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EPILEPSY IN NONHUMAN PRIMATES

Leah Croll[1], **Charles A. Szabo**[2], **Noha Abou-Madi**[3], **Orrin Devinsky**[1]

[1]NYU, Neurology

[2]UTHSCSA, Neurology

[3]Cornell University College of Veterinary Medicine, Department of Clinical Sciences

Abstract

Objectives—Non-human primates (NHP) are model organisms for understanding the pathophysiology and treatment epilepsy therapy in humans, while data from human patients informs the diagnosis and treatment of NHP with seizures and epilepsy. We reviewed the literature and surveyed veterinarians at zoos and NHP research centers to 1) better define the range of seizures and epilepsy in NHP, 2) understand how NHPs can inform our knowledge of human epilepsy pathophysiology and treatment, and 3) identify gaps of knowledge and develop more effective guidelines to treat seizures and epilepsy in NHP.

Methods—We searched PrimateLit, Pubmed, and Google Scholar for studies on experimental models of epilepsy in NHP and on naturally-occurring seizures and epilepsy in NHP in captivity. We also created a survey to assess methods to diagnose and treat epilepsy in NHP. This survey was sent to 41 veterinarians at major international zoos and research facilities with NHP populations to study seizure phenomenology, diagnostic criteria for seizures and epilepsy, etiology, and anti-seizure therapies in NHP.

Results—We summarize the data from experimental and natural models of epilepsy in NHP and case reports of epilepsy of unknown origin in captive primates. We also present survey data collected from veterinarians at 8 zoos and 1 research facility. Experimental data from NHP epilepsy models is abundant, while data from primates who develop epilepsy in the wild or in zoos is very limited, constraining our ability to advance evidence-based medicine.

Significance—Characterization of seizure or epilepsy models in NHP will provide insights into mechanisms and new therapies which cannot be addressed by other animal models. NHP research will better inform species-specific diagnoses, and outcomes

Keywords

seizure; baboon; antiepileptics

Corresponding author: Leha Croll, NYU Langone Health, Neurology, 333 E 38th St, New York, NY 10016-4576, (646) 501-7070, leah.croll@nyumc.org.

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We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

1. Introduction

The neurobiological and phylogenetic proximity of nonhuman primates (NHP) and humans suggests that neurological disorders in primates can inform our understanding of human disorders while advances in human therapies can be adapted in primate care. Primate brains provide the closest parallels to the genetic, neurochemical, neurophysiological and cytoarchitectonic features of human brains, and are excellent models of physiology and disease[1]. Epilepsy occurs naturally in NHP – spontaneously (i.e., presumed genetic) and from symptomatic (structural) causes such as trauma and infection. In humans, focal epilepsies account for 20–66% of incident epilepsies in population-based studies of all ages[2]. A cause sf epilepsy is identified in 14–39% of cases; most have no identifiable cause[2]. Research in NHP may help us to better understand the underlying pathophysiology of human epilepsies and inform their treatment. Our knowledge of epilepsy in NHP comes primarily from two sources: experimental models of epilepsy and animals in captivity or research facilities who develop seizures or epilepsy.

The literature on seizures and epilepsy occurring in NHP in captivity or animal research facilities who develop symptomatic (structural) epilepsy or epilepsy of unknown origin is limited to case reports and small series. We need research to further assess the safety and efficacy of therapies and protocols for seizures, epilepsy and status epilepticus in NHP. By contrast, there is considerable data from experimental epilepsy models.

NHP resemble humans more closely genetically, physiologically and anatomically than any other animal model[1]. Our objective is to provide an overview of experimental epilepsy models in NHP, natural epilepsy models in NHP in research facilities, and the diagnosis and management of seizures and epilepsy in NHP in zoos, as research in NHP can build our knowledge of epilepsy pathophysiology, diagnosis, and treatment in both NHP and humans.

2. Methods

We systematically examined data on: the range of seizure phenomenology, the diagnosis of seizures and epilepsy, causes of seizures and epilepsy, and management of seizures/epilepsy in NHP.

2.1 Literature search for studies of epilepsy in NHP

We searched Pubmed and Google Scholar for studies on experimental models of epilepsy in NHP and on naturally-occurring seizures and epilepsy in NHP in captivity. Our Pubmed search used combinations of keywords relating to 1) epilepsy 2) seizures 3) NHP. We also searched for specific species i.e., "*Gorilla gorilla*" AND "seizure" and for all years available. The search was restricted to studies on NHP in English. There was no limitation on year published or type of article. We also searched the reference lists of all relevant studies (backward citation searching). We also used Google and Google Scholar to perform these searches and for forward citation searching.

We searched PrimateLit Database (accessed 11/1/2018) on primatology (University of Wisconsin-Madison Libraries) for "epilepsy" or "seizure," which yielded >1,000 results.

Restricting the search to English articles for all years and article types yielded ~800 articles, from which we selected those on experimental epilepsy models that didn't overlap with our Pubmed and Google searches, and included all case reports of epilepsy or seizures in NHP in captivity.

2.2. Survey of Zoos and Research Facilities with Primates

We sent our survey to lead veterinarians at 35 international zoos and 6 research facilities. Questions included background information on the animal care facility and the primates it cares for, including demographic and clinical information of NHPs with seizures. We asked about the seizure semiology, diagnostic work up, the efficacy of ASMs and other treatments used, other medical history in the affected animal, and descriptions of any craniofacial trauma or episodic behavioral changes suggesting possible seizure activity.

3. Results: Nonhuman primate models of epilepsy

Multiple NHP models of epilepsy have been extensively studied in natural and experimental models of focal and generalized epilepsy (Table 1). These models studied the pathophysiology and neurophysiology underlying epileptic seizures, as well as anti-seizure therapies in NHP. We included models based on their relevance to understanding human epilepsies and their applications for further research.

3. 1 The study of epileptogenesis in experimental models

The alumina gel-induced rhesus monkey model of focal epilepsy was an early NHP mode[3]. Initial studies investigated the role of the inhibitory neurotransmitter, γ-aminobutyric acid (GABA) in epileptogenesis. Immunocytochemistry for GABA-synthetic enzyme, glutamate decarboxylase (GAD), revealed significant destruction of GABAergic neurons and GABA receptors at chronic cortical epileptic foci[2, 3]. Other studies showed that the loss of GAD-positive terminals and neuronal somata occurs clinical seizure onset in monkeys[3] suggesting that loss of GABAergic innervation contributes to the focal epilepsy pathogenesis.

