

Study of the pathophysiology of demyelination in an experimental model: Correlation of lesion volume with T2, apparent diffusion coefficient (ADC) and fractional anisotropy (FA)

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INTRODUCTION: The pathological features associated with multiple sclerosis (MS) alter the water content and tissue biochemistry in the region of demyelination. Evaluation of the complete course of disease evolution and the activity at various stages of demyelination and remyelination is thus necessary to understand the pathophysiology. However, this is not feasible in humans due to difficulty in identifying the exact location and the onset of the disease and hence, experimental model studies are necessary. Measurement of MR parameters like relaxation times aid in unambiguous identification of the tissue type as well as give an insight into the pathophysiology and biochemistry of myelination [1]. Pathologic processes that alter tissue organization by altering the barriers to water molecular motion cause abnormal diffusivity as well as affect their direction of diffusion. Diffusion imaging (DWI) and diffusion tensor imaging (DTI) provide a quantitative measure of water diffusion in tissues by the measurement of apparent diffusion coefficient (ADC) and fractional anisotropy (FA), respectively. In our previous study [2] we reported sequential monitoring of the variation in ADC and FA values during the complete process of de- and re-myelination. The aim of the present study was to monitor the lesion volume during the de- and re-myelination phases and to correlate it with T2, ADC and FA values.

MATERIALS AND METHODS: 1% Lysophosphatidylcholine was administered by stereotaxic injection in the internal capsule (ic) area of the rat brain (n = 30, male Wistar; b.w. = 150 to 250 gms) to induce demyelination. MR experiments were carried out at 4.7 T (BIOSPEC Bruker, Germany) using a 72 mm resonator as transmit/receive coil. The rats were sequentially monitored using T2 mapping and diffusion imaging at various time periods of de- and re-myelination. T2 maps were generated using a multi-slice SE with 16 TEs (range 25 to 400 ms) and TR = 5 sec. DWI and DTI experiments were carried out using the following parameters: TR/TE = 3000/38.3 ms. While for DWI, six 'b' values (range 0-1000 s/mm²) were used and for DTI 30 diffusion directions and three 'b' values (0, 250, and 855.27 s/mm²) were used. Due to mortality, not all rats could be monitored at all time points. Lesion volume was calculated by determining the area of the lesion multiplied by the slice thickness and the total volume (in mm³) was reported. T2, ADC and FA values were calculated from the lesion area as well as from the unaffected contralateral ic area by selecting uniform circular ROIs of 4 pixels (area = 0.0039 cm²) and their average values are reported. Pearson correlation was used to correlate the lesion volume with T2, ADC and FA values. Institute animal ethics committee approved the study.

RESULTS: Demyelination appeared as hyperintense area in the ic on T2-weighted image in 18/30 rats (Fig. 1). During demyelination, the lesion size increased from day 3 (14.6 mm³) till day 11 (30% increase). Subsequently from day 15, the size decreased and at day 20 it was 8.4 mm³. Complete disappearance of the lesion was observed in one rat that was monitored on day 26, indicating complete remyelination. ADC and T2 of lesion showed a gradual increase while FA decreased with the progression of demyelination. Thereafter, from day 15, T2 and ADC decreased and FA increased indicating remyelination (see Table 1). Pearson correlation between lesion volume with T2 as well as with ADC revealed a positive correlation with a correlation coefficient of 0.92 and 0.87, respectively while a negative correlation was observed between lesion volume and FA with a correlation coefficient of 0.94 (Fig. 2).

DISCUSSION: Our results showed an increase in the size of the demyelination lesion from its onset (day 3) to day 11 indicating damage to the myelin sheath. This initiates an inflammatory response leading to an infiltration of the inflammatory cells in and around the lesion. Additionally extra-cellular water gets accumulated in these regions resulting in edema which increases T2, ADC and the lesion volume. Simultaneously, FA decreased during this period as the nerve fibers tends to lose its anisotropy due to myelin damage [2]. In-vitro studies on experimental allergic encephalomyelitis showed prolonged T2 during the pre-acute stages of demyelination due to edema accompanied with a transient change in the blood-brain barrier [3]. Increased ADC and reduced FA during demyelination have also been reported in both human and animal models of MS [4, 5]. Progressive decrease in lesion size was observed from day 15 onwards till remyelination. One rat studied till day 26 showed complete disappearance of the lesion. These observations suggest that as myelin reforms there is reduction of inflammatory response and the extracellular water content leading to decrease of lesion size. As a consequence, ADC and T2 values reduced during remyelination and were similar to those observed in contralateral ic region while the FA value increased and reached normal values. Pearson correlation showed that the lesion size has a positive correlation with T2 and ADC values and a negative correlation with FA. In conclusion, our data indicated that quantitative estimate of MR parameters like T2, ADC and FA and their correlation with the lesion size can be used to characterize the different stages of de- and re-myelination and thus provide useful information on its pathophysiology.

