Demonstration of Restricted Diffusion Early in the Development of Inflammatory/Demyelinating Lesions - A multiparametric MR Study

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INTRODUCTION

In multiple sclerosis (MS) magnetic resonance imaging (MRI) techniques are needed that mirror the underlying acute and chronic pathology better than conventional MRI. We demonstrate a novel finding consisting of restricted diffusion in the very early phase of inflammatory-demyelinating lesion development.

MATERIALS and METHODS

Two patients were studied serially: (A) a 19 year old man with clinically definite MS and (B) a 30 year old woman with probable MS (previous episode of optic neuritis 3 months earlier) who both presented with clinical relapses ((A) right hemiparesis; (B) hemianopia, left hemiparesis)). They were studied over 4 months with MRI (on days: (A) 0, 2, 5, 7, 10, 12, 18, 20, 25, 62, 85, 115; (B) 0, 5, 7, 11, 16, 23, 33, 65, 93, 121) and volume selective MR $1H^+$ spectroscopy (MRS) (3 studies each):

1. a) Proton density-, T_2-, T_1-weighted, b) isotropic diffusion-weighted (DW) EPI (5 *b* values=0-1000s/mm^2), c) Magnetisation Transfer Ratio (MTR) (FLASH 3D, 40 ms/ 5 ms/ FLIP 12 ^{0}), d) T_1-weighted 5 and 15 minutes after 0.2 mmol/kg ("double dose") Gadodiamid-DTPA. 2. MRS (TR 1500 ms/TE 10+135 ms, 2 cm^3)

RESULTS

Both patients showed a very similar sequence of MR changes in 8 newly active lesions (∅>1cm) developing in 4 stages over the observation period (figure 1):

1. Days 0-5: Initial minimal T_2 hyperintensity, slight MTR reduction and strongly restricted diffusion (up to ADC = 0.39 x 10^{-9}m^2/s, standard deviation), and only very faint enhancement on delayed post-contrast scans
2. days 3-7: increase of T_2 hyperintensity, increase of the degree of contrast enhancement and increase of ADC to normal values ('pseudo-normalisation')
3. up to 4 weeks: further ADC elevation (ADC = 0.6-1.2 x 10^{-9}m^2/sec), pronounced MTR reduction, prominent enhancement on early post-contrast scans
4. after 4 weeks: partial reversal of T_2 hyperintensity and ADC elevation, increase of MTR and resolution of enhancement.

MRS demonstrated N-acetyl-aspartate (NAA) reduction and prominent free lipid and lactate peaks (day 4 (A) day 6(B)) in 2 lesions with restricted diffusion.

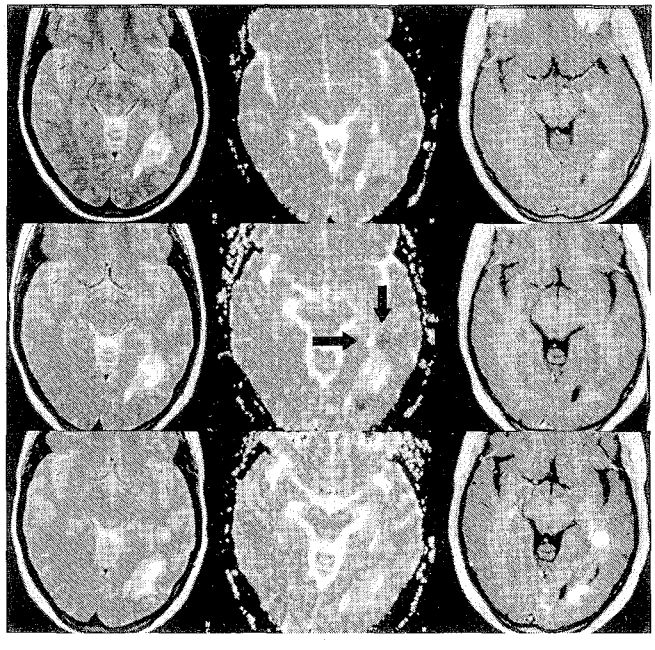
Both patients received each 2 courses of i.v. methylprednisolon ((A) 250mg, 500mg days 2-9 (B) 500mg, 750mg days 2-9) after the first MRI examination. Contrast enhancement stopped immediately for 3 weeks in patient A after steroid treatment and was reduced in patient B, while the reduced ADC showed no comparable change. Clinical symptoms progressed for 9 and 5 days, respectively, before a steady nearly complete resolution of symptoms occurred over 2 to 4 months. Both patients showed elevated CSF cell counts and positive oligoclonal bands.

DISCUSSION

Restricted diffusion delineated a short, very early phase of lesion evolution. While lesions progressed to the typical acute oedematous appearance (strong T_2 hyperintensity and blood-brain-barrier disruption) the ADC increased in parallel to 'pseudo-normal' and increased values. Increased diffusion in acute lesions is in agreement with histological observations of widened extracellular spaces due to vasogenic inflammatory oedema.

In contrast to this there is no obvious explanation for restricted diffusion in early MS lesions. From experimental models of cerebral ischaemia and status epilepticus it is known that diffusion-weighted (DW) MRI can demonstrate restricted diffusion associated with shrinkage of the extracellular space and cytotoxic cell swelling induced by energy depletion (through an intracellular rise of lactate due to anaerobic glycolysis followed by depolarisation). In MS lesions the aggressive inflammatory milieu may cause energy depletion (e.g. through mitochondrial dysfunction induced by proinflammatory cytokines). We found pathological lactate peaks that may indicate a critical energy state in MS lesions. Lactate peaks could also be associated with hypercellularity, a recognised feature in early lesion development occasionally with prominent lymphocytic and microglial cell infiltrates and cell swelling in activated astrocytes. The slight changes of T_2 and post-contrast MRI indicating increase of BBB permeability might have been sufficient for cell migration into developing lesions. It is conceivable that dense cellular infiltrates reduce the extracellular space and thereby restrict diffusion before this effect is counterbalanced by the development of inflammatory vasogenic oedema. Both mechanisms (disturbances of energy metabolism/hypercellularity) might act together.

Figure 1
A newly developing lesion with restricted diffusion on ADC map (arrows, row 2, middle), on follow-up strong T_2 hyperintensity, increased ADC and prominent contrast enhancement.



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