The diagnosis of MS requires demonstration of disease dissemination in space and time and is based on diagnostic criteria such as the recently revised McDonald criteria.1 With their 2001 revision, the McDonald criteria formally have included MRI in the diagnostic workup of patients with suspected MS.2 Since then, the relevance of MRI for diagnosis and disease monitoring has further increased owing to continuous improvements of MRI scanners and sequences. Nevertheless, there is a clinicoradiologic dissociation in MS, i.e., some patients with high lesion load experience a relatively mild disease course, whereas others with few abnormalities on conventional MRI fare far worse. In a few patients who do fulfill the current McDonald Criteria and who have received a tentative diagnosis of MS, brain MRI remains unremarkable. This raises the obvious question of whether such MRI-negative patients indeed have MS or another autoimmune CNS disorder.

In this issue of Neurology® Neuroimmunology & Neuroinflammation, Takewaki et al.3 report on 11 patients identified from a single MS center cohort of 550 patients who fulfilled the 2010 McDonald criteria, but had normal conventional MRI of the brain and the spinal cord. These patients had a mean age of 41.5 years, a mean disease duration of 12.6 years, and a median Expanded Disability Status Scale score of 6, indicating severe disability. Clinically, patients presented with involvement of the pyramidal system and visual impairment as well as with somatosensory, autonomic, and cognitive symptoms. All patients responded to immunotherapy with IV methylprednisolone and/or plasmapheresis. Diffusion tensor imaging (DTI) revealed extensive white matter abnormalities, and the frequency of plasmablasts in the peripheral blood was significantly increased in these patients. The authors conclude that the identified patients might have a distinct autoimmune disease entity that they propose to be called ”Normal-appearing Imaging-associated, Neuroimmunologically Justified, Autoimmune Encephalomyelitis (NINJA).”4

Current diagnostic criteria for MS allow for an early diagnosis and treatment of the patients, facilitated by a high sensitivity of the criteria. However, the specificity of these criteria is only modest.2 In addition, MRI criteria were developed to identify patients at risk for MS and not to differentiate MS from other conditions. These factors can contribute to misdiagnosing patients with MS, especially when white matter abnormalities associated with migraine or small vessel ischemic disease are present.1 In contrast, Takewaki et al. report on patients with disorders mimicking MS that do fulfill the diagnostic criteria, but have a normal conventional MRI. In addition, the CSF cell count and immunoglobulin G index were normal, and oligoclonal bands were absent in these patients. Electrophysiologic studies showed abnormalities in only 4 of 8 studied patients. Given this discrepancy between multifocal clinical presentation and protracted disease courses on the one hand and negative MRI and CSF findings on the other, these patients are additionally at risk of being diagnosed with somatoform disorders. Clearly, good clinical judgment should guide (tentative) diagnosis and early initiation of immunotherapy in these patients.

What do these patients suffer from then? The extensive diagnostic workup that included exclusion of a wide range of other autoimmune, infectious, degenerative, and neoplastic
In summary, the relevant work by Takewaki et al. identified MRI-negative patients with an MS mimicking disorder that is likely of autoimmune origin. This study hopefully stimulates other groups to identify similar patients and investigate them ideally in prospective study designs that include extended autoimmune diagnostic workup and advanced structural and functional imaging. In the future, the majority of these patients likely can be diagnosed based on a molecular classification.10

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