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Yulin Ge, Meng Law, Joseph Herbert and Robert I. Grossman

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Case Report

Prominent Perivenular Spaces in Multiple Sclerosis as a Sign of Perivascular Inflammation in Primary Demyelination

Yulin Ge, Meng Law, Joseph Herbert, and Robert I. Grossman

Summary: In this study, we describe prominent perivenular spaces as a sign that is seen on high-resolution (512×512) transverse T2-weighted MR images in patients with multiple sclerosis. The observed widening of perivenular space is depicted as a stringlike hyperintensity projecting radially and aligned with multiple sclerosis lesions (usually small), following the course and configuration of deep venular structures. This widening may be an important sign in differentiating primary (ie, in multiple sclerosis) from secondary causes of demyelination.

Perivascular inflammation is a critical event in the pathogenesis and evolution of multiple sclerosis lesions. We describe prominent perivenular spaces that appear to be associated with and may be useful as a sign in differentiating multiple sclerosis from other white matter diseases.

Case Reports

The MR imaging examinations were performed in 3 patients with clinically definite diagnoses of relapsing-remitting multiple sclerosis on a 3T MR unit. High-resolution (matrix, 512×512) axial dual-echo fast spin-echo images (proton attenuation and T2-weighted with TR/TE1/TE2, 7900/17/119) were obtained with a section thickness of 3.0 mm and no gap. The pixel size was $0.43 \times 0.43 \text{ mm}^2$. In addition, axial FLAIR images (TR/TE/TI, 9010/92/2500) and postgadolinium T1-weighted images (TR/TE, 600/27) were also obtained in the same fashion as dual-echo images in these patients.

Case 1. A 43-year-old woman with a clinically definite diagnosis of multiple sclerosis for 3 years developed recent numbness and abnormal sensation in the lower extremities. MR imaging of the brain showed 5 hyperintense lesions on T2-weighted images with no evidence of enhancement on postcontrast T1-weighted images. Three of these 5 lesions demonstrated this “prominent perivenular spaces” sign. As shown in Figure 1, prominent perivenular spaces were identified associated with several multiple sclerosis lesions in this patient. The imaging appearance of these perivenular spaces include the following: 1) Abnormal stringlike hyperintensities located in

the periventricular or subcortical regions are best visualized on dual-echo T2-weighted fast spin-echo sequences. 2) Unlike the Virchow-Robin space, these enlarged perivenular spaces do not follow the lenticulostriate arteries as extensions of the subarachnoid space; they appear to follow the course and configuration of deep venular structures. 3) These spaces are usually shown to be most prominent adjacent to lesion plaques (usually small) and project radially outward. 4) Unlike Virchow-Robin spaces, these stringlike hyperintensities are not isointense to cerebrospinal fluid as shown on FLAIR imaging that is demonstrated in Figure 1.

Case 2. A 51-year-old woman started with numbness in the left hand 6 years ago and had a clinical diagnosis of relapsing-remitting multiple sclerosis. Clinical examination revealed sensory problems extending from the left elbow distally and the left side of the body, as well as lower extremity weakness. The expanded disability status scale was 2.0. MR imaging of the brain showed prominent perivenular spaces signs at the level of the lateral ventricle associated with 2 lesions on proton attenuation and T2-weighted images (Fig 2A). These dilated perivascular spaces extended from lesions outwardly as a cluster of linear hyperintensities on T2-weighted images. Prominent perivenular spaces were not found in all lesions in this patient.

Case 3. A 33-year-old woman was diagnosed with relapsing-remitting multiple sclerosis and optic neuritis for 2 years. There were 3 lesions detected on MR imaging of the brain, including 1 nodular enhancing lesion in the left occipital lobe. Prominent perivenular spaces signs were depicted in both sides of parietal subcortical white matter regions as cluster-appearing hyperintensities on T2-weighted images (Fig 2B). They demonstrated purely enlarged perivenular spaces without apparent association with lesions.

