Secondary involvement of optic radiation in Leber's hereditary optic neuropathy

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Introduction

Leber's hereditary optic neuropathy (LHON) is a mitochondrial disease characterized by the peculiar preferential involvement of the small axons serving central vision, colour vision and high spatial frequency contrast sensitivity; these fibers form the papillomacular bundle (1). It is defined, along with the dominant optic atrophy (DOA), as a non-syndromic mitochondrial optic neuropathy, and both present clinically with visual loss and optic nerve atrophy reflecting retinal ganglion cell (RGC) degeneration as the only or at least primary pathological feature (1). Mitochondrial optic neuropathies may also occur in more complex syndromes such as Friedreich's ataxia (FRDA), in which a diffusion-weighted imaging (DWI) study has demonstrated an involvement not only of the optic nerve but also of the optic radiation (OR) (2). Recently a voxel-based morphometry (VBM) study pointed toward OR impairment in LHON patients also, without concluding whether pathogenesis was primary or secondary (3). Therefore, the aim of this study was to use DWI to investigate the optic radiation in LHON patients and healthy carriers.

Methods

22 LHON patients (17 males; age 33±11, mean ± SD; 14 with 11778G>A, 7 with 3460G>A, and 1 with 14484T>C mutation), 11 healthy carriers (5 males; age 45±15; 8 with 11778G>A and 3 with 3460G>A mutation) and 22 healthy controls (16 males; age 37±17) were studied in a 1.5 T GE Signa Horizon LX whole-body scanner. Structural imaging included T1- and T2-weighted fast spin-echo scans. Axial DW images were obtained (slice thickness = 5 mm, inter-slice gap = 1mm) using a single-shot EPI sequence (matrix size = 192x192). Orthogonal x, y and z diffusion-encoding gradients were applied with gradient strengths corresponding to b-values of 300, 600 and 900 s/mm^2. In addition, images without diffusion weighting were acquired, corresponding to b = 0 s/mm^2 and exhibiting T2-contrast. Distortions in the DW-EPI images due to gradient-induced eddy currents were corrected using the image registration software FLIRT (4). Due to the nature of the distortions, the degrees of freedom were restricted to translation, scaling, and shearing along the phase encoding direction. Possible head movements were corrected using image registration of each volume to the first restricting degrees of freedom to translation and rotation. Mean diffusivity (MD) was determined pixel-wise using a least-squares fit using the program DTIFIT (4). In order to avoid contamination of the MD values for grey and white matter by the much higher values of cerebral spinal fluid (CSF) during further evaluation, pixels containing CSF were masked from the MD map. This was accomplished using the FAST algorithm (4) for a two-class segmentation based on the corresponding T2-weighted EPI images. Regions of interest (ROIs) **(Fig. 1)** were determined by segmentation of the left and right ORs (5) on three slice using the T2-weighted EPI images and were copied on the ADC maps to obtain the mean ADC values. One-way ANOVA followed by post-hoc LSD test was used for comparison between groups. To investigate the effect of genetic, demographic and clinical parameters (gender, mutation, age at onset, disease duration, history of recovery of visual acuity) on DWI data we used a multiple regression with a backward stepwise method to obtain a significant model. For all analyses, only P values less than 0.05 after Bonferroni correction for multiple comparisons were accepted as statistically significant.

Results

Right- and left-side MD values were not statistically different for OR ROIs and are reported as mean. ANOVA detected a group difference ($P < 0.01$) and post hoc testing revealed an increase in OR MD of LHON patients compared with both healthy carriers ($P < 0.05$) and healthy controls ($P < 0.01$) with a clear overlap between groups **(Fig. 2)**. Healthy carriers and healthy controls did not differ among themselves. In LHON patients multiple regression analysis led to a significant model including only two varibles, history of recovery of visual acuity (negative correlation) and disease duration (positive correlation)($P < 0.05$) **(Table)**.

Discussion

Our results confirm the observation of a retrochiasmatic involvement in LHON patients. This alteration is mild and is evident only in a part of the affected subjects and not in healthy carriers. Furthermore, lack of recovery of visual acuity and longer disease duration are associated with the increase of MD in ORs of LHON patients. Whereas all these data we can conclude that MD changes regard only the patients with longer disease duration and absence of recovery of visual acuity. Thus they may represent secondary alterations, reflecting a downstream effect rather than a primary effect of the mitochondrial dysfunction.

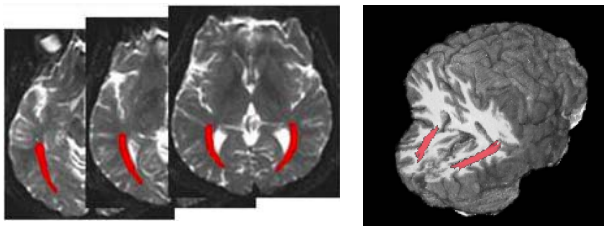

Figure 1. Manual segmentation of ROIs including optic radiation (left) and their 3D reconstruction on a registered T1 image (right)

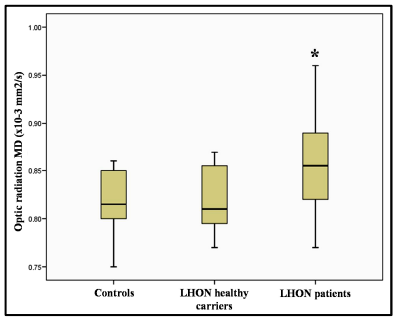

Figure 2. Box-plot of MD values of optic radiations controls LHON healthy carriers and LHON patients. (Each box shows the median, quartiles, extreme values; * = P<0.05).

Table. MD values at level of OR in the LHON patients, LHON healthy carriers and controls with group comparison results (first two sections). The third part of the table shows the multiple regression model.

One-way ANOVA				
ROI	**LHON patients MD (x10^{-3} mm^2/s)**	**LHON carriers MD (x10^{-3} mm^2/s)**	**Controls MD (x10^{-3} mm^2/s)**	***P***
Optic radiation*	0.86±0.04	0.82±0.04	0.82±0.03	*<0.01*
Post-hoc LSD test				
LHON patients *vs* healthy controls				*<0.01*
LHON patients *vs* LHON carriers				*<0.05*
LHON carriers *vs* healthy controls				*n.s.*

Multiple regression (backward stepwise method)	OR MD values in LHON patients
Model	*R = 0.54; P < 0.05*
Disease duration	*R = 0.39; P = 0.06*
History of recovery of visual acuity	*R = -0.47; P = 0.028*

* = mean of left and right MD values. Values are reported as mean and standard deviation

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