Retrograde retinal damage after acute optic tract lesion in MS

The anterior visual pathway is frequently affected in multiple sclerosis (MS), but how axonal damage extends from the site of the lesion to neuronal bodies in the retina or lateral geniculate nucleus is poorly understood. Thanks to optical coherence tomography (OCT), it is possible to map and quantify the retrograde diffusion of axonal damage to the retina.[1] Lesions in the anterior optic pathway promote significant atrophy of retinal nerve fibre layer (RNFL), which develops in the first 3 months after damage and remains stable after 3 months. Moreover, it has been recently demonstrated that retinal damage in MS is complex and may distinctly affect retinal layers, combining either layer thinning (suggesting the presence of synapse loss and neuronal loss) or layer thickening (suggesting the presence of oedema and inflammation). In fact, the analysis of the ganglion cell/inner plexiform layer (ganglion cell layer (GCL) +inner plexiform layer complex (IPL)) and inner nuclear layer (INL) better correlates with functional disability and prognosis than with RNFL atrophy.[2] Acute focal lesions of the optic tracts are infrequently recognised in MS, and they constitute an excellent opportunity to study retrograde axonal degeneration. Previous studies with OCT have shown the homonymous hemimacular atrophy ipsilateral to the optic tract lesion as a specific pattern of retinal atrophy in optic tract lesions,[3] with a preferential impact on the GCL.[4]

METHODS

A patient with relapsing–remitting MS presented with non-painful, new onset, acute bilateral visual deficit. Automated visual field tests demonstrated non-congruent bilateral homonymous right hemianopsia (figure 1A). Visual acuity (Snellen chart) and colour test (Hardy Rand and Rittler plates) were normal. 3T brain MRI showed a new 10-mm lesion on fluid attenuated inversion recovery in the area corresponding to the left optic tract that showed gadolinium enhancement (figure 1B). She was treated with intravenous methylprednisolone. Before starting the prospective evaluation, we obtained written informed consent from the patient.

We performed OCT (Spectralis, Heidelberg Engineering) for each eye with macular raster scan centred on the fovea (matrix size 20°×20°, 25 sections of 240 µm; 6-mm ring area was used to calculate sector retinal thickness). Central 1-mm diameter area corresponding to the fovea was excluded to facilitate the calculation of average measurements at baseline, 5th and 10th month after onset. Retinal layers were automatically segmented by the in-built software of the equipment (Spectralis Viewer software, V.5.7, with Segmentation Editor (β version)) and manually corrected by a trained neurologist (IG). GCL and IPL layers were considered as a single complex (GCL+IPL) as

