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Featured Article

The pattern of amyloid accumulation in the brains of adults with Down syndrome

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Abstract

Introduction: Adults with Down syndrome (DS) invariably develop Alzheimer's disease (AD) neuropathology. Understanding amyloid deposition in DS can yield crucial information about disease pathogenesis.

Methods: Forty-nine adults with DS aged 25–65 underwent positron emission tomography with Pittsburgh compound–B (PIB). Regional PIB binding was assessed with respect to age, clinical, and cognitive status.

Results: Abnormal PIB binding became evident from 39 years, first in striatum followed by rostral prefrontal-cingulo-parietal regions, then caudal frontal, rostral temporal, primary sensorimotor and occipital, and finally parahippocampal cortex, thalamus, and amygdala. PIB binding was related to age, diagnostic status, and cognitive function.

Discussion: PIB binding in DS, first appearing in striatum, began around age 40 and was strongly associated with dementia and cognitive decline. The absence of a substantial time lag between amyloid accumulation and cognitive decline contrasts to sporadic/familial AD and suggests this population's suitability for an amyloid primary prevention trial.

Keywords: Alzheimer's disease; Down syndrome; Amyloid; PIB; PET; Dementia; Striatum; Preclinical

1. Introduction

Adults with Down syndrome (DS) invariably develop senile plaques, composed of β-amyloid peptide (Aβ), indistinguishable from the histopathology of sporadic Alzheimer's disease (AD) [1,2], and have a high risk for the development of early onset dementia [3] with estimated age-specific prevalence rates increasing from 20% to 50% in the fifties to 30% to 75% in those aged >60 years [4]. Comparable levels of amyloid can be observed in the brains of individuals with DS without dementia to those seen in typically developing individuals with AD dementia [3]. It is now believed that amyloid deposition in the typically developing population with sporadic AD can occur more than a decade before the clinical symptoms of dementia appear [5,6].

Similar to autosomal-dominant AD, people with DS are genetically predisposed to increased amyloid accumulation; in DS, this is the result of triplication of the amyloid

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precursor protein gene, located on chromosome 21. DS is therefore a genetic example of Aβ overproduction, making it a highly complementary study group to the autosomally inherited forms of AD that are presently being investigated by the Dominantly Inherited Alzheimer Network (DIAN) [7] or in the large single kindred of the Alzheimer Prevention Initiative Autosomal Dominant Alzheimer's Disease study [8]. DS can yield crucial information about the generalizability of the pattern of cerebral amyloid accumulation across different genetically determined forms of AD. Furthermore, being a candidate group for amyloid primary prevention trials—particularly because DS is more prevalent than autosomally inherited AD—it is of critical importance to first understand the behavior of amyloid in the DS population so as to best optimize the timing of such studies.

Positron emission tomography (PET) imaging with ligands such as [^{11}C]–Pittsburgh compound–B (PIB) enables in vivo quantification and localization of fibrillar Aβ deposits [9]. Previous amyloid PET studies have reported widespread cortical binding in people with DS after about the age of 40 years [10–15] (Table 1). In younger individuals, imaging has generally shown an absence of amyloid binding, although some single isolated cases have been reported with focal striatal binding [12–14]. These previous studies have used large anatomic regions of interest (ROI) in relatively small numbers of participants, making a more fine-grained and systematic study of amyloid accumulation across different brain areas highly desirable. Moreover, with the exception of the pilot study [10] that was the precursor to the present work, all previous amyloid PET analyses in DS used standardized uptake value ratios of static images; the present study utilized the more robust method of calculating non–displaceable binding potential (BP_{ND}) from dynamic image data. This report, therefore, characterizes in detail the evolution of PIB binding in cortical and subcortical regions of the DS brain.

2. Methods

2.1. Study design and participants

Forty-nine participants with DS aged 25–65 volunteered to take part and successfully completed the neuropsychological assessments and the imaging protocol of this study. Participants were identified via services for people with intellectual disabilities in England and Scotland, through the Down Syndrome Association or following responses to our Web site. All received an easy-to-read information pack containing a leaflet and a DVD (see: https://www.youtube.com/user/downsproject/videos). Participants were screened for any contraindications to magnetic resonance imaging (MRI)/PET scanning. All participants had previously received a clinical diagnosis of DS based on having the characteristic phenotype. In addition, 33 participants had been karyotyped as part of a pervious study, and all were confirmed to have full trisomy 21.

Table 1
Previous amyloid PET studies in individuals with DS and the main findings of amyloid binding

Study	Amyloid agent	Participants with DS	Age range (y)	Youngest amyloid positive participant	Methods	Regions with increased amyloid binding in DS
(Landt et al. 2011) [10]	^{11}C–PIB	8	25–59	45	Scan 0–90 min after injection, BP_{ND} estimated with cerebellum as reference region, region-specific positive-binding thresholds	5/8: Anterior and posterior cingulate, calcarine, prefrontal, superior parietal. Hippocampus (2/8).
(Sabbagh et al. 2011) [12]	^{18}F-Florbetapir	1	55	NA	Scan 50–60 min after injection, SUVR estimated using cerebellum reference region	Frontal, temporal, parietal, anterior and posterior cingulate, precuneus, striatum, thalamus
(Handen et al. 2012) [13]	^{11}C–PIB	7	20–44	38	Scan 40–60 min after injection, SUVR using cerebellum reference region; region-specific positive-binding thresholds	Striatum (2/7); frontal, anterior cingulate, precuneus/posterior cingulate, lateral temporal lobe (1/7)
(Hartley et al. 2014) [14]	^{11}C–PIB	63 (none with symptoms of dementia)	30–53	NA	Scan 50–70 min after injection, SUVR using subcortical white matter and cerebellum reference region, region-specific positive-binding thresholds	Striatum (21/63); anterior cingulate (13/63); precuneus, frontal and lateral temporal cortex (12/63); parietal cortex (8/63)
(Jennings et al., 2015) [15]	^{18}F-Florbetaben	39	40–56	40–44	Scan 100–120 min after injection, SUVR using cerebellum reference region, composite region positive-binding threshold	Composite region (frontal, lateral temporal, anterior and posterior cingulate, parietal, occipital): 1/14 (40–44 y); 6/15 (45-49 y); 7/10 (≥50 y)

Abbreviations: PET, positron emission tomography; DS, Down syndrome; BP_{ND}, non–displaceable binding potential; NA, not applicable; ^{11}C–PIB, ^{11}C–labeled Pittsburgh Compound–B; SUVR, standardized uptake value ratio.

NOTE. Amyloid agents refer to amyloid-specific PET radiotracers: ^{11}C–PIB and two ^{18}F–labeled amyloid radiotracers (Florbetapir and Florbetaben). A study by Nelson et al. [11] utilized a mixed amyloid/tau tracer and was thus not investigated in detail.