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. who discuss ω-3 fatty acid levels and markers of accelerated brain aging. Docosahexaenoic acid (DHA), an ω-3 fatty acid, activates the retinoid X receptor (RXR) signaling pathway. 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. 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. 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, the majority of patients with Gaucher disease and GBA mutation carriers never develop PD. 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. 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 stated: “There is no obvious clear distinction between simple Mendelian and complex traits.”

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

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

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