



INFLAMMATION CHRONIQUE DE BAS GRADE, STATUT APOE4, ALZHEIMER

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Association of Chronic Low-grade Inflammation With Risk of Alzheimer Disease in ApoE4 Carriers.

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Abstract

IMPORTANCE: The association between peripheral inflammatory biomarkers and Alzheimer disease (AD) is not consistent in the literature. It is possible that chronic inflammation, rather than 1 episode of inflammation, interacts with genetic vulnerability to increase the risk for AD.

OBJECTIVE: To study the interaction between the apolipoprotein E (ApoE) genotype and chronic low-grade inflammation and its association with the incidence of AD.

DESIGN, SETTING, AND PARTICIPANTS: In this cohort study, data from 2656 members of the Framingham Heart Study offspring cohort (Generation 2; August 13, 1971–November 27, 2017) were evaluated, including longitudinal measures of serum C-reactive protein (CRP), diagnoses of incident dementia including AD, and brain volume. Chronic low-grade inflammation was defined as having CRP at a high cutoff level at a minimum of 2 time points. Statistical analysis was performed from December 1, 1979, to December 31, 2015.

MAIN OUTCOMES AND MEASURES: Development of AD and brain volumes.

RESULTS: Of the 3130 eligible participants, 2656 (84.9%; 1227 men and 1429 women; mean [SD] age at last CRP measurement, 61.6 [9.5] years) with both ApoE status and longitudinal CRP measurements were included in this study analysis. Median (interquartile range) CRP levels increased with mean (SD) age (43.3 [9.6] years, 0.95 mg/L [0.40–2.35 mg/L] vs 59.1 [9.6] years, 2.04 mg/L [0.93–4.75 mg/L] vs 61.6 [9.5] years, 2.21 mg/L [1.05–5.12 mg/L]; $P < .001$), but less so among those with ApoE4 alleles, followed by ApoE3 then ApoE2 genotypes. During the 17 years of follow-up, 194 individuals (7.3%) developed dementia, 152 (78.4%) of whom had AD. ApoE4 coupled with chronic low-grade inflammation, defined as a CRP level of 8 mg/L or higher, was associated with an increased risk of AD, especially in the absence of cardiovascular diseases (hazard ratio, 6.63; 95% CI, 1.80–24.50; $P = .005$), as well as an increased risk of earlier disease onset compared with ApoE4 carriers without chronic inflammation (hazard ratio, 3.52; 95% CI, 1.27–9.75; $P = .009$). This phenomenon was not observed among ApoE3 and ApoE2 carriers with chronic low-grade inflammation. Finally, a subset of 1761 individuals (66.3%) underwent brain magnetic resonance imaging, and the interaction between ApoE4 and chronic low-grade inflammation was associated with brain atrophy in the temporal lobe ($\beta = -0.88$, SE = 0.22; $P < .001$) and hippocampus ($\beta = -0.04$, SE = 0.01; $P = .005$), after adjusting for confounders.

CONCLUSIONS AND RELEVANCE: In this study, peripheral chronic low-grade inflammation in participants with ApoE4 was associated with shortened latency for onset of AD. Rigorously treating chronic systemic inflammation based on genetic risk could be effective for the prevention and intervention of AD.

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“Résultats : 1 227 hommes et 1 229 femmes [âge moyen à la dernière mesure de la protéine C-réactive (PCR) 61,6 ans] dont le statut ApoE a été évalué et dont la PCR a été mesurée longitudinalement, ont été inclus dans cette étude. Au cours des 17 années de suivi, 194 personnes (7,3 %) ont développé une démence, dont 152 (78,4 %) étaient atteintes de la maladie d'Alzheimer. L'ApoE4 couplé à une inflammation chronique de bas grade, définie comme un taux de CRP de 8 mg/L ou davantage, étaient associés à un risque accru de maladie d'Alzheimer (MA), surtout en l'absence de maladies cardiovasculaires (rapport de risque 6,63). On a aussi constaté un risque accru d'apparition précoce de la MA comparativement aux porteurs d'ApoE4 sans inflammation chronique (rapport de risque 3,52). Ce phénomène n'a pas été observé chez les porteurs d'ApoE3 et d'ApoE2 présentant une inflammation chronique de bas grade.

Conclusions et pertinence : Dans cette étude, l'inflammation périphérique chronique de bas grade chez les participants porteurs d'ApoE4 a été associée à une latence réduite pour déclencher la MA. Le traitement rigoureux de l'inflammation systémique chronique prenant le risque génétique en compte pourrait être efficace pour la prévention et le traitement de la MA.”