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# A Retrospective Study on Canine Epilepsy: Etiological Distribution, Therapeutic Outcome, and Survival Time

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**Abstract :** The purpose of this study was to investigate the etiological distribution, therapeutic outcome, and survival time in canine epilepsy. The medical records of 57 epileptic dogs were reviewed for the evaluation of etiological distribution. Among them, 27 dogs (47%) and 30 dogs (52%) had idiopathic epilepsy (IdE) and structural epilepsy (StE), respectively. Twenty-nine dogs (IdE: 16 dogs, StE: 13 dogs) were evaluated for therapeutic outcome and survival time. The incidence of generalized epileptic seizure (IdE, 56% vs. StE, 44%; $P = 0.043$) and the median seizure frequency at the time of first presentation (IdE, 2.0/month vs. StE, 13.3/month; $P < 0.01$) were significantly different between the two groups. Although pre-treatment seizure frequency and duration were not different, the median duration of seizure in the IdE group (0.5 min) was significantly shorter than that in the StE group (3 min) after treatment ($P < 0.01$). In addition, the median frequency of seizure was relatively lower in the IdE group (0.25/month) compared to the StE group (2.00/month) following antiepileptic therapy ($P = 0.053$). The median survival time of the IdE group (1.5 years [95% CI, 1.0-2.3 years]) was significantly longer than that of the StE group (0.4 year [95% CI, 0.2-1.3 years]) ($P < 0.01$). The information on etiological data and intracranial lesions may be useful for predicting treatment response and prognosis in epileptic dogs.

***Key words*** **:** dog, idiopathic epilepsy, seizure, structural epilepsy, antiepileptic therapy.

## Introduction

In the veterinary field, epilepsy is one of the most common chronic and functional neurological disorder. Epilepsy is defined as a neurological disease, which causes the prominent clinical sign of seizures (3). The causes of epilepsy can be classified as idiopathic and structural (8).

Idiopathic epilepsy (IdE) is a disease in which epilepsy occurs without any underlying disorder caused by an identifiable cerebral pathology (3,20). IdE can be classified into three sub-groups: 1) genetic epilepsy, 2) suspected genetic epilepsy, and 3) epilepsy of unknown cause. On the other hand, structural epilepsy (StE) is characterized by epileptic seizures caused by underlying cerebral pathology, including vascular, inflammatory/infectious, traumatic, anomalous/developmental, neoplastic, and degenerative diseases (3). Prognosis of both IdE and StE is known to be varied because it is difficult to predict this for individual patients. However, the seizure-control prognosis of dogs with StE is less predictable than that of dogs with IdE, and some evidence suggests that dogs with StE have a shorter survival time and a greater resistance to antiepileptic drugs than dogs with IdE (22,24).

The International League Against Epilepsy (ILAE), the human epilepsy organization, established the classification and terminology of epilepsy. Based on this information, many dynamic studies have been conducted on several aspects (4,12). However, in veterinary medicine, the terminology and classification of epilepsy have not been established precisely because the diagnostic methods for the neurologic patients in human medicine are not routinely used in veterinary neurology clinics (7). Especially in South Korea, the veterinary literature on canine epilepsy is limited, which deals with research on the etiological distribution and survival studies. To the best of our knowledge, the information on canine epilepsy in the veterinary literature of South Korea is based on inadequate statistical analysis or isolated case reports (6,16-19,21).

The purpose of this study was to investigate the etiological distribution, therapeutic outcome, and survival time of dogs with IdE and StE.

## Materials and Methods

### Case selection

The medical records of 62 dogs with seizure were reviewed from all dogs presented to the Veterinary Medical Center, Chungbuk National University from April 2013 until July 2017. According to the International Veterinary Epilepsy Task Force (IVETF) consensus, epilepsy is defined as two or more seizures occurring at least 24 h apart (10). To ensure the diagnosis of epilepsy, dogs with seizures occurring only on one day were excluded from this study. Although repetitive seizures occur over time, reactive seizures due to extracranial

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disorders, including metabolic diseases or toxins are not considered to be epilepsy. Thus, the dogs were excluded if they were diagnosed with seizures caused by diseases such as hepatic encephalopathy, hypoglycemia, and electrolyte disorders.