This alumina gel temporal lobe epilepsy (TLE) model in rhesus monkeys produced parallel pathology, behavior, and EEG features to human chronic TLE[4]. Another TLE model was developed by inducing status epilepticus in pig-tailed macaque *(Macaca nemestrina)* with unilateral entorhinal infusions of bicuculline[5]. This model may inform the effects of prolonged seizures during infancy and the origins of human TLE. A status epilepticus model was generated by intravenous bicuculline in adolescent baboons (*Papio papio)* to study the effects of seizure-induced brain injury with or without hypoxia[6].

3.2 The study of potential seizure therapies in experimental models

The alumina gel-induced rhesus macaque (*Macaca mulatta*) model of focal epilepsy has assessed the efficacy of anti-seizure medications (ASMs). Phenytoin and phenobarbital reduced seizure frequency and severity in these monkeys[7]. Animals given pharmacologic prophylaxis had only partial seizures whereas control animals exhibited secondarily generalized tonic-clonic seizures (GTCS). This model compared the efficacy of valproic acid (VPA) and ethosuximide (ESM)[8]. Low dose VPA reduced seizure frequency, duration, and

severity but a higher dose was required to attenuate focal motor seizures. Long-term seizure frequency was reduced with high VPA plasma levels. Ethosuximide exacerbated seizure frequency. Clonazepam (CZP), like VPA, controlled secondarily GTCS at low doses, while partial or focal motor seizures were controlled only at higher doses[9]. Seizure frequency was reduced with high doses of VPA or CZP, even after cessation of the ASM. The enduring effects of VPA after medication discontinuation was first demonstrated in this primate model[8]. These studies established ASM efficacy for seizure prophylaxis and suggest that long-term risk modification requires high doses. This model was also used to evaluate vagus nerve stimulation (VNS) to treat seizures. Chronic VNS Therapy reduced seizure frequency but not severity nor interictal epileptiform discharges (IEDs)[10].

3.3 Natural model of idiopathic generalized epilepsy with photosensitivity

The propensity for visual stimuli, such as flashing lights, to trigger seizures, or photosensitivity, was originally encountered in wild red baboons (Papio hamadryas papio)[11]. The ability to replicate seizures in a laboratory setting by taking advantage of photosensitivity provided an attractive opportunity to better understand mechanisms underlying photoepileptic responses and test treatments. Intermittent light stimulation (ILS) triggers generalized interictal epileptic discharges over the frontocentral regions, as well as seizures, beginning with myoclonic jerking of the eyelids, then spreading to the lower face, neck, trunk, and upper and lower extremities[11]. These myoclonic seizures can develop into GTC seizures. Similar to humans, photosensitivity is increased by hyperventilation and stress, and maximal in the morning hours, especially upon awakening. In both species, spontaneous IEDs are more likely when the animal is relaxed with closed eyes[12]. Photosensitive baboons also exhibit spontaneous myoclonic, absence and GTC seizures, but electroclinical data is more limited[13].

3.4 Epidemiology of generalized photosensitive epilepsy in baboons

Photosensitivity occurs in 60% of red baboons from western Africa[1], and reportedly more prevalent than in *Papio h. anubis* and *Papio h. cynocephalus*[14]. Photosensitivity was observed in about 40% of baboons (*P.h. cynocephalus/anubis, hamadryas/anubis*, and *papio/Anubis*) with spontaneous GTCS, and in 40% of animals with spontaneous generalized interictal discharges on scalp EEG[13].

The Southwest National Primate Research Center (SNPRC) in San Antonio, Texas has ~2000 baboons, including *P.h. anubis*, *P.h. anubis/cynocephalus* crosses, *P.h. hamadryas*,*P.h. papio*. The SNPRC houses the oldest and largest captive baboon pedigree, spanning seven generations. The prevalence of seizures is 26% and recurrent seizures is 15%[15]. Seizure incidence was 25/1000 baboon years (2.5%), much higher than in humans (135/100,000 person years or 0.135%). Most baboons have childhood or adolescent-onset of GTCS, and scalp EEG reveal generalized IEDs with 4–6 Hz spike- or polyspike-and-wave discharges. As the seizures occur predominantly in sleep or upon awakening, the number of witnessed seizures underestimate actual seizure counts[15]. Caretakers can recognize intense seizures and peri-ictal behavioral changes or injuries; brief and often mild myoclonic seizures, especially eyelid myoclonus, or absence seizures are missed unless observed by a caretaker. Craniofacial trauma, such as brow lacerations or bruising, related to seizure-induced falls,

serve as useful adjunct for identifying seizures[16]. Based upon the electroclinical findings, there are striking parallels between this baboon epilepsy syndrome and juvenile myoclonic epilepsy (JME) in humans[13].

While the natural history of epilepsy in the baboon is uncharted, epileptic baboons have shorter life expectancy than nonepileptic controls[17]. Some epileptic baboons die suddenly and unexpectedly in the colony. On pathological exam they are found to have pulmonary edema, similar to humans with sudden unexpected death in epilepsy (SUDEP). As no other reasons for death are noted on necropsy, the epileptic baboon is thought to serve as a natural animal model for SUDEP.

3.5 Seizure pathophysiology in baboons

Developments in structural and functional neuroimaging offer an excellent opportunity for studying the brain networks involved in photosensitivity and spontaneous ictal or interictal epileptic discharges. $H_2{}^{15}O$-PET and resting-state fMRI have been used to map photoepileptic responses, networks underlying interictal discharges and network responses to antiseizure therapies[18,19]. Neuroimaging has also informed the planning of intracranial electrode placement and ongoing histopathological analyses, which are not possible in people with idiopathic generalized epilepsies[19]. Intracranial EEG confirmed functional neuroimaging findings that, in addition to the frontocentral cortices, the parietal and occipital regions are involved in the epileptic network, and that multiregional focal discharges occur alongside generalized interictal epileptic discharges. Ictal discharges, though generalized appear to be triggered by focal discharges from frontal, parietal or occipital cortices. Post-mortem neuropathological studies also identify more diffuse cell loss in the epileptic baboon brains, including decreased cortical neurons in sensorimotor, frontal and parietal cortices compared to controls[20]. It is unclear whether the cell-loss in affected baboons may be related to seizure activity or cortical developmental anomalies.

