Neurobiology of Aging 70 (2018) 18–29

Contents lists available at ScienceDirect

Neurobiology of Aging

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

The contribution of small vessel disease to subtypes of Alzheimer's disease: a study on cerebrospinal fluid and imaging biomarkers

Daniel Ferreira [a,*], Sara Shams [b,c], Lena Cavallin [b,c], Matti Viitanen [a], Juha Martola [b,c], Tobias Granberg [b,c], Mana Shams [b,c], Peter Aspelin [b,c], Maria Kristoffersen-Wiberg [b,c], Agneta Nordberg [d,e], Lars-Olof Wahlund [a,e], Eric Westman [a,f]

[a] Division of Clinical Geriatrics, Department of Neurobiology, Care Sciences, and Society, Centre for Alzheimer Research, Karolinska Institutet, Stockholm, Sweden
[b] Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden
[c] Department of Radiology, Karolinska University Hospital, Stockholm, Sweden
[d] Department of Neurobiology, Care Sciences, and Society, Centre for Alzheimer Research, Translational Alzheimer Neurobiology, Karolinska Institutet, Stockholm, Sweden
[e] Department of Geriatric Medicine, Karolinska University Hospital, Stockholm, Sweden
[f] Department of Neuroimaging, Centre for Neuroimaging Sciences, Institute of Psychiatry, Psychology, and Neuroscience, King's College London, London, UK

ARTICLE INFO

Article history:
Received 20 March 2018
Received in revised form 10 May 2018
Accepted 22 May 2018
Available online 30 May 2018

Keywords:
Alzheimer's disease
Subtypes
Small vessel disease
Magnetic resonance imaging
Neurodegeneration
Cerebrospinal fluid biomarkers

ABSTRACT

We investigated whether subtypes of Alzheimer's disease (AD), that is, typical, limbic-predominant, hippocampal-sparing, and minimal atrophy AD, had a specific signature of small vessel disease and neurodegeneration. Four hundred twenty-three clinically diagnosed AD patients were included (161 typical, 121 limbic-predominant, 70 hippocampal-sparing, 71 minimal atrophy). One hundred fifty-six fulfilled a biomarkers-based AD diagnosis. White matter hyperintensities and cerebral microbleeds (CMB) had the highest prevalence in limbic-predominant AD, and the lowest prevalence in minimal atrophy AD. CMB existed evenly in lobar and deep brain areas in limbic-predominant, typical, and hippocampal-sparing AD. In minimal atrophy AD, CMB were mainly located in brain lobar areas. Perivascular spaces in the centrum semiovale were more prevalent in typical AD. Small vessel disease contributed to the prediction of Mini-Mental State Examination. Minimal atrophy AD showed highly pathological levels of cerebrospinal fluid Aß$_{1-42}$, total tau, and phosphorylated tau, in the absence of overt brain atrophy. Cerebral amyloid angiopathy seems to have a stronger contribution to hippocampal-sparing and minimal atrophy AD, whereas hypertensive arteriopathy may have a stronger contribution to typical and limbic-predominant AD.

© 2018 Elsevier Inc. All rights reserved.

1. Introduction

The clinical syndrome of Alzheimer's disease (AD) is heterogeneous and often harbors multiple neuropathologies (Boyle et al., 2018; Schneider et al., 2007). Autopsy data of more than 1000 participants have recently shown that 65% of the subjects had AD pathology at autopsy, whereas only 43% received a clinical diagnosis of AD during life (Boyle et al., 2018). Furthermore, AD pathology rarely occurred in isolation (only in 9% of the participants), because most cases had mixed pathology (44% had other neurodegenerative and vascular pathology and 40% had at least 1 type of vascular pathology) (Boyle et al., 2018). The low accuracy of the clinical diagnosis together with the progress made in biomarkers research has led to a shift in the definition of AD as a biological construct (Jack et al., 2018). Accordingly, amyloid positivity is mandatory for the diagnosis of AD (Jack et al., 2018; McKhann et al., 2011). Furthermore, recent data shows that not only the presence of neurofibrillary tangles (NFT) is relevant, but also the spatial distribution of the NFT in the brain, together with corresponding patterns of atrophy (Ekman et al., 2018; Murray et al., 2011; Whitwell et al., 2012).

