Voxel-based analyses of diffusion-tensor imaging in Fabry disease

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Running Title: Voxel-based DTI in Fabry Disease

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Key words: Fabry disease, voxel-based DTI, Diffusion-tensor Imaging
ABSTRACT

Background: Fabry disease (FD) is a lysosomal storage disorder that is associated with marked cerebrovascular disease. Conventional MRI shows an extensive load of white matter lesions (WMLs) already at an early stage in FD.

Objective: Investigator independent and sensitive quantification of brain structural changes in clinically affected men and women with FD.

Methods: The authors performed a voxel-based analysis of diffusion tensor images (DTI) in 25 FD patients and 20 age-matched normal controls.

Results: DTI revealed significant increases of cerebral white matter diffusivity (MD) in FD patients that were pronounced in the periventricular white matter. Even the subgroup of patients without significant WMLs-load (n = 18) showed increased diffusivity in the cerebral white matter. In gray matter areas MD elevation could only be detected in the posterior part of the thalamus, independently from visible pulvinar alterations on the T1-weighted images. Voxel-based anisotropy (FA) measurements did not differ significantly between patients and controls.

Conclusions: The present study demonstrates the clinical feasibility of voxel-based analysis of DTI as a sensitive tool to quantify brain tissue alterations in FD. The pattern of increased brain tissue diffusivity is probably due to microangiopathic alterations mainly affecting the long perforating arteries.
INTRODUCTION

Fabry disease (FD) is a rare X-linked hereditary lysosomal storage disease. Deficiency of α-galactosidase A activity leads to accumulation of neutral glycosphingolipids, particularly in vascular endothelial and smooth muscle cells of various organs. Along with progressive renal and cardiac dysfunction, clinical CNS involvement mainly due to cerebral vasculopathy leading to serious complications like stroke at a rather early age has been confirmed by clinical studies and neuroimaging. The most prominent brain structural findings in FD are severe progressive white matter lesions (WMLs) that are detectable by T2- and FLAIR-weighted images using conventional MRI.

Focussing on WMLs and quantifying structural cerebrovascular involvement by visual rating scales on conventional MRI is comprised by limited accuracy. Investigation of brain structure, especially the detection of typical patterns of brain structural involvement as well as the assessment of the natural course of these affections, is of importance for a better understanding of the brain’s pathophysiology and to study potential effects of new treatment options like the enzyme replacement therapy (ERT) in FD.

There is evidence that diffusion-tensor imaging (DTI) is more accurate and more sensitive in quantifying structural brain alterations than other assessments in conventional MR-technique. The principal parameters derived from diffusion tensor analysis are fractional anisotropy (FA) and mean diffusivity (MD). Reduced water diffusion parallel to axonal tracts represented by FA is an indicative of axonal degeneration. Furthermore, MD that measures randomized mean water diffusion is a representative DTI parameter for ultrastructural brain tissue alterations. Thus, DTI provides a promising tool for detection of early ultrastructural cerebral changes in FD.

The preferences of diffusivity measurements in FD patients have been previously demonstrated. One study demonstrated global elevation of the average diffusion constant (ADC) in cerebral tissue of men with FD. Moreover, analyzing DTI with Regions-of-Interest (ROI) we previously showed significant elevations of white matter diffusivity (MD) even in those Fabry patients without significant WMLs. However ROI-based analysis is time-consuming, investigator dependent and does usually not cover the whole brain.

To investigate the feasibility of the investigator independent structural data processing procedures which cover the whole brain we analyzed DTI data of Fabry patients using a voxel-based approach. In this way, brain structural differences can be detected by voxel-wise comparison of normalized DTI maps between patient and control groups.
SUBJECTS & METHODS

Patients

We enrolled 25 clinically affected FD patients (10 men, mean age 36.1 ± 12 years; 15 women, mean age 36.7 ± 11.5 years), and 20 age-matched healthy controls (12 men, mean age 34.4 ± 10.2 years; 8 women, mean age 36 ± 9.4). 22 patients and 18 controls were part of our previously published ROI-based study 6. All patients were recruited at the Children’s Hospital, University Mainz. For the enzymatic and molecular diagnosis of FD standard methods were used as generally recommended 21. The average clinical stage of FD patients was moderate. None of the patients had end-stage renal failure or underwent renal dialysis. Table 1 shows patient characteristics. Inclusion criteria have been described previously 6 11. At the time of assessment, 20 patients were under current treatment with enzyme replacement therapy (ERT) or were about to start ERT (5 patients, two patients with previous ERT). Age-matched controls were recruited by advertisement and underwent a structured interview and physical examination to exclude cerebral diseases as well as clinically manifest psychiatric disorders or significant organic dysfunction. The study was approved by the local Ethics Committee, and all subjects gave written informed consent.

