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Short Report

Cerebral small vessel disease in middle age and genetic predisposition to late-onset Alzheimer's disease

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Abstract

Introduction: Cerebral small vessel disease (CSVD) is associated with late-onset Alzheimer's disease (LOAD) and might contribute to the relationship between apolipoprotein E ε4 (*APOEε4*) and LOAD, in older people. However, it is unclear whether CSVD begins in middle age in individuals genetically predisposed to LOAD.

Methods: We assessed the relationship between radiological markers of CSVD, white matter hyperintensities and microbleeds, and genetic predisposition to LOAD in a cross-sectional analysis of cognitively normal subjects aged 40–59 years recruited from the PREVENT Dementia study.

Results: Microbleed prevalence was 14.5%, and mean ± standard deviation white matter hyperintensity percentage of total brain volume was 0.41 ± 0.28%. There was no significant association between *APOEε4* carrier status or history of parental dementia and white matter hyperintensity volume ($P = .713$, .912 respectively) or microbleeds ($P = .082$, .562 respectively) on multiple regression.

Discussion: Genetic predisposition to LOAD, through *APOE* genotype or AD family history, is not associated with CSVD in middle age.

Keywords: Dementia; White matter hyperintensity; Cerebral microbleed; MRI; Cerebral small vessel disease; Middle age; Risk factors

1. Introduction

Cerebral small vessel disease (CSVD) is associated with late-onset Alzheimer's disease (LOAD) in older people [1] and might contribute to the relationship between *APOEε4* and LOAD [2]. Furthermore, dominantly inherited Alzheimer's disease (AD) is associated with regionally increased white matter hyperintensity burden decades before symptom onset when cognition is normal [3], raising the possibility that CSVD might be an early feature in the pathogenesis of AD. However, it is unknown whether CSVD similarly begins in middle age in individuals genetically predisposed to LOAD.

We assessed the relationship between key markers of CSVD (white matter hyperintensities and cerebral microbleeds [CMBs]) seen on 3T magnetic resonance imaging

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(MRI) and genetic predisposition to LOAD in cognitively normal subjects aged 40–59 years recruited from the PREVENT Dementia study [4].

Unexpectedly, we found that CSVD is not associated with the main genetic predisposition to LOAD (*APOEε4* carrier status) or dementia family history in cognitively normal middle-aged subjects.

2. Methods

2.1. Setting and participants

Data were available from PREVENT Dementia subjects; full details of the study are described elsewhere [4], but participants are cognitively normal, middle-aged (40–59 years) subjects with or without parental Alzheimer's/mixed dementia. 160 participants were included for white matter hyperintensity analysis and 157 (of the same 160 participants) for CMB analysis. The research was approved by the London-Camberwell St Giles NHS Ethics Committee. All subjects provided written informed consent.

2.2. MRI acquisition

All subjects were scanned on a 3T Siemens-Verio scanner. MRI parameters are described in the Supplementary Material. All MRIs were reported by a neuroradiologist and analyzed using ITK-SNAP software in random order by a single rater blinded to all study data including clinical and genetic information.

2.3. White matter hyperintensity analysis

White matter hyperintensity volumes were quantified using Statistical Parametric Mapping (SPM8) on fluid-attenuated inversion recovery MRIs using an automated, validated method [5,6]. Following brain segmentation, white matter hyperintensity volumes were calculated by applying an intensity threshold of 1.2 times the modal intensity. Fluid-attenuated inversion recovery segmentations were manually checked for errors and corrected (Fig. 1A–1C).

2.4. CMB analysis

The number of CMBs at each topographical location were rated using the Microbleed Anatomical Rating Scale [7] on susceptibility-weighted imaging MRIs (Figs. 1D and 1E). To increase accuracy, only definite CMBs were included in statistical analyses.

To examine the accuracy of CMB ratings, 40 participants (including those with and without CMBs) were independently rated by a second reader (a neuroradiologist) blinded to clinical information. The intraclass correlation coefficient for definite CMBs was 0.95, indicating excellent interrater reliability. To examine intrarater reliability, each participant was rated twice at 2 weeks apart, yielding an intraclass correlation coefficient of 0.98.

2.5. Statistical analysis

For statistical analysis, SPSS 23 was used. Statistical significance was defined as $P < .05$ with Bonferroni correction.

To answer whether white matter hyperintensity burden (defined as "total white matter hyperintensity volume as a percentage of total brain volume" [WMH]) was associated with genetic predisposition to LOAD, we performed bivariate analyses against WMH using Mann-Whitney *U* test for categorical participant characteristics (gender, *APOEε4* carrier status, *APOEε2* carrier status, and parental AD/mixed dementia) and Spearman rank correlation coefficient for continuous participant characteristics (age, number of years of education). These six participant characteristics were then included in multiple linear regression against $\log_{10}$WMH.

To answer whether CMB burden (defined as "presence of at least one definite CMB" or "definite CMB presence") was associated with genetic predisposition to LOAD, we performed bivariate analyses against definite CMB presence using Pearson's χ^2 test (or, if insufficient sample size, Fisher's exact test) for categorical participant characteristics and binomial logistic regression for continuous participant characteristics. These six participant characteristics were then included in multiple logistic regression against definite CMB presence.

(See online Supplement for additional methodological details).

3. Results

On bivariate analysis (Mann-Whitney *U* test), median WMH did not differ significantly ($U = 1506$, $z = -0.284$, $P = .776$) between patients with (0.39%) and without (0.39%) definite CMBs.

Mean (standard deviation) WMH was 0.41% (0.28) in the study cohort. The only participant characteristic associated with WMH on bivariate analysis (Table 1) was age Q4 ($r_s = 0.216$, $P = .006$); gender ($P = .034$, WMH greater in male subjects) did not survive Bonferroni correction ($P < .008$). Similarly, in multiple linear regression against $\log_{10}$WMH (Table 1), only age ($t = 2.426$, $P = .016$) added significantly to the model; *APOEε4* carrier status ($t = 0.369$, $P = .713$) and parental AD/mixed dementia ($t = -0.111$, $P = .912$) did not.

The prevalence of CMBs in the study cohort was 14.5%. This is comparable to the few existing studies that have measured CMB presence in middle-aged participants [8]. No participant characteristic was associated with definite CMB presence on bivariate analysis (Table 2); the association with age at baseline ($W = 6.590$, $P = .010$) did not survive Bonferroni correction ($P < .008$). In multiple logistic regression against definite CMB presence (Table 2), only age at baseline was significantly ($W = 5.800$, $P = .016$) associated. *APOEε4* carrier status ($W = 3.030$, $P = .082$) and parental AD/mixed dementia ($W = 0.336$, $P = .562$) were not significantly associated with definite CMB presence.