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Diffusion-weighted imaging in acute demyelinating myelopathy

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Abstract
Introduction Diffusion-weighted imaging (DWI) has become a reference MRI technique for the evaluation of neurological disorders. Few publications have investigated the application of DWI for inflammatory demyelinating lesions. The purpose of the study was to describe diffusion-weighted imaging characteristics of acute, spinal demyelinating lesions.
Methods Six consecutive patients (two males, four females; aged 28–64 years) with acute spinal cord demyelinating lesions were studied in a prospective case series design from June 2009 to October 2010. We performed magnetic resonance imaging studies from 2 to 14 days from symptom onset on the patients with relapsing remitting multiple sclerosis (n=3) or clinically isolated syndrome (n=3). Main outcome measures were diffusion-weighted imaging and apparent diffusion coefficient pattern (ADC) of acute spinal cord demyelinating lesions.
Results All spinal lesions showed a restricted diffusion pattern (DWI+/ADC−) with a 24% median ADC signal decrease. A good correlation between clinical presentation and lesion site was observed.
Conclusion Acute demyelinating spinal cord lesions show a uniform restricted diffusion pattern. Clinicians and neuroradiologists should be aware that this pattern is not necessarily confirmatory for an ischaemic aetiology.

Keywords Inflammatory myelopathy · Demyelination · DWI · Multiple sclerosis · MRI

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Introduction

Diffusion-weighted imaging (DWI) has become a reference magnetic resonance imaging (MRI) technique for the evaluation of neurological disorders, such as stroke [1], tumours and radiation treatments [2, 3], infectious diseases [4], epilepsy [5], transient global amnesia [6] and migraine [7]. Only few publications, however, have investigated the application of DWI for acute inflammatory demyelinating lesions of the central nervous system [8–13].

Acute demyelinating brain lesions are mainly reported to have an increased DWI signal (DWI+) and an increased apparent diffusion coefficient (ADC+) [14–16] with a strong and peculiar time dependence. The ADC value rapidly increases when a new gadolinium-enhancing lesion appears; the ADC progressively decreases with Gd vanishing within 2 months. Moreover, the ADC value is known to increase at the lesion site up to 6 months prior to Gd enhancement [9, 10]. These time-related changes reflect the underlying pathological processes at the blood–brain barrier with disruption (acute vasogenic oedema, active demyelination and acute axonal loss) and subsequent repair (resolution of inflammation and oedema) even in normally appearing white matter (initial perivascular inflammation with myelin, oligodendrocytes and axonal alterations, microglia activation, increased tissue water content) [10].

So far, however, observations were made only in brain inflammatory lesions. In this paper, we report the DWI characteristics of six consecutive patients with spinal cord inflammatory lesions. From our observations, it appears that in this region, lesions have slightly different characteristics with respect to diffusion, exhibiting hyperintense signal in the DWI and reduced ADC values (DWI+/ADC−), therefore appearing similar to ischaemic lesions.

Materials and methods

Spinal MRI examinations were performed with DWI sequences in six consecutive patients (two males, age range 28–64) seen at our institution from June 2009 to October 2010. Patients were referred either for an acute isolated demyelinating myelopathy (clinically isolated syndrome, CIS) or for a spinal attack in the context of a previously diagnosed, clinically defined multiple sclerosis (MS). The MRI studies were performed between 2 and 14 days from symptom onset

Clinical evaluation

Clinical evaluation included the following observations:

