Neurobiology of Aging 44 (2016) 108–113

Contents lists available at ScienceDirect

Neurobiology of Aging

journal homepage: www.elsevier.com/locate/neuaging

Effect of age at onset on cortical thickness and cognition in posterior cortical atrophy

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ARTICLE INFO

Article history:
Received 4 December 2015
Received in revised form 30 March 2016
Accepted 16 April 2016
Available online 25 April 2016

Keywords:
Posterior cortical atrophy
Age at onset
Neuroimaging
Cortical thickness
Atypical Alzheimer disease

ABSTRACT

Age at onset (AAO) has been shown to influence the phenotype of Alzheimer's disease (AD), but how it affects atypical presentations of AD remains unknown. Posterior cortical atrophy (PCA) is the most common form of atypical AD. In this study, we aimed to investigate the effect of AAO on cortical thickness and cognitive function in 98 PCA patients. We used Freesurfer (v5.3.0) to compare cortical thickness with AAO both as a continuous variable, and by dichotomizing the groups based on median age (58 years). In both the continuous and dichotomized analyses, we found a pattern suggestive of thinner cortex in precuneus and parietal areas in earlier-onset PCA, and lower cortical thickness in anterior cingulate and prefrontal cortex in later-onset PCA. These cortical thickness differences between PCA subgroups were consistent with earlier-onset PCA patients performing worse on cognitive tests involving parietal functions. Our results provide a suggestion that AAO may not only affect the clinico-anatomical characteristics in AD but may also affect atrophy patterns and cognition within atypical AD phenotypes.

1. Introduction

Alzheimer's disease (AD) is a neurodegenerative disease that typically presents with insidious and progressive memory loss and early atrophy in the hippocampus and medial temporal lobes (McKhann et al., 2011). Histopathologically, AD is characterized by the deposition of β-amyloid neuritic plaques, and intraneuronal neurofibrillary tangles, which typically first appear in entorhinal, limbic, and then neocortical regions and which are associated topographically with neuronal loss (Braak and Braak, 1991; Gomez Isla et al., 1997). The age at onset (AAO) of the disease has increasingly been recognized as a factor that may influence both the pattern of atrophy and the clinical symptoms in patients with AD (Kaiser et al., 2012). Early-onset AD, traditionally defined as onset before 65 years, differs from late-onset AD in that the pattern of cerebral atrophy in these younger individuals is more widespread, less prominent in medial temporal regions and more severe in posterior cingulate, temporo-parietal areas, and precuneus (Frisoni et al., 2005, 2007). Early-onset AD patients also show greater cortical atrophy and hypometabolism than late-onset AD at the same disease clinical stage (Kim et al., 2005). From a pathological point of view, studies have reported larger burden of pathology in younger patients (Marshall et al., 2007) and more widespread and more pronounced burden outside the medial temporal lobe compared with patients with late-onset AD. Atypical variants of AD are also commonly associated with an early AAO (Greicius et al., 2002) and more often present with nonmemory symptoms including visuospatial function, apraxia, and language deficits (Galton et al., 2000; Schott and Warren, 2012; Van der Flier et al., 2011).

Posterior cortical atrophy (PCA) is the most common atypical form of AD. It is characterized by insidious and gradual visual complaints in the absence of primary ocular disease (see Crutch et al., 2012 for a review). Symptoms typically progress over time to include other functions such as praxis and calculation and memory, whereas insight is relatively preserved until later stages

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0197-4580/
http://dx.doi.org/10.1016/j.neurobiolaging.2016.04.012

(Tang-Wai et al., 2004). PCA patients show atrophy mainly in parieto-occipital regions (Lehmann et al., 2011) with atrophy patterns progressing to a more global pattern with advancing disease stage (Lehmann et al., 2012). Pathologically, patients with PCA show fairly similar appearances to typical AD, although there are differences in the distribution of the pathological changes, with greater density of neurofibrillary tangles described in the parietal and occipito-temporal junction, and lower amyloid burden in the hippocampus (Hof et al., 1997; Tang-Wai et al., 2004). Although PCA is typically considered a young-onset form of AD, it can also occur in older patients. However, the pathophysiological underpinning of different ages at onset remains unknown.

In this study, we aimed to investigate the effect of AAO on cortical thickness in PCA. As early AAO in AD has been linked to a higher proportion of focal phenotypes, we expected individuals with earlier-onset PCA to show a more focal presentation compared with those with later-onset PCA. We therefore hypothesized that PCA patients with earlier AAO would have greater loss in cortical thickness in posterior regions compared with later-onset PCA.

