

## Original Research

# Cerebral Amyloid Angiopathy in an Aged Sooty Mangabey (*Cercocebus atys*)

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A 26-y-old male sooty mangabey (*Cercocebus atys*) was found at necropsy to have a moderate degree of cerebral amyloid  $\beta$  (A $\beta$ ) angiopathy in superficial and parenchymal blood vessels of the brain. Senile (A $\beta$ ) plaques were absent, as were neurofibrillary tangles and other signs of neurodegeneration. Affected blood vessels were arterial, capillary, and, less frequently, venous in nature. Histologically, the A $\beta$ 40 isoform was more prevalent than was A $\beta$ 42. As in humans but unlike in squirrel monkeys, the density of lesions in this mangabey increased along a rostral-to-caudal gradient. Therefore mangabeys appear to conform to the general tendency of nonhuman primates by developing cerebral A $\beta$  angiopathy in the absence of other indices of Alzheimer-type neuropathology.

**Abbreviations:** A $\beta$ , amyloid  $\beta$ ; CAA, cerebral amyloid angiopathy; GFAP, glial fibrillary acidic protein; Iba 1, microglia-expressed calcium-binding protein.

One of the most common microvasculopathies in the aging human brain is cerebral amyloid angiopathy (CAA), a disorder in which various aggregation-prone proteins accumulate in the walls of parenchymal and meningeal blood vessels.<sup>4,9</sup> Most often, the amyloidogenic protein is amyloid  $\beta$  (A $\beta$ ), a cleavage product of the A $\beta$  precursor protein and the essential component of senile plaques in Alzheimer disease.<sup>15,43</sup> In the brain vasculature, the basal lamina is a primary site of A $\beta$  deposition.<sup>25,35</sup> Severely affected arterioles show a loss of smooth muscle cells in the tunica media, a weakening of the vascular wall and a propensity to rupture.<sup>3,34</sup> CAA thus increases the risk of intracerebral bleeding and may be responsible for as much as 20% of nontraumatic hemorrhagic stroke in elderly humans.<sup>15,18,35</sup> CAA is present to various degrees in virtually all cases of Alzheimer disease,<sup>15,16,21</sup> but it also occurs independently.<sup>24</sup> As is the case for other proteopathies, advancing age is a significant risk factor for CAA.<sup>8,19</sup>

In humans, CAA most often affects the arteries and arterioles of the brain, particularly those in the leptomeninges and cortex.<sup>2,25</sup> CAA is less frequent in veins and capillaries,<sup>25</sup> but capillary CAA can be prominent in some cases.<sup>26,33</sup> The occipital lobe is affected most often<sup>1,32,37</sup> but all cortical regions are vulnerable. CAA is variable in occurrence in the cerebellum and uncommon in deep telencephalic gray structures, white matter, and the brainstem,<sup>36</sup> except in severely affected cases.<sup>32</sup>

Although its specific role in the pathogenesis of Alzheimer disease remains uncertain, there is now strong evidence that dementia is exacerbated by CAA.<sup>14</sup> Furthermore, CAA is independently linked to cognitive decline both in rare familial cases<sup>20</sup> and in older humans with idiopathic CAA.<sup>2,20</sup> Despite the prevalence

of cerebrovascular amyloidosis in elderly humans, surprisingly little is known about its effect on the brain, in part because of a paucity of natural animal models that closely mimic the human disorder.<sup>17,38</sup>

Nonhuman primates offer a unique opportunity to view CAA from a comparative perspective, given that they normally generate human-sequence A $\beta$  and develop severe cerebral A $\beta$  amyloidosis in old age, generally in the absence of other changes that characterize Alzheimer disease.<sup>12</sup> Nonhuman primates have the additional advantage that, compared with humans, their relatively small brains enable exhaustive regional analysis of microscopic lesions, something that, for practical reasons, is seldom undertaken in the human brain. Here we present the first investigation of age-associated brain changes in sooty mangabeys, focusing in particular on A $\beta$  deposition and related abnormalities. One of the 2 aged mangabeys analyzed had A $\beta$  deposition in the brain which was almost exclusively in the form of CAA. Remarkably, the vessel types affected and the regional distribution of CAA more closely resembled the pattern seen in humans than that in other nonhuman primates, particularly squirrel monkeys.<sup>6</sup> Differences and similarities in CAA among primate species could provide fresh insights into the development of cerebral amyloidosis and related disorders in older humans.

