ELSEVIER

Neurobiology of Aging 33 (2012) 1023–1033

NEUROBIOLOGY OF AGING

www.elsevier.com/locate/neuaging

Early and late onset Alzheimer's disease patients have distinct patterns of white matter damage

Elisa Canu[a], Giovanni B. Frisoni[b], Federica Agosta[a], Michela Pievani[a,b], Matteo Bonetti[c], Massimo Filippi[a,*]

[a] *Neuroimaging Research Unit, Institute of Experimental Neurology, Division of Neuroscience, Scientific Institute and University, Ospedale San Raffaele, Milan, Italy*

[b] *IRCCS, Centro San Giovanni di Dio - Fatebenefratelli, Brescia, Italy*

[c] *Service of Neuroradiology, Istituto Clinico Città di Brescia, Brescia, Italy*

Received 24 March 2010; received in revised form 29 July 2010; accepted 20 September 2010

Abstract

We investigated patterns of white matter (WM) loss in 18 early onset (EO) and 24 late onset (LO) Alzheimer's disease (AD) patients compared with 42 healthy controls (HC), and explored relationships of WM atrophy and apolipoprotein E (ApoE) genotype. Subjects underwent magnetic resonance imaging (MRI). Patterns of WM were assessed using voxel-based morphometry. Compared with healthy controls, LOAD patients had a selective parahippocampal WM loss, while EOAD patients experienced a more widespread pattern of posterior WM atrophy. The distinct regional distribution of WM atrophy reflected the topography of gray matter (GM) loss. ApoE ε4 status was associated with a greater parahippocampal WM loss in both AD groups. The greater WM atrophy in EOAD than LOAD fits with the evidence that EOAD is a more aggressive form of the disease. The ApoE ε4 effect on WM damage in AD is restricted to specific WM regions and does not seem to be related to age of onset.

Keywords: Alzheimer's disease; Early onset; White matter; Atrophy; VBM

1. Introduction

The term early onset (EO) Alzheimer's disease (AD) refers to patients who meet the criteria for AD (McKhann et al., 1984) and show onset of symptoms before the age of 65 years. Compared with the more frequent late onset (LO) AD, EOAD patients present with a more rapid clinical and cognitive decline and an earlier multidomain cognitive impairment, including language, visuospatial, and executive function deficits (Rogaeva, 2002). In these patients, memory deficits are variable and often not predominant (Klunemann et al., 2002; Maurer et al., 1997). Neuroimaging studies showed greater hypoperfusion (Hanyu et al., 1995), hypometabolism (Ichimiya et al., 1994; Mielke et al., 1992; Sakamoto et al., 2002; Yasuno et al., 1998), and gray matter (GM) atrophy (Frisoni et al., 2005, 2007; Ishii et al., 2005) in the parietal and dorsal temporal regions of EOAD patients, with a relative sparing of the hippocampus, when compared with LOAD patients.

While the majority of the neuroimaging studies on AD were restricted to the investigation of the GM damage, a growing body of evidence suggests that AD is associated with white matter (WM) loss mainly affecting the posterior portion of the corpus callosum, cingulum, and temporoparietal regions (Chaim et al., 2007; Double et al., 1996; Stoub et al., 2006; Teipel et al., 2002). Diffusion tensor magnetic resonance imaging (MRI) studies in AD patients reported WM microstructural abnormalities of the temporal, parietal, and frontal lobes as well as in the corpus callosum (Bozzali

* Corresponding author at: Neuroimaging Research Unit, Institute of Experimental Neurology, Division of Neuroscience, Scientific Institute and University Hospital San Raffaele, Via Olgettina, 60, 20132 Milan, Italy. Tel.: +39 02 26433033; fax: +39 02 26435972.

E-mail address: m.filippi@hsr.it (M. Filippi).

0197-4580/$ – see front matter © 2012 Elsevier Inc. All rights reserved.
doi:10.1016/j.neurobiolaging.2010.09.021

et al., 2002; Fellgiebel et al., 2005; Head et al., 2004; Rose et al., 2000; Stahl et al., 2007; Teipel et al., 2007). At present, the potential mechanisms leading to WM damage in AD are still poorly understood. Postmortem studies suggested that WM degradation in AD could be secondary to GM pathology or may be a primary myelin damage associated with oligodendrocyte death and reactive gliosis (Bronge et al., 2002; Englund, 1998; Englund and Brun, 1990; Englund et al., 1988; Sjobeck and Englund, 2003; Sjobeck et al., 2005). There is, to date, no evidence that age at onset of the disease influences WM loss in AD patients.

