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MRI Techniques Could Help Distinguish Between MS and Migraine

Using a combination of imaging methods could prevent misdiagnoses and aid the administration of effective treatment.

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STOWE, VT—Some patients with migraine receive an inappropriate diagnosis of multiple sclerosis (MS). The two disorders share certain clinical and radiologic features, and misdiagnosis is a significant problem. Using MRI scanners widely available to clinicians, researchers are developing several imaging techniques that can provide an objective basis for distinguishing between MS and migraine, according to an overview provided at the Headache Cooperative of New England's 28th Annual Stowe Headache Symposium.

The imaging techniques evaluate different aspects of MS pathology, said Andrew J. Solomon, MD, Associate Professor of Neurological Sciences at the University of Vermont College of Medicine in Burlington. The techniques have been automated to a large extent, which reduces the need for human interpretation of data. The incorporation of machine learning could further aid differential diagnosis.

Andrew J. Solomon, MD

Grounds for Confusion

Various similarities between migraine and MS increase the likelihood of misdiagnosis. The two disorders are chronic and entail attacks and remissions. Both are associated with changes in brain structure and white matter abnormalities that may be subclinical.

In a study of patients with migraine by Liu et al, between 25% and 35% of participants met MRI criteria for dissemination in space for MS, depending on how lesions were defined. The first report of

natalizumab-associated progressive multifocal leukoencephalopathy occurred in a patient who, on autopsy, was found not to have had MS. In a 1988 study, Engell and colleagues found that of 518 consecutive patients who had died with a diagnosis of clinically definite MS, the diagnosis was incorrect for 6%.

In 2005, Carmosino and colleagues evaluated 281 patients who had been referred to an MS center and found that 67% of them did not have MS. The investigators identified 37 alternative diagnoses, of which migraine was the second most common. About 10% of participants had a final diagnosis of migraine.

In a recent survey, Dr. Solomon and colleagues asked more than 100 MS specialists whether they had seen patients who had had a diagnosis of MS for more than one year, but, on evaluation, determined that they did not have MS. Approximately 95% of respondents answered affirmatively. About 40% of respondents reported having seen three to five such patients in the previous year.

The current diagnostic criteria for MS rely on clinicians to interpret clinical and radiologic data and contain many caveats regarding their application, said Dr. Solomon. The criteria "were not developed to differentiate MS from other disorders," but to predict which patients with an initial neurologic syndrome typical for MS will subsequently develop MS, he added. Physicians who are unfamiliar with the diagnostic criteria may misapply them and make an incorrect diagnosis.

The Central Vein Sign

Autopsy studies have indicated that MS lesions generally center around veins. Researchers have recently been able to visualize these veins within MS lesions using 7-T MRI. This finding, which investigators have called the central vein sign, could be a way to distinguish MS from other disorders. But 7-T MRI generally is not available to clinical neurologists. In 2012, scientists at the NIH developed a method that combines T2* imaging, which helps visualize veins, and fluid-attenuated inversion recovery (FLAIR) imaging that visualizes MS lesions. This method visualizes veins within lesions, or central vein sign, using 3-T MRI, which is more commonly available to clinical neurologists. The researchers called this sequence FLAIR*, and numerous studies have suggested that it may differentiate MS from other diagnoses.

Dr. Solomon and collaborators tested this technique on a group of 10 patients with MS who had no other comorbidities for white matter disease and 10 patients with migraine and white matter abnormalities who also had no other comorbidities for white matter disease. The mean percentage of lesions with central vessels per participant was 80% in patients with MS and 34% in migraineurs. The patients with migraine had fewer juxtacortical, periventricular, and infratentorial lesions, compared with patients with MS.

Because researchers have used various definitions of the central vein sign, Dr. Solomon and colleagues published a consensus statement to improve the interpretation of the imaging findings. They recommended that neurologists disregard periventricular lesions and concentrate on subcortical and white matter lesions that are visible from two perspectives.

Another limitation of this diagnostic imaging technique is that it "requires evaluation of every single lesion to determine if a central vein was present," said Dr. Solomon. He and his colleagues developed a simplified algorithm that required the examination of three lesions. To test this algorithm, they examined their original cohort plus 10 patients with MS and comorbidities for white matter disease (eg, migraine or hypertension) and 10 patients who had been misdiagnosed with MS (most of whom had migraine). Three blinded raters examined three lesions chosen at random from each MRI. This method had a 0.98 specificity for MS and a sensitivity of 0.52. The study demonstrated problems with inter-rater reliability, however.

Dr. Solomon later collaborated with researchers at the University of Pennsylvania to develop a machine learning technique that could identify the central vein sign. When they applied the technique to the expanded cohort of 40 patients, it identified the sign accurately with an area under the curve of about 0.86. The central vein sign may be a good biomarker for MS, and using this automated technique to assess 3-T MRI images appears to be clinically applicable, said Dr. Solomon.

