Thesis for the degree of Master of Veterinary Medicine

A Retrospective Study of Epileptic Small-breed Dogs Diagnosed on Magnetic Resonance Imaging in Jeju

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Abstract

Seizures are the most common neurological condition in dogs. Magnetic resonance imaging (MRI) is one of the most reliable diagnostic tool for neurological symptoms such as seizures.

Objectives: To identify the proportion of neurological disorders and clinical responses to antiepileptic medical treatment in small-breed dogs in Jeju that underwent brain MRI. The medical records and MRI images (MAGNETOM Sempra 1.5T, Siemens, Germany) of 70 small-breed dogs referred to Jeju National University between September 2021 and April 2023 were retrospectively evaluated. Records describing the prescribed antiepileptic drugs including phenobarbital, levetiracetam, gabapentin, zonisamide, and diazepam were also evaluated. The proportions of neurological disorders diagnosed using brain MRI were as follows: idiopathic epilepsy (IE) in 22 dogs (31.4%), meningoencephalitis of unknown origin (MUO) in 14 dogs (20.0%), tumors in 8 dogs (11.4%),

hydrocephalus in 5 dogs (7.2%), and others in 21 dogs (30.0%). For dogs that lasted treatment over 30 days (26 dogs), we evaluated the initial clinical response to antiepileptic drugs (AEDs). Additionally, 17/26 dogs (65.4%) treated with AED showed a complete response, 6/26 dogs (23.1%) showed a partial response, and 3/26 dogs (11.5%) showed no response. For dogs that were diagnosed with MUO or IE (36 dogs), we evaluated 365-day survival rate. Notably, 8/36 dogs (22.2%) with MUO or IE died within 365 days of presentation, 24/36 dogs (66.7%) survived beyond 365 days or were alive during the research period, and 4/36 dogs (11.1%) were lost to follow-up. Before 2021, patients with neurological symptoms in Jeju were unable to receive MRI. However, since September 2021, patients in Jeju underwent MRI imaging. This is the first retrospective study for dogs performed brain MRI in Jeju.

Keywords: Epilepsy, MRI, Antiepileptic drugs, Jeju, Dog

Ⅰ. Introduction

Seizures are common neurological disorders in veterinary medicine. Epilepsy is a brain disorder characterized by at least two unprovoked epileptic seizures with a minimum of 24 hours separation. Epileptic seizures are defined as sudden transient episodes of convulsions caused by abnormal neuronal activity in the brain [2]. Epileptic seizures are categorized to reactive epilepsy, structural epilepsy, and non-structural epilepsy. A reactive epilepsy is defined as a natural response by the normal brain to a transient disturbance in function caused by metabolic or toxic conditions [3]. Structural epilepsy is categorized as vascular, inflammatory, infectious, traumatic, anomalous, developmental, neoplastic, or degenerative. In contrast, idiopathic epilepsy is only classified as non-structural epilepsy. Current recommendations state that dogs presenting with seizures should undergo magnetic resonance imaging (MRI) and exclude reactive seizures.

MRI is an important diagnostic tool as it helps detect structural intracranial lesions with relatively high sensitivity and specificity [21]. In Jeju Island (South Korea), accurate diagnosis of neurological disorders is challenging because of the absence of MRI equipment. However, in September 2021, the Jeju National Teaching Hospital initiated the first MRI equipment to enable imaging of the neurological system for diagnostic purposes.

This study aimed to evaluate the prevalence of neurological disorders in Jeju, their management with antiepileptic drugs (AEDs), and the survival rate of each condition.

Ⅱ. Materials and Methods

1. Animals

The electromedical records (EMRs) from the Internal Medicine Department of Jeju National Teaching Hospital from September 2021 to April 2023 were evaluated for dogs under 20kg body weight that underwent brain MRI. Data retrieved from the EMRs included the dogs breed, age, sex, neuter status, body weight, chief complaint, laboratory findings, neurological examination, and MRI findings.

2. Inclusion criteria and group assignment

Patients were included in this study if they had a brain MRI on presentation and at least one of the following neurological symptoms: (1) epilepsy (having at least two unprovoked epileptic seizures > 24 hours apart), (2) cluster seizure (two or more seizures occurring within 24 hours), (3) generalized or focal epileptic seizure, (4) vestibular dysfunction, (5) ataxia, (6) paraparesis or tetraparesis, and (7) other symptoms such as pain or dropped jaw [2,4].

