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Original Research

Relationship Between Epilepsy and Colpocephaly in Baboons (*Papio hamadryas*)

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Brain MRI scans revealed various occipital horn variants in a pedigreed baboon colony consisting of *Papio hamadryas anubis* and its hybrids. We retrospectively characterized these variants and evaluated their relationships to epilepsy phenotypes and scalp EEG findings. MRI scans (3D, T1-weighted) from 208 baboons (female, 134 female; male, 74; age [mean ± 1 SD], 16 ± 5 y) were reviewed; 139 (67%) of these animals also underwent scalp EEG previously. Occipital horn variants included elongation (extension of the occipital ventricle behind the mediobasal origin of the calcarine fissure), which affected 23 baboons (11%; 7 bilateral, 9 left, 7 right), and elongation with enlargement (colpocephaly), which occurred in 30 baboons (14%; 7 bilateral, 11 left, 12 right). The incidence of the occipital horn variants did not differ according to age or prenatal or perinatal history. Colpocephaly was associated with craniofacial trauma but not with witnessed seizures. Abnormal scalp EEG findings, including interictal epileptic discharges, did not differ significantly among the occipital horn morphologies. This study is the first radiologic description of occipital horn variants, particularly colpocephaly, in baboons. Whereas colpocephaly is frequently associated with other radiologic and neurologic abnormalities in humans, it is mostly an isolated finding in baboons. Because craniofacial trauma can occur in the setting of seizure-related falls, its increased association with colpocephaly may reflect an increased risk of seizures or of traumatic brain injuries due to seizures. Colpocephaly in baboons needs to be characterized prospectively radiologically, neurologically, histopathologically, and genetically to better understand its etiology and clinical significance.

Abbreviations: CFT, craniofacial trauma; IED, interictal epileptic discharge

Colpocephaly was originally described in humans as a congenital enlargement of the posterior aspect of the lateral ventricle, particularly relative to the size of the frontal horns.[2,22] The isolated or relative enlargement of the occipital horns is pathologically associated with diminished periventricular white matter, and in congenital cases is thought to be due to a developmental disruption of glial cell migration.[7] Colpocephaly is commonly encountered associated with congenital insults, including hypoxia or infection, premature low-birth–weight deliveries, and chromosomal abnormalities.[9,12,14] It is radiologically associated with periventricular white matter abnormalities, extending into the centrum semiovale, and can be associated with a full or partial agenesis of the corpus callosum. In addition, colpocephaly can be associated with decreased cerebral volume, cortical atrophy, cerebellar atrophy, optic nerve and cortical dysplasia, and periventricular nodular heterotopias. Neurologically, children with colpocephaly may have developmental delay or cognitive impairment, visual or sensorimotor deficits, spasticity and seizures,[2,9,12,14] although in hereditary cases, additional radiologic and neurologic findings may be absent.[3,13] A few case reports of acquired colpocephaly exist, but these typically are associated with obstructive or normal pressure hydrocephalus, resulting in disproportionate enlargement of the occipital horns.[14]

In a baboon colony housed at the Southwest National Primate Research Center at the Texas Biomedical Research Institute (San Antonio, TX), MRI has been used to evaluate morphometric changes associated with brain development and aging, as well as the heritability of brain volume and structure.[11,15] There has been no formal population-based assessment of MRI variants or abnormalities in other NHP species. The baboon colony at the center currently comprises about 1500 baboons.[18] In addition, the colony features the largest captive baboon pedigree in the world, including 2000 baboons, stretching across 6 to 8 generations and consisting of primarily olive baboons (*Papio hamadryas anubis*) and their hybrids). Genetic generalized epilepsy is prevalent in this pedigree, phenotyped clinically or by scalp EEG (or both) in about 700 baboons.[18,19]

Brain pathology studies have reported hydrocephalus and porencephaly in this baboon pedigree,[6] but variants limited to the occipital horns were not described. We here characterized 2 variants, one defined as an elongation of the occipital horns of the lateral ventricles and the second representing concentric or eccentric enlargement of the occipital horns, associated with cystic dilation of the elongated ventricles into the occipital, pericalcarine, white matter. The clinical significance of these findings, including potential etiologic factors and association with various epileptic phenotypes, was evaluated in this study.