Thalamic Volume

Thalamic atrophy is common in the early stages of relapsing-remitting MS. The thalamus also is implicated in migraine. Although studies have examined volumetric brain changes in migraine, none has examined thalamic volume specifically, said Dr. Solomon.

He and his colleagues used an automatic segmentation method to analyze thalamic volume in their cohort of 40 patients. Analysis of variance indicated that thalamic volume was significantly smaller in patients with MS, compared with patients without MS. When the researchers used a thalamic volume less than 0.0077 as a cutoff, the technique's sensitivity and specificity for the diagnosis of MS were 0.75.

Recent data suggest that thalamic atrophy in MS does not result from thalamic lesions, but from diffuse white matter abnormalities. Like the central vein sign, thalamic atrophy may reflect MS pathophysiology and could be incorporated into MS diagnostic criteria, said Dr. Solomon.

Cortical Lesions

Autopsy and MRI studies have shown that cortical lesions are characteristic of MS, but MRI studies have suggested that migraineurs generally do not have cortical lesions. Although neurologists can see

these lesions in vivo on 7-T MRI, 3-T MRI is not as sensitive and makes cortical lesion detection challenging.

In 2017, Nakamura and colleagues found that ratio maps of T1- and T2-weighted 3-T MRI, images that are acquired in routine clinical care for MS, could identify areas of cortical demyelination. Dr. Solomon and colleagues tested whether this method could distinguish MS from migraine. They defined a z score of less than 3 as an indication of low myelin density. When they examined the cohort of 40 patients, they were able to correlate areas with z scores below the cutoff with cortical lesions that were visible on conventional imaging. The technique accurately distinguished patients with MS from patients with migraine.

None of these emerging imaging techniques is 100% accurate. In the future, however, combining several of these techniques in conjunction with tests of blood biomarkers such as microRNA could accurately distinguish between MS and other disorders with high specificity and sensitivity, Dr. Solomon concluded.

—Erik Greb

Suggested Reading

Carmosino MJ, Brousseau KM, Arciniegas DB, Corboy JR. Initial evaluations for multiple sclerosis in a university multiple sclerosis center: outcomes and role of magnetic resonance imaging in referral. *Arch Neurol <https://www.ncbi.nlm.nih.gov/pubmed/15824257>* . 2005;62(4):585-590.

Engell T. A clinico-pathoanatomical study of multiple sclerosis diagnosis. *Acta Neurol Scand <https://www.ncbi.nlm.nih.gov/pubmed/?term=a+clinico-pathoanatomical+study+of+multiple+sclerosis>* . 1988;78(1):39-44.

Liu S, Kullnat J, Bourdette D, et al. Prevalence of brain magnetic resonance imaging meeting Barkhof and McDonald criteria for dissemination in space among headache patients. *Mult Scler <https://www.ncbi.nlm.nih.gov/pubmed/23380650>* . 2013;19(8):1101-1105.

Nakamura K, Chen JT, Ontaneda D, et al. T1-/T2-weighted ratio differs in demyelinated cortex in multiple sclerosis. *Ann Neurol <https://www.ncbi.nlm.nih.gov/pubmed/?term=nakamura+k+chen+jt+ann+neurol+2017>* . 2017;82(4):635-639.

Sati P, Oh J, Constable RT, et al. The central vein sign and its clinical evaluation for the diagnosis of multiple sclerosis: a consensus statement from the North American Imaging in Multiple Sclerosis Cooperative. *Nat Rev Neurol <https://www.ncbi.nlm.nih.gov/pubmed/?term=The+central+vein+sign+and+its+clinical+evaluation+for+the+diagnosis+of+multiple+scler*

osis%3A+a+consensus+statement+from+the+North+American+Imaging+in+Multiple+Sclerosis+Cooperative> . 2016;12(12):714-722.

Solomon AJ, Klein EP, Bourdette D. "Undiagnosing" multiple sclerosis: the challenge of misdiagnosis in MS. *Neurology <https://www.ncbi.nlm.nih.gov/pubmed/22581930>* . 2012;78(24):1986-1991.

Solomon AJ, Schindler MK, Howard DB, et al. "Central vessel sign" on 3T FLAIR* MRI for the differentiation of multiple sclerosis from migraine. *Ann Clin Transl Neurol <https://www.ncbi.nlm.nih.gov/pubmed/26900578>* . 2015;3(2):82-87.

Solomon AJ, Watts R, Dewey BE, Reich DS. MRI evaluation of thalamic volume differentiates MS from common mimics. *Neurol Neuroimmunol Neuroinflamm <https://www.ncbi.nlm.nih.gov/pubmed/28761906>* . 2017;4(5):e387.

/ysUvv5AigyKAkbh3N9RmN8JlVJEuGKUBhCJbVLc1BI1gMGHIYBux/+v556W4UUzzusSQQ5
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microbiome-differ-patients-relapsing&m=web&rt=nr&rc=Recency&rid=61f16d8e-
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