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.

1. Tan ZS, Harris WS, Beiser AS, et al. Red blood cell omega-3 fatty acid levels and markers of accelerated brain aging. Neurology 2012;78:658–664.
2. de Urquiza AM, Liu S, Sjoberg M, et al. Docosahexaenoic acid, a ligand for the retinoid X receptor in mouse brain. Science 2000;290:2140–2144.
3. Cramer PE, Cirrito JR, Wesson DW, et al. ApoE-directed therapeutic rapidly clear B-amyloid and reverse deficits in AD mouse models. Science Epub 2012 Feb 9.

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.

Red Blood Cell Omega-3 Fatty Acid Levels and Markers of Accelerated Brain Aging

Steven R. Brenner

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