WriteClick: Editor's Choice

Editors' Note: Responding to the study by Matsuzaki et al., which found an association between high cholesterol levels and Alzheimer disease (AD) pathology, Dr. Mascitelli et al. suggest the alternative interpretation that statin therapy may be responsible for the increased risk of dementia in these patients. The authors counter that, while they did not address this question directly, most other studies on the subject have not found a significant association between statin use and AD risk. Drs. Park and Koltzenburg point out that small sample size and broader inclusion criteria may explain why Burakgazi et al. found that oxaliplatin causes only mild axonal loss, compared to previous studies that showed more significant amplitude reductions. They also comment that the reductions in intraepidermal nerve fiber density are surprising and that these findings should be replicated in a larger population. Authors Klassen and Ahlskog respond to Dr. Rosenbaum's inquiry, clarifying that the normal pressure hydrocephalus patients in their study were assessed with videotaped gait examinations before and about 30 minutes after high-volume lumbar puncture as part of their diagnostic evaluation.

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

ASSOCIATION OF ALZHEIMER DISEASE PATHOLOGY WITH ABNORMAL LIPID METABOLISM: THE HISAYAMA STUDY

Luca Mascitelli, Udine, Italy; Stephanie Seneff, Cambridge, MA; Mark R. Goldstein, Naples, FL: Matsuzaki et al.[1] found that dyslipidemia may increase the risk of plaque-type pathology, and suggested that adequate control of cholesterol, in addition to the control of diabetes, might contribute to a strategy for the prevention of Alzheimer disease (AD). However, the most significant result reported in this study is that the highest quartiles of low-density lipoprotein (LDL), total cholesterol/high-density lipoprotein (HDL), LDL/HDL, and non-HDL cholesterol showed increased risk for neuritic plaque compared to the lowest quartiles, where cholesterol status was measured at least 10 years prior to plaque measurement. After correcting for major confounding variables, there was no significant difference for the middle quartiles compared to the lowest. A plausible explanation for this finding might also be that statin therapy, more likely to be used in those with high cholesterol, could be the main cause of the increased risk of dementia. Otherwise, this study is inconsistent with other studies that have shown an inverse relationship between cholesterol levels and mental decline in the elderly.[2,3] Furthermore, such an interpretation would confirm the results reported in the Cardiovascular Health Study,[4] where "ever used statins" were associated with a 1.21 hazard ratio for dementia, and "previously used statins" were associated with a 2.5-fold increased risk compared to "never used statins."

Author Response: Kensuke Sasaki, Toru Iwaki, Fukuoka, Japan: Mascitelli et al. question whether statin use could be an important confounding factor for the risk of Alzheimer pathology. They stated that "previously used statins" were associated with a 2.5-fold increased risk compared to "never used statins" in the Cardiovascular Health Study.[4] However, most related studies including the Cardiovascular Health Study itself claimed no significant association of statins with a risk of AD.[4–6] Moreover, the Rotterdam Study reported that statins are associated with a reduced risk of AD.[7] We did not directly evaluate the risk of statin use because it was difficult to determine separately the impact of high cholesterol and statin use in our observational study.[1] Currently, we do not know if statin therapy may cause increased risk of AD. It is plausible that adequate control of metabolism and lifestyle modifications may lessen the need for statin therapy and may contribute to a strategy for the prevention of AD. Ongoing analyses in the Hisayama Study for the association between dyslipidemia and AD, in relationship to many confounding factors, may contribute to further clarification.

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LONGITUDINAL ASSESSMENT OF OXALIPLATIN-INDUCED NEUROPATHY

Susanna B. Park, Martin Koltzenburg, London, UK: The small sample size may have contributed to the finding of Burakgazi et al.[1] that oxaliplatin produces only mild axonal loss yet others have identified significant axonal loss (greater than 50% amplitude reduction).[2] It is possible that the inclusion of patients with baseline neuropathic symptoms (TNS score $\geq$4) led to a floor effect with respect to changes in sensory amplitudes and nerve function following oxaliplatin.

It was also interesting that reductions in intraepidermal nerve fiber density (IENFD) were reported. These are typically utilized to examine small fiber neuropathy.[3] Given the prominent large fiber dysfunction identified in oxaliplatin-treated patients by clinical and neurophysiologic assessments, the finding of small fiber loss is unexpected. The IENFD changes may be too small to be clinically observable through quantitative sensory testing,[4] but may be interesting in terms of the pathophysiologic basis for the development of neuropathy. As such, it is important to replicate this finding in a larger sample.

Finally, the impact of long-term nerve damage remains critical, particularly in the adjuvant setting. These results are similar to previous studies where oxaliplatin produced a long-lasting neuropathy,[2,5] in contrast to the previously held view of reversibility within 6 months.

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NORMAL PRESSURE HYDROCEPHALUS: HOW OFTEN DOES THE DIAGNOSIS HOLD WATER?

Richard B. Rosenbaum, Portland, OR: This article[1] and the accompanying podcast were excellent. Can the authors clarify how soon after the high volume lumbar puncture the patient is examined and how long the effect lasts? For example, is test sensitivity lost if the examination is done 1 hour after the lumbar puncture?

Author Response: Bryan T. Klassen, Rochester, MN: At our institution, the patients are evaluated with videotaped gait examinations immediately before and shortly after (~30 minutes) the high volume lumbar puncture. They are generally seen the following day by the physician who elicits the patient/family's impression of results, views the videos, and repeats the examination. The decision to proceed with surgery was based upon a clearly favorable response to the lumbar puncture, whether or not this was sustained the following day. We did not have sufficient data to explore the question of how the test's sensitivity changes over time.

1. Klassen BT, Ahlskog JE. Normal pressure hydrocephalus: how often does the diagnosis hold water? Neurology 2011; 77:1119–1125.

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

Association of alzheimer disease pathology with abnormal lipid metabolism: the hisayama study

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