Published in final edited form as:

Mult Scler. 2012 December ; 18(12): 1745–1753. doi:10.1177/1352458512445407.

Acute demyelinating lesions with restricted diffusion in multiple sclerosis

Konstantin E Balashov¹ and Eric Lindzen²

¹Department of Neurology, UMDNJ, Robert Wood Johnson Medical School, New Brunswick, NJ, USA

²Department of Neurology, SUNY at Buffalo, Buffalo, NY, USA

Abstract

Background and objectives—It is widely accepted that typical acute demyelinating lesions in relapsing–remitting multiple sclerosis (RRMS) exhibit vasogenic edema with increased diffusion, as demonstrated by an increased apparent diffusion coefficient on MRI. In contrast, acute ischemic lesions demonstrate cytotoxic edema with restricted diffusion. Recent reports have documented selected cases of acute demyelinating lesions exhibiting restricted diffusion (ADLRD) in MS. We aimed to assess the morphologies, distributions, signal characteristics and changes over time of nine ADLRD. An additional goal was to obtain clinical correlations and relate our findings to all previously published case reports describing ADLRD.

Methods—A retrospective case series study was performed at two academic centers. MRI characteristics of nine ADLRD found in six RRMS patients were compared with typical active symptomatic contrast-enhancing lesions with increased or normal diffusion in control RRMS patients.

Results—The average size of ADLRD was not significantly different from typical lesions. A periventricular location and faint signal on T2-weighted images were significantly more common for ADLRD compared with typical lesions. Two patients with ADLRD on initial MRI exhibited new ADLRD on their follow up scans.

Conclusion—Our results and review of prior published cases suggest that ADLRD represent a new variant of MS lesion. The restricted diffusion that is a characteristic of ADLRD on MRI is a new challenge in the differential diagnosis of stroke in young adults. The pathogenesis of ADLRD remains to be understood.

Keywords

multiple sclerosis; magnetic resonance imaging; diffusion magnetic resonance imaging; relapsing–remitting multiple sclerosis; demyelinating diseases; brain edema

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Corresponding author: Konstantin E Balashov, MD, PhD, Department of Neurology, UMDNJ, Robert Wood Johnson Medical School, 125 Paterson Street, 6th Floor, New Brunswick, NJ 08901, USA. kbalashov@yahoo.com.

Conflict of interest statement

The authors declare no conflicts of interest in preparing this article.

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Introduction

Multiple sclerosis (MS) is the leading cause of neurological disability in young adults.¹ In 85% of patients, MS initially follows a relapsing–remitting course (RRMS) and is associated with acute demyelinating lesions (ADLs).² It is widely accepted that although ADLs in MS patients may occasionally demonstrate increased diffusion weighted imaging (DWI) signal, this is seen in conjunction with an increased, rather than decreased, apparent diffusion coefficient (ADC) on MRI.^{3–6} Bright signal on both DWI and ADC in acute MS lesions has been postulated to be due to peripheral and central vasogenic edema⁷ that increases the lesional ADC value, while also resulting in hyperintense DWI signal due to a ‘T2 shine through’ effect. In contrast, while acute ischemic stroke lesions also demonstrate increased DWI signal, they exhibit a reduced, or dark, signal on ADC maps, consistent with restricted diffusion due to early cytotoxic edema. This imaging appearance in the acute stage of ischemia is followed by a return of ADC to ‘pseudonormal’ values at approximately 1 week.⁸

Recently, several separate clinical cases of MS or clinically isolated syndrome (CIS) with ‘atypical’ ADL exhibiting restricted diffusion (hyperintense on DWI, hypointense on ADC) on brain MRI were described by us⁹ and three other independent groups.^{10–12} Similar to ischemic stroke lesions, the ‘atypical’ ADLs also developed increased ADC on follow-up MRI. Here, we analyze nine ADLs with reduced ADC found in six RRMS patients and correlate our findings with the other groups.^{10–12} Our analysis suggests that ADL with restricted diffusion (ADLRD) represent a new variant of MS lesion that differs from ‘typical’ MS lesions based on lesion location, MRI characteristics and a tendency to reoccur. The restricted diffusion exhibited by ADLRD on MRI represents a new challenge in the differential diagnosis of stroke in young adults.