Three distinct subtypes based on the spread of NFT in the brain have been described (Murray et al., 2011). Typical AD has rather balanced NFT counts in the hippocampus and the association

Equal contribution Daniel Ferreira, Sara Shams.

* Corresponding author at: Centre for Alzheimer Research, Division of Clinical Geriatrics, Department of Neurobiology, Care Sciences, and Society, Karolinska Institutet, NEO, Floor 7th, Room 7833, Blickagången 16, 141 52 Huddinge, Sweden. Tel.: +46 7 201 28 047; fax: +46 8 585 85 470.
E-mail address: daniel.ferreira.padilla@ki.se (D. Ferreira).

0197-4580/$ – see front matter © 2018 Elsevier Inc. All rights reserved.
https://doi.org/10.1016/j.neurobiolaging.2018.05.028

cortex, whereas limbic-predominant AD has NFT counts predominantly in the hippocampus, and hippocampal-sparing AD has NFT counts predominantly in the association cortex. These subtypes can be tracked in vivo by investigating corresponding atrophy patterns on structural magnetic resonance imaging (MRI) of the brain (Whitwell et al., 2012). Several studies have confirmed them in independent cohorts by using a variety of advanced MRI techniques for data analysis and clustering (Byun et al., 2015; Dong et al., 2017; Hwang et al., 2015; Noh et al., 2014; Park et al., 2017; Poulakis et al., 2018; Risacher et al., 2017; Varol et al., 2017; Zhang et al., 2016). In addition, we have recently validated a method to easily determine these subtypes in clinical practice by applying visual rating scales of regional brain atrophy (Ekman et al., 2018; Ferreira et al., 2017). A fourth subtype with no or minimal atrophy has also been identified (Byun et al., 2015; Dong et al., 2017; Ferreira et al., 2017; Poulakis et al., 2018).

Another contributor to heterogeneity in the clinical syndrome of AD is small vessel disease (Boyle et al., 2018). Cerebral amyloid angiopathy (CAA, i.e., amyloid deposition in vessel walls) and hypertensive arteriopathy (i.e., hypertensive small vessel damage) are the 2 most common forms of small vessel disease (Pantoni, 2010). Both cause microvascular frailty and are associated with cognitive decline and increased mortality. CAA mainly affects brain lobar areas, and hypertensive arteriopathy mainly affects deep brain areas, although certain overlap exists (Shams et al., 2017a). Because the microvasculature affected is too small to be studied per se, different MRI measures are used as surrogate markers of small vessel disease (Wardlaw et al., 2013). These MRI markers have been associated with amyloid and tau levels in the cerebrospinal fluid (CSF) (Shams et al., 2017a), as well as with amyloid PET binding (Park et al., 2013).

Previous research on AD subtypes has focused on gray matter atrophy, mostly in the cortex and the hippocampus (Byun et al., 2015; Dong et al., 2017; Ferreira et al., 2017; Hwang et al., 2015; Murray et al., 2011; Noh et al., 2014; Park et al., 2017; Varol et al., 2017; Whitwell et al., 2012; Zhang et al., 2016). Small vessel disease as a contributor to AD subtypes has only been marginally investigated, and its role in determining subtype is unknown. We aimed to fully characterize AD subtypes with regards to small vessel disease, amyloid, NFT, and neurodegenerative pathology, to bring to light the implications of small vessel disease in AD heterogeneity. We investigated a large cohort of clinically diagnosed AD patients because core clinical criteria are still the cornerstone. However, as explained previously, the clinical diagnosis of AD is inaccurate and often shows a mismatch with the biomarkers-based diagnosis of AD. Thus, we also classified our patients into amyloid positive and amyloid negative and characterized these 2 groups. Reporting our data for both a clinical diagnosis and a biomarkers-based diagnosis can be of interest from a clinical and research perspective and may be relevant to better understand how small vessel disease contributes to heterogeneity in these groups.