The diagnosis of IdE was made on the basis of three tiers (10). Tier 1: signalment (an age at initial epileptic seizure onset ranging from 6 months to 6 years, a family history of idiopathic epilepsy), unremarkable findings of physical and neurological examinations between the ictal phases, unremarkable blood tests, and urinalysis. Tier 2: unremarkable fasting and post-prandial bile acids, unremarkable imaging results, including brain MRI and/or CT, and normal cerebrospinal fluid (CSF) analysis. Tier 3: identification of ictal or inter-ictal EEG abnormalities.

The StE was diagnosed by identifying one or more identifiable structural lesions in the brain through history taking, physical and neurological examinations, clinical pathology tests, and MRI/CSF findings (10). Structural abnormalities of the brain resulting in epileptic seizures included various vascular, inflammatory, infectious, traumatic, anomalous, developmental, neoplastic, and degenerative diseases.

Overall, 57 dogs were enrolled in this study. The number of dogs diagnosed with IdE and StE was 27 and 30, respectively. All dogs were included in the analysis of the etiological distribution. Of these, 29 dogs (IdE: 16 dogs, StE: 13 dogs) were included in the evaluation of therapeutic outcome and survival time.

**Etiological distribution**

The etiological distribution was evaluated using the following data: 1) sex; 2) presence of neurological signs (except seizure); 3) specific seizure pattern (isolated seizure, cluster seizure, or status epilepticus); 4) seizure type (focal or generalized); 5) body weight; 6) age at initial seizure onset; and 7) seizure frequency at the first presentation.

**Therapeutic outcome and survival time**

The variables for evaluating the effectiveness of antiepileptic treatments were as follows: 1) period of treatment; 2) pre-treatment seizure frequency; 3) post-treatment seizure frequency; 4) pre-treatment seizure duration; 5) post-treatment seizure duration; 6) success rate of seizure control; 7) survival time; and 8) lifespan. The survival time was defined as the time from the beginning of the anti-epileptic treatment to the present time. The lifespan is the time from birth to the present time, which is synonymous with age.

**Statistical analysis**

For statistical comparisons between IdE and StE, Fisher's exact tests were used for categorical data (gender, neurological sign, specific seizure pattern, and seizure type) and Wilcoxon rank sum tests were used for continuous data (body weight, initial age, initial seizure frequency, period of treatment, pre- and post-treatment seizure frequency and duration, and reduction in frequency and duration of seizures). The Fisher's exact test was performed for the comparison of the success rate of seizure control, which was analyzed based on the sub-classification of the reduction rate in seizure frequency (seizure control failed, reduced frequency of seizures from 0% to 50%, reduced frequency of seizures from 50% to 100%, and seizure free). The Kaplan-Meier method with log-rank test was used to estimate the median survival time and the median lifespan for all cases of IdE and StE. Dogs alive at the time of follow-up were censored. Values of $P < 0.05$ were considered significant. All statistical analyses were performed using the SAS Version 9.4 (SAS Institute Inc., Cary, NC, USA).

**Table 1.** Etiological distribution of dogs with idiopathic and structural epilepsy

| Variables | | IdE ($n = 27$) | StE ($n = 30$) |
|---|---|---|---|
| Gender [N (%)] | Male | 14 (56) | 11 (44) |
| | Female | 13 (40.6) | 19 (59.8) |
| Neurological status [N (%)] | Normal | 21 (75) | 7 (25) |
| | Abnormal | 6 (20.7) | 23 (79.3)* |
| Specific seizure pattern [N (%)] | Isolated | 10 (58.8) | 7 (41.2) |
| | Cluster | 12 (54.6) | 10 (45.5) |
| | SE | 5 (31.3) | 11 (68.8) |
| | Cluster & SE | - | 2 (100) |
| Seizure type [N (%)] | FES | 4 (40) | 6 (60) |
| | GES | 23 (56.1)* | 18 (43.9) |
| | FEvG | - | 2 (100) |
| | FES & GES | - | 4 (100) |
| Median Body weight [kg (IQR)] | | 4.8 (4.4)* | 2.8 (2.3) |
| Median Age at initial seizure onset [years (IQR)] | | 3.9 (4.6) | 7.9 (7.5) |
| Mean Seizure frequency at first presentation [seizures/month (IQR)] | | 2.0 (11.0) | 13.3 (27.0)* |

IdE, idiopathic epilepsy; IQR, interquartile range; FES, focal epileptic seizure; FEvG, focal epileptic seizure evolving into generalized seizure; GES, generalized epileptic seizure; SE, status epilepticus; StE, structural epilepsy; *$P < 0.05$ (Wilcoxon rank sum test and Fisher's exact test).

