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Florbetapir PET, FDG PET, and MRI in Down syndrome individuals with and without Alzheimer's dementia

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Abstract Because Down syndrome (DS) is associated with amyloid β (Aβ) deposition, we characterized imaging measurements of regional fibrillar Aβ burden, cerebral metabolic rate for glucose (rCMRgl), gray matter volumes (rGMVs), and age associations in 5 DS with dementia (DS/AD+), 12 DS without dementia (DS/AD−), and 9 normal controls (NCs). There were significant group differences in mean standard uptake value ratios (SUVRs) for florbetapir with DS/AD+ having the highest, followed by DS/AD−, followed by NC. For [18F]-fluorodeoxyglucose positron emission tomography, posterior cingulate rCMRgl in DS/AD+ was significantly reduced compared with DS/AD− and NC. For vMRI, hippocampal volumes were significantly reduced for the DS/AD+ compared with DS/AD− and NC. Age-related SUVR increases and rCMRgl reductions were greater in DS participants than in NCs. DS is associated with fibrillar Aβ, rCMRgl, and rGMV alterations in the dementia stage and before the presence of clinical decline. This study provides a foundation for the studies needed to inform treatment and prevention in DS.

Keywords: Down syndrome; Florbetapir; FDG-PET; PET; Dementia; Alzheimer's disease; Imaging

1. Introduction

Down syndrome (DS) is characterized by partial to complete trisomy of chromosome 21, developmental delay, and other developmental abnormalities. DS is also associated with a significant increase in the risk of Alzheimer's disease (AD) [1]. This increased AD risk is generally believed to be because of trisomy of the amyloid precursor protein (APP) gene, which resides on the distal arm of chromosome 21. Presumably, the possession of an extra copy of the APP gene induces APP overexpression, accounting for the virtually universal presence of fibrillar amyloid β (Aβ) peptide neuropathology in autopsied DS patients over the age of 35 years [2,3].

AD dementia occurs in approximately 10% to 25% of persons with DS in their 40s, 20% to 50% of those in their 50s, and 60% to 75% of those over the age of 60 years

Conflicts of Interest: All authors declare that they have no material conflicts of interest with respect to the present study, as defined by the ICMJE guidelines.

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[2–4]. Due especially to improvements in the treatment of DS-related cardiac anomalies, more persons with DS are living to older ages [5]. Given their increased risk for AD, there is a critical and largely unmet need to characterize the clinical and biomarker changes associated with the preclinical and clinical stages of AD in DS individuals.

To date, the best established brain imaging methods for the preclinical and clinical evaluation of AD include positron emission tomography (PET) measurements of fibrillar Aβ burden, reductions in regional PET measurements of the cerebral metabolic rate for glucose (CMRgl), and magnetic resonance imaging (MRI) measurements of regional and whole-brain volumes. These imaging techniques have been used successfully in a small number of studies to detect and track characteristic brain alterations in DS [6–17]. To our knowledge, although, no reported studies have yet characterized all three measurements in the assessment of DS patients, and only one has reported findings in DS individuals with (DS/AD+) and without AD dementia (DS/AD−) [6].

The primary objective in this small cross-sectional study was to use PET measurements of fibrillar Aβ burden, PET measurements of regional CMRgl, and MRI measurements of hippocampal and regional gray matter volumes to identify age-related brain imaging alterations associated with preclinical and clinical AD dementia in individuals with DS. Clinical, functional, and neuropsychological findings provided secondary outcomes of interest. These findings could establish a cohort for the longitudinal research of AD biomarker assessments in DS and help set the stage for the evaluation of interventions to treat and prevent AD dementia in this at-risk population.

2. Methods

2.1. Subjects

Five DS participants with the clinical diagnosis of Alzheimer's dementia (DS/AD+), 12 DS participants without the clinical diagnosis of Alzheimer's dementia (DS/AD−), and 9 normal controls (NCs) were enrolled in the study (Table 1). Participants and/or their caregivers/legal guardians provided informed consent, and the participants were studied under protocols approved by our organization's Institutional Review Board. DS/AD+ participants met *DSM-IV* and NIA-Alzheimer's Association diagnostic criteria for AD dementia by informant report of progressive cognitive decline with clear historical evidence of functional decline from premorbid abilities [18]. DS/AD− participants had neither evidence of progressive cognitive nor functional decline.

"Although the standard diagnostic criteria from the *DSM-IV* are not modified specifically for individuals with intellectual disability, it is stated within these criteria that change from a previous level of function is required for a diagnosis. Specifically, "The cognitive deficits in Criteria A1 and A2 (memory, language, executive functioning, etc.) each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning". The study lead here is a neurologist with a large number of patients in his practice and is familiar with premorbid deficits in DS (on average). We were careful to query parents/caregivers about noted changes in their daily life, much like is emphasized in a number of dementia screeners for ID currently in development (NTG screener from the National Task Group on Intellectual Disabilities and Dementia Practices—not available at the start of this study)."

The DS/AD+ and DS/AD− subjects had no history of epilepsy or seizures and their neurological examinations were nonfocal. NC participants were cognitively normal, without trisomy 21, and matched for age to the DS/AD− group. All DS subjects were confirmed by chromosome testing to have trisomy 21. Exclusion criteria included a lifetime history of another neurodegenerative disease, vascular dementia, or psychiatric disorders. Except as noted later, a medical history, physical examination, clinical evaluation, functional and neuropsychological testing, chromosome testing, and brain imaging were performed in all subjects. One DS/AD− participant withdrew consent after florbetapir PET scan and was not subsequently assessed by MRI. An additional DS/AD+ subject, who was severely impaired and agitated during imaging procedures, was excluded from the study due to extremely poor PET and MRI imaging quality. All other participants were evaluated with both florbetapir PET and MRI.

2.2. Clinical, functional and neuropsychological tests

All participants completed the Dementia Questionnaire for People with Learning Disabilities (DLD) [19], the Mini-Mental State Examination (MMSE) [20], the Brief Praxis Test [21], the severe impairment battery (SIB) [22], and the Vineland Adaptive Behavior Scale, second edition (see Table 1) [23]. Premorbid IQ estimation was not available from records, nor was it assessed as part of the study.

2.3. [18F] Florbetapir PET acquisition and preprocessing

Florbetapir PET imaging was used to assess mean cortical-to-pontine florbetapir standard uptake value ratios (SUVRs) as the primary outcome measure of fibrillar Aβ burden. As in our previous florbetapir study [7], participants underwent a 10-minute emission scan 50 minutes after intravenous injection of 10 mCi (370 MBq) of [18F] florbetapir. Scans were performed on a Siemens Biograph XVI HiRez PET/CT scanner. The images were reconstructed using an iterative reconstruction algorithm (4 iterations, 16 subsets), with a 5-mm full-width at half-maximum Gaussian filter, and were corrected for radiation attenuation and scatter. If significant patient motion was observed, another 10-minute scan was acquired. SPM8 (http://www.fil.ion.ucl.ac.uk/spm/) was used to linearly and nonlinearly deform