How predictive of dementia are inflammatory biomarkers in late midlife?

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Few topics in neurology have generated as much recent debate as the use of biomarkers in prediction of cognitive decline and dementia in cognitively normal individuals. Since substantial brain damage has already occurred by the time a clinical diagnosis of dementia is made, this may be too late for any effective intervention. Inflammatory markers have been identified as potentially useful biomarkers in predicting and monitoring progression of cognitive decline until dementia.[1]

In this issue of *Neurology*®, Singh-Manoux et al.[2] present a large study evaluating whether 2 midlife blood biomarkers, interleukin-6 (IL-6) and C-reactive protein (CRP), predict subsequent cognitive decline. IL-6, but not CRP, predicted cognitive decline, particularly in the reasoning domain and overall cognition (Mini-Mental State Examination).[2] This study is valuable and timely, supplementing prior studies showing that a high level of CRP, IL-6, or tumor necrosis factor–α is associated with an increased risk of Alzheimer disease (AD) and cognitive decline.[3] The changes even in midlife are unlikely to be attributable to a preclinical disorder but may be associated more generally with aging. Now that several studies from large populations have been published, it is useful to consider several core questions in cognitive decline risk prediction.

The Singh-Manoux et al. study reinforces the concept that significant associations of average inflammatory biomarkers between declining and nondeclining groups do not ensure that these biomarkers will be useful for individual risk prediction. There was a relatively high proportion of false-positives and false-negatives around any IL-6 cutpoint. Despite the group differences, measurement of IL-6 in midlife is highly unlikely to be useful in clinical practice on an individual level.

Multimarker studies provide an opportunity for head-to-head comparisons of biomarker performance. Surprisingly, the best-known acute phase reactant, CRP, often fares worse than other biomarkers in these comparisons. In several large multimarker studies,[4–6] including the present one,[2] CRP was not a predictor of cognitive decline. Why might IL-6 be a better predictor of cognitive decline than CRP? There are several possibilities. Intuitively, the association could present a dilution effect due to the long time interval between time sampling and the time of outcome adjudication, which could be of differing import for each biomarker, and more evident for CRP. IL-6 is intimately involved in several pathophysiologic processes of the nervous system that could contribute to white matter changes and neurodegeneration.[7] If IL-6 production is upregulated or induced by the general aging process or by other conditions that occur in aging, it is possible that these changes participate in the pathologic processes associated with different forms of dementia. Elevated IL-6 affects lipid metabolism and triglyceride production, and stimulates the hypothalamic–pituitary–adrenal axis, which is associated with central obesity, hypertension, and insulin resistance; all of these factors are associated with an increased risk of dementia.[8] It is plausible that the effect starts early in the natural history of cognitive decline, in contrast to CRP. In fact, when CRP was measured earlier than the other inflammatory markers, other investigators have also found no association between CRP and an increased risk of dementia.[6] In this study, CRP may not have been indicative of cognitive status years later, only because it was assayed too early before it could have a pathophysiologically relevant effect.

Furthermore, there are 2 distinct isoforms of CRP. Native CRP (nCRP) is a pentameric oligoprotein and acute phase reactant that is produced during inflammatory disease. nCRP can be dissociated irreversibly to form free subunits or monomeric CRP (mCRP) that has lower aqueous solubility, becomes tissue-associated, and accumulates in brain microvessels, thus potentiating inflammatory microenvironments and promoting progression of dementia.[9] The existence of mCRP but not nCRP in the brains of patients with AD strongly indicates that actual commercially available assays are probably unsuitable for measuring biomarkers and their associated risk for cognitive decline. CRP in human plasma is routinely

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measured by light-scattering immunoassays that are based on agglutination reactions involving formation of bridges between antibodies and antigens. The crosslinked structure required to achieve aggregate formation is most efficiently produced by polyvalent antibodies and antigens with multiple antigenic determinants. In the case of CRP, the dissociation of a pentameric molecule reduces the number of antigenic determinants per antigen molecule, and thus the number of viable antibody-binding sites per molecule.[10] Consequently, the efficiency of the formation of a crosslinking structure and the intensity of light scattering will decrease, resulting in attenuated detection of the monomeric protein, especially in assays using monoclonal antibodies.[10] Only the production and characterization of antibodies capable of distinguishing between nCRP and mCRP will allow us to identify biologically active mCRP and add substantially to our diagnostic ability. For these reasons, without appropriate assays, several cautionary notes should be made when drawing conclusions from such work.

In spite of these weaknesses, there are important strengths in using peripheral inflammatory markers as potential predictors of cognitive decline. Circulating inflammatory state biomarkers are more appropriate because they are less invasive than lumbar puncture, are less costly than brain amyloid imaging, and can be easily assessed repeatedly in a primary care clinic setting. However, because of the weight of evidence directly linking inflammation to the numerous pathologic changes of cognitive decline and dementia, perhaps they could be used to indicate an increased susceptibility for neurodegeneration or cognitive decline. If heightened risk is indicated, a more complete risk profile could be obtained.

Given the current evidence, are inflammatory biomarkers useful in predicting cognitive decline? The answer is probably "No," as there are still many unanswered questions regarding their use. Further longitudinal studies with large and well-characterized sample collections relating inflammatory biomarker level to cognitive function are necessary to define more precisely the links between systemic inflammation and cognitive decline.

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