Conflict of Interest Disclosures: Dr Jack has provided consulting services for Eli Lily and owns stock in Johnson and Johnson.

REFERENCES

1. Gordon BA, Blazey T, Su Y, et al. Longitudinal β-amyloid deposition and hippocampal volume in preclinical Alzheimer disease and suspected non–Alzheimer disease pathophysiology [published online August 22, 2016]. *JAMA Neurol*. doi:10.1001/jamaneurol.2016.2642.

2. Sperling RA, Aisen PS, Beckett LA, et al. Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*. 2011;7(3):280-292.

3. Jack CR Jr, Knopman DS, Weigand SD, et al. An operational approach to National Institute on Aging-Alzheimer's Association crtiteria for preclinical Alzheimer disease. *Ann Neurol*. 2012;71(6):765-775.

4. Jack CR Jr, Wiste HJ, Weigand SD, et al. Amyloid-first and neurodegeneration-first profiles characterize incident amyloid PET positivity. *Neurology*. 2013;81(20):1732-1740.

5. Jack CR Jr, Wiste HJ, Knopman DS, et al. Rates of β-amyloid accumulation are independent of hippocampal neurodegeneration. *Neurology*. 2014;82(18):1605-1612.

6. Knopman DS, Jack CR Jr, Wiste HJ, et al. Selective worsening of brain injury biomarker abnormalities in cognitively normal elderly persons with β-amyloidosis. *JAMA Neurol*. 2013;70(8):1030-1038.

7. Knopman DS, Jack CR Jr, Lundt ES, et al. Evolution of neurodegeneration imaging biomarkers from clinically normal to dementia in the Alzheimer disease spectrum. *Neurobiol Aging*. In press.

8. Jack CR Jr, Wiste HJ, Weigand SD, et al. Age-specific population frequencies of cerebral β-amyloidosis and neurodegeneration among people with normal cognitive function aged 50-89 years: a cross-sectional study. *Lancet Neurol*. 2014;13(10):997-1005.

9. Jack CR Jr, Wiste HJ, Weigand S, et al. Different definitions of neurodegeneration produce similar frequencies of amyloid/neurodegeneration biomarker group findings. *Brain*. 2015;138(pt 12):3747-3759.

10. Nelson PT, Head E, Schmitt FA, et al. Alzheimer's disease is not "brain aging": neuropathological, genetic, and epidemiological human studies. *Acta Neuropathol*. 2011;121(5):571-587.

11. Crary JF, Trojanowski JQ, Schneider JA, et al. Primary age-related tauopathy (PART): a common pathology associated with human aging. *Acta Neuropathol*. 2014;128(6):755-766.

12. Jagust W. Vulnerable neural systems and the borderland of brain aging and neurodegeneration. *Neuron*. 2013;77(2):219-234.

13. Yeoman M, Scutt G, Faragher R. Insights into CNS ageing from animal models of senescence. *Nat Rev Neurosci*. 2012;13(6):435-445.

14. Jack CR Jr, Wiste HJ, Weigand SD, et al. Age, sex, and APOE ε4 effects on memory, brain structure, and β-amyloid across the adult life span. *JAMA Neurol*. 2015;72(5):511-519.

15. Barnes J, Ridgway GR, Bartlett J, et al. Head size, age and gender adjustment in MRI studies: a necessary nuisance? *Neuroimage*. 2010;53(4):1244-1255.

Status Epilepticus and Brain Atrophy
Shrinkage Is a Growing Problem

Andrew J. Cole, MD

There is general agreement among neurologists, emergency physicians, and intensivists that status epilepticus is a medical emergency; that the longer status goes on, the more difficult it is to stop; and that as the status moves up the severity spectrum from simple status to refractory status requiring treatment with an anesthetic to super-refractory status requiring more than 1 course of anesthetic treatment, the lower the likelihood of successful treatment and the higher the mortality.[1] In this issue of *JAMA Neurology*, Hocker and colleagues[2] present a retrospective study demonstrating the evolution of apparent brain atrophy in a series of adult patients treated at the Mayo Clinic with so-called super-refractory status epilepticus (SRSE). Patients with an overt anoxic ischemic etiology, epilepsia partialis continua, and absence of status were excluded. This series of 19 patients, culled from 42 who met the authors' diagnostic criteria for SRSE, were selected for study based on the availability of magnetic resonance imaging (MRI) scans at prespecified points in time. The authors use a straightforward metric, percentage change in the ventricular brain ratio (ΔVBR), to quantify change in brain volume between 2 scans, one obtained within 2 weeks of onset of SRSE and the second within 6 months of resolution of SRSE but at least 1 week after the initial scan. The main findings stated by the authors are that in all patients studied, measurable brain atrophy developed between the 2 scans obtained, and amount of atrophy was positively correlated with duration of anesthetic therapy, negatively correlated with patient age, and not correlated with functional outcome. Curiously, no table of case-wise data are provided, making it difficult for readers to inspect the case-by-case association between degree of ΔVBR and duration, etiology, treatment, or even age of the specific patients.

