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Alzheimer disease-like neuropathologic changes in a geriatric baboon (*Papio hamadryas*)

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ABSTRACT

Importance: Alzheimer's disease (AD) is the most common cause of dementia in the elderly with the incidence rising exponentially after the age of 65 years. Unfortunately, effective treatments are extremely limited and definite diagnosis can only be made at autopsy. This is in part due to our limited understanding of the complex pathophysiology, including the various genetic, environmental, and metabolic contributing factors. In an effort to better understand this complex disease, researchers have employed nonhuman primates as translational models.
Case Presentation: This report aims to describe the AD-like neuropathology in the brain of a 37-year-old female baboon (*Papio hamadryas*), which at the time of her death made her the oldest hamadryas baboon at any member institution of the Association of Zoos and Aquariums. A diagnostic necropsy was performed, and the brain was evaluated for neurodegenerative disease. Frequent amyloid-β deposits were identified, consistent with what has been described in other geriatric nonhuman primates. Phospho-tau pathology, including neurofibrillary tangles, a feature not well-described in other primate models, was also abundant.
Conclusions and Relevance: Our results suggest that more detailed, prospective, longitudinal studies are warranted utilizing this particular species to see if they represent a viable model for human brain aging.

Keywords: Hamadryas; Alzheimer disease; Aβ plaque; neurofibrillary tangles; glial tau; neuropathology

INTRODUCTION

Nonhuman primates (NHPs) are important translational models of human disease due to their highly conserved genomic sequence; humanoid anatomy; physiology and molecular pathways; susceptibility to similar infectious, metabolic, and other diseases; and similarities

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Conflict of Interest

The authors declare no conflicts of interest.

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in aging. Amyloid-β (Aβ) accumulation with age is typical in the primate brain, as are functional decrements in cognition and mobility [1-5]. While several NHPs develop Aβ deposits, neurofibrillary tangles (NFTs), important features of Alzheimer's disease (AD) that are associated with neuronal death, are either sparse of absent in most. Few studies have investigated neurodegenerative pathologies in baboons. Herein, we present the case of a geriatric 37-year-old female hamadryas baboon (*Papio hamadryas*) diagnosed with diffuse cerebral Aβ plaques, frequent Aβ angiopathy, and multifocal brain neurofibrillary tangles and glial tauopathy. These intriguing findings confirm the previously documented similarities between brain aging in humans and nonhuman primates and also raises the consideration for further studies to elucidate the viability of hamadryas baboons as a model for early AD-like neuropathology.

CASE PRESENTATION

A captive-born (February 11, 1983) female hamadryas baboon was received by the Phoenix Zoo in 1989 and subsequently euthanized on October 7, 2020 due to advanced age and several comorbidities. At the time of euthanasia, this spayed female was receiving non-steroidal anti-inflammatory drugs (NSAIDs) for vertebral spondylosis and kyphosis and multijoint osteoarthrosis. She had a right-sided cataract with posterior lens luxation, polypoid oral growths, and dental disease with attrition. She was treated for thoracic puncture and secondary bacterial pneumonia in 2013. In the last years of her life, keepers recorded a declining quality of life, with brief episodes of abnormal behavior (similar to dementia/brief forgetfulness), lethargy, progressive decreases in appetite, and fluctuating weight with chronic poor body condition. For euthanasia, the animal was anesthetized with ketamine/medetomidine/midazolam via blow dart in the right pelvic limb. Numerous boluses of intravascular euthasol were administered over the course of 30 min until there was cessation of cardiac activity. Subsequently, a diagnostic postmortem examination was performed by a board-certified veterinary anatomic pathologist.

External examination showed moderate sarcopenia, multifocal alopecia/hypotrichosis, periorbital erythema, and two oral polypoid nodules. Both ears had cauliflower deformities (conspecific trauma) on the dorsal pinnas. Internal examination demonstrated various aging-related pathologies in various organ systems. The vertebral column had multifocal bridging spondylosis, which was most severe in the distal lumbar and proximal-to-mid thoracic vertebrae, and vertebral ankylosis of the cervical and thoracic segments. The humeri and femora joints had degenerative changes, including fibrillation and osteophytes. Focal fibrous adhesions were between the left caudal lung lobe and the left dorsolateral parietal pleura at ribs 11 to 13. The left adrenal gland had a well-demarcated medullary tumor. The left thyroid gland lobe had multifocal tumors. The heart demonstrated mild endocardiosis on the tricuspid and semilunar valves. The kidneys and the pancreas had numerous multifocal cysts that were up to 2 cm in diameter in the kidney and involved 50% of the pancreatic parenchyma. Grossly, the brain was unremarkable other than areas of dural ossification; no significant atrophy or edema was appreciated.