The included dogs underwent physical and neurological examinations, complete blood count (CBC), serum biochemistry, and thoracic radiography. The patient's complete medical history and additional blood analysis were performed to exclude reactive epilepsy due to conditions such as hyperammonemia, hypoglycemia, or severe azotemia [16]. Some dogs underwent echocardiograms to exclude cardiogenic cause of syncope.

The dogs were then included in Group 1 if they had a

neurological diagnosis and all the dogs in group 1 that were placed on antiepileptic drugs (AEDs) and follow-up for at least 30 days were assigned to Group 2. Additionally, dogs in group 1 diagnosed with meningoencephalitis of unknown origin (MUO) and idiopathic epilepsy (IE) were assigned to Group 3.

3. Diagnostic testing and categories

MRI examinations were performed using the 1.5T scanner (Magnetom Sempra; Siemens Healthineers, Munich, Germany). The following sequences were obtained from all patients: T1 and T2 - weighted images (T1W, T2W), fluid-attenuated inversion recovery (FLAIR), and post-contrast T1W images after intravenous injection of 0.01 mmol/kg of gadoterate meglumine (Clariscan; GE Healthcare AS, Oslo, Norway). Trained veterinarians administered standard anesthesia. All measurements were performed by either a trained veterinarian or veterinary radiologist. All diagnosis were confirmed by diplomate of the Korean College of Veterinary Internal Medicine (DKCVIM).

Cerebrospinal fluid (CSF) was collected via the cisterna magna for analysis, including polymerase chain reaction (PCR), to identify the infective agent. However, CSF analyses were not available for all dogs related to anesthesia or technical problem.

MRI findings included abnormalities associated with inflammation, degeneration, neoplasm, hemorrhage, and ischemia. Dogs with meningoencephalitis of unknown origin (MUO) were diagnosed based on the criteria used by Granger *et al* [7]. Briefly, intracranial focal, multifocal or diffuse lesion in T2W, CSF pleocytosis (hypercellular with > 50% mononuclear cells) and negative for infectious diseases. Dogs

were diagnosed with hydrocephalus based on the findings reported by Laubner *et al* [13]. Briefly, ventricle/brain ratio > 0.6 with morphological abnormalities indicative of increased intraventricular pressure. Dogs with brain tumors were diagnosed based on previous studies [1, 12, 19]. Briefly, lesion location, signal intensities and contrast inhancement implicate brain tumor type and combination of signalment, history and CSF analysis. However, histopathologically confirmation was not performed in any dog with suspected brain tumor in this study. Patients were diagnosed with idiopathic epilepsy if there were no specific abnormalities on MRI.

4. Antiepileptic drug (AED) response

Dogs in Group 2 began AEDs therapy on the day of diagnosis. The AEDs included phenobarbital, gabapentin, levetiracetam, zonisamide, and diazepam. Data on the clinical response to treatment and adverse events were obtained from telephone conversations with the owners or records from re-examination.

Treatment responses were divided into three categories: complete response (CR, resolution of neurological symptoms), partial response (PR, > 50% reduction in the frequency of neurological symptoms), and no response (NR, neither CR nor PR).

5. Survival rate

Data on dogs included in Group 3, date of death and cause or current patient status were obtained via telephone conversations with the owners and evaluated. Dogs were divided into three categories: those

who died within 365 days, those who survived beyond 365 days or were alive at the time of investigation, and those who were lost to follow-up.

Ⅲ. Results

1. Signalment and diagnostic findings

A total of 72 dogs met the inclusion criteria (Figure 1).

