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Chronically raised C-reactive protein is inversely associated with cortical β-amyloid in older adults with subjective memory complaints

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ABSTRACT

Background: Inflammation promotes amyloidogenesis in animals and markers of inflammation are associated with β-amyloid (Aβ) in humans. Hence, we sought to examine the cross-sectional associations between chronically elevated plasma C reactive protein (CRP) and cortical Aβ in 259 non-demented elderly individuals reporting subjective memory complaints from the Multidomain Alzheimer Preventive Trial (MAPT).

Methods: Cortical-to-cerebellar standard uptake value ratios were obtained using [^{18}F] florbetapir positron emission tomography (PET). CRP was measured in plasma using immunoturbidity. Chronically raised CRP was defined as having 2 consecutively high CRP readings (> 3 mg/l ≤ 10 mg/l) between study baseline and the 1 year visit (visits were performed at baseline, 6 months, 1 year and then annually). Associations were explored using adjusted multiple linear regression.

Results: Chronically raised CRP was found to be inversely associated with cortical Aβ (B-coefficient: −0.054, SE: 0.026, p = 0.040) and this association seemed to be specific to apolipoprotein E (Apo E) ε4 carriers (B-coefficient: −0.130, SE: 0.058, p = 0.027). CRP as an isolated reading measured closest to PET scan was also inversely associated with cortical Aβ when CRP was treated as a dichotomized variable (high CRP $>$ 3 mg/l $\leq$ 10 mg/l, B-coefficient: −0.048, SE: 0.023, p = 0.043).

Conclusions: Our preliminary findings suggest that inflammation might be beneficial in the early stages of Alzheimer's disease as the immune systems attempts to combat Aβ pathology particularly in ApoE ε4 carriers. Investigating the temporal relationships between cerebral Aβ and a panel of inflammatory markers would provide further evidence as to whether chronic inflammation might modulate amyloidogenesis in vivo.

1. Background

There is a growing body of evidence to suggest that chronic low grade inflammation is central to the pathogenesis of Alzheimer's disease (AD) (Bolós et al., 2017; McGeer and McGeer, 2013; McGeer and McGeer, 1999). Inflammation promotes amyloidogenesis in cell culture (Lee et al., 2015) and animal models (Lee et al., 2008; Philippens et al., 2017) and microglia accompany β-amyloid (Aβ) plaques in mild cognitive impairment (MCI) (Parbo et al., 2017) and AD (Edison et al., 2008). Other markers of inflammation including complement activation products (Eikelenboom et al., 1989; Eikelenboom and Stam, 1982), interleukin 6 (Strauss et al., 1992) and C-reactive protein (CRP) (Iwamoto et al., 1994) have also been associated with Aβ plaques. Furthermore, cytokines (Liao et al., 2004; Yamamoto et al., 2007) and CRP induce Aβ formation in vitro (Bi et al., 2012).

In this study, we have explored for the first time the cross-sectional associations between cortical Aβ and chronically raised plasma CRP. The association of CRP with Aβ in human brain has received scant research attention, although studies using Rules Based Medicine (RBM) panels have shown that CRP is not associated with brain Aβ levels (Burnham et al., 2014; Kiddle et al., 2012). However, it might be that an isolated CRP reading does not best capture the chronically inflamed state. Hence, we hypothesised that chronically raised CRP, used as a proxy-marker of sustained persistent inflammation, would be associated with increased cortical Aβ load. We also explored the role of apolipoprotein E (ApoE) ε4 status, the main genetic risk factor

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associated with sporadic AD (Corder et al., 1993), on the relationship of chronically raised CRP with Aβ.

2. Methods

2.1. The Multidomain Alzheimer Preventive Trial: standard protocol approvals, registrations and ethics

Data were obtained from an ancillary [^{18}F] florbetapir positron emission tomography (PET) study carried out as part of the Multidomain Alzheimer Preventive Trial (MAPT); a large phase III, multicentre, randomized, placebo-controlled trial (Vellas et al., 2014) (registration: NCT00672685). The trial had a four arm design comprising a placebo group and three treatment groups; omega 3 polyunsaturated fatty acid (n − 3 PUFA) supplementation, multidomain intervention (involving nutritional and exercise counselling and cognitive training) plus placebo and n − 3 PUFA supplementation plus multidomain intervention (n = 1680). MAPT was designed to assess the efficacy of the interventions in slowing cognitive decline in older adults at risk of dementia. In the main analysis of MAPT, no significant effects of any of the interventions were found on cognition compared to placebo after adjustment for multiple testing (Andrieu et al., 2017). Both the MAPT and PET sub-study were approved by the ethics committee in Toulouse (CPP SOOM II) and have therefore been performed in accordance with the 1964 Declaration of Helsinki and its later amendments. Written consent was obtained from all participants.

2.2. Participants

A total of 271 subjects participated in the MAPT-[^{18}F] florbetapir ancillary study. At inclusion, participants were community-dwelling, men and women without dementia, aged ≥70, and who met at least one of the following criteria: spontaneous memory complaints, limitation in executing ≥1 Instrumental Activity of Daily Living, or slow gait speed (≤0.8 m/s). Two participants were excluded because they developed dementia at the clinical assessment closest to PET (Clinical Dementia Rating (CDR) ≥ 1). Subjects with CRP levels > 10 mg/l indicative of acute infection or trauma were excluded from the analysis (Ridker, 2003). Thus, a total of 259 subjects were included in the analyses described here.

