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White matter hyperintensities predict amyloid increase in Alzheimer's disease

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Abstract

Impaired amyloid clearance probably contributes to increased amyloid deposition in sporadic Alzheimer's disease (AD). Diminished perivascular drainage due to cerebral small-vessel disease (CSVD) has been proposed as a cause of reduced amyloid clearance. White matter hyperintensities (WMHs) are considered to reflect CSVD and can be measured using fluid-attenuated inversion recovery (FLAIR) magnetic resonance imaging (MRI). Amyloid deposition can be determined *in vivo* using Pittsburgh compound B ([^{11}C]PiB) positron emission tomography (PET). We aimed to elucidate the association between WMH and the progression of amyloid deposition in patients with AD. Twenty-two patients with probable AD underwent FLAIR-MRI and [^{11}C]PiB-PET examinations at baseline (BL) and after a mean follow-up (FU) interval of 28 months. The relationship between BL-WMH and the progression of cerebral amyloid between BL and FU was examined using a regions-of-interest (ROI) approach. The region-specific variability of this relationship was analyzed using a voxel-based method. The longitudinal analysis revealed a statistically significant association between the amount of BL-WMH and the progression of amyloid load between BL and FU (p = 0.006, adjusted R^2 = 0.375, standardized coefficient β = 0.384). The association was particularly observed in parieto-occipital regions and tended to be closer in regions adjacent to the brain surface. According to our knowledge, this is the first *in vivo* study in human being supporting the hypothesis that impaired amyloid clearance along perivascular drainage pathways may contribute to β-amyloid deposition in sporadic AD. The extent of WMH might be a relevant factor to be assessed in antiamyloid drug trials.

Keywords: Alzheimer's disease; White matter hyperintensities; Positron emission tomography; Pittsburgh compound B; Prospective study

1. Introduction

The characteristic histopathological features of Alzheimer's disease (AD) include senile plaques and neurofibrillary tangles in conjunction with loss of neurons and synapses (Braak and Braak, 1991; Thal et al., 2002.). The major constituent of senile plaques is amyloid-β peptide (Aβ).

Mutations leading to an overproduction of Aβ are recognized as a major cause of aggregation of the peptide in early-onset familial AD (Hardy and Selkoe, 2002). However, the reasons for β-amyloid deposition in late-onset sporadic AD are less clear (Duyckaerts et al., 2009). One hypothesis is that an impaired clearance of β-amyloid contributes to cerebral amyloid deposition (Thal, 2009). This notion is strengthened by the finding that AD patients had identical β-amyloid production rates but decreased β-amyloid clearance rates relative to normal control subjects (Mawuenyega et al., 2010). From animal studies, it is known that molecules contained in the interstitial fluid (ISF) are cleared from the brain via different pathways. Whereas ISF of white matter seems to be preferentially drained

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into the cerebrospinal fluid (CSF) directly, the ISF of gray matter appears to flow outward via perivascular spaces, which are located alongside cerebral arteries, and to empty into cervical lymph nodes (Carare et al., 2008; Szentistvanyi et al., 1984; Weller, 1998; Zhang et al., 1992). The latter drainage pathway could be impaired in late-onset AD. As a consequence, amyloid may be less efficiently cleared from the brain and become deposited in the form of β-amyloid plaques.

White matter hyperintensities (WMHs) detected in free fluid-suppressing and tissue fluid-sensitive magnetic resonance imaging (MRI) sequences such as fluid-attenuated inversion recovery (FLAIR) are considered to reflect pathology of small cerebral arteries, which cannot be imaged directly (Pantoni, 2010). From a histopathological perspective, WMHs are considered to be a consequence of thickening and sclerosis of arterial small vessel walls associated with the accumulation of extracellular matrix components. Such changes in vessel walls might lead to impaired perivascular drainage of molecules including Aβ (Huang et al., 2010). However, our knowledge of the etiology of WMH is still evolving.

The amount and progression of amyloid deposition during the course of AD can be monitored using positron emission tomography (PET) by means of the radiotracer [^{11}C]PiB (Pittsburgh compound B) (Grimmer et al., 2010). The progression is accelerated by the ε4 allele of the apolipoprotein E (ApoE) gene in a gene dose-dependent fashion (Grimmer et al., 2010).

