Restricted diffusion preceding gadolinium enhancement in large or tumefactive demyelinating lesions

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Summary

Although restricted diffusion without coincident contrast enhancement is most commonly associated with cerebral ischemia, large or tumefactive multiple sclerosis (MS) lesions may demonstrate this pattern initially, followed by subsequent gadolinium (Gd) enhancement. The clinical and MRI characteristics of 3 patients with MS with this imaging pattern are reviewed. All patients had brain MRI lesions >1 cm in diameter, in locations consistent with new neurologic symptoms, and with prominent restricted diffusion but no Gd enhancement. Demyelinating lesion etiologies were supported by CSF findings, laboratory exclusion of alternative diagnoses, lesion evolution, or additional lesions characteristic of MS on brain MRI. Follow-up imaging within 2–4 weeks showed decreased restricted diffusion with patchy Gd enhancement which resolved on subsequent imaging. This imaging evolution may reflect early demyelination prior to inflammation-associated blood-brain barrier disruption.

Diffusion-weighted MRI is used as part of the imaging protocol in both suspected multiple sclerosis (MS) and cerebral ischemia. Restricted diffusion is characterized by decreased apparent diffusion coefficient (ADC) values and typically displayed as hypointensity on ADC imaging sequences. ADC signal reduction is the MRI hallmark of acute ischemia, though demyelinating lesions, neoplasms, and infectious masses can demonstrate restricted diffusion,¹ and discriminating between these etiologies based on MRI characteristics can be challenging. The time course of these processes (ranging

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from acute to chronic progressive) and the presence or absence of gadolinium (Gd) enhancement aids in the differentiation.

The majority of cases of acute demyelinating lesions reported with restricted diffusion have been relatively easy to distinguish from ischemia due to the simultaneous presence of Gd enhancement.²⁻⁴ Several of the remaining cases either have not commented on Gd enhancement at the time of ADC reduction^{5,6} or reported the absence of simultaneous Gd enhancement and lacked close temporal follow-up.⁴ Two recent studies reported cases of restricted diffusion in demyelinating lesions with subsequent progression of Gd enhancement, but the evolution of enhancement was not a focal point of discussion.^{7,8} We present 3 examples of acute demyelinating lesions with decreased ADC followed by Gd enhancement which presented to our clinic over a 9-month interval.

CASE REPORTS

Case 1

A 28-year-old man presented with abrupt onset of slurred speech after a couple of days of mild facial weakness and dysphagia. He was afebrile, and initial neurologic examination showed

Figure 1 Case 1

MRI evolution (A-C): MRI 2 days after symptom onset: fluid-attenuated inversion recovery (FLAIR), apparent diffusion coefficient (ADC), and T1-weighted sequence post gadolinium (T1 + Gd); (D-F) MRI 22 days later.

Figure 2 Case 2

MRI evolution (A–C): MRI <1 day after symptom onset; (D–F) MRI 31 days later. ADC = apparent diffusion coefficient; FLAIR = fluid-attenuated inversion recovery; Gd = gadolinium.

profound facial and tongue weakness, mild left hemiparesis, and bilateral ankle clonus. His first brain MRI—within hours of symptom worsening—showed multiple white matter hyperintensities on fluid-attenuated inversion recovery (FLAIR) images (figure 1, A–C). Several lesions had mass effect, the largest of which was a right posterior frontal region lesion with patchy Gd enhancement. Posterior to this lesion was an area of restricted diffusion (reduced ADC) without Gd enhancement. Spine MRI was normal, but MS diagnosis was supported by negative infectious and malignancy workup, and CSF notable for an elevated immunoglobulin G (IgG) index and CSF-specific oligoclonal bands. He was treated empirically with IV methylprednisolone (MP) for 5 days with an incomplete response and subsequently received 6 plasma exchange (PLEX) treatments with good response. Brain MRI at the completion of IVMP (not shown) showed resolution of Gd enhancement in the large right frontal lesion and persistent but diminished restricted diffusion in the adjacent lesions, still without contrast enhancement. Brain MRI was repeated after PLEX treatments (figure 1, D–F), 22 days after initial imaging, and showed evolution of Gd enhancement and increased ADC signal where previous ADC reduction was observed.

Case 2

A 26-year-old woman presented with headaches and positive visual phenomena of colors and shapes. Visual field testing indicated a left homonymous hemianopsia, and brain MRI after 2 days of symptoms revealed multiple FLAIR hyperintensities (figure 2, A–C). A right occipital lesion, less apparent on the FLAIR sequence, showed restricted diffusion with peripheral areas of reduced ADC and no Gd enhancement. She had a negative malignancy workup, and CSF studies revealed unique oligoclonal bands. She received 3 days of IVMP with improvement in visual fields. Repeat MRI 1 month after initial imaging (figure 2, D–F) showed resolution of Gd enhancement in the right frontoparietal lesion but interval development of enhancement in the right occipital lesion with increased ADC signal. She was clinically stable but because of the MRI findings, was treated with a second course of IVMP for 5 days. MRI 2 months

Figure 3 Case 3

MRI evolution (A–C): MRI <1 day after symptom onset; (D–F) MRI 9 days later. ADC = apparent diffusion coefficient; FLAIR = fluid-attenuated inversion recovery; Gd = gadolinium.

after initial imaging showed improved but persistent Gd enhancement of the right occipital lesion. She initiated therapy with natalizumab. Four months after the initial MRI, repeat imaging revealed no new lesions and no abnormal Gd enhancement.