3.6 The study of potential seizure therapies in baboons (Papio papio)

Early studies in the natural GGE model of epilepsy in the baboon evaluated the efficacy of antiseizure medications in the setting of photosensitivity[6]. Similar to the experimental seizure models, phenobarbital and benzodiazepines, including diazepam and clonazepam were the most efficacious in suppressing photoparoxysmal and -convulsive responses, whereas carbamazepine, phenytoin and ethosuximide were deemed not as effective in the treatment of generalized myoclonic seizures. Valproic acid was effective only at much higher doses than required in humans for successful treatment of seizure types associated with idiopathic generalized epilepsy[21]. But even at subtherapeutic doses, valproic acid alters the epileptic networks, as demonstrated in a recent functional MRI study[18]. There are surprisingly no studies evaluating the effects of chronic antiseizure medications on spontaneous seizure activity in the epileptic baboon. Nonetheless, in a recent study, high-frequency microburst VNS therapy demonstrated efficacy in reducing spontaneous GTCS frequency in epileptic baboons monitored continuously by video[22].

The antiseizure medication, ketamine, on the other hand, may induce spontaneous interictal epileptic discharges and reduce seizure threshold at subtherapeutic doses (intramuscular

injections of 4–6 mg/kg)[13]. The seizures are mainly myoclonic seizures, and rarely convulsive in character. If convulsive seizures occur, they are usually briefer than the spontaneous GTCS, and may be repetitive[13,22,23]. Intramuscular ketamine exceeding 8 mg/kg raises seizure thresholds and suppresses photosensitivity[23]. Inhibition of the negative feedback influencing glutamatergic activity via antagonism of presynaptic glutamate receptor activity results in a proconvulsive effect, while at higher ketamine doses, the glutamatergic effects may be suppressed by saturation of the postsynaptic glutamate receptors[24]. Interestingly, ketamine is currently recommended for treatment of refractory SE in humans[25]. Proconvulsants, such as allyl-glycine, which inhibits GABA synthesis, or the GABA-receptor antagonist bicuculline, were routinely used in previous decades to reliably provoke photoconvulsive responses in NHP studies[6,11,12].

3.7 Future directions of research in natural model of generalized epilepsy of unknown origin

Identification of genes underlying photosensitivity and epilepsy is an important goal in the baboon model for idiopathic generalized epilepsy. Baboons in the SNPRC pedigree have a 26% prevalence of GTCS[15]. No genes have been identified although the heritability of GTCS (0.33, $p<0.0000001$) and IEDs (0.19, $p<0.002$) strongly supports a genetic contribution (CAS, personal communication, July 19, 2018). Genetic and epigenetic studies are underway to determine their contribution to photosensitivity and epilepsy in the baboons. Identifying baboons at high genetic risk for epilepsy will facilitate research into the developmental aspects of the epilepsy, including epileptogenesis. In addition to evaluating antiepileptogenic therapies, the epileptic baboon can be utilized to provide targets for neurostimulation or neurochemical interventions. Finally, this model can provide important insights into the co-morbidites of idiopathic generalized epilepsy, including social and behavioral consequences of seizures and SUDEP.

4. Results: Seizures and epilepsy of unknown cause in nonhuman primates

Our literature searches yielded very few case reports of seizures of unknown origin in captive NHP. We were unable to find any case reports of seizures observed in wild NHP. Of the available case reports, only one paper addressed seizure therapies (see section 4.1 below). However, unpublished data was available on GTCS between 1993 and 2005 in non-baboon primates at the SNPRC. This data is described in section 4.2 below.

Multiple case reports of secondary seizures in captive NHP were found in our literature searches (see table 2). Examples include: 14 cases of amaurotic epilepsy in primates at the National Zoological Park and 2 cases in primates at the Antwerp Zoo, found to be due to lead poisoning on necropsy[26]; grand mal seizures in a 22-year-old western lowland gorilla at the North Carolina Zoo due to amoebic meningoencephalitis caused by *Balamuthia mandrillaris*[27].

4.1 Potential seizure therapies in nonhuman primate patients

Controlling sporadic seizures, recurrent seizures (epilepsy) and status epilepticus in NHP is a challenge for animals in captivity and in primate research facilities. Phenobarbital remains the primary ASM used in zoos to treat primates and most other animals with epilepsy[28]. However, the pharmacokinetics and dosage required for safe and effective seizure control in NHP remains poorly defined. Side effects of phenobarbital in humans include lethargy, impaired cognition, dizziness, unsteadiness, rash and other allergic reactions, soft tissue changes (Dupuytren's contracture, frozen shoulder), and teratogenicity.

The Milwaukee County Zoo reported on different ASM regimens for apes[28]. Breakthrough seizures were common with phenobarbital monotherapy, which was not considered an ideal ASM as most animals required adjunctive or alternative therapies including acetazolamide, carbamazepine, and levetiracetam. Oral contraceptives reduced seizures in some female apes with catamenial epilepsy. In three cases, adjunctive ASMs improved seizure control with a reduction in phenobarbital dosage[28].

4.2 Survey of Zoos and Research Facilities with Primates

We surveyed lead veterinarians at 35 international zoos and 6 research facilities with NHPs. The questions included background information about the animal care facility and primates cared for, demographic and clinical information of individuals with seizures, seizure semiology, diagnostic work up, efficacy of ASMs and other treatments, medical history in affected animals, and descriptions of any craniofacial trauma or episodic behavioral changes suggestive of possible seizure activity.

Eight of 35 (22%) zoo veterinarians and 1/6 research facilities responded. Of the 8 zoo responders, 3 reported no history of seizures in any primates. Two of five responders who had seizures in primates provided medical records, which we reviewed. Table 3 summarizes the zoo data; 18 NHPs with single or recurrent seizures. Affected primates included lemurs, colobuses, tamarins, orangutans, bonobos, and gorillas.

