REGIONAL PATTERNS OF BRAIN GRAY AND WHITE MATTER ABNORMALITIES IN PATIENTS WITH HEREDITARY OPTIC NEUROPATHIES: DOMINANT OPTIC ATROHPY *VS* LEBER HEREDITARY OPTIC NEUROPAHTY

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INTRODUCTION

- Dominant optic atrophy (DOA) and Leber's hereditary optic neuropathy (LHON) are the two most common hereditary optic neuropathies.[1,2]
- Clinical manifestations:
  - DOA: slowly progressive, painless, bilateral visual loss;
  - LHON: rapid, bilateral and severe loss of central vision.
- Genetic background:
  - DOA: OPA1 gene mutations;
  - LHON: mitochondrial DNA mutations.
- Anterior visual pathways involvement:
  DOA and LHON: damage of the retinal ganglion cells (RGCs) and their axons in the optic nerve.
- CNS involvement:
  - DOA: atrophy of the anterior optic pathway and distributed brain white matter (WM) microstructural abnormalities;[3,4]
  - LHON: selective atrophy along the entire visual pathways, from the optic nerve to the primary visual cortex.[4,5,6]

OBJECTIVE

The aim of our study was to apply voxel-wise methods to compare the regional patterns of gray matter (GM) and WM abnormalities between patients with DOA and LHON and assess the correlations between GM/WM abnormalities and patients' disease duration and neuro-ophthalmologic variables.

METHODS

Subjects

We studied 19 patients with DOA, 16 patients with LHON and 20 healthy controls (HC).

Table 1 summarizes the main demographic and clinical characteristics of the study groups.

Table 1.	Controls	DOA patients	LHON patients	DOA *vs* controls	LHON *vs* controls	DOA *vs* LHON
No. of subjects	20	19	16			
Women/Men	10/10	10/9	13/3	0.8	0.05*	0.04*
Mean age (range) [years]	40 (24-59)	43 (22-64)	35 (20-60)	0.4	0.2	0.04**
Mean disease duration (range) [years]	-	26 (2-55)	7 (1-33)	-	-	<0.001**

* Fisher exact test
** Mann-Whitney U tests

Neuro-ophthalmologic examination

- LogMar visual acuity (VA) assessment;
- Standardized Automated Perimetry: Humphrey Mean Deviation measurement;
- Optical coherence tomography: average peripapillary and temporal quadrant Retinal Nerve Fiber Layer (RNFL) measurements.

Neurologic examination

Brain MRI acquisition (3.0 Tesla Philips Intera scanner): axial FLAIR, T2-weighted TSE, 3D T1-weighted FFE and DT MR sequences.

MRI analysis

- Brain WM lesions were identified and T2 lesion volumes (LV) quantified using a local thresholding segmentation technique (Jim 6.0).
- FLAIR scans were used to increase confidence in lesion identification.
- On 3D T1-weighted images, volumetric scaling factors (Vscal) were derived using the SIENAx software.

Voxel-Based Morphometry analysis (SPM12, DARTEL)

Segmentation in WM and GM. Normalization to the GM population templates. Jacobian modulation. Smoothing: 8-mm FWHM isotropic Gaussian kernel. Normalization to MNI space.[7]

Diffusion tensor (DT) MRI analysis

- Corrections for eddy currents, estimation of DT, creation of fractional anisotropy (FA) and mean diffusivity (MD) maps.
- TBSS analysis (FTD tool): individual FA images were non-linearly registered to the FMRIB58-FA atlas; thinning of the resulting mean FA image to create a WM tract "skeleton"; individual subject FA maps were warped onto this group skeleton for statistical comparisons by searching perpendicular from the skeleton for maximum FA values; similar approach for the MD, axial (AD) and radial diffusivity (RD).[8]

Between-group comparisons

- **Differences in demographic and clinical variables** (SPSS):
  T-test, Kruskall-Wallis test, Mann-Whitney test and Fisher exact test.
- **Differences of GM and WM volumes** (SPM8) ($p<0.001$ uncorrected):
  Two-sample t test and ANOVA test (adjusted for Vscal, age and sex).
- **Voxel-wise differences of DT MRI metrics (FA, MD, AD, RD)** (FDT tool) (Threshold Free Cluster Enhancement $p<0.05$): permutation method (5000 permutations, randomised program within FSL) and two-sample t tests (adjusted for age and sex).

Correlation analysis (SPM8, FTD tool): linear regression analysis (Threshold Free Cluster Enhancement $p<0.05$ and $p<0.001$ uncorrected).

RESULTS

Neurologic examination

- Normal in all subjects.
- None of the patients had extraocular neurological complications.

Table 2 summarizes the main neuro-ophthalmologic findings of DOA and LHON patients.