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Materials and Methods

MRI studies were performed in 208 (134 female, 74 male) baboons (*Papio hamadryas anubis*, *Papio hamadryas cynocephalus*, and their hybrids) with a mean (± 1 SD) age of 16 ± 5 y (Table 1). All but 8 baboons came from a captive baboon pedigree housed at the Southwest National Primate Research Center. The baboons were scanned under different research protocols, most for a genetic study evaluating the heritability of brain volume and structure,[11,15] and the others as part of structural or functional neuroimaging studies in epileptic baboons.[16,21] Although there were no neurologic exclusion criteria regarding the first cohort, the 180 baboons selected for the heritability studies for brain volumes had a minimal age of 6 y, when the baboon brain is fully developed.[15] The remaining 28 animals were selected for a voxel-based morphometry study comparing epileptic with asymptomatic, control baboons. All of the baboons underwent high-resolution (isotropic 500 µm) MRI of the cerebrum at the Research Imaging Institute (University of Texas Health Science Center at San Antonio, San Antonio, TX). The baboons were intubated after administration of intramuscular ketamine (5 to 10 mg/kg) or valium (10 mg) or both and then anesthetized by using isoflurane 1% (minimal alveolar concentration, 1 to 1.5).[15,16] During MRI acquisition, the baboons were intubated and connected to a ventilator (Aestiva 5, Datex-Ohmeda, GE Healthcare, Little Chalfont, United Kingdom), and heart rate, pulse oximetry, and respiratory rates were monitored during anesthesia. An optimized, motion-corrected, high gray matter:white matter contrast (approximately 25%), high signal-to-noise ratio (approximately 25) protocol was developed for a 3-T scanner (TRIO, Siemens, Erlangen, Germany) using an 8-channel primate head coil. The MRI scans were evaluated for cortical and subcortical abnormalities simultaneously in 3 dimensions. The occipital horn variants were classified as *elongated* when they extended beyond the coronal plane demarcated by the basomedial origin of the calcarine sulcus (Figure 1) or as *enlarged* when the elongated occipital horns were also concentrically or eccentrically widened relative to the frontal horns (Figure 2). Enlargement in baboons was most consistent with colpocephaly in humans. All of the variants were confirmed with regard to their classification by 2 investigators (CB, who is board-certified in neuroradiology, and CAS). In addition, the MRI scans of the baboons with occipital horn variants, particularly colpocephaly, were reviewed for additional structural abnormalities of the cortical or subcortical gray or white matter structures.

We performed a retrospective case-detection survey of veterinary records to evaluate the age, sex, prenatal or perinatal conditions, gestational age at birth, and subsequent clinical histories of all of the baboons with the occipital horn variants. Pregnancies were documented by daily observation of female baboons in breeding cages, with the date of conception (first day of pregnancy) defined as 2 d before a female's sex skin swelling began to decrease.[8] The gestational age was confirmed subsequently by ultrasonography.[4] The charts were screened for references to witnessed seizures (whether spontaneous [unprovoked] or provoked by ketamine or handling), abnormal neurologic exam, any treatments for head injuries (particularly brow or muzzle lacerations, which are often but not exclusively related to falls during seizures), and observations of periictal behaviors, including confusion, decreased responsiveness, and lethargy.[18] Measurements of total cerebral brain volume were available in 174 (84%) of the baboons from earlier studies.[11,15] The risk of epilepsy, according to the presence or absence of interictal epileptic discharges (IED) occurring spontaneously or secondary to intermittent light stimulation (photosensitivity) on scalp EEG, was available in 139 (67%) baboons. In all of these studies, the baboons were treated in strict accordance with the US Public Health Service's *Guide for the Care and Use of Laboratory Animals*[10] and the Animal Welfare Act.[1] This study was approved by the IACUC of the University of Texas Health Science Center at San Antonio and Texas Biomedical Research Institute.