MR data acquisition

All data were obtained on a 1.5 Tesla system with gradients of 40 mT/m (Magnetom Sonata; Siemens). Apart from the acquisition of routine T1– (TR/TE: 600ms/25ms, Matrix 256 x 256) PD/T2-weighted (TR/TE1/TE2: 4500ms/15ms,100ms, Matrix 256 x 256), FLAIR-weighted (TR/TE 9000ms/108 ms, slice thickness 6mm, Matrix 512 x 448) images and 3D-MP RAGE (TR/TE: 1900ms/16ms, Matrix 512 x 512) data sets, we used a transverse diffusion-weighted single-shot spin-echo echo-planar based sequence with gradients along 6 non-collinear directions (TR/TE= 8000/105 ms, b=0 and 1000 s/mm², matrix 128 x 128, slice thickness 3 mm without gap (voxel size 1.8 x 1.8 x 3.0 mm) and 6 averages. The transverse slices were aligned to the AC-PC line (anterior – posterior commissure) and covered the whole brain, except the top 6 mm.

With matter lesion classification

WMLs-load was classified on FLAIR-images using a simplified previously described visual rating scale 11 : 0 = no WML, 1 = mild WMLs (up to five single, non-confluent lesions), 2 = significant WMLs (more than 5 or confluent).

DTI data post-processing

The MR-DTI data-sets were transferred to a Linux x86 Workstation for post-processing. The diffusion tensors were computed using an in-house programme based on the algorithm of Basser et al. 22. The decomposition of the diffusion tensor (D) in an eigensystem was accomplished by symmetric bi-diagonalization followed by QR-reduction, implemented using the respective functions as supplied with the GSL (GNU Scientific Library). Mean Diffusivity (MD) is the mean of the diffusion tensor eigenvalues \([D_{xx}+ D_{yy}+ D_{zz}]/3 \text{ given in } \text{mm}^2/\text{s}\]. Fractional Anisotropy (FA) is the standard deviation of eigenvalues from the MD normalized by square norm of the eigenvalues 22. Both indices were plotted voxel by voxel as MD and FA index maps.
Image processing – voxel-based DTI

A voxel-based analysis of parameters derived from magnetic resonance diffusion tensor imaging (MR-DTI) was employed and based on the Voxel-Based Morphometry implemented with SPM2 software optimized for white-matter. First, a template was created by normalizing all images to standard space (EPI template, International Consortium for Brain Mapping) which approximates the Talairach and Tournoux space. In a second step all images were normalized using the customized template. For the creation of the customized template all non-diffusion weighted images from the DTI data-sets (B0 images) were normalized to the standard anatomical space. Every B0 image was segmented in its gray and white matter volumes. All white matter volumes were normalized to the white matter template accompanying SPM2 and the resulting normalization parameters were applied to the respective raw B0 images. A new B0 template was created by averaging all normalized B0 images. All normalized B0 images were again segmented and the resulting volume images were averaged.

The customized gray matter, white matter and CSF templates were set up as the a priori brain tissue distribution probability maps used in the segmentation procedure. All B0 images were segmented using the customized Bayesian Priors. The white matter image volumes were normalized to the customized white matter template and the respective volume images of FA, MD and B0, lying in native space, were transformed accordingly to the resulting normalization parameters.

Image segmentation and threshold

Partial volume effects can be reduced by segmenting the normalized FA and MD images into CSF, gray matter, and white matter compartments. The segmentation algorithms for defining gray and white matter were based on a probability of greater than 0.80 according to Medina et al. Thus, only voxels surviving this threshold were included in the group analyses. The individual gray and white matter masks were then combined and applied to individual MD and FA maps.

Since MD is markedly higher in CSF than in the brain tissue, a threshold procedure can be effectively used to additionally eliminate partial volume effects due to CSF in the segmented MD maps. Therefore an empirically set cutoff threshold of MD = 1050 x 10^-6 mm^2/s equalling about 3 standard deviations above the mean measured tissue MD value (774 ± 96 x 10^-6 mm^2/s) was applied. With this conservative threshold especially those critical MD values from periventricular border zones were excluded which in part were significantly elevated in patient versus control comparisons.