Unpublished seizure data on NHP species outside the baboon colony was available from an epidemiological study at SNPRC (NIH/NINDS 1 R01 NS047755–01). The clinical database (CAMP) and necropsy records between 1993 and 2005 identified suspected or witnessed seizures in 44 NHP: 2 grivets (*Chlorocebus aethiops*, both female), 2 marmosets (*Callithrix jacchus*, one female), 13 rhesus monkeys (*Macaca mulatta*, 9 female), 27 cynomolgus monkeys (*Macaca fascicularis*, 19 female), and two chimpanzees (*Pan troglodytes*, 1 female). One grivet with chronically elevated enzymes, experienced a single seizure associated with ketamine at age 9 years, the other had a spontaneous seizure at age 8 years. Both marmosets had Langur Herpes Virus infections; seizures were witnessed only when handled by staff. The rhesus and cynomolgus monkeys exhibited spontaneous seizures, usually isolated, and suspected seizures based on craniofacial trauma or being found down in the cage, or induced by ketamine. The mean age of onset in the rhesus monkeys was 6.5 (range 0.5–11) years, excluding 2 animals with only ketamine-induced seizures. Four had ≥2 seizures; 7 had suspected seizures only. Four had terminal seizures, usually related to infection. The mean age of onset of epilepsy in the cynomolgus monkeys was 3 (range 0.5–

11), excluding animals without a birthdate (N=3) and with only ketamine-induced seizures (N=4). All but three cynomolgus monkeys had single witnessed or suspected events, and these three had two events each. Four monkeys had seizures suspected based upon craniofacial trauma, and 2 had seizures associated with handling. In three cases, seizures may have resulted from chronic infections, and in 14 seizures onset was within 2 months of euthanasia, performed due to infection or anemia. Two chimpanzees had seizures. One had three spontaneous GTCS (ages 13, 18 and 19 years). She had idiopathic thrombocytopenic purpura, cerebral artery stenosis and intracardiac fibrosis, with brain hemorrhages at autopsy. The second was found confused and diagnosed postictal after his first seizure; but his mental status deteriorated; he was euthanized and autopsy revealed meningoencephalitis. Like the grivets, marmosets and macaques, who had largely symptomatic seizures, the two chimpanzees had symptomatic epilepsy. None of these animals underwent EEG and chronic ASMs were not administered.

5. Discussion

There is a serious knowledge gap with respect to the diagnosis and treatment of seizures or epilepsy in NHP. This study aimed to collect information from Pubmed and Google searches, and from zoos and primate research facilities, to better understand the overall approach taken by veterinarians in these respective settings. It is clear that treatment is provided on a case-by-case basis utilizing anti-seizure medications (ASMs) that are effective in humans. Some of these medications are metabolized differently by NHPs than in humans, but veterinarians often extrapolate from human medicine to NHP patients when diagnosing and treating epilepsy[28]. This can be problematic, however, as species differences in drug metabolism and toxicity between different NHPs and between NHPs and humans have not been studied[29]. There is little information with respect to diagnosis and classification of the seizures. The epileptic baboon demonstrates the only well-documented and classified natural NHP model of idiopathic generalized epilepsy with photosensitivity, affecting most of the known baboon subspecies. In canines, the 2015 International Veterinary Epilepsy Task Force, proposing a classification system for epilepsy and epileptic seizures adapted from the International League Against Epilepsy[30], demonstrates a collaborative effort which would also benefit the managements of NHP patients. Developing a common terminology between human and veterinary neurologists and neuroscientists will facilitate both clinical and research efforts.

The limitations to collecting data on NHP are numerous. Collecting this type of data is challenging since the detection, classification and quantification of seizures requires close observation, and is often limited to convulsive seizures and peri-ictal behavioral changes or injuries. Recognition of more subtle seizure types, such as focal seizures with alteration of awareness, absence or myoclonic seizures is tenuous without access to continuous video-EEG monitoring. Epileptic NHPs may be dangerous to house with other NHPs as they are not only at risk for seizure-related injuries, but also abuse by other cage-mates. Care and management for NHPs is expensive and challenging, and ethically, in the absence of treatment, is difficult to justify quality of life of NHPs with seizures.

Experimental and natural models of epilepsy in NHP have advanced our understanding of mechanisms and therapies (see Table 1). The experimental models provided insight into the electrophysiology underlying absence seizures and focal epileptogenesis. The most extensively studied natural model, the epileptic baboon, advanced understanding of photosensitivity and reflex seizures pathophysiology, assessment ASMs, and the clinical and neuropathological effects of convulsive status epilepticus[11]. Furthermore, the genetic similarities between NHP and humans make NHPs uniquely valuable models of epilepsy. While the no specific epilepsy genotypes have been identified in the baboon or other NHP, once they become established, these models could provide useful platforms to study epileptogenesis and developmental aspects underlying or associated with epilepsy. There are several other advantages of NHP models for epilepsy. In contrast to rodent and mouse models, the epileptic baboon demonstrates seizure types and semiologies as well as ictal and interictal EEG findings consistent with idiopathic epilepsies in humans. NHP are better suited for neuroimaging studies than murine and rodent models, due to their larger brain volumes, similar neuroanatomy and brain connectivity to humans. Furthermore, since NHP can be trained to perform cognitive and fine motor tasks, relevant behavioral and treatment effects can be assessed and are readily translated to humans. Ideally, behavioral training also needs to be implemented for to reduce the need for sedation during neuroimaging and electrophysiological procedures.

Several decades ago, the development of genetic and experimental murine and rodent epilepsy models marginalized interest in the baboon model due to their lower cost, wider availability, miniaturization of equipment, and ethical concerns. And currently, ASM screening are utilizing even smaller and less expensive animal models, including zebra fish, Caenorhabiditis elegans and drosophila melanogaster[31]. Alternatively, canine epilepsy models can assess long-term focal seizure detection and neurostimulation[32] as well as studies on the mechanisms underlying genetic generalized epilepsy with myoclonus and photosensitivity[33] and the progressive myoclonic epilepsy associated with Lafora Disease[34]. Dogs are expensive to maintain but easy to purchase and handle. Dogs could become valuable for gene discovery, since many canine epilepsies are idiopathic (presumed genetic), genetic variation is reduced within breeds, and similarities between dog and human genomes[35]. The DIRAS1 gene linked to Rhodesian Ridgeback's photosensitive epilepsy[34] and mutations in the ADAM23 gene causing familial partial epilepsy in Belgian Shepherds are some examples. Eight mutations for canine progressive myoclonic epilepsies occur in orthologs of human genes[35]. Similarly, NHLRC1 was identified as causing Lafora disease in Miniature Wire-haired Dachshunds[36].

Still, our limited understanding of seizure and epilepsy in NHP species is an important untapped resource. NHP research will not only improve care of NHP with epilepsy, but also inform our understanding of human epilepsy. Hence, there is a need for more coordinated and systematic data collection between zoos and research facilities to identify research opportunities. Current research of NHP epilepsy models is limited by potential differences between humans and NHP in neurophysiology, pharmacodynamics, and target biology. The relevance of the respective NHP models for the investigation of human epilepsy needs to be critically considered. Critically, investigation of epilepsy and seizures in NHP must satisfy

the highest ethical standards, and that NHP are not used in high-risk studies, in inappropriate studies or in studies adequately suited for smaller animals or models.