Materials and methods

Patients

A retrospective review of clinical charts and MRI scans was approved by the Institutional Review Boards of the State University of New York at Buffalo and the UMDNJ-Robert Wood Johnson Medical School. All subjects had a previously established diagnosis of MS based on 2005 revisions to the McDonald Criteria¹³ or of the CIS based on CHAMPS criteria.¹⁴ Each patient included in the study was comprehensively evaluated at one of two specialized MS centers with exclusion of common diseases that could mimic MS. At least one high-resolution brain MRI scan of sufficient quality for neuroimaging analysis, with the following pulse sequences, was required for inclusion: fluid-attenuated inversion recovery (FLAIR), pre- and post-contrast T1-weighted imaging (T1WI), ADC and DWI. ADLRD were defined as intracerebral white matter lesions exhibiting restricted diffusion on DWI with corresponding decreased ADC, in the context of an acute clinical exacerbation. Surveillance for cases fitting the inclusion criteria was conducted by ECL at the Buffalo study site over a 6-month period and by KEB at UMDNJ-RWJMS over a 10-month period. In total, six RRMS patients with nine ADLRD were identified. They are described in Table 1. As controls, we reviewed brain MRI studies of 27 RRMS patients with 57 contrast-enhanced lesions exhibiting increased or normal diffusion based on DWI and ADC sequences. To be included in the analysis, control lesions could not be incidental findings on patients who were not acutely symptomatic, and symptomatic control lesions could be found on brain MRI no more than 5 days after the symptom onset. Using these criteria, 50 out of 57 contrast-enhanced lesions surveyed for the control dataset were excluded, with seven symptomatic enhancing lesions not exhibiting restricted diffusion (typical acute demyelinating lesions) being compared with ADLRD in the final analysis (Table 2). The MS patients with ADLRD and MS patients with typical lesions had a similar mean age.

Three of the six MS patients with ADLRD were above the age of 50. Based on available medical records, none of the patients with ADLRD was diagnosed with stroke, peripheral vascular disease or myocardial infarction before or after ADLRD were found. There were no other imaging findings on MRI suggestive of a possible vascular occlusive or vasculopathic etiology (chronic lacunar infarctions, wedge-shaped or vascular-territory ischemic lesions, hemorrhages). IV steroids were not given for at least 1 month prior to the initial MRI.

MRI technique and volumetric analysis

All of the MRI protocols used in this study were clinically standardized and validated. Scans obtained at SUNY and at UMDNJ-RWJMS were obtained at 1.5 and 3.0 T magnetic field strengths. A uniform time delay of 5 minutes following contrast injection was utilized prior to acquisition of the T1-weighted post-contrast images at both of the study sites. DWI was always performed prior to contrast administration. Source data for the diffusion-weighted images and ADC maps was obtained in three orthogonal directions with b values of 1000 s/mm² to obtain essentially pure diffusion-based contrast while maintaining an acceptable signal-to-noise ratio.¹⁵ Slice thicknesses of the axial images used in the analysis (FLAIR, T1 pre- and post-contrast, DWI with ADC) varied between 3.0–6.5 mm (with inter-slice gap included) at SUNY and 4.8–6.5 mm at UMDNJ-RWJMS. Quantitative lesion analysis (volume and maximum axial diameter) was carried out on DICOM-formatted MR image files using a clinically validated imaging software package incorporating manual area tracing and length measurement tools (ClearCanvas Workstation, Toronto, ON, Canada). Manual tracing, area and length measurements of lesions were conducted exclusively by the authors (EL, KEB), both of whom have clinical expertise and certification in neuroimaging. The volume was calculated for each lesion by summing its traced area on all intersecting image slices of a given pulse sequence and multiplying this value by the sum of the slice thickness and interslice gap. Maximum lesion diameters were obtained by measuring the maximum distance that a straight line could be drawn between two points along a lesion's perimeter in the axial plane.