As FA is even more susceptible to errors arising from partial volumes a cutoff was applied for combined gray and white matter segmented FA maps excluding all FA values under 0.25. FA of CSF and cortical gray matter is typically below 0.2. The processed FA and MD maps were then smoothed using an isotropic Gaussian filter (full width half maximum 10 mm).

Calculation of mean global FA and MD

Independent of voxel-based DTI, mean global FA and MD values were directly calculated from original diffusion tensor images after using the described FA and MD thresholds and gray and white matter segmentation.
Statistical analysis

Voxel-wise group differences in MD and FA were calculated using unpaired Student’s t-tests in SPM2. An uncorrected p < 0.001 on voxel level was selected as a threshold of significance. The amount of adjacent voxels with significant MD elevations was represented in total cluster size. Determination of the location of clusters demonstrating significantly different DTI values was accomplished by converting the x, y, z coordinates for the peak voxel within a cluster from the Montreal Neurological Institute (MNI) coordinates used in SPM2 analyses to Talairach coordinates using MSU - MNI Space Utility software (http://www.ihb.spb.ru/~pet_lab/MSU/MSUMain.html). This software programme also identified nearest lobar and Brodmann area locations.

Further statistical analysis was performed with SPSS software package version 12.0 (SPSS, Chicago, IL, 2003). Descriptive data are reported as means and standard deviations (SD). The analyzed mean global FA and MD values did not show any significant deviation from normal distribution (Kolmogorov-Smirnov tests, P > 0.74); hence, parametric tests were used. Comparisons (FD vs. controls) for mean global MD and FA values of gray and white matter segments of all 45 studied subjects were carried out using unpaired Student’s t-tests. Association of clinical features with imaging parameters of the patient group was analysed using univariate analysis (ANOVA) or binary logistic regression with age as covariate. Spearman’s rank ($r_s$) and partial ($r_p$) correlation coefficient were calculated for correlations of WMLs-load, age and global FA and MD values in FD patients and controls. The level of statistical significance was set at two-tailed $\alpha = 0.05$. 
RESULTS

The age-dependent WMLs-load in patients was clearly exceeding those of controls (see table 2). There were significant correlations between WMLs-load and mean global MD ($r_s = 0.558, p = 0.004$) and FA ($r_s = -0.493, p = 0.012$) of the white matter and between age and mean global MD of the white matter ($r_s = 0.431, p = 0.031$) in FD patients. However, these correlations did not remain significant when age and WMLs-load were alternatively excluded using partial correlation. Only age itself correlated significantly with WMLs-load ($r_s = 0.661, p < 0.001$) of FD patients. Furthermore, association of clinical symptoms (angiokeratoma, neuropathic pain, cerebrovascular events, cardiovascular and renal dysfunction) and the imaging parameters of the patient group was analysed using univariate analysis with age as covariate (ANOVA). None of the analysed parameters (see table 1) had a significant effect on the WMLs-load or on DTI parameters in FD patients. Moreover, using a binary logistic regression neither WMLs-load nor global MD or FA values were found to be predictive for cerebrovascular events in our study group.

Using voxel-based DTI analysis MD differed significantly ($p < 0.001$, uncorrected) between FD and controls (table 3A; figure 1A). MD values were significantly increased mainly in regions of the frontal, temporal, central and parietal white matter (table 3A; figure 1A).

In gray matter regions significant MD increases could only be detected in the posterior thalamus bilaterally ($p<0.001$, uncorrected; table 3A; figure 1A). Thalamic diffusivity elevation remained significant after exclusion of two male patients who showed pulvinar hyperintensities on T1-weighted images and three patients with visible thalamic lesions on the T1- or T2-weighted images.

Even FD patients without significant WMLs ($n = 18$) showed a significant MD ($p < 0.001$, uncorrected; table 3B; figure 1B) increase in similar localizations but with a lower total cluster size of around 23%.

In contrast to the significant diffusivity alterations, no anisotropy (FA) differences could be detected comparing gray and white matter segmented FA maps of FD patients and controls.
DISCUSSION

In the present study we used DTI and voxel-based analyses to quantify brain structural changes in FD.

The most prominent finding was a marked disseminated increase of cerebral white matter diffusivity (MD) in Fabry patients while fractional anisotropy (FA) did not differ significantly between patients and controls.

