

Extensive and strong increase of radial diffusivity in human hypomyelinating disorders

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Introduction. Hypomyelination refers to a permanent and substantial deficit of myelin in the brain. It forms an important group of childhood white matter (WM) disorders with numerous causes that often remain unknown.¹ Hypomyelination is diagnosed based upon successive, conventional MRIs: WM is mildly hyperintense on T₂-weighted images; signal intensity on T₁-weighted images varies between mildly hypointense, isointense, and hyperintense, depending on the amount of myelin that is deposited. On follow-up MRI no progression of myelination is seen. Hypomyelination is a good model to study the effect of lack of myelin on axial and radial diffusivity (AD and RD).

Material and methods. DTI (1.5T, Siemens Sonata, EPI, 1 b0 and 12 b750 volumes (12 directions), TR/TE 6700/81 ms, 49 contiguous slices, isotropic 2.5mm voxels) was obtained in 25 patients with either a known or an unclassified hypomyelinating disorder (14F/11M, mean age 12.3y, range 0.8 – 47y) and 44 age-matched controls. The diffusion tensor was calculated with FSL4.1. Tract-based spatial statistics (TBSS) was used to compare FA, MD, AD, and RD along the tracts in both groups (using randomise, with age as covariate, mean skeleton obtained from group-target and thresholded above FA of 0.2).² DTI values were extracted from the voxels within the skeleton that were abnormal for all DTI-metrics, and for ROIs in splenium and body of the corpus callosum, and bilaterally in the posterior limb of the internal capsule (PLIC).

Results. TBSS showed extensive changes in all DTI parameters. FA was reduced in patients with hypomyelinating disorders compared to controls in as much as 96% of the whole skeleton, at a t_{corrected}-corrected threshold p<0.01. RD was increased in 93% of the skeleton, and MD in 84% of the skeleton. AD was increased to a much smaller extent: only 20% of the skeleton. These areas were confined to the splenium, a small part of the genu, the corona radiata, parts of the superior longitudinal fasciculus, and parts of the thalamic radiation (see figure).

Results from the area which was abnormal for all DTI-metrics (20% of the skeleton) are shown in the upper part of the table. FA and MD had a relative change of ±24%, the relative increase in RD was as large as 35%. Although all voxels within this ROI had significantly increased AD, the relative change was only 13%. In the small ROI in the splenium (a subset of the 20%-skeleton-ROI) changes were more pronounced, with especially large increases of RD. The small ROIs in the body of the corpus callosum and the PLIC bilaterally did not overlap with the 20%-skeleton-ROI, and AD was similar in patients and controls. However, RD was still largely increased in these ROIs, causing the increase of MD and the decrease of FA.

Discussion and conclusion. This study showed that in human hypomyelinating disorders RD is severely affected in large parts of WM, also in regions without changes in AD. Although our patient cohort consisted of several different hypomyelinating disorders, we observed a relatively uniform picture, especially when considering the large age range of the patients.

Possibly, reported diffusivity values in the splenium are overestimated, because no partial volume correction was performed on the data. Considering the thin corpus callosum of some patients and the acquired 2.5mm isotropic voxels, CSF will influence the results in this area,^{3,4} as evidenced by the larger variance in patients. The method of free water elimination might correct for this problem.⁵ However, the largest part of the skeleton is not influenced by partial volume with CSF, as also evidenced by the unchanged values for AD even in the body of the corpus callosum.

Histopathology in hypomyelinating disorders typically shows a lack of myelin and relatively well preserved axons.⁶ In combination with the extensive and strong abnormalities in RD this supports the interpretation of this diffusivity parameter in terms of myelin density, which was originally based on animal studies.⁷ Of course, the relationship in humans has also been suggested by a change of RD during early development, but changes in AD occur simultaneously.⁸ Recently, a small reduction of RD was observed regionally after neural stem cell transplantation in patients with Pelizaeus-Merzbacher disease, possibly due to myelin formation.⁹ In most clinical situations a change in RD is preceded, accompanied, or followed by a change in AD, such that the effects are not easy to distinguish. The current data do show clear changes in RD, consistent with a lack of myelin, while AD remains unaffected.

To conclude, in hypomyelinating disorders there are more extensive and larger increases of RD compared to AD, supporting a relationship between RD and myelin density in human leukoencephalopathies.

References

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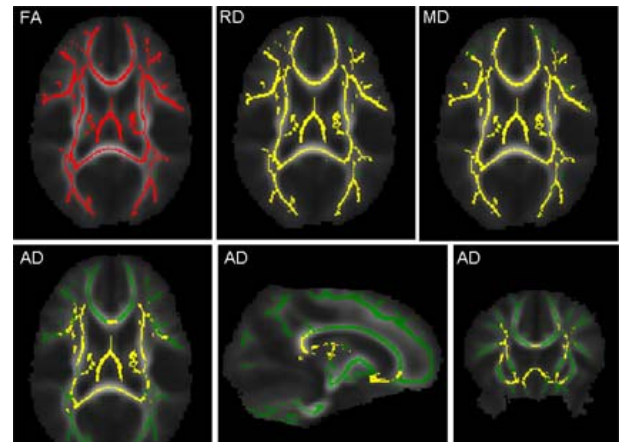


Figure: decreased FA (red) and increased diffusivities (yellow) at t_{corrected}-corrected p<0.01 in patients with hypomyelination vs. controls overlaid on skeleton (green).

Table: DTI metrics (mean ± SD) for hypomyelination, controls, and their differences. MD, AD, RD in 10⁻⁵mm²/s.

| | hypomyelination | controls | abs.diff. | rel.diff. |
|---------------------|-----------------|-------------|-----------|-----------|
| 20% of skeleton | | | | |
| FA | 0.31 ± 0.05 | 0.40 ± 0.05 | -0.09 | -24% |
| MD | 115 ± 15 | 93 ± 11 | 23 | 24% |
| AD | 154 ± 15 | 135 ± 9 | 18 | 13% |
| RD | 97 ± 16 | 72 ± 12 | 25 | 35% |
| splenium c.callosum | | | | |
| FA | 0.45 ± 0.14 | 0.75 ± 0.10 | -0.30 | -40% |
| MD | 149 ± 52 | 91 ± 21 | 58 | 64% |
| AD | 226 ± 54 | 188 ± 22 | 38 | 20% |
| RD | 111 ± 53 | 43 ± 22 | 68 | 157% |
| body c.callosum | | | | |
| FA | 0.46 ± 0.10 | 0.64 ± 0.10 | -0.18 | -28% |
| MD | 123 ± 16 | 104 ± 16 | 19 | 19% |
| AD | 190 ± 20 | 190 ± 12 | 0 | 0% |
| RD | 89 ± 19 | 61 ± 20 | 29 | 47% |
| bilateral PLIC | | | | |
| FA | 0.54 ± 0.08 | 0.62 ± 0.06 | -0.08 | -12% |
| MD | 88 ± 7 | 83 ± 6 | 5 | 6% |
| AD | 149 ± 10 | 150 ± 5 | -2 | -1% |
| RD | 57 ± 9 | 49 ± 7 | 9 | 18% |