IMAGE OF THE MONTH

Neuropsychiatric Systemic Lupus Erythematosus

Imaging can play an important role in ruling out other causes of neuropsychiatric systemic lupus erythematosus (NPSLE), which could be caused by SLE-mediated organ dysfunction, infection, medication side effects, metabolic abnormalities, or an unrelated condition, according to Dr. Patricia C. Cagnoli, a rheumatologist at the University of Michigan in Ann Arbor.

"You have to figure out if the [NPSLE] symptoms are related to the lupus," Dr. Cagnoli said. But "we don't have any specific imaging technique that can tell you that."

The diagnostic approach also depends in part on the presentation. Are the symptoms focal or acute or more diffuse? For example, in the case of acute symptoms, CT can help rule out ischemic strokes, large tumors, and massive bleeds—the most acute and urgent conditions that would require immediate treatment/surgery. If a patient has more diffuse symptoms, infection should be ruled out first with a lumbar puncture in addition to imaging.

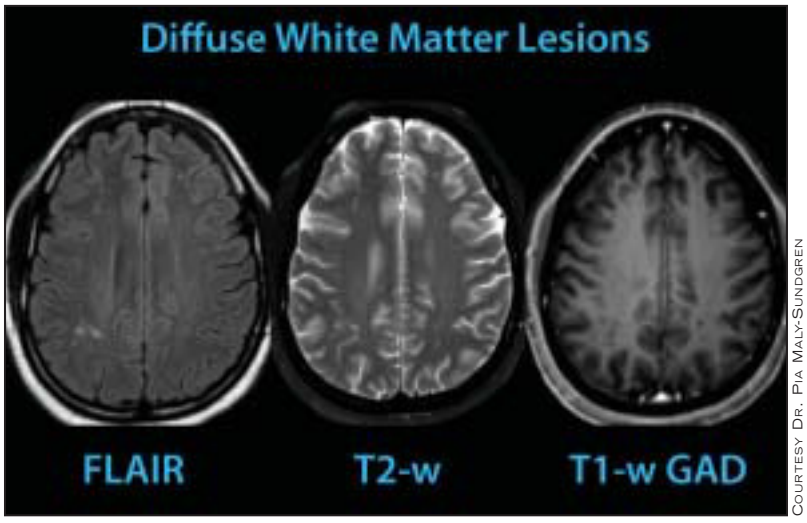
"MRI is probably the cornerstone imaging technique to use in the diagnosis of neuropsychiatric lupus," Dr. Cagnoli said. Multiple imaging sequences and intravenous administration of contrast are employed to accurately delineate abnormal areas in the brain. "More often than not, MRI will reveal several lesions that were not detected by CT scanning." These areas of new injury are likely capable of responding to treatment and healing in ways that cannot be seen by CT.

MRI also frequently identifies small bright spots in the subcortical white matter that are of uncertain significance and are sometimes referred to as "unidentified bright objects," or UBOs.

"Most of the patients with neuropsychiatric lupus will have these hyperintense white matter lesions, but so do apparently normal individuals," she said.

These lesions are not specific to NPSLE. It's not uncommon for patients to have small white-matter lesions on MRI that are considered to be areas of possible demyelinization, similar to multiple sclerosis. In fact, patients are often referred to Dr. Cagnoli's group to help determine if patients have MS or lupus with CNS involvement. MS lesions tend to be bigger, to coalesce, and to progress quickly.

However, imaging is only part of the picture. "It's the rest of your physical assessment, your clinical impression, your laboratory evaluation that will tell you, in the end, what it is," she said.



Courtesy Dr. Pia Maly-Sundgren

MRI shows NPSLE lesions with fluid attenuated inversion recovery (FLAIR), T2-weighted, and T1-weighted, gadolinium contrast sequences.

Functional MRI techniques such as MR spectroscopy, diffusion-weighted imaging, and diffusion tensor imaging (DTI) are beginning to reveal which patients have functional abnormalities.

When comparing structural and functional MRI, "you have a normal conventional MRI and you see already evidence of neuronal loss or brain injury in the functional MRI," Dr. Cagnoli said.

The researchers hope to use these techniques to identify patients with preclinical NPSLE–type lesions, in order to begin treatment as early as possible. "Eventually, our hope is that we might be able to treat these patients sooner rather than later," she said. "One of the problems we have with [NPSLE] is trying to identify those patients" who require earlier and more aggressive treatment, "as opposed to those patients who can benefit from a more conservative approach."

NPSLE requires treatment not just for the neuropsychiatric symptoms, with antipsychotics for psychosis as an example, but also for the underlying SLE, with immunosuppressants and high doses of corticosteroids. "So you treat the symptom—psychosis is the symptom in this case—but also the underlying mechanism, which is the lupus," said Dr. Cagnoli, who is also the associate director of the Michigan Lupus Program.

She and several colleagues are currently enrolling patients in a pilot study to evaluate whether MR spectroscopy, MR perfusion imaging, and MR DTI can detect alterations in brain function distinctive for NPSLE and compare the findings with those found in an existing cohort of 20 normal, healthy controls.

