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Featured Article

An inflammatory and trophic disconnect biomarker profile revealed in Down syndrome plasma: Relation to cognitive decline and longitudinal evaluation

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Abstract

Introduction: Given that Alzheimer's pathology develops silently over decades in Down syndrome (DS), prognostic biomarkers of dementia are a major need.
Methods: We investigated the plasma levels of Aβ, proNGF, tPA, neuroserpin, metallo-proteases and inflammatory molecules in 31 individuals with DS (with and without dementia) and in 31 healthy controls. We examined associations between biomarkers and cognitive decline.
Results: Aβ40 and Aβ42 were elevated in DS plasma compared to controls, even in DS individuals without dementia. Plasma Aβ correlated with the rate of cognitive decline across 2 years. ProNGF, MMP-1, MMP-3, MMP-9 activity, TNF-α, IL-6, and IL-10 were higher in DS plasma, even at AD-asymptomatic stages. Declining plasma Aβ42 and increasing proNGF levels correlated with cognitive decline. A combined measure of Aβ and inflammatory molecules was a strong predictor of prospective cognitive deterioration.
Conclusions: Our findings support the combination of plasma and cognitive assessments for the identification of DS individuals at risk of dementia.

Keywords: Alzheimer's disease; Amyloid-β; Biomarker; Blood; Down syndrome; Inflammation; Nerve growth factor; Metallo-proteases; MMP-3; MMP-9; Plasma; proNGF

1. Introduction

Down syndrome is a genetic disorder caused by a complete or segmental trisomy of chromosome 21, resulting in moderate-to-severe intellectual disability from early life and cognitive decline with advancing age [1,2]. Given the triplication of the amyloid precursor protein (APP) gene on chromosome 21, individuals with Down syndrome inexorably exhibit a gradual and silent accrual of Alzheimer's disease pathologic hallmarks over decades, including amyloid-β (Aβ) plaques, neurofibrillary tangles, inflammation, and central nervous system (CNS)

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cholinergic deficits [3–8]. The prevalence of dementia increases progressively with age in Down syndrome, reaching ≥75% in subjects aged 55–60 years [9–11]. Thus, from a genetic perspective, individuals with Down syndrome represent a population at high risk of Alzheimer's disease.

Diagnosing dementia in Down syndrome is challenging, given the need to dissect the underlying intellectual disability from age-related cognitive decline and is also limited by a paucity of diagnostic criteria and cognitive screening tools [12]. Thus, reliable biomarkers that signal the evolution of a silent Alzheimer pathology are presently of utmost medical relevance.

In the sporadic Alzheimer's disease population, Aβ and tau biomarkers in cerebrospinal fluid (CSF) and positron emission tomography amyloid imaging have demonstrated significant diagnostic utility in identifying Alzheimer's disease at its prodromal stages [13,14]. This has prompted recommendations for their use in the screening and monitoring of patients in clinical trials of disease-modifying drugs [15–18]. However, from a clinical perspective, there is a need to investigate biomarkers in other body fluids, as lumbar puncture is associated with discomfort and many patients consider it invasive, which complicates follow-up analyses. Consequently, blood is a preferred source of biomarkers for routine patient screening. However, the relation between blood analytes, Alzheimer's pathology, and cognitive decline remains elusive.

In Alzheimer's disease and Down syndrome, there is a progressive degeneration of basal forebrain cholinergic neurons [8,19–27], which depend on nerve growth factor (NGF) for their phenotypic maintenance [28,29]. Recent studies demonstrated a compromise of the NGF metabolic pathway in Alzheimer's disease [30,31] and Down syndrome brains [32], providing a mechanistic rationale to explain the degeneration of these neurons in such disorders (reviewed in [33,34]). The impaired maturation of the NGF precursor (proNGF) was associated with reduced levels of tissue plasminogen activator (tPA) and increased levels of its inhibitor neuroserpin; enzymes involved in proNGF cleavage [33,35]. The availability of NGF is further compromised by the over-activation of matrix metallo-protease 9 (MMP-9), which is a NGF-degrading protease [33,35]. Given that the cholinergic neurons are the key in the modulation of higher CNS functions [36], the investigation of biomarkers signaling a CNS trophic compromise is of therapeutic significance.

Neuroinflammation is an early pathologic hallmark of Down syndrome [37,38] and Alzheimer pathologies [39–41], although the precise neuroinflammatory phenotypes may be different in both disorders [42]. In transgenic models of amyloid pathology, an early pro-inflammatory process precedes the development of amyloid plaques and is associated with the intraneuronal accumulation of Aβ oligomers [43–45]. Notably, pro-inflammatory mediators (e.g., tumor necrosis factor-α (TNF-α) and MMP-3) can promote MMP-9 activation [46–49] suggesting that an early CNS inflammation could potentially affect NGF metabolism in Alzheimer's disease and Down syndrome brains.

Thus, this study is a comprehensive investigation of biomarkers of amyloid pathology, NGF metabolism, and inflammation in plasma from individuals with Down syndrome and nontrisomic cases. A 2-year prospective longitudinal follow-up was carried out to investigate whether the circulating levels of amyloid, inflammatory, and NGF-related markers, or their change over time, would bear a relationship with cognitive decline and dementia onset in Down syndrome.

2. Materials and methods

Additional details are available as Supplementary Material.

2.1. Study cases

Participants included 62 members of a community-based cohort of individuals from the region of Sicily, Italy. All were native to the island and of European origin. Over 60 people with Down syndrome were screened during the first 6 months of the study and 31 consented to give blood. Karyotyping showed full trisomy in all Down syndrome participants. Recruitment was done by clinicians at the Institute for Research on Mental Retardation and Brain Ageing (IRCSS) in Troina, Enna, Italy, and at ANFFAS-Catania, Catania, Italy, after family or personal written informed consent. Procedures were approved by the Research Ethics Committee at the IRCSS and by the Institutional Review Board of McGill University, Canada.

The Down syndrome group included 21 subjects who did not show a clinically relevant cognitive decline at study initiation, referred to as "DS" and classified as Alzheimer Should read Alzheimer's disease (AD) asymptomatic based on the Dementia Scale for Down syndrome (DSDS) [12,50,51] and on the *International Classification of Diseases*, *Tenth Revision* (ICD-10) criteria [52,53]. The Down syndrome cohort also included a group of 10 individuals with a prior diagnosis of probable Alzheimer's disease referred to as "DS + AD". The control group, "HC", consisted of 31 age-matched volunteers, free of karyotype abnormalities and of cognitive or neurological deficits. The age range of all participants in our study population (HC, DS, and DS + AD) was between 17 and 60 years. Table 1 illustrates further demographic information.

2.2. Clinical assessment and neuropsychological evaluation in the Down syndrome population

Participants received a general physical and neurological examination. Diagnosis of probable Alzheimer's disease was made according to ICD-10 criteria, as established by the Working Group for the Establishment of the Criteria for the Diagnosis of Dementia in Individuals with