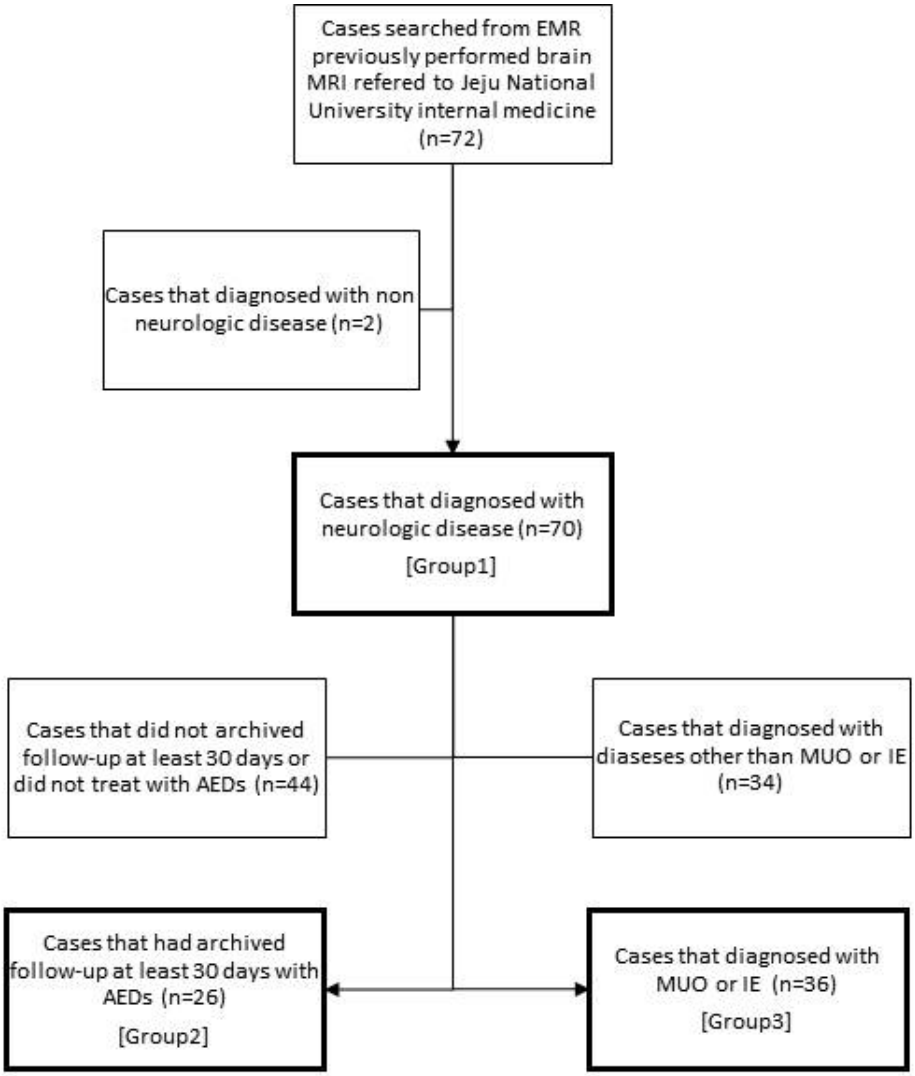

Figure 1. Flow diagram of the current study for group 1, group 2, and group 3. EMR, electronic medical record; MRI, magnetic resonance imaging; AED, antiepileptic drug; MUO, meningoencephalitis of unknown etiology; IE, idiopathic epilepsy

Two dogs were diagnosed with non-neurological diseases (one with inflammatory myopathy and one with immune-mediated polyarthritis) were excluded. Group 1 included 70 dogs diagnosed with neurological diseases (Table 1), including 37 male dogs (6 intact, 31 neutered) and 33 female dogs (11 intact, 22 neutered). The dogs had a median age of 9 years (range: 1-16 years old) and median body weight of 4.2 kg (range: 1.6-19.2 kg).

Table 1. Signalment of the dogs included in Group 1

Variables	Overall (n = 70)	MUO (n = 14)	IE (n = 22)	Hydroce-phalus (n = 5)	Brain tumor (n = 8)	Others (n = 21)
Sex						
Male	6	1	3	0	2	0
Male neutered	31	8	7	2	4	11
Female	11	3	3	1	0	4
Female neutered	22	2	9	2	2	8
Body weight (kg)						
median	4.2	3.1	5.1	3.3	5.2	5.0
range	1.6-19.2	1.6-19.2	1.8-16.1	1.9-8	2.3-10.2	2.8-18.0
Age at onset (year)						
median	9	5	6	10	10	9
range	1-16	1-14	2-16	9-14	7-13	1-14

MUO, meningoencephalitis of unknown etiology; IE, idiopathic epilepsy

In Group 1, the most common diagnoses were idiopathic epilepsy (IE, n = 22), meningoencephalitis of unknown origin (MUO, n = 14), hydrocephalus (n = 5), and suspected brain tumors (n = 8), including 4 cases of meningioma, 2 cases of glial tumors, and 2 cases of pituitary tumors. Twenty-one dogs were included in others with diagnoses including traumatic brain injury (TBI, n = 4), cervical intervertebral disc disease (n = 4), paroxysmal dyskinesia (n = 4), suspected metastasis of carcinoma (n = 2), idiopathic vestibular disease (n = 1), peripheral nerve sheath tumor (n = 1), inflammatory myelopathy (n = 1), idiopathic facial paralysis (n = 1), sudden acquired retinal degeneration (SARD, n = 1), brain infarction (n = 1), and suspected brain abscess (n = 1).

