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Striatal morphology in early-onset and late-onset Alzheimer's disease: a preliminary study

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ABSTRACT

We investigated volume and shape changes in the striatum (caudate, putamen, and nucleus accumbens) of 18 early-onset (EOAD) and 18 late-onset (LOAD) Alzheimer's Disease patients compared with 2 control groups age- and sex-matched to each patient group, and explored the relationship between striatal atrophy and apolipoprotein E (*APOE*) genotype. EOAD patients showed significant shape changes in the left and right ventral putamen ($p < 0.05$, corrected for multiple comparison with permutation tests). LOAD patients showed significant reductions in the left and right nucleus accumbens volumes ($p < 0.05$; Mann–Whitney test) and shape ($p < 0.05$; permutation test). Caudate abnormalities were detected in EOAD and LOAD patients in terms of local enlargements and reductions ($p < 0.05$ for the left and right, permutation test). When *APOE* was considered, significant differences were detected between LOAD $\varepsilon 4$ carriers and noncarriers in the left and right caudate ($p < 0.05$, permutation test). These results suggest distinct patterns of striatal pathology in EOAD and LOAD patients, the dorsal striatum being involved in EOAD and the ventral striatum in LOAD.

1. Introduction

An increasing amount of evidence indicates that early-onset and late-onset Alzheimer's Disease (AD) represent distinct clinical and pathological disease subtypes. AD patients developing symptoms after the age of 65 (LOAD) typically show memory impairment and prominent medial temporal lobe (MTL) atrophy (Filippi et al., 2012; Frisoni et al., 2005, 2007). Patients developing symptoms before age 65 (EOAD) show a greater occurrence of atypical symptoms (visuospatial, executive, and attentional function deficits) and greater neocortical atrophy (Balasa et al., 2011; Frisoni et al., 2005, 2007; Ishii et al., 2005; Karas et al., 2007; Shiino et al., 2006, 2008; Smits et al., 2012). The LOAD atrophy profile is consistent with the prototypical pattern of AD progression, originating from the MTL and limbic cortex and spreading to the neocortex (Braak and Braak, 1990). Even so, the typical profile of atrophy in EOAD follows a distinct pattern: earlier and more pronounced neocortical atrophy and later and less pronounced MTL atrophy; this pattern is also supported by recent neuropathological investigations (Murray et al., 2011). These observations have made it possible to identify specific clinical pathological correlates of early-onset and late-onset forms of AD and have important implications when using imaging biomarkers as surrogate outcomes in clinical trials.

Recent observations in familial EOAD have opened new perspectives on the pathological correlates of atypical AD. Studies in subjects carrying genetic mutations causative for AD show that the first site of pathological changes is the striatum (Klunk et al., 2007; Koivunen et al., 2008; Remes et al., 2008; Villemagne et al., 2009) leading to the hypothesis that striatal pathology might be a prominent phenotype in familial EOAD. In sporadic AD, post-mortem studies show that the striatum is affected by amyloid and tau pathology (Braak and Braak, 1990; Mann, 1991; Thal et al., 2002), and in vivo assessment of striatal atrophy demonstrated reduced putamen and caudate volumes (Barber et al., 2002; de Jong et al., 2008; Madsen et al., 2010) affecting primarily their anterior portions (de Jong et al., 2011; Karas et al., 2007; Looi et al., 2010; Madsen et al., 2010; Rombouts et al., 2000). No study, however, has investigated striatal atrophy in EOAD and LOAD. This distinction might be relevant for at least 2 reasons. First, sporadic EOAD shares several clinical features with familial EOAD (an earlier disease onset and greater occurrence of atypical symptoms than in LOAD) and therefore might share the same pathological phenotype. Second, the structural and functional organization of the striatum suggests

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a possible differential involvement of this structure in EOAD and LOAD. The striatum modulates 'atypical' and 'typical' AD functions (Albin et al., 1989; Alexander et al., 1986). The dorsal striatum, including the putamen and caudate, is part of the motor circuit and is primarily associated with sensorimotor disturbances (Alexander et al., 1986); the ventral striatum, including the nucleus accumbens, is part of the limbic circuit and is involved in behavior and memory functions (Alexander et al., 1986) and has been shown to be specifically vulnerable in typical AD (Suenaga et al., 1990). Considering the distinct clinical profiles of EOAD and LOAD, it can be hypothesized that striatal pathology might involve distinct nuclei in the 2 AD subtypes.

Based on this background, the present study aimed to assess the topography of striatal abnormalities in EOAD and LOAD. Using a shape-based approach, we outlined the nucleus accumbens, putamen, and caudate nucleus, and compared the volume and shape changes between each AD subtype and age- and sex-matched control subjects. Furthermore, we conducted a preliminary analysis to investigate whether the Apolipoprotein E (*APOE*) genotype influenced the pattern of striatal abnormalities. Because *APOE* genotype influences the pattern of cortical and MTL atrophy in AD (Pievani et al., 2009; Wolk et al., 2010) and might interact with age at onset in modulating the clinical phenotype (Van der Flier et al., 2011), we explored possible differences between $\varepsilon 4$ carriers and noncarriers in AD subgroups.