## Materials and Methods

**Subjects.** Three sooty mangabeys (*Cercocebus atys*) were studied: a 32-y-old female, a 26-y-old male, and a 19-y-old female. All animals were from the colony of the Yerkes National Primate Research Center, and their birthdates were known. The maximal lifespan of sooty mangabeys is unknown, but we are aware of no reports of animals of known age that have lived longer than 32 y. According to the presence of age-associated changes and based on our knowledge of the life history of other Old World simians, particularly macaques,<sup>42</sup> we conclude that the 26-y-old and

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32-y-old mangabeys can be considered aged, and the 19-y old animal is middle-aged. Given the paucity of information on lifespan in this species, the maximal potential lifespan of mangabeys may be somewhat greater than 32 y.

All 3 animals were diabetic at the time of euthanasia. Due to the difficulty treating diabetes in a colony setting, the decision was made to euthanize these mangabeys. Necropsy revealed marked islet amyloid polypeptide (amylin) amyloidosis in the pancreas of all subjects. In addition to diabetes, the following clinical and pathologic findings were noted. The 32-y-old female was diagnosed with severe age-related kyphosis and acute onset of hindlimb lameness; necropsy revealed the presence of advanced endometrial carcinoma. The 26-y-old vasectomized male was found to have age-related glomerulosclerosis, chronic fibrosing cardiomyopathy, and chronic lymphoplasmacytic colitis. The 19-y old female was diagnosed with endometriosis, lethargy, persistent inappetence, firm abdomen and decreased hematocrit; at necropsy, severe hemoperitoneum and endometriosis were evident.

The mangabeys were euthanized via sodium pentobarbital overdose (2.22 mg/kg IV), and tissues were collected at necropsy, in accordance with federal and institutional guidelines for the humane care and use of experimental animals. The Yerkes Center is fully accredited by AAALAC.

**Histochemistry.** The brains were immersion-fixed in 4% paraformaldehyde for a minimum of 2 wk. Subsequently, they were coronally slabbed, dehydrated, embedded in paraffin wax, and sectioned at 10  $\mu$ m thickness. Tissues were deparaffinized and rehydrated by heating at 60 °C for 45 min followed by immersion in xylene and a graded (descending) series of ethanol to water. Antigen retrieval for A $\beta$  involved treating in 100% formic acid for 10 min, and that for Iba1 and glial fibrillary acidic protein (GFAP) involved heating sections in sodium citrate buffer at 100°C for 30 min.

Coronally sliced tissue sections were matched for the 3 mangabeys and included the following regions: anterior frontal lobe; midfrontal and anterior temporal lobes; posterior frontal, mid-temporal, and anterior parietal lobes; occipital lobe; and cerebellum and brainstem. Sections were immunostained with the following antibodies: clone 6E10 (1:10,000) mouse monoclonal antibody (Covance, Princeton, NJ) raised against residues 1 to 16 of the A $\beta$  peptide; rabbit polyclonal antibodies R163 and R165 (both at 1:1000) to the C-terminal amino acids of A $\beta$ 40 and A $\beta$ 42, respectively; mouse monoclonal antibody CP13 (1:5000) to phosphoserine 202 of Tau (courtesy of Dr Peter Davies, Albert Einstein College of Medicine, Bronx, NY); mouse monoclonal antibody to Iba1 (1:1000; Wako Chemicals USA, Richmond, VA), a calcium-binding protein that is upregulated in activated microglia; and a mouse monoclonal antibody to GFAP (1:1000; Dako, Carpinteria, CA; see reference 27 for details regarding antibodies). GFAP- and Iba1-stained sections were counterstained with thioflavin S to assess the relationship between activated glial cells and thioflavin-positive amyloid deposits.

