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Localization of cerebral hypoperfusion in dogs with refractory and non-refractory epilepsy using [99mTc] ethyl cysteinate dimer and single photon emission computed tomography

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ABSTRACT. To evaluate the localization of functional deficit area in epileptogenic zones of the brain in seven refractory and seven non-refractory epilepsy dogs using technetium 99m labeled with ethyl cysteinate dimer and interictal single photon emission computed tomography [^{99m}Tc-ECD SPECT] co-registration with Magnetic Resonance Imaging (MRI). Regions showing perfusion deficits in the SPECT images were analyzed by using the standard semiquantitative evaluation method to compare the level of cortical perfusion to the maximum number of counts within the cerebellum (max C), considered the area of reference. This study showed that SPECT imaging revealed abnormalities in several regions of the brain in both epilepsy groups. The refractory epilepsy dogs showed more frequency area of hypoperfusion in temporal lobe than non-refractory group with not statistically significance (P=0.28). The result suggests the lesion in temporal might be relevance with refractory epilepsy in canine patients.

KEY WORDS: dog, drug-resistant epilepsy, ethyl cysteinate dimer, single photon emission computed tomography

Many reports estimated prevalence of epileptic seizures in dogs between 0.5% and 5.7% [6, 14, 21]. Approximately 30% of canine epileptic patients have refractory epilepsy [16]. The definition of refractory epilepsy is defined as failure of adequate trials of two tolerated, appropriately chosen and used antiepileptic drug schedules (whether as monotherapies or in combination) to reach sustained seizure freedom [10] or partial therapeutic success [18]. Canine refractory epilepsy is also described as medically intractable or pharmacy- resistant. An uncontrollable seizure in dogs contributing to increase mortality rates by sudden unexpected death in epilepsy (SUDEP) [19]. Present, the number of canine seizure patients in Thailand which frequently suffering from drug-resistant epilepsy is increasing. Therefore, presurgical evaluation of epileptogenic zone is the most important.

The definition of epileptogenic zone defined as the minimum amount of cortex to produce seizure freedom. The seizure freedom is also the ideal goal of epilepsy treatment in veterinary medicine. When the epileptogenic zone can be localized accurately, the patients can be treated by the surgical techniques for complete seizure control and increase quality of life especially in refractory patients. In theoretic the epileptogenic zone contains of five cortical abnormal 'zones': symptomatogenic, irritative, seizure-onset, structurally abnormal (epileptogenic lesion) and functional deficit. Recently, these zones can be differentiated by proper multimodalities including ictal video monitoring, interictal non-invasive or invasive electroencephalography (EEG), ictal video-EEG, magnetoencephalography, structural and functional Magnetic Resonance Imaging (MRI), or Nuclear Imaging [5]. Although an intracranial EEG evaluation is regarded as the gold standard for localizing the epileptogenic zone in human, some limitations accompany the use of scalp EEGs and even intracranial EEGs in dogs. Ictal single photon emission computed tomography

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(SPECT) hyper-perfusion and interictal SPECT hypo-perfusion zone are reliable techniques in localizing the epileptogenic focus [13]. The brain SPECT can become a useful diagnostic tool and provide better insight into the neurobiology of epilepsy in human and dogs [11, 13]. Furthermore, SPECT is commonly used in evaluations of hyper perfusion zones in human patients suffering from refractory focal seizures [7, 8]. In human medicine, the surgical removal of epileptogenic zone is proved for treatment refractory epilepsy. Consequence, high technology and advanced surgical techniques were introduced in veterinary field. The surgical method for refractory epilepsy will be the option for the canine patients in near future. Therefore, the special technique such as interictal SPECT will be the essential technique for detect functional deficit area in epileptogenic zone before considering the appropriate treatment method. At present day, no reports using interictal SPECT to evaluate functional deficit zone detection in canine refractory epilepsy. The objective of this study is to evaluate hypoperfusion zones in canine refractory epilepsy and develop the practical protocol and analysis software of interictal SPECT co-registered to MRI technique.

