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ALZHEIMER DISEASE

CSF levels of mitochondrial DNA—a new biomarker for preclinical Alzheimer disease?

Reduced levels of cell-free mitochondrial DNA (mtDNA) in cerebrospinal fluid (CSF) could be a novel biomarker of preclinical Alzheimer disease (AD), according to a new study.

The pathological changes underscoring clinical AD begin decades before manifestation of dementia. Current biomarkers of the preclinical stage are brain and CSF levels of amyloid-β (Aβ) and CSF levels of tau, but exactly how these measures relate to disease onset is poorly defined. For the current study, Ramon Trullas and colleagues chose to focus on CSF levels of mtDNA, which can be accurately measured using PCR.

Individuals were selected from a cohort of 282 patients at a hospital unit for AD and other cognitive disorders, and were classified according to cognitive status and CSF concentrations of Aβ and tau. "We hypothesized that mtDNA might be released into the CSF by damaged synapses and could, therefore, be a biomarker of neurodegeneration," says Trullas. "We expected to find high CSF levels of mtDNA in patients with AD, but instead we found the opposite."

> "...regulation of mtDNA content [could be] a convergence point in the pathophysiology of AD..."

In asymptomatic at-risk individuals (classic biomarker evidence of AD but no cognitive impairment) and symptomatic patients with sporadic AD, CSF mtDNA levels were significantly lower than in healthy age-matched controls. Moreover, in young asymptomatic carriers of mutations in presenilin-1 (*PSEN1*) that cause familial AD, CSF concentrations of mtDNA were reduced relative to those in mutation-free family members.

"These findings suggest that, independently of aetiology, regulation of mtDNA content is a convergence point in the pathophysiology of AD," suggests Trullas. Patients with frontotemporal dementia—a disease that is clinically similar to AD—did not show changes in CSF mtDNA.

To investigate early mtDNA changes in the brain, the researchers studied cortical neurons from mice harbouring human *PSEN1* mutations. Neurons harvested well before manifestation of AD symptoms showed significant reductions in mtDNA copy number.

"Our results highlight a potential biomarker for preclinical AD and generate a new hypothesis that mtDNA depletion is a fundamental biological process in this disease," concludes Trullas.

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Original article Podlesniy, P. *et al.* Low CSF concentration of mitochondrial DNA in preclinical Alzheimer's disease. *Ann. Neurol.* doi:10.1002/ana.23955