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Commentary on Oeckl et al., "Serum Beta-Synuclein Is Higher in Down Syndrome and Precedes Rise of <fc>pTau181</fc>"

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People with Down syndrome (DS) develop Alzheimer disease (AD) neuropathology by the time they are 40 years of age with clinical signs of dementia developing approximately 10-15 years later [1-3]. Given the age-dependency of AD progression, following cohorts of people with DS can provide insights into early biomarkers of neurodegeneration in prodromal stages. Also, by extension, outcomes from studies with people with DS may inform temporal events in late-onset AD. To improve our understanding of AD onset and progression in DS and to facilitate the development and validation of novel disease-modifying drug candidates against AD in DS, we need easily accessible and well-validated biomarkers.

Whilst reliable cerebrospinal fluid (CSF) and imaging biomarkers for AD pathologies and neurodegeneration have been available for some time, the field has recently been galvanized by the development of blood-based biomarkers[4]. This is a rapidly evolving area of research with several studies pointing to plasma proteins changing prior to onset of dementia.[5,6] Sensitive blood-based assays for phosphorylated tau forms (pTau) for use as blood biomarkers of AD-related tau pathophysiology have been developed. A ratio of 42 to 40 amino acid-long amyloid β (Aβ42/Aβ40) in plasma reflects cerebral Aβ pathology. Neurofilament light (NfL) can also be measured in blood and reflects general neurodegeneration. Finally, serum or plasma levels of glial fibrillary acidic protein (GFAP) reflect astrocytic activation in the brain, which increases in response to Aβ pathology and other neurodegenerative brain changes. These biomarkers have been investigated in longitudinal cohorts of sporadic and familial AD, and in recent years, also in DS[7]. As it is the case in AD, plasma Aβ42/Aβ40 and total-tau, at least with currently available methods, have shown low diagnostic performance. Additionally, plasma pTau181 has been proven to differentiate people with DS with and without dementia with high accuracy, but no better than NfL[6]. The high diagnostic performance of NfL, in addition to its stability in pre-analytical handling and the fact that it can be measured by robust assays used in clinical routine in many European countries, has pointed to plasma NfL as the best biomarker for diagnosis of AD in DS[8]. However, more studies are needed to determine if other biomarkers, different than those used for sAD—for example, related to synaptic, inflammatory, metabolic, or oxidative stress imbalances—could be earlier or more accurate biomarkers for dementia in DS[7].

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In the article by Oeckl [9] and colleagues, plasma and serum samples from a cohort of 61 people with DS ranging in age from 23 to 58 years of age, with 14 with a consensus diagnosis of dementia. A group of neurotypical controls (n=23, 32-54 years of age) were included for comparison. Plasma pTau181 was measured using the Quanterix platform and serum β-synuclein, a novel blood-based biomarker for synaptic dysfunction in AD and related neurodegenerative dementias, was assayed using immunoprecipitation-mass spectrometry. The authors report that ptau181 was increased only in the symptomatic group with DS relative to asymptomatic people and neurotypical controls. β-Synuclein was increased in asymptomatic people with DS, further increased in symptomatic people with both groups being higher than controls. β-Synuclein and ptau181 blood levels correlated with cognition; higher levels of β-synuclein and pTau181 were associated with poorer scores on the CAMCOG-DS scale. A striking result is the age-association of β-synuclein and pTau181, which appears to be exponential rather than linear. The authors conclude the β-synuclein is altered early in AD in DS and within the prodromal stages.

People with DS show significant neuron loss with age (by structural neuroimaging[10] and autopsy studies[11,12]) and AD and a loss of other synapse proteins such as synaptophysin[13-15]. Synaptojanin 1, a presynaptic protein coded on chromosome 21 is overexpressed in DS[16], suggesting possible imbalances in synapse function that could lead to memory dysfunction and hippocampal hyperexcitability (work in mice)[17]. Although α-synuclein in Lewy bodies is observed in the brains of people with DS[11,18], β-synuclein described in the current study as a marker of synapse dysfunction has received little attention, and there are no studies regarding protein levels in the brains of people with DS, suggesting this could be an area of future focus.

This is an important study that may identify a novel biomarker for DS that may reflect early neurodegenerative changes reflecting synapse degeneration, prior to the development of cognitive decline. Interestingly, serum β-synuclein is already higher in younger nondemented adults with DS relative to neurotypical controls, raising the question of whether this event also has a neurodevelopmental basis. There is some evidence to suggest that β-synuclein may be protective and inhibits aggregation by α-synuclein, implicated in Lewy body disease [19]. Although the gene for β-synuclein is not on chromosome 21, overexpression of chromosome 21 genes may lead to modifications in the expression levels of genes on other chromosomes.

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Author Contributions

EH and HZ Contributed equally to this commentary.

Potential Conflicts of interest

Nothing to report.

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