Apolipoprotein E (ApoE) is the major genetic risk factor for sporadic AD (Raber et al., 2004). This gene is on chromosome 19 which codes for a lipid transport protein, and has 3 major alleles (ε2, ε3, and ε4). Carriers of at least 1 ε4 allele have an increased risk of developing AD, as well as an associated dose-related decrease in age of onset (Farrer et al., 1997) and an increase of rate of cognitive decline (Cosentino et al., 2008). Neuroimaging studies have reported greater medial temporal lobe atrophy, particularly involving the hippocampus, in AD patients who are ε4 carriers vs. non carriers (Agosta et al., 2009; Geroldi et al., 1999; Hashimoto et al., 2001; Juottonen et al., 1998; Lehtovirta et al., 1995; Pievani et al., 2009). More recently, increased WM vulnerability in healthy individuals carrying the ApoE ε4 allele has been suggested (Bartzokis et al., 2007; Persson et al., 2006). To our knowledge, the only study investigating the ε4 effect on WM damage in AD focused on WM hyperintensities in patients with late age at onset (Bronge et al., 1999), showing a strong relationship between the ApoE ε4 allele and WM alterations in AD.

In this study, we investigated the patterns of WM loss in EOAD and LOAD patients compared with healthy controls. Consistent with their patterns of GM damage (Frisoni et al., 2005, 2007; Ishii et al., 2005), we hypothesized that LOAD patients would show a preferential WM loss in the medial temporal regions, while EOAD patients would have a more widespread involvement of the posterior parietotemporal WM. We also addressed whether ApoE ε4 allele carrier status interacts with age at onset in determining WM loss in AD patients.

2. Methods

2.1. Subjects

Eighteen EOAD and 24 LOAD patients, meeting the criteria for probable AD (McKhann et al., 1984), were recruited from the Translational Outpatient Memory Clinic (TOMC) of the IRCCS Centro San Giovanni di Dio Fatebenefratelli, Brescia, Italy. None of them had a family history suggestive of an autosomal dominant disease. Patients were matched on an individual basis for dementia severity as measured by the Clinical Dementia Rating (CDR) (Hughes et al., 1982) and for disease duration. When more than 1 matching LOAD patient was available, the 1 with the closest matching Mini Mental State Examination (MMSE) was chosen. Forty-two healthy controls (HC) were included and matched to the EOAD and LOAD patients based on age and gender. All participants underwent: history taking, laboratory examinations, physical and neurological examination, neuropsychological assessment, and MRI scan. Patient's history was taken with a structured interview from patients' relatives and age at onset was estimated from the caregiver's report of memory disturbances exceeding episodic forgetfulness (Frisoni et al., 1996). The local ethics committee approved the study. Written informed consent was obtained from all the subjects prior to enrollment into the study.

2.2. Neuropsychological assessment

Neuropsychological investigation assessed: global cognitive functioning with the MMSE (Folstein et al., 1975), visuospatial functions with the Rey figure copy test (Caffarra et al., 2002), frontal-executive functions with the Trail Making test (Amodio et al., 2002), and learning with Rey's word list immediate and delayed recall (Carlesimo et al., 1996), and Rey figure delayed recall (Caffarra et al., 2002) tests.

2.3. Genetic analysis

ApoE genotyping was carried out as previously described (Hixson and Vernier, 1990).

2.4. Image acquisition and analysis

Using a 1.0 Tesla scanner (Philips Gyroscan, Philips, Eindhoven, The Netherlands), the following sequences were obtained from all subjects: axial dual-echo (DE) (repetition time [TR] = 2000 ms, echo time [TE] = 8.8/110 ms, flip angle = 90°, field of view [FOV] = 230 mm^2, matrix size = 256 × 256, slice thickness = 5 mm, no gap); axial fluid-attenuated inversion recovery (FLAIR) (TR = 5000 ms, TE = 100 ms, flip angle = 90°, FOV = 230 mm^2, matrix size = 256 × 256, slice thickness = 5 mm, no gap); and high-resolution sagittal 3D gradient echo (TR = 20 ms, TE = 5 ms, flip angle = 30°, FOV = 220 mm^2, matrix size = 256 × 256, slice thickness = 1.3 mm).

WM hyperintensities (WMHs), if any, were identified on dual-echo and fluid-attenuated inversion recovery scans. An experienced observer reviewed the severity of WM hyperintensities according to the age-related WM change scale (Wahlund et al., 2001).

2.5. Voxel based morphometry

Voxel based morphometry (VBM) analysis was performed using the Statistical Parametric Mapping software (SPM8; Functional Imaging Laboratory, University College London, London, UK. Available at: http://www.fil.ion.ucl.ac.uk/spm/software/spm8/): (1) T1-weighted images were segmented using the VBM5.1 toolbox (Structural Brain Imaging Group, University of Jena, Jena, Germany. Available at: http://dbm.neuro.uni-jena.de/beta-version-of-vbm51-toolbox/) (Ashburner and Friston, 2005) to produce