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White matter atrophy in Alzheimer's disease variants

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Abstract

Background: In comparison with late-onset Alzheimer's disease (LOAD, onset, >65 years), early-age-of-onset Alzheimer's disease (EOAD, onset, <65 years) more often presents with language, visuospatial, and/or executive impairment, often occurring earlier than a progressive memory deficit. The logopenic variant of primary progressive aphasia (lv-PPA) and posterior cortical atrophy (PCA) have recently been described as possible atypical variants of EOAD. Lv-PPA is characterized by isolated language deficit, whereas PCA is characterized by predominant visuospatial deficits. Severe hemispheric gray matter (GM) atrophy associated with EOAD, lv-PPA, and PCA has been described, but regional patterns of white matter (WM) damage are still poorly understood.

Methods: Using structural magnetic resonance imaging and voxel-based morphometry, we investigated WM damage in patients with EOAD (n = 16), PCA (n = 13), lv-PPA (n = 10), and LOAD (n = 14) at presentation and 72 age-matched control subjects.

Results: In patients with EOAD, PCA, and lv-PPA, WM atrophy was centered on the lateral temporal and parietal regions, including the cingulum and posterior corpus callosum. Compared with control subjects, patients with lv-PPA showed more severe left parietal damage, and patients with PCA showed more severe occipital atrophy. Moreover, patients with EOAD had greater cingulum atrophy compared with those with LOAD. LOAD showed WM damage in the medial temporal regions and less extensive hemispheric involvement.

Conclusion: Patterns of WM damage in EOAD, lv-PPA, and PCA are consistent with the clinical syndromes and GM atrophy patterns. WM injury in AD atypical variants may contribute to symptoms and disease pathogenesis.

Keywords: Alzheimer's disease; White matter damage; Cerebral network; Age of onset; Voxel-based morphometry

1. Introduction

Alzheimer's disease (AD) can present with distinct clinical profiles, depending on the age of onset. Typical late-onset AD ([LOAD], >65 years) presents with the classical progressive amnesic syndrome, whereas early-age-of-onset AD ([EOAD], <65 years) is often characterized by atypical manifestations with greater impairment in attention, executive, language, and visuospatial functions at the time of presentation.

Furthermore, we have demonstrated previously [1] that two relatively focal, early-onset (usually before 65 years) clinical syndromes—posterior cortical atrophy (PCA) [2] and the logopenic variant of primary progressive aphasia (lv-PPA) [3]—are often clinical variants of AD pathology and can thus be considered clinical variants of EOAD.

PCA is characterized by initially isolated, progressive impairment of higher order visual and visuospatial skills, which usually manifest as visual agnosia, prosopagnosia, environmental disorientation, and elements of Balint's syndrome [4,5]. Consistent with their clinical presentation, patients with PCA show brain damage in the parietal

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occipital and posterior temporal cortices, which is often more prominent in the right hemisphere [6–9].

Lv-PPA is a progressive language disorder characterized by slow speech, sentence repetition, and comprehension deficits, and relative sparing of motor speech, grammar, and single-word comprehension. Significant atrophy is located in the left posterior temporoparietal region [10].

A growing number of imaging studies are exploring white matter (WM) damage in typical LOAD, mainly reporting widespread WM abnormalities and tissue loss in the temporal, parietal, and frontal lobes, as well as in the corpus callosum [11]. Despite the clinical interest for the younger onset form of AD, very few studies have explored the in vivo pattern of WM involvement in EOAD [12], as well as in lv-PPA [13,14], and PCA [15–17].

The aim of the current study was to explore the patterns of WM atrophy in EOAD and in its atypical lv-PPA and PCA variants, and to compare them with that of typical LOAD. We hypothesized that younger patients would show preferential WM loss in the posterior neocortical brain regions, and that such a pattern would be more global and symmetrical in EOAD, and centered on the lateral parietal regions, with right and left lateralization in PCA and lv-PPA, respectively. In contrast, we expected that patients with LOAD would have a more circumscribed involvement of the medial temporal WM.