In the present study, we sought *in vivo* evidence for a pathophysiological model, which assumes that impaired amyloid clearance results in increased amyloid deposition in the brain. We addressed the following questions:

(1) Is the amount of WMH used as an indicator of impaired perivascular drainage associated with the progression of amyloid load in AD patients;

(2) Is there a regional variability of this association;

(3) Can an association between WMH and amyloid load also be demonstrated by cross-sectional baseline measurement; and

(4) Does the ApoE genotype have an effect on WMH?

Additional analyses were performed to determine whether the data support the clearance hypothesis or rather favor the assumptions that WMHs are caused by amyloid deposition or that during the course of AD, amyloid accumulation and WMH formation coexist but are unrelated.

2. Methods

2.1. Patient recruitment, inclusion and exclusion criteria

Recruitment and inclusion criteria of the patient sample have been described elsewhere (Grimmer et al., 2010). Briefly, outpatients with very mild-to-moderate dementia, as rated on the Clinical Dementia Rating scale (CDR; 0.5–2) (Morris et al., 1989), who fulfilled National Institute of Neurological Disorders and Stroke–Alzheimer's Disease and Related Disorders Association (NINCDS-ARDRA) diagnostic criteria for probable AD (McKhann et al., 1984) were included. They had been referred for the diagnostic evaluation of cognitive impairment by general practitioners, neurologists, psychiatrists, or other institutions, and had undergone a standardized diagnostic procedure including the Mini-Mental State Examination (MMSE) (Folstein et al., 1975) and ApoE genotyping (Zivelin et al., 1997). To enhance the likelihood of underlying AD pathology, cranial positron emission tomography with 2-deoxy-2-[^{18}F]fluoro-D-glucose ([^{18}F]FDG-PET) findings typical for AD were also required for inclusion (Hoffman et al., 2000; Jagust et al., 2007), that is, hypometabolism in the temporo-parietal and posterior cingulate cortex with relative sparing of the primary sensomotor cortex on visual inspection (Minoshima, 2003). All patients underwent cranial MRI on a 1.5-T scanner to assess structural brain abnormalities, and only patients in whom a FLAIR sequence suitable to evaluate WMH was available were considered for analysis. In addition, [^{11}C]PiB-PET was used to assess brain amyloid burden. All patients underwent a follow-up examination including MRI with FLAIR and PET imaging after a mean interval of 28 ± 5.7 months.

2.2. Brain imaging

Structural MRI, [^{18}F]FDG-PET, and [^{11}C]PiB-PET of the brain were obtained at baseline and at follow-up examinations using standard procedures (Grimmer et al., 2009a,b, 2010). The [^{11}C]PiB images were coregistered to high-resolution MRI scans and normalized to the Montreal Neurological Institute (MNI) space using the warping parameters of the MRI to obtain interindividually comparable images.

FLAIR sequences comprised the following parameters: repetition time (TR) = 9000 ms; echo time (TE) = 105 ms, inversion time (TI) = 2500 ms, and 3-mm slices.

Using the standard reference tissue model (Ziolko et al., 2006), a relative measure of cerebral [^{11}C]PiB uptake was obtained by calculating a cerebral cortex to cerebellar vermis (C/cv) ratio of each patient's [^{11}C]PiB Standardized Uptake Value (SUV) 40–70-min scan to control for between-subjects differences in tracer uptake using standard methods (Grimmer et al., 2009a,b, 2010). [^{11}C]PiB increase was calculated by subtracting baseline C/cv ratio from the ratio at follow-up.

The amount of subcortical WMH was assessed by visual inspection using a standard semiquantitative score that considered both number and size of lesions (Scheltens et al., 1993). We favored a visual rating over automatic routines to avoid false-positive classifications, for example, of lacunar infarcts. Scores for regional subcortical WMH (range, 0–6) were obtained for the frontal, temporal, parietal, and occipital white matter of each side separately and added to one total score. Assessment of WMH was conducted by an experienced neuroradiologist (F.A.) blinded to time point of examination, patient identification, and all clinical and other imaging data. To reduce inter-rater variability, all ratings