Introduction: X-linked Adrenoleukodystrophy (ALD) is a neurodegenerative disorder that results from mutations in the ABCD1 gene and manifests in a wide clinical spectrum of phenotypes. About 60% of male carriers develop the most severe form leading to cerebral rapid progressive inflammatory demyelination, neurological dysfunction, and death within few years. Effective treatments are available but carry high toxicity. Onset and disease course of cerebral ALD are unpredictable and make clinical management challenging. Based on recent in-vivo and in-vitro data, we set out to assess changes in microvascular perfusion of white matter using dynamic susceptibility contrast magnetic resonance imaging (DSC-MRI).

Methods: Twenty-four patients with cerebral adrenoleukodystrophy were evaluated between 2006 and 2015. Microvascular flow patterns, determined as capillary transit time distribution (CTH), were estimated from raw DSC-MRI perfusion data. Regions of interest (ROIs) were drawn in co-registered maps (A: non-enhancing T2-hyperintense core, B: T1-post contrast enhancing rim, and C: T2- hyperintense perilesional WM, D: adjacent normal appearing white matter and distant normal appearing white matter: dNAWM). For available longitudinal data, ROIs were drawn based on areas converting to T2-hyperintensity on follow-up imaging and non-converting adjacent regions.

Results: In patients with cerebral ALD we found distinct zonal abnormalities in microvascular perfusion with increased CTH in Zones A and C, while the contrast enhancing rim (Zone B) showed homogenized capillary flow and increase permeability consistent with inflammatory vasodilation. Furthermore, perilesional white matter (Zone D) while normal appearing as determined on structural imaging, revealed microvascular perfusion abnormalities (n=34; ANOVA between group differences p=0.0002, post hoc analysis with Dunnett’s correction: dNAWM vs. A, p<0.0001; dNAWM vs. B, p=0.5648; dNAWM vs. C, p=0.0057; dNAWM vs. D, p=0.0406). Analysis of longitudinal data showed that increased CTH predicts lesion progression as demonstrated by T2 hyperintensity on follow up imaging. (n=12, mean±SEM 3.4±0.5 converting vs 2.1 ± 0.3 non-converting, p=0.0381)

Conclusion: MR microvascular perfusion showed zonal abnormalities in white matter demyelinating lesions of patients with cerebral ALD. These capillary flow changes extend beyond the lesion edge to the adjacent normal appearing white matter as determined by structural imaging and predict lesion progression. Moreover, we found that capillary transit time distribution abnormalities determined by DSC-MRI can detect cerebral disease more than 6 months before conventional MRI sequences. Our study suggest changes in microvascular perfusion play an crucial role in the pathophysiology of cerebral ALD and could serve as a biomarker to identify patients at high risk of developing cerebral disease.

(no table selected)
Figure 2: Three-year-old asymptomatic male patient with X-linked adrenoleukodystrophy, who underwent frequent MRI screening for cerebral conversion. While structural imaging showed no abnormal signal changes at his second visit, analysis of the perfusion data acquired at this time revealed increased heterogeneity of microvascular flow patterns within the splenium of the corpus callosum. Follow up imaging 7 months later showed early manifestation of cerebral adrenoleukodystrophy in the corresponding region.