Brain white matter involvement in OPA1-dominant optic atrophy and Leber's hereditary optic atrophy: a DTI study

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Target audience Neurologists and neuroradiologists interested in the pathophysiology of the non-syndromic mitochondrial optic neuropathies, OPA1-dominant optic atrophy (*OPA1*-DOA) and Leber's hereditary optic atrophy (LHON).

Purpose While both LHON and OPA1-DOA are characterized by optic nerve atrophy as the only or prevalent pathological feature, with an early and preferential involvement of the small fibres in the papillomacular bundle,[1] recent brain magnetic resonance imaging (MRI) studies have also shown abnormalities of the optic radiation in LHON patients, confirmed by post-mortem investigation,[2] suggesting a trans-synaptic degeneration. The aim of the present study was to investigate whole brain white matter of *OPA1*-DOA patients, compared LHON patients and healthy controls, using diffusion tensor imaging, to detect subtle structural alterations.

Methods *Subjects.* 19 adult subjects with *OPA1*-DOA (aged 21 – 60 years), 17 with LHON (aged 25 – 55 years) and 18 healthy controls (aged 24 – 55 years) were studied. No subject studied showed evidence of white matter lesions on conventional MR images. 11 LHON and 9 *OPA1*-DOA patients were on idebenone therapy.

Acquisition protocol. Each subject underwent an MRI examination protocol using a 1.5 T GE Signa scanner, including T2-weighted Fast Low-Angle Inversion Recovery,T2-weighted Fast Spin Echo, T1-weighted volumetric imaging (FSPGR; TR/TE 12.3/5.2 ms; 1 mm isotropic resolution), Diffusion Tensor imaging (DTI; TR/TE 104/82 ms; 64 acquisitions with non-collinear field gradients b-value=900 mm^2 s^{-1}; axial oblique FOV 32 cm; 128×128 in-plane resolution; 3 mm slices).

Analysis protocol. Imaging data were processed to provide voxelwise estimates of tensor parameters, including mean diffusivity (MD) and fractional anisotropy (FA). Statistical analysis was focused on identifying areas of altered white matter compared with controls, and relate such alterations to clinical and genetic variables. Non-parametric statistical inference was performed for major white matter (WM) tracts, using the software TBSS (FSL, University of Oxford), based on a GLM framework, with cluster-free enhancement, yielding voxelwise probability estimates adjusted by controlling the family-wise error rate.

A single-sided T-test was used to detect neuro-degeneration (FA reductions and MD increases for patients compared to controls), separately for each patient group, using age and sex as covariates. Voxels showing a difference at $p<0.05$ after correction were deemed to be significantly altered. For both patient groups, subject age was used to perform a regression analysis. In addition, a regression on control subject age was performed as a baseline check. We also included data on idebenone therapy as a further regressor, although idebenone dosage (and duration of therapy) was variable between subjects.

Results Both *OPA1*-DOA and LHON patients showed significant increases in white matter MD and decreases in FA compared with controls. For both patient groups, FA was more severely affected in almost all areas. The number of voxels with a significant difference in terms of diffusivity parameters was considerably higher in *OPA1*-DOA patients than in LHON patients (30.3% of WM skeleton vs 5.5% for FA; 29.2% vs 0.5% for MD). Furthermore, in the LHON patients, half of these voxels were within the optic radiation with the remainder in other white matter areas, of which the acoustic radiation was the most consistent, bilaterally, but also superior corona radiata, superior longitudinal fasciculus and medial corpus callosum only on the right side (Figure 1A).

The results were consistently different in *OPA1*-DOA patients where only a fifth of the voxels affected belonged to the optic radiation, while the majority were distributed evenly throughout the whole white matter including several areas not affected in LHON patients and involving almost all bundles within the supratentorial and infratentorial compartments (Figure 1B).

Exploratory regression analyses revealed a highly significant reduction in FA with age in *OPA1*-DOA patients, in almost al l areas considered. The regression of FA on subject age for both the control group and the LHON patients was negative, strengthening the likelihood that the positive finding for *OPA1*-DOA patients was group specific.

Considering LHON patients the only significant regression analysis was for idebenone therapy showing that the patients taking idebenone had lower MD values compared to controls within the anterior cingulum, genu of corpus callosum, olfactory tracts bilaterally, and in the left prefrontal white matter compared with untreated patients. An effect of therapy was not observed in the *OPA1*-DOA patients.
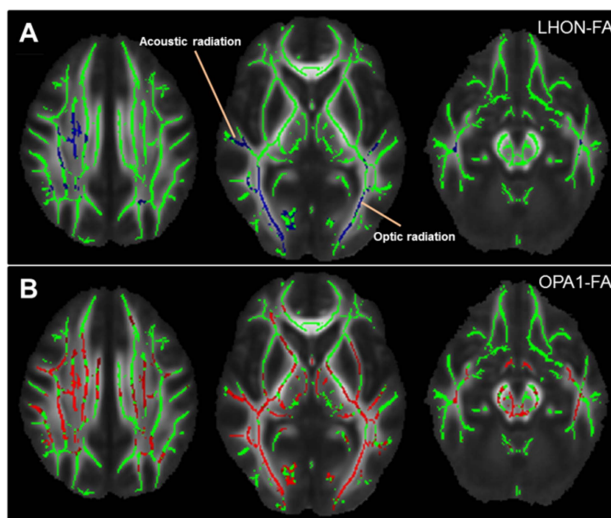

Fig. 1: Representative axial slices showing areas for which FA was significantly reduced in patient groups (corrected p < 0.05) on the TBSS skeleton (green) projected onto the mean FA map. (A) LHON FA < control FA (blue) (B) OPA1-DOA FA < control FA (red)

Discussion and Conclusions LHON patients presented a preferential involvement of the optic radiations and of the acoustic radiations detected by DTI possibly due to trans-synaptic degeneration, with a protective effect of idebenone therapy. *OPA1*-DOA patients presented a widespread involvement of white matter, detected by DTI, supporting the view of a multi-systemic disorder.[3] The correlation between diffusivity abnormalities and the age of these patients also supports the hypothesis of a congenital and developmental disorder.

References
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