Statistical analysis

Figures were generated and statistical analysis performed with a GraphPad package from GraphPad Software, Inc., La Jolla, CA. The results are presented as mean $\pm$ SEM. The *t* test and Fisher's exact test using two-tailed *p*-values were utilized.

Results

Patients with ADLRD

All six patients with ADLRD (Table 1) had clinically definite RRMS, with the onset of clinical symptoms between 33 days to 16 years prior to ADLRD being identified on MRI for the first time. Patient age varied from 21 to 62 years old. Five patients with ADLRD were females and one patient was male. Six ADLRD, one for each patient, were found on initial MRI scans obtained at the time of an acute attack and three ADLRD were noted on follow-up MRI of two patients (Table 3). Patient #1 was found to have two additional ADLRD on follow-up MRI (Figure 1 and Table 3, lesions 1B and 1C) and patient # 4 was found to have one more ADLRD (Table 3, lesion 4B) located in the hemisphere opposite to the location of the ADLRD that was present on the initial MRI, published earlier.⁹ Seven out of nine ADLRD exhibited contrast-enhancement (e.g. lesions 1A and 1B in Figure 1 and Lesion 5 in Figure 2). Two ADLRD, both located in the parietal periventricular region, did not exhibit contrast enhancement (Figure 1, Lesions 1C and Figure 2, Lesion 5).

Lesion hypointensity on the ADC map of most ADLRD was homogeneous. However, the largest ADLRD, seen in patient #5, exhibited two subregions of differentially decreased

diffusion on the ADC map (Figure 2): strongly hypointense ADC signal in the posterior-medial portion of the lesion correlating with faintly hyperintense T2 signal, and faintly hypointense ADC signal present in the anterior-lateral portion of the lesion correlating with strongly hyperintense T2 signal. It is not clear if this heterogeneity in the ADC values occurred within a single lesion or was due to two separate overlapping ADLRD at different stages of natural progression in time (see below).

Natural progression of ADLRD

Serial scans revealed aspects of the natural progression of one ADLRD (lesion 3). Initially, the ADLRD exhibited a very faint, small contrast-enhanced signal on post-contrast T1 and faint T2-hyperintense signal on FLAIR (Figure 2A and B). Restricted diffusion (hyperintense DWI signal and hypointense ADC) was present at this time point (Figure 2C and D). The lesion volume on DWI and FLAIR is larger than the volume of the lesion on ADC; 'T2 shine through' effect may have contributed to increased volume of the lesion on DWI relative to ADC. On the follow-up MRI scan performed 17 days after the initial study, the contrast-enhanced portion of the lesion and T2-hyperintense signal on FLAIR progressed, both being brighter and larger, possibly reflecting progressively increased permeability of the blood-brain barrier and increasing vasogenic edema. The area of enhancement on post-contrast T1 then became smaller with time, based on comparison of the images at day 30 and day 17 (not shown), while the prominent T2-weighted signal remained stable. Restricted diffusion had resolved by day 17 and continued to be absent at day 30, with remaining bright signal on DWI being secondary to a T2 shine through effect. In lesion 3, the overall pattern was therefore of contrast-enhancement persisting substantially longer than restricted diffusion. Of the four ADLRD which could be reevaluated on follow-up MRI (within 10 days to 4 months), three acquired a strong T2-hyperintense signal and one lesion resolved (Table 3).

Clinical symptoms and ADLRD

Of nine ADLRD, five lesions exhibited locations corresponding to new clinical symptoms (Table 1). Three ADLRD lesions found on follow-up MRI (Table 3, Lesions 1B, 1C and 6) were asymptomatic. Exact dates of new clinical symptom onset were available for four symptomatic ADLRD (Table 3, lesions 1A, 4A, 4B and 5), two of which were detected on MRI performed 2–4 days after symptom onset and two of which were seen on MRI performed within 1 day of symptom onset. Symptomatic ADLRD converted to lesions with normal or increased diffusion on all follow up MRI scans performed 13 days or more following onset of symptoms (e.g. Table 3, lesions 4A and 3). In patient 4, the first MRI scan performed without ADC 2 days prior to clinical symptom onset (published earlier⁹) revealed contrast-enhanced lesions; these exhibited restricted diffusion on the second MRI which was performed 5 days later (Table 1, ADLRD 4A).