- *History and neurological examination* using the Expanded Disability Status Scale scoring [17] performed by a neurologist with expertise in MS
- *Blood tests*: routine haematological and haematochemical tests, inflammatory parameters; serum protein iso-electro-focusing (IEF), lactate, B_{12} and folate dosing, thyroid function; autoimmune screening (ANA, ENA-screen, anti-DNA, ANCA; anti-gliadin, anti-endomisium, anti-transglutaminase antibodies), thrombophilic screening (lupus anticoagulant, anti-beta2 glycoprotein, anti-cardiolipin antibodies), infective screening (HIV, *Borrelia burgdorferi*, *Treponema pallidum*, *Mycoplasma pneumoniae* and *Mycobacterium tuberculosis*, CMV, EBV, HSVI/II, VZV, HBV, HCV)
- *Routine urine test*
- *Lumbar puncture* with cerebrospinal fluid (CSF) leucocyte, glucose and protein counts; CSF protein, immuno-electro-focusing (IEF)
- *Sarcoidosis screening*: CSF and blood angiotensin-converting enzyme, chest X-ray
- *Somatosensory-*, *motor- and visual-evoked potentials*
- *Cerebral and spinal MRI*

MRI techniques

Spinal MRI images were obtained using a scanner operating at 1.5 T (Siemens Sonata Maestro Class, Siemens Medical Systems, Erlangen, Germany). The patients underwent a conventional clinical protocol followed by a diffusion imaging sequence during the same scanning session.

Conventional MRI A conventional diagnostic protocol, used to corroborate the diagnosis and to identify the exact anatomical location of the lesions, was performed. It consisted of the following sequences (obtained with a 3-mm slice thickness, 10% gap between slides, field of view (FOV) 250×250 mm^2):

- Sagittal T1-weighted (T1W) images, repetition time (TR) 584 ms, echo time (TE) 12 ms, image matrix (IM) 256×512, flip angle (FA) 180
- Sagittal T2-weighted (T2W) images, TR 3,100 ms, TE 104 ms, IM 256×512, FA 180
- Sagittal proton density (PD)-weighted images, TR 3,300 ms, TE 11 ms, IM 256×512, FA 150
- Axial T2W Medic 2D (cervical spine), TR 837 ms, TE 27 ms, IM 163×256, FA 30
- Axial T2W turbo spin echo (TSE) (dorsal spine), TR 4,260 ms, TE 97 ms, IM 197×51, FA150

In addition, the following images were acquired 5 min after the injection of 0.1 mmol/kg gadolinium-diethylenetriamine pentaacetic acid with 3-mm slice thickness:

- Sagittal T1W turbo TSE fat saturation (FS), TR 400 ms, TE 11 ms, IM 269×384, FA180
- Axial T1W TSE FS, TR 690 ms, TE 11 ms, IM 208×256, FA 180

Diffusion imaging The diffusion imaging protocol consisted of a pre-contrast axial DWI single-shot echo-planar imaging sequence with *b* values of 0, 500 and 1,000 s/mm^2 and diffusion sensitivity in three orthogonal directions (TR 3,000 ms, TE 83 ms, FOV 250×250 mm, in-plane resolution 1.3×1.3 mm^3, slice thickness 3 mm, number of averages 4). The signal from the three diffusion directions was averaged in order to obtain a single image per slice and *b* value. Direction-independent ADC maps were generated from the axial DWI through a monoexponential pixelwise fit by software supplied by the manufacturer.

Image evaluation

The anatomical locations of the lesions were identified on the conventional MR images, in order to correctly determine the corresponding spot on the axial diffusion-weighted images. The size of the lesions was measured on the sagittal (for the cranio-caudal extension) and axial (for the transversal dimensions) T2W images, by assimilating the lesion to an ellipsoid and measuring the main axes.

The DWI with the highest *b* value was used in order to determine the boundaries of each lesion and draw the region of interest, which was automatically coregistered on the ADC maps. The mean ADC value inside the lesion was considered for the evaluation and compared to the one of healthy tissue obtained from the homologous contralateral spinal region as a reference. In the case of median lesions, corresponding areas at one vertebral body above or below were used for comparison.

Images were evaluated by a neuroradiologist (ST) and a neurologist with expertise in neuroradiology (CG). In the case of discordant interpretation of images, the neuroradiologist's opinion was considered.