2. Methods

2.1. Participants and assessment

AD cases were recruited from the outpatients of the IRCCS Istituto Centro San Giovanni di Dio Fatebenefratelli, in Brescia, Italy. Each subject underwent history-taking, laboratory exams, a physical and neurological exam, a neuropsychological assessment, and magnetic resonance image (MRI) scanning, as described previously (Frisoni et al., 2007). In addition, cerebrospinal fluid sampling was performed in a subsample of participants, as detailed elsewhere (Frisoni et al., 2009). Briefly, history was taken with a structured interview from patients' relatives (usually spouses) and age at onset was estimated from the caregiver's report of memory disturbances exceeding the episodic forgetfulness that might be regarded as usual for the patient or report of other progressive cognitive disturbances (language, praxis, orientation, visuospatial skills) (Frisoni et al., 1996). Laboratory exams included complete blood count, chemistry profile, thyroid function, B_{12} and folic acid, and electrocardiogram. The neuropsychological assessment included the Mini Mental State Examination (MMSE; Folstein et al., 1975), Rey's word list (immediate and delayed recall; Carlesimo et al., 1996), Rey figure copy and delayed recall (Caffarra et al., 2002), letter and category fluency (Novelli et al., 1986), token test (De Renzi and Vignolo, 1962; Spinnler and Tognoni, 1987), and Trail Making Test Parts A and B (Amodio et al., 2002; Reitan, 1958). Motor symptoms were assessed with the Extrapyramidal Symptoms Scale (Richards et al., 1991).

Subjects were eligible if they had a diagnosis of AD according to core clinical criteria for probable AD (McKhann et al., 2011). Exclusion criteria were: (1) evidence of depression or disthymia; (2) abnormal laboratory test results; (3) other major systemic, psychiatric, or neurological illnesses; and (4) other causes of focal or diffuse brain damage on MRI scan (e.g., lacunae and extensive cerebrovascular disorders). According to these criteria, 18 AD patients with disease onset before the age of 65 (EOAD) were eligible for the study, and 18 AD patients with disease onset after the age of 65 (LOAD) were then matched 1:1 to EOAD patients by dementia severity as measured by the Clinical Dementia Rating (Hughes et al., 1982). When more than 1 matching LOAD patient was available, the one with the closest matching MMSE was chosen. None had a family history suggestive of autosomal dominant AD. All patients with cerebrospinal fluid data available (25%; $n = 9$) showed abnormal amyloid beta(1–42) levels according to the established cutoff (normal levels >500 pg/mL; Sjögren et al., 2001).

Healthy control subjects were selected from subjects enrolled in an ongoing study, described in detail elsewhere (Galluzzi et al., 2009). Exclusion criteria were the presence of any clinical, neurological, or neuropsychological impairment, and of cerebrovascular disease. Because EOAD and LOAD differ for age, we selected 2 control groups, matched for age and sample size to each patient group, as follows. Controls were matched 1:1 to AD patients based on age and sex, thus obtaining a control group for EOAD ($n = 18$; YC) and a control group for LOAD ($n = 18$; EC). When more than 1 matching control was available, the one with the closest matching educational level was chosen. Written informed consent was obtained from patients and control subjects. No compensation was provided for participating in the study. The study was approved by the local ethics committee.

2.2. Genetic analysis

Genomic DNA was extracted from whole-blood samples of subjects according to standard procedures. *APOE* genotyping was carried out by polymerase chain reaction amplification and HhaI restriction enzyme digestion. The genotype was resolved on 4% Metaphor Gel (BioSpa) and visualized by ethidium bromide staining (Hixson and Vernier, 1990).

2.3. MRI

MRI scans were acquired on a 1.0 T scanner (Philips Gyroscan, Philips, Eindhoven, The Netherlands) at the Neuroradiology Unit of the Hospital "Citta' di Brescia," in Brescia, Italy. The following sequences were acquired: (1) high-resolution T1-weighted sagittal gradient echo (repetition time = 20 ms, echo time = 5 ms, flip angle = 30°, field of view = 220 mm, acquisition matrix = 256 × 256, and slice thickness = 1.3 mm); and (2) axial fluid attenuated inversion recovery (repetition time = 5000 ms, echo time = 100 ms, flip angle = 90°, field of view = 230 mm, acquisition matrix = 256 × 256, slice thickness = 5 mm). White matter (WM) hyperintensities, if any, were identified on the fluid attenuated inversion recovery scans according to the age-related WM change scale (Wahlund et al., 2001).

2.4. Striatal volumetry

The nucleus accumbens, caudate nucleus, and putamen were manually traced by a single tracer, blind to clinical, neuropsychological, and MRI findings, following an optimized protocol based on landmarks and criteria defined in established protocols (Gunning-Dixon et al., 1998; Hokama et al., 1995; Makris et al., 1999). A detailed description of the criteria used can be found elsewhere (Boccardi et al., in press). The 3-D images were preprocessed according to procedures previously described (Frisoni et al., 2007). Briefly, the images were reoriented along the anterior-posterior commissure (AC-PC) line, normalized to a customized template with a 12-parameter affine transformation, and resampled to 1-mm isotropic voxels. Tracings were carried out with the MultiTracer software (http://www.loni.ucla.edu/Software/MultiTracer) on the reoriented, normalized, 1-mm thick coronal brain sections, from posterior to anterior, while simultaneously checking the sagittal and axial planes (Fig. 1 shows the striatal nuclei outlined on scans of representative EOAD and LOAD