Therapy effects in cerebral folate transport deficiency with hypomyelination monitored by multimodal quantitative MR-Imaging

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Target audience: clinicians in the fields of neuropediatrics, neurology and neuroradiology, as well as clinical MR-researcher.

Introduction

Myelin-sensitive quantitative (q) MRI techniques are of growing importance to study white matter (WM) disorders in childhood [1]. Cerebral folate transport deficiency, caused by mutations in the *folate receptor 1* (*FOLR1*) gene, is a treatable WM disorder with hypomyelination and late infantile onset [2]. Prevalent clinical features include developmental regression, movement disturbances and epilepsy, which improve under folinic acid therapy [3]. We report a serial qMRI study of the effects of folinic acid therapy in a patient with profound hypomyelination due to cerebral folate transport deficiency. Magnetization transfer (MT) and diffusion tensor imaging (DTI) provided parameter maps related to myelination. The purpose was i) to monitor the underlying WM changes during therapy and their correlation with the clinical course and ii) to validate those parameters as possible surrogate markers for further therapeutic trials.

Patient and Methods

One boy with cerebral folate transport deficiency (*FOLR1:* p.Q118X, p.C175X) [3] and severe clinical phenotype has been treated with folinic acid by now over 4.2 yrs which ameliorated the symptoms. The concomitant serial qMR studies at a 3T clinical scanner (TRIO, Siemens, Erlangen) included high-resolution 3D MRI (T1-w(eighted) MP-RAGE, T2-w variable flip-angle TSE), DTI (single-shot STEAM MRI at 2.2 mm resolution, b=950 s/mm^2, 24 gradient directions, 2.2 mm slice thickness) and 3D MT imaging at 1.25 mm isotropic resolution (3D FLASH, TE/TR/α=4.9/25 ms/5°; 12.8 ms Gaussian MT-pulse of 540° applied 2.2 kHz of resonance). By means of two reference FLASH scans with predominant PD-w (TR/α=25 ms/5°) and T1-w (TR/α=11 ms/15°), we obtained maps of the percentage MT saturation caused by a single MT-pulse, a semi-quantitative MT parameter insensitive to T1 and RF inhomogeneities [4]. Regions of interest (ROI) in genu, splenium and frontal WM were analysed using MRIcro.

Table: Quantitative ROI analysis of MT (percent unit) and FA in genu

Age (yrs)/ Patient	Time of therapy (yrs)	MT	FA
3.9	0	1.88*	0.61
4.4	0.5	1.96*	0.44
4.9	1	2.26*	n.d.
5.3	1.4	2.48*	0.53
5.5	1.6	2.27*	0.52
6	2.1	2.54	0.86
6.6	2.7	2.82	0.87
7.1	3.2	2.84	0.88*
7.6	3.7	2.83	0.84
8.1	4.2	2.76	n.d.
Ctrls. (n=12) 6.3 ± 2.5		2.95 ± 0.21	0.65 ± 0.11

Ctrls.: controls, n.d.: not done; control values as mean±SD, *>2SD.

Results

T1-w and T2-w (**row 1**) images showed mild WM alterations indicative of hypomyelination (**Fig. B**) compared to an age-matched control (**Fig. A**). These partially subsided over the following 3.7 yrs (**Fig. C, D;** control **Fig. E**). In contrast, the initial MT saturation map (**row 2**) revealed distinct, widespread reduction (**Fig. B** compared to **Fig. A**). However, MT increased subsequently (**Fig. C, D**) and reached values within control ranges in genu (**Table**) and splenium but not in frontal WM (compare to **Fig. E**). The patient's MT histograms (**row 3**) (**Fig. B-D**) lacked the mode at 2.5% ascribed to myelinated WM (**Fig. A, E**)**.** Over time, the main mode shifted towards higher values while the zero peak reflecting cerebrospinal fluid (CSF) abated (**Fig. C, D**). Fractional anisotropy (FA) maps demonstrated similar courses, although without reaching significance in genu (**Table**).

Discussion and Conclusion

QMRI indicated an advancement of myelination under folinic acid therapy which was paralleled by clinical improvement. While this is only qualitatively reflected by T1-w and T2-w images, the MT maps demonstrated striking contrast changes and enabled detailed spatial evaluation. MT histograms might mirror the consequent increase of brain volume and reduction of CSF space. Although myelination is associated only with part of the MT effect, MT saturation may provide a valuable parameter to monitor therapy effects. For further evaluation, the MR protocol is currently applied to 2 more patients with cerebral folate transport deficiency.

Figure:

row 1: T2-w TSE image

row 2: colour coded MT saturation maps

row 3: histogram of MT saturation

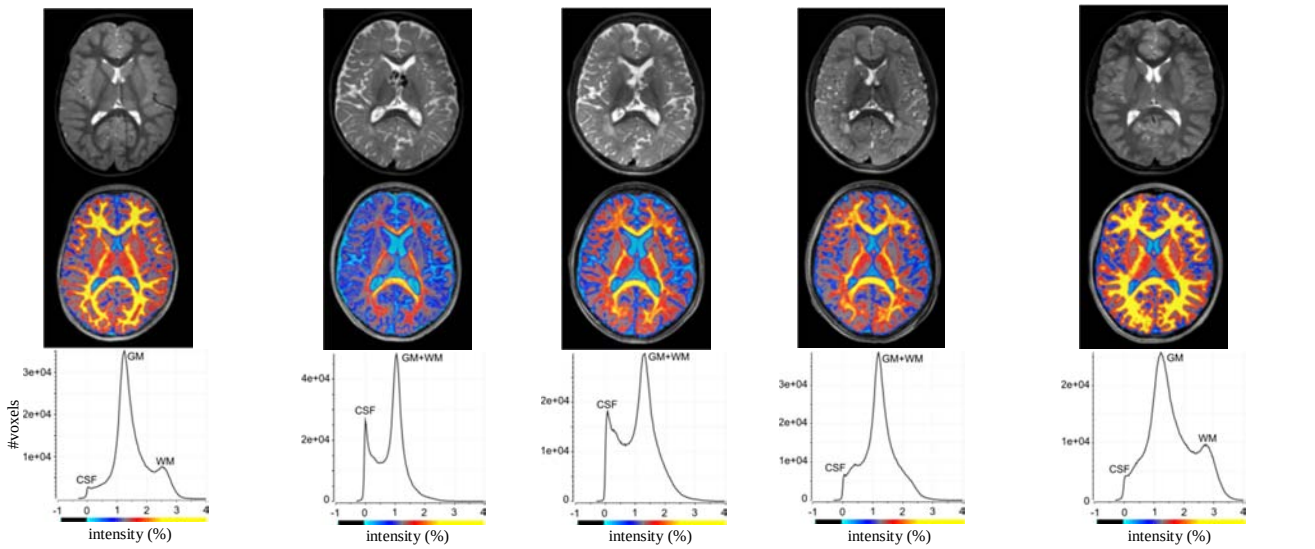

Fig. A: **control**, age 3 yrs

Fig. B: **patient**, age 3.9 yrs no therapy

Fig. C: **patient**, age 6 yrs 2.1 yrs of therapy

Fig. D: **patient**, age 7.6 yrs 3.7 yrs of therapy

Fig. E: **control**, age 10.2 yrs

References: 1. Dreha-Kulaczewski et al., *J Magn Reson Imaging* 2012: Aug 21 (Epub), 2. Steinfeld et al., *Am J Hum Genet* 2009;85:354, 3. Grapp et al., *Brain* 2012;135:2022, 4. Helms et al., *Magn Reson Med* 2008;59:667.