Results

Three patients (n. 1, 2 and 3) were affected with relapsing remitting multiple sclerosis (RR-MS), and three (n. 4, 5 and 6) had a CIS with spinal presentation highly suggestive for MS at the first evaluation time point. Patient n. 4 converted to clinically defined MS within 1 year following the occurrence of a second relapse. Patient n. 5, a 28-year-old female, had a typical inflammatory demyelinating presentation with subacute onset (over hours), CSF oligoclonal bands and MRI lesion morphology typical for demyelinating diseases, namely posterior, incomplete acute transverse myelopathy spreading through less than two vertebral bodies. Patient n. 6 had a similar clinical picture as patient n. 5 (Table 1). Extensive autoimmune, infectious, thrombophilic, endocrine and vitamin screening did not show any significant abnormalities, and CSF cell counts and protein were within normal range for all patients.

We observed a good agreement between clinical presentation and lesion site for all patients (Table 1). All acute symptomatic lesions revealed by MRIs performed within 2 weeks since symptom onset showed a restricted diffusion signal that was confirmed by an ADC drop (mean ADC signal decrease −28.7±15.9%; median −24.2%; range −12.8, −57.8%) (Table 2). Gadolinium enhancement was present in five out of six lesions (Table 1, Fig. 1).

Illustrative case (patient n. 4): a 30-year-old female presented at our emergency department on June 2009 because of intense and progressive neck pain; subacute hypoesthesia of her right side involving her face below the zygomatic bone, right arm, gluteal and genital areas; loss of left arm dexterity and urinary urgency. Her medical history was unremarkable except for migraine with aura. Neurological examination revealed a left brachio-crural spinothalamic syndrome and a right brachio-crural motor-ataxic syndrome, both spreading contralaterally within 24 h. The spinal MRI showed a C2 right, postero-lateral lesion with increased T2-weighted signal and without contrast enhancement; DWI sequences revealed a restricted diffusion signal with corresponding ADC map drop. The result from her brain MRI was normal; more than five oligoclonal bands were identified by CSF IEF. An extensive autoimmune, infectious, endocrine, thrombophilic and vitamin screening, cell and protein CSF counts were normal. The patient was treated with a high-dose steroid course with partial recovery. She was clinically stable for the subsequent year; follow-up MRIs did not show any cerebral or spinal lesions. In June 2010, the patient experienced a new right visual disturbance suggestive of optic neuritis. Besides the typical clinical presentation, the diagnosis of optic neuritis was confirmed by pathological visual-evoked potentials; a cerebral MRI showed four new, inactive white matter lesions. A diagnosis of clinically definite multiple sclerosis was made. New symptoms completely subsided after a high-dose steroid course. An immuno-modulating agent was added to therapy.

Discussion

We report on DWI findings of six consecutive patients with an acute inflammatory demyelinating myelopathy in the context of a defined RR-MS and CIS who had their spinal MRI performed within 2 weeks from last relapse. All the described spinal lesions were characterized by a restricted diffusion pattern with 24% median ADC signal decrease. From a clinical standpoint, this outlines how DWI+/ADC− pattern does not necessarily imply an ischaemic myelopathy as previously suggested [18].

In all patients, a good correlation between clinical presentation and lesion site was observed, thus confirming the acute symptomatic nature of the lesions. To our knowledge, this is the first report on DWI characterization of a series of acute, inflammatory demyelinating spinal lesions.