Comparably to our previously published ROI-based DTI findings diffusivity elevations were pronounced in the periventricular white matter. Crutchfield et al. 7 also found that most cerebral abnormalities in FD were located in the periventricular deep white matter. These areas are supplied by long perforating arteries of small caliber. Thus, our results support the assumption of pronounced and relevant dysfunction of these vessels in FD. In contrast, other studies suggested that cerebral abnormalities were pronounced in the posterior artery territory 9 mainly due to cerebral macroangiopathy which can not be supported by our data.

Concordantly to our previously published ROI-based DTI findings and other published brain imaging studies 5 6 8 32 voxel-based assessed diffusivity elevations were still significant after exclusion of 7 patients with a significant WMLs-load. This indicates that measurable elevations of interstitial water content and myelin rarification as degenerative changes of the brain tissue in FD probably emerge before WMLs are detectable on conventional images.

Moreover, we found significant diffusivity elevations in the posterior part of the thalamus suggesting structural vulnerability at least in this area of the posterior circulation in FD. Increased signal intensity on T1-weighted images has been repeatedly described in the pulvinar regions (“pulvinar sign”) 33 34 . But, as the diffusivity differences did not disappear after excluding the two patients who showed the “pulvinar sign” on T1-weighted images, MD elevations and pulvinar sign in FD do not seem to refer to a same pathophysiological mechanism. One can speculate that increased CBF in the posterior artery territory predisposes to thalamic calcification as well as to degenerative tissue rarification or increase of thalamic water content that eventually represents as T1 weighted signal increase in the pulvinar 33 34 . On the other hand retro- and anterograde deafferentation due to remote cerebral lesions like WMLs might be a cause for distinct MD elevations in the thalamus 35 that need further investigation.

Using voxel-based measurements we were able to analyze the entire gray matter compartment. Interestingly, beside widespread white matter affection no diffusivity changes were found in the gray matter. This finding underlines the theory that CNS dysfunction in FD is mainly due to insufficiency of the long perforating arteries resulting predominantly in structural changes of the periventricular deep white matter 5 7 13 36 . Conversely it is known from autopsy studies that glycolipid deposition can not only be found in blood vessel walls but also in specific small neuronal populations in the CNS in FD 37 38 . These pathological intra-neuronal changes that are not known to have a functional correlate might potentially not be detectable with DTI.

Different from the discussed marked diffusivity (MD) changes white matter anisotropy (FA) indicating disturbances of nerve fiber integrity was not significantly altered in FD.
Quantification of global MD and FA values of the white matter compartment revealed no significant association with age, clinical symptoms or WMLs-load. Only age, but not the clinical symptoms affected WMLs-load significantly. Thus, our findings support previous notions of the close relation between age and the early progression of WMLs-load in FD. Unexpectedly, cerebrovascular events as well as cerebrovascular risk factors like renal and cardiac dysfunction were not significantly related to the brain structural disturbances, which is probably due to the small study group. The previous finding of an increased WMLs-load in young stroke patients with FD compared to other young cryptogenic stroke patients points at the connection of early structural alterations and ischemic events in FD.

Beside the small study sample size one limitation of the present study clearly are artefacts due to misregistration, low signal to noise ratio (SNR) and potential volume contamination of the voxel-based DTI approach. These especially affect FA more than MD values in a template-based method. Thus, in addition to the assumption that an increase of interstitial water content within the white matter in FD results in an increase of diffusivity (MD) while the fiber integrity (FA) is not yet significantly disturbed, the dissociation of MD and FA findings could also be influenced by these technical limitations. For more conservative restriction of partial volume artefacts due to CSF contamination data processing was additionally refined using a threshold approach in DTI maps according to previous studies.
CONCLUSION

Voxel-based diffusion tensor analyses of FD patients revealed significant elevations of brain tissue diffusivity mainly in the periventricular deep white matter. This pattern of diffusivity alterations that is probably due to microangiopathy could be detected independently from visible WMLs in FLAIR-weighted MR images. Additionally, MD elevations were detected in the posterior region of the thalamus.

As an investigator independent MR-technique voxel-based DTI analysis could demonstrate its favourable sensitive properties to quantify brain tissue alterations in FD. In the future longitudinal assessments using our approach could be used to quantify the cerebral involvement and its clinical relevance in the course of FD and related disorders by providing for example further information about the predictive value of early ultrastructural diffusivity changes on cerebrovascular events and by monitoring the cerebral effects of enzyme replacement therapy and other potential treatment options.