2. Methods

2.1. Subjects

Eligible subjects were identified by searching the database at the University of California at San Francisco (UCSF), Memory and Aging Center for patients meeting criteria for AD, PCA, and lv-PPA. Clinical diagnosis was based on a multidisciplinary evaluation including a history and neurological examination by a neurologist, caregiver interview by a nurse, and a neuropsychological test battery by a neuropsychologist. The diagnosis of probable AD was based on standard research criteria [18] in which memory impairment is required, even if in younger patients it does not have to be the main symptom. Then, based on the age of onset (age at the first symptom as reported by patient and caregivers), patients with AD were divided into EOAD (<65 years) and LOAD (>65 years). Memory impairment constituted the main clinical complaint in older patients. As expected [19], younger patients with AD presented at first evaluation with important attention/executive, visuospatial, praxis, and language deficits, whereas memory deficits, when present early, were often not considered the major cause of functional impairment. The following diagnostic criteria were applied, respectively, for PCA and lv-PPA: criteria by McMonagle et al. [20] and Alladi et al. [21], and criteria by Gorno-Tempini et al. [10].

Thirty right-handed patients with AD (16 EOAD and 14 LOAD) were included. The group size (16/14) was chosen to preserve similar power for the EOAD (mean age, 61 years) and LOAD (mean age, 78 years) analyses. Thirteen patients with PCA (mean age, 61 years) and 10 patients with lv-PPA (mean age, 63 years) were also identified (Table 1). To be included in the study, patients with needed to have undergone high-quality magnetic resonance imaging (MRI) within 6 months of the first clinical evaluation. No patient had a clear dominant family history of dementia or psychiatric diseases. During the diagnostic procedure, conventional magnetic resonance (MR) images were used to exclude other causes of focal or diffuse brain damage, including extensive WM disease. All the patients but those with LOAD were included in our previous article [1].

As previously reported [1], positron emission tomography with the amyloid beta tracer 11C-labeled Pittsburgh Compound-B study was conducted in a subgroup of patients: three with PCA, four with lv-PPA, and seven with EOAD. Autopsies were performed at UCSF for three additional patients—one with PCA, one with lv-PPA, and one with EOAD—showing, in all cases, amyloid deposition (on positron emission tomography) or AD pathology at autopsy.

Seventy-two healthy subjects, with no history of neurological or major psychiatric disorders (longstanding Axis I psychiatric disorder), were studied (younger control subjects: 38 women, 27 men, mean age of 61 years; older control subjects: 21 women, 10 men, mean age of 73 years).

Table 1
Demographic and global cognitive assessment data (at time of the scan) for patients and control subjects

	PCA	lv-PPA	EOAD	LOAD	Control subjects
No. of subjects	13	10	16	14	72
Female/male, n	8/5	4/6	6/10	6/8	42/30
Mean age at MRI, y (SD)	61 (8.2)	63.5 (7.2)	60.7 (3.7)	78.3 (5.6)*	62.3 (10.4)
Right-/left-handed, n	11/2	9/1	15/1	14/0	68/5
Education, y (SD)	15.1 (2.9)	17.2 (3.6)	15.8 (4.1)	15.8 (2.8)	17.6 (2.4)
Disease duration, y (SD)	3.3 (1.9)	3.3 (2.1)	4 (2.3)	3.6 (1.4)	—
MMSE score, (SD)	20.6 (7.0)	20.5 (4.4)	21.3 (5.6)	22.9 (6.9)	29.8 (0.4)†

Abbreviations: EOAD, early-onset Alzheimer's disease; LOAD, late-onset Alzheimer's disease; Lv-PPA, logopenic variant of primary progressive aphasia; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging; PCA, posterior cortical atrophy; SD, standard deviation.

*$P < .001$ versus early-onset forms.

†$P < .001$ versus patients.