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Neuroimaging

Longitudinal changes in amyloid positron emission tomography and volumetric magnetic resonance imaging in the nondemented Down syndrome population

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Abstract

Introduction: Down syndrome (DS) arises from a triplication of chromosome 21, causing overproduction of the amyloid precursor protein and predisposes individuals to early Alzheimer's disease (AD).
Methods: Fifty-two nondemented adults with DS underwent two cycles of carbon 11-labeled Pittsburgh compound B ([^{11}C]PiB) and T1 weighted magnetic resonance imaging (MRI) scans 3.0 ± 0.6 years apart. Standard uptake value ratio (SUVR) images (50–70 minutes; cerebellar gray matter [GM]) and GM volumes were analyzed in standardized space (Montreal Neurological Institute space).
Results: 85% of PiB(−) subjects remained PiB(−), whereas 15% converted to PiB(+), predominantly in the striatum. None reverted from PiB(+) to PiB(−). Increases in SUVR were distributed globally, but there were no decreases in GM volume. The PiB positivity groups differed in the percent rate of change in SUVR [PiB(−): 0.5%/year, PiB converters: 4.9%/year, and PiB(+): 3.7%/year], but not in GM volume.
Discussion: Despite the characteristic striatum-first pattern, the global rate of amyloid accumulation differs by pre-existing amyloid burden and precedes atrophy or dementia in the DS population, similar to general AD progression.

Keywords: Down syndrome; Alzheimer's disease; Longitudinal; Amyloid PET; PiB

1. Introduction

Down syndrome (DS) is the most common genetic developmental disability (approximately 14.5 in every 10,000 live births [1]), and among other things, the triplicate copy of chromosome 21 leads to higher levels of amyloid precursor protein (APP) mRNA in DS brains compared with healthy controls [2]. In postmortem studies, elevated amyloid burden is apparent in adults with DS as early as their 20s and is nearly ubiquitous by their 40s in the same chemical form observed in Alzheimer's disease (AD) postmortem studies in the general population [3–5]. The combined effects of advances in medical procedures, better standard of care, and increased resource availability have led to a dramatic increase in life

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expectancy, which is currently in the 60s, compared to approximately 9 years in the early 20th century [6].

Specific localization and sufficient density of amyloid-β plaques, often regarded as a consequence of reduced clearance of amyloid-β, are a neuropathologic hallmark of AD [7]. Thal staging of amyloid-β plaques in the general population suggests a hierarchical pattern with five phases. Nondemented cases may exhibit phases 1 through 3 in which phase 1 begins in the neocortex, phase 2 spreads to the allocortex, and phase 3 includes the diencephalic nuclei, striatum, and cholinergic nuclei of basal forebrain. Proven AD cases typically exhibit phases 3 through 5, where phase 4 involves several brainstem nuclei and phase 5 includes the cerebellum [8].

In <1% of all AD cases, there is a deterministic genetic predisposition to overexpression of amyloid-β and an early age of onset for dementia (<65 years) [9]. Autosomal dominant AD (ADAD) results from genetic mutations in APP (chromosome 21; 10–15% of ADAD cases), presenilin-1 (PSEN1; chromosome 14; 18%–50%), or presenilin-2 (PSEN2; chromosome 1; <5%) [10]. An interesting finding in individuals with ADAD is the striatum-dominant pattern of amyloid accumulation, regardless of mutation type [11,12]. In our previous cross-sectional study in the nondemented DS population, patterns of carbon 11-labeled Pittsburgh compound B ([^{11}C]PiB) binding demonstrated the elevated striatal binding in the absence of elevated neocortical binding [13]. These data suggest that a striatum-dominant pattern of amyloid-β plaque deposition in ADAD and DS may be a result of amyloid overproduction, consistent with other work [12–16].

