Seven-Tesla Magnetic Resonance Imaging

New Vision of Microvascular Abnormalities in Multiple Sclerosis

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Background: Although the role of vascular pathology in multiple sclerosis (MS) lesions was suggested long ago, the derivation of these lesions from the vasculature has been difficult to assess in vivo. Ultrahigh-field (eg, 7-T) magnetic resonance imaging (MRI) has become a tool for assessing vascular involvement in MS lesions owing to markedly increased image resolution and susceptibility contrast of venous blood.

Objective: To describe the perivenous association of MS lesions on high-resolution and high-contrast 7-T susceptibility-sensitive MRI.

Design: Case study.

Setting: University hospital.

Patients: Two women with clinically definite relapsing-remitting MS.

Results: We demonstrated markedly enhanced detection of unique microvascular involvement associated with most of the visualized MS lesions with abnormal signals on and around the venous wall on 7-T compared with 3-T MRI.

Conclusions: These findings, which have never been shown on conventional fields of MRI, not only allow for direct evidence of vascular pathogenesis in MS in vivo but also have important implications for monitoring lesion activity and therapeutic response.

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REPORT OF CASES

Two female patients with clinically definite relapsing-remitting MS (patient 1 was aged 54 years and patient 2 was aged 39 years) had received initial diagnoses 6 and 7 years earlier, respectively, based on Poser criteria.3 Both had Expanded Disability Status Scale scores of 2.0; neither had used steroids within the previous 3 months; and neither had received immunomodulating medication within 2 years of the current imaging study. They gave informed consent for participation.

PATIENT 1

Patient 1 first experienced MS symptoms with mild muscle stiffness in her lower extremities and since then has had repeated exacerbations of various symptoms, including bilateral lower extremity weakness and paresthesias, vertigo, ataxia, diplopia, and dysphagia. At the time of the first 7-T MRI study, patient 1 reported mildly disabling physical symptoms, visual disturbance, and no change in symptomatology at follow-up.
PATIENT 2

Patient 2 first experienced MS symptoms of visual disturbance and has experienced visual changes, headache, fatigue, and clumsiness. During the course of the disease, the patient's symptoms have fluctuated in intensity, though she claims to have been asymptomatic at the time when the current MRI was performed. Two age-matched, healthy female volunteers were included as controls.

MAGNETIC RESONANCE IMAGING

Both patients underwent MRI at 7 T. Patient 1 had follow-up studies at 7 T and 3 T with gadolinium-enhanced imaging 9 months later. Before imaging, global shimming was performed to optimize the static field homogeneity. Two-dimensional, high-resolution, T2*–weighted (gradient-recalled echo) imaging was acquired in the axial plane with the following imaging parameters: repetition time/echo time/flip angle=500 ms/25 ms/35°, slice thickness=2 mm, acquisition matrix=1024 × 1024 mm², and pixel size=0.23 × 0.23 mm². This sequence was optimized to best visualize both venous structures and lesions. In addition, T2- and T1-weighted imaging was also performed. For comparison, in the follow-up studies of patient 1, MRI was performed at 3 T right after the 7-T scan. This includes T2-weighted (repetition time/echo time=8000 ms/119 ms) and T2*-weighted (repetition time/echo time/flip angle=900 ms/25 ms/35°) as well as gadolinium-enhanced, T1-weighted imaging with 2-mm–thick slices and 0.69 × 0.69 mm² pixel size.

RESULTS

Seven-tesla, susceptibility-sensitive, T2*-weighted imaging, which allows for an unprecedented resolution (pixel size, 0.23 × 0.23 mm²) and contrast of even rather small vascular structures, clearly delineates the intimate association between lesions and veins in MS. In our 2 patients with relapsing-remitting MS, we demonstrated a total of 80 MS lesions, 58 and 22 lesions independently. All lesions showed a strict perivascular distribution, following the form, orientation, and course of the vessels (this feature being best noted in small lesions) (Figure 1). The diameter of veins associated with lesions ranged from 0.3 mm to 0.7 mm.

