Optic neuritis drives bidirectional trans-synaptic axonal degeneration in multiple sclerosis

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Background. Analysis of the optic pathway may help to clarify the mechanisms involved in grey matter damage in MS. We investigated the relationship between white matter inflammation and neurodegeneration to achieve evidence of trans-synaptic degeneration in the optic pathway in MS at clinical onset. To overcome the effect induced by optic neuritis (ON) in the optic pathway, by disease duration and by concomitant medications, we focused on patients with no history of ON.

Objective. We studied whether white and grey matter inflammatory pathology could determine trans-synaptic degeneration even at clinical onset and in absence of iptic neuritis.

Materials an Methods. MS 3T MRI scans consisted in the following sequences: 3D-T1, 3D- Fluid Attenuated Inversion Recovery (3D-FLAIR), 3D-Double Inversion recovery (3D-DIR). Visual (V1, V2, V3, V4 and V5) cortical thickness (TH) and volume were analyzed on T1-3D sequences by means of ANTs; furthermore, lateral geniculate body (LGB) volume was calculated. 3D-DIR sequences allowed the measurement of cortical lesions volume (i.e. Grey Matter Lesion Volume, GMLV) and percentage (GMLV in a specific visual area/ grey matte volume of the specific visual area) in each visual cortical area. The Optic radiation white matter lesion volume (WMLV), also expressed by percentage (optic radiation WLMV/optic radiation volume), was evaluated on 3D-FLAIR sequences. The MRI methods are summarized in Figure 1. Global peripapillary retinal nerve fiber layer (g-RNFL) TH, the 6 RNFL-sectors (TI, T, TS, NS, N and NI) THs, the Macular (foveal, inner ring, outer ring) Volumes and THs were analysed by optic coherence tomography (OCT). OCT parameters were obtained also in a cohort of Healthy Control (HC).