Case 3

A 43-year-old woman developed right-sided paresthesias and clumsiness which quickly worsened after evolving over a couple of days. The initial brain MRI was performed upon symptom worsening (figure 3, A–C) and revealed a FLAIR hyperintensity extending from the posterior limb of the left internal capsule to the left corona radiata with an incomplete rim of peripheral restricted diffusion and no Gd enhancement. CSF studies showed elevated IgG index and CSF-specific oligoclonal bands. She was treated with 4 days of IVMP without significant symptomatic improvement, and then 5 courses of PLEX with a good response. Follow-up MRI (figure 3, D–F) 9 days after initial imaging showed resolution of the lesion's restricted diffusion and development of central patchy Gd enhancement. The enhancement was still present but decreased on brain MRI 5 weeks after initial MRI.

DISCUSSION

We report 3 patients with initial MRI studies within 48 hours of symptom onset or abrupt worsening showing areas of restricted diffusion, in patterns ranging from the lesion borders to homogeneously reduced ADC signal. Two of the patients had lesions which appeared tumefactive on imaging while the other had a large lesion with relatively severe symptoms. All patients had normal spine MRI but CSF studies consistent with immune-mediated demyelinating disease. Gradient-echo or susceptibility-weighted imaging sequences from each patient (not shown) did not demonstrate lesion hypointensity, suggesting that the ADC patterns were not due to susceptibility effect from blood, iron-containing macrophages, or other inflammatory free radicals. The abnormal ADC resolved in 1 patient as early as 9 days later, while another patient lacked full resolution of restricted diffusion at day 8 after initial MRI but had resolution on follow-up MRI at day 22. Following restricted diffusion on initial MRI,

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subsequent Gd enhancement was seen in the patients on follow-up MRI 9–31 days later. All 3 patients were placed on disease-modifying therapies and remained clinically and radiologically stable at 1-year follow-up intervals.

Imaging studies are increasingly relied on for the diagnosis of MS, making it necessary to identify the range of imaging patterns seen in MS, particularly potential uncommon atypical patterns. Although acute MS lesions are typically associated with increased diffusion, there are several reports of demyelinating lesions with restricted diffusion, usually associated with active inflammation indicated by Gd enhancement. Recent articles^{7,8} describe acute MS lesions with areas of restricted diffusion where Gd enhancement was present but progressed on follow-up imaging. We extend those findings by showing that in tumefactive lesions and large demyelinating lesions, restricted diffusion can precede the onset of Gd enhancement. This observation makes the important clinical point that not all lesions with restricted diffusion in the absence of Gd enhancement are ischemic, particularly in younger patients without significant vascular risk factors. Acute ischemic strokes frequently show Gd enhancement in the days to weeks following symptom onset,⁹ but our cases demonstrate that the pattern of restricted diffusion preceding Gd enhancement is also possible in demyelinating disease.

The majority of acute MS lesions do not demonstrate restricted diffusion even when captured in early stages. Multiple serial diffusion-weighted imaging studies^{10,11} show a typical pattern of increased diffusion in normal-appearing white matter of future lesions prior to Gd enhancement. Potential reasons for the increased diffusion include focal edema increasing the size of extracellular space and subtle early myelin loss.^{3,10} The serial imaging studies^{10,11} highlight the concept of tissue changes occurring prior to inflammatory blood–brain barrier disruption manifested by Gd enhancement. This evolution of demyelinating lesions is also demonstrated by our cases, though the tissue change is diffusion restriction and more dramatic.

The etiology of the early restricted diffusion in these MS lesions is unknown, and multiple hypotheses have been raised. It is postulated that myelin fragments and reduced fiber tract organization may restrict water diffusion.⁸ Another theory, based on immunopathology studies of acute MS lesions which have identified heterogeneous mechanisms of tissue damage,^{12,13} is that restricted diffusion reflects activated microglia and oligodendrocyte apoptosis prior to infiltration of bloodborne inflammatory cells. The physical clustering of microglia and release of excitotoxins leading to oligodendrocyte injury with associated cytotoxic edema (similar to that seen in ischemia) may be responsible for initial restricted diffusion. Proinflammatory cascades in acute MS inflammation can lead to mitochondrial dysfunction and decreased energy production resulting in cell death that may also contribute to the pattern of restricted diffusion.¹⁴ It has been proposed that acute demyelinating lesions with restricted diffusion are a newly identified variant of MS lesions,⁴ but there is some variability among such lesions, particularly in the degree and distribution of diffusion restriction.⁸ Although not all tumefactive MS lesions demonstrate restricted diffusion, the majority of reported demyelinating lesions with reduced ADC are larger than typical lesions and often have a tumefactive appearance. They may also

appear more likely to produce severe or stroke-like symptoms,^{2,5–7,15} clinically consistent with the MRI findings. The acute development of relatively severe symptoms in our cases resulted in rapid clinical evaluation and imaging, which allowed identification of ADC reduction prior to the occurrence of Gd enhancement.

Inflammatory demyelination should be included in the differential diagnosis of hypointense lesions on ADC sequences. Short-interval (2–4 weeks) follow-up MRI looking for subsequent lesion evolution characteristic of acute demyelination should be considered in young patients without vascular risk factors presenting with such lesions.

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