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Cerebral microbleeds and age-related macular degeneration: The AGES-Reykjavik Study

Chengxuan Qiu^{a,b,*}, Mary Frances Cotch^c, Sigurdur Sigurdsson^d, Gudny Eiriksdottir^d,
Fridbert Jonasson^{e,f}, Ronald Klein^g, Barbara E.K. Klein^g, Tamara B. Harris^a, Mark A. van
Buchem^h, Vilmundur Gudnason^{d,e}, and Lenore J. Launer^a

^aLaboratory of Epidemiology, Demography and Biometry, National Institute on Aging, National Institutes of Health (NIH), Bethesda, Maryland ^bAging Research Center, Karolinska Institutet-Stockholm University, Stockholm, Sweden ^cDivision of Epidemiology and Clinical Applications, National Eye Institute, NIH, Bethesda, Maryland ^dIcelandic Heart Association, Kopavogur, Iceland ^eFaculty of Medicine, University of Iceland, Reykjavik, Iceland ^fDepartment of Ophthalmology, National University Hospital, Reykjavik, Iceland ^gDepartment of Ophthalmology and Visual Sciences, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin ^hDepartment of Radiology, Leiden University Medical Center, Leiden, The Netherlands

Abstract

We test the hypothesis that cerebral microbleeds (CMB) and age-related macular degeneration (AMD), both linked to amyloid- β deposition, are correlated. This study includes 4205 participants (mean age 76.2; 57.8% women) in the AGES-Reykjavik Study (2002–2006). CMB were assessed from magnetic resonance images and AMD from digital retinal images. Data were analyzed with multinomial logistic models controlling for major confounders. Evidence of CMB was detected in 476 persons (272 with strict lobar CMB and 204 with non-lobar CMB). AMD was detected in 1098 persons (869 with early AMD, 140 with exudative AMD, and 89 with pure geographic atrophy). Early and exudative AMD were not associated with CMB. The adjusted odds ratio of pure geographic atrophy was 1.62 (95% confidence interval 0.93–2.82, $P=0.089$) for having any CMB, 1.43 (0.66–3.06, $P=0.363$) for strict lobar CMB, and 1.85 (0.89–3.87, $P=0.100$) for non-lobar CMB. This study provides no evidence that amyloid deposits in the brain and AMD are correlated. However, the suggestive association of geographic atrophy with CMB warrants further investigation.

Keywords

Age-related macular degeneration; Cerebral microbleeds; Amyloid- β ; The AGES-Reykjavik Study

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*Corresponding author at: Aging Research Center, Karolinska Institutet, Gävlegatan 16, SE-113 30 Stockholm, Sweden. Tel.: +46 8 6905816; fax: +46 8 690 5954. chengxuan.qiu@ki.se (C. Qiu).

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Appendix A: Supplementary data. Supplementary data associated with this article can be found, in the online version, at

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1. Introduction

Cerebral microbleeds (CMB) seen on magnetic resonance images (MRI) are confirmed histopathologically to be hemosiderin deposits due to minor blood leakage through small-vessels. Lobar CMB indicate leakage due to cerebral amyloid angiopathy (CAA), the deposits of amyloid- β (A β) in cerebral microvasculature. A β deposits have also been detected in retinal drusen associated with advanced stages of age-related macular degeneration (AMD) (Anderson et al., 2004), suggesting A β involvement in the progression of drusen to late AMD. Here, we test the hypothesis that A β deposits in the brain and retina may be correlated by examining the association of AMD with CMB.

2. Methods

Participants are from the Age, Gene/Environment Susceptibility (AGES)-Reykjavik Study (Harris et al., 2007). Briefly, a random sample ($n=5764$) of survivors of the original Reykjavik Study cohort was examined during 2002–2006 for the AGES-Reykjavik Study. Of them, 1559 persons were excluded due to lack of brain or retinal imaging data, leaving 4205 (73.0%) for the current analysis. The AGES-Reykjavik Study was approved by the ethics authorities of the Icelandic Heart Association and the National Institute on Aging of US NIH.

Digital fundus images were acquired following standard protocol (Jonasson et al., 2011). AMD signs on retinal images were assessed using EyeQ Lite. AMD was categorized as early AMD (soft drusen, pigmentary abnormalities, large soft drusen or large soft indistinct drusen in the absence of late AMD) and late AMD (exudative AMD and geographic atrophy [GA]).

Brain MRI scans (T1-weighted 3D spoiled gradient-echo sequence; PD/T2-weighted fast spin-echo sequence; fluid attenuated inversion recovery sequence; T2*-weighted gradient-echo type echo-planar sequence optimized to maximize the susceptibility effect of hemosiderin [time to echo 50 ms; repetition time 3050 ms; flip angle 90°; field of view 220 mm]) on all eligible participants were acquired on a 1.5T Signa Twinspeed System. CMB were first scored by radiologists, then, trained raters accessed the database and recorded each bleed by locations.

We used multinomial logistic models to estimate the odds ratio (OR) and 95% confidence interval (CI) of AMD related to presence or distribution of CMB, controlling for age and sex.

3. Results

Of the 4205 participants, evidence of CMB was detected in 476 persons (272 with strict lobar and 204 with non-lobar CMB). AMD was detected in 1098 persons (869 with early AMD, 140 with exudative AMD, and 89 with pure GA). AMD was significantly associated with older age, lower education, and smoking, but not with sex, body-mass index, hypertension, diabetes, total cholesterol, and total WMH volume (Supplementary Table 1).

Neither early nor late AMD was significantly associated with CMB (Supplementary Table 2). When late AMD was further categorized as exudative AMD and pure GA, pure GA was marginally associated with CMB (OR 1.62, 95% CI 0.93–2.82, $P=0.089$). The OR of pure GA for strict lobar CMB was 1.43 (0.66–3.06, $P=0.363$) and for non-lobar CMB was 1.85 (0.89–3.87, $P=0.100$). There was no significant association of exudative AMD with CMB. Stratified analysis did not show significant differences by sex in the association between AMD and CMB.

4. Discussion

This study shows no association of CMB with early and exudative AMD, but a suggestive association with pure GA. We expected a stronger association of AMD with lobar CMB due to presence of CAA in this region, but the observed association was slightly stronger for non-lobar than for strict lobar CMB. Several population studies have examined the association of AMD with clinical stroke and WMH, but the results are mixed. This is the first report on the association of AMD with CMB. Although A β is implicated in the pathogenesis of both AMD and CAA, the lack of association of AMD with CMB seems plausible. Firstly, A β peptides in drusen may be of retinal pigment epithelial (RPE) origin because RPE is an abundant source of A β precursor protein. However, A β assemblies in drusen are not equivalent to oligomeric amyloid assemblies in the aging brain (Anderson et al., 2004). Secondly, the molecular compositions of A β deposits in the brain and retina appear to be different because the A β assemblies in drusen are more heterogeneous than cerebral oligomeric A β assemblies. Finally, A β deposits in both the brain and retina may be simply correlated through the aging process. However, given that high amounts of amyloid β are observed in GA eyes at the edges of atrophy, the suggestive association of pure GA with CMB warrants further investigation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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