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Similar pattern of atrophy in early- and late-onset AD

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Abstract

Background: Previous research on structural changes in early-onset Alzheimer's disease (EOAD) and late-onset Alzheimer's disease (LOAD) have reported inconsistent findings.

Material: Study participants (N = 145) included 63 patients with AD, (24 patients with EOAD [aged ≤65 years], 39 patients with LOAD [aged >65 years]), 25 healthy controls aged ≤65 years, and 57 healthy controls aged >65 years.

Methods: In the present substudy of the Gothenburg MCI study, 1.5 T scans were used to estimate lobar and hippocampal volumes using FreeSurfer.

Results: Hippocampal atrophy is the most prominent feature of both EOAD and LOAD compared with controls. Direct comparison between EOAD and LOAD showed that the differences between the groups did not remain after correcting for age.

Discussion: Structurally, EOAD and LOAD does not seem to be different nosological entities. The difference in brain volumes between the groups compared with controls is likely due to age-related atrophy.

Keywords: Early-onset AD; Late-onset AD; MRI; Neuroimaging; Hippocampus

1. Introduction

Alzheimer's disease (AD) is the most common type of dementia and is believed to account for approximately 50 to 70% of all cases of dementia [1]. AD is characterized by typical neuropathological changes, neurofibrillary tangles, and senile plaques, gradually spreading throughout the brain [2]. Traditionally, AD is categorized as either early-onset Alzheimer's disease (EOAD, age ≤65 years) or late-onset Alzheimer's disease (LOAD, age >65 years). EOAD is thought to have a faster rate of progression and shows a greater neuropathological burden than LOAD [3]. Cognitively, LOAD is characterized by a classic AD profile with impaired semantic memory function as the most prominent finding whereas EOAD may present a more atypical profile with apraxia and impaired visuospatial functions [4]. Structural imaging studies have been performed to elucidate whether EOAD is AD with an earlier starting point or if EOAD should be regarded as a different nosological entity. The interpretation of these imaging studies is complicated by generally small group sizes and different methodological approaches. Although not consistent, most studies have reported a higher degree of neocortical atrophy in EOAD compared with LOAD [5–9]. Although some studies do not find a difference in hippocampal atrophy between EOAD and LOAD [9,10], most studies report more pronounced hippocampal atrophy in LOAD [5,6,8,11].

A better understanding of the structural brain changes taking place in AD and their relation to age at onset would be useful to improve inclusion criteria in future intervention studies and also for increasing the etiological/nosological

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understanding of the disease. Furthermore, as patients with dementia diseases often undergo an incipient phase when differential diagnostics can be difficult, information on patterns of atrophy in AD at different ages of onset will be highly valuable.

The aim of the present study is to investigate if EOAD and LOAD have different patterns of atrophy compared with healthy controls of similar age and also by direct comparison between EOAD and LOAD.

2. Materials

2.1. The Gothenburg MCI study

The Gothenburg MCI study is a clinically based longitudinal study that aims at identifying neurodegenerative, vascular, and stress-related disorders before the development of dementia [12]. The Gothenburg MCI study is approved by the Local Ethics Committee (diary number: L091-99, 1999; T479-11, 2011). Inclusion requires subjective and/or objective (by an informant) verifications of a progressive cognitive impairment for more than 6 months, age $\geq$50 and $\leq$ 79 years, and Mini–Mental State Examination (MMSE) score $\geq$18. Exclusion criteria are acute/instable somatic disease, severe psychiatric disorder, or substance abuse.

Healthy controls were recruited from senior citizens' organizations. Controls were not included if they had subjective or objective signs of cognitive disorder as assessed with the aforementioned procedure or fulfilled any of the aforementioned exclusion criteria.

2.2. Classification

Patients' degree of decline was staged according to the Global Deterioration Scale (GDS). GDS classification is made by means of checklists and instruments for cognitive symptoms [12]. The guidelines for the classification used are as follows: for GDS 4 (mild dementia) participants should have MMSE $\leq$ 25, CDR sum of boxes $>$ 1.0, I-FLEX $>$ 3, and two or more positive outcomes on variables 13 to 20 of STEP [13]. When the guidelines are not applicable, a consensus decision among physicians at the clinic is made to determine appropriate GDS score. All patients classified as GDS 4 were further assessed by a specially trained physician for specific dementia diagnosis. Anamnestic and clinical symptomatology and the presence of cerebral white matter changes determined by a modified version of the Fazekas scale were taken into account in the diagnostic procedure [14]. If the diagnosis cannot be unambiguously determined, then it is further discussed and established in a clinical consensus meeting. AD is diagnosed using the NINCDS-ADRDA criteria for AD [15]. For an AD diagnosis, the patient must have at most only mild white matter changes and predominant temporoparietal lobe symptoms. This was done to ensure that no patients with mixed dementia were classified as AD. Only patients with GDS 4 and an AD diagnosis were included in the present study. The guidelines and diagnostics are described in detail in a previous publication [12].

2.3. The present study

The present study is a substudy of the Gothenburg MCI study. An additional inclusion criterion for all participants was a magnetic resonance imaging scan using a Siemens Symphony 1.5 T scanner available for analysis. Patients also had to be classified as GDS 4 and subsequently received an AD diagnosis according to the NINCDS-ADRDA criteria.

The total patient group (N = 145) consisted of 63 patients with AD and 94 healthy controls. Of the 63 AD patients, 24 were $\leq$65 years and classified as EOAD, and 39 were $>$65 years, that is, LOAD. Of the healthy controls, 25 were $\leq$65 years, and 57 were $>$65 years. Patients with mixed dementia or vascular dementia were not included in the study.

3. Methods

A 1.5 T scanner (Siemens Symphony, Erlangen, Germany) was used for the magnetic resonance data acquisition. FreeSurfer volumetry was performed on T1 3D IR/GR images (repetition time 1610 ms, echo time 2.38 ms, flip angle 15°, coronal slices, field of view 250 mm $\times$ 203 mm, slice thickness 1 mm, pixel spacing 0.49 mm $\times$ 0.49 mm, and matrix size 512 $\times$ 416).

Cerebrospinal fluid (CSF) samples were collected by lumbar puncture. CSF T-tau and amyloid β 42 levels were determined using a sandwich enzyme-linked immunosorbent assay constructed to measure T-tau or amyloid β 42 [16].

3.1. FreeSurfer

Brain volumes were measured using the automated segmentation software, FreeSurfer, version 5.3.0, which is freely available for download online [17]. The FreeSurfer analyses were performed on a computing cluster running 64 bit CentOS 6. These analyses were performed on nodes based on Supermicro X9DRT Intel E5-2670 (Sandy Bridge) running at 2.6 GHz. A few analyses were also performed using a MacPro 3.1 with 64 bit 2 GHz $\times$ 2.8 GHz quad-core Intel Xeon processors and Mac OSX 10.8.5.

The calculation of surface volumes in FreeSurfer begins with an affine alignment to the MNI305 atlas, an intensity normalization, and removal of the skull [18,19]. Voxels are then classified as white matter or nonwhite matter by a threshold classification that is refined by some assumptions of the classification of the given voxel and its neighboring voxels [18]. Seed points in corpus callosum and the pons from the atlas alignment are then used to find two cut planes to separate the hemispheres and to remove subcortical structures [18]. A white matter surface is then generated for each hemisphere by the outer boundary of the white matter volume and some refinement based on intensities gradients [18,20]. The pial surface is then deformed outward from