alzheimer's research&therapy

COMMENTARY

Inflammation in the Alzheimer's disease cascade: culprit or innocent bystander?

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Abstract

The strongest known risk factors for late-onset Alzheimer disease (LOAD) remain a positive family history and the *APOE* ε4 allele. van Exel and colleagues used these known risk factors to identify high- and low-risk samples of middle-aged persons in whom they compared levels of inflammatory and vascular risk factors. They observed that, compared with controls, middle-aged offspring of families with a parental history of LOAD had higher blood pressures, lower ankle-brachial indices (measure of peripheral atherosclerosis), and increased production of proinflammatory cytokines in lipopolysaccharide-stimulated whole blood samples, associations that were independent of *APOE* genotype. This study adds to the growing body of evidence linking inflammatory mechanisms to Alzheimer disease risk and, especially when considered in light of the recently described association of genetic variation in the complement receptor 1 (*CR1*) gene with LOAD, suggests that inflammatory biomarkers (whether causal or incidental) could be measured and perhaps used to risk-stratify middle-aged persons for early preventive and therapeutic interventions.

While the blood-brain barrier restricts the flow of blood-borne ions, molecules, and cells into the neural tissue, protecting the central nervous system from insult and injury, it also diminishes the utility of measuring circulating biomarkers to study changes that may be happening within the brain. However, peripheral blood monocytes and macrophages actively cross the blood-brain barrier and hence may better reflect inflammation within the neuropil. Thus, whereas three large population studies failed to relate circulating levels of inflammatory markers, such as C-reactive protein (CRP), to risk of cognitive decline and clinical Alzheimer disease (AD) [1-3], one of these, the Framingham Study, reported an association between the increased production of cytokines (interleukin-1 [IL-1] and tumor necrosis factor-alpha) by peripheral blood monocytes and an approximately twofold increase in risk of incident AD [3].

Although late-onset AD (LOAD) in patients older than 65 years of age appears to be strongly heritable, a substantial proportion of this heritability remains unexplained by known genetic and environmental factors [4]. The strongest known risk factors for LOAD remain a positive family history and the *APOE* ε4 allele. van Exel and colleagues [5] use these known risk factors to identify high- and low-risk samples of middle-aged persons in whom they compare levels of inflammatory and vascular risk factors. In this Dutch study, they observed that middle-aged persons with a parental history of LOAD had adverse levels of certain vascular risk factors (higher systolic and diastolic blood pressures and a lower ankle-brachial index) and greater production of proinflammatory cytokines in lipopolysaccharide-stimulated whole blood samples when compared with middle-aged persons whose parents were known to be free of dementia. While the APOE ε4 allele genotype was more frequent among offspring with parental AD compared with controls, these findings were independent of APOE genotype. The investigators did not link higher blood pressures and markers of inflammation to cognitive performance, neuroimaging findings, or other surrogate markers of accelerated brain aging. This and the fact that the participants were too young to develop clinical dementia due to AD (mean age of 48.9 years) limit the interpretation of their study findings. However, a few prior studies have linked peripheral inflammation to lower brain volumes, to baseline cognitive function, and to greater cognitive decline [6-8]. In the Framingham Study, among persons who had at least one APOE ε4 allele, verified parental dementia resulted in smaller total brain volumes [9] and lower scores on verbal memory tasks. Thus, among persons with an increased genetic risk for

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AD based on APOE status, there are clearly additional genetic influences, one of which may be complement receptor 1 (*CR1*), a gene that could modify an individual's response to inflammation-inducing environmental stimuli [10]. Studies have also shown that aging alone can cause an increase in peripheral cytokine concentrations [11].

Cytokine dysregulation can lead to neuronal injury through a variety of mechanisms, including altered neurotransmission, apoptosis, and activation of microglia and astrocytes, which in turn lead to production of free radicals, complement factors, glutamate, and nitric oxide [12]. Postmortem studies of AD brains demonstrated the presence of acute-phase inflammatory reactants (including CRP, proinflammatory cytokines, and activated complement cascade proteins) in the senile plaques and neurofibrillary tangles that are the pathologic hallmarks of AD [13,14]. The concentrations of inflammatory markers in these areas are intense, with levels higher than those seen in infarcted hearts, atherosclerotic plaques, or replaced joints [15]. Although it is unclear whether these proinflammatory cytokines are etiopathologically involved in the AD cascade or are merely innocent bystanders, findings that implicate cytokines in the expression and processing of β-amyloid precursor protein [16,17] and the promotion in turn by fibrillar β-amyloid of the production of proinflammatory cytokines by microglial and monocytic cell lines [18] suggest that inflammation may amplify several steps of the amyloid cascade. Beyond β-amyloid, IL-1 has been demonstrated to increase neuronal tau phosphorylation [19].

Initially, a number of observational population-based cohort studies [20] had linked intake of nonsteroidal anti-inflammatory drugs (NSAIDs) to a lowered risk of developing AD. However, a recent meta-analysis failed to observe any association of either the serum-amyloid lowering (SALA) or the non-SALA NSAIDs with a lower risk of AD [21]. Randomized placebo-controlled clinical trials also failed to demonstrate a beneficial effect of the NSAIDs, either rofecoxib or naproxen, or more recently the amyloid-lowering NSAID, tarenflurbil, on the progression of AD [22,23]. These negative results do not, however, exclude the possibility that at a different dose, at an earlier stage of the disease, or in a subgroup of patients (perhaps defined by genetic factors and PBMC [peripheral blood mononuclear cell] production of inflammatory markers), these drugs may show benefit. The finding by van Exel and colleagues [5] of elevations in proinflammatory cytokine production during early middle-age in persons with a family history of AD also suggests the possibility that a longer period of anti-inflammatory intervention may have yielded a different result. In addition, their observation of higher blood pressures in this at-risk group implies that vascular risk factors may act in concert with increased inflammation to enhance the risk for AD; hence, their potential synergistic interaction needs to be considered in future clinical trials.

In summary, this study adds to the growing body of evidence linking inflammatory and vascular mechanisms to AD risk and provides some biological insights into the known increase in AD risk associated with a positive family history. It is premature to make clinical recommendations based on this study alone, but if these results can be extended to include incident AD and validated in other cohorts, they may help refine risk prediction. They may also help identify future 'environmental' primary or secondary prevention targets, both vascular and inflammatory, for people with genetic susceptibility to AD. Furthermore, these data suggest that studies of anti-inflammatory interventions might be best undertaken in subgroups at highest risk of AD, perhaps persons with a positive family history, at least one APOE ε4 allele, and documented mild cognitive impairment. Such trials should plan to carefully document the genetic, vascular risk factor, and inflammatory status of subjects to identify whether the putative therapies could be beneficial in selected subgroups.

Abbreviations

AD, Alzheimer disease; CRP, C-reactive protein; IL-1, interleukin-1; LOAD, late-onset Alzheimer disease; NSAID, nonsteroidal anti-inflammatory drug; SALA, serum-amyloid lowering.

Competing interests

The authors declare that they have no competing interests.

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