Discussion

Perivascular inflammation is a critical event in the pathogenesis and evolution of multiple sclerosis lesions, and the association of vascular injury and multiple sclerosis lesions has long been recognized. In 1916, James W. Dawson, a histologist, first described periventricular lesions that extend from the ependymal surface of the ventricles along large collecting central veins (1), which appear fingerlike and are now often referred to as “Dawson’s fingers.” This has been confirmed by histopathologic studies in which an intense perivenular cuffing by lymphocytes and monocytes in lesion plaques was found in active acute lesions (2, 3). Such perivenular inflammation has also been thought to play a primary role in the disruption of the blood-brain barrier, in myelin breakdown, and in the formation of new lesions.

Although the lesion-vein relationship has been identified in postmortem studies for many years, few studies have demonstrated it in vivo. Recently, using

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From the Department of Radiology (Y.G., M.L., R.I.G.), New York University School of Medicine, New York, NY; and the Department of Neurology (J.H.), Hospital for Joint Disease, New York University School of Medicine, New York, NY.

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Address correspondence to Yulin Ge, MD, Department of Radiology, New York University Medical Center, 560 First Avenue, OBH-D-120 (C&D Bldg.), New York, NY 10016.

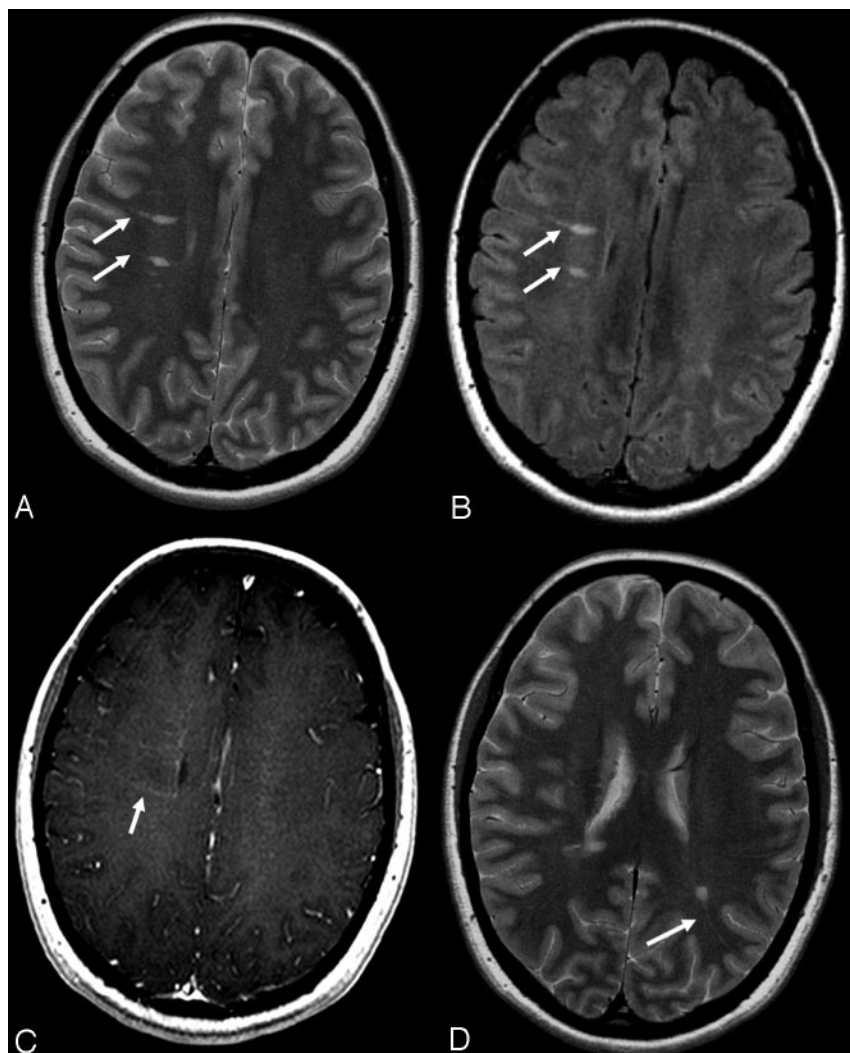


FIG 1. "Prominent perivenular spaces" sign in a 43-year-old patient with multiple sclerosis. (A) Proton attenuation image (TR/TE, 7900/17) shows a widening perivenular space as stringlike hyperintensity (arrows) projecting radially from 2 small multiple sclerosis lesions following the course and configuration of deep venular structures. (B) FLAIR MR image (TR/TE/TI, 9010/92/2500) shows the increased intensity (arrows) (not cerebrospinal fluid intensity) within these prominent perivenular spaces. (C) Enhanced T1-weighted image (TR/TE, 600/27) shows an enhancing vein (arrow) in one lesion. (D) Proton attenuation image shows another lesion (arrow) with this prominent perivenular spaces sign.