ACKNOWLEDGEMENTS

We thank the patients and volunteers who took part in our study.
REFERENCES


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<tr>
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<th>Fabry Disease</th>
<th>Controls</th>
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<tr>
<td>N (women)</td>
<td>25 (15)</td>
<td>20 (8)</td>
</tr>
<tr>
<td>Age (years)*</td>
<td>36.4 ± 11.5 (19-55)</td>
<td>35.1 ± 9.7 (22-55)</td>
</tr>
<tr>
<td>Cerebrovascular events</td>
<td>N = 5 (20%)</td>
<td>0</td>
</tr>
<tr>
<td>Neuropathic pain</td>
<td>N = 20 (80%)</td>
<td>0</td>
</tr>
<tr>
<td>Angiokeratoma</td>
<td>N = 13 (52%)</td>
<td>0</td>
</tr>
<tr>
<td>Cardiac dysfunction</td>
<td>N = 20 (80%)</td>
<td>0</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>N = 13 (52%)</td>
<td></td>
</tr>
<tr>
<td>Arrhythmias</td>
<td>N = 7 (28%)</td>
<td></td>
</tr>
<tr>
<td>Left ventricular hypertrophy</td>
<td>N = 1 (5%)</td>
<td></td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td>N = 20 (80%)</td>
<td>0</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>N = 4 (16%)</td>
<td></td>
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<tr>
<td>Proteinuria</td>
<td>N = 16 (64%)</td>
<td></td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)*</td>
<td>0.92 ± 0.41</td>
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Table 2: White Matter Lesion (WML) Quantification in Fabry patients and controls

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<tr>
<th>WML-Classification</th>
<th>Male Fabry patients</th>
<th>Female Fabry patients</th>
<th>Male controls</th>
<th>Female controls</th>
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<tr>
<td></td>
<td>N</td>
<td>Age</td>
<td>N</td>
<td>Age</td>
</tr>
<tr>
<td>No WML</td>
<td>4</td>
<td>26.8 ± 7.0</td>
<td>7</td>
<td>30.7 ± 11.0</td>
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<tr>
<td>Mild WMLs</td>
<td>2</td>
<td>30.0 ± 4.0</td>
<td>5</td>
<td>39.4 ± 9.6</td>
</tr>
<tr>
<td>Significant WMLs</td>
<td>4</td>
<td>48.5 ± 5.7</td>
<td>3</td>
<td>46.0 ± 10.1</td>
</tr>
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Table 3: Talairach space-derived distribution of white matter regions with increased diffusivity (MD; \( p < 0.001 \) uncorrected) in FD patients with (A) and without (B) significant WMLs compared to age-matched controls

### A

<table>
<thead>
<tr>
<th>Centroid voxels</th>
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<th>cluster size</th>
<th>Location: adjacent gray matter region (Brodmann area( ^\ddagger ))</th>
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<tr>
<td>X (-25) Y (-14) Z (28)</td>
<td>4.76</td>
<td>13453</td>
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<td>1265</td>
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<td>2336</td>
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<tr>
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<td>3.99</td>
<td>269</td>
<td>right frontal lobe superior frontal gyrus (9)</td>
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<tr>
<td>X (15) Y (-22) Z (-2)</td>
<td>3.93</td>
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### B

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<td></td>
<td></td>
<td>(Brodmann area‡)</td>
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<tr>
<td>X  Y  Z*</td>
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<td>231</td>
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<td>-14  -87 -7</td>
<td>3.71</td>
<td>196</td>
<td>left occipital lobe lingual gyrus (18)</td>
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</table>
LEGEND OF TABLES AND FIGURES

Table 1: * mean ± SD (range);

Table 2: White Matter Lesion Quantification in Fabry patients and controls
Mild WMLs = single, non-confluent bright lesions; Significant WMLs = multiple (> 5) or confluent lesions

Table 3: Talairach space-derived distribution of white matter regions with significantly increased diffusivity (MD; p < 0.001 uncorrected) in FD patients with (A) and without (B) significant WMLs compared to age-matched controls
* Talairach coordinates; † only T scores > 3.6 presented; ‡ nearest identified Brodmann area of significantly increased MD

Figure 1: Voxel-based comparison of diffusivity (MD) between FD patients with (A) and without (B) significant WMLs and age-matched controls
Significant MD elevations are projected on transverse sections (3mm distance) of FA template. (A) MD values were significantly increased mainly in regions of the frontal, temporal, central and parietal white matter (p < 0.001, uncorrected). In gray matter regions significant MD increases could be detected in the posterior thalamus bilaterally. (B) FD patients without significant WMLs (n = 18) showed significant MD increase in similar localizations but with a lower total cluster size.
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