Age at scanning, normalized brain volumes, and gestational age at birth (available only for the baboons with the occipital horn variants) were compared by using 2-sided Student *t* tests ($\alpha < 0.05$). Association of occipital horn elongation or enlargement with sex, clinical history of seizures, craniofacial trauma (CFT), and scalp EEG findings, such as IED and photosensitivity, were calculated by using 2-sided Fisher exact tests (www.vassarstats.net).

Results

We reviewed the MRI scans of 208 baboons and identified occipital horn variants in 53 (25%) animals, 23 (11%) with occipital horn elongation and 30 (14%) with occipital horn enlargement (colpocephaly; Table 1, Figures 1 and 2). Occipital horn elongation was bilateral in 7 baboons, left-sided in 9, and right-sided in 7. Colpocephaly was bilateral in 7 baboons, left-sided in 11, and right-sided in 12. Among the cases with unilateral enlargement, only 1 (4%) baboon had elongation of the contralateral occipital horn. Review of gray and white matter structures in the baboons with occipital horn variants did not reveal global ventriculomegaly or frontal horn enlargements, cerebellar developmental abnormalities, or agenesis of the corpus callosum. In the baboons with colpocephaly, thinning of the corpus callosum was suspected in 2 cases, and bilateral thinning of the occipital cortices (possible due to volume averaging related to the underlying ventricle), left occipital cortical atrophy, bilateral enlargement of the temporal horns, and bilaterally decreased signal in the basal ganglia (suggestive of calcification), each was noted in individual baboons. In addition, one female baboon had a single periventricular subependymal gray matter lesion, which was suggestive of a heterotopic nodule. In the baboons with occipital horn elongation, only one baboon had bilaterally enlarged temporal horns. In comparison, baboons with normal occipital horns demonstrated bilateral temporal horn enlargement in 11 cases, basal ganglia signal reductions in 5 baboons, and unilateral occipital cortical atrophy and cerebellar atrophy each in one case. No significant differences in age or normalized brain volumes were found among the 3 groups.

There were no significant differences in gestation between baboons with occipital horn elongation compared with colpocephaly, although data were limited to 29 baboons, and the overall gestational age at birth was not different from previously published normative data of healthy female baboons (namely 6 mo or 180 d).[8] No prenatal or perinatal developmental or postnatal abnormalities were noted in the groups with the occipital horn variants, and vision was decreased in only one baboon with occipital horn elongation. Elongation of the occipital horns was significantly associated with the female gender compared to the group with normal occipital horns (Fisher exact test, 2-tailed, $P < 0.02$). Clinical data were available for 163 (78%) baboons. A history of physical trauma, including bruising, lacerations, or

Table 1. Demographic, radiologic, and electroclinical data among 208 baboons

	Normal occipital horn (n = 155)	Elongated occipital horn (n = 23)	Colpocephaly (n = 30)
Age (y) at MRI	16 ± 6	15 ± 5	15 ± 4
Sex	97 female,[a] 58 male[a]	18 female,[a] 5 male[a]	19 female, 11 male
Normalized total cerebral volume	192 ± 4 cm^3 (n = 130, 84%)	192 ± 4 cm^3 (n = 14, 61%)	193 ± 4 cm^3 (n = 30, 100%)
Lateralization of variants	not available	7 bilateral, 9 left, 7 right	7 bilateral, 11 left, 12 right
Gestational age at birth	not available	182 ± 7 d	179 ± 7 d
Perinatal complications	not available	none	none
Clinical history	n = 106	n = 23	n = 30
Seizures	17 (16%)	4 (17%)	5 (17%)
Craniofacial trauma	29 (27%)[a]	6 (26%)	14 (47%)[a]
Seizures or craniofacial trauma	46 (43%)	6 (26%)	17 (57%)
EEG	n = 107	n = 17	n = 18
Interictal epileptic discharges	56 (52%)	9 (53%)	6 (33%)
Photosensitivity	29 (27%)	4 (24%)	4 (22%)

[a]Values are significantly (Fisher Exact Test, 2-tailed, $P < 0.05$) different.