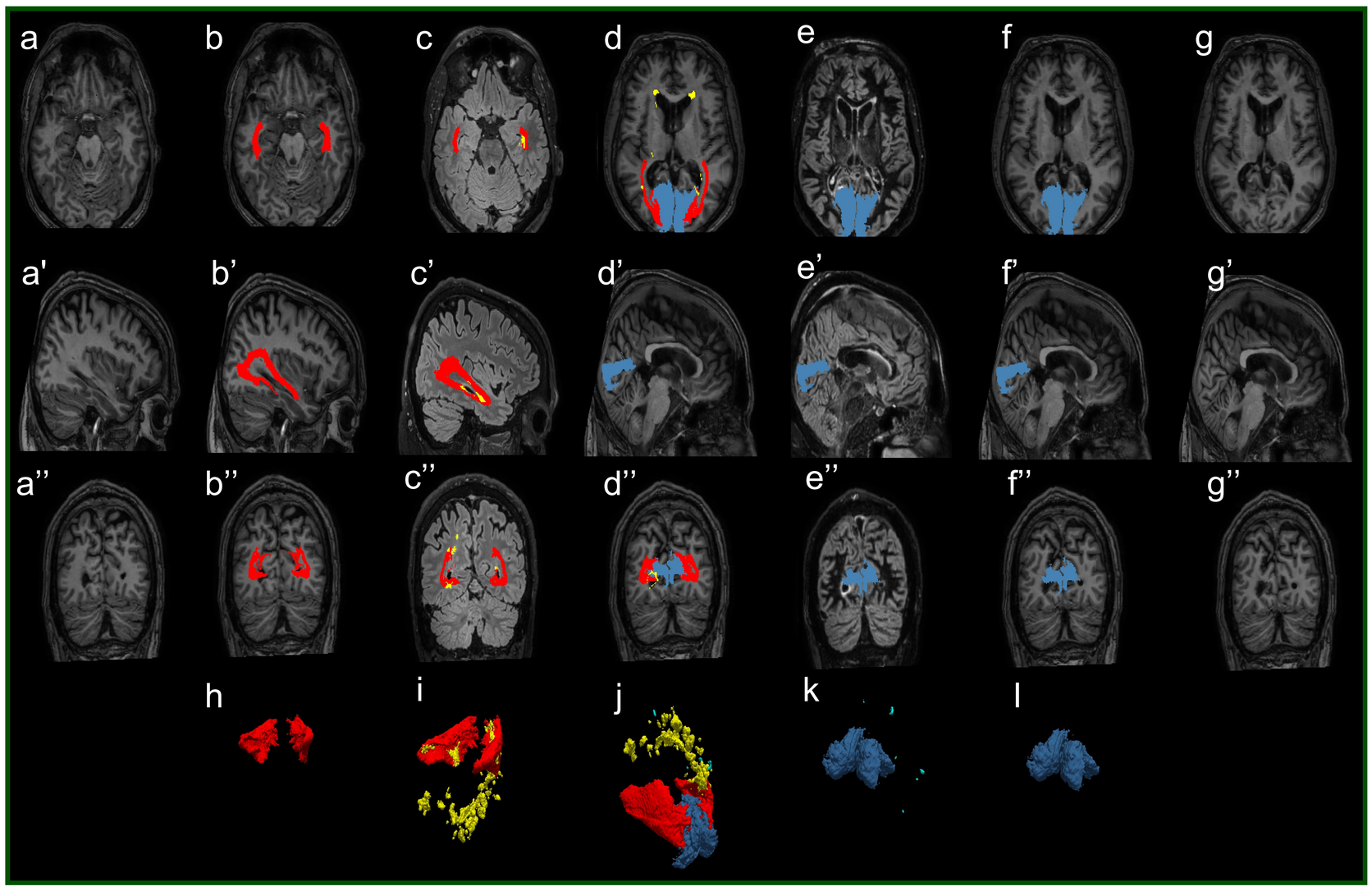

Figure 1. T1-3D (Figure a, a', a'', g, g', g'') images were recorded by the software fsl within the space NMI in order to reconstruct three-dimensionally , applying the Jülich probabilistic atlas, both the optical radiation (threshold: 0.20, Figure h) and the visula cortex (V1 is shown in l). The volume of interest (VOI) corresponding to the areas of white matter demyelination were selected through the program mricron by a team of neurologists using MRI 3D-FLAIR sequences (Figure c) for white matter lesions and MRI 3D-DIR sequences for cortical lesions (Figure e). These volumes were calculated by counting the voxels in each VOI and have been converted to mm^3. Finally, white matter lesion volume whitine the optic radiation (i) and cortical lesion volume within each Visual Area (V1 in k) were calculated by the software by merging the 3D reconstruction of optical radiation or Visual Areas with the VOI (Figure j).

3. Correlation analysis. No correlation between visual cortical areas (V1, V2, V3, V4 and V5) thickness or volume and white (optic radiation WMLV and WMLV%) and grey matter (GMLV in V1, V2, V3, V4 and V5, expressed also as percentage) focal inflammation was observed. LGB volume did not correlate with any white matter or grey matter inflammatory parameters. Only a mild correlation between LGB and ipsilateral T-RNFL was found (r:0.3, $p<0.001$). No correlation between retinal and white or grey matter parameters were detected. Multivariate analysis failed to explain any RNFL or Macular thickness values based on MRI parameters; moreover, Visual Cortex Thickness was not explained by any MRI or OCT parameters.

Results.

1. Study Population. 56 clinically isolated syndromes/early relapse-onset MS with a mean disease duration of 4.0±3.5 months and 31 HC were enrolled in the studied. No difference for age (p=0.7) or gender (p=0.5) was observed within the two groups.

2. OCT parameters in healthy control and MS patients. No difference was disclosed within the two groups for any OCT parameter considered. Table 1 summarized mean values and standard deviation in the two groups.

	HC	CIS/eRRMS
Temporal Inferior-RNFL	148.9 ± 20.1	149.1 ± 19.6
Temporal-RNFL	72.2 ± 9.5	70.6 ± 12.6
Temporal Superior-RNFL	138.2 ± 14.5	137.3 ± 19.3
Nasal inferior-RNFL	112.9 ± 23.5	116.0 ± 26.9
Nasal-RNFL	72.1 ± 13.5	75.1 ± 15.3
Nasal Superior-RNFL	109.0 ± 16.9	111.4 ± 21.3
Foveal Volume	0.2 ± 0.0	0.2 ± 0.0
Foveal thickness	270.1 ± 22.3	270.1 ± 19.3
Inner Ring Volume	2.1 ± 0.1	2.1 ± 0.1
Inner Ring Thickness	341.1 ± 11.6	341.5 ± 15.3
External Ring Volume	6.3 ± 0.2	6.4 ± 0.3
External Ring Thickness	295.4 ± 15.4	300.0 ± 13.7
Macular Volume	8.4 ± 0.3	8.5 ± 0.4
Macular Thickness	298.3 ± 10.3	301.0 ± 13.3

Table 1 OCT paramaeters in healthy control (HC) and CIS/eRRMS patients. No difference was observed within tjhese two groups

Conclusions. No evidence of trans-synaptic degeneration was found at clinical onset in the optic pathway of MS patients having no history of ON. In these patients trans-synaptic degeneration may occur in later disease phases.

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