2.3. [^{18}F] florbetapir positron emission tomography (PET)

PET scans were performed once during MAPT in volunteers using [^{18}F] florbetapir (Vellas et al., 2014; Del Campo et al., 2016). All data acquisitions were begun 50 min after injection of a mean of 4 MBq/kg weight of [^{18}F]-Florbetapir. Radiochemical purity of [^{18}F]-Florbetapir was always superior to 99.5%. Standard uptake value ratios (SUVRs) were generated from semi-automated quantitative analysis using the cerebellum as a reference. Cortical-to-cerebellar SUVRs (cortical-SUVRs) were obtained using the mean signal of the following cortical regions: frontal, temporal, parietal, precuneus, anterior cingulate, and posterior cingulate as previously described (Joshi et al., 2012). A quality control based on semi-quantification process was also performed. The median and interquartile range (IQR) for the time interval between baseline and PET-scan (in months) was 15.5 (IQR: 9.7–25.2).

2.4. CRP assessment in plasma

Plasma samples were collected at baseline and at the 6, 12, 24 and 36 month visits in MAPT and stored at −80 °C. CRP was subsequently measured using immunoturbidity according to standard protocols. CRP values were determined against a standard curve and were expressed in mg/l. High CRP readings, indicative of inflammation, were defined as > 3 mg/l ≤ 10 mg/l and acute inflammation was defined as CRP > 10 mg/ml (Ridker, 2003).

2.5. Confounding variables

On the basis of data availability and the literature on dementia (Alzheimer's Association, 2016), we selected the following confounders: age at PET-scan assessment, gender, educational level, cognitive status assessed at the clinical visit closest to PET-scan (Clinical dementia rating (CDR): scores 0 or 0.5), time interval between baseline and PET scan (in months), MAPT group allocation (4 groups: placebo, multidomain intervention plus placebo, n − 3 PUFA supplementation and multidomain intervention + n − 3 PUFA supplementation) and ApoE ε4 genotype (carriers of at least one ε4 allele versus non-carriers).

2.6. Statistical analysis

Descriptive statistics are presented as mean ± standard deviation or absolute values/percentages as appropriate. We ran multiple linear regression analysis to evaluate the cross-sectional relationship between chronically raised CRP and cortical Aβ to model protracted chronic inflammation. Subjects were categorized as having chronically raised CRP levels if they had 2 consecutively high CRP readings (> 3 mg/l ≤ 10 mg/l) between study baseline and the 1 year visit (visits were performed at baseline, 6 months and 1 year then annually). We also used multiple linear regression analysis to assess the cross-sectional associations of cortical Aβ with plasma CRP measured closest to PET examination adjusting for all confounders. CRP was analysed as a dichotomized variable according to a cutoff of > 3 mg/l above which was considered as elevated CRP (Ridker, 2003) and as a continuous variable (subjects with CRP levels > 10mg/l were excluded). To explore the role of ApoE ε4 genotype on the association between chronically raised CRP and cortical Aβ we ran multiple linear regression stratified according to ApoE ε4 genotype (carriers versus non-carriers) and adjusted for all confounders. Using multiple linear regression adjusted for all confounders we also explored the association of chronically raised CRP stratified according to baseline non-steroidal anti-inflammatory drug (NSAID) usage. NSAIDS were defined using the Anatomical Therapeutic Chemical (ATC) classification system as all drugs in the following classes: M01AA, M01AB, M01AC, M01AE. M01AG, M01AH and M01AX. There was no correction for multiple comparisons: $p < 0.05$ was considered statistically significant. Statistical analyses were performed using SAS software version 9.4 (SAS Institute Inc., Cary, NC).

3. Results

3.1. Sample characteristics

Clinical and demographic characteristics of the study participants are shown in Table 1. The mean age of the participants was around 76 years and approximately 60% of the subjects were female. Participants exhibited a high educational level and just less than half had a CDR score of 0.5. Approximately one quarter of the subjects were ApoE ε4 carriers and 39% of the subjects were Aβ positive using a threshold of mean cortical SUVR ≥ 1.17 (Del Campo et al., 2016; Fleisher et al., 2011). A total of 49 participants (out of 246: 19.9%) had chronically raised CRP levels and 13 (26.5%) of these were Aβ positive. A total of 67 participants (out of 259: 25.9%) exhibited CRP levels > 3 mg/l ≤ 10 mg/l at the clinical visit closest to PET scan and 18 (26.9%) of which were Aβ positive.

3.2. Investigation of the relationship between plasma CRP and cortical Aβ

There was a statistically significant cross-sectional association of chronically raised CRP with cortical Aβ load after adjustment for all confounders (Table 2). Similarly, plasma CRP levels measured closest to PET examination (as an isolated reading) were significantly associated with cortical Aβ when CRP was treated as a dichotomized variable, but not as a continuous variable (Table 3).