Overall, we were able to identify several symptomatic ADLRD within the first 24 hours and up to 4 days after the onset of clinical symptoms. The time course for one lesion demonstrates that restricted diffusion can be present for at least 5 days after contrast-enhancement is first noted on MRI. Restricted diffusion for all ADLRD resolved on follow-up MRI done 13 or more days after the onset of clinical symptoms

MRI characteristics of ADLRD compared with active symptomatic lesions without restricted diffusion

We compared the MRI characteristics of the nine ADLRD lesions found in six RRMS patients (five females, one male, average age 41.0 ± 6.6 years old) with 'typical' symptomatic contrast-enhanced lesions not exhibiting restricted diffusion in seven control RRMS patients (seven females, average age 41.7 ± 4.0 years old). Inclusion criteria for the

patients and control enhanced lesions analyzed in this study are documented in the materials and methods section. Only control symptomatic lesions documented on MRI within 5 days of the new neurological symptom onset were included, as the interval between the onset of clinical symptoms (or the appearance of a new contrast-enhanced lesion) and the documentation/appearance of symptomatic ADLRD on MRI was 5 days or less (Table 3). The lesion characteristics of each group are described in Tables 3 and 4, respectively. ADLRD had an average size (1.75 ± 0.35 cm) which was not significantly different from 'typical' active lesions in the controls (1.0 ± 0.18 cm), ADLRD also exhibited an average T2-weighted lesion volume (3.61 ± 1.65 cm³) which was not significantly different from control enhanced lesions (1.82 ± 1.38 cm³). However, a periventricular location was more common for ADLRD (eight out of nine lesions) as compared with control lesions (zero out of seven lesions, $p = 0.0014$ based on Fisher's exact test). In addition, faint T2-hyperintense signal was characteristic of ADLRD (five out of nine lesions) as compared with control lesions without restricted diffusion, which all had strong T2 signal ($p = 0.0337$ based on Fisher's exact test).

Discussion

In this study, we extend previous descriptive reports of ADLRD in patients with relapsing forms of MS by investigating the radiological characteristics of nine ADLRD in six patients. Strengths of this study include its size, being the largest single sample of such lesions yet described. We were able for the first time to statistically compare the imaging characteristics of ADLRD with typical acute MS lesions exhibiting normal or increased diffusion. We have also summarized the characteristics of all previously published ADLRD in comparison with our own findings.

Limitations of this study include slight variations in the MRI protocols employed. Higher field strength MRI scanners are more sensitive at detecting tissue voxels exhibiting restricted diffusion due to their typically higher gradient strengths and higher signal-to-noise ratio. In the case of our study, the potential differences in the detection limits between the 1.5 and 3 T scanners were minimized by employing validated manufacturer protocols for DWI. The relatively large slice thicknesses of the images used were felt to be sufficient to provide volumetric data appropriate to our study design, a retrospective case series.

Although the radiological phenotype of ADLRD adds to the differential diagnostic considerations when evaluating acute vascular events, such events are relatively uncommon before the 6th decade and establishment of a small cohort of age-matched controls with acute vascular events was felt to be outside of the scope of this study. The contrast-enhancement associated with seven out of nine DWI-positive lesions in our cases would have been atypical for classical ischemic stroke. Although one Crohn's disease patient and one patient with diabetes mellitus were included in the analysis, both diseases are not uncommon in MS patients.^{16,17} However, ischemia is difficult to diagnose clinically when it occurs in the deep white matter. It remains a possibility that ADLRD have an ischemic component, or are purely ischemic. Future studies with application of new imaging techniques may clarify this issue.

