Diffusion Tensor Imaging and ^{1}H-MR spectroscopy for evaluation of methotrexate leukoencephalopathy in a patient with Acute Lymphoblastic Leukemia

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Purpose: Acute methotrexate (MTX)-induced leukoencephalopathy (MIL) is a rare [1], but potentially severe complication of leukemia treatment [2,3]. Conventional imaging techniques are quite insensitive in detecting early parenchymal abnormalities; therefore, initial imaging diagnosis relies on diffusion-weighted imaging, which typically shows significantly restricted water diffusion in lesion areas [4]. Since diffusion tensor imaging (DTI) and proton magnetic resonance spectroscopy (MRS) are known to provide valuable information about the integrity and quality of myelin [5,6], our purpose was to determine whether the use of these techniques may shed new light on the yet poorly understood underlying histopathological processes and their dynamics in MIL based on serial observations in a well worked-up patient.

Patient and Methods: A 16 year-old male with acute T-cell lymphoblastic leukemia (ALL) and evidence of CNS involvement developed severe MTX-induced toxicity on day 20 of intrathecal (i.t.) induction therapy. Neurological examination revealed right hemiplegia, facial weakness and dysarthria. Because symptoms recovered under leucovorin/aminophylline treatment and withdrawal of MTX, an additional dose of i.t.-MTX was given on day 42. Shortly after this dose, the patient developed left hemiparesis and ptosis with worsening dysarthria. MTX was withdrawn again from the treatment plan. During the almost 8-month-long follow-up period, 13 MRI scans were performed, 11 of which included DTI (TRSE-EPI, 12 directions, 4 averages) and 4 included MRS (2D-CSI, PRESS, TE:135). Using the Diffusion Toolbox in SPM2, apparent diffusion coefficient (ADC), fractional anisotropy (FA) and eigenvalue ($\lambda 1$, $\lambda 2$–3) maps were calculated and coregistered. For quantitative DTI analysis one ROI that included the entire lesion area across 7 adjacent slices was defined for both hemispheres. Postprocessing of MRS data was performed on a Multimodality Workstation (Siemens Medical Systems, Erlangen, Germany).

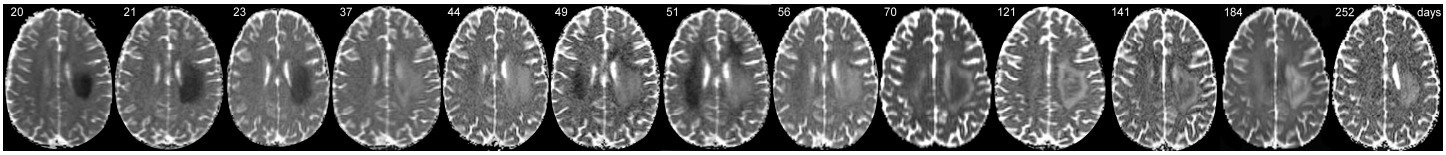

***Fig.1**: Serial ADC images during 252 days of follow-up. Initially, restricted diffusion was present within the left hemisphere only, but after re-challenge with MTX it also appeared on the right side. While some abnormalities resolved, suggesting reversibility, ADC remained elevated on the left, indicating permanent tissue damage.*

Results: From days 21 to 23, visible abnormalities were limited to the left cerebral hemispheric WM, wherein ADC was found to be considerably low (223.3 μm^2/ms) (**Fig.1**) while FA remained normal (0.45). By day 37, ADC far exceeded the normal range (766.2 μm^2/ms) while FA decreased to 0.17 (**Fig.2**). On rechallenge with MTX (day 42), similar additional lesions appeared within the right centrum semiovale. Now, ADC decreased in lesion areas of both hemispheres, followed by a moderate decline of FA on the right side only (0.38). Subsequently, ADC and FA values became fairly stable, but remained clearly abnormal on the left ($ADC_{left/right}$=626.3/472.0 μm^2/ms, $FA_{left/right}$=0.18/0.43). Eigenvalue analysis yielded a proportional decrease of λ_1 and $\lambda_{2\text{-}3}$ within the right hemispheric lesion, while $\lambda_{2\text{-}3}$ increased more markedly than λ_1 within the left hemisphere. MRS revealed increased Cho/NAA ratios within both hemispheres during follow-up, but these were more pronounced on the left side (**Table 1**).