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References

1. Charles Akos S. Primate Models of Neurological Disease. The Laboratory Primate. Elsevier; 2005 p. 467–86.
2. Banerjee PN, Filippi D, Allen Hauser W. The descriptive epidemiology of epilepsy—A review. Epilepsy Res. 2009; 85(1):31–45. [PubMed: 19369037]
3. Houser CR, Harris AB, Vaughn JE. Time course of the reduction of GABA terminals in a model of focal epilepsy: a glutamic acid decarboxylase immunocytochemical study. Brain Res. 1986; 383(1–2):129–45. [PubMed: 3094829]
4. Ribak CE, Seress L, Weber P, et al. Alumina gel injections into the temporal lobe of rhesus monkeys cause complex partial seizures and morphological changes found in human temporal lobe epilepsy. J Comp Neurol. 1998; 401(2):266–90. [PubMed: 9822153]
5. Gunderson VM, Dubach M, Szot P, et al. Development of a Model of Status epilepticus in Pigtailed Macaque Infant Monkeys. Dev Neurosci. 1999; 21(3–5):352–64. [PubMed: 10575259]
6. Meldrum BS, Anlezark G, Balzamo E, et al. Photically induced epilepsy in Papio papio as a model for drug studies. Adv Neurol. 1975; 10:119–32. [PubMed: 1170711]
7. Lockard JS, Congdon WC, DuCharme LL, et al. Prophylaxis with Diphenylhydantoin and Phenobarbital in Alumina-Gel Monkey Model. Epilepsia. 1976; 17(1):37–47. [PubMed: 817891]
8. Lockard JS, Levy RH, Congdon WC, et al. Efficacy Testing of Valproic Acid Compared to Ethosuximide in Monkey Model: II. Seizure, EEG, and Diurnal Variations. Epilepsia. 1977; 18(2): 205–24. [PubMed: 406139]
9. Lockard JS, Levy RH, Congdon WC, et al. Clonazepam in a Focal-Motor Monkey Model: Efficacy, Tolerance, Toxicity, Withdrawal, and Management. Epilepsia. 1979; 20(6):683–95. [PubMed: 115680]
10. Lockard JS, Congdon WC, DuCharme LL. Feasibility and Safety of Vagal Stimulation In Monkey Model. Epilepsia. 1990; 31(s2):S20–6. [PubMed: 2226362]
11. Menini C, Silva-Barrat C. The Photosensitive Epilepsy of the Baboon In: Zifkin BJ, Beaumanoir A, Rowan AJ, editors. Reflex Epilepsies and Reflex Seizures: Advances in Neurology Lippincott-Raven Publishers; 1998 p. 29–47.
12. Naquet R, Valin A. Experimental Models of Reflex Epilepsies In: Zifkin BJ, Beaumanoir A, Rowan AJ, editors. Reflex Epilepsies and Reflex Seizures: Advances in Neurology Lippincott-Raven Publishers; 1998 p. 15–28.
13. Szabó CÁ, Knape KD, Leland MM, et al. Electroclinical phenotypes in a pedigreed baboon colony. Epilepsy Res. 2013; 105(1–2):77–85. [PubMed: 23499213]
14. Killam EK, Stark LG, Killam KF. Photic-stimulation in three species of baboons. Life Sci. 1967; 6(15):1569–74. [PubMed: 4963371]
15. Szabo CA, Knape KD, Leland MM, et al. Epidemiology and characterization of seizures in a pedigreed baboon colony. Comp Med. 2012; 62(6):535–8. [PubMed: 23561888]
16. Szabo CA, Knape KD, Leland MM, et al. Craniofacial trauma as a clinical marker of seizures in a baboon colony. Comp Med. 2014; 64(2):135–9. [PubMed: 24674589]
17. Ákos Szabó C, Knape KD, Michelle Leland M, et al. Mortality in captive baboons with seizures: A new model for SUDEP? Epilepsia. 2009; 50(8):1995–8. [PubMed: 19389147]

18. Salinas FS, Szabõ CÁ. Resting-state functional connectivity in the baboon model of genetic generalized epilepsy. Epilepsia. 2015; 56:1580–9. [PubMed: 26290449]
19. Szabó CÁ, Salinas FS, Leland MM, et al. Baboon model of generalized epilepsy: Continuous intracranial video-EEG monitoring with subdural electrodes. Epilepsy Res. 2012; 101(1–2):46–55. [PubMed: 22480914]
20. Young NA, Szabo CA, Phelix CF, et al. Epileptic baboons have lower numbers of neurons in specific areas of cortex. Proc Natl Acad Sci. 2013; 110(47):19107–12. [PubMed: 24191031]
21. Ehlers CL, Killam EK. Circadian periodicity of brain activity and urinary excretion in the epileptic baboon. Am J Physiol Integr Comp Physiol. 1980; 239(1):R35–41.
22. Szabó C, Salinas FS, Papanastassiou AM, et al. High-frequency burst vagal nerve simulation therapy in a natural primate model of genetic generalized epilepsy. Epilepsy Res. 2017; 138:46–52. [PubMed: 29059589]
23. Ákos Szabó C, Leland M, Sztonák L, et al. Scalp EEG for the diagnosis of epilepsy and photosensitivity in the baboon. Am J Primatol. 2004; 62(2):95–106. [PubMed: 14983467]
24. Moghaddam B, Adams B, Verma A, et al. Activation of Glutamatergic Neurotransmission by Ketamine: A Novel Step in the Pathway from NMDA Receptor Blockade to Dopaminergic and Cognitive Disruptions Associated with the Prefrontal Cortex. J Neurosci. 2018; 17(8):2921–7.
25. Höfler J, Trinka E. Intravenous ketamine in status epilepticus. Epilepsia. 2018; 59:198–206. [PubMed: 30146731]
26. Zook BC, Sauer RM, Garner FM. Acute amaurotic epilepsy caused by lead poisoning in nonhuman primates. J Am Vet Med Assoc. 1972; 161(6):683–6. [PubMed: 4626776]
27. Sato H, Une Y, Kawakami S, et al. Fatal Baylisascaris Larva Migrans in a Colony of Japanese Macaques Kept by a Safari-Style Zoo in Japan. J Parasitol. 2005; 91(3):716–9. [PubMed: 16108577]
28. Gerlach T, Clyde VL, Morris GL, et al. Alternative Therapeutic Options for Medical Management of Epilepsy in Apes. J Zoo Wildl Med. 2011; 42(2):291–4. [PubMed: 22946407]
29. West GB. The importance of quantitative systemic thinking in medicine. Lancet. 2012; 379(9825): 1551–9. [PubMed: 22516561]
30. Berendt M, Farquhar RG, Mandigers PJJ, et al. International veterinary epilepsy task force consensus report on epilepsy definition, classification and terminology in companion animals. BMC Vet Res. 2015; 11(1).
31. Cunliffe VT, Baines RA, Giachello CNG, et al. Epilepsy research methods update: Understanding the causes of epileptic seizures and identifying new treatments using non-mammalian model organisms. Vol. 24, Seizure. 2015 p. 44–51. [PubMed: 25457452]
32. Howbert JJ, Patterson EE, Stead SM, et al. Forecasting seizures in dogs with naturally occurring epilepsy. PLoS One. 2014; 9(1):e81920. [PubMed: 24416133]
33. Wielaender F, Sarviaho R, James F, et al. Generalized myoclonic epilepsy with photosensitivity in juvenile dogs caused by a defective DIRAS family GTPase 1. Proc Natl Acad Sci. 2017; 114(10): 2669–74. [PubMed: 28223533]
34. Swain L, Key G, Tauro A, et al. Lafora disease in miniature Wirehaired Dachshunds. PLoS One. 2017; 12(8):e0182024. [PubMed: 28767715]
35. Potschka H, Fischer A, Von Rüden EL, et al. Canine epilepsy as a translational model? Epilepsia. 2013; 54(4):571–9. [PubMed: 23506100]
36. Ekenstedt KJ, Oberbauer AM. Inherited epilepsy in Dogs. Top Companion Anim Med. 2013; 28(2):51–8. [PubMed: 24070682]
37. Marcus EM, Watson CW. Symmetrical Epileptogenic Foci in Monkey Cerebral Cortex: Mechanisms of Interaction and Regional Variations in Capacity for Synchronous Discharges. Arch Neurol. 1968; 9(1):9(1) 99–116.
38. Marcus EM. Epileptogenic effects of cobalt in Macca mulatta: unilateral and bilateral cortical foci. Epilepsia. 1972; 13(2):343–4.
39. Tenney JR, Marshall PC, King JA, et al. FMRI of generalized absence status epilepticus in conscious marmoset monkeys reveals corticothalamic activation. Epilepsia. 2004; 45(10):1240–7. [PubMed: 15461678]

