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SHORT COMMUNICATION

A familial spontaneous epileptic feline strain: A novel model of idiopathic/genetic epilepsy

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Summary A spontaneous epileptic model of cats has not been described previously. Recently, we identified familial epileptic cats and investigated their clinical features. These epileptic cats are healthy except for the presence of recurrent seizures that are typically a focal limbic seizure with secondary generalization. Furthermore, generalized seizures were induced by vestibular stimulation in some cats. This spontaneous epileptic cat strain may be a valuable model for idiopathic/genetic epilepsy.

Introduction

In epilepsy research, feline epilepsy/seizure models are produced by various methods including kindling (Shouse et al., 2004), kainic acid (KA) (Ben-Ari, 1985; Tanaka et al., 1992), penicillin (Cortez and Snead, 2006), pentylentetrazol (Testa and Gloor, 1974; Magistris et al., 1988), and trauma (Pitkänen et al., 2006). However, these models are artificial seizure models and do not replicate spontaneous epilepsy completely.

On the other hand, genetic models that manifest spontaneous epilepsy from gene mutations are an essential model of idiopathic epilepsy. Typical genetic epilepsy models include the photosensitive baboon (Papio papio) (Jobe and Browning, 2006a), audiosensitive mouse (Fuller and Sjursen, 1967), tottering mouse (Green and Sidman, 1962),

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El mouse (Imaizumi et al., 1959; Suzuki and Nakamoto, 1977), genetically epilepsy prone rat (GEPR) (Jobe and Browning, 2006b), genetic absence epilepsy rat from Strasbourg (GAERS) (Marescaux et al., 1992), and dogs (Löscher, 1997; Morita et al., 2002; Lohi et al., 2005). However, no report has described a feline genetic and/or spontaneous epilepsy model.

Recently, we identified two generations of cats showing spontaneous seizures induced by specific stimulations, such as removing the cat from a cage, in a closed colony of a commercial trader of laboratory animals. In the present study, we investigated clinical features of these epileptic cats to evaluate their value as a model of epilepsy and to establish a spontaneous epileptic cat strain colony.

Methods and results

Animals and the pedigree analysis

This study was approved by the Animal Care and Use Committee of Nippon Veterinary and Life Science University.

The pedigree of the epileptic cats and their blood relation was drawn based on individual records (including sex, birthday, parents, and medical information) from the trader. The familial closed colony consisted of 166 cats, of which 23 cats (16 males with 14 alive and 7 females with 5 alive) were epileptic. The pedigree of the epileptic cats is shown in Fig. 1. Of the epileptic cats, 14 were investigated in the present study. These epileptic cats (18—68 months old; 2.6—4.3 kg) consisted of 5 females and 9 males. They were confirmed to be healthy except for recurrent seizures by various clinical examinations; including general physiology, neurology, hematology, serum chemistry, electrolytes, blood gas, urinalysis, serological tests for major viruses and Toxoplasma, tandem mass screening, cerebrospinal fluid analysis, and brain MRI using a 1.5 T system.

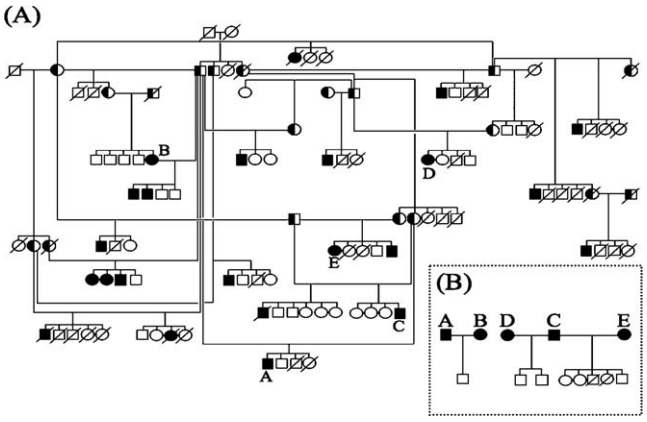

Figure 1 (A) Pedigree of the spontaneous feline epileptic strain (partially omitted). (B) The small pedigree for attempting the inbreeding of epileptic cats. All 23 affected cats representing both sexes were born from unaffected parents, consistent with an autosomal recessive mode of inheritance. Square = male; circle = female; completely black symbol = affected cat. Half blackened symbols = suspected carrier; a slash shaded symbol = dead or unknown medical records (already released).

As determined from the pedigree, all of the epileptic cats were born from clinically normal parents. Therefore, we hypothesized that the epileptic cats were recessive homozygotes and their parents were heterozygote (autosomal recessive), and the chi-square test was performed under the assumption of simple Mendelian inheritance. The chi-square test did not exclude our hypothesis.

Seizure semiology

From the medical records of the trader, 7 of the 14 epileptic cats showed an initial seizure at 4—12 months old. For the remaining 7 cats, an accurate age of their initial seizure was unavailable. However, all of the epileptic cats showed some seizures by 2 years old.

To investigate their seizure semiology, 24-h continuous video monitoring was performed for 2 months in each of the 14 epileptic cats. Each recorded seizure was reviewed clinically, and counted for frequency and duration. Furthermore, we performed stimulation tests to investigate whether the seizures could be induced by vestibular stimulation. The method of vestibular stimulation was to swing the carry cage manually up, down, right and left for 2 min. This stimulation test was performed once a month for a 3-month period.

Under the 2-month monitoring, spontaneous seizures were recognized in 6 of 14 epileptic cats (43%), with a frequency of 0.5—19 seizures/month. Most of the spontaneous seizures occurred during sleep and began as arrest and attention behavior. Gradually, head turning, unilateral facial twitching, salivation and circling were observed, and the spontaneous seizures developed into secondary generalized tonic—clonic convulsions. After the generalized convulsion, most of the cats showed a postictal phase with twilight state with or without postictal paresis (Supplementary Movie 1). The total duration of the spontaneous seizures averaged 4—5 min.

Vestibular stimulation-induced seizures were observed in 6 of the 14 epileptic cats (43%), and its frequency varied from 1 to 3 seizures during the 3-month observation period (30—100%). The seizures occurred during the stimulation test and began as generalized tonic—clonic convulsion followed by a postictal phase (Supplementary Movie 2).

Spontaneous and stimulation-induced seizures were observed in 2 cats. Four epileptic cats did not show any seizures for the 2 months continuous and 3 months stimulation periods. However, they did show some spontaneous seizures out of the observation period.

Interictal EEG

Interictal scalp-EEG under sedation (medetomidine) and/or anesthesia (inhalation of sevoflurane) was performed in the 14 epileptic cats. EEGs showed frequent interictal discharges (IIDs) consisting of spikes and sharp waves (Fig. 2A). Most IIDs appeared dominantly in the uni- and/or bilateral temporal—parietal regions and were occasionally generalized. Unfortunately, there were no animals that showed an ictal EEG.

Inbreeding

In order to investigate whether these epileptic cats will be able to establish and sustain as a colony, we attempted inbreeding between 3 pairs of epileptic cats (shown in the pedigree corresponding to each alphabet in Fig. 1). As a result, we successfully inbred the epileptic cats, and obtained 6 presumed homozygotic kittens (Fig. 1B). Five kittens were born from cat C and E, but one was stillborn and one with teratosis of the lumbar spinal cord (myeloschisis) was euthanized at 1 day after birth. The six surviving kittens grew normally, and are 5—14 months old at present. Although these kittens have not yet shown any clinical seizures, they did show temporal—parietal and occasionally generalized IIDs