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Quantitative Neuroimaging Advances in the Measurement of Brain Injury but Not Brain Function in Systemic Lupus Erythematosus

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Appenzeller and colleagues¹ study contributes important information about a successful methodological approach to understand one manifestation of the brain injury that occurs in some patients with systemic lupus erythematosus (SLE), namely, the “hyperintense white matter lesions.” Borrowing from the successful strategy used in advancing the understanding disease burden in multiple sclerosis, Appenzeller and colleagues¹ have demonstrated that the quantitative magnetic resonance imaging measure of total load of white matter (WM) lesions is a useful biomarker that correlated with a history of central nervous system (CNS) symptoms, serum anti-phospholipid antibody levels, and total steroid dose at baseline imaging. The study design in 120 patients and 44 healthy control subjects is solid, and includes the basic foundations for any study of SLE, including strict disease criteria for diagnosis, description of associated illnesses and pharmacological therapy history, sex- and age-matched control subjects without neurological or psychiatric illness, attention to disease duration, activity, and damage, as well as timing of the onset of new symptoms. Importantly, SLE patients with concomitant disease(s) capable of affecting the CNS were excluded from this study.

Although the follow-up examination was not part of a formal longitudinal design, the authors’ obtained repeat imaging data in 80 of the initial 120 patients, and 42 patients in this group had symptoms referable to the CNS. They report that 38% of the SLE patients with repeat scans demonstrated an increased load in the WM lesions; approximately 43% of those with normal initial neuroimaging had new imaging abnormalities at follow-up, and 33% of those with abnormal initial imaging had developed additional abnormalities. The substantial number of patients with new WM lesions or progression of the WM lesions suggests the existence of a distinct subset of patients who are vulnerable to CNS injury. This is consistent with a recent in-depth study following changes in cognitive function in a group of SLE patients over a 5-year period.² A small subset of these patients demonstrated clear cognitive deterioration and differed substantially from the rest of the cohort in whom there was no

significant cognitive change despite exacerbations and remissions of SLE disease activity. Longitudinal changes in WM lesion load demonstrated by the quantitative magnetic resonance imaging assessment tool used in this study may contribute to our understanding of underlying disease mechanism in progressive brain injury in SLE patients.

The clinical implications and significance of the presence and progression of WM lesions that Appenzeller and colleagues¹ reported remain to be fully explored. They collected “a battery of standardized neuropsychological tests” at baseline and found, not unexpectedly, that cognitive impairment was observed significantly more frequently in patients with WM lesions than in those without. There was only brief mention of follow-up cognitive testing as a functional correlate of the progression in imaging abnormalities. A key to modern models of brain function is connectivity, and so one might suppose that patients with WM damage and loss of brain connectivity would display cognitive and emotional impairments that include deficits of processing speed, attention, vigilance, multistep problem solving, memory and mood, and perhaps occasionally, a specific vivid, disconnection syndrome. Given Appenzeller and colleagues’¹ remarkable quantification scheme, a correlation with WM lesion size across one or all of the general cognitive and emotional domains would have been important. Equally useful would be a correlation between development of new WM lesions across the cognitive and emotional domains.

Alternatively, a failure to find a correlation between structural WM injury and cognitive performance or emotional status would have been equally instructive. The quantitative information about the WM injury is impressive, but it is likely that SLE pathogenesis also affects gray matter. Many of the diverse autoantibodies to blood elements, endothelium, neuronal receptors, and membrane proteins^{3, 4} found in SLE have been associated with vasculopathy, with or without inflammation, and altered blood flow or direct neuronal destruction.⁵ There are a number of neuroimaging studies, including this groups’ past work, that demonstrate cerebral atrophy.^{6, 7} Other recent pioneering work, requiring confirmation, has begun to test the relation of a number of emerging neuroimaging techniques and disease activity.^{8–10} Some of these studies have generated information not only about whole-brain gray matter^{9, 11, 12} but also about specific gray matter regions of interest, such as the amygdala,¹³ and found that SLE patients with neurological symptoms had significantly diminished regional apparent diffusion coefficients compared with healthy control subjects. A single imaging method may be too limited, even one that is systematically applied as successfully as in Appenzeller and colleagues’¹ study.

Another dilemma that Appenzeller and colleagues’¹ work raises is the possibility that disease activity index and steroid dosage simply reflect the burden of disease (non-CNS and CNS) that had been treated previously. Indeed, both the number of lesions and total volume of the lesions correlated with disease damage assessed by standardized measures. A reevaluation of the clinical symptoms of the patients with CNS disease and categorization into subgroups based on pathoanatomic localization of disease may be useful in unraveling this complicated web.

With a developing awareness of the vast array of autoantibodies that destroy brain directly, as well as other brain destructive mechanisms, “lumping” patients within the broad realm of

“neuropsychiatric” lupus had clinical usefulness but contributes little to pathogenesis of CNS abnormalities. Appenzeller and colleagues¹ approach of quantifying CNS burden is an excellent start point among a myriad of relatively small group studies with categorical neuroimaging information; longitudinal characterization of symptoms and brain injury may reveal disease mechanism and eventual treatments that are more specific than current immunological suppression, anticoagulants, and antidepressants.

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