Although many cerebral white matter lesions are asymptomatic,^{18–20} the observation of acute enhanced lesions on MRI is nevertheless a fairly frequent occurrence in busy MS clinics. In light of this, and the relative rarity of ADLRD, it is felt to be unlikely that they simply represent a hyperacute phase in the development of 'typical' MS lesions. Further decreasing the likelihood that ADLRD simply represent an early phase of 'typical' MS lesion development is the fact that typical contrast-enhanced MS lesions have normal or increased diffusion seen even on days 1–5 after the onset of symptoms (Table 4).

In all of our clinical cases, the restricted diffusion in ADLRD converted to normal or increased ADC signal on follow-up MRI done 13 or more days after the onset of clinical symptoms. This is consistent with the findings of Rovira et al. who described two ADLRD with decreased ADC signal observed up to 10 days after symptom onset.¹² The mechanism of ADLRD conversion to a subacute lesion with increased diffusion is not clear. One may hypothesize that pleiotropic factors, e.g. vascular endothelial growth factor, released in acute MS lesions²¹ lead to neovascularization which, in turn, may be associated with increased ADC values.²²

The ADLRD described in this paper had less hyperintense T2 signal and were more commonly detected in the periventricular region compared with 'typical' active MS lesions. Some of the MS patients who had ADLRD on their initial MRI developed new ADLRD in another location on follow-up imaging, which raises the question of whether there may be a phenotypic predisposition for ADLRD in some individuals. Taking the above findings into consideration, we suggest that ADLRD represent a new variant of acute MS lesion. Contrast-enhancement is a hallmark of biologically active lesions in MS.^{23,24} This reflects a breakdown in the blood-brain barrier, which predisposes to focal vasogenic edema. In turn, vasogenic edema is associated with increased diffusion and, therefore, bright voxels on ADC maps, which is the 'typical' imaging appearance for acute MS plaques.³ In a number of previous studies, a higher ADC has been reported in T2-weighted MS lesions than in areas of normal appearing white matter.²⁵ In contrast, ADLRD in the RR MS patients described in this paper had hypointense ADC signal discovered on MRI performed up to 4 days after the onset of clinical symptoms. The MRI features of the 9 ADLRD found in 6 RRMS patients in the present study were consistent with 4 other ADLRD previously found in 4 patients by 3 independent groups.^{10–12} A summary of the clinical and MRI features of all 13 ADLRD is presented in Table 5. In addition to our study and those described above, other reports have noted that lesional ADC values may be altered. While it was previously shown in human studies that enhancing lesions exhibited lower ADC values compared with those that were non-enhanced,^{26,27} the average ADC values of both types of MS lesion were increased in comparison to normal-appearing white matter. In a primate study of experimental allergic encephalomyelitis, demyelinating lesions in the internal capsule exhibited decreased diffusion MR image signal with the diffusion-sensitizing gradient in all three orthogonal directions.²⁸ Recently, a restricted diffusion pattern has been found in acute demyelinating spinal cord lesions.²⁹

Based upon the scanning intervals used in our study, it is uncertain whether two of the ADLRD that did not enhance (Lesions 1C and 5), represent a phase of ADLRD development occurring before or after the possible onset of contrast enhancement, or whether these lesions never enhanced. Certain T2-weighted lesions of demyelinating pseudotumor, an acute fulminant variant of MS, may lack contrast enhancement for up to 7 days in the acute phase.²⁴ The patients with non-enhanced ADLRD did not have an immediate follow-up MRI, which could potentially have revealed development of contrast-enhancement. Alternatively, breakdown of the blood–brain barrier may have been present, but not extensive enough to be detected by the conventional single-dose contrast technique employed in this case series.

