Treatment Strategy Studies in Canine and Feline Refractory Epilepsy

Summary of Doctoral Thesis

Yuji Hamamoto

Graduate School of Veterinary Medicine and Life Science

Nippon Veterinary and Life Science University

Epilepsy is one of the most common neurological disorders in mammals, particularly humans and dogs. In general, the treatment of epilepsy is based on antiepileptic drugs (AEDs). However, in cases that do not respond to applicable AEDs, which are known as 'refractory epilepsy' or 'drug-resistant epilepsy,' epilepsy surgery is often the next resort. Epileptic surgery has been successfully used for treating patients with refractory epilepsy, but not yet to be established in veterinary medicine. Thus, it is essential to establish surgical indication criteria in dogs and cats with refractory epilepsy.

The epileptogenic zone (EZ) is defined as "area of cortex that is necessary and sufficient for initiating seizures and whose removal (or disconnection) is necessary for complete abolition of seizures". As the most important concept in epilepsy surgery, an accurate localization of the EZ is required preoperatively for successful treatment, and can be achieved using approached of multiple modalities. The EZ consists of five abnormal cortical zones including the (1) symptomatogenic zone, which can be detected by seizure semiology; (2) irritative zone detected by interictal electroencephalography (EEG) and magnetoencephalography (MEG); (3) seizure-onset zone detected by ictal video-intracranial EEG and single photon emission computed tomography (SPECT); (4) structural abnormal zone detected by structural magnetic resonance imaging (MRI); and (5) functional deficit zone detected by functional imaging such as interictal SPECT, photon emission tomography, and MRI.

Currently, there is no established methodology to detect the EZ in veterinary medicine. The familial spontaneous epileptic cat (FSEC), which was discovered in 2009, is the only spontaneous epileptic feline family with a genetic background, and is considered as an animal model of human mesial temporal lobe epilepsy (MTLE), where the EZ is located in the hippocampus and/or amygdala. Human MTLE is the most common refractory epilepsy requiring epilepsy surgery. Thus, using FSECs to validate the methodology for detecting the EZ is an optimal approach in veterinary medicine. The main purpose of this study series was to introduce epilepsy surgery as a new treatment of refractory epilepsy in veterinary medicine. Therefore, I investigated the risk factors for survival in dogs and cats with epilepsy to determine indications for epilepsy surgery (Chapter 2), and validated advanced MRI techniques to detect the EZ using FSECs (Chapters 3–5). Additionally, I performed anterior temporal lobectomy (ATL), which is a common surgical technique in patients with MTLE, in healthy dogs in order to assess the surgical procedure and complications (Chapter 6).

Chapter 2: Retrospective epidemiological study of canine and feline epilepsy in Japan

To determine the surgical indication criteria, this chapter retrospectively investigated the etiological distribution of canine and feline cases with epilepsy that had been referred to the teaching hospital in Japan. The risk factors for survival in dogs with idiopathic epilepsy were (1) seizure frequency of ≥ 0.3 seizures/month and (2) focal epileptic seizures. The seizure frequency of ≥ 0.3 seizures/month is considered one of the criteria for canine refractory epilepsy. Epilepsy surgery is applicable to dogs with detectable EZ. Additionally, since focal epileptic seizures are caused by brain regional electrical hyperactivity, it is conceivable that dogs with focal epileptic seizures often have detectable EZ. Therefore, this chapter proposed the indication criteria for epilepsy surgery in dogs as cases with high frequency epileptic seizures (≥ 0.3 seizures/month) who are resistant to applicable AEDs and/or cases who have a detectable EZ (i.e., focal epilepsy).

Chapter 3: Detection of the structural abnormal zone in FSECs using voxel-based morphometry

Voxel-based morphometry (VBM) has been developed as a statistical morphometric imaging analysis method to locate brain abnormalities in humans. Standard VBM analysis requires the normalization to a standard template in order to evaluate abnormal regions in the same coordinates. In this chapter, feline standard template and tissue probability maps were created from 38 healthy cats. However, the olfactory bulb, which was included in the gray matter, was segmented to cerebrospinal fluid due to segmentation errors. Standard VBM analysis using these templates was performed to evaluate structural abnormal zone in FSECs compared with healthy cats (control). When comparing between the FSEC and control groups, there were no significant differences in any of the regions. However, the individual analysis revealed that 5/25 FSECs showed decreased hippocampus and/or amygdala, which are suspected as the EZ. This chapter indicated that standard VBM analysis can detect the abnormal structural zone in FSECs, and may be useful as a non-invasive technique to detect structural abnormalities with high reproducibility in veterinary medicine.