MATERIALS AND METHODS

Animal population

Fourteen dogs of all ages which have 2 or more seizure were included in this study. These epileptic dogs were divided into two groups: 7 dogs in the refractory epileptic group and 7 dogs in the non-refractory epileptic group.

Inclusion criteria for the refractory group were the dogs who have failed response after several therapeutic antiepileptic drugs trial, and the frequency of seizure was reduced less than 50% of total seizure frequency. The refractory groups were treated in which more than 2 antiepileptic drugs including Phenobarbital, Potassium Bromide, Gabapentin and Levetiracetam. All dogs in this group had adequate therapeutic drug level before using the combination of the antiepileptic drugs. The duration of antiepileptic drug therapy was more than 6 months.

The dogs in non-refractory epileptic (well-controlled seizure symptom) group included the dogs that had free period of seizure, or the number of seizures was reduced as 50% or more than 50% of total seizure frequency.

Exclusion criteria for both groups are the dogs had structural epilepsy type or higher anesthesia risk or/and the dogs which had epilepsy concurrent with systemic disease such as kidney disease, hepatic disease.

The time between the last seizure and the SPECT acquisition was set within 2 weeks in this study [13]. Clinical neurologic examinations, laboratory profile testing, and interictal SPECT were performed on all dogs in the epilepsy group.

Ethical approval and informed consent from the owner

All experimental protocols were approved by the Animal Ethics Committee of the Kasetsart University (Protocol No. ACKU 02060). The purposes of the research, the risks of anesthesia, the complication such as anaphylactic after injection the tracer were explained to all the owners before the dogs went to diagnose with scintigraphy.

Radiotracer

All dogs received intravenous fluids for 10 min prior to the injection of the tracer to avoid stress during this procedure. The environment was free of noise with dimmed light to avoid provoking anxiety in the animals. The injected activity of 99m technetium-ethyl cysteinate dimer (^{99m}Tc-ECD) was approximately 740–925 mBq (20–25 mCi) per dog [13].

Anesthetic protocol

Ten min after the tracer injection, the dogs were premedicated with dexmedetomidine 375 mcg/m^2 intravenously (I.V.) (DEXDOMITOR®, Zoetis, Kalamazoo, MI, USA). Anesthesia was induced 25 min after premedication, using 2–5 mg/kg propofol I.V. and maintenance with 2% isoflurane. SPECT acquisition started at 35–40 min after the radiopharmaceutical injection.

SPECT

All dogs were positioned in sternal recumbency with their heads as close to the detectors as possible. SPECT was performed by using a dual-head gamma camera (Symbia E, Siemens, Erlangen, Germany) equipped with parallel holes collimators for Low Energy High-Resolution (LEHR). The total acquisition time in the step-and-shoot mode (120 steps, 10 sec/step, 3 degrees per step) through a 360-degree rotation on a 128 × 128 matrix was 15 min. Images were reconstructed by using dedicated ordered subset expectation maximization (OSEM), algorithm (iterative 8, subset 8), zoom mode 1.5. Gaussian filter and Chang's attenuation correction method were applied.

MRI

MRI was performed on all patients for rule out brain lesion using 1.5T MAGNETOM ESSENZA (Siemens) scanners in transverse, dorsal and sagittal projections. The routine examination protocol included a TSE/T2-weighted, T2 FLAIR and 3D MPRAGE sequence with 256 × 256 matrix. The Interictal SPECT data were fitted to the 3D MPRAGE sequence with the help of auto-fusion tool available in Syngo® software (Syngo®, SIEMENS Healthineers, Erlangen, Germany).

