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Electroclinical phenotypes in a pedigreed baboon colony

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Summary This is the first large-scale epidemiological study evaluating the prevalence of interictal epileptic discharges (IEDs) and photosensitivity (PS) recorded by scalp EEG in a natural nonhuman-primate model of photosensitive, generalized epilepsy. Scalp EEG was used to characterize electroclinical phenotypes in a large baboon pedigree housed at the Southwest National Primate Research Center at the Texas Biomedical Research Institute (Texas Biomed) based upon IEDs and photosensitivity. Scalp EEG studies including intermittent light stimulation (ILS) were performed in 671 baboons. Clinical histories were available for 531 (79%) of the animals. The EEG studies lasted 53 (±11) min, during which the baboons were lightly sedated with intramuscular ketamine doses of 5.6 (±0.8) mg. The animals were further classified according to electroclinical phenotypes recorded by scalp EEG: presence or absence of IEDs, seizures and photoparoxysmal or photoconvulsive responses. Effects of age, gender, and species on EEG phenotypes were compared using (Chi-square, two-sided, $\alpha < 0.05$). Sensitivity and specificity of IEDs and photosensitivity to detect a history of seizures was calculated. Generalized IEDs and photosensitivity were identified in 324 (49%) and 156 (23%) pedigreed baboons, respectively. Only photosensitivity was associated with gender, significantly increased in males. Otherwise, while IEDs were marginally more prevalent among males, there were no other significant associations of IEDs or photosensitivity with age or subspecies. Photosensitivity was significantly associated with IEDs, with demonstrating a possible association with gender and subspecies. Of 531 baboons with histories of clinical events, 91 (17%) had witnessed seizures and 269 (51%) were asymptomatic. IEDs demonstrated sensitivity and specificity of 62% and 57%, and photosensitivity of 40% and 83%, for prediction of seizures, respectively. While these EEG findings mirror the high prevalence of seizures in the colony, the sensitivity and specificity of scalp EEG may have

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been affected by ketamine's ability to lower the threshold for IEDs and seizures, particularly in animals predisposed to epilepsy. Photosensitivity provides a specific biological marker for epilepsy in future epidemiological, genetic, behavioral and histopathological studies.

Introduction

The baboon represents a natural model of photosensitive, generalized epilepsy (Killam, 1979). Spontaneous seizures have been reported in the baboon, but the interest in this model was fueled by the high prevalence of photosensitivity, or the ability to trigger seizures with intermittent light stimulation (ILS). Early studies aimed to dissect the epileptic networks underlying photosensitivity (Naquet and Meldrum, 1972). Although semiological and electroencephalographic (EEG) data were recorded by several groups (Fischer-Williams et al., 1968; Corcoran et al., 1979), data were limited on the epidemiology and electroclinical classification of the seizures in wild or captive baboon colonies.

The Southwest National Primate Research Center (SNPRC) of the Texas Biomedical Research Institute (TBRI) in San Antonio, Texas, currently sustains about 2000 baboons, including *P.h. anubis* (PHA), *P.h. anubis*/*cynocephalus* crosses (PHX), *P.h. hamadryas*, *P.h. papio* and other subspecies or crosses. The SNPRC is distinguished as housing the largest colony of baboons of any national primate center, and is home to the oldest and largest captive baboon pedigree, consisting of over 2000 animals and spanning as many as seven generations (Rogers and Hixson, 1997). Spontaneous seizures have been witnessed since the inception of the pedigree five decades ago (Killam et al., 1967). Because of the ability to observe baboons in large cages and detailed record-keeping, the SNPRC provides an ideal setting to study the epidemiology of seizures. Despite historical breeding across subspecies, seizures are widespread. The seizure prevalence of 26% was recently reported, and, in 15%, seizures tend to recur (Szabó et al., 2012a). This figure may underestimate the true prevalence, as the baboons are not under constant observation, and seizures, particularly if nocturnal, may go unnoticed. Furthermore, some of the baboons may exhibit predominantly eyelid myoclonia or absence seizures, which are difficult to recognize by untrained observers, while in others, craniofacial trauma may represent seizure-related injuries (Szabó et al., 2012a).

This is the first large-scale epidemiological study evaluating the prevalence of interictal epileptic discharges (IEDs) and photosensitivity (PS) in a large pedigree of baboons. A previous scalp EEG studies in a smaller group of animals selected from this pedigree, demonstrated that the natural epilepsy of the baboon model closely resembles one of the most common epilepsy syndromes in humans, juvenile myoclonic epilepsy (JME; Szabó et al., 2004, 2005). The seizures are generalized myoclonic or tonic–clonic in character, present chiefly in adolescence, occur predominantly in the morning and can be provoked by stress, handling and ketamine administration. These EEG studies documented a high prevalence of eyelid myoclonia even in baboons without other witnessed seizure types. Generalized IEDs were prevalent in the pedigree. The IEDs consisted predominantly of 4–6 Hz spike- or polyspike-and-wave discharges, even in asymptomatic baboons. A few young baboons, ages 4 years old and younger, demonstrated IEDs of 2–3 Hz frequency, while IEDs of 6–7 Hz were exhibited in a few adult animals.

In this study, scalp EEG findings will be presented for 671 baboons, 531 of which also have clinical information regarding seizures. The purpose of this study is to correlate EEG findings, including the presence or absence of IEDs, recorded seizures and photosensitivity, with demographic data (age, gender and subspecies) and clinical history (history of provoked or unprovoked seizures).

Methods

Six hundred seventy-one baboons belonging to *P.h. anubis* and hybrid subspecies were evaluated with scalp EEG, and classified according to interictal and ictal EEG traits, as well as photosensitivity. Of the 671 baboons undergoing scalp EEG studies, 452 (67%) were females, 219 (33%) were males, 425 (63%) belonged to PHA, 219 (33%) to PHX and the remaining 27 (4%) to other subspecies (Table 1). Their mean age at the time of the EEG study was 13 (range 0.5–33) years old, their mean weight was 21 (±7) kg. The selection of the baboons included a broad representation across the pedigree. However, because of some baboons, particularly younger animals, presenting with severe seizures, as well as older animals that were never witnessed to have seizures and were either ill or near to termination, were preferentially referred for EEG studies, some demographic and clinical biases were unavoidable. The baboons were treated in strict accordance with the U.S. Public Health Service's *Guide for the Care and Use of Laboratory Animals* (Committee for the Update, 2011) and the *Animal Welfare Act*. This study was approved by the Institutional Animal Care and Use Committees of UTHSCSA and Texas Biomed.

Clinical information was obtained from a computerized database, and complemented by the review of veterinary records, particularly in animals whose computerized records were inconclusive (Szabó et al., 2012a). Seizures were determined in animals demonstrating generalized motor activity during the ictus or based upon postictal findings of confusion reported in the chart. Spontaneous, unprovoked seizures were classified separately from seizures were provoked either by ketamine anesthesia or handling. Epilepsy was only diagnosed in baboons with at least two witnessed, unprovoked seizures.

Scalp EEG

The methods for the scalp EEG studies were described by our group previously (Szabó et al., 2004, 2005). The surface electrodes are placed according to the standard international 10–20 electrode placement system at FP1, FP2, T8,