Briefly, immunohistochemical staining was performed as follows: sections were first incubated in 3% H<sub>2</sub>O<sub>2</sub> and methanol for 10 min and then blocked with 2% normal serum and 0.2% Tween in 1 $\times$  PBS for 90 min. Subsequently the tissue was incubated in primary antibodies in a blocking solution (2% normal serum and 0.2% Tween in 1 $\times$  PBS) overnight at 4 °C. Finally, antigen-antibody complexes were enhanced with an avidin-biotin-peroxidase system (Vectastain Elite ABC kit, Vector Laboratories, Burlingame, CA) and visualized by using the chromogen diaminobenzidine.

Control sections were run simultaneously, including positive controls (Alzheimer patient brain samples, previously confirmed) and negative controls (omission of the primary antibody).

Additional sections were stained with standard histochemical markers, including the Campbell-Switzer silver stain for Alzheimer-associated lesions, Luxol fast blue for myelin, Perls Prussian blue stain for iron, and hematoxylin and eosin.

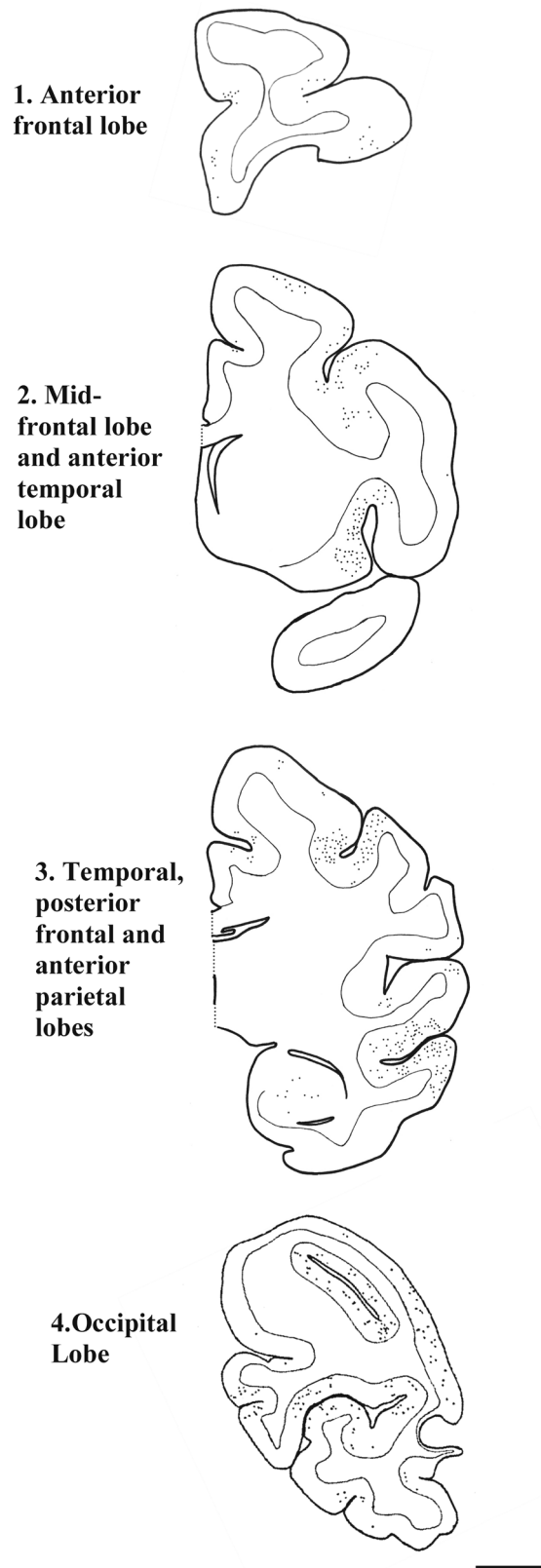
**Analysis.** Sections were analyzed for the presence of A $\beta$  deposits at all coronal levels in the 3 mangabeys. Only one mangabey, the 26-y-old male, showed A $\beta$  deposits, so the lesions in this animal were mapped in representative sections, one for each region (Figure 1) by using a microscope-based mapping system equipped with ImageScope software (Aperio, Vista, CA). All immunoreactive profiles were counted, with the caveat that separate profiles in a given section may represent segments of a single vessel. Vascular lesions were characterized further in regard to the size and location of the vessel. Specifically, superficial blood vessels were defined as any vessels lying outside of the cortex, and intracortical blood vessels were defined as any blood vessels in cortical layers 1 to 6 (that is, between the cortical surface and the white matter; no positive vessels were found in white matter). Capillaries were defined as blood vessels with diameters of approximately 10  $\mu$ m or less. We also searched all sections for parenchymal A $\beta$  in senile plaques but found none. To estimate the relative numbers of A $\beta$ 40- and A $\beta$ 42-positive vessels, a subset of adjacent sections from the 26-y-old monkey were immunostained with antibodies R163 and R165 to A $\beta$ 40 and A $\beta$ 42, respectively.