Interpretation

The regions showing perfusion deficits in SPECT image of all epilepsy dogs were analyzed by 1 veterinary radiologist and 1 medical technician. Our study used a standard semi-quantitative evaluation method that was modified from Misko *et al.* [15]

to compare the level of cortical perfusion to the maximum number of counts within the cerebellum (max C). Briefly, the brain standard perfusion deficits (SPD) including areas in which the number of counts per single pixel was less than 50% of the max C within the temporal lobe cortex, and the rest of the cerebral cortex was less than 70% of max C. Intelligent imaging software were used for analysis of perfusion deficits. For the fusion of the MRI and interictal SPECT images, the location of the SPD changes was determined on transverse, sagittal and dorsal sections using a 10-color scale for encoding the interictal SPECT images to allow the visualization of the cut-off levels of 50% of max C. Individual those SPD foci/areas with perfusion deficit overlying cortical area of at least 0.10 cm^3 were engaged into account for the analysis. The average number of count region of interest (av ROI) of each SPD was also compared with the average number of counts in the same region in the opposite cerebral hemisphere, and the difference >15% were regarded as True Perfusion Deficit (TPD) [15].

Statistical analysis

The results were reported as the median, range, or percentage (%). The correlation coefficient of the group means was calculated and compared by using digital statistical software (SPSS 19.0 for Windows, Chicago, IL, USA). The frequency of hypoperfusion area founded by SPECT was estimated by a logistic regression and fisher extract test to predict the outcome of the ratio between the refractory group and the non-refractory group. The analysis of the differences in age, body weight, seizure duration between the refractory group and the non-refractory group was performed by nonparametric statistics (Moses Test of Extreme Reaction) at a significance level of 0.05. Seizure duration described by the duration from the day of first seizure present to the day which the dog went to SPECT scan.

RESULTS

Clinical characteristics of the epileptic dogs

Fourteen epileptic dogs participated in this study. There were five males and nine females. Several breeds were presented: 6 beagles, 3 crossbreeds, 1 poodle, 1 Chihuahua, 1 French bulldog, 1 Pomeranian, and 1 Miniature. Seven epileptic dogs had a history of refractory epilepsy (seizure presented frequently the same or more progression as before treatment), and 7 dogs had non-refractory epilepsy (Seizure free period or seizure present less than 50% of total number seizure). General data regarding the factors associated with seizures are presented in Table 1.

In refractory groups, four epileptic dogs had focal onset seizures with secondary generalization, and the other three dogs had generalized seizures. In non-refractory groups, two epileptic dogs had focal onset seizures with secondary generalization, and the other five dogs had generalized seizures. All epileptic dogs were on treatment with antiepileptic drugs. The non-refractory groups were treated with phenobarbital monotherapy and the refractory groups were treated in which more than 2 antiepileptic drugs including Phenobarbital, Potassium Bromide, Gabapentin and Levetiracetam.

A summary of the characteristic data of the refractory and non-refractory epileptic dogs were presented in Table 2. The median age and weight tended to differ between the refractory and non-refractory epileptic dogs, but no statistically significant differences were observed. Nonetheless, the epilepsy duration was statistically significantly different between the refractory and non-refractory epileptic dogs (P<0.001).

Table 1. Summary of the clinical characteristics and neuroimaging findings of 14 epileptic dogs

Pt/Sex	Breed	Seizure identity	Seizure symptoms	MRI finding	Interictal SPECT lesion (TPD)	Frequency of seizure (time/month)	
						Pre-treatment	Post-treatment
Group: Refractory epilepsy							
1/F	Crossbreed	SFS	Restlessness, salivation	Normal	Left temporal, occipital and hippocampus	1	3
2/F	Crossbreed	SFS	Stretch leg, vocal, twitching leg	Normal	Right temporal	2	2
3/F	Crossbreed	SFS	Vocal, seeking attention, circling	Normal	Right frontal and left occipital	2	6
4/F	Beagle	GS	Tonic clonic convulsion	Normal	Right temporal and hippocampus	1	6
5/F	Miniature	GS	Tonic clonic convulsion	Normal	Left temporal	3	17
6/M	Beagle	SFS	Abnormal walking	Normal	Right temporal	3	30
7/ M	Chihuahua	GS	Tonic clonic convulsion	Normal	Right parietal	1	7
Group: Nonrefractory epilepsy							
1/ M	Beagle	SFS	Twitching leg, drop tail	Normal	Right temporal	2	1
2/F	Beagle	GS	Tonic clonic convulsion	Normal	Right frontal	12	0
3/ M	Beagle	GS	Tonic clonic convulsion	Normal	Right parietal	1	0
4/ M	French bull	SFS	Anxiety, Restlessness, salivation	Normal	Left parietal and occipital	5	2
5/F	Beagle	GS	Tonic clonic convulsion	Normal	Right parietal and left occipital	1	0
6/F	Pom	GS	Tonic clonic convulsion,	Normal	Right occipital	3	1
7/F	Poodle	GS	Tonic clonic convulsion	Normal	Left parietal	1	0