REFERENCES: [1] Vite CH et al. AJNR Am J Neuroradiol. 2008; 29 1(2):308-13; [2] K. Balasubramanian et al. Proc Intl Soc Magn Res Med 2009; 3256 [3] Karlik SJ et al. Magn Reson Med. 1990; 14(1):1-11 [4] Valsasina P et al. NeuroImage 2005; 26; 822-828. [5] DeBoy CA. et al. Brain 2007; 130; 2199-2210.

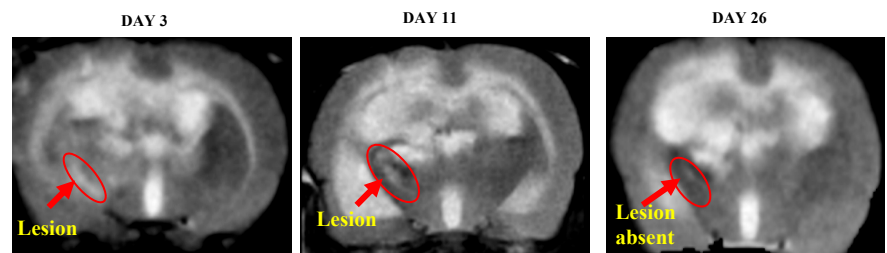


Fig. 1: T2-W images showing demyelination on day 3 and 11 and remyelination on day 26

Table 1: Variation in T2, ADC and FA during various stages of de- and re-myelination

	Day 3	Day 5	Day 7	Day 11	Day 15	Day 20
Lesion volume (mm ³)	14.6 (n = 13)	17.4 (n = 13)	18.7 (n = 13)	19.0 (n = 8)	9.9 (n = 4)	8.4 (n = 3)
T2 (ms)	86 ± 8.2 (n = 11)	110.6 ± 13 (n = 12)	113.3 ± 16.4 (n = 13)	122.2 ± 22.6 (n = 8)	95.6 ± 12.4 (n = 3)	67.3 ± 6.1 (n = 3)
ADC (mm ² /s)	958 ± 147.2 (n = 14)	1136.8 ± 188 (n = 12)	1182 ± 186.5 (n = 12)	1342 ± 200.7 (n = 8)	1016.8 ± 195 (n = 4)	667 ± 78.5 (n = 3)
FA	0.28 ± 0.03 (n = 13)	0.25 ± 0.03 (n = 13)	0.24 ± 0.03 (n = 10)	0.17 ± .03 (n = 6)	0.34 ± 0.03 (n = 3)	0.47 ± 0.02 (n = 2)

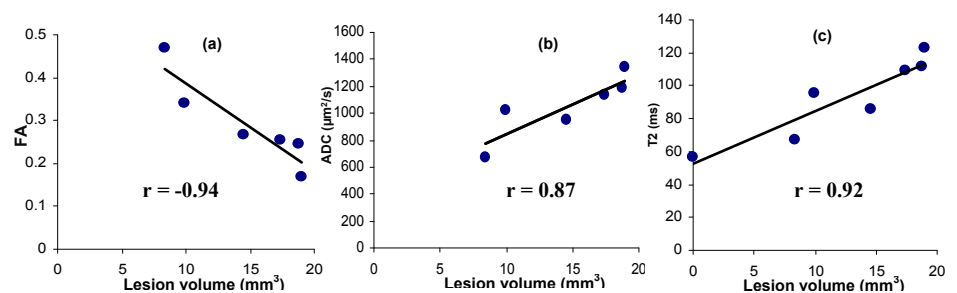


Fig. 2: Correlation of lesion volume with (a) FA (b) ADC and (c) T2 values at various stages of de- and re-myelination