Cerebrospinal Fluid Biomarkers

Cerebrospinal fluid biomarkers for Alzheimer's disease in Down syndrome

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Abstract

Down syndrome (DS), present in nearly six million people, is associated with an extremely high risk to develop Alzheimer's disease (AD). Amyloid-β and tau pathology are omnipresent from age 40 years onward, but clinical symptoms do not appear in all DS individuals. Dementia diagnostics is complex in this population, illustrating the great need for predictive biomarkers. Although blood biomarkers have not yet proven useful, cerebrospinal fluid (CSF) biomarkers (low amyloid-β42, high t-tau, and high p-tau) effectively contribute to AD diagnoses in the general population and are increasingly used in clinical practice. Surprisingly, CSF biomarkers have been barely evaluated in DS. Breaking the taboo on CSF analyses would finally allow for the elucidation of its utility in (differential) diagnoses and staging of disease severity. A sensitive and specific biomarker profile for AD in DS would be of paramount importance to daily care, adaptive caregiving, and specific therapeutic interventions.

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1. Introduction: Down syndrome at high risk for Alzheimer's disease

Down syndrome (DS), present in nearly six million people worldwide, is the main genetic cause of intellectual disability in humans with a live birth prevalence of approximately one in 650 to 1000 [1,2]. DS is caused by the triplication of chromosome 21, hence trisomy 21. In addition to the intellectual disability, people with DS face an extremely high risk to develop dementia because of Alzheimer's disease (AD) later in life. By the age of 65, 68% to 80% of DS individuals develop AD [3] compared with about 11% of those aged >65 years in the general

(nonintellectually disabled) population [4]. Because of improved medical care, DS life expectancy has increased tremendously in the last century: from 9 years in 1929 to an actual average life expectancy of 61.1 years for men and 57.8 years for women [5]. Consequently, dementia has become evident in the aging DS population, being a major challenge in current daily care.

The high risk for AD in DS is generally attributed to the triplication of the amyloid precursor protein (APP) gene, encoded on chromosome 21. The APP protein is cleaved by β- and γ-secretase into amyloid-β (Aβ) peptides, the main constituent of the amyloid plaques found in AD. Overproduction of the APP protein, and thus increased formation of its splicing product Aβ, is present from birth onward, resulting in early Aβ accumulation and deposition in the brain (Fig. 1). Plaque formation has been reported to start with deposition of the longer Aβ1–42 fragments, already observed in a 12-year-old child with DS, later followed by