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This study reaffirms that prolonged status epilepticus is bad for the brain. On its face, the study suggests that there should be an urgency to resolving SRSE and so limiting the exposure to anesthetics and associated insults with the hope of lessening fixed structural decline in brain volume. Any such conclusion, however, must be tempered by the lack of control for premorbid function, etiology, and specific treatment, especially in the context of studies cited by the authors describing potential toxicity of various anesthetic and antiepileptic agents.[3] It is particularly surprising that there is a poor correlation of ΔVBR with the modified Rankin Scale score as a measure of outcome. Two possibilities are that extrinsic variables such as etiology or specific anesthetics used, or intrinsic patient-specific characteristics are more powerful determinates of functional outcome than the degree of observed apparent relative brain atrophy compared with baseline assessment. The authors freely admit that the number of patients studied is small, and the spectrum of etiologies and treat-

ments used is broad. Less obvious, however, are the limitations intrinsic to the methods used.

ΔVBR is clearly defined in the report but relies on comparisons of a change in volume of a small structure (the lateral ventricles) with the change in volume of a large structure (total brain area).[4] Median VBR observed in the study was 0.06 on the initial scan and 0.08 on the follow-up study, yielding a ΔVBR of approximately 25%. Although this figure is striking, it does not imply a 25% loss of brain volume, because VBR may change as the result of an increase in ventricular area, a decrease in whole brain area, or a combination of both. It would have been instructive for the authors to provide a table listing the actual measured ventricular and whole brain areas, along with some measurement of interobserver variability, to allow the reader to better consider the significance of the ΔVBR observed. Furthermore, the influence of measurement error, sampling error related to noncongruent slices, and the ratio technique that magnifies the apparent size of ΔVBR based on the division of a very small number by a relatively much larger number call into question the ability of the technique to truly resolve relative amounts of injury between patients.

An equally important limitation of the study is the lack of serial scans, beyond the requisite acute and posttreatment studies. Because the primary outcome measure is dependent on the assessment of lateral ventricle area on a single slice, assessing the possibility that increased ventricular area is transient, perhaps due to altered cerebrospinal fluid pressure dynamics, would be important. Equally interesting is the question of whether whatever process underlies the apparent atrophy acquired during treatment progresses beyond the acute phase. Only long-term follow-up scans could address these questions, but the answers may be of even greater interest than this well-presented initial study.

ARTICLE INFORMATION

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REFERENCES

1. Shorvon S, Ferlisi M. The treatment of super-refractory status epilepticus: a critical review of available therapies and a clinical treatment protocol. *Brain*. 2011;134(pt 10):2802-2818.

2. Hocker S, Nagarajan E, Rabinstein AA, Hanson D, Britton JW. Progressive brain atrophy in super-refractory status epilepticus [published online August 15, 2016]. *JAMA Neurol*. doi:10.1001/jamaneurol.2016.1572.

3. Sutter R, Marsch S, Fuhr P, Kaplan PW, Rüegg S. Anesthetic drugs in status epilepticus: risk or rescue? a 6-year cohort study. *Neurology*. 2014;82(8):656-664.

4. Herrmann EK, Hahn K, Kratzer C, von Seggern I, Zimmer C, Schielke E. Status epilepticus as a risk factor for postencephalitic parenchyma loss evaluated by ventricle brain ratio measurement on MR imaging. *AJNR Am J Neuroradiol*. 2006;27(6):1245-1251.

Do ω-3 Fatty Acids Regulate Cerebral β Amyloid?

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Numerous epidemiologic studies suggest that dietary consumption of fish or of ω-3 fatty acids (the putative "active ingredient" in fish) may reduce the risk of late-life dementia including Alzheimer disease (AD). However, clinical trials have failed to demonstrate disease-modifying effects in mild to moderate AD,[1,2] diminishing enthusiasm for ω-3s for brain health during aging. A study in this issue of *JAMA Neurology* by Yassine et al[3] revisits this topic with a clinical study aimed at testing the hypothesis that the ω-3 fatty acid docosahexaenoic acid (DHA) has clinically relevant "antiamyloid" effects in the aging brain.

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Docosahexaenoic acid has received particular attention because it is the most abundant polyunsaturated fatty acid in the brain, playing an important structural role in synapses while also modulating a number of signaling pathways. Brain DHA levels are also modulated by dietary intake, so it is plausible for dietary DHA to alter brain concentrations and affect downstream targets including brain pathology and function. Transgenic mouse studies from 2 different laboratories using 2 different strains of mice previously showed that DHA administration was associated with lower cerebral β amyloid.[4,5] These preclinical data, combined with the epidemiologic data, motivated a large multicenter National Institute on Aging–funded trial of DHA to slow the progression of AD. Sadly, DHA failed to slow cognitive decline during an 18-month period in nearly 400 patients with mild to moderate AD.[2] In light of the view that any antiamyloid therapy may need to be initiated prior to the onset of dementia to be clinically effective, it will come as no surprise that DHA, a putative antiamyloid agent, failed to modify the disease course in a study population that had dementia at baseline. The idea of "earlier" intervention with DHA has been discussed, but it is challenging to reinvigorate interest in a failed treatment strategy, regardless of the viability of the argument, because clinical trials are such expensive and labor-intensive ventures.

However, the Yassine et al study[3] has the potential to rekindle interest in the therapeutic potential of DHA by presenting clinical evidence in support of the transgenic mouse studies indicating that DHA consumption is associated with reduced cerebral amyloid. Yassine and colleagues took advantage of an