The stereologic point-counting method<sup>22</sup> was used to determine the total area of the neocortex in each mapped section, which then served as the 2-dimensional reference space for calculating A $\beta$  lesion density. Briefly, an image of the entire tissue section was captured at low magnification and the cortical areas were outlined using ImageScope software. A symmetrical grid of + symbols was superimposed on an image of the tissue section. Each + represented a micrometer-calibrated square of known area; symbols overlying the area of interest were counted manually to calculate the total area of the cortex in that section.<sup>22</sup> The density of A $\beta$  lesions was determined by counting the number of lesions per unit area (mm<sup>2</sup>) of interest.

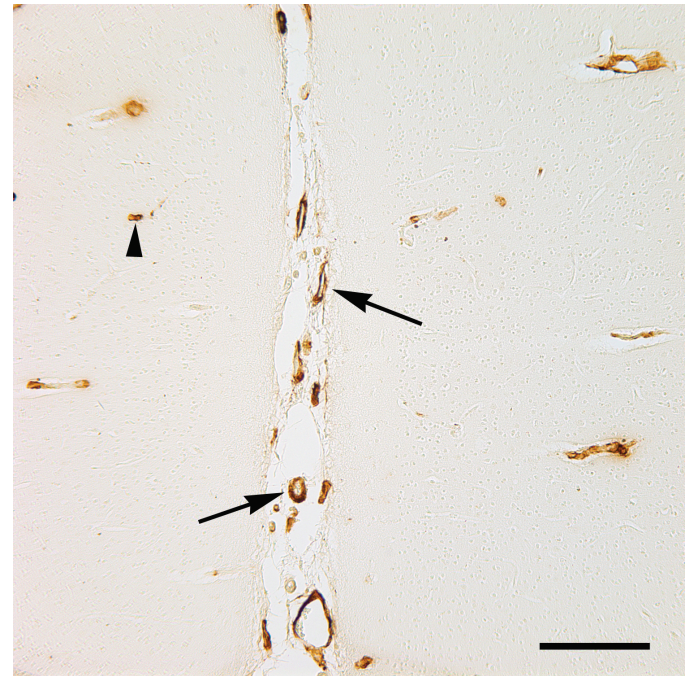
## Results

**A $\beta$  deposition in a male mangabey.** Of the 3 animals analyzed, only the 26-y-old male mangabey displayed  $\beta$ -amyloid deposition, and in the regions sampled the deposits occurred exclusively within the walls of cerebral blood vessels. Senile plaques and tauopathy were not observed in any mangabey, either by immunostaining or Campbell-Switzer silver staining. Because the brains of the 19- and 32-y-old mangabeys showed little frank pathology and no A $\beta$  deposition, our analysis focused on the affected 26-y-old mangabey.