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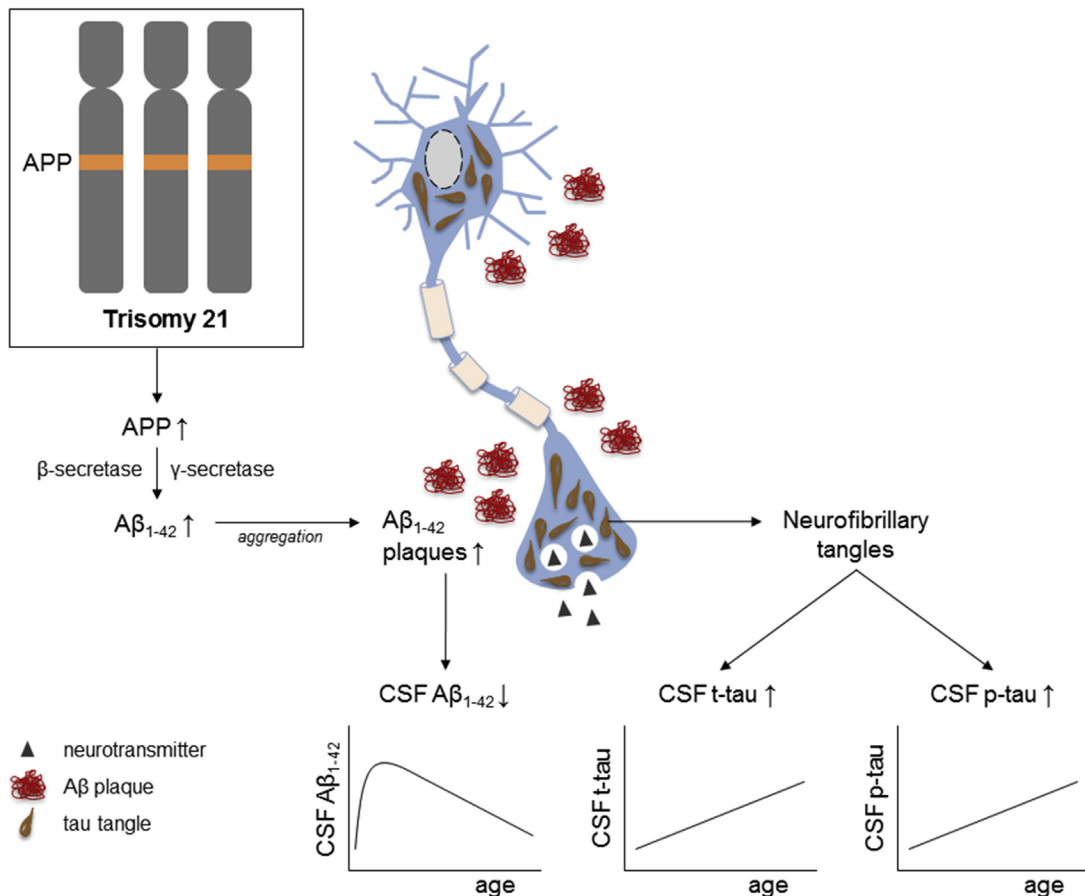
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Fig. 1. Schematic illustration of AD neuropathology and related changes in CSF biomarkers in DS. DS is caused by trisomy 21. The *APP* gene is encoded on chromosome 21, causing an overproduction of the APP protein in DS from birth onward. The enzymes β- and γ-secretase cleave the APP protein into Aβ peptides, which aggregate into plaques. The longer Aβ1–42 fragments are most prone to aggregate. Extensive neuropathology, that is, extracellular plaques, but also intracellular neurofibrillary tangles consisting of p-tau and t-tau, increases strongly in the third and fourth decade of life in virtually all DS individuals. These neuropathologic hallmarks are reflected by altered levels of CSF biomarkers. The CSF AD profile (low levels of Aβ42, and high levels of p-tau and t-tau) demonstrates high sensitivity and specificity in the general population. Whether a similar biomarker profile is useful for AD in DS remains to be elucidated. The very limited number of small-sized CSF studies in DS suggests that CSF Aβ1–42 increases in early childhood when the aggregation of Aβ1–42 into plaques is still relatively low. Once the deposition of Aβ1–42 into plaques augments (i.e., reduced clearance from the brain), CSF Aβ1–42 gradually decreases. In contrast, CSF t-tau and p-tau both correlate positively with age in DS. Abbreviations: Aβ, amyloid-β; APP, amyloid precursor protein; CSF, cerebrospinal fluid; DS, Down syndrome; p-tau, phosphorylated tau; t-tau, total tau.

formation of more compacted fibrillary plaques that contain Aβ1–40 as well [6]. Neuropathologic studies showed that the abundance of amyloid plaques and neurofibrillary tangles—the second hallmark of AD pathology—increases strongly in the third and fourth decade of life. By the age of 40 years, pathology is omnipresent in virtually all persons with DS, meeting the neuropathologic criteria for AD [7,8]. Interestingly, a 78-year-old DS woman with a partial trisomy 21 lacking the third copy of the *APP* gene was found to display neither symptoms of dementia nor evident AD pathology [9], illustrating the central role of the triplication of the *APP* gene.

Strikingly, despite the presence of pathology from midlife, not all DS individuals develop clinical dementia symptoms, thus complicating the prediction and monitoring of (the course to) dementia [10]. Indeed, DS individuals may reach their 70s free of dementia symptoms [11]. Therefore, diagnosing AD in DS is relatively difficult compared with the general population considering the (variable extent of) intellectual disability, pre-existing behavior, and comorbidities that might be misinterpreted as dementia symptoms. Differentiating among low(er) cognitive capacities because of the intellectual disability, cognitive decline because of normal aging, and deterioration because of AD is a fairly complex endeavor, heavily relying on clinical observations and caregiver reports [10,12].

Consequently, an objective biomarker profile for AD in DS would greatly aid the diagnostic procedure and contribute to more sensitive and earlier diagnoses. In fact, predicting the onset and monitoring the progression of AD in DS is of paramount importance to daily care. It would contribute to awareness and understanding among caregivers and relatives, leading to increased acceptance—the starting point for adaptive caregiving: allocating additional