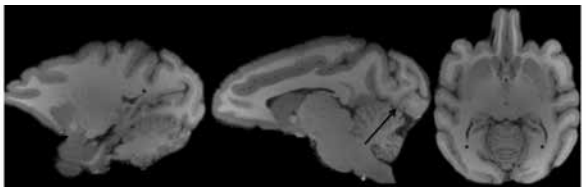

Figure 1. Normal occipital horn configuration on MRI. Two sagittal slices and an axial slice of a 3D, T1-weighted MRI study. The black arrow indicates the landmark for differentiating occipital horn elongation (mesiobasal onset of the calcarine sulcus). Black asterisks indicate the occipital horns.

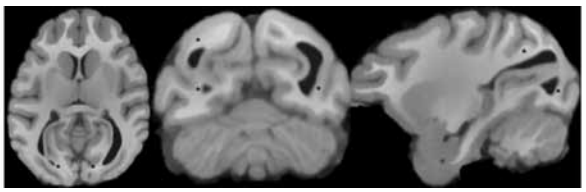

Figure 2. Enlarged occipital horns (colpocephaly) on MRI. Axial, coronal, and sagittal slices of a 3D, T1-weighted MRI study depicting elongated, eccentrically enlarged occipital horns. Black asterisks indicate the occipital horns.

mutilation, was reported in a majority of baboons, but CFT specifically was reported in 49 (24%) baboons. Compared with baboons with normal occipital horns, colpocephaly was significantly associated with CFT (Fisher exact test, 2-tailed, $P < 0.05$, and IED were more prevalent among baboons with normal (56%) or elongated occipital horns (53%) than in baboons with colpocephaly (33%), but intergroup differences were not statistically significant. No significant associations were found between elongation or colpocephaly and seizures or photosensitivity.

Discussion

This study is the first structural MRI description of variants of the occipital ventricular horns, particularly colpocephaly, in the largest captive baboon (*P. h. anubis* and its hybrids) pedigree in the world. Although ventriculomegaly has been described in pathologic studies,[6] colpocephaly affecting only the occipital horns has not been reported. No definitive causes, including congenital, perinatal, and acquired causes, or associated comorbidities were noted in the baboons with either occipital horn elongation or enlargement. At the same time, this pedigree contains a large number of baboons with genetic generalized epilepsy, presenting with witnessed seizures and CFT, which is a sensitive (but not specific) marker for seizure-related falls.[19] Compared with normal occipital or elongated occipital horns, colpocephaly was significantly associated with CFT but not with other clinical or scalp EEG features.[19,17] Baboons with a history of witnessed seizures or with neurologic disorders apparently were not referred for MRI investigation in the earlier studies,[11,15] but because CFT was not previously demonstrated to be associated with seizure activity,[17] these baboons were still referred for scanning. Therefore, if seizures are closely linked to colpocephaly, it is likely that this radiologic or pathologic finding may be more prevalent in the pedigree, and, in cases with severe neurologic impairment, the neuroimaging findings might resemble those described in humans.[2,7,9,12,14,22] In addition to the increased prevalence of CFT, the minimal overlap between unilateral colpocephaly and contralateral occipital horn elongation suggests differences in the etiology and potential clinical significance of the 2 occipital horn variants.

Colpocephaly in humans pertains to a configuration of the lateral ventricles, in which the occipital horns are enlarged compared with the frontal horns. Some studies have proposed quantitative measures, such as a 3:1 ratio of occipital to frontal horn diameter, but the same studies also have used merely qualitative measures in their classification.[5,14] Colpocephaly in humans tends to be associated with multiple radiologic and neurologic abnormalities.[9,12,14] Colpocephaly in baboons, in contrast, appears to be an isolated finding in most cases. The only clinically significant association was with CFT, which is often a marker of seizure activity. Because all of the epileptic baboons in the colony have generalized IED on scalp EEG, which are interictal markers of genetic generalized epilepsy, it is unlikely that colpocephaly is the cause of their epilepsy; instead colpocephaly may simply lower the seizure threshold compared with that in baboons with normal or elongated occipital horns. Given that closed head injuries are not a cause of colpocephaly in humans, the likelihood that

colpocephaly would be acquired due to seizure-related falls in baboons is small.[5] Because isolated colpocephaly typically is inherited in humans and is very unlikely to be acquired, it is possible that the condition similarly has a genetic origin in baboons.[3,13] Future studies could reveal a genetic link between genetic generalized epilepsy and colpocephaly in baboons.