F, female; M, male; SFS, simple focal seizure; GS, generalized seizure; SPECT, single photon emission computed tomography; TPD, true perfusion deficits. 0=not found seizure before single photon emission computed tomography.

Table 2. Summary of the characteristic data of the refractory and nonrefractory epileptic dogs

Variable	Refractory group (n=7)	Non-refractory group (n=7)	*P*-value
Age (month)	63 (28–96)	60 (12–67)	0.704
Body weight (kg)	17 (12–41)	14 (2.3–19.4)	0.296
Age at seizure onset (month)	36 (4–90)	28 (8–59)	0.867
Duration of Epilepsy (month)	24 (6–36)	12 (8–48)	0.000[a)]

The data are presented as the median and range (minimum–maximum value). n=number of dogs per group.
a) Significant difference between the groups, $P \leq 0.05$).

SPECT findings

By interictal SPECT co-registration with MRI, 9 epileptic dogs showed focal TPD and 5 dogs showed multifocal TPD. In conclusion, 20 TPD regions were frequently found in 14 epileptic dogs. The region frequently hypoperfusion were temporal (6/20, 30%), frontal (2/20, 10%), parietal (5/20, 25%), occipital (5/20, 25%) and hippocampus (2/20, 10%).

The refractory epileptic dogs more frequent exhibited focal perfusion deficits in the temporal lobe 5 of 7 dogs (71%) than the non-refractory epileptic dogs 1 of 7 dogs (14%). Hippocampal hypoperfusion was observed on the ipsilateral side of the temporal lobe in 2 refractory epileptic dogs.

The difference in frequency of hypoperfusion zone was analyzed by using logistic regression and fisher extract test. The frequency of hypoperfusion zone in the temporal region were not statistically significantly different between the refractory and non-refractory groups (P=0.28).

MRI, SPECT, and SPECT co-registration with MRI images of the refractory epileptic dogs' group with temporal lobe hypoperfusion were shown in Fig. 1. The location of SPD changes was determined on dorsal sections obtained by the fusion of the MR and interictal SPECT images by using a 10-color scale as shown in Fig. 2. The fusion of the MR and interictal SPECT images showed hypoperfusion in the hippocampus of refractory epileptic dogs by using Syngo® MI software for data analysis as shown in Fig. 3.

DISCUSSION

The present study described the clinical characteristics and evaluated the localization of hypoperfusion zones in canine refractory epilepsy by using interictal SPECT co-registered to MR images. The results revealed that the brain lesions in the refractory epileptic dogs showed greater hypoperfusion in the temporal region than those in the non-refractory epileptic dogs, which the difference is not statistically significant. Previously, several human studies have shown that temporal lobe epilepsy is the most common type of medical refractory epilepsy and often responds satisfactorily to surgical treatment [20, 23]. Besides, study of brain perfusion parameters in dogs with idiopathic epilepsy by magnetic resonance imaging had shown that decreased blood perfusion of the brain in piriform lobe, thalamus, and temporal cerebral cortex [4]. Although, our result was consistent with previous several human and dog studies. However, the exact mechanisms underlying the pharmaco-resistance of temporal lobe epilepsy in dogs are poorly understood.