**Table 2.** Evaluation of therapeutic outcome after seizure control in dogs with idiopathic and structural epilepsy

| Variables | IdE ($n = 16$) | StE ($n = 13$) |
|---|---|---|
| Median Period of treatment [months (IQR)] | 13.0 (20.5)* | 3.0 (10.0) |
| Median Pre-treatment SF [seizures/months (IQR)] | 4.7 (10.5) | 15.0 (22.0) |
| Median Post-treatment SF [seizures/months (IQR)] | 0.3 (2.3) | 2.0 (4.8)† |
| Median Pre-treatment SD [minutes (IQR)] | 2.0 (2.0) | 2.0 (1.5) |
| Median Post-treatment SD [minutes (IQR)] | 0.5 (0.7) | 3.0 (4.0)* |

IdE, idiopathic epilepsy; IQR, interquartile range; SD, seizure duration; SF, seizure frequency; StE, structural epilepsy; †$P = 0.053$, *$P < 0.05$ (Wilcoxon rank sum test).

**Table 3.** Comparison of the success rate of seizure control between the IdE and StE groups based on the reduction rate of seizure frequency

| Variables | IdE ($n = 16$) | StE ($n = 13$) |
|---|---|---|
| Number of dogs with treatment failures [N (%)] | 1 (6.3) | 1 (7.7) |
| Number of dogs with ≥ 0% < 50% reduction in SF [N (%)] | 2 (12.5) | 3 (23.1) |
| Number of dogs with ≥ 50% < 100% reduction in SF [N (%)] | 9 (56.3) | 8 (61.5) |
| Number of dogs with 100% reduction in SF [N (%)] | 4 (25) | 1 (7.7) |

IdE, idiopathic epilepsy; SF, seizure frequency; StE, structural epilepsy; No significant difference between IdE and StE groups ($P > 0.05$, Fisher's exact test).

## Results

### Etiological distribution

When comparing clinical and demographic features of the IdE and StE groups, presence of neurological signs except seizure (IdE, 21% vs. StE, 79%; $P < 0.0001$), generalized epileptic seizure (IdE, 56% vs. StE, 44%; $P = 0.043$), median body weight (IdE, 4.8 kg vs. StE, 2.8 kg; $P = 0.014$), and median seizure frequency at the time of first presentation (IdE, 2.0/month vs. StE, 13.3/month; $P = 0.008$) were significantly different in incidence (Table 1). Specific seizure pattern did not differ between the two groups (cluster seizure, $P = 0.426$; status epilepticus, $P = 0.151$). Additionally, no significant difference was found in sex ($P = 0.293$) and age at initial seizure onset ($P = 0.072$).

### Therapeutic outcome

The median period of treatment was significantly longer in the IdE group (13 months) than that in the StE group (3 months) ($P = 0.016$) (Table 2). Although pre-treatment seizure frequency ($P = 0.104$) and duration ($P = 0.877$) were not different between the two groups, the median duration of sei-