Acute demyelinating brain lesions are mainly reported to have a DWI and ADC increased signal [14–16], while only a minority of them (20–30%) show an ADC drop [11, 19, 20] arising the differential diagnosis with ischaemic stroke [1, 21]. When present, the ADC drop in MS brain lesions is around 20–30%, thus quantitatively less pronounced than typical acute ischaemic ADC decrease (40–50%) [11]. Beyond time dependence, this diffusion pattern seems to be related to lesion size and inflammatory process extent. While smaller acute inflammatory lesions are more frequently reported to be DWI+/ADC+, deriving from the T2 enhancement effect arising from vasogenic oedema, larger or pseudotumoural ones can be DWI+/ADC− or even with different combinations of DWI/ADC signals [8, 11, 13]. Three main hypotheses have been put forward to explain diffusion signal in these cases, namely swelling of the myelin sheaths, high content of inflammatory cells and

Table 1 Demographic and clinics-radiological characteristics of the patients

Patient no.	Sex	Age (years)	Clinical subtype	Disease duration (years)	Clinical presentation	Time between symptom onset and MRI exam (days)	EDSS	T2	DWI/ADC	Gd	Brain MRI	OB
1	M	64	RR-MS	28	Right b-c motor sy	6	7	+	+/−	+	>9 T2W lesions, Gd-	>5
2	F	31	RR-MS	8	Bi-brachial tinglings, left brachial motor sy	14	3.5	+	+/−	+	>9 T2W lesions, Gd-	>5
3	M	44	RR-MS	15	Urinary urgency, posterior legs sensory sy	8	3	+	+/−	+	9 T2W lesions, Gd-	>5
4	F	30	CIS	0	Brown–Sequard sy, incontinence	6	2.5	+	+/−	−	Normal	>5
5	F	28	CIS	0	V3 and tetra ataxic sensory sy	2	3.5	+	+/−	+	Normal	>5
6	F	57	CIS	0	Ataxic paraparesis, (T10 sensory level)	3	3.5	+	+/−	+	>9 T2W lesions, 2 Gd+ lesions	>5

RR-MS relapsing remitting multiple sclerosis, *CIS* clinically isolated syndrome, *C* cervical, *T* thoracic, + DWI or ADC increase, Gd enhancing; − DWI or ADC decrease, Gd not enhancing; *OB* oligoclonal bands, *sy* syndrome

cytotoxic oedema following secondary ischaemic damage and release of inflammatory cytokines leading to mitochondrial dysfunction [11, 22–25].

We observed a 24% median ADC signal reduction in our spinal series, which is in line with the ADC drop in MS brain lesions reported in literature [8, 11]. This pattern is also qualitatively similar to the diffusion pattern described in acute ischaemic spinal lesions (DWI+ADC−) [26–28]. Regarding the extent of the ADC drop, however, there are no clear-cut reference values in ischaemic spinal lesions. Values are reported to vary from 20–30% in the series of Küker et al. [27] to 35–50% in the series by Thurnher et al. [28]. The very high prevalence of DWI+/ADC− presentation in our small cohort (six out of six patients) compared to acute inflammatory brain lesions (around 20–30%) might be explained by specific spinal features of inflammation. First, the spinal cord has an extremely rich venous drainage [29], with a tissue venular density similar to periventricular areas; there is strong evidence in literature for a perivenular distribution of inflammation as well as for periventricular intense inflammation in MS [30]. Second, the spinal cord has a relatively fixed position ensured by ligament connections, and it is thus particularly susceptible to micro-traumatic injury precipitating inflammation processes. Therefore, although small in diameter, spinal lesions can share the diffusion signal of MS larger/pseudotumoural/stroke-like lesions (DWI+/ADC−) due to the pronounced inflammatory process taking place [8, 11, 13, 31, 32]. Another factor that may contribute to the high prevalence of DWI+/ADC− pattern in our cohort could be related to the fact that the examination was conducted in the very early phase of the inflammatory process [11]. Actually, some of the published studies concerning diffusion signal evolution in time in MS patients are based on a fixed MRI schedule, independent from clinical correlates, i.e. relapses; a short, very early phase of ADC drop can thus be missed [9, 10, 20].