2. Materials and methods

2.1. Participants

Patients with a clinical diagnosis of AD (N = 423) undergoing investigation between January 2006 and December 2011 as part of the Karolinska Imaging Dementia Study (Shams et al., 2015), were recruited for this study. Other diagnoses, such as dementia with Lewy bodies, vascular dementia, alcohol-related dementia, mild cognitive impairment, etc., were excluded. Further exclusion criteria for the present study were insufficient MRI scan quality, inability to undergo an MRI investigation, or a history of traumatic brain injury.

All patients underwent a thorough investigation, including neuropsychological examination and brain MRI. The APOE ε4 genotype and CSF biomarkers were available for 152 and 280 patients, respectively. Diagnosis was determined in multidisciplinary rounds according to the International Statistical Classification of Diseases and Related Health Problems–10th Revision (ICD-10), based on all the available clinical information, including comprehensive cognitive testing. MRI was used to exclude potential non-AD causes of cognitive impairment. The visual rating scales described further down were only applied for research purposes (i.e., the scales were not part of the diagnostic procedure). CSF was available for a percentage of the patients, also for research purposes (i.e., CSF biomarkers were not part of the diagnostic procedure). The ICD-10 criteria are thus similar to the core clinical criteria of the 2011 National Institute on Aging–Alzheimer's Association criteria of AD (McKhann et al., 2011). Please see these 2 diagnostic criteria in Supplementary Table 1.

For the aims of the present study, patients with available CSF data were rediagnosed into 2 separate groups according to the research criteria of the 2011 National Institute on Aging–Alzheimer's Association criteria (McKhann et al., 2011) (Supplementary Table 1): the amyloid-positive subsample, including amyloid-positive (CSF $A\beta_{1-42} \leq 550$) patients, with no mixed or unspecified dementia according to the ICD-10 coding, and no large brain infarctions; and the amyloid-negative subsample, including amyloid-negative (CSF $A\beta_{1-42} \leq 550$) patients.

Written informed consent was obtained from the patients or a legal guardian. Ethical approval was obtained from the Regional ethics board in Stockholm, Sweden, in accordance with the Declaration of Helsinki.

2.2. Magnetic resonance imaging, regional brain atrophy, and small vessel disease

Susceptibility-weighted imaging and/or T2* gradient recalled echo, as well as conventional T1-weighted, T2-weighted, and fluid-attenuated inversion recovery sequences were performed. Three MRI scanners (Siemens, Erlangen, Germany) at the Radiology Department of Karolinska University Hospital, Stockholm, Sweden, were used. Scanner specifications and scanning parameters are provided elsewhere (Shams et al., 2015).

Regional brain atrophy was assessed with visual rating scales as previously detailed (Ferreira et al., 2015b). Medial temporal atrophy (MTA) was assessed with the Scheltens' scale (Scheltens et al., 1992), posterior atrophy (PA) with the Koedam's scale (Koedam et al., 2011), and atrophy in the frontal lobe with the global cortical atrophy scale–frontal subscale (GCA-F) (Ferreira et al., 2015a). Reliability (weighted κ) in 120 random cases was as follows: Intra-rater (L.C.): MTA-left = 0.94, MTA-right = 0.89, PA = 0.88; GCA-F = 0.83; Inter-rater (L.C. vs. rater 2): MTA-left = 0.71, MTA-right = 0.70; PA = 0.88, GCA-F = 0.79. Raters were blinded to patient information and each other's ratings.

Small vessel disease imaging markers were all assessed according to the STRIVE (Wardlaw et al., 2013). Cerebral microbleeds (CMB) were analyzed according to the Microbleed Anatomical Rating Scale (Gregoire et al., 2009). Cortical superficial siderosis was rated as linear, gyriform, and hypointense (Charidimou et al., 2015). The total burden of white matter hyperintensities (WMH) was rated with the Fazekas scale (Fazekas et al., 1987), and its topography with the age-related white matter changes scale (Wahlund et al., 2001). Lacunes were defined as 3–15 mm CSF-filled cavities, with a hyperintense rim on fluid-attenuated inversion recovery. Perivascular spaces (PVS) were rated in the centrum semiovale and basal ganglia according to a standardized scale (Potter et al., 2015). Image analysis was performed by 2 raters (JM and SS), blinded to

Download English Version:

https://daneshyari.com/en/article/6802804

Download Persian Version:

https://daneshyari.com/article/6802804

Daneshyari.com