This study found hippocampal hypoperfusion on the same side as the temporal lobe hypoperfusion in 2 refractory epileptic dogs, which indicated that hippocampal hypoperfusion lesions may be an epileptogenic network alteration in refractory epileptic dogs. Previous studies in humans have suggested that the progression of hippocampal atrophy leads to the development of an epileptogenic network and aggravates repeated seizures [3]. Nonetheless, only one study using an animal model of drug-resistant epilepsy has discovered a significant loss of hippocampal neurons in the CA1, CA3c/CA4 and dentate hilus of rats with drug-resistant epilepsy [22]. In this study, our finding of hippocampal perfusion deficit was consistent with the findings reported by Kuwabara *et al*. who demonstrated hippocampal atrophy in epileptic dogs by using volumetric MRI [9]. Additionally, Lorincz *et al.* found increasing hippocampal T2 values in an evaluation of T2 relaxometry in epileptic dogs [12]. On the contrary, only one study in dog reported that temporal lobe epilepsy, as described in humans, was not a typical cause of refractory epilepsy because of the lack of evidence of neuronal loss in the hippocampus in dogs with drug-resistant epilepsy [1]. In future, these hippocampal network properties altered by temporal lobe epilepsy in dogs could lead to the observed refractory nature of this condition.

In this study demonstrated that the duration of epilepsy (age at SPECT acquisition minus age at epilepsy onset) in the refractory group was statistically significantly different from that in the non-refractory group (P=0.000). Our finding was consistent with recent study in human that showed an increasing atrophy of the ipsilateral hippocampus due to neuronal loss in refractory patients with longer epilepsy duration. In addition, they also demonstrate an increased probability of exhibiting an abnormal distribution of the granular cells in the dentate gyrus [2].

Although, intracranial electroencephalography is regarded as the primary goal in epilepsy localization, but there was no reported about an accurate method before intracranial electroencephalography examination in dogs. The interictal SPECT is one of the methods to evaluate epileptogenic zone from function deficit zone but this technique developed to evaluate brain function. Since epilepsy is a functional disorder of the brain, it is logical to presume that SPECT might be useful to diagnose epilepsy, in addition to EEGs [5]. The other modalities such as Positron Emission Tomography and functional MRI are detected the epileptogenic zone, there are a distinct lack of reports in epileptic veterinary patients. Moreover, there are very limited in several factors such as costs, facilities, and licensing regulation in veterinary medicine [5].

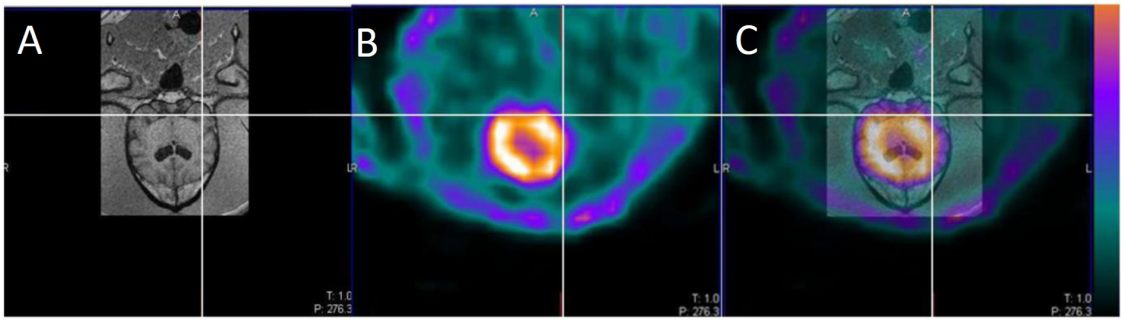

Fig. 1. (A) Magnetic Resonance Imaging (MRI), (B) single photon emission computed tomography (SPECT) and (C) co-registration with MRI images of the patient 5 in refractory epileptic group with focal hypoperfusion deficits at the left temporal lobe (cross line). Color scale bar: Brightness=hot area, Darkness=cold area.