Chapter 4: Changes in the interictal and early postictal diffusion and perfusion magnetic resonance parameters in FSECs

In abnormal cortical zones, the seizure-onset zone is the most approximated region to EZ. However, examinations such as ictal SPECT and video-intracranial EEG are difficult to perform in veterinary medicine. This study measured the status of cerebral diffusion and perfusion in FSECs in the interictal and early postictal states using diffusion and perfusion MRI, and detected the functional deficit zone and spread seizure onset zone. When comparing the interictal state between FSECs and healthy cats, the hippocampus of FSECs showed hypoperfusion. Additionally, the early postictal state of FSECs showed hippocampal hypodiffusion and hyperperfusion in addition to amygdaloid hyperperfusion compared to the interictal state. These results indicated that diffusion and perfusion MRI can identify the EZ. Furthermore, perfusion MRI is a particularly sensitive technique to detect an epileptic seizure and the spreading of the seizure onset zone. Thus, cerebral diffusion and perfusion should be evaluated using MRI to detect the EZ in veterinary medicine.

Chapter 5: Detection of epileptogenic laterality and changes in cerebral metabolism by applying zonisamide in FSECs using magnetic resonance spectroscopy

Proton magnetic resonance spectroscopy (^{1}H-MRS) is a non-invasive technique used to measure cerebral metabolism. In this chapter, I investigated the metabolism in the thalamus of FSECs and healthy cats. Additionally, the metabolic changes caused by treatment with zonisamide (ZNS) were measured in cats to evaluate the effect of ZNS on the cat epileptic brain. When comparing the metabolism in the left and right thalamus of FSECs, total N-acetyl aspartate (tNAA) showed significant asymmetry. In addition, tNAA in the right thalamus was significantly lower in FSECs than in healthy cats. Since decreased tNAA indicates neural cell loss, we considered that decreased tNAA in the right thalamus in FSECs was caused by epilepsy. Therefore, ^{1}H-MRS may be a useful technique to detect the EZ laterality. The results also indicated that the glutamate and glutamine complex was significantly decreased by chronic administration of ZNS. This change may be caused by the inhibition of glutamate release, which is suspected as one of the pharmacological effects of ZNS. Therefore, ZNS may be an effective AED for cats with epilepsy to control epileptic seizures.

Chapter 6: Surgical procedure and complications of ATL in healthy dogs

Patients with refractory MTLE have often been subjected to ATL surgery, which is a resection surgery that removes the anterior temporal lobe including the rostral hippocampus and amygdala. To my knowledge, there are no reports describing ATL in dogs and cats. In this chapter, I performed ATL in healthy dogs to evaluate the surgical procedure and its complications. Five of 7 dogs (71%) showed a successful resection of the anterior temporal lobe following ATL. However, one dog died suddenly during skin suture (unknown cause), while the remaining two dogs were euthanized during the operation due to uncontrollable hemorrhage from the middle cerebral artery. The most common complications following ATL included atrophy of the ipsilateral temporal muscle and absent or decreased contralateral menace response. However, there were no complications in the dog who survived the procedure without detectable iatrogenic injury on postoperative MRI. Thus, ATL may be established as surgical treatment in dogs with epilepsy provided that the success rate is improved using equipment such as ultrasonic surgical aspirator and navigation system, which are used in human microsurgery.

Recent years have witnessed remarkable development in veterinary medicine. Thus, it is expected that a turning point in epilepsy surgery will soon take place in the treatment of canine and feline epilepsy. Epilepsy surgery will be a gleam of hope for dogs and cats with refractory epilepsy. Furthermore, epilepsy surgery may contribute to a better understanding of the pathophysiology of epilepsy. Finally, I believe that this study provided useful information to establish epilepsy surgery in veterinary medicine for application in the near future.