ELSEVIER

Alzheimer's & Dementia ■ (2018) 1-8

Alzheimer's & Dementia

Featured Article

Early striatal amyloid deposition distinguishes Down syndrome and autosomal dominant Alzheimer's disease from late-onset amyloid deposition

Ann D. Cohen[a,*,1], Eric McDade[b,c,1], Brad Christian[d], Julie Price[e,f], Chester Mathis[e], William Klunk[a,b], Benjamin L. Handen[a]

[a]*Department of Psychiatry, University of Pittsburgh School of Medicine*
[b]*Department of Neurology, University of Pittsburgh School of Medicine*
[c]*Department of Neurology, Washington University School of Medicine*
[d]*Department of Medical Physics, University of Wisconsin–Madison School of Medicine*
[e]*Department of Radiology, University of Pittsburgh School of Medicine*
[f]*A. A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital*

Abstract

Introduction: The objective of this study was to evaluate amyloid β (Aβ) deposition patterns in different groups of cerebral β amyloidosis: (1) nondemented with amyloid precursor protein overproduction (Down syndrome); (2) nondemented with abnormal processing of amyloid precursor protein (preclinical autosomal dominant Alzheimer disease); (3) presumed alteration in Aβ clearance with clinical symptoms (late-onset AD); and (4) presumed alterations in Aβ clearance (preclinical AD).
Methods: We performed whole-brain voxelwise comparison of cerebral Aβ between 23 Down syndrome, 10 preclinical autosomal dominant Alzheimer disease, 17 late-onset AD, and 16 preclinical AD subjects, using PiB-PET.
Results: We found both Down syndrome and preclinical autosomal dominant Alzheimer disease shared a distinct pattern of increased bilateral striatal and thalamic Aβ deposition compared to late-onset AD and preclinical AD.
Conclusion: Disorders associated with early-life alterations in amyloid precursor protein production or processing are associated with a distinct pattern of early striatal fibrillary Aβ deposition before significant cognitive impairment. A better understanding of this unique pattern could identify important mechanisms of Aβ deposition and possibly important targets for early intervention.

Keywords: Down syndrome; Autosomal dominant Alzheimer dementia; Pittsburgh compound B; Striatum; Diffuse plaque; Aβ42

1. Introduction

Although the exact cause for the deposition of cerebral amyloid β (Aβ) plaques remains uncertain, two main mechanisms are currently proposed: altered processing or overproduction of amyloid precursor protein (APP)—as in autosomal dominant Alzheimer's disease (ADAD) or Down syndrome (DS)—and impaired clearance—as in the case of late-life Aβ deposition seen in preclinical AD (pre-AD), mild cognitive impairment, and late-onset AD (LOAD). It is probable that similar mechanisms contribute to both early- and late-onset forms of AD. However, it is clear that genetic disorders associated with the overproduction or altered enzymatic processing of APP are associated with a very high risk of AD two to three decades earlier than that typical for LOAD.

The pathological features are similar for all forms of AD, but those with ADAD and DS have been shown to have an

[1]These authors contributed equally to this work.
*Corresponding author. Tel.: (412) 246 6251.
E-mail address: cohenad@upmc.edu

https://doi.org/10.1016/j.jalz.2018.01.002
1552-5260/

increase in the Aβ42/40 ratio compared to LOAD [1–3]. In addition, Aβ PET studies in ADAD have identified a distinct pattern of early striatal deposition not commonly seen in LOAD, which was confirmed in a recent autopsy study [4]. If this is related to an increased production of APP, it might be expected that a similar pattern would be identified in DS [5].

Therefore, we evaluated the early PiB-PET Aβ deposition patterns in four different groups of subjects with evidence of cerebral β amyloidosis: (1) nondemented with APP overproduction (DS); (2) nondemented with abnormal processing of APP (preclinical ADAD [pre-ADAD]); (3) presumed alterations in Aβ clearance (pre-AD); (4) presumed alteration in Aβ clearance with clinical symptoms (LOAD). It was hypothesized that the pre-AD pattern of amyloid deposition in individuals with DS would be similar to that of those with pre-ADAD.