CSF samples were analyzed in 22 dogs (28.9%), and all PCR samples were negative. CSF samples of 8 dogs were analyzed wtih CSF pleocytosis,

Twenty-eight dogs (40%) had a history of generalized seizures. Additionally, Of the dogs with idiopathic epilepsy (IE, 68.1%) were more likely to present with a history of generalized seizures than those with other diagnoses.

2. Relationship between age and the presence of structural brain lesions

The brain MRI findings for each case were classified as follows: structural lesions (MUO, brain tumor, hydrocephalus, TBI, cervical intervertebral disc disease, suspected metastasis of carcinoma, peripheral nerve sheath tumor, inflammatory myelopathy, brain infarction, and suspected brain abscess) and non-structural lesions (IE, PD, idiopathic vestibular disease, idiopathic facial paralysis, and SARD). A total of 35 dogs were included in the structural brain lesion group

and the remaining dogs were included in the non-structural brain lesion group.

Of the dogs with structural brain lesions, 8 dogs (22.9%) were ≤ 6 years old and 27 (77.1%) were > 6 years old. Of the dogs without structural brain lesion, 17 dogs (48.6%) were ≤ 6 years old and 18 (51.4%) were > 6 years old (Figure 2).

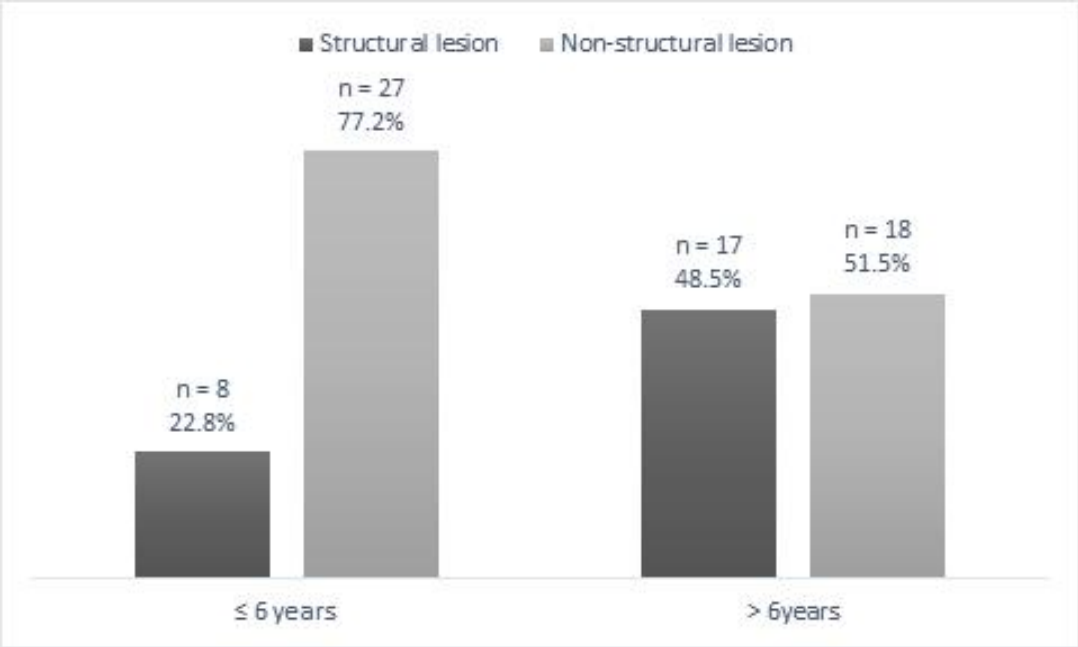

Figure 2. Comparison of age categorized by presence of structural brain lesion in Group 1. Thirty five dogs exhibited brain structural lesion while 35 dogs exhibited absence of brain structural lesion. According to the International Veterinary Epilepsy Task Force(IVETF) diagnostic approach, non brain structural lesion is frequently characterized by a clinical onset below the age of 6 years. In contrast, dogs with brain structural lesion is frequently characterized by a clinical onset over the age of 6 years.