Microscopic examination of the internal organs showed various age-related pathologies. The kidneys showed significant renal interstitial fibrosis, chronic inflammation, glomerular dropout, and tubular atrophy. The sampled pancreas showed numerous simple cysts containing macrophages and eosinophilic material. The pedunculated oral masses were

composed primarily of dense fibrous tissue covered with squamous epithelium. The liver demonstrated sinusoidal aggregates of mononuclear cells, most consistent with extramedullary hematopoiesis. The heart had scattered interstitial fibrosis, variable cardiomyocyte karyomegaly, and multifocal intramyocardial arteries with mural sclerosis. The left adrenal gland had a benign medullary pheochromocytoma. The left thyroid gland lobe had multiple benign adenomas.

Hematoxylin and eosin stained sections of the brain showed overall mild neuronal loss and gliosis, frequent neuronal lipofuscin accumulation, and perivascular pigment-laden macrophages and mineral deposits, which were especially prominent in the thalamus. Scattered foci of meningothelial hyperplasia were noted in the arachnoid layer of the meninges. Several congophilic parenchymal deposits were identified scattered throughout the cerebrum and expanding arteriole walls. Formalin-fixed paraffin-embedded tissue blocks (n = 6) from the brain were sent to a board-certified neuropathologist for subsequent evaluation. The sections evaluated included frontal and temporal neocortex, basal ganglia, hypothalamus, brainstem, and cerebellum. Unstained slides cut from these blocks were stained with a modified Bielschowsky silver stain as well as immunohistochemical stains for Aβ (6e10), phospho-tau (AT8), and phospho-TDP43 (ID3). There were parenchymal Aβ deposits in the neocortex, limbic regions, and basal ganglia. Most of the plaques were diffuse/primitive; however, there were some that were neuritic (**Fig. 1**). Numerous leptomeningeal and intraparenchymal arterioles and arteries demonstrated amyloid deposition, consistent with amyloid angiopathy. In terms of tau pathology, there were readily identified cortical tangles (**Figs. 1** and **2**). Glial tau was identified in numerous areas within the cortex, white matter, subpial and subventricular regions; it generally appeared astrocytic in morphology. In some regions it was more pronounced including the fornix and middle cerebellar peduncle (**Fig. 3**). Scattered NFTs were within the basal ganglia and there was extensive brainstem tau pathology, which was a mixture of NFTs and glial tau pathology. Silver staining demonstrated moderate-to-focally frequent diffuse plaques and occasional neuritic plaques. Immunostains for phospho-TDP43, an abnormal protein frequently seen in the limbic structures of humans of advanced age and commonly colocalized with phospho-tau, were negative.

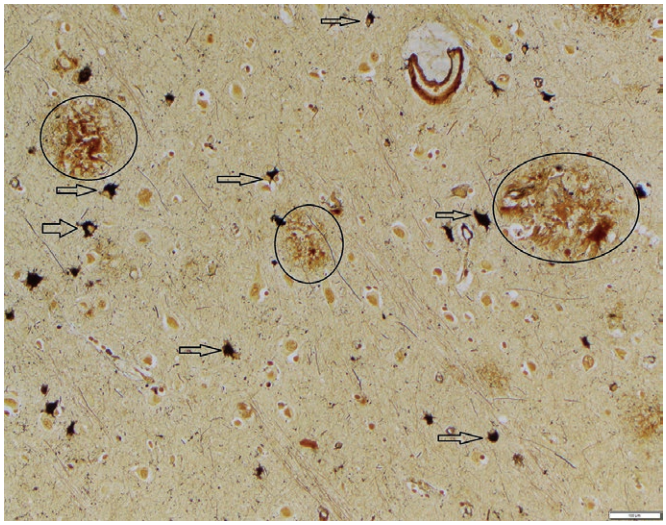

Fig. 1. Bielschowsky silver-stained section of amygdala. Representative mature neuritic plaques are circled; representative neurofibrillary tangles are pointed out with arrows. Scale bar: 100 μm.

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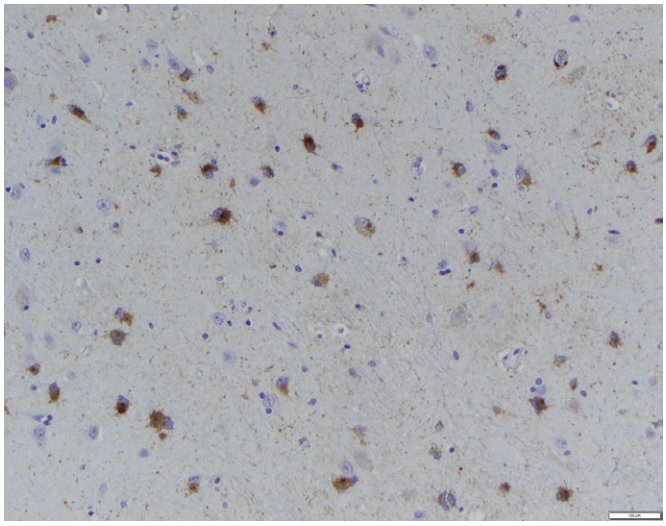

Fig. 2. Inferior temporal lobe stained with AT8 (phospho-tau). Numerous neuronal cytoplasmic inclusions representing neurofibrillary tangles are demonstrated with positive immunoreactivity. Scale bar: 100 μm.