2. Methods

2.1. Design and participants

Following approval from the University of Pittsburgh and the University of Wisconsin-Madison Institutional Review Boards, all subjects were recruited through three ongoing studies of ADAD, DS (Pittsburgh and Wisconsin), and normal aging that included in vivo PiB-PET and cognitive/functional performance (Pittsburgh) with a modified Mini Mental State Examination. Further details of subject recruitment, cognitive, and functional evaluation and determination of clinical diagnosis are provided in previous publications [6–8]. Ten pre-ADAD subjects ≥18 years of age were included in the present study representing predominantly presenilin-1 mutation carriers as well as APP gene mutations. The DS subjects (n = 23) were ≥30 years of age. The pre-AD subjects (n = 16) and the LOAD subjects (n = 17) were ≥65 years of age and were matched to each other for both age and sex. ADAD gene mutations were confirmed through an approved commercial testing facility (Athena Diagnostics®, Worcester, MA) and chromosome 21 triplication was confirmed in all DS participants. All subjects underwent detailed cognitive and functional evaluations as well as magnetic resonance imaging (MRI) and PiB-PET imaging. For the purposes of this study, only those subjects determined to be nondemented, based on a standard neuropsychological test battery, designed to assess those areas of cognition known to be impaired in LOAD and also to be sensitive to mild cognitive impairment [9] were included in the pre-ADAD and pre-AD groups. All DS participants had a mental age ≥30 months (based upon the Stanford-Binet 5th edition [10]) and score in the asymptomatic range (<3 CCS score) on the Dementia Scale for Down Syndrome [11]. The Dementia Scale for Down Syndrome is an informant-completed 60-item questionnaire focused on symptoms of dementia in DS. It has been found to have good sensitivity and specificity [11]. None of the adults with DS were taking memory enhancement or AD medications or had a medical or psychiatric condition that would impair cognitive functioning. Preclinical dementia stage in DS was established by a caregiver report and the use of a standardized interview for dementia in DS. Only subjects considered to be regionally PiB-positive based on methods described previously were included in this study [12].

2.2. Imaging

MRI was performed with GE Medical Systems (Wisconsin) and Siemens Magnetom Trio (Pittsburgh). A volumetric MRI using the Alzheimer's Disease Neuroimaging Initiative sequence [13] was performed at the time of the PiB-PET scan for the purposes of coregistration, region of interest (ROI) placement, and atrophy correction. PET imaging was performed on a Siemens/CTI ECAT HR+ PET Scanner with a Neuro-insert (CTI PET Systems, Knoxville, TN) in a three-dimensional mode. The [C-11] PiB was injected intravenously (12–15 mCi, over 20 s, specific activity ∼1–2 Ci/μmol), and PET scanning was performed from 40 to 70 minutes postinjection (six 5-minute frames). The baseline full resolution MR was resliced along the AC-PC line and downsampled to PET voxel space. After addressing any motion, the PiB-PET data were summed to form a static image and coregistered to the downsampled MR image. The PiB-PET data were averaged over 50 to 70 minutes postinjection, and the analysis used a standardized uptake value ratio (SUVR) with cerebellar gray matter as reference [14]. Global PiB was computed as the average SUVR of the following regions: anterior cingulate, striatum, prefrontal cortex, lateral temporal cortex, parietal cortex, and precuneus cortex [14–16]. Here after, we refer to these six ROIs as the AD regions as they were derived from areas typically demonstrating high Aβ burden. PiB positivity was defined regionally based on an SUVR value above the cutoff in any one (or more) of these six regions.

For each subject, the structural MRI was visually inspected for any artifacts or abnormalities. The structural MRI was segmented and normalized to the Montreal Neurological Institute space with the unified-segment procedure in SPM8 [17]. For voxel-based analyses, the averaged 50- to 70-minute PiB-PET images were then coregistered to the segmented-normalized MRI and visualized for appropriate registration.

2.3. Statistical analysis and parametric imaging methods

Appropriate descriptive and inferential statistics were used to compare groups including Student *t-tests* and chi-squared tests. For the between-group comparison, we performed separate voxel-level *t*-tests across the entire brain with a global mean scaling to explore the effect of group status on PiB retention using SPM8. The statistical threshold was a false discovery rate of $P < .05$. The SUVR values from the AD region ROIs were compared across all groups using an ANOVA with Bonferroni's