be improved by application of phased-array surface coils, image averaging, high field strength MRI, computer-based postprocessing analysis, magnetic resonance spectroscopy, and functional MRI.[5] Anatomical magnetic resonance neuroimaging does not identify structural lesions in all human patients.[30] Therefore, other functional methods used in human epileptology, such as positron emission tomography and ictal single photon emission computed tomography, also might offer better visualization of epileptogenic foci or secondary changes in the brains of dogs with idiopathic epilepsy.[30]

Footnotes

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