

Effects of Age on CSF and Plasma Biomarkers in a Nonhuman Primate Model of Early Alzheimer's Pathology

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BACKGROUND

African green vervet monkeys (*Chlorocebus aethiops sabaeus*) are a non-human primate model of early Alzheimer's disease (AD) neuropathology, in which we previously demonstrated brain amyloid β ($A\beta$) deposition and phosphorylated tau associations with reduced brain volume, glucose metabolism, and physical function (gait speed), along with PHF tau staining but a paucity of true neurofibrillary tangles (NFTs). These characteristics provide an ideal opportunity for investigation of the early pathogenesis of the disease during a period when interventions may be more effective at preventing AD progression. We have been evaluating multisystem cognitive and physical function along with metabolic, physiologic, and biochemical phenotypes in an aging colony of monkeys supported by an NIA R24. Similar to humans, vervets experienced numerous age-related changes including declines in physical and cognitive function, social isolation, and impairments in carbohydrate metabolism, among other characteristics. The purpose of the present study was to determine the effects of age on CSF and plasma biomarkers of AD and related dementias.

METHODS

Subjects were members of the Aging Vervet Cohort, which consists of 46 middle aged - to elderly female vervet monkeys (9-29 years). Biannual CSF and blood were collected longitudinally over 5 years. Previously we reported negative associations between age and CSF $A\beta_{42}$ and $A\beta_{40}$. Here we assessed CSF and plasma NfL, GFAP, p-tau181, and p-tau217 using single and multiplex assays from Meso Scale Discovery. Generalized linear mixed models, accounting for repeated measures within individuals, were used to determine effects of age. Repeated-measures correlations were used to evaluate associations between CSF and plasma biomarkers.

Associations Between Age and ADRC Fluid Biomarkers

Biomarker	CSF						Plasma					
	Ln. Trans	Estimate	SE	t value	p		Ln. Trans	Estimate	SE	t value	p	
AB_{1-40}	no	-50.410	48.9	-1.031	0.308		no	2.23	1.14	-1.97	0.056	
AB_{1-42}	no	-5.006	5.75	-0.871	0.388		yes	0.006	0.009	0.067	0.502	
AB_{42-40}	no	-0.001	0.003	-0.345	0.731		yes	0.006	0.007	-0.79	0.435	
pTau ₁₈₁	yes	0.054	0.023	2.380	0.021		no	-0.083	0.23	-0.36	0.583	
pTau ₂₁₇	yes	0.090	0.024	3.769	<0.001		no	-0.086	0.30	-0.29	0.775	
NfL	yes	0.134	0.028	4.723	<0.001		yes	0.077	0.017	4.52	<0.0001	
GFAP	yes	0.115	0.042	2.728	0.007		yes	-0.003	0.031	0.10	0.923	
pTau ₁₈₁ : AB_{42}	yes	0.065	0.026	2.465	0.017		yes	-0.022	0.023	-0.92	0.227	
pTau ₂₁₇ : AB_{42}	yes	0.099	0.028	3.525	0.001		yes	-0.01	0.024	-0.43	0.673	

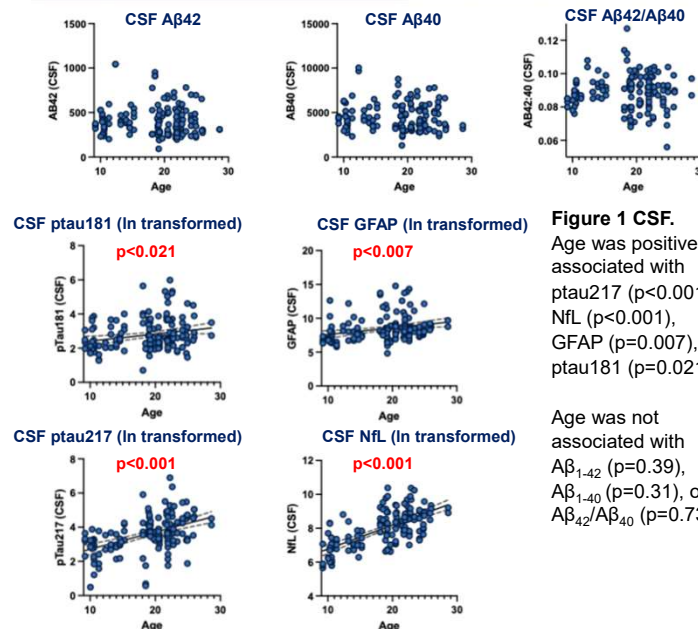


Figure 1 CSF. Age was positively associated with ptau217 ($p<0.001$), NfL ($p<0.001$), GFAP ($p=0.007$), & ptau181 ($p=0.021$).

Age was not associated with AB_{1-42} ($p=0.39$), AB_{1-40} ($p=0.31$), or AB_{42}/AB_{40} ($p=0.73$).

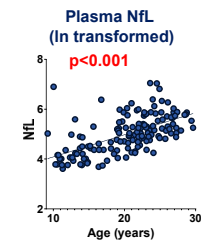


Figure 2 Plasma: NfL increased with age ($p<0.001$), and CSF and plasma NfL levels were correlated ($p=0.023$). Other plasma ADRC markers were not significantly correlated with age.

RESULTS

CSF: age was positively associated ptau217 ($p<0.001$), NfL ($p<0.001$), GFAP ($p<0.007$), and ptau181 ($p<0.021$). Adjusting ptau181 and ptau217 for $A\beta_{42}$ did not influence the ptau relationships with age.

Plasma: NfL increased with age ($p<0.001$), and CSF and plasma NfL levels were correlated ($p<0.023$). Age was not associated with other plasma markers ($p>0.2$).

CONCLUSIONS

African green/ vervet monkeys experienced age-related changes in CSF biomarkers comparable to that seen in humans. Analyses are underway to assess ADRC biomarker relationships with cognitive function, neuroimaging, post-mortem pathology, and other relevant phenotypes.

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