40. Kopeloff L, Barrera E, Kopeloff N. Recurrent convulsive seixzures in animals produced by immunologic and chemical means. Am J Psychiatry. 1942; 98:881–902.
41. Wada JA, Tsuchimochi H. Cingulate Kindling in Senegalese Baboons, Papio papio. Epilepsia. 1995; 36(11):1142–51. [PubMed: 7588460]
42. Wada JA, Mizoguchi T, Osawa T. Secondarily generalized convulsive seizures induced by daily amygdaloid stimulation in rhesus monkeys. Neurology. 1978; 28:1026–36. [PubMed: 106328]
43. Hong Z, Yang TH, Tang MH, et al. A novel kindling model of temporal lobe epilepsy in rhesus monkeys induced by Coriaria lactone. Epilepsy Behav. 2013; 29(3):457–465. [PubMed: 24100251]
44. Perez-Mendes P, Blanco MM, Calcagnotto ME, et al. Modeling epileptogenesis and temporal lobe epilepsy in a non-human primate. Epilepsy Res. 2011; 96(1–2):45–57. [PubMed: 21620680]
45. Chen N, Liu C, Yan N, et al. A Macaque Model of Mesial Temporal Lobe Epilepsy Induced by Unilateral Intrahippocampal Injection of Kainic Acid. PLoS One. 2013; 26(8):e72336.
46. Riefenberg S, Lammey M, Sleeper M, et al. Diagnosis and treatment of epilepsy in an adult captive female chimpanzee (Pan troglodytes). [Abstract]. J Am Assoc Lab Anim Sci JAALAS. 2010; 49(1):80.
47. Diseases Cousins D. and injuries in wild and captive gorillas. Int Zoo Yearb. 1972; 49(1):211–218.
48. Baird J Jr Eclampsia in a lowland gorilla. GORILLA Gaz. 1993; 7(1):10.
49. Trupkiewicz J, McNamara T, Cook R, et al. Cerebral infarction associated with coarctation of the aorta in a lowland gorilla (Gorilla gorilla). In: AAZV [AM ASSOC ZOO VET] ANNUAL PROCEEDINGS. 1993 p. 110–1.
50. Machotka S, Chapple FI, Stookey J. Cerebral tuberculosis in a rhesus monkey. J Am Vet Med Assoc. 1975; 167:648–50. [PubMed: 809394]
51. Villano J, Carney E, Cooperm T, et al. Acute hemiparesis in a cynomolgus macaque (Macaca fascicularis). [Abstract]. J Am Assoc Lab Anim Sci JAALAS. 2010; 49(1):91.
52. Kornegay R, Baldwin T, Pirie G. Herpesvirus encephalitis in a ruffed lemur (Varecia variegatus). J ZOO Wildl Med. 1993; 24(2):196–203.
53. Anonymous. Acute amaurotic epilepsy in monkeys. Int ZOO Yearb. 1962; 3:123–4.
54. Gjeltema JL, Troan B, Muehlenbachs A, et al. Amoebic meningoencephalitis and disseminated infection caused by Balamuthia mandrillaris in a Western lowland gorilla (Gorilla gorilla gorilla). J Am Vet Med Assoc. 2016; 248(3):315–21. [PubMed: 26799111]
55. Yoshizawa K, Nakao K, Habiro M, et al. Cerebromalacia with epilepsy and cortical blindness in a laboratory Japanese macaque (Macaca fuscata). Toxicol Pathol. 2010; 38(7):1058–63. [PubMed: 20884816]
56. García A, Nambiar PR, Marini RP, et al. Staphylococcal meningoencephalitis, nematodiasis, and typhlocolitis in a squirrel monkey (Saimiri sciureus). J Med Primatol. 2009; 38(5):377–81. [PubMed: 19737242]
57. Hobson DJ, Turner PV. Spontaneous pancreatic islet cell tumor in a black and white colobus monkey (Colobus guereza kikuyuensis). J Med Primatol. 2008; 37(Suppl. 1):11–5. [PubMed: 18269522]
58. Zöller M, Grevot A, Mätz-Rensing K, et al. Leucoencephalopathy with cerebral calcinosis in a young chimpanzee (Pan troglodytes) - A case report. J Med Primatol. 2007; 36(6):385–90. [PubMed: 17976045]
59. Helke KL, Denver MC, Bronson E, et al. Disseminate cryptococcosis in a guenon (Cercopithecus ascanius). Vet Pathol. 2006; 43(1):75–8. [PubMed: 16407492]
60. Landolfi JA, Wellehan JFX, Johnson AJ, et al. Fatal human herpesvirus type 1 infection in a white-handed gibbon (Hylobates lar). J Vet Diagnostic Investig. 2005; 17(4):369–71.

