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Commentary: is Alzheimer's disease uniquely human?

Caleb E. Finch^{a,*} and Steven N. Austad^b

Caleb E. Finch: cefinch@usc.edu

^aDavis School of Gerontology and Department of Biological Sciences, University of Southern California, Los Angeles, CA, USA

^bDepartment of Biology, University of Alabama at Birmingham, Birmingham, AL, USA

Abstract

That Alzheimer's disease (AD) might be a human-specific disease was hypothesized by Rapoport in 1989. Apes and humans share an identical amyloid beta (A β) peptide amino acid sequence and accumulate considerable A β deposits after age 40 years, an age when amyloid plaques are uncommon in humans. Despite their early A β buildup, ape brains have not shown evidence dystrophic neurites near plaques. Aging great ape brains also have few neurofibrillary tangles, with one exception of 1 obese chimpanzee euthanized after a stroke who displayed abundant neurofibrillary tangles, but without the typical AD distribution. We discuss the need for more exacting evaluation of neuron density with age, and note husbandry issues that may allow great apes to live to greater ages. We remain reserved about expectations for fully developed AD-like pathology in the great apes of advanced ages and cautiously support Rapoport's hypothesis.

Keywords

Alzheimer's disease; Aging; Chimpanzee; Gorilla; Obesity; Life span

Great apes, although the longest lived primates and our closest relatives, are the least documented for brain aging. As early as 1989, Rapoport hypothesized that Alzheimer's disease (AD) was phylogenetically novel in humans (Rapoport, 1989; Rapoport and Nelson, 2011). Fewer than 50 brains of elderly captives have been studied in histopathologic detail (Finch and Austad, 2012; Gearing et al., 1997, 1996; Hof et al., 2002; Rosen et al., 2008; Selkoe et al., 1987), but no brains of wild apes have been brought to light. Of the classic plaque and tangle markers for AD in captive apes, some amyloid beta (A β) was present in cerebral vessels and as diffuse deposits; however, neurofibrillary tangles (NFTs) were few, giving little evidence of tauopathy. The consensus of these reports, based mainly on chimpanzees, is that brain aging was very mild in great apes at ages after 40 years that are demographically equivalent to human ages of 80–90 years in economically developed countries (Fig. 1).

These findings on the great apes seem anomalous because extensive studies of several monkey species showed extensive A β deposits (lemur, marmoset, and macaque) (reviewed in Hof et al., 2002; Finch and Austad, 2012; Morrison and Baxter, 2012); aging baboons even show hyperphosphorylated tau (Schultz et al., 2000). Moreover, the amino acid sequences of both the amyloid precursor protein and the tau protein are identical in humans and chimpanzees. But then in 2008, the field was startled by a case report of an elderly chimpanzee.

In the *Journal of Comparative Neurology*, Rebecca Rosen et al. (2008) described a 41-year-old female chimpanzee from the Yerkes Primate Center that was euthanized after incurring a left hemisphere stroke. Unexpectedly, this brain had abundant NFTs with classic tau-immunoreactive paired helical filaments, as exactly characterized with current immunoreagents and by electron microscopy. A set of normal control chimpanzee brains aged 41–56 years had “little abnormal tau immunoreactivity.” A β and NFTs were most abundant in prefrontal cortex, with least in the occipital cortex, whereas the hippocampus had much fewer plaques and NFTs than cerebral cortex. There was no obvious relation of the amyloid or tauopathy to the stroke, which mainly affected temporal, parietal, and occipital lobes. DNA sequencing did not detect mutations associated with human tauopathies. The medical history included a normal magnetic resonance imaging brain scan 2 years before the stroke but also showed long standing hypercholesterolemia and moderate obesity. Further, stroke cases have not been studied for amyloid and tauopathies. A survey of primate centers and zoos participating in the Chimpanzee Species Survival Plan identified at least 10 more stroke cases (Jean et al., 2012) but did not define the frequency of stroke incidence.

Gorillas have recently rejoined this discussion. Perez et al. (2013) reported, on brains from the Great Ape Aging Project, which provides zoo specimens that died “of natural causes,” again in the *Journal of Comparative Neurology*. All 5 gorillas aged 42–55 years (the oldest gorilla known) had definitive A β ₄₂ containing plaques in multiple regions of the cerebral cortex, as well as cerebrovascular amyloid. Plaque density was progressive with aging: absent below age 25 years, very modest at 32 years, and increasingly prevalent at 42–55 years, with the oldest showing the most advanced pathology. Thioflavin S and other markers of fibrillar amyloids were more prevalent in the cerebrovasculature than in plaques, consistent with aging chimpanzees (Rosen et al., 2008). All plaques were immunoreactive for oligomeric A β . Tau-like neuronal lesions (SMI-34 and Alz50 positive) were scattered in neocortex and hippocampus.

These findings may be compared with those in the Braak's benchmark studies of “random” human brain autopsies (Braak and Braak, 1997), which reported that 90% of brains younger than 50 years were “devoid of amyloid.” Thus, the A β buildup in the brains of all 5 gorillas 42 years suggests an earlier onset than in humans, but still below full-blown AD pathology.