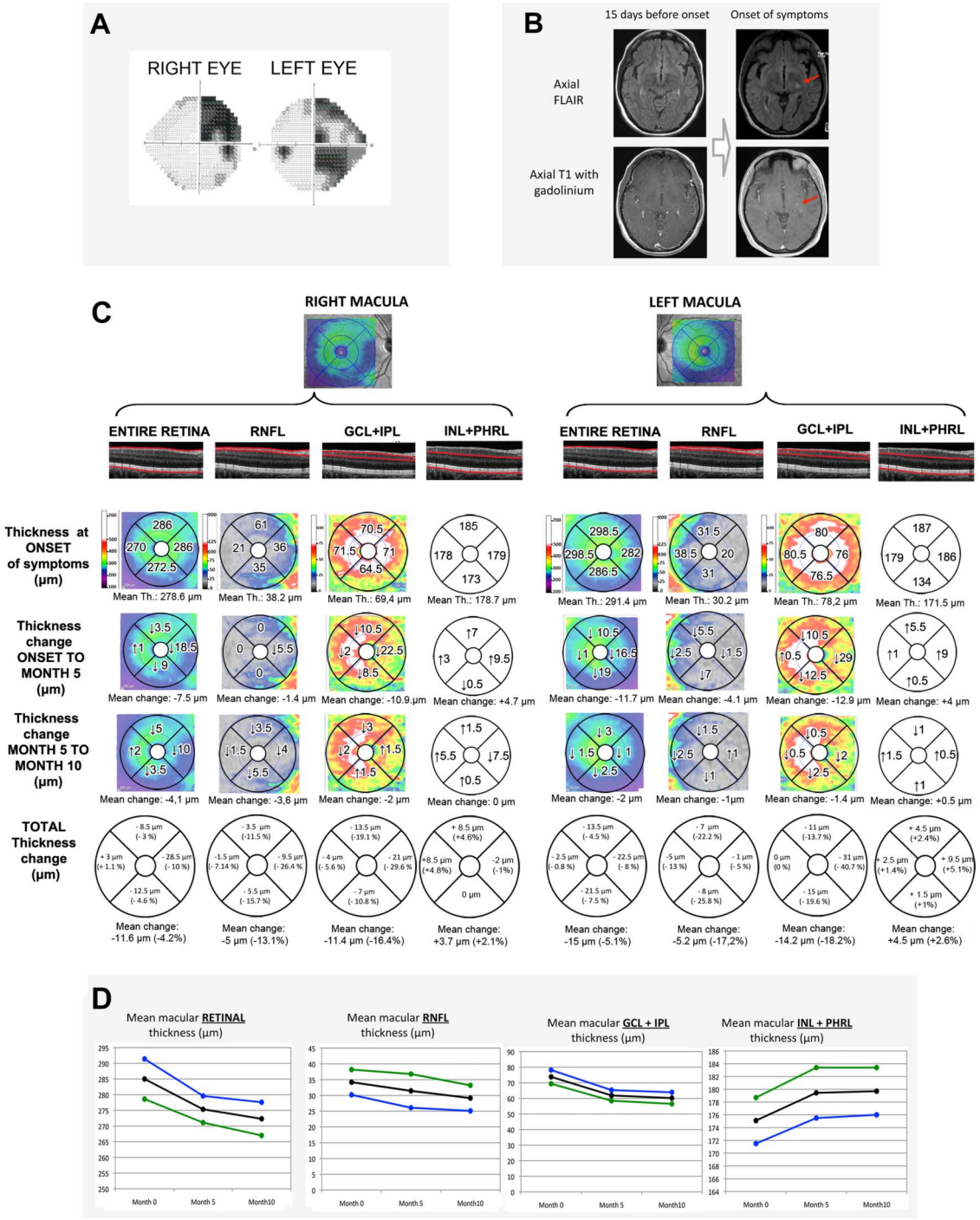

Figure 1 (A) Automated visual field analysis showing the characteristic non-congruent right homonymous hemianopsia; (B) brain MRI showing a focal lesion around left optic tract on axial FLAIR and axial T1 with gadolinium; (C) optical coherence tomography measures for retinal layers in every macular sector of each eye at relapse onset, by 5th and 10th month. Numbers within macular grids represent thicknesses at baseline (first grid row) and in-between period changes (rest of grid rows). Colour scales represent topographical distribution of thicknesses for layers; (D) temporal evolution of retinal thickness over 10 months for the entire retina, RNFL, GCL+IPL and INL+PHRL. Mean measurements of the right eye are represented by green lines, the left eye by blue lines and the mean of both by black lines. GCL+IPL, ganglion cell layer+inner plexiform layer complex; INL+PHRL, inner nuclear layer+photoreceptor layer complex; RNFL, retinal nerve fibre layer.

described by Saidha *et al*.[2] The thicknesses of RNFL, GCL+IPL and the entire retina were measured for every macular sector of each eye. INL, layers accounting for photoreceptors (PHRP), pigment epithelium and Bruch's membrane were considered as a single complex (INL+PHRP), the thickness of which was calculated by subtracting the RNFL and GCL+IPL thicknesses from the retinal thickness.