In patient 1 on initial 7-T scans, we found that 34 of 58 total lesions were small (<15 mm²) and of these, 23 and 11 were associated with well-defined and ill-defined central veins, respectively. In the 24 remaining large lesions, 11 of these had well-defined central veins and 13 had obscured central veins, including 3 T1 black holes. Several small lesions showed subtle abnormal signal intensities strictly at the perivascular spaces, with well-defined central veins as well as small lesions with relatively obscured veins and large lesions with well-defined and ill-defined vessels (Figure 1). In Figure 2, white matter tracts, such as those of the optic radiations, being well depicted on 7-T
imaging, allowed us to accurately visualize MS lesions along a venous distribution, rather than following the course of the fiber tracts (Figure 2B). Compared with the healthy control (Figure 2A), there was marked increase in iron deposition in the basal ganglia and thalamic areas in patient 1 shown on 7-T scans (Figure 2B). In addition, a lesion embedded within the cortical sulcus was found on 7-T but not on 3-T images (Figure 2B). On 3-T, T2*-weighted imaging (Figure 2C), the perivenous association of lesions and abnormal iron deposition were poorly detected compared with 7-T MRI with the similar sequence acquisitions.

On 9-month's follow-up imaging at 7T in patient 1, we noted the same number of total lesions and also found that of the 34 small lesions counted, 5 had increased whereas 3 had decreased in size, with the 26 remaining lesions demonstrating no change (Figure 3). On 3-T gadolinium-enhanced scans, we did not note any contrast enhancement corresponding to lesions observed on 7-T imaging (Figure 3). In addition, venous vasculature associated with lesions was not visualized on either gradient-echo or T2-weighted imaging at 3 T.

In patient 2, we noted 16 small and 6 large lesions. Of these small lesions, 13 had well-defined veins in their centers and 3 had indistinct veins, as seen in Figure 4. All except 1 of the large lesions were associated with indistinct central veins.

**COMMENT**

In 1916, James W. Dawson described thin and linear periventricular lesions (Dawson fingers) oriented around the
long axis of central veins at the initial stages of MS. Since Dawson, additional histological evidence has confirmed a close association between the inflammatory nature of MS plaques and microvasculature abnormalities. Very few studies, however, have delineated the precise derivation of lesions from vascular changes in vivo.

Ultrahigh-field (7-T) systems have provided sophisticated imaging to improve the fundamental quantities underlying image resolution and contrast and have allowed for a more detailed and accurate examination of neuropathologic changes in disease processes such as MS. The 7-T MRI analysis in our 2 patients with MS revealed a total of 80 MS lesions on T2*-weighted series, with most lesions associated with centrally coursing veins. Close examination revealed subtle abnormalities in signal intensities in strict perivenous fashion in many of these lesions. This feature was especially true in smaller lesions than in larger ones. We suggest that these small lesions represent an early stage of MS plaque development, marked by beginnings of transendothelial migration of vascular inflammatory cells of lymphocytes and macrophages without apparent blood-brain barrier breakdown. In the current study, this angiocentric pattern of MS lesions was found in a greater number of smaller lesions in the absence of blood-brain barrier breakdown or contrast enhancement on MRI, which was previously thought to be the first and earliest detectable inflammatory activity on imaging. In addition, the increase in some of these signal abnormalities around veins on follow-up 7-T imaging (Figure 3) suggests lesion growth associated with vascular involvement.

Our findings established that approximately half of the total MS lesions in our 2 patients were small with well-defined central veins and that these diffuse, subtle signal abnormalities may correspond to early vascular changes, which may result in early ischemic injury leading to subsequent hypoxic injury to myelin and neuronal cells. This represents the first time in vivo that such
subtle vascular involvements have been diffused in nature. As shown with corticosteroids recommended for acute exacerbations to shorten duration and reduce inflammation and in immunomodulatory drugs to prevent progression and new lesion formation, markedly improved detection of these lesions on 7-T MRI will have substantial ramifications on monitoring lesion development and therapeutic response.

On follow-up studies in patient 1, we found a change in size in 8 of 34 (23.5%) small lesions over a period of 9 months, with 14.7% increased and 8.8% decreased in size. Such changes in size in these small lesions may represent dynamic vascular inflammatory activity. In addition, we did not find any enhancement in association with all lesions visualized on 7-T imaging in this patient, suggesting relatively minor vascular damage due to the lower amounts of inflammatory activity. Therefore, using ultrahigh-field MRI for precise characterization of microvascular abnormalities may allow for immediate pharmacologic intervention directed at these perivascular changes.

In summary, our study, on the basis of increased detection of small and subtle perivenous or venous wall signal changes at 7 T (attributable to high field strength), may in fact describe the earliest detectable vascular changes possible before blood-brain barrier breakdown. The appreciation and assessment in vivo of early microvascular involvement in lesions is important in diagnosis, monitoring lesion progression, and determining therapeutic efficacy.