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Genetics

Monoaminergic impairment in Down syndrome with Alzheimer's disease compared to early-onset Alzheimer's disease

Alain D. Dekker[a,b], Yannick Vermeiren[a,b], Maria Carmona-Iragui[c,d], Bessy Benejam[d], Laura Videla[d], Ellen Gelpi[e], Tony Aerts[b], Debby Van Dam[a,b], Susana Fernández[d], Alberto Lleó[c], Sebastian Videla[d,f], Anne Sieben[b], Jean-Jacques Martin[b], Netherlands Brain Bank[g], Rafael Blesa[c], Juan Fortea[c,d], Peter P. De Deyn[a,b,h,*]

[a]*Department of Neurology and Alzheimer Research Center, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands*
[b]*Laboratory of Neurochemistry and Behaviour, Institute Born-Bunge, University of Antwerp, Wilrijk, Antwerp, Belgium*
[c]*Department of Neurology, Hospital de la Santa Creu i Sant Pau, Biomedical Research Institute Sant Pau, Universitat Autonoma de Barcelona, Barcelona, Spain*
[d]*Down Medical Center, Catalan Down Syndrome Foundation, Barcelona, Spain*
[e]*Neurological Tissue Bank—Biobanc, Hospital Clinic Barcelona, Institut d'Investigacions Biomediques August Pi i Sunyer, Barcelona, Spain*
[f]*Faculty of Health and Life Sciences, Department of Experimental and Health Sciences, Universitat Pompeu Fabra, Barcelona, Spain*
[g]*Netherlands Institute for Neuroscience, Amsterdam, The Netherlands*
[h]*Department of Neurology and Memory Clinic, Hospital Network Antwerp (ZNA) Middelheim and Hoge Beuken, Antwerp, Belgium*

Abstract

Introduction: People with Down syndrome (DS) are at high risk for Alzheimer's disease (AD). Defects in monoamine neurotransmitter systems are implicated in DS and AD but have not been comprehensively studied in DS.

Methods: Noradrenaline, adrenaline, and their metabolite 3-methoxy-4-hydroxyphenylglycol; dopamine and its metabolites 3,4-dihydroxyphenylacetic acid and homovanillic acid; and serotonin and its metabolite 5-hydroxyindoleacetic acid were quantified in 15 brain regions of DS without AD (DS, n = 4), DS with AD (DS+AD, n = 17), early-onset AD (EOAD, n = 11) patients, and healthy non-DS controls (n = 10) in the general population. Moreover, monoaminergic concentrations were determined in cerebrospinal fluid (CSF)/plasma samples of DS (n = 37/149), DS with prodromal AD (DS+pAD, n = 13/36), and DS+AD (n = 18/40).

Results: In brain, noradrenergic and serotonergic compounds were overall reduced in DS+AD versus EOAD, while the dopaminergic system showed a bidirectional change. For DS versus non-DS controls, significantly decreased 3-methoxy-4-hydroxyphenylglycol levels were noted in various brain regions, though to a lesser extent than for DS+AD versus EOAD. Apart from 3,4-dihydroxyphenylacetic acid, CSF/plasma concentrations were not altered between groups.

Discussion: Monoamine neurotransmitters and metabolites were evidently impacted in DS, DS+AD, and EOAD. DS and DS+AD presented a remarkably similar monoaminergic profile, possibly related to early deposition of amyloid pathology in DS. To confirm whether monoaminergic alterations are indeed due to early amyloid-β accumulation, future avenues include positron emission tomography studies of monoaminergic neurotransmission in relation to amyloid deposition, as well as relating monoaminergic concentrations to CSF/plasma levels of amyloid-β and tau within individuals.

Keywords: Alzheimer's disease; Cerebrospinal fluid; Dementia; Dopamine; Down syndrome; Monoamines; MHPG; Neurotransmitter; Noradrenaline; Plasma; Serotonin; Trisomy 21

The authors have declared no conflict of interest.

*Corresponding author. Tel.: +31 50 361 4650; Fax: ■■■.

E-mail address: p.p.de.deyn@umcg.nl

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1. Introduction

People with Down syndrome (DS), or trisomy 21, have an exceptionally high risk to develop Alzheimer's disease (AD): 68%–80% of people are diagnosed with dementia by the age of 65 years [1]. The additional copy of chromosome 21, encoding the amyloid precursor protein (APP), causes overproduction of amyloid-β (Aβ) peptides. Very early in life, intracellular Aβ accumulation takes place in neurons, followed by extracellular Aβ aggregation and subsequent deposition in characteristic Aβ plaques [2–5]. In DS brains, not only plaques but also neurofibrillary tangles are omnipresent from the age of 40 years [6]. The onset of clinical dementia symptoms, however, is subject to a marked variation in time [7,8]. Because the dementia diagnosis in DS is complex, among others due to comorbidities, pre-existing intellectual disability, and behavior [9], sensitive and specific biomarkers for AD in DS would be very valuable. In the general non-DS population, the so-called "AD profile" (low Aβ42, high total-tau, and high phosphorylated-tau) in cerebrospinal fluid (CSF) has proven useful as a diagnostic aid [10]. However, the clinical utility in DS has not been demonstrated yet [11]. Therefore, the study of alternative biomarkers for AD in DS receives vast attention.