—Kerri Wachter

MS-Like Syndromes Slow Pediatric Brain Growth, Cognition

BY JEFF EVANS

SEATTLE — Children and adolescents who have an acute demyelinating syndrome or multiple sclerosis may experience lasting impairment in brain growth or cognition, according to two prospective studies.

In one study, Dr. Douglas L. Arnold and his fellow researchers found a slower-than-expected rate of brain growth over 1 year in children with a history of one acute demyelinating event.

In a second study of children and adolescents with multiple sclerosis, Christine Till, Ph.D., and her coinvestigators found total brain volume of T2 lesions on MRI was significantly associated with cognitive impairment, which occurred in about one-third of the subjects.

"These findings are important because they indicate an effect of inflammatory activity on cognitive function," particularly on tests that depend on integrated neural networks or efficient communication across multiple brain regions, she said.

Dr. Arnold of the Montreal Neurological Institute and Hospital at McGill University, Montreal, and his associates compared brain volume changes over 1 year using T1-weighted MRI scans in 31 children with acute demyelinating syndromes (ADS) and in 31 healthy age- and gender-matched control patients from the National Institutes of Health MRI Study of Normal Brain Development (www.brain-child.org). The children had a mean age of 10 years (range of 4-16 years). None was on immunomodulatory therapy during the study, because they had experienced only one clinical event. Only a few children had residual physical deficits from transverse myelitis.

The rate of brain growth decreased in both groups during the year and tended to level off after 10 years of age. Before 10 years of age, ADS patients did not show atrophy, but instead showed a failure of age-anticipated brain growth. The rate of brain growth was significantly lower in 13 ADS patients younger than 10 years than it was in 12 healthy control patients (0.62%/year vs. 2.26%/year), Dr. Arnold reported at the annual meeting of the American Academy of Neurology.

However, no difference was found in the rate of brain growth after 10 years of age in 18 ADS patients (0.18%/year) and 19 healthy control patients (0.06%/year).

There appears to be a "heightened vulnerability of the more immature CNS to inflammatory brain injury, despite the capacity of younger brains to adapt … [or] respond to injury of certain sorts. This inflammation seems to interrupt some critical developmental processes and result in this failure of age-anticipated growth," he said.

The researchers are acquiring additional data to find any corresponding neuropsychological changes and to determine whether there is any spatial localization of the changes in brain growth.

Dr. Arnold and some of his coinvestigators reported receiving research support and personal compensation from companies that manufacture drugs for MS.

The study was supported by the Multiple Sclerosis Scientific Research Foundation of Canada and the Canadian Institutes of Health Research.

In the second study, Dr. Till and her colleagues looked for signs of cognitive impairment in 32 children who presented to the pediatric MS clinic at the Hospital for Sick Children, Toronto, during 2007-2008.

Prior studies in children have shown reductions in processing speed, memory, attention, and executive function, which generally occur with greater severity at a younger age of onset and with longer disease duration.

But the "association between cognitive impairment and MRI lesion load has not been investigated in children with MS," said Dr. Till, of the department of psychology at York University, Toronto.

Of the 32 patients, 3 were excluded from the analysis because of excessive head motion during the MRI scans, and 1 patient was excluded because of a change in diagnosis. The remaining 28 patients (22 females) were a mean of 16 years old and had a mean disease duration of 4.5 years with a relapsing-remitting course. Their median Expanded Disability Status Scale Score was 1 and 23 (82%) of them were receiving disease-modifying treatment during the study.

Of the 28 children, 10 (36%) had cognitive impairment, which Dr. Till and her associates defined as scores more than 1.5 standard deviations below the mean for their age on at least 3 of the 17 different tests in the battery. Attention and processing speed were the most commonly impaired measurements. More than 20% of the children had impaired visuomotor integration on a test that required them to copy designs of increasing complexity as well as a test that assessed cognitive flexibility and working memory.

The cognitively impaired children were younger at disease onset than were cognitively normal children (9.7 years vs. 12.5 years). Children who were cognitively impaired also had experienced a longer disease duration than did those who were cognitively normal (6.1 years vs. 3.7 years). However, the differences in both comparisons did not reach statistical significance ($P = .07$).

Total brain T2 lesion volume was most strongly correlated with attention, processing speed, and a global cognitive composite score. But total brain T1 lesion volume did not correlate with any of the neuropsychological testing outcomes.

In multiple linear regression models, age at disease onset was the main significant predictor of verbal intelligence and processing speed, accounting for 23%-37% of the total variation in the two. The addition of total brain lesion volume to these models accounted for another 4%-11% of the total variation.

The total brain T2 lesion volume was the main significant predictor of the global cognitive composite score as well as scores on the sustained visual attention test, after controlling for covariates.

Dr. Till said she had no conflict of interest to disclose. Two of her research collaborators disclosed receiving compensation for speaking for manufacturers of drugs for MS. ■