EDITORIAL

Cerebrospinal Fluid Vascular Endothelial Growth Factor

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In this issue of *JAMA Neurology*, Hohman et al[1] provide new insights into a biomarker related to cognitive performance in advanced age. They report that elevated levels of vascular endothelial growth factor (VEGF) in cerebrospinal fluid (CSF) are associated with improved hippocampal volume, episodic memory, and executive function. Moreover, statistical analyses were applied to test how the CSF levels of β-amyloid 42 and tau may interact with CSF VEGF levels to help predict neurocognitive factors in their sampled research participants. Hohman and colleagues report on analyses from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database, which comprises neuroimaging, CSF, and neurocognitive longitudinal data on 279 patients, regrettably without corresponding autopsy data.

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The study by Hohman et al[1] leverages the strengths of the ADNI study, including longitudinal follow-up of the research volunteers as well as granular detail in the neurocognitive assessments. Certain characteristics of the study are important to take into consideration, including the fact that the research participants derive from many geographically distinct sites, which likely introduces some variability in the data owing to the "multiple hands" involved while also probably increasing the generalizability of the outcome measures since the study is less prone to bias from an idiosyncratic approach from any given individual or laboratory. Their scatterplots help to show both the promise and the challenges of using a biomarker with such a high degree of variability in a population. Furthermore, some of the findings are difficult to fully comprehend at this point, such as why the CSF VEGF levels do not differ much between the control, mild cognitive impairment, and Alzheimer disease (AD) groups at baseline. There have been reports about how VEGF in the CSF may correlate with late-life brain disease; for example, an association between CSF VEGF levels and cognitive status was described in the ADNI.[2,3] Although Hohman and colleagues[1] are relatively new to the field of CSF biomarker analyses, their fresh perspective and rigorous statistical analyses are impressive and important.

The new study by Hohman et al[1] contributes to an evolving story by providing novel insights at the key clinical research nexus of AD, cerebrovascular disease (CVD), biomarkers, and neurocognitive features of the brain diseases of aging. Clinical research on Alzheimer-type cognitive impairment is in a state of flux. There is an evolving understanding of 2 key ideas: first, the clinical symptoms and signs that a layperson refers to as *Alzheimer's disease* is a syndrome caused by many different aging-related brain conditions; second, there is a need for better clinical biomarkers to accurately diagnose which disease is occurring in a given individual. It is worthwhile to reflect on why some of the common assumptions in the field are now known to be incorrect.

Recent years have seen improved study designs in autopsy series, including longitudinal evaluations capturing detailed clinical information. This improvement is paired with state-of-the-art neuropathologic assessments. Improved clinicopathologic correlations have shifted the emphases to incorporate a broad spectrum of clinical and pathologic features as opposed to clinical research that for too long was characterized by overdichotomization of complex disease features (eg, demented/nondemented cognitive status or AD/normal pathologic status). As a result of this paradigm shift, certain persistent myths, such as there being poor correlation between cognitive status and AD-type plaque and tangle pathology, are being explained and/or refuted.[4] Among individuals in advanced old age, it is the norm for the brain to harbor more than one neuropathologically defined disease entity, the presence of which has been associated with cognitive impairment. These common disease entities (in approximate descending order of prevalence) include CVD; primary age-related tauopathy; AD; α-synucleinopathy; transactive response-DNA binding protein 43 pathologies, including hippocampal sclerosis of aging; and other less common diseases.[4-6] Although not the most prevalent, AD tends to cause the most morbidity. In contrast, CVD and primary age-related tauopathy abnormalities are practically universal in older individuals but can have a more subtle effect on cognition.

There is scant hope of either treating a disease in an individual or even testing drugs that might treat the disease if one cannot confidently diagnose an individual's brain diseases during his or her lifetime. Current clinical biomarkers—neuroimaging or CSF analyses—generally focus on 2 types of markers: amyloidosis and neuronal injury. There is general agreement in the clinical research community that a combination of these markers being positive provides a signature that indicates extant AD pathology. However, armed only with an *APOE* genotype and a Folstein Mini-Mental State Examination[7] ("old-school" biomarkers that may outperform some new tests), most clinicians could do quite well in this regard.

The difficulty is in assessing the presence and severity of non-AD diseases. A recent survey[8] of European AD diagnosticians showed that the most frequently used biomarker for clinical AD diagnosis among survey participants was medial temporal lobe atrophy as observed neuroradiographically; this test may predict cognitive symptoms, although there is great overlap between AD and other completely different, prevalent, and high-morbidity diseases, such as hippocampal sclerosis of aging. Thus, we are only beginning to refine our tools

to diagnose non-AD diseases that affect many patients and/or clinical trials. We know even less about disease modifiers that synergize or otherwise interact with AD.

In this context of an evolving research field, Hohman et al[1] leave open to interpretation the significance of their intriguing findings and the usefulness with regard to clinical practice. Newly emerging analyses from the ADNI and other data sets are beginning to appreciate the extent and contributions of cerebrovascular and other mixed pathologic features in this presumed pure cohort of individuals at risk for AD, mild cognitive impairment of the AD type, and AD.[9] Yet mechanisms remain enigmatic and invite many additional questions. Is VEGF an AD disease modifier? Does VEGF in CSF provide a substrate for helping to understand challenging notions, such as cognitive reserve and brain resilience, perhaps intrinsic biological properties of the person's brain even before the disease process began? Or, alternatively, does the level of CSF VEGF (and perhaps other growth factors and agents) provide a biomarker signature for a subset of cases with a neuropathologically definable disease combination (ie, AD with CVD)? The latter idea seems worthy of consideration. Intriguingly, in animal models, VEGF levels in CSF are associated with altered susceptibility to experimental stroke, and in clinical studies,[10,11] a similar correlation is observed directly linked to different subtypes of human CVD. Given these considerations, we agree with the statement of Hohman et al[1]: "Future work leveraging arterial spin labeling–magnetic resonance imaging data and measures of VEGF would be useful in clarifying the role of cerebral blood flow alterations as a possible mediator of VEGF effects on brain aging."

ARTICLE INFORMATION

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