MRS	Right hemisphere				Left hemisphere			
(day)	Cho	NAA	Cr	Cho/NAA	Cho	NAA	Cr	Cho/NAA
23	1.73	3.52	1.64	0.49	1.98	2.13	1.53	0.92
37	0.23	0.37	0.25	0.61	0.42	0.21	0.30	1.97
121	0.34	0.45	0.25	0.76	0.55	0.22	0.36	2.56
252	1.57	2.24	1.09	0.70	1.88	0.39	0.78	2.56

***Table 1 (right)**: Summary of MRS results. Numeric values for brain metabolites were obtained from voxels covering hemispheric white matter lesion areas*

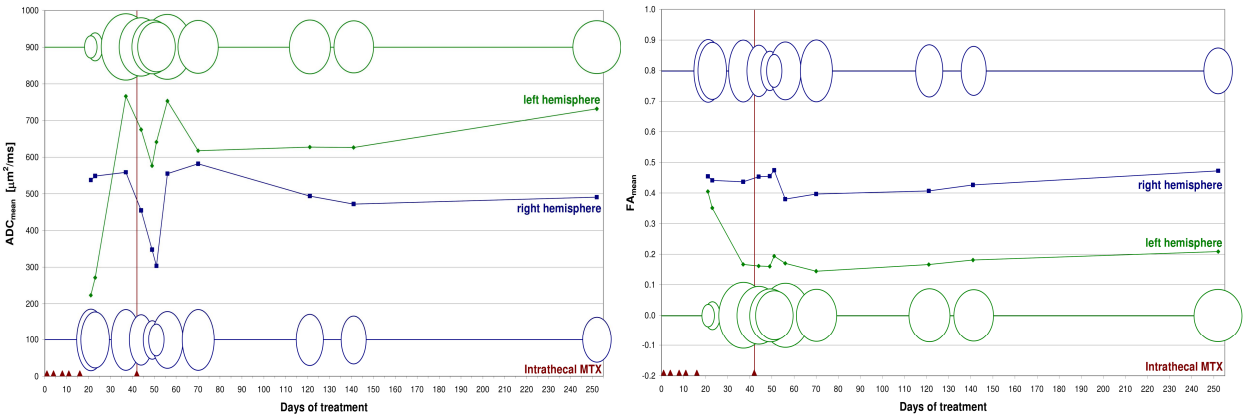

***Fig.2**: Temporal evolution of ADC (left) and FA (right) values within hemispheric lesion areas during the course of acute MTX-induced leukoencephalopathy. The ellipses illustrate the magnitudes of Eigenvalues λ_1 in conjunction with the mean of λ_2 and λ_3 at each time point on both sides. The red triangles indicate the days of i.t.-MTX administration.*

Conclusion: In a patient with acute MTX neurotoxicity, we observed a rapid decline of ADC followed by a somewhat delayed decrease of FA within the left hemispheric WM lesion shortly after the onset of neurological symptoms. The same pattern was found for the right hemisphere after rechallenge with MTX. The initial dramatic decrease of ADC values may correspond to intramyelinic edema (vacuolating myelinopathy), cytotoxic tissue damage, or their combination [6]. Although axonal dystrophy without damage to oligodendrocytes is a well-known histopathological pattern in acute MIL [7], our analysis of eigenvalues suggests that the initial uncoupling of ADC and FA changes indicates a sequence of distinct histopathological events: first, for a short period of time, dominant myelin damage with relatively intact axons, followed by involvement of the neuroaxonal unit. Our data support that ADC and FA have the potential to normalize after MTX withdrawal [8]. However, a strong decline of FA likely indicates permanent damage to both the neuroaxonal unit and the myelin sheath. The consequent loss of tissue matrix is reflected in a persistent ADC elevation. Similar to previous reports on MRS [9], we also found an increasing Cho/NAA ratio in lesion areas, indicating a significant and prolonged membrane turnover, initially due to myelin breakdown and perhaps subsequently to myelin build-up as well in the context of repair mechanisms (remyelination). Again, these changes appear to be more substantial in areas of more profound tissue damage. Although diffusion abnormalities do not necessarily indicate permanent tissue damage and may not prompt a mandatory modification of treatment regimen [10], our findings suggest that close monitoring of ADC, FA and spectroscopy data may help differentiate reversible from irreversible tissue damage early on. To confirm this hypothesis, future studies need to include further analysis of eigenvalues and a larger patient cohort for determining cut-off values to separate reversible and irreversible forms of MTX neurotoxicity.

References: **[1]** Reddick WE et al. (2005) *AJNR* 26:1263 **[2]** Rubnitz JE et al. (1998) *Leukemia* 12:1176 **[3]** Shuper A et al. (2000) *Childs Nerv System* 9:573 **[4]** Sandoval C et al. (2004) *AJNR* 24:1887 **[5]** Rollins N et al. (2007) *Pediatr Radiol* 37:769 **[6]** Khong PL et al. (2003) *AJNR* 24:1181 **[7]** Hendin B et al. (1974) *Cancer* 33:468 **[8]** Haykin ME et al. (2006) *J Neurooncol* 76: 153 **[9]** Chu WCW et al. (2003) *Radiology* 229:659 **[10]** Eichler AF et al. (2007) *Neurooncology* 9:373