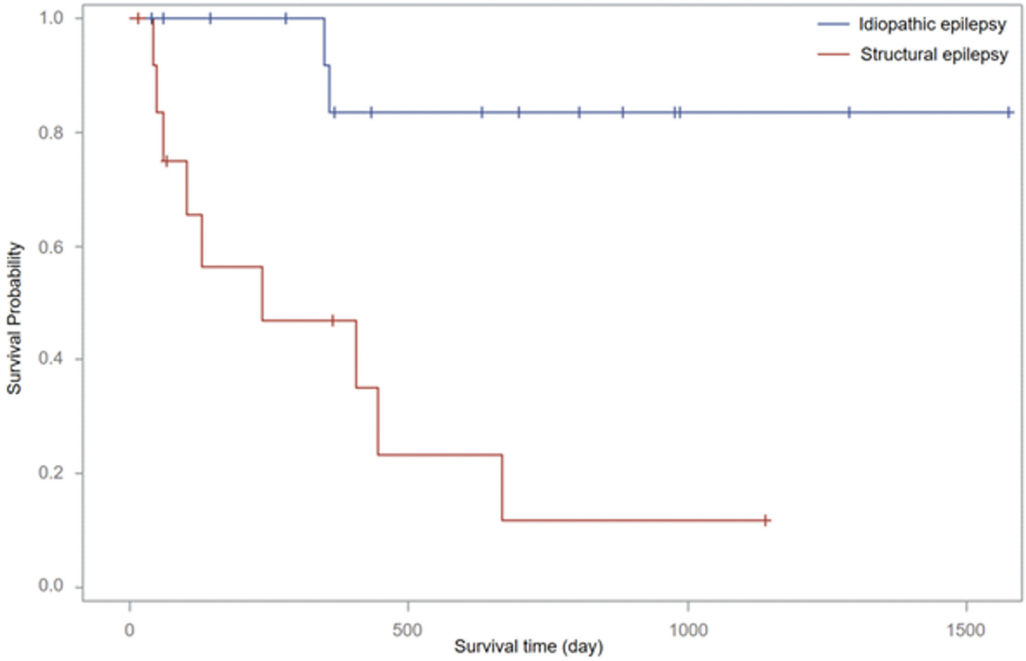


**Fig 1.** Kaplan-Meier curves of survival time in dogs with idiopathic and structural epilepsy based on the time of initiation of treatment. Hash marks indicate censored data.

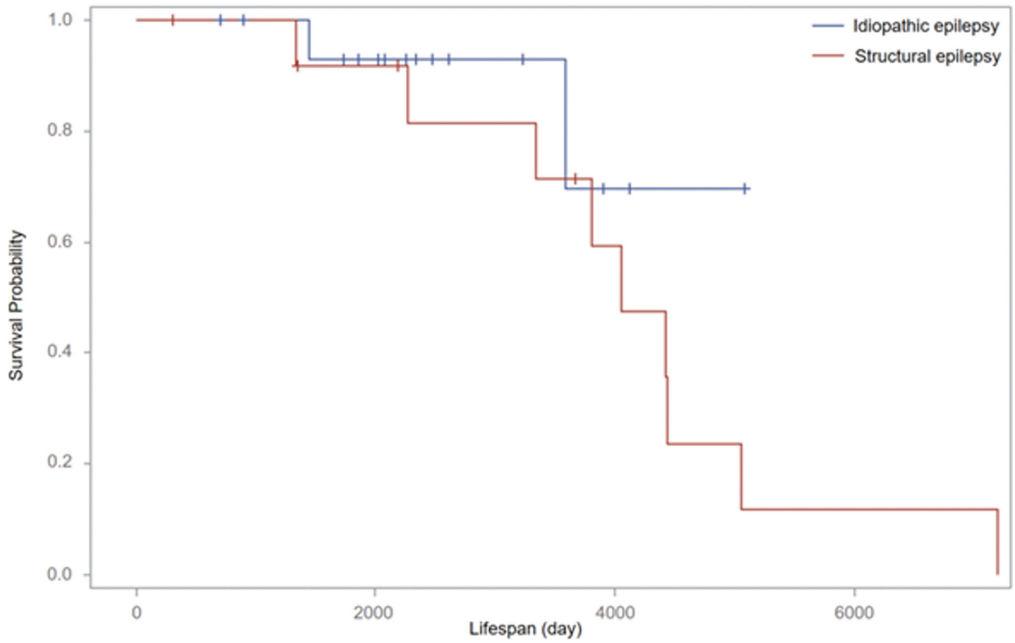


**Fig 2.** Kaplan-Meier curves of lifespan in dogs with idiopathic and structural epilepsy based on the time of birth. Hash marks indicate censored data.

zure in the IdE group (0.5 min) was significantly shorter than that in the StE group (3 min) after treatment ($P = 0.006$). In addition, the median frequency of seizure was relatively lower in the IdE group (0.25/month) that in the StE group (2.00/month) following therapy ($P = 0.053$). When the success rate of seizure control was evaluated, no significant differences were observed between the IdE and StE groups (Table 3).