Our findings have implications also for the clinical practice. Once a myelopathic syndrome is recognized, neurologists rely mainly on clinical and radiological criteria to differentiate between an inflammatory and ischaemic origin. A clearly defined sensory level and clinical progression to nadir between 4 h and 21 days after symptom onset are usually suggestive of an inflammatory aetiology [33]. In the case of diagnostic uncertainty, restricted diffusion imaging has been evocated as confirmatory for an ischaemic origin [18]. The results of our small series question this conclusion leaving the differential diagnosis open at least in the acute setting.

Table 2 ADC measures, spinal lesion site and size, spinal cord measures

Patient n.	ADC value ($\times 10^{-5}$ mm^2/s)	ADC reference ($\times 10^{-5}$ mm^2/s)	Reduction (%)	Lesion site	Lesion size (mm)	Spinal cord max and min diameters (mm)	Spinal cord cross-sectional area (mm^2)
1	88.2±6.3	114.6±5.4	−33	C2, left paramedian	14×6.7×5.7 (irregular shape)	11.8×7.9	66.73
2	102.2±3.4	127.6±20	−19.9	C2 postero-lateral, left	9.8×5×4.6	10.2×6.2	54.67
3	72.2±19.2	91.2±6.3	−21	T7–8 postero paramedian, right	15.8×7.2×5.6	8.2×6.8	37.32
4	55.8±3.2	77±1.7	−27.5	C2, right postero-lateral	11.9×8×7	10.2×8.6	62.87
5	42.2±5.0	100±3.6	−57.8	C4–5, postero median	5×3.6×2.5	12.8×10.8	82.33
6	109±7.1	125±5.4	−12.8	T11–T12 central	18.2×6.1×6.4	9.4×7.4	49.24

Absolute ADC value at lesion sites. Percentage decrease in ADC signal is referred to the homologous spinal unaffected regions (see text)

