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Featured Article

Neuronal exosomes reveal Alzheimer's disease biomarkers in Down syndrome

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Abstract

Introduction: Individuals with Down syndrome (DS) exhibit Alzheimer's disease (AD) neuropathology and dementia early in life. Blood biomarkers of AD neuropathology would be valuable, as non-AD intellectual disabilities of DS and AD dementia overlap clinically. We hypothesized that elevations of amyloid β (Aβ) peptides and phosphorylated-tau in neuronal exosomes may document preclinical AD.
Methods: AD neuropathogenic proteins $A\beta_{1-42}$, P-T181-tau, and P-S396-tau were quantified by enzyme-linked immunosorbent assays in extracts of neuronal exosomes purified from blood of individuals with DS and age-matched controls.
Results: Neuronal exosome levels of $A\beta_{1-42}$, P-T181-tau, and P-S396-tau were significantly elevated in individuals with DS compared with age-matched controls at all ages beginning in childhood. No significant gender differences were observed.
Discussion: These early increases in $A\beta_{1-42}$, P-T181-tau, and P-S396-tau in individuals with DS may provide a basis for early intervention as targeted treatments become available.

Keywords: Intellectual disability; Down syndrome; Alzheimer's disease; Blood biomarkers; Neuronal exosomes; Hyperphosphorylated tau; Amyloid-β

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1. Introduction

Down syndrome (DS) is the most common nonlethal aneuploidy in humans caused by complete or partial trisomy of chromosome 21 [1]. In addition to intellectual disability and atypical development often observed in DS, the prevalence of dementia is significantly higher, with onset at an earlier age than in the general population [2]. A strong candidate mechanism is the amyloid β (Aβ) precursor protein (*APP*) gene that is located on chromosome 21 and triplicated in people with DS, giving rise to toxic amyloid peptides at an early age [3]. Amyloid pathology has been observed as early as 15 years of age in postmortem brain samples from individuals with DS [4]. By age 40, amyloid plaques and neurofibrillary tangles are present in sufficient numbers for a postmortem pathological diagnosis of Alzheimer's disease (AD) [5]. Age-related increases in both soluble and insoluble Aβ peptides $A\beta_{1–40}$ and $A\beta_{1–42}$ within frontal cortex have been described in older individuals with DS and are correlated with increased oxidative stress, suggesting that other pathological pathways are at play as well [6]. The presence of AD pathology in younger individuals with DS is relatively unknown because of, in part, a paucity of brain tissue available for study at earlier age epochs. Biomarkers that reflect AD pathology at earlier ages are thus of considerable interest because neuroprotective therapies will eventually target younger individuals with DS.

Neuropathological biomarkers of AD, including $A\beta_{1–40}$ and $A\beta_{1–42}$, have been detected in brain tissue and cerebrospinal fluid (CSF) decades before onset of dementia in the general population [7] and in DS [8]. Performing lumbar punctures in those with DS is challenging; thus, there is a need for the development of reliable blood-based biomarkers for AD in this population. Most cell types in the body, including neurons, release small endosomally derived vesicles, known as exosomes [9,10]. Exosomes contain proteins, messenger RNA, and microRNA that play a prominent role in cellular signaling, removal of unwanted proteins, and transfer of cellular pathogens to other cells [8]. Because of their small size, secreted exosomes diffuse into biological fluids (blood, CSF, and urine) and circulate in the interstitial space, both in the brain and the periphery [11]. Neuronal exosomes have unique neuron-specific surface markers, which enable targeted examination from circulating biological fluids [10,12,13].

APP processing occurs in exosomes [14–17], and it has been suggested that exosomes play a role in Aβ clearance [18]. Exosomes receive APP from early endosomes after cleavage into Aβ peptides, which are secreted from the cells in exosomes [18]. Neuronal exosomes contain Aβ peptide products and tau and transmit these to neighboring cells, other brain regions, and the circulatory system, suggesting that neuronal exosomes extracted from either plasma or CSF can specifically assess relevant neuropathological processes within CNS neurons [19,20]. Other findings indicate that AD biomarkers in neuronal exosomes accurately predict onset of dementia as early as 10 years before symptom onset in patients with sporadic AD or frontotemporal dementia [10,21]. Exosomal biomarkers have not been analyzed in individuals with DS. In this study, we hypothesized that neuronal exosomes obtained from blood in DS would have elevated levels of Aβ peptides and phosphorylated-tau (P-tau) that could document a preclinical AD phase in the DS population.

The results presented here are from an international collaboration, including investigators from Hospital de la Santa Creu i Sant Pau in Barcelona (Spain), University of California at Irvine (UCI), Barrow Neurological Institute and Banner Sun Health Research Institute (Arizona), the Linnaeus University and the Karolinska Institutet in Sweden, and Medical University of South Carolina (MUSC). The aims were to examine alterations in exosome AD biomarkers in children, young adults, and older adults with DS in comparison with age-matched non-DS controls and also whether AD biomarkers were altered in individuals with DS that display dementia.

2. Methods

2.1. Subject and blood accrual

Blood samples were obtained from 84 individuals (Table 1). Participants either had a normal chromosomal count (control) or were trisomic for chromosome 21 (DS). The older adult DS group (>35 years) consisted of individuals with DS, independent of dementia status. This group was subdivided into two groups: 1) noncognitively impaired (NCI) and 2) those with early or with fully symptomatic dementia. Because samples were collected from several different clinics, assessed with slightly different cognitive batteries, primary outcomes did not include correlation

Table 1
Participant demographics

Groups	Diagnosis	*n*	Male/female	Average age (y) ± SEM	Age range (y)
Young controls (8–35)	NCI	9	4/5	15 ± 2.5	8–27
Adult controls (>35)	NCI	28	13/15	55 ± 1.7	43–77
Young DS (8–35)	NCI	14	8/6	19 ± 2.2	8–31
Adult DS (>35)		33	18/15	51 ± 0.8	43–62
Subgroups	NCI	16	10/6	51 ± 1.1	43–60
	Early or fully symptomatic dementia	17	8/9	51 ± 1.4	43–62

Abbreviations: SEM, standard error of the mean; NCI, noncognitively impaired; DS, Down syndrome.