2. Methods

2.1. Participants

This study involved a total of 98 PCA patients. Patients were recruited at 3 specialist centers: 81 patients at the Dementia Research Centre (DRC) at the National Hospital for Neurology and Neurosurgery London (UK), 9 patients at the University Hospital Virgen del Rocio (HUVR) Memory Disorders Unit (Spain), and 8 patients at University of California San Francisco (UCSF) Memory and Aging Center (US). Informed consent was obtained from all subjects and the study had local ethics committee approval. All patients met clinical diagnostic criteria for PCA (Mendez et al., 2002; Tang-Wai et al., 2004), fulfilled criteria for probable AD (Dubois et al., 2014; McKhann et al., 1984, 2011), and had to have a suitable MRI scan available. Patients at UCSF and HUVR were only included if they had undergone the same neuropsychological battery as patients from the DRC. For all centers, patients underwent comprehensive neurological examination. AAO was ascertained by asking participants or their caregivers when they first experienced symptoms. A group of 91 control subjects was included for comparison of the imaging data, matched for gender, age, scanner field strength, and site (64 DRC, 19 HUVR, and 8 UCSF). Demographics and clinical data are shown in Table 1.

2.2. Background neuropsychological testing

Detailed neuropsychological assessment was available for 68 of the 98 participants (52 DRC, 9 HUVR, 7 UCSF) and consisted of the mini-mental state examination (MMSE; Folstein et al., 1975), digit span forward and backward, short Recognition Memory Test (Warrington, 1996), graded difficulty arithmetic test (Jackson and Warrington, 1986), graded difficulty spelling test (Baxter and Warrington, 1994), assessment of apraxia through gesture production, and the subtest of figure-ground discrimination, fragmented letters, object decision, dot counting, and number location from the Visual Object And Space Perception Battery (Warrington and James, 1991).

Table 1
Demographics of the control group, total sample of PCA, and earlier- and later-onset PCA subgroups

	Controls	PCA	PCA ≤ 58	PCA > 58	*p*
N	91	98	49	49	
Gender	33 m/58f	40 m/58f	14 m/35f	26 m/23f	—
Age	64 ± 5	64 ± 7	58 ± 4	68 ± 5	<0.0001
Age at onset	—	59 ± 7	53 ± 3	63 ± 5	<0.0001
MMSE	—	19 ± 2	18 ± 5	21 ± 5	0.04
Disease duration, y	—	4.8 ± 0	5 ± 2	5 ± 2	0.77
Scanner (3T, 1.5T)	51, 40	53, 45	27, 22	26, 23	—

Data shown as mean (standard deviation).
Key: MMSE, mini-mental state examination; PCA, posterior cortical atrophy.

2.3. Image acquisition and processing

T1-weighted volumetric MR scans were acquired on 5 different scanners (two 3T Trio (DRC and UCSF), 1.5T Intera (HUVR), and two 1.5 Signa units [DRC]) using spoiled gradient recalled or gradient echo (MPRAGE) sequences. The scans consisted of full brain coverage coronal or sagittal slices running between 124 and 208 contiguous slices of 1.5 or 1.0 mm. Full details of imaging parameters are shown in the Supplementary Methods, and site and scanner distribution in earlier and later PCA are shown in Supplementary Table 1. For patients with neuropsychological assessment, all scans were performed within 6 months from cognitive testing. All scans were transferred to a Linux workstation for analysis.

Cortical thickness measurements were made using the freely available software Freesurfer, version 5.3.0 (http://surfer.nmr.mgh.harvard.edu/). The detailed procedure for the surface construction has been described and validated in previous publications (Dale et al., 1999; Fischl and Dale, 2000). Briefly, the image processing included intensity normalization, removal of nonbrain tissue, segmentation, surface inflation, and topological correction. Cortical thickness was then calculated as the closest distance from the grey/white boundary to the grey/CSF boundary at each vertex on the surface. Cortical thickness was smoothed with a 20-mm full-width at half height Gaussian kernel to reduce local variations in the measurements for further analysis. Surfaces were checked and manual edits were performed in cases of gross inaccuracies using the Freesurfer editing tools. Values for estimated total intracranial volume were also obtained from Freesurfer.

2.4. Statistical analysis

Both neuropsychological and neuroimaging data were analyzed using 2 different approaches: (1) comparing earlier- and later-onset PCA by splitting the PCA sample using the median AAO = 58 years as the cut-off value, and (2) using AAO as a continuous variable within the whole PCA sample.

2.4.1. Neuropsychological testing

The normality of score distribution was investigated for each neuropsychological test using the Kolmogorov–Smirnov test, and differences between groups were calculated using unpaired *t* test or *U* Mann–Whitney where scores were not normally distributed. Correlation between cognitive scores and AAO was performed using Spearman's correlation coefficient. Additional analyses were conducted correcting for MMSE and disease duration (in 2 separate models).

2.4.2. Cortical thickness

2.4.2.1. Controls versus PCA and earlier- versus later-onset PCA. Regional cortical thickness variations between controls and PCA, and earlier- and later-onset PCA were assessed using a vertex-by-vertex general linear model performed with the Surfstat software for Matlab (http://www.stat.uchicago.edu/~worsley/surfstat/). Cortical thickness was modeled as a function of group (controls, earlier-onset PCA, later-onset PCA), controlling for age (mean centered), gender, total intracranial volume, site, and field strength. Group differences between controls and PCA subgroups were corrected for multiple comparisons (family-wise error [FWE], $p < 0.05$), whereas