In this context, we previously analyzed monoamine neurotransmitters and metabolites in serum of 151 elderly DS individuals with AD (DS+AD) and without AD (DS), but also in a nondemented DS group at blood sampling that developed dementia over time (converters). Remarkably, serum levels of the primary noradrenergic metabolite 3-methoxy-4-hydroxyphenylglycol (MHPG) were strongly decreased in DS+AD, but also in converted DS individuals. Individuals with MHPG levels below median had a more than 10-fold increased risk of developing dementia, suggesting that decreased serum MHPG levels may be predictive for conversion to AD [12].

Blood biomarkers, however, are subject to (confounding) peripheral effects. CSF biomarkers are generally regarded better indicators of biochemical changes in the central nervous system because of their direct contact with the extracellular space [13]. Very few studies have investigated CSF biomarkers in (moreover small) DS cohorts [11], including two on monoamines [14,15]. Although a few postmortem studies were conducted several decades ago, a comprehensive profile of central monoaminergic changes in DS+AD is not established yet. Indeed, monoamines were quantified in a limited number of brain regions from a few DS cases with often long postmortem delays (PMDs). For instance, cell loss in the locus coeruleus (LC), major source of noradrenaline (NA), and reduced NA concentrations have been reported in elderly DS cases [16–23], but an integrated study of regional changes in NA, dopamine (DA), serotonin (5-HT), and their primary metabolites is lacking. Vermeiren et al., for example, investigated monoaminergic profiles in a variety of postmortem brain regions in early-onset AD patients (EOAD) compared with age- and gender-matched control subjects. In EOAD patients, lower levels of serotonergic compounds were found in amygdala and hippocampus, complemented by lower NA levels in the prefrontal cortex and amygdala. No differences in MHPG levels could be observed [24].

To the best of our knowledge, this study is the first to comprehensively evaluate monoaminergic alterations in (1) postmortem brain tissues and (2) (paired) CSF/plasma samples from DS individuals with and without AD. Noradrenergic (NA; adrenaline; MHPG), dopaminergic (DA; 3,4-dihydroxyphenylacetic acid [DOPAC]; homovanillic acid [HVA]), and serotonergic (5-HT; 5-hydroxyindoleacetic acid [5-HIAA]) compounds were quantified using reversed-phase HPLC (RP-HPLC). In one of the largest collections Q3 of DS brain tissue (n = 21), 15 regions of DS cases without and with a neuropathologically confirmed diagnosis of AD (DS and DS+AD, respectively) were analyzed and compared with EOAD patients and healthy controls in the general population. Second, we report the monoaminergic results in (paired) CSF/plasma samples obtained from the largest DS cohort to have undergone lumbar punctures, comparing DS without dementia (DS), DS with prodromal AD (DS+pAD), and DS with clinically diagnosed AD (DS+AD).

2. Materials and methods

2.1. Postmortem samples

2.1.1. Study population

In total, postmortem samples from 21 elderly DS individuals were obtained from the Netherlands Brain Bank (NBB), Netherlands Institute for Neuroscience (Amsterdam, The Netherlands), the Neurological Tissue Bank—Biobanc, Hospital Clinic Barcelona—Institut d'Investigacions Biomediques August Pi i Sunyer (IDIBAPS; Barcelona, Spain), and the Institute Born-Bunge (IBB; Antwerp, Belgium). Specifically, brain samples from nine DS+AD individuals were obtained from the NBB (open access: www.brainbank.nl). All material has been collected from donors for or from whom written informed consent for a brain autopsy and the use of the material and clinical information for research purposes had been obtained by the NBB. Moreover, the IDIBAPS provided samples of two DS and five DS+AD donors for whom written informed consent was obtained from the next of kin. The study was approved by the Hospital Clinic de Barcelona Ethics Committee and in accordance with Spanish legislation. Finally, the IBB provided samples of DS (n = 2), DS+AD (n = 3), EOAD patients (n = 11), and healthy controls without neurological disease (n = 10). Since DS+AD presents early in life, we identified EOAD patients and controls <75 years of age as comparison groups. Ethical approval was granted by the medical ethics committee of the Hospital Network Antwerp (ZNA, approval numbers 2805 and 2806). The study was