WriteClick: Editor's Choice

Editors' Note: In WriteClick this week, Dr. Hachinski applauds authors Deramecourt et al. for attempting to quantify cerebrovascular burden in their study and suggests ways to correlate their quantitative vascular index with cognitive data. The authors agree with Dr. Hachinski regarding the limitations of their study and clarify their goals. In reference to "Red blood cell ω-3 fatty acid levels and markers of accelerated brain aging" by Tan et al., Dr. Brenner details the molecular pathways behind how increased docosahexaenoic acid (DHA), an ω-3 fatty acid, can lead to improved cognitive function. Drs. Sidransky and Hart explain why they disagree with the conclusion of Anheim et al. that *GBA* should be considered a dominant causal gene with reduced penetrance for Parkinson disease.

Megan Alcauskas, MD, and Robert C. Griggs, MD

RED BLOOD CELL OMEGA-3 FATTY ACID LEVELS AND MARKERS OF ACCELERATED BRAIN AGING

Steven R. Brenner, St. Louis: I read the article by Tan et al.[1] who discuss ω-3 fatty acid levels and markers of accelerated brain aging. Docosahexaenoic acid (DHA), a long chain polyunsaturated ω-3 fatty acid, activates the retinoid X receptor (RXR) signaling pathway.[2] The RXR agonist, bexarotene, has recently been found to clear β-amyloid deposits from brains of Alzheimer disease mouse models, by transcriptionally inducing apoE through nuclear peroxisome proliferator activated receptors and liver X receptors in coordination with RXR. Activation of RXR stimulated physiologic Aβ clearance mechanisms and resulted in rapid reversal of Aβ-induced deficits.[3] Higher levels of the ω-3 fatty acid, DHA, through activation of the RXR signaling pathways, may result in increased apoE and subsequent clearance of soluble β-amyloid, resulting in improved cognitive function and inhibition of brain aging.

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PENETRANCE OF PD IN GLUCOCEREBROSIDASE GENE MUTATION CARRIERS

Ellen Sidransky, P. Suzanne Hart, Bethesda, MD: In their study, Anheim et al.[1] attempt to estimate the penetrance of Parkinson disease (PD) among *GBA* mutation carriers by studying familial PD. They determined that the PD penetrance in *GBA* carriers was approximately 30% at age 80 under a dominant model, and concluded that families could be counseled that *GBA* can be considered a dominant causal gene with reduced penetrance. We are troubled by this conclusion.

While *GBA* is an important risk factor for parkinsonism,[2] the majority of patients with Gaucher disease and *GBA* mutation carriers never develop PD.[3] Data from a large Gaucher Registry demonstrated that among patients homozygous for GBA mutations, the probability of developing PD before age 70 was 5%–7%, and 9%–12% before age 80.[4] In the study by Anheim et al., ascertainment bias could be inflating the penetrance assessment. But our concern actually runs deeper, and relates to attaching labels to modes of inheritance in such instances.

It is becoming increasingly clear that the boundaries between what were once considered "simple" Mendelian disorders and complex disorders are often quite blurred. In a 2000 editorial, Drs. Dipple and McCabe[5] stated: "There is no obvious clear distinction between simple Mendelian and complex traits: genetic diseases represent a continuum with diminishing influence from a single primary gene influenced by modifier genes, to increasingly shared influence by multiple genes." Thus, categorizing *GBA*-associated parkinsonism as a Mendelian trait may be unnecessary and confusing.

We fear that a health care provider might communicate a dominant mode of inheritance without fully understanding the complexity of the situation.

This may prompt unnecessary anxiety in a patient population already at risk for a recessive disorder.

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3. Sidransky E. Heterozygosity for a Mendelian disorder as a risk factor for complex disease. Clin Genet 2006;70:275–282.
4. Rosenbloom B, Balwani M, Bronstein JM, et al. The incidence of parkinsonism in patients with type 1 Gaucher disease: data from the ICGG Gaucher Registry. Blood Cells Mol Dis 2011;46:95–102.
5. Dipple KM, McCabe ER. Phenotypes of patients with "simple" Mendelian disorders are complex traits: thresholds, modifiers, and systems dynamics. Am J Hum Genet 2000; 66:1729–1735.

STAGING AND NATURAL HISTORY OF CEREBROVASCULAR PATHOLOGY IN DEMENTIA

Vladimir Hachinski, London, Canada: This recently published study makes a laudable attempt at quantification of the cerebrovascular burden as well as one that tries to conform to the recommended standards of doing so.[1,2]

The major limitation is that the vascular burden is not correlated with cognition. This is particularly relevant when considering those who do not have dementia. Schneider et al.[3] have shown that isolated vascular lesions, amyloid plaques, and Lewy bodies are relatively common in elderly individuals. However, it is the combination that multiplies the likelihood that many will develop dementia.

This study could be complemented by trying to correlate whatever cognitive data are available in the brain banks of the 2 centers with the vascular burden and also with the presence or absence of the *APOE4* allele, correlating not only the likelihood of amyloid deposition, but also with the development of atherosclerotic vascular disease.

Another possible approach is to take the vascular index developed by the authors and apply it as a hypothesis to existing clinical pathologic studies that have clinical, imaging, and pathologic data.

This study is welcome, given the increased recognition of the vascular component of cognitive impairment in the elderly, which at the moment is the only component that is both treatable and preventable.[4]

Author Response: Raj N. Kalaria, Newcastle upon Tyne, UK; Vincent Deramecourt, Lille, France: We welcome Dr. Hachinski's views on these longstanding issues, which have dogged the cerebrovascular disease field. Currently, when it seems we should quantify all we examine, how should we relate brain vascular pathology to cognitive dysfunction?

Our first goal was to establish a conceptual model that vascular pathology can be "measured" in all types of dementias.[1] This step would advance the field by reconsidering previous strategies[5] and guidelines[2] yet still refining the oft-quoted work of Tomlinson et al.[6] We have not only shown which lesions are relevant including microinfarction but hopefully provided a clear means to achieve quantification without major modifications in ongoing protocols in various centers.

We recognize the limitations of our study. It is expected that the proof of this concept will eventually be revealed from correlative analyses of large cohorts with brain autopsy collections such as the Honolulu Asia Aging Study USA, Cognitive Function in Ageing Study UK, Europe Brain Net II, and Brains for Dementia UK.

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Author disclosures are available upon request (journal@neurology.org).

Penetrance of PD in Glucocerebrosidase Gene Mutation Carriers

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