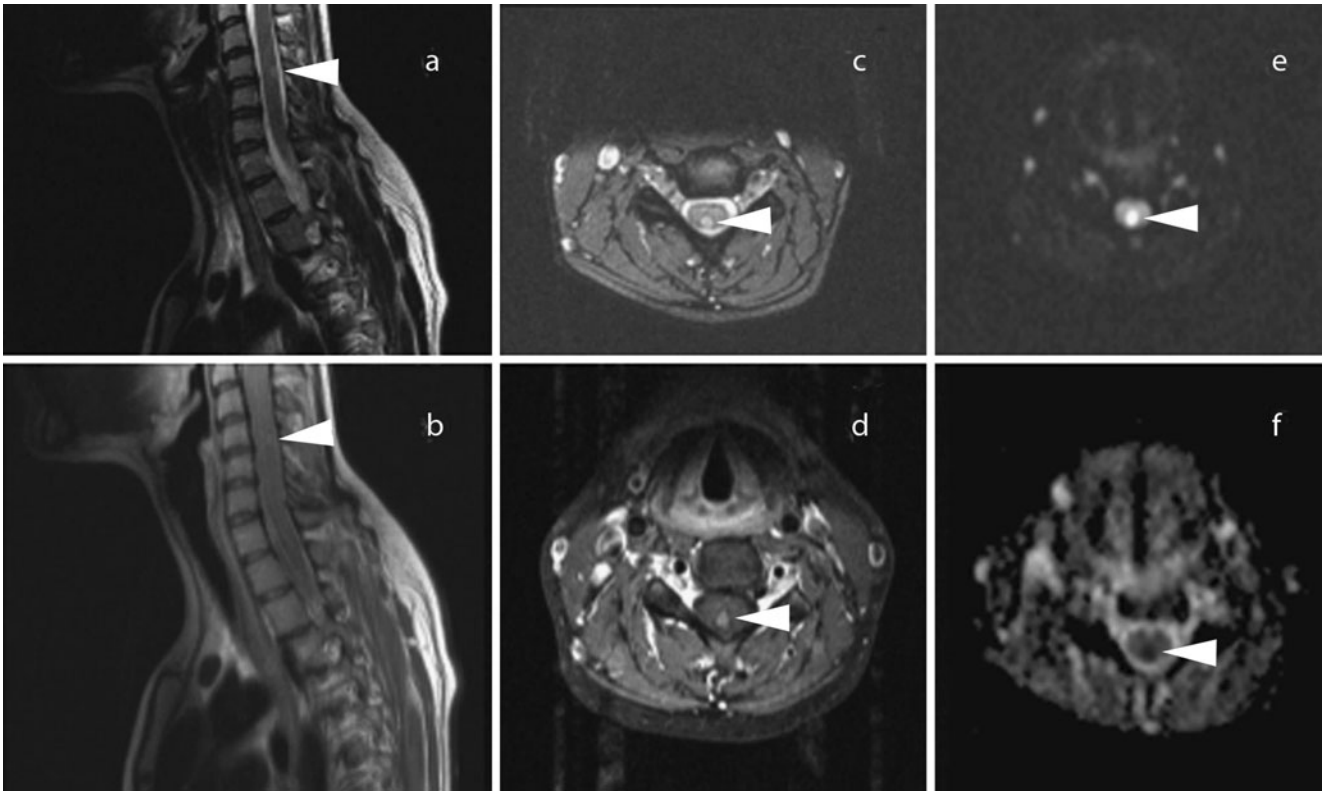

Fig. 1 Patient n. 5, spinal MRI: hyperintense, intramedullary, postero-medial lesion, C4–5 lesion on T2 and PD-weighted images (**a**, **b** sagittal sequences). Corresponding axial spinal T2-weighted (**c**) and Gd-enhanced, T1-weighted sequences (**d**) showing Gd enhancement at lesion level. Diffusion images showing DWI+ (**e**) and ADC− (**f**) pattern

The main limitation of our study is the small sample size. The prevalence of patients with acute spinal cord demyelinating lesions in our region is rather low, and correspondingly, the number of patients with this condition seen in our hospital is quite small, not allowing us to perform any robust statistical analysis. As already reported in publications by other authors [26–28, 34], we cannot exclude that a certain variability in the quantification of the ADC drop is due to the high grade of technical difficulties in spinal diffusion sampling (low signal-to-noise ratio, unfavourable field homogeneity, CSF and blood pulsation artefacts, small lesion size with respect to resolution) [18]. The calculation of the ADC from three directions only, which might not be perfectly aligned with the fibre orientation, associated to the physiological variation of diffusivity and the marked local anatomical variability depending on spinal morphological measures [35–37], might also explain the high variability of reference ADC values. Thus, ADC value of the lesions has to be interpreted in comparison with normal-appearing white matter and not as absolute index. Nonetheless, the pattern homogeneity we found (DWI+ADC−) in all our six patients argues against major technical limits. Another limitation is that our diffusion analysis protocol does not give any information about the diffusion direction. The fibre direction in the spinal cord being very well defined, a more complete diffusion tensor imaging approach could potentially be beneficial from an investigational point of view. However, our work reflects a more clinical approach which employs a routine and faster protocol as time for performing diagnostic scans is a limited resource in the acute clinical setting. Under this aspect, the usage of higher field strengths (3 T and above) might be beneficial. At higher fields, T2 and T2* decays are faster, making echo-planar imaging-based techniques like conventional DWI more prone to artefacts; however, this loss can be compensated by the gain of signal-to-noise ratio, which in turn can be used to apply parallel imaging and other acceleration techniques in order to reduce scan time.

In conclusion, we report here a uniform diffusion-weighted imaging behaviour of acute spinal cord demyelination with a restricted diffusion presentation. We hypothesize that the lesion location is a leading factor in determining diffusion signals in these cases. Clinicians and neuro-radiologists should be aware that a DWI+/ADC− pattern in an acute myelopathy setting is not necessarily confirmatory for an ischaemic aetiology [18].

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Conflict of interest We declare that we have no conflict of interest.

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