One of the strengths of the current study was the ability to correlate the occipital horn variants with scalp EEG findings. Scalp EEG findings were used to confirm the diagnosis of epilepsy in this pedigree, and, with the exception of rare cases, the IED were generalized in distribution (even in cases of unilateral occipital horn elongation or colpocephaly).[19] According to the association with CFT, we expected IED to be increased in the colpocephalic group, but the prevalence of IED actually appeared to be decreased in that group compared with the other groups. Scalp EEG probably demonstrates a bias toward recording of generalized IED over more circumscribed, focal discharges potentially emanating from the frontocentral or parietooccipital regions, mainly because of the baboons' smaller brain volume and relatively thicker skulls compared with humans'. Indeed, intracranial EEG recordings of baboons with genetic generalized epilepsy reveals a combination of generalized and multifocal IED, with a predominance of episodes from the parietooccipital regions.[20] Although the implanted baboons in the cited study[20] did not include animals with occipital horn variants, it is possible that enlargement of the occipital horn may interfere with the generation or synchronization of generalized IED, which may be the reason for the lack of association between IED and colpocephaly. However, photosensitivity (that is, the ability to trigger seizures or IED with intermittent light stimulation) seems to be equally as prevalent in baboons normal occipital horn morphology and with occipital horn enlargement, suggesting that that occipitofugal pathways required for the expression of photoparoxysmal or photoconvulsive responses are not critically affected by colpocephaly. To better understand the interaction between colpocephaly and electroclinical phenotypes, resting-state functional MRI, ideally with simultaneous EEG recording, might help elucidate any altered connectivity of the primary visual cortices as well as the occipital nodes of the epileptic network.

One of the main weaknesses of the current study was its reliance on a retrospective analysis of veterinary records as the main source for historical and clinical data. Retrospective data are often incomplete, and the rare neurologic or behavioral assessments did not shed light on the potential clinical effects of occipital horn anomalies. As mentioned earlier, it is likely that baboons with clinically or neurologically significant deficits or severe epilepsy were not included in the larger MRI cohort, thus excluding subjects that may have conformed to human case reports of colpocephaly. In a prospective study, visual deficits might be elicited in some of the baboons with ectatic enlargement of the ventricles, extending to the occipital pole, and, in several cases, to the primary visual cortices. In addition, a prospective study would more effectively confirm an association between seizures and colpocephaly.

Another weakness of this study was that MRI assessments were limited to T1-weighted sequences, which were reviewed in 3D. T2-weighted, particularly fluid-attenuated inversion-recovery sequences, are more sensitive for the detection of cortical developmental and subcortical white matter abnormalities and might help reveal etiologic mechanisms. Furthermore, to better define the structural consequences and clinical significance of the occipital horn variants, and colpocephaly in particular, quantitative measures should be applied, such as ventricular measurements comparing occipital and frontal horn diameters with occipital horn measures; these measurement further need to be correlated with occipital lobe volume, calcarine cortical thickness, and the diameter of the corpus callosum. Finally, with in a prospective study, baboons with colpocephaly can be identified for eventual histopathologic evaluation to better define the underlying etiology.

In summary, colpocephaly was identified as a radiologic finding in a subset of pedigreed baboons. Although colpocephaly presented as an isolated phenomenon, frequently even unilaterally, in this sample, MRI evaluation of baboons with more severe neurologic impairment might have identified other brain developmental abnormalities associated with colpocephaly. Clinically, colpocephaly may increase the risk for seizures by lowering the seizure threshold. Because of the apparent lack of other radiologic or neurologic abnormalities in these baboons as well as in humans with inherited colpocephaly, the presentation of colpocephaly might, at least in part, be genetically determined. Because these baboons are pedigreed, heritability of the occipital horn anomalies needs to be evaluated. Finally, a prospective MRI study that includes baboons with congenital neurologic or behavioral disorders, the use of multiple MRI sequences, and the correlation of electroclinical and MRI findings with histopathology will determine the pathophysiology that underlies colpocephaly.

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