Amyloid-β plaque accumulation precedes dementia, but the causal relationship is still unknown, as some cases never develop dementia despite the presence of plaques. In the DS population, the prevalence of dementia increases rapidly after the age of 30 years. It is estimated to be as high as 33% among individuals with DS aged 30 to 39 years, 55% among those aged 40 to 59 years, and 77% for individuals above the age of 60 years [17]. By comparison, the prevalence of dementia in the general population is estimated as 4% below 65 years, 15% between 65 and 74 years, 43% between 75 and 84 years, and 38% over the age of 85 years [18].

A comparison of DS adults with age-matched controls demonstrated a distinct pattern of gray matter (GM) reductions in hippocampus and adjacent medial temporal lobe that were independent of age and most likely reflect the abnormal brain morphology resulting from developmental disability [19]. In addition, others have suggested that age-related reductions in overall brain and GM volumes are not present until the onset of dementia [20]. GM reductions in allocortex and association neocortex in the nondemented DS population have been demonstrated using voxel-based morphometry, suggesting neuronal loss during the AD pathophysiologic process [21].

Knowledge of the disease course would inform future studies and therapeutic trials for which the DS population is a prime candidate. Moreover, findings regarding the natural history of amyloid-β accumulation and GM atrophy in the nondemented DS population may be generalizable to the predementia phase of any AD case. This study aims to identify the direction, magnitude, and regional distribution of changes in amyloid burden and GM volume in nondemented adults with DS.

2. Methods

2.1. Participants

The complete cohort (N = 81) was confirmed to be trisomic for chromosome 21 using genetic testing and recruited from a number of programs serving adults with DS and developmental disabilities (e.g., mailings to disability programs, fliers in DS clinics, research registries) located within 3 to 5 hours of the two performance sites (Waisman Center, University of Wisconsin-Madison; University of Pittsburgh Medical Center). Inclusion criteria included receptive language ≥3 years. Exclusion criteria included having a prior diagnosis of dementia, conditions that might contraindicate magnetic resonance imaging (MRI) (e.g., claustrophobia, metal in the body), and having a medical or psychiatric condition that impaired cognitive functioning.

Participants were assessed for dementia using the Down syndrome Dementia Scale (DSDS). Three individuals from the complete cohort received a cognitive cutoff score (CCS) >3 and were removed from analyses (N = 81 − 3 = 78). One individual had a CCS of 3 at entry but was included based on lower early and middle tally score on the DSDS, suggesting dementia was not present [22].

Out of the 78 nondemented participants, 52 (30–50 years old) completed two cycles of imaging and neuropsychologic evaluation (3.0 ± 0.6 years apart). Demographic information for the study cohort is summarized in Table 1. *APOE* ε4 allele information was obtained by genetic testing. The remaining subjects with only one cycle of data will be transitioned to a newly National Institutes of Health–funded biomarker study, Neurodegeneration in Aging Down Syndrome.

2.2. MRI acquisition

T1 weighted MRIs were acquired on a 3.0T GE SIGNA 750 (University of Wisconsin-Madison) or a 3.0T Siemens Magnetom Trio (University of Pittsburgh Medical Center). The SIGNA 750 acquisition used a high-resolution volumetric-spoiled gradient sequence (inversion time/echo time/repetition time = 450/3.2/8.2 ms, flip angle = 12°, slice thickness = 1 mm no gap, and matrix size = 256 × 256 × 156), whereas the Magnetom Trio acquisition used a magnetization-prepared rapid acquisition gradient echo sequence (inversion time/echo time/repetition time = 900/2.98/2300 ms, flip angle = 9°, slice thickness = 1.2 mm, matrix size = 160 × 240 × 256).

2.3. Positron emission tomography acquisition

On-site chemical synthesis of [^{11}C]PiB yielded high specific activity (≥2 mCi/nmol). Up to 15 mCi of [^{11}C]PiB was delivered intravenously via bolus injection (over 20–30 seconds) into the antecubital vein. Positron emission tomography