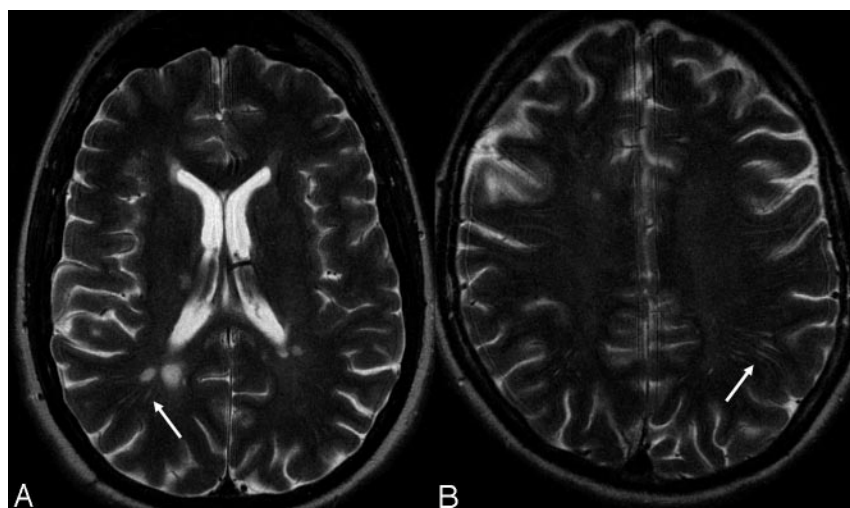


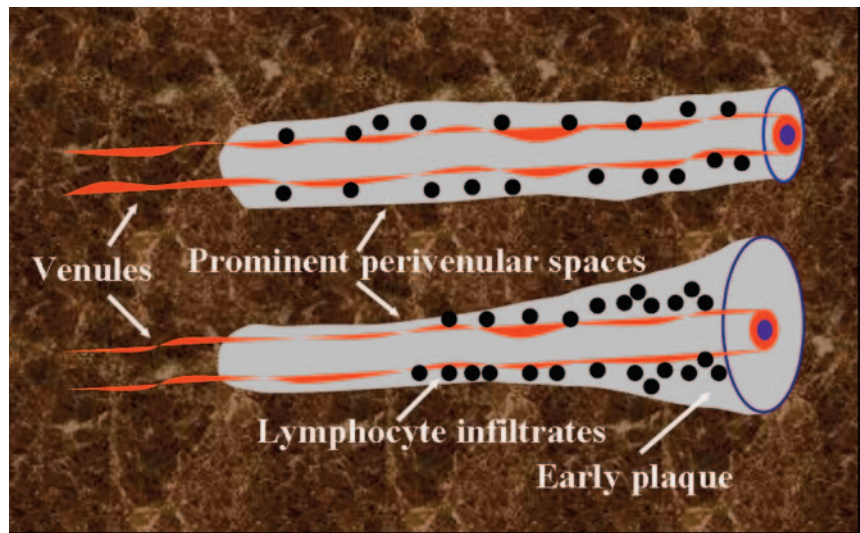
FIG 2. (A) "Prominent perivenular space" sign (arrow) follows the central course of the veins along which the lesions spread on T2-weighted image (TR/TE, 7900/119) in a 51-year-old patient. (B) Prominent perivenular spaces sign (arrow) without apparent association with lesions on T2-weighted image in a 33-year-old patient.

a complex MR venography technique after contrast material administration, Tan et al (4) showed that almost all lesions in the periventricular region were centered on small veins. We describe the prominent perivenular spaces sign on the basis of conventional routine MR imaging in patients with multiple sclerosis.

This sign is best identified on high-resolution T2-weighted images. It has implications in potentially differentiating primary from secondary demyelinating diseases on the basis of conventional MR imaging.