**Vessel types affected by  $\beta$ -amyloid deposition.** All A $\beta$  deposits in the 26-y-old mangabey were vascular in nature, affecting both leptomeningeal and intracortical blood vessels. The majority of A $\beta$ -positive superficial vessels were arteries or arterioles, and amyloidotic blood vessels within the cortex were predominantly small arterioles or capillaries (Figures 2 and 3). Given the vessels' size and the thickness of the vascular walls, it was apparent that a small number of veins were affected also. At more rostral levels, intracortical vessel profiles clearly outnumbered leptomeningeal vessels, but in the occipital lobe the relative amounts of intracortical and leptomeningeal CAA were similar (Table 1). Staining of



**Figure 1.** Topographic distribution of vascular A $\beta$  deposits (dots) in a 26-y-old sooty mangabey. The brainstem segments analyzed were devoid of A $\beta$  immunoreactivity and are not pictured. Antibody, antiA $\beta$  clone 6E10; bar, 5 mm.



**Figure 2.** Cerebral A $\beta$  angiopathy in the occipital neocortex of a 26-y-old mangabey. The arrows indicate 2 large superficial vessels in a sulcus, and the arrowhead marks a small parenchymal capillary. Antibody, antiA $\beta$  clone 6E10; bar, 200  $\mu$ m.

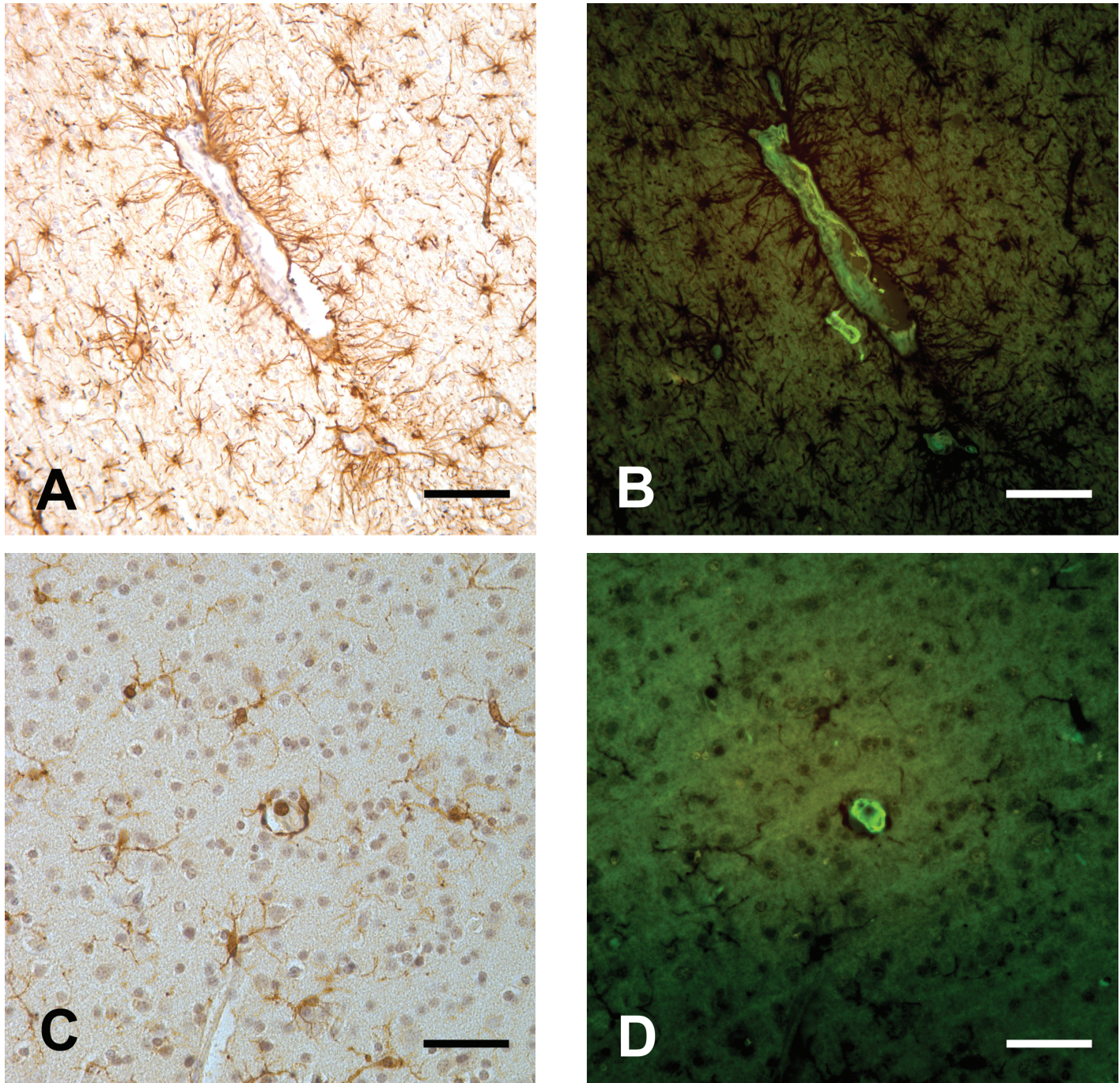
adjacent sections for A $\beta$ 40 and A $\beta$ 42 (the 2 main isoforms of A $\beta$ ) indicated that most CAA was immunopositive for A $\beta$ 40, whereas A $\beta$ 42 immunoreactivity was less frequent, as has been reported for other primate species.<sup>7</sup>