Table 2.			DOA patients	LHON patients	p value
Mean VA	Mean LogMAR VA (range)		0.59 (0.2)	0.81 (0.2)	0.5
	No. of affected eyes with ↓ values		32 (84%)	28 (87%)	-
SAP	Average Mean Deviation (range) [dB]		-6.5 (-30.8, -0.98)	-13.6 (-32.9, -2.03)	0.02*
OCT	**Average RNFL thickness**	Mean values (range) [μm]	69.8 (53-88)	61.9 (36-92)	0.2
		No. of affected eyes with ↓ values	35 (92%)	32 (100%)	-
	Temporal RNFL thickness	Mean values (range) [μm]	44.7 (31-81)	43.6 (28-68)	0.8
		No. of affected eyes with ↓ values	36 (95%)	32 (100%)	-

MRI analysis

- Non-specific brain focal T2-hyperintense lesions:
  - 5 (31%) LHON patients (mean T2 LV=0.1 ml, SD=0.3) (**Figure 1A**);
  - 10 (53%) DOA patients (mean T2 LV=0.7 ml, SD=1.8) (p=0.2) (**Figure 1B**).
- One DOA patient had focal lesions along the optic radiations (ORs) (**Figure 1B**).
- One DOA patient had diffuse hyperintensities along the Ors (**Figure 1B**).

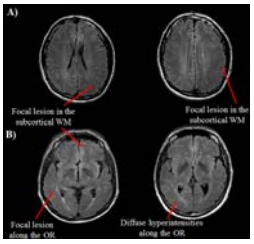

Figure 1. WM abnormalities in LHON (A) and DOA (B) patients.

Voxel-Based Morphometry analysis

Analysis of regional WM volumes

- LHON and DOA patients *vs* controls: compared to controls, LHON and DOA patients had significant WM atrophy of the chiasm and optic tracts (**Figure 2A**).
- LHON *vs* DOA patients and controls: compared to controls and DOA patients, LHON patients had significant WM atrophy of the left optic radiation (**Figure 2B**).

Analysis of regional GM volumes

- LHON patients *vs* controls: compared to controls, LHON patients had significant GM atrophy of the left primary visual cortex (**Figure 3**).
- DOA patients *vs* controls and DOA patients *vs* LHON patients: no significant GM volume differences were found between DOA patients and controls and between DOA and LHON patients.

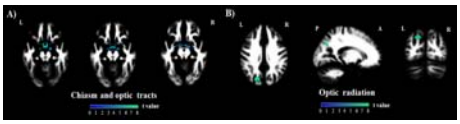

Figure 2. WM volume differences between LHON and DOA patients *vs* controls (A) and between LHON patients *vs* DOA patients and controls (B). Regions of decreased WM volume are shown according to a blue-green scale.

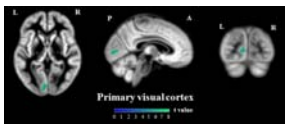

Figure 3. GM volume differences between LHON patients *vs* controls. Regions of decreased GM volume are shown according to a blue-green scale.

DT MRI analysis

- LHON patients *vs* controls: compared to controls, LHON patients had significantly decreased FA, increased MD and RD in the WM of the bilateral optic radiation (**Figure 4A**).
- DOA patients *vs* LHON patients and controls: compared to LHON patients (**Figure 4B**) and controls (**Figure 4C**), DOA patients had significantly decreased MD, AD and RD in the WM of the cerebellum, brainstem, thalamus and fronto-occipital-temporal lobes.

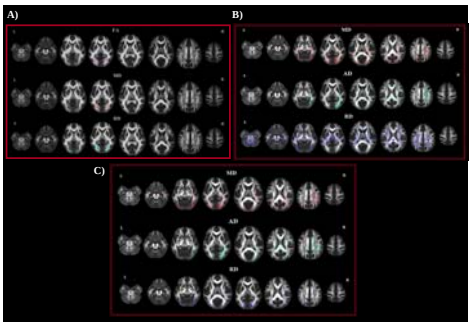

Figure 4. WM microstructural abnormalities between LHON patients *vs* controls (A), DOA patients *vs* controls (B) and DOA *vs* LHON patients (C). Areas of significantly decreased WM FA (purple), MD (orange), RD (turquoise) and areas of increased WM MD (red), AD (green) and RD (blue).

Correlation analysis

No significant correlation was found between WM/GM abnormalities and DOA/LHON patients' clinical (disease duration) and neuro-ophthalmologic variables (VA, mean deviation, average and temporal RNFL measurements).

CONCLUSIONS

- Both LHON and DOA patients had an involvement of the anterior visual pathways, possibly due to Wallerian and trans-synaptic degeneration phenomena, which in turn are a consequence of a primary degeneration of the RGCs.
- In LHON patients, structural damage extends selectively to the posterior optic pathways with a sparing of other brain regions.
- In DOA patients, tissue damage did not spread to the ORs and visual cortex. Conversely, a pattern of diffuse cerebral and cerebellar WM microstructural abnormalities was found in these patients.
- All of this suggests that different molecular defects and genetic inheritance might lead to different patterns of regional structural brain abnormalities in patients with hereditary optic neuropathies.

REFERENCES

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