**Survival time**

Among 57 dogs with epilepsy, 29 dogs were enrolled in the analysis of survival time. At the end of the study period (August 2017), 12 dogs were alive and 4 dogs were dead in the IdE group whereas 4 dogs were alive and 9 dogs were dead in the StE group. The median survival time of the IdE group (1.5 years [95% CI, 1.0-2.3 years]) was significantly longer than that in the StE group (0.4 years [95% CI, 0.2-1.3 years]) ($P = 0.0006$) (Fig 1). However, no significant difference was found in the median lifespan between the IdE (6.3 years [95% CI, 5.2-8.7 years]) and StE (10.1 years [5% CI, 6.1-12.2 years]) groups ($P = 0.253$) (Fig 2).

## Discussion

This study demonstrated etiological features, treatment responses, and prognosis of canine epilepsy by comparing the clinical data obtained from dogs with IdE and StE.

In the specific seizure pattern, no significant difference was found between the IdE and StE groups. However, the prevalence of generalized epileptic seizure was significantly higher in the IdE group than that in the StE group. In a previous study, the prevalence of generalized epileptic seizure was not different between IdE and StE groups (1), while in another study, a relatively high prevalence of generalized type was noted in dogs with StE (15). Additionally, in a recent study of dogs with StE, 93% of dogs had generalized epileptic seizures and 7% of dogs had focal epileptic seizures (10). Based on these results, the seizure type alone may not be enough to differentiate canine epilepsy.

At the seizure onset, the median age of the StE group (7.9 years) was relatively older than that of the IdE group (3.9 years), and this result was similar to that of a previous study (IdE, 6 months to 7 years; StE, older than 7 years) (15). Additionally, the mean seizure frequency of the StE group was significantly higher than that of the IdE group at the first presentation. The relatively late onset and frequent occurrence of seizure may contribute to shorten the survival time of dogs with StE.

Before attempting an antiepileptic therapy, seizure frequency and duration were not different between the two groups. However, both these indexes of the StE group were significantly higher and longer, respectively than those of the IdE group after the treatment. Additionally, seizure duration of the StE group was increased by 1.5 times following antiepileptic therapy. These results suggest that the therapeutic response of the IdE group is better than that of the StE group. The longer treatment period of the IdE group may have been influenced by the relatively high responsiveness to antiepileptics in comparison with the StE group.

The success of seizure control is defined as more than 50% reduction in the seizure frequency, and this study shows 82% and 69% of the success rates in the IdE and the StE group, respectively. As these rates were not different between the two groups, the seizure frequency could be halved by antiepileptic therapy in epileptic dogs with or without intracranial lesions. Previous studies reported that the success rates ranged from 58% to 80% in dogs with IdE (5,9,11,23,25). In the present study, 9 dogs (56%) of the IdE group and 10 dogs (77%) of the StE group were treated with two kinds of antiepileptics at least, while monotherapy was applied to refrac-

tory cases of IdE previously (5,9,11,23,25). Multi-drug therapy and low tolerance of the cases may contribute to relatively high success rates in this study.

The median survival time of the IdE group (1.5 years) was significantly longer than that of the StE group (0.4 years) whereas the median lifespan was not different between the IdE (6.3 years) and the StE groups (10.1 years). These results suggest that therapeutic response and onset-age of the IdE group was better and earlier than those of the StE group. These aspects could be proved by the data of etiological distribution and therapeutic outcome in this study.

In comparison with previous studies (2,13-15), the survival time and the lifespan are relatively shorter in the present study. The main reason for this difference is a short study period (approximately 4 years). In fact, 75% and 31% of the treated dogs were still alive at the end of the study period in the IdE and the StE groups, respectively.

This study had the following limitations: 1) small sample size (n = 57), 2) incompleteness of clinical data due to observer variability, and 3) short study period. In the future, a well-organized study is necessary with more epileptic dogs for a longer period.

This retrospective study shows that etiological features, treatment responses, and prognosis are different between dogs with IdE and StE. Therefore, the information on etiological data and intracranial lesions may be useful for predicting treatment responses and prognosis in epileptic dogs.

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