**Topographic distribution of CAA.** CAA in the mangabey was distributed in a focal, patchy pattern (Figure 1), with many lesions clustering around various cortical sulci (Figures 1 and 2). The overall density of CAA exhibited an increasing rostral-caudal gradient, with the highest density of CAA in the cortex and leptomeninges of the occipital lobe (Tables 1 and 2). Some CAA was present in the amygdala, but little was seen in the hippocampal formation, and none in the white matter, basal ganglia, diencephalon, cerebellum, or brainstem.

**Other changes in the brain.** Immunostaining for astrocytes and microglia revealed abundant activated glial cells in close proximity to thioflavin-positive vessels, an indicator of a focal inflammatory response (Figure 3). Perls Prussian blue staining revealed a small amount of superficial and intracortical hemosiderin. Luxol fast blue staining showed no obvious abnormalities in myelin.

## Discussion

We report the case of an aged male sooty mangabey with cerebral  $\beta$ -amyloid angiopathy that was distributed irregularly throughout many regions of the neocortex. Vascular  $\beta$  amyloid is common in other nonhuman primate species,<sup>12,23</sup> but there were 3 unusual aspects of cerebral A $\beta$  deposition in the mangabey. First, we did not detect any senile plaques in the sections that we examined. In squirrel monkeys, which typically develop a preponderance of CAA, senile plaques do occur,<sup>6,40,41</sup> and CAA and plaques also coexist in other primate species.<sup>12,23,39</sup> It therefore is possible that senile plaques would be present in more severely affected



**Figure 3.** (A) Astrocytes associated with a thioflavin-positive blood vessel. GFAP immunostain; thioflavin S and hematoxylin counterstain. (B) This image shows the same section as in panel A, but thioflavin S is visualized under fluorescence illumination. (C) Microglial cells near a thioflavin-positive blood vessel. Iba1 immunostain; thioflavin S and hematoxylin counterstain. (D) This image shows the same section as in panel D, but thioflavin S is visualized under fluorescence illumination. Bar, 100  $\mu$ m (A, B), 50  $\mu$ m (C, D).

mangabeys. Second, whereas in squirrel monkeys there is a clear rostral predominance of CAA,<sup>6</sup> the sooty mangabey had more CAA in the occipital lobe, a pattern resembling stage 1 CAA in humans.<sup>32</sup> Finally, compared with squirrel monkeys, the mangabey showed a greater proportion of CAA in larger vessels, often superficial arteries and arterioles. This pattern, in conjunction with the relatively modest overall amount of CAA, is again reminiscent of the earliest stages of human CAA.<sup>32</sup>