3. AEDs clinical response

Twenty-six dogs were included in Group 2 (follow-up at least 30 days) (Table 2).

Table 2. Comparison of AEDs and clinical response categorized by MUO, IE, and others in Group 2

Variables	Overall (n = 26)	MUO (n = 9)	IE (n = 9)	Others (n = 8)
CR (%)	17/26	5/9	6/9	6/8
	65.4%	55.6%	66.7%	75%
PR (%)	6/26	3/9	2/9	1/8
	23.1%	33.3%	22.2%	12.5%
NR (%)	3/26	1/9	1/9	1/8
	11.5%	11.1%	11.1%	12.5%

AED, antiepileptic drug; MUO, meningoencephalitis of unknown etiology; IE, idiopathic epilepsy; CR, complete response; PR, partial response; NR, no response

All dogs in this group were treated with AEDs (including phenobarbital, levetiracetam, gabapentin, zonisamide, and diazepam). Of these, 16 dogs (61.5%) received combination therapy (phenobarbital, gabapentin, and zonisamide), and 10 dogs received monotherapy (phenobarbital (n = 7), gabapentin(n = 1), levetiracetam (n = 1), and diazepam (n = 1)).

Dogs in Group 2 were categorized into MUO, IE, and other conditions such as brain tumor or hydrocephalus based on their diagnoses. Responses within 30 days of treatment initiation were recorded in 17 dogs (65.4%), PR in 6 dogs (23.1%), and NR in 3 dogs (11.5%).

4. Survival rate

Thirty-six dogs diagnosed with MUO or IE were included in Group 3 (Table 3).

Table 3. Cases that diagnosed to MUO or IE were classified according to their 365-day survival rate in Group 3

Variables	Overall (n = 36) %	MUO (n = 14) %	IE (n = 22) %
Death within 365 days	8/36	6/14	2/22
	22.2%	42.9%	9.1%
Survived over 365 days or alive during research period	24/36	6/14	18/22
	66.7%	42.9%	81.8%
Loss to follow up	4/36	2/14	2/22
	11.1%	14.2%	9.1%

MUO, meningoencephalitis of unknown etiology; IE, idiopathic epilepsy

Additionally, eight dogs (22.2%; MUO, n = 6 and IE, n = 2) died at home or were euthanized at the owner's request for deteriorating neurological signs within 365 days of presentation. Twenty-four dogs (66.7%; MUO = 6, IE = 18) survived for over 365 days. Of these dogs, six dogs (MUO = 2, IE = 4) that were alive during the research period and did not complete the 365-day follow-up were also included. Four dogs (11.1%; MUO = 2, IE = 2) were lost to follow-up.

Patients with IE had a 365-day survival rate of 81.8%, whereas those with MUO had a survival rate of 42.9%. In this study, the IE group exhibited a higher 365-day survival rate than the MUO group.

Ⅳ. Discussion

This study evaluated the prevalence of neurological diseases following the introduction of the first MRI equipment in Jeju, the response to AEDs for each specific disease, and the 365-day survival rates between patients with MUO and IE. According to a previous large-scale study including 900 dogs that underwent MRI for epileptic seizures, 53.8% of the study population was diagnosed with presumed IE [9]. Another study found that 41% of the study population had IE [15]. In the present study, 31.4% of the study population had IE, which is a relatively low prevalence compared to previous studies. According to previous large scale study in United Kingdom, most common breeds identified in IE were Labrador retriever, Border collie, and Staffordshire bull terrier [5]. And previous study in Japan, most common breeds identified in IE were Chihuahua, Miniature Dachshund, and Yorkshire terrier [10]. Maltese, Chihuahua, and mixed breed were most common breeds identified in this study, we might assume that breed distribution would provide different prevalence of IE.

According to a previous study, the prevalence of IE is higher in males than females [9]. However, in the present study, no significant sex-related differences were observed. The relationship between sex hormones and seizures is well described in human population, whreas, less well described in canine population [23]. Further studies would be required.

