Brain morphometry in late-infantile Metachromatic Leukodystrophy

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Introduction

Metachromatic Leukodystrophy (MLD) is a rare metabolic disorder leading to white matter (WM) demyelination and rapid neurological deterioration. Children with the late-infantile form show first clinical symptoms during the first years of life and undergo a rapid neurological deterioration with loss of motor function as a key feature [1]. Death occurs within the first decade of life as no causal therapy is available yet [2]. However, as therapeutic options evolve, it seems essential to understand and quantify progression of the natural disease course.

In MLD, the demyelination can sensitively be detected as WM signal hyperintensities on T2-weighted images [3]. Automated morphometric analyses techniques are known to be objective and make use of computer algorithms in order to assist more complex volumetric measurements. With demyelination and atrophy being the main features of morphological brain changes in MLD [3], a multispectral segmentation approach was chosen for this study, in order to make use of the improved T2-contrast for demyelination within the WM and the higher spatial resolution and good gray/white matter tissue contrast of T1-weighted images. The aim of this study was to assess cerebral volumetric changes in comparison to normal controls and in relation to the disease course.

Methods

Overall, 18 patients (19 MRIs) with late-infantile MLD (mean age 35.5 ± 9.81 months, range 20 to 59) and 48 typically developing children (39.29 ± 10.90 months) of the same age range were included. Patient data was collected as part of a natural history study of the German Leukodystrophy network (Leukonet) and from a therapeutic phase I/II trial concerning enzyme replacement in Copenhagen, Denmark [4]. Control MRI data of typically developing children used in this study were obtained from the Pediatric MRI Data Repository created by the NIH MRI Study of Normal Brain Development [5]. MRI sequences of patients and controls were acquired on 1.5 T Siemens and GE scanners using a high-resolution T1-weighted (voxel size 1x1x1mm) and a lower-resolution T2-weighted axial sequence (slice thickness typically 3-4mm).

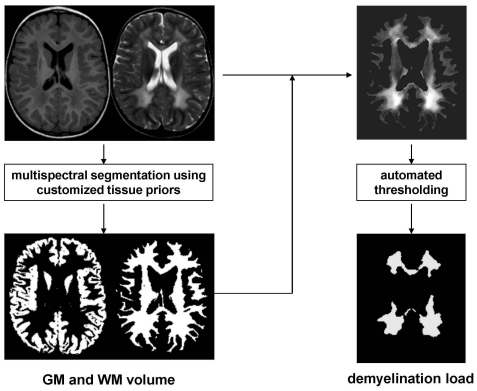

Figure 1

Summary of the methodological approach for segmentation. *In a first step multispectral image segmentation results in GM and WM image volumes. In a second step, the WM segment is applied to the T2-weighted image and an automated intensity threshold within the WM of the T2-weighted image is calculated in order to separate normal appearing and demyelinated WM (demyelination load).*

An automated multispectral segmentation of gray matter (GM) and WM volumes was performed using T1- and T2-weighted sequences (Figure 1). This segmentation algorithm is implemented as "New Segmentation" in SPM8 and is an extension of the "Unified Segmentation" model [6]. From the healthy controls, tissue priors for segmentation were created using the template-O-matic toolbox as implemented in SPM8 [7]. Within the WM of T2-weighted images of the patients, an automated intensity threshold using a Gaussian mixture model together with a hidden Markov Random Field approach was applied in order to quantify the 'demyelination load' (volume of demyelinated WM). These volumetric parameters were validated using manual segmentation and analyzed in relation to the clinical course and loss of motor function.

Results

WM volumes of the patients did not differ from controls, although their growth curves appeared different. GM volume of patients, however, was clearly below those of normally developing children (Student's t-test, p<.001; Figure 2). The demyelination load (corrected for total WM volume) was found to increase after disease onset and correlated positively with deterioration of motor function (rho=0.69, p<.001) and disease duration (correlation coefficient.65, p=.003; Figure 3). Validation yielded good agreement between manual and automated measurements of demyelination load: volume agreement was estimated with an ICC of 0.987 (0.967-0.995) and the spatial overlap with a median dice coefficient of 0.77 (0.09-0.87).

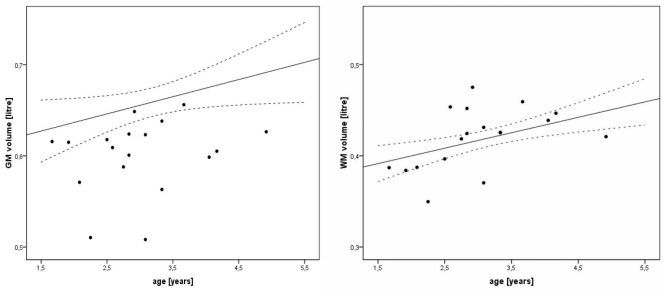

Figure 2: GM (left) and WM (right) volumes *of controls (mean of linear regression line and its 95% confidence intervals) and patients (single dots) showing less GM volume in patients, whereas WM volume was not different.*

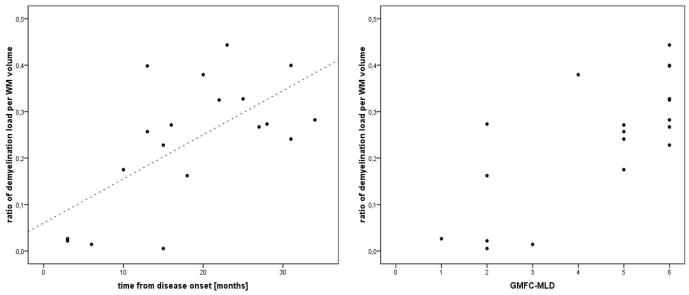

Figure 3: Demyelination load *as a fraction of the total WM volume versus time from disease onset (left) and versus deterioration of motor function assessed with a standardized motor score (GMFC-MLD, [1]; right).*

Discussion

The automated segmentation method reliably quantified cerebral volumetric changes. Interestingly, GM volume was found to be reduced already early during the disease course when compared with healthy controls, whereas their total WM volume did not differ. This supports the idea that neuronal dysfunction caused by neuronal storage plays an additional role in the disease process, in addition to the more obvious WM demyelination. The demyelination load increased with disease duration and motor deterioration. These data may serve as reference for therapeutic intervention.

References

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