RESULTS

At 10-month follow-up, we observed a mean reduction of 4.7% (13.3 µm) in bilateral mean macular thickness: 4.7% (11.6 µm) in the right eye (contralateral to optic tract lesion) and 5.2% (15 µm) in the left eye (ipsilateral to the lesion) (figure 1C and online supplementary figure S1). This atrophy reproduced the specific pattern observed in optic tract

lesions with homonymous hemimacular atrophy that was congruent with the left optic tract lesion. This atrophy was mainly due to GCL+IPL thinning (13.6 µm reduction (18.4%) in bilateral average thickness compared to baseline) with the same homonymous hemimacular pattern seen for the entire retina. RNFL atrophy (5.05 µm reduction bilaterally (14.8%) compared to baseline) was more severe in the nasal sector of the right macula (26.4% reduction compared to baseline) and in the inferior and superior sectors of the left macula (25.8% and 22.2%, respectively, compared to baseline). We observed that most of the macular atrophy (9.6 µm, 75.6% of total thinning) happened during the first 5 months (figure 1D). Interestingly, while most of the GCL+IPL atrophy (11.9 µm, 87.5% of total thinning) happened in the first 5 months, RNFL atrophy developed more slowly and progressively along 10 months (54.4% of the reduction happened in the first 5 months). In addition, we found an increase in the INL+PHRL thickness (4.3 µm (2.5%) reduction in bilateral average thickness compared to baseline) in the first 5 months that remained stable until month 10. This increase was particularly notable in the temporal sectors, with a mean thickening of 9 µm (4.9%) after 10 months. No microcystic macular oedema was observed in the INL or PHRL at any time.

DISCUSSION

This case illustrates that axonal damage due to optic tract lesion may extend in a retrograde manner to the retina with different dynamics and effects into the different retinal layers. The fact that most of the thinning of GCL+IPL happens in the first months when RNFL atrophy extends longer suggests that functional axonal abnormalities may influence neuronal survival even before axons are definitively lost in the RNFL. If true, this clearly indicates that early monitoring of ganglion cell loss would be relevant to evaluate dynamics of neuronal damage. Finally, we observed a thickening of macular INL+PHRL layers that would be, especially for temporal sectors, above the expected axial resolution (3.9 µm) and test–retest variability of total macular thickness segmentation (1 µm) of our equipment.[5] This finding may suggest the presence of pathological abnormalities like oedema or inflammation in these layers, a phenomenon that could constitute the response of glial cells to axonal and neuronal loss in the neighbouring layers. These results would require further validation.

Iñigo Gabilondo,[1] María Sepúlveda,[1] Santiago Ortiz-Perez,[1,2] Elena Fraga-Pumar,[1] Elena H Martínez-Lapiscina,[1] Sara Llufriu,[1] Nuria Solá,[1] Albert Saiz,[1] Bernardo Sanchez-Dalmau,[1,2] Pablo Villoslada[1]

[1]Department of Neurology, Center of Neuroimmunology, Institute of Biomedical Research August Pi i Sunyer (IDIBAPS), Hospital Clinic of Barcelona, Barcelona, Spain
[2]Department of Ophthalmology, Hospital Clinic of Barcelona, Barcelona, Spain

Correspondence to Dr Pablo Villoslada, Department of Neurology, Hospital Clinic of Barcelona, Villarroel 170, Barcelona 08036, Spain; pvilloslada@clinic.ub.es

Contributors IG, EFP and SOP performed OCT studies and analysis; MS, SL, NS and AS performed patient evaluation; PV and BSD reviewed data and wrote the manuscript.

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Competing interests Iñigo Gabilondo has received travel and accommodation expenses from Novartis for national and international congresses. Maria Sepulveda has no conflicts of interest to disclose. Santiago Ortiz-Pérez has received consultancy fees from Novartis. Elena Martínez-Lapiscina has received travel and accommodation expenses from Novartis, Biogen, Teva, Sanofi Aventis, Lundbeck and Bayer for national and international congresses. Elena Fraga-Pumar, Sara Ilufriu and Nuria Sola have no conflicts of interest to disclose. Albert Saiz has received remuneration for consulting services and for giving lectures from Bayer-Schering, Merck-Serono, Biogen-Idec, Sanofi-Aventis, Teva Pharmaceutical Industries and Novartis. Bernardo Sanchez-Dalmau has received travel and accommodation expenses from Novartis for national and international congresses. PV has received consultancy fees from Roche, Novartis, MedImmune, TFS, Heidelberg Engineering, Digna Biotech and Neurotec Farma and research grants from Novartis and Roche and is founder and hold stocks in Bionure Farma.

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