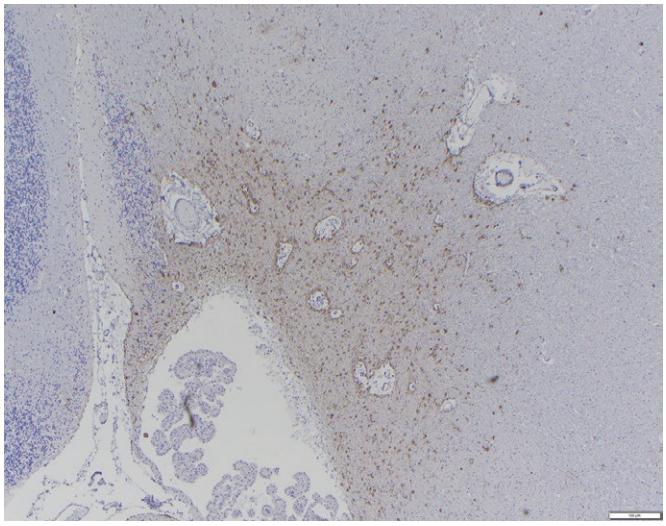

Fig. 3. Inferior cerebellar peduncle stained with AT8 (phospho-tau). A discrete area is shown in the subventricular region with numerous immunoreactive astrocytic profiles. Scale bar: 100 μm.

DISCUSSION

The neuropathologic findings in this 37-year-old female hamadryas baboon showed Aβ plaques and neurofibrillary tangles throughout the brain. To our knowledge, this is the oldest baboon to have a formal neurodegenerative workup presently in the literature. This pattern of neurodegeneration is remarkably similar to advanced human AD and further advocates for the use of nonhuman primates as useful animal models for human aging. Several large-scale, cross-sectional studies have characterized the degree and location of amyloid plaque deposition in aged old world monkeys, including rhesus and cynomolgus macaques [6-8]. Latimer et al. [3] demonstrated Aβ plaque pathology in a well-characterized, deeply-phenotyped cohort of aged vervets. Interestingly, while some degree of paired helical filament tau immunoreactivity was observed in the vervet model, neurofibrillary tangles were rare. In fact, some studies have suggested that nonhuman primates do not develop the

widespread, mature neurofibrillary tangles of AD, limiting the extent of the degree of utility NHPs can act as a comparative model for human AD pathology. Several larger scale studies have shown than tau pathology is either sparse or absent in other nonhuman primates including chimpanzees [9], orangutans [10], squirrel monkeys [11], and rhesus monkeys [8,12,13]. Notwithstanding, there are occasional reports in the literature that do describe various degrees of spontaneous phospho-tau pathology, including dystrophic neurites, pre-tangles, and tangles in various species; however, most of these are case reports or small case series and the described tau pathology is usually sparse and limited to certain brain regions. There are few detailed studies of aged baboon brain in which neurodegenerative pathologies have been assessed. In contrast to studies of other NHPs, the tau pathology in this case was a prominent feature, in addition to Aβ plaque deposition, potentially mirroring human AD pathology more so than many other NHP species that have been studied. More than 20 years ago, Schultz et al. [14] demonstrated that abnormal tau development featured prominently as a function of age in a cohort of 50 baboons, in addition to plaque deposits and described NFTs in a 26-year-old and a 30-year-old baboon. Additionally, this case showed that while tau pathology was not entirely homologous to human brains in terms of location and pattern of deposition, the baboon model did show an important characteristic of human tauopathy: the phenomenon of selective vulnerability [14,15]. As such, baboons may be a potential model for age-related tauopathies, including AD. There has been little follow-up study since the Schultz et al.'s study in the past two decades, leaving the potential to further utilize these animals as models of human brain aging momentarily untapped. The ultimate value of this potential model depends on the outcome of additional studies of other baboon cohorts with further characterization at the ultrastructural, genetic, behavior, and neuropathologic levels. Prospective longitudinal studies are needed where cohorts of hamadryas baboons are extensively characterized, including brain imaging, cognitive and physical testing, AD fluid biomarker analyses, and ultimately, necropsy. These types of studies will help investigate relationships with behavior and AD-like neuropathology in aging members of this species, which will ultimately help evaluate their utility as a model of human brain aging. Limitations of this case report include the relative lack of antemortem data regarding cognitive status or physical function on this animal. Additionally, the effects of longstanding NSAID on the development of neuropathology in animal are unknown.

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