The pathophysiological basis for the restricted diffusion seen in ADLRD requires further study. It has been hypothesized that excitotoxicity mediated by glutamate is involved in the induction of cytotoxic edema for a number of neurological conditions including diffuse axonal injury, Wallerian degeneration and ischemic stroke.¹⁰ Restricted diffusion also occurs in some CNS infections, such as herpes encephalitis and Creutzfeldt–Jakob disease¹⁰ as well as hypercellular tumors.³⁰ The question of whether restricted diffusion in ADLRD may be due in part to an inflammatory infiltrate or cytotoxic edema involving

oligodendrocytes is raised by the imaging appearance of lesions in fulminant demyelinating processes such as tumefactive MS and progressive multifocal leukoencephalopathy, in which peripheral restricted diffusion seen along the advancing edges^{31,32} of such lesions corresponds to where these demyelinating processes are thought to be most acute or active.

Recently, Lassmann suggested that vascular pathology may be a primary cause of demyelinating lesion formation in a subset of MS patients, as those lesions showed profound similarities to tissue alterations found in acute white matter ischemic stroke.³³ If focal ischemic processes contribute to the pathogenesis of ADLRD, then their DWI signal characteristics are easily explainable. If ischemia was not the cause, then possible cellular substrates for the restricted diffusion mentioned above, in addition to other components of the inflammatory cascades in MS would need to be investigated: for example, could early leukocyte migration or the effects of cytokines upon preexisting oligodendrocytes, astrocytes or microglia within the perivenular white matter of a developing lesion play a role in restricting water diffusion within the affected tissue?

We conclude that ADLRD represent a new variant of MS lesion. Our data suggest that ADLRD are different from typical MS lesions based on lesion location, MRI signal characteristics and a tendency towards reoccurrence. The finding of a potential new variant of lesion in MS has two main implications. First, it adds another differential diagnostic consideration when evaluating acute subcortical white matter strokes, especially in young patients. Second, it suggests etiological heterogeneity in the development of acute multiple sclerosis lesions. A prospective study should be undertaken to verify our results and to serve as a next step in the elucidation of ADLRD clinical and radiological characteristics, as well as to investigate the possible relationship between the presence of ADLRD and clinical prognosis.

Acknowledgments

Funding

KEB's research activity was supported in part by the NINDS/NIH (grant number K23NS05255).

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Figure 1.

Recurrent ADLRD in patient #1: An acute demyelinating lesion adjacent to the body of the left lateral ventricle exhibits restricted diffusion (hypointense pixels on ADC map, hyperintense signal on diffusion weighted imaging) in conjunction with faint ring-enhancement (hyperintense signal on T1-weighted imaging post-contrast). Follow-up MRI 9 weeks later reveals a second acute ring-enhanced lesion exhibiting restricted diffusion in the right frontal lobe (Lesion 1B) and a third periventricular lesion in the left parietal lobe that exhibits restricted diffusion but does not enhance (Lesion 1C).

Figure 2.

Acute demyelinating lesions exhibiting restricted diffusion (ADLRD). MRI shows ADLRD 3, patient #3 (A,B,C,D) and ADLRD 5, patient #5 (E,F,G,H) as seen on FLAIR (A, E), T1WI post IV contrast (B, F), ADC (C, G) and DWI (D, H). ADLRD 3 exhibits faint contrast-enhancing signal (B, thin black arrows); ADLRD in patient #5 is non-enhancing (F). There is a strongly hypointense ADC signal in the posterior-medial portion of lesion 5 associated with faint T2-hyperintense signal (G and E, white thick arrow) and faintly hypointense ADC signal in the anterior-lateral portion of the lesion associated with strongly hyperintense T2 signal (G and E, black thick arrow). Multiple chronic, small T2 hyperintense lesions are seen in both patients on FLAIR (A, E).

Table 1
Multiple sclerosis patients with acute demyelinating lesions with restricted diffusion.