With respect to breed size, patients with inflammatory diseases were more prevalent in smaller breeds (< 10kg) than with other diseases [9, 11]. However, in this study, the majority of the included dogs

weighed less than 10kg, with the exception of three dogs. Notably, there were no significant differences in body weight. We assume that study population was small that even if certain breeds (Maltese, Chihuahua, Shih tzu, and Yorkshire terrier) related to non-infectious inflammatory condition included in this study [11]. Histopathological confirmation should be performed, but clinical signs respond to immune-suppressive therapy would support suspected MUO diagnosis [7]. Further studies would be required.

According to a previous study, dogs with IE, 44% of included dogs presented generalized seizures [6]. In this study, dogs with IE, 68.1% of included dogs presented generalized seizures. Sex hormones especially estrous cycle and testosterone affected seizure occurrence in intact dogs [22, 23]. However in this study, dogs with IE, 22% of included dogs were intact that we mignt assume that other specific factor triggers seizures other than sex hormone.

According to the IVETF diagnostic consensus proposal, dogs with structural lesions showed a higher seizure onset age (7.6 ± 3.4 years) compared to those without structural lesions (3.3 ± 2.1 years) [4]. Additionally, dogs under the age of 6 without structural lesions exhibited a higher prevalence of epileptic symptoms than those with structural lesions. Similarly, the prevalence of dogs under the age of 6 years without structural lesions was 48.6%, whereas that of dogs with structural lesions was 22.9% as seen in a previous study. We might recommand that dogs with epileptic seizure over the age of 6 years to perform brain MRI and CSF analysis than dogs under the age of 6 years to evaluate inflammatory, infectious, or neoplastic.

Phenobarbital, zonisamide, and levetiracetam are approved as first-line AED for the management of seizures in the ACVIM consensus

statement [17].

Phenobarbital is a well-tolerated AED for chronic use in veterinary medicine. Previous studies have shown that phenobarbital monotherapy is potentially effective in reducing seizures [8, 20]. The combination of phenobarbital, gabapentin, and zonisamide was most commonly used in the present study and achieved a higher CR rate than phenobarbital monotherapy. No significant differences were observed in the response to AEDs for each diagnosis. We might suggest that phenobarbital is recommandable AED to manage epileptic seizure.

According to previous study, comparing the median survival times of dogs with idiopathic epilepsy and those with epilepsy associated with intracranial lesions, the former had a longer survival time [14]. Similarly, the present study showed that dogs diagnosed with IE had a higher 365-day survival rate (81.8%) than dogs diagnosed with MUO (42.9%). In one study, 56% of dogs diagnosed with MUO either died or were euthanized due to failure to respond to treatment, while another study found that 25% of the 116 dogs included in the study died or were euthanized within 7 days after diagnosis [14, 18]. In this study, 21.4% of dogs had died within 7 days after diagnosis with a similar outcome of previous studies. Additionally, 6/14 dogs (42.9%) diagnosed with MUO died within 365 days. Dogs diagnosed with MUO have relatively poor survival outcomes.

This study had several limitations. First, the retrospective design of this study has innate limitations. Treatment varied among dogs based on clinical signs and veterinarian preferences. Second, the number of included cases was small and statistical analyses were not performed including survival curve that further study would be needed to provide reliability. And, Six of the dogs (MUO = 2 and IE = 4) were still alive

when the survival analysis was completed, thus, the exact survival rate could not be established making the interpretations limited. Third, histopathological confirmation of the definitive diagnosis was not performed in any case. MRI interpretation and clinical data may support confidence in MRI diagnosis [21]. However, biopsy should be performed when feasible to obtain accurate diagnosis and determine prognosis [19]. Finally, not all patients underwent CSF analysis to support inflammatory, neoplasia, and idiopathic.

Ⅴ. Conclusion

The prevalence of disorders in small-breed dogs with epilepsy in Jeju was similar to that reported in previous studies. Briefly, IE is most common neurologic disease in Jeju with most common breeds identified in IE were Maltese, Chihuahua and mixed breed. Notably, 68% of dogs younger than 6 years old did not have structural brain lesions, whereas 32% had structural brain lesions. This support that dogs older than 6 years old recommand to perform CSF analysis. In this study, phenobarbital was the first treatment option with tolerable mono-or combination therapy. In addition, patients with IE had a higher 365-day survival rate than patients with MUO. However, further studies should be performed to obtain the prognoses for each neurological disorder on Jeju Island.