Key Points

- Data from experimental NHP epilepsy models is abundant, but not from primates developing epilepsy in the wild or in zoos.
- NHP research informs our understanding of the pathophysiology, genetics, and management of epilepsy in NHP as well as humans.

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Table 1.

Summary of natural and experimental models of focal and generalized epilepsy in NHP.

Model	Induction of Seizures or Epilepsy	Clinical Manifestations	EEG Findings	Applications	Human Relevance
Experimental Models of Generalized Epilepsy					
Acute absence seizures in rhesus monkeys[37]	Bilateral cortical application of conjugated estrogens	Absence, myoclonic and GTC seizures	GSWC (3 Hz)	Seizure mechanisms	Absence epilepsy
Chronic absence epilepsy in rhesus monkeys[38]	Bihemispheric pial application of cobalt powder	Absence, in some cases GTC seizures	GSWC	Electroclinical monitoring of epilepsy	Absence epilepsy
Marmoset model of absence SE[39]	Subcutaneous injection of γ-butyrolactone	Absence-like behavioral arrest, orofacial myoclonus, and LOA	GSWC (3 Hz)	Antiepileptic drug trials, seizure mechanisms.	Absence epilepsy
Baboon of convulsive status epilepticus[6]	Intravenous bicuculline, gallamine, allylglycine, pentylenetetrazol	Generalized convulsive SE	Generalized SE patterns	Mechanisms of SE induced brain injury	Complications of SE
Experimental Models of Focal Epilepsy					
Focal epilepsy in rhesus monkeys[40]	Sensorimotor application of $Al(OH)_3$ gel	Focal motor seizures	Focal spikes or SWC (mainly at injection site)	Mechanisms of focal SE	Epilepsia partialis continua
Focal epilepsy in rhesus monkeys[7]	Subpial (pre- and postcentral gyrus) injection of $Al(OH)_3$	Focal motor with secondary GTC seizures	Focal spikes and sharp waves	Epileptogenesis model, mechanisms, anti-seizure drug and VNS trials	Posttraumatic
Temporal lobe epilepsy in rhesus monkeys[4]	$Al(OH)_3$ injections intohippocampus, amygdala, entorhinal cortices, and temporal neocortex	Focal dyscognitive with secondary GTC seizures, evolving to SE	Focal ictal and interictal spikes with eventual propagation ipsi- & contralaterally	Epileptogenesis model, mechanisms and anti-seizure drug and antiepileptogenic interventions	Temporal lobe epilepsy
Temporal lobe epilepsy in pig-tailed monkeys[5]	SE induced by entorhinal infusions of bicuculline	Focal SE, late focal dyscognitive seizures	Focal SE, focal seizures and spikes	Epileptogenesis model, mechanisms and anti-seizure drug and antiepileptogenic interventions	Temporal lobe epilepsy
Cingulate kindling in baboons[41]	Electrical kindling of cingulate	Focal SE, late focal seizures with secondary GTC seizures	Focal SE, repetitive focal and bilateral spikes	Epileptogenesis model	Cingulate epilepsy
Amygdaloid kindling in rhesus monkeys[42]	Electrical kindling of amygdala	Focal SE, late focal seizures with secondary GTC seizures	Focal SE, focal seizures and spikes	Epileptogenesis model	Temporal lobe epilepsy
Coriaria lactone rhesus monkey model of TLE[43]	Repeated intramuscular *Coriaria* lactone injection	Autonomic changes, eventual GTC seizures	Focal seizures, spikes and PSP, with bilateral propagation	Epileptogenesis model, mechanisms and anti-seizure drug and antiepileptogenic interventions	Temporal lobe epilepsy
Pilocarpine marmoset model of epilepsy[44]	SE induced by intraperitoneal pilocarpine injections	SE with late focal dyscognitive seizures	Focal seizures, spikes, with bilateral propagation	Epileptogenesis model, mechanisms and anti-seizure drug	Temporal lobe epilepsy

Model	Induction of Seizures or Epilepsy	Clinical Manifestations	EEG Findings	Applications	Human Relevance
				and antiepileptogenic interventions	
Macaque model of temporal lobe epilepsy[45]	Kainic acid injections intrahippocampally	Focal motor and GTC seizures	Focal seizures, spikes, with bilateral propagation	Epileptogenesis model, mechanisms and anti-seizure drug and antiepileptogenic interventions	Temporal lobe epilepsy
Natural Model of Genetic Generalized Epilepsy					
Genetic generalized epilepsy in baboons[11,13, 15, 18]	Spontaneous seizuresor induced by photic stimulation	Generalized myoclonic, absence and GTC seizures	Generalized ictal patterns, GSWC and generalized PSP on scEEG, (generalized & multifocal on Ic EEG)	Mechanisms, anti-seizure drug and VNS trials, cognitive and behavioral effects of VNS and anti-seizure drugs, BOLD effects of anti-seizure drugs	Idiopathic generalized epilepsy (JME), photosensitive epilepsy

GTC generalized tonic-clonic, *GSWC* generalized spike-and-wave complexes, *SE* status epilepticus *Al(OH)3* aluminium hydroxide, *PSP* polyspikes, *ScEEG* scalp EEG, *ICEEG* intracranial EEG.

Table 2.