Patient #	Age/Sex	Type of MS	Time from first clinical attack	Spinal cord lesions on MRI	Laboratory results (ANA, B12, Lyme, RPR)	Disease modifying treatment at the time of MRI	Other Medications	History of disorders other than MS
1	51/F	RR	3 years	Yes	Normal	Natalizumab	Modafinil, zolpidem, naproxen, bupropion, simvastatin	Anxiety, depression, hypercholesterolemia
2	52/F	RR	16 years	Yes	RPR was not done. Other tests were normal	None	Bupropion	Mononucleosis, depression
3	62/M	RR	6 years	No	ANA titer was elevated (1:320). There was no other evidence suggestive of lupus or Sjögren's syndrome. B12 not available. Lyme and RPR were normal	None	Fluoxetine, baclofen, clonazepam, temazepam, hydrocodone	Anxiety, depression, chronic low back pain
4	21/F	RR	33 days	No	Normal	None	None	None
5	30/F	RR	15 years	Yes	Normal	Glatiramer acetate	Oxybutinin, lansoprazole, sertraline	Depression, GERD, urinary incontinence, Crohn's disease
6	30/F	RR	2 years	Yes	Normal	None	Insulin, simvastatin, sertraline	Depression, diabetes, hypercholesterolemia

ANA, anti-nuclear antibody; RR, relapsing–remitting; GERD, gastroesophageal reflux disease; RPR, rapid plasma reagin.

Table 2

Control patients with acute symptomatic lesions.

#	Age/Sex	Type of MS	Disease modifying treatment	Other Medications	History of conditions other than MS
1	39/F	RR	None	Fexofenadine	Seasonal allergy
2	48/F	RR	None	Xanax	Anxiety
3	50/F	RR	Interferon-beta 1a	Hydrochlorothiazide, metoprolol	Anxiety, hypertension
4	20/F	RR	Interferon-beta 1b	Acetaminophen, aspirin, caffeine	Migraine
5	48/F	RR	None	None	Hypertension
6	40/F	RR	Glatiramer acetate	None	None
7	47/F	RR	Interferon-beta 1a	Zolpidem	Insomnia

Table 3

Acute demyelinating lesions with restricted diffusion characteristics.

Lesion #	Lesion location	Size (cm) [*]	Volume ^{**} (cm ³)	IV contrast signal	Signal on T2WI	Corresponding new symptom at the time of ADLRD	Interval from the onset of new symptoms to MRI	Time to and the lesion characteristics at the follow up MRI
1A ^{***}	Periventricular (left frontal)	1.18	1.36	Yes	Faint	Right-sided hemiparesis and dysarthria	4 days	2 months later: Resolution of restricted diffusion and T2WI signals and contrast-enhancement of T1WI
1B	Corona radiata (right frontal)	0.98	0.22	Yes	Strong	Asymptomatic.	N/A	Not available
1C	Periventricular	1.06	0.36	No	Strong	Asymptomatic.	N/A	Not available
2 ^{****}	Periventricular	1.05	0.68	Yes	Strong	Not available	N/A	Not available
3	Periventricular (left frontal lobe)	2.2	4.4	Yes	Faint	Low extremity weakness with gait ataxia	Less than 1 week but the exact date is not available	17 days later: Increased enhancement on T1WI, strong hyperintense T2WI signal. Resolution of restricted diffusion.
4A	Periventricular (right frontal lobe)	1.59	1.87	Yes	Faint	Left leg weakness	3 days	30 days: Faint residual enhancement on T1WI. Hypointense T1WI and hyperintense T2WI signals.
4B	Periventricular (left frontal lobe)	2.95	8.67	Yes	Faint	Right leg weakness	1 day	5 days before: Contrast-enhancing lesion on T1WI and faint T2 signal could be seen. DWI was not performed.
5	Periventricular (left parietal-occipital junction)	3.83	14.57	No	Faint	Visual symptoms	1 day	10 days later: Increased central contrast enhancement on T1WI. Strong hyperintense signal on T2WI and ADC.
6	Periventricular (left frontal)	0.9	0.36	Yes	Strong	Asymptomatic	N/A	Not available

^{*} Size of the lesion was measured as the longest axis of the lesion's T2 signal on the axial slice exhibiting the largest lesion area on FLAIR, except in cases 1C and 5 where the T2 signal of ADLRD was confluent with old lesions and lesion size was measured on DWI.

^{**} The volume of the lesions was measured as T2 signal volume on FLAIR, except in cases 1C and 5 where the T2 signal of ADLRD was confluent with old lesions and the volume of DWI signal was measured.