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제주도에서 자기공명영상으로 진단된 간질증상 소형견에 대한 후향적 연구

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요약

간질은 개의 가장 흔한 신경학적 문제 중 하나이다. 한편, 자기 공명 영상은 간질을 포함한 신경 증상을 보이는 환자를 진단하는 데 가장 신뢰되는 도구 중 하나이다. 본 연구의 목적은 제주도의 간질증상 소형견 중에서 뇌 자기공명영상을 촬영 후 각 질병 비율을 확인하고 항경련제 치료에 대한 임상 반응을 평가하는 것이다. 2021년 9월부터 2023년 4월까지 제주대학교 동물병원을 방문한 70마리의 소형견의 의료 기록 및 자기공명영상 이미지를 후향적으로 수집하였다. 간질 관리를 위해 페노바비탈, 레베티라세탐, 가바펜틴, 조니사마이드 또는 디아제팜과 같은 항경련제가 처방되었다. 뇌 자기공명영상으로 진단된 질병은 특발성 간질 22마리 (31.4%), 원인불명의 뇌수막염 14마리 (20.0%), 종양 8마리 (11.4%), 수두증 5마리 (7.2%), 기타 21마리 (30.0%) 였다. 간질 증상으로 30일 이상 치료를 시작한 개 26마리 중 17마리 (65.4%)가 완전한 치료반응을 보였다. 26마리 중 6마리 (23.1%)는 부분적 치료반응을 나타내었고, 26마리 중 3마리 (11.5%)는 치료반응이 나타나지 않았다. 또한 원인불명의 뇌수막염 또는 특발성 간질로 진단된 개 36마리 중에서 365일 생존률을 평가하였다. 36마리 중 8마리 (22.2%)가 365

일 이내에 사망했고, 36마리 중 24마리 (66.7%)가 365일을 초과하여 생존했거나 연구기간 동안 생존했으며, 36마리 중 4마리 (11.1%)는 추적이 소실되었다. 2021년 이전에는 제주에서 신경 증상이 있는 환자들이 자기공명영상을 촬영하지 못한 상황이었으나 2021년 9월부터는 제주의 환자들이 자기공명영상 촬영을 시작하게 되었다. 이는 제주지역에서 뇌 자기공명영상 촬영한 개를 대상으로 한 최초의 후향적 연구이다.

주요어: 간질, 자기공명영상, 항경련제, 제주, 개

감사의 글

길면 길다고 할 수 있고 짧다면 짧다고 할 수 있는 2년간의 대학원 생활을 잘 마무리할 수 있도록 도와주신 교수님, 동기들 그리고 제주대학교 동물병원 진료진들에게 감사의 인사를 먼저 올립니다.

제가 하고 싶은 일을 묵묵히 뒤에서 지지해주고 사랑으로 보듬어주신 부모님과 동생에게 감사의 마음을 담습니다. 공부에 집중할 수 있게 된 것은 부모님의 끊임없는 관심과 사랑 덕분임을 이 감사의 글을 통해 올립니다.

학부 졸업 후 1년간 인턴생활을 하면서 제가 생각했던 것과 많이 다른 현실에 좌절 후 방황하고 있을 때 제가 가야할 길을 알려주시고 받아주신 송우진 지도교수님께 감사의 인사를 드립니다. 외과의를 꿈꿔왔던 저를 내과의의 길로 잘 이끌어주셨고 현재 그 길을 선택한 것에 매우 만족하고 있습니다.

항상 저희를 생각해주시고 진료에 집중하여 성장할 수 있게 도와주시는 윤영민 교수님께도 감사드립니다. 교수님의 보살핌 덕에 저와 동기들 모두 값진 진료경험과 지식을 얻었습니다.

논문을 쓰는 동안 부족한 부분을 많이 채워주시고 놓친 부분을 세세히 보살펴주신 김명철 교수님께도 감사의 인사를 드립니다. 교수님의 피드백은 제가 큰 힘이 되었습니다.

진료를 보면서 동고동락했던 병원 식구들과 동기들, 선후배 선생님들에게도 많은 도움을 받았습니다. 이 인연은 잊지 않고 잘 간직하겠습니다.

마지막으로 대학원 생활동안 얻은 지식과 경험은 앞으로 큰 자산으로 여길 것이고 이 모든 것은 제 주변의 감사한 인연들 덕분에 좋은 결실을 이루게 될 것이라 생각합니다. 이 경험을 토대로 앞으로 나아가 더 나은 수의사가 될 수 있도록 더욱 성장하겠습니다.

크나큰 감사의 마음을 담아.

2024년 2월

김민건