It is not surprising that we failed to detect  $\beta$ -amyloid deposition in the 19-y-old mangabey, given that rhesus monkeys, another Old World species, only begin to show A $\beta$  deposits in their early 20s (although, as in all nonhuman primates, interindividual variation is high).<sup>12</sup> However, contrary to expectation, the 32-y-old female mangabey was devoid of A $\beta$  deposition of any kind. The reasons for this discrepancy are unknown at this time. Perhaps A $\beta$  deposition in mangabeys is influenced by their sex, although

**Table 1.** Overall density (no./mm<sup>2</sup>) of vascular A $\beta$  deposits in the cortex at 4 coronal brain levels of a 26-y-old mangabey

Cortical region	Superficial	Intracortical	Total
Anterior frontal	0.22	0.67	0.59
Anterior—mid	0.56	0.94	1.5
Posterior—mid	0.69	0.84	1.64
Occipital	1.26	1.17	2.37

See Figure 1 for a description of the cortical regions.

**Table 2.** Density (no./mm<sup>2</sup>) of A $\beta$ -immunoreactive capillaries and larger vessels in the cortex at 4 coronal brain levels of a 26-y-old mangabey

Cortical region	Affected capillaries	Affected larger vessels
Anterior frontal	0.86	0.03
Anterior—mid	0.71	0.37
Posterior—mid	1.04	0.60
Occipital	1.38	1.04

See Figure 1 for a description of the cortical regions.

it is interesting to note that A $\beta$  deposition is more aggressive in female mice that bear a transgene for the human A $\beta$ -precursor protein than in their male counterparts.<sup>5</sup> The issue of sex-associated differences in the pathogenesis of A $\beta$  deposition deserves greater attention in all primate species.

Several distinct isoforms of A $\beta$  have been observed in which modifications occur at the C and N termini.<sup>44</sup> The most common isoforms vary in length due to differential cleavage at the C terminus of A $\beta$  and accordingly are referred to as A $\beta$ 40 (40 amino acids long) and A $\beta$ 42. Interestingly, much more A $\beta$ 40 than A $\beta$ 42 is produced in the brain, but A $\beta$ 42 has a stronger tendency to aggregate and appears to be the dominant component of extracellular plaques.<sup>11,29</sup> In contrast, A $\beta$ 40 generally predominates in CAA in humans.<sup>4</sup> Although the A $\beta$  of nonhuman primates is similar in amino acid sequence to that of humans, the A $\beta$ 40 isoform is relatively more abundant in the aged simian brain.<sup>7,28</sup> Both isoforms of the A $\beta$  peptide, A $\beta$ 40 and A $\beta$ 42, were present in the affected vasculature of the mangabey we present; as in other primates (including humans), A $\beta$ 40 was detected more frequently within the CAA. This finding—that both A $\beta$ 40 and CAA are more common in nonhuman primates—suggests that the ratio of A $\beta$ 40:A $\beta$ 42 may influence the pathobiology of the peptide with regard to the risk for both CAA and Alzheimer disease. As in nearly all other nonhuman primates examined (with the exception of a single chimpanzee),<sup>27</sup> none of the mangabeys that we examined showed evidence of human-like neurofibrillary tangles.

An intriguing feature of A $\beta$ -amyloidosis in the simian brain is that different species have different patterns of A $\beta$  deposition, despite the fact that all primates studied to date have a human-like A $\beta$  sequence.<sup>12,39</sup> Furthermore, A $\beta$  aggregation plays a fundamental role in the development of Alzheimer disease in humans,<sup>11,13,30</sup> but no nonhuman species has yet been shown to develop the full clinicopathological phenotype that defines Alzheimer disease.<sup>12,17</sup> Even so, CAA can exacerbate cognitive decline in the elderly.<sup>2,10,25,32</sup> Comparative analysis of the factors that govern the accumulation of A $\beta$  in the primate brain could yield new insights both into cerebrovascular A $\beta$  amyloidosis and into the uniquely human vulnerability to Alzheimer disease.

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