The first character of each lesion identifier corresponds to the patient number; a second character is used for lesion identifiers in patients with more than one ADLRD either on the initial scan, or on follow-up scans.

3.0 T MRI was used for Lesion #2. All other studies were performed using 1.5 T MRIs.

ADRLD, acute demyelinating lesions exhibiting restricted diffusion; DWI, diffusion weighted imaging; FLAIR, fluid-attenuated inversion recovery; T1WI, T1-weighted imaging; T2WI, T2-weighted imaging; ADC, apparent diffusion coefficient

Table 4

Characteristics of control symptomatic MS lesions without restricted diffusion.

#	Lesion location	Lesion size (cm) [*]	Lesion volume (cm ³) ^{**}	Enhancement	Signal on T2WI	Main symptom at time of new active lesion	Interval between onset of new symptoms and initial MRI ^{***}
1	Corona radiata (frontal)	1.07	0.29	Yes	Strong	Contralateral weakness	2 days
2	Corona radiata (frontal)	0.85	0.39	Yes	Strong	Contralateral weakness	1 day
3	Internal capsule	1.48	10.04	Yes	Strong	Contralateral weakness	3 days
4	Corona radiata (frontal)	0.44	0.5	Yes	Strong	Contralateral weakness	4 days
5	Pons	1.79	1.25	Yes	Strong	Unilateral CN VI palsy	3 days
6	Pons	0.58	0.105	Yes	Strong	Double vision	5 days
7	Juxtacortical (left dorsolateral prefrontal)	0.8	0.19	Yes	Strong	Abnormal executive function, disorientation	3 days

^{*} Size of the lesion was measured on FLAIR images as the longest axis of the lesion's T2-hyperintense signal within the axial slice exhibiting the largest lesion area.

^{**} Measured as the T2-hyperintense signal volume on FLAIR.

^{***} 1.5 T MRI was used in all described studies

FLAIR, fluid-attenuated inversion recovery; T1WI, T1-weighted imaging

Table 5

Summary of 13 acute demyelinating lesions with restricted diffusion reported in 10 patients ^{*}.

Parameter	Range of values	Comments
Diagnosis at the time of ADLRD occurrence	RRMS ($n = 8$) or CIS ($n = 2$)	One patient with CIS progressed to RRMS in 10 months. ¹²
Patient age	From 13 to 62 years old	
Patient gender	9 females and 1 male	
How large were ADLRD compared with 'typical' MS lesions?	ADLRD had larger size with many lesions having a 'tumefactive' appearance.	
What were the most common lesion locations?	Only supratentorial ADLRD were reported. Periventricular location was very common (in 77% of all cases)	
Are ADLRD contrast- enhanced?	82% of ADLRD exhibited contrast-enhancement	Based on 11 ADLRD seen on MRI that included IV contrast. Two ADLRD ^{10,11} were from MRI studies that were performed without IV contrast.
What was the relationship with MS symptoms?	69% of ADLRD were symptomatic	
When was restricted diffusion observed?	From 2 hours to 10 days after onset of symptoms	1 ADLRD was seen within 2 hours, ¹¹ 4 ADLRD were seen within 1 day, 1 ADLRD was seen within 3 days and 1 ADLRD was seen within 4 days. Two lesions seen within 1 day were also found to have restricted diffusion after 10 days. ¹²
What was the earliest time point at which ADLRD converted to a 'typical' lesion appearance with increased diffusion?	13 days after onset of symptoms	No MRI scans were obtained on day 11 or 12 after onset of symptoms.
Can ADLRD reoccur in the same patient at a different location?	Yes	Based on two cases described in this manuscript.

^{*} Based on both nine ADLRD from six patients presented in the Results section and four ADLRD from four clinical cases reported by other authors.^{10–12}

ADLRD, acute demyelinating lesions exhibiting restricted diffusion; CIS, clinically isolated syndrome; RRMS, relapsing–remitting multiple sclerosis