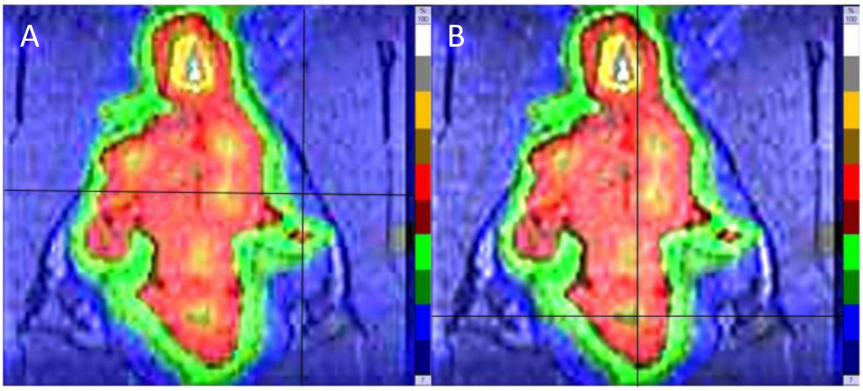

Fig. 2. The location of Standard Perfusion Deficit (SPD) changes of the patient 1 in refractory group on dorsal sections of the Magnetic Resonance Imaging (MRI) and interictal single photon emission computed tomography (SPECT) fusion images by using a 10-color scale bar (the right of each picture) were shown. (A) The location of SPD changes at left temporal lobe (Cross line). (B) The visualization of the cut-off levels of 50% of maximum cerebellum count/pixel (cross line).

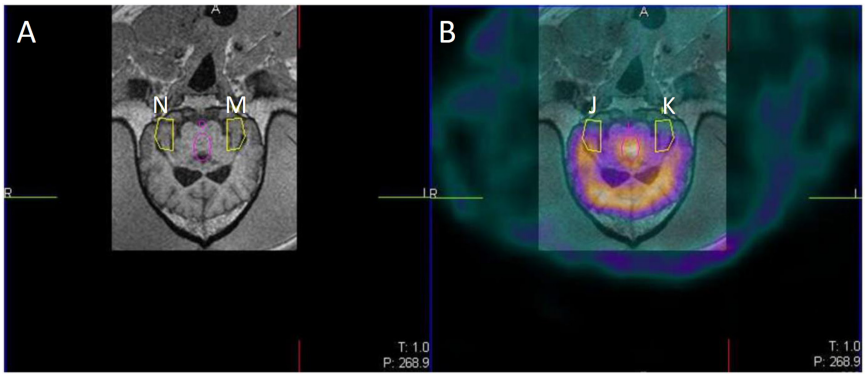

Fig. 3. Magnetic Resonance Imaging (MRI) and interictal single photon emission computed tomography (SPECT) co-registered with MRI images from patient 1 in refractory group showed the average number of count Region Of Interest (av ROI) of left hippocampus (K) that compared with the average number of counts in the same region in the opposite area (J). The difference >15% indicated the presence of a True Perfusion Deficit (TPD). K=114 count/pixel, J=178 count /pixel, max C=251 count/pixel (ellipse). The cortical area of at least 0.10 cm^3 was engaged.

Previous studies have shown quantitative data by representation of the average count per pixel and standard deviation between groups. However, all several studies did not show individual data [13, 17]. Moreover, the summation of data between groups of epilepsy dog could not specify the true perfusion deficit foci in individual dogs. Furthermore, one of our proposals in this study developed a feasibility method to localize epileptic foci in each dog for pre-surgical evaluation with considering surgical seizure freedom in future. In our suggestion, the use of the difference of 15% as being representative for TPD by Misko *et al.* [15] was

more optimally studied individual dog for localization of functional deficit zone in canine refractory epilepsy.

A major limitation of epilepsy in dogs is the dependency on the owner to observe and describe the symptom of seizures. The number of subtle clinical signs in humans that give a clue to the origin of the epileptic focus, can never be confirmed in animals due to the lack of supervision during the seizures. Another major limitation of a small number of epilepsy dogs in this study.

In conclusion, this study demonstrated that SPECT imaging revealed abnormalities in several regions of the brain in dogs with refractory epilepsy. Interestingly, the findings showed hypoperfusion in the temporal area that have a high number of frequencies in the dogs with refractory more than non-refractory epilepsy. Finally, the researchers would like to suggest that the functional deficit in temporal lobe might be one of the pathophysiology of canine refractory epilepsy.

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