The abnormally dilated and increased signal intensity in the perivenular spaces is likely to be lesion-

FIG 3. Schematic drawing illustrates the perivenular inflammatory infiltrates that cause lesion formation and enlarged perivenular spaces in multiple sclerosis. The prominent perivenular spaces can be with (bottom vessel) or without (top vessel) lesion association.



related (Fig 1, 24), indicating not only that the lesion may be involved in the dilation of the perivenular space but also the presence of inflammatory activity along this space (Fig 3). Because the increased signal intensity within the perivenular space is not suppressed on FLAIR imaging (Fig 1B), the perivenular spaces are unlikely to be cerebrospinal fluid, but rather may represent inflammatory activity or perivenular lymphocytic cuffing. Histopathologically, Fog (5) demonstrated that nearly 91% of lesions have a perivenous origin; however, in our 3 patients, not all multiple sclerosis lesions demonstrated these prominent perivenular spaces signs. This finding may be related to 3 factors. The first factor may be due to the extent of inflammatory activity in the lesion without increasing water content within the perivenular spaces. The second factor, potentially accounting for poor conspicuity of prominent perivenular spaces in some lesions, is that these lesions have become so large that the tissue adjacent to the venules also demyelinate, resulting in obscuration of the perivenular spaces. The third is that some vessels are too small or have become occluded, leading to the difficulty in detecting them. Prominent perivenular spaces were also observed unassociated with lesions (Fig 2B), seen as a cluster of ramifying vascular structures with increased signal intensity. In the absence of apparent associated lesions, this observation may be indicative of local perivenular low-grade inflammation in normal-appearing white matter, preceding new lesion development (Fig 3). This concern can be addressed by following these prominent perivenular spaces in longitudinal studies.

On the basis of the anatomic knowledge and venography of the periventricular cerebral veins (4, 6), the prominent perivenular spaces appearing as radially aligned projections are consistent with the orientation of the periventricular vein in the brain. Therefore they are not likely to represent true Virchow-Robin spaces, which are actually periarterial spaces. Virchow-Robin spaces are extensions of the subarachnoid space that accompanies arteries entering brain

parenchyma, therefore containing cerebrospinal fluid and would follow cerebrospinal fluid signal intensity, which can be suppressed on FLAIR imaging; whereas prominent perivenular spaces are not suppressed on FLAIR, indicating that the increased signal intensity is not cerebrospinal fluid. In addition, the Virchow-Robin space is usually observed in the basal ganglionic region because of the enlarged space around penetrating arteries at the level of or close to the anterior commissure (7). The observation that prominent perivenular spaces in multiple sclerosis are not Virchow-Robin spaces has clinical implications in improving our specificity in making a diagnosis of primary demyelination.

In our study, the lesions associated with prominent perivenular spaces did not show enhancement on postcontrast T1-weighted imaging. Although we do not fully understand the cause, the observed widening of perivenular spaces on MR imaging seems to be more prominent at the early stage of lesion development, when the lesion is small and the blood-brain barrier has not been disrupted (Fig 14). There is often a faint linear enhancement along the perivascular space, as shown in Figure 1C, which we believe is venous enhancement due to slow flow of intravenous contrast material that further confirms that the observed prominent perivenular spaces are in fact perivenous.

Because the clinical radiologic diagnosis of multiple sclerosis is still challenging as a result of the nonspecific appearance of multiple sclerosis plaques on T2-weighted imaging, the prominent perivenular spaces may be a sign we can identify on conventional MR imaging to increase our clinical suspicion for multiple sclerosis. Although perivascular spaces can become more prominent with age, in part due to atrophy of the white matter, the finding of prominent perivenular spaces in younger patients with a potential diagnosis of primary demyelination should increase our clinical suspicion. Recent advances in faster high-resolution MR imaging enable us to demonstrate more anatomic and pathologic detail in multiple sclerosis lesions, especially when high-field scan-

ners (8) become more widely used in the clinical setting, resulting in significantly increased signal-to-noise ratio and spatial resolution. It is likely that as high-field high-resolution scanners allow visualization of smaller structures in the brain, the criteria for making a diagnosis of multiple sclerosis may change. This study provides imaging evidence that multiple sclerosis lesions develop in the perivenular region, resulting in a prominent perivenular spaces sign that may be useful in the diagnosis of lesion development of multiple sclerosis disease.

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