We note a conspicuous gap: Neither report commented on neuron death or neuron loss nor used the broad term neurodegeneration to describe their findings. Perez et al. (2013) noted “...the normal appearing Alz50-ir neurons in close association with Abeta plaques... (and) ...absence of dystrophic neurites surrounding plaques.” Notably, neither report measured

synapse density or synaptic markers. We appreciate their caution in skirting the crucial issue: can age-related amyloid and NFT arise without neurodegeneration including the neuron death that is so dramatic even in early stages of AD? Abeta plaques in human AD brains show focal synaptic deficits, dystrophic dendrites, and aberrant sprouting near (Grutzendler et al., 2007; Guevara et al., 2004; Masliah et al., 1991, 2003). Thus, the apparently normality of neurons and dendrites near plaques in aging gorilla brains seems to depart from a body of evidence on human AD brains. We briefly note that transgenic rodent models of AD with familial dominant mutations also show focal dendritic dystrophies with emergent A β deposits (Kirkwood et al., 2013; Spires-Jones et al., 2007) but without notable tauopathy or obvious neuron death. These partial AD phenotypes arise in relatively young hosts that do not represent later aging processes of normative genotypes.

The great ape histochemical studies, while carefully done, have not yielded conclusions about neuron loss. We need exacting stereological analysis of aging great ape brains for neuronal and dendritic density in relation to A β deposits. We may anticipate species differences, as shown by optical fractionator stereology, whereas entorhinal cortex neurons of macaques were stable across the life span (Gazzaley et al., 1997), aging dogs incur 30% neuron loss (Siwak-Tapp et al., 2008). Moreover, the macaques showed substantial individual brain-to-brain variation in neuron density. As noted to us by a reviewer, few of the available brain specimens of great apes at advanced ages were sampled for stereological analysis of neuron numbers. Nonetheless, existing specimens could be fruitfully analyzed for local neuron density. Unfortunately, the current funding and regulatory climate does not favor such studies, despite their fundamental importance.

Besides needing more detailed data on neuron density, further information is needed on Abeta multimeric structures. For example, formic acid extraction for the most highly polymerized Abeta forms showed exponential increases of A β ₄₀ and A β ₄₂ in normal human brains, starting before age 50 years (Fukumoto et al., 2004), an age when modest levels of A β are histochemically detected (Braak and Braak, 1997). Moreover, formic acid extracts of temporal and occipital cortex showed as much or more A β ₄₀ and A β ₄₂ in aged monkeys and chimpanzee as in human AD (Rosen et al., 2011). Intriguingly, the binding of the Abeta imaging ligand Pittsburgh Compound B to brain homogenates (isotonic, no detergents, or formic acid) was much higher in AD cortex than in human controls or in primates, including the individual chimpanzee with NFTs noted previously from Rosen et al. (2008). Pittsburgh Compound B binds with less affinity to synthetic A β fibrils or to A β deposits in hAPP transgenic mouse brains than to A β amyloid from AD brains, suggesting its preferential binding to pathogenic conformations of A β multimers. We may anticipate species differences in proteins that influence Abeta assembly, for example, clusterin (Oda et al., 1995; Yu and Tan, 2012). We also note the expanding role of A β , a highly conserved peptide from fish to humans. Its broad age-related increase may be related to roles in innate immunity (Condic et al., 2014; Soscia et al., 2010) and to inflammatory processes arising in many tissues independently of specific pathology (Finch, 2007; Franceschi and Campisi, 2014; Park et al., 2009).

Husbandry could also contribute to species differences in neurodegeneration. As noted previously, the great apes have shown much less degenerative brain changes with age in

contrast to monkeys and some prosimians. Thus, we must wonder whether the husbandry for the captive great apes is optimized. Cage space can have a major influence on brain aging, for example, monkeys reared in small cages had several-fold more amyloid and 20% less synaptophysin at later age (Merrill et al., 2011). Herbivorous species such as gorillas pose special problems because we do not know which micronutrients are obtained from diets that include various parts of more than 100 species of plants. Moreover, gorillas, like other apes tend to become obese in captivity (Less et al., 2014). Clinical grade elevation of blood cholesterol is common in captive great apes on a wide range of diets (reviewed in Finch and Stanford, 2004, Table 3A). Although sudden death from heart failure is common in captive great apes, it may arise more frequently from fibrotic cardiomyopathy (Varki et al., 2009; Great Ape Heart Project, 2012) than from ischemic cardiovascular disease (Manning, 1943; Murphy et al., 2011). The relationship of various heart conditions to conditions of captivity is poorly understood. Recent interventions to reduce gorilla obesity in zoos with a low-starch diet showed benefits to insulin regulation even in the short term (Less et al., 2014). We anticipate continued increase in the longevity of captive species as husbandry becomes more refined.

In conclusion, we cannot yet conclude that AD, with its severe but regionally selective neurodegeneration and neuron loss, is uniquely human, because of the need for further evaluation of neuron density. We may err on the side of caution because the experienced investigators of the published studies would seem likely to have noticed if there was neurodegeneration or neuron loss at the gross level of early clinical AD. We must also ask, could the advanced ages reached by modern humans introduce yet undefined factors of aging that trigger evolutionarily novel neurodegenerative processes? Although improved husbandry may further extend life spans of captive great apes, we remain reserved on whether AD levels of neurodegenerative brain amyloidosis and tauopathies will emerge at later ages.

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Fig. 1. Survival curves for captive gorillas (Allman et al., 1998) and for the US population in 2010 (Human Mortality Database, www.mortality.org).