Summary of case reports and case series of epilepsy or seizures in NHP in captivity

Case reports and case series				
Species	**Clinical signs**	**Diagnosis**	**Treatment**	**Outcome**
1 Chimpanzee[46]	Multiple syncopal-like episodes with intermittent associated grand mal seizure activity	By exclusion (loop recorder ruled out cardiac abnormalities) Idiopathic epilepsy	Phenytoin and gabapentin	Successful treatment
Multiple lowland gorilla[47]	Epileptic seizures	Presumptive trauma at birth		
1 Lowland gorilla[48]	Grand mal seizures 3 weeks before delivery	Eclampsia	Magnesium sulfate	Recovered and gave birth
2 Bonobos[28] 1 Lowland gorilla[28]	Seizures of increased frequency	Seizure-generating effects of estrogen (corresponding with ovulation) Hydrocephalus	Phenobarbital, acetazolamide, Levetiracetam, extended-cycle oral contraceptive Phenobarbital, carbamazepine	Decreased frequency of seizures
1 Lowland gorilla[49]	Progressive left focal seizures and left hemiparesis; Status epilepticus leading to right hemiplegia and debilitation	Cerebrovascular disease secondary to aortic coarctation	Acyclovir, phenobarbital, valproic acid, midazolam	Euthanasia
1 Rhesus monkey[50]	Seizures of increased frequency	Cerebral tuberculosis		Euthanasia
1 Cynomolgus monkey[51]	Partial seizures and right hempresis	Post-surgical changes	fluid therapy, phenytoin, dexamethasone, and antibiotics	Recovered with treatment, euthanized later
1 Black and white ruffled lemur[52]	Chronic intermittent lameness and paresis progressing to convulsions with nystagmus, anisocoria, and profuse salivation	Herpesvirus encephalitis		Died
Multiple species of non-human primates[53]	Signs of acute amaurotic epilepsy	Unknown	Diphenyl hydantoin sodium	
16 Rhesus macaques[26]	Signs of acute amaurotic epilepsy	Lead poisoning		
1 lowland gorilla[54]	Obtunded mentation with grand mal seizures	Amoebic meningoencephalitis and disseminated infection caused by Balamuthia mandrillaris	Antimicrobials and steroids	Died
1 Japanese Macaque[55]	Cortical blindness and GTCs	Unknown	diazepam and phenobarbital	Died
1 Guyanese squirrel monkey[56]	Inappetence and weakness preceded seizures	Staphylococcal meningoencephalitis, nematodiasis, and typhlocolitis	diazepam, pentobarbital, methyl prednisolone, flunixin meglumine, cimetidine, and enrofloxacin	Died
1 Black and white colobus monkey[57]	marked depression, paresis, whole body tremors, and ataxia“severe seizures”	Pancreatic islet cell tumor		Died
1 Chimpanzee[58]	Convulsions and severe paralysis	Leucoencephalopathy with cerebral calcinosis	antibiotics, vitamins, corticoids and anti-inflammatory drugs	Died

Case reports and case series				
Species	**Clinical signs**	**Diagnosis**	**Treatment**	**Outcome**
1 Red-tailed guenon[59]	inappetance, lethargy, and seizures	Disseminate cryptococcosis		Died
1 White-handed gibbon[60]	weak, disoriented, ataxic, seizures	human herpesvirus type 1 infection		Died

Table 3.

Summary of survey responses and relevant medical records sent by participating DVMs

Zoo	# of Cases	Species	Age (yr), sex	Semiology	Diagnostic work up, if any	Treatments tried, if any
1	4	Ring-tailed lemur	8 F	5+ seizures with loss of consciousness and cramps		Dexamethasone injections, effect unknown
		Ring-tailed lemur	13 F	3+ seizures associated with fall and unresponsiveness	Neoplasia suspected (animal had abdominal mass)	Etelefrine, effect unknown
		Ring-tailed lemur	15 M	2 seizures with cramps lasting a few minutes		
		Vervet monkey	5 M	1 episode with fall from tree and twitching		
2	7	Black and white ruffled lemur	4 M	1 seizure triggered by ketamine		
		Red ruffled lemur	10 M	1 seizure with hypersalivation while recovering from anesthesia		
		Angola Colubus	10 M	1 seizure associated with ketamine, years later multiple seizures with confusion/ disorientation	MRI revealed right-sided dural mass	Diazepam given to break seizures
		Black and white Colobus	<1 M	Multiple seizures associated with anesthesia		Diazepam given to break seizures
		Black and white Colobus	1 F	1 seizure following arrest and resuscitation during surgery		Diazepam given to break seizures
		Bearded emperor tamarin	4 F	Several grand mal seizures following fight with sibling	Bloodwork unrevealing, on necropsy found to have large subdural hemorrhage	Seizures did not respond to diazepam, animal arrested
		Sumatran Orangutan	31 F	2 petit mal seizures involving head and arm	Radiographs revealed a fetus with head down lodged in the pelvis Found to have islet cell tumor on necropsy	Vets removed fetus, animal arrested shortly afterwards
3	0					
4	0					
5	0					
6	2	Unspecified	Details of this case privileged			
		Red ruffled lemur	24 F	Unknown	Unknown	Phenobarbital with good effect
7	2	Western Lowland Gorilla	<1 M	Many left focal seizures over lifetime with collapse and shaking of arms and legs, post-ictal lethargy	MRI and CT at 10yrs showed R frontal atrophy and calcified gyri; Serum and CSF antibody titers to HSV1 and EBV were consistently elevated; necropsy revealed cerebrovascular disease and infarction of R cerebral hemisphere and thalamus	Initially controlled with phenytoin, later switched to phenobarbital due to severe gingival hyperplasia, then switched to VPA due to drowsiness Acyclovir was given for possible encephalitis

Zoo	# of Cases	Species	Age (yr), sex	Semiology	Diagnostic work up, if any	Treatments tried, if any
		Western Lowland Gorilla	42 M	Many seizures, initially presented with status epilepticus, subsequently had behavioral changes (aggression)	Elevated serum toxoplasma and HSV titers; MRI with left temporal lobe encephalomalacia	Phenobarbital, gabapentin later added for better behavioral and seizure focus control Acyclovir was given for possible encephalitis
8	3	Bonobo	36 F	Multiple seizures occurring during menses	Bloodwork and CSF studies unrevealing; CT with several mineralized foci in cerebrum and cerebellum	Phenobarbital; acetazolamide; OCP
		Bonobo	36 F	Multiple seizures occurring on days of ovulation	CT and MRI grossly normal	Phenobarbital, later changed to keppra due to adverse effects; OCP
		Western Lowland Gorilla	<1 M	Multiple seizures occurring every 1–4 hours	Bloodwork unrevealing, CT with hydrocephalus	initially treated with phenobarbital and dilantin, later switched to carbamazepine

All animal care facilities who participated in our study will remain anonymous

Number of cases refers to the known number of nonhuman primates with history of observed seizures in each facility. Cases may be from animals currently at the facility or from animals who were previously at the facility.

Age pertains to age at onset of first observed seizure

MRI magnetic resonance imaging; *CT* computerized tomography; *CSF* cerebrospinal fluid; *HSV* herpes simplex virus; *EBV* Epstein-Barr virus; *VPA* valproic acid; *OCP* oral contraceptive pill