Retinal periphlebitis is associated with multiple sclerosis severity

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ABSTRACT

Objectives: To assess the association of primary retinal inflammation, namely retinal periphlebitis (RP) and microcystic macular edema, with clinical, brain, and retinal imaging biomarkers of multiple sclerosis (MS) severity.

Methods: One hundred patients with MS underwent a neurologic and ophthalmic examination, MRI, and optical coherence tomography. Disability was assessed using the Expanded Disability Status Scale at baseline and after a 1-year follow-up. The normalized brain volume, the normal-appearing gray matter volume, and T1 lesion volume were assessed at baseline as radiologic biomarkers of disease severity. Retinal nerve fiber layer thickness and macular volume at baseline were used as surrogate markers of axonal damage. We used general linear models adjusted for sex, age, disease duration, and MS treatment to compared adjusted means of these parameters among patients with RP and patients without primary retinal inflammation.

Results: Five patients showed RP, 2 showed microcystic macular edema, and the retina was normal in the remaining 93. Patients with RP had a tendency toward a higher adjusted-mean Expanded Disability Status Scale score at baseline and disability progression after a 1-year follow-up compared with patients without primary retinal inflammation. These patients also had a higher adjusted-mean T1 lesion volume (adjusted differences: 10.4, 95% confidence interval [CI]: 0.6 to 20.2; $p = 0.038$) and lower T1 brain volume (adjusted differences: −68, 95% CI: −139 to 2; $p = 0.059$). Patients with RP had a lower adjusted-mean retinal nerve fiber layer thickness (adjusted differences: −13.4, 95% CI: −24.4 to −2.3; $p = 0.018$) and a trend toward lower macular volume.

Conclusions: These results support the role of RP as a biomarker of MS severity. ***Neurology***® **2013;81:877-881**

GLOSSARY

CI = confidence interval; **EDSS** = Expanded Disability Status Scale; **MME** = microcystic macular edema; **MS** = multiple sclerosis; **MV** = macular volume; **OCT** = optical coherence tomography; **ON** = optic neuritis; **RNFL** = retinal nerve fiber layer; **RP** = retinal periphlebitis.

Multiple sclerosis (MS) causes axonal degeneration, determining disease severity. Retinal periphlebitis (RP) is a vasculitis that affects the peripheral retina in approximately 10% of patients with MS. The presence of RP is associated with a higher disease activity in relapses and gadolinium-enhancing lesions.[1] Additionally, optical coherence tomography (OCT) has identified retinal nerve fiber layer (RNFL) atrophy and a decreased macular volume (MV) as axonal damage markers in MS.[2–4] Moreover, OCT enabled identification of microcystic macular edema (MME) in 0.5% to 5% of patients with MS and it seems to be associated with MS activity or previous optic neuritis (ON).[2] In this study, we assessed the association between primary retinal inflammation (RP and MME) and clinical (Expanded Disability Status Scale [EDSS]) and imaging (brain and retinal) biomarkers of disease severity to evaluate their suitability as biomarkers in MS.

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METHODS **Standard protocol approval and patient consent.** The Research Ethics Committee approved the study and all participants provided their written informed consent.

Study design. The MS-VisualPath cohort is an ongoing cohort of patients with MS (aged 18–55 years) conducted at the Hospital Clinic of Barcelona. The recruitment started in December 2010 and it is permanently opened. Patients with psychiatric or other neurologic diseases or any ocular disease/treatment/surgery were excluded. Patients were excluded if they had ON in the 6 months before inclusion. At baseline and yearly thereafter, patients undergo a complete neurologic and ophthalmologic examination including OCT and MRI.

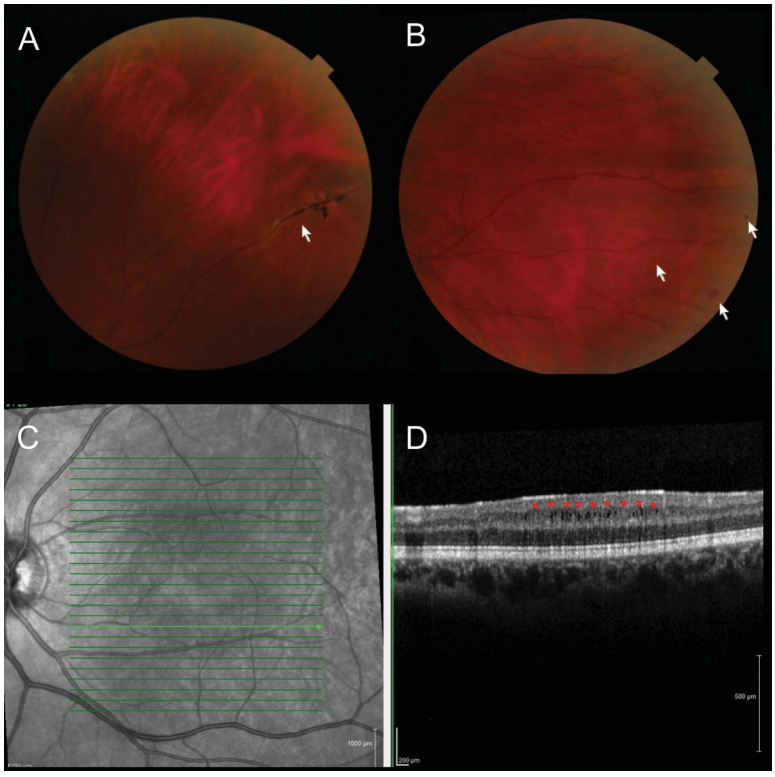
Clinical assessment. We collected demographic (sex and age) and MS-related variables (onset and diagnosis date, disease type and duration, ON history, MS treatment, and disability assessed by EDSS). The presence of prior ON was assessed in the subjects' medical history and confirmed by careful ophthalmologic assessment, MRI of the optic nerve (T2 sequence), and/or by identifying abnormal (a mean plus 1 SD of the interocular asymmetry of registered ON cases) asymmetry in the RNFL by OCT and in the mean deviation of the visual field. We measured high- and low-contrast monocular visual acuity using ETDRS (Early Treatment Diabetic Retinopathy Study) charts. Color vision was tested using Hardy-Rand-Ritter pseudoisochromatic plates, as previously described.[5] A full ophthalmic examination, including pupil dilation with tropicamide 1%, was also performed.

Optical coherence tomography. Spectral domain retinal OCT (Spectralis; Heidelberg Engineering, Carlsbad, CA) was performed as previously described.[5] RNFL and MV were considered as mean value of both eyes except for patients with an ON history in whom only the fellow eye's value was considered.

Magnetic resonance imaging. MRI study was performed using a 3T scanner (Trim Trio; Siemens, Malvern, PA). We obtained a 3-dimensional structural T1 magnetization-prepared rapid-acquisition gradient echo sequence. T1 lesion masks were manually created from T1 scans using ITK-SNAP software. Brain tissue volume, normalized for patient's head size, was evaluated with SIENAX, which was fully automated once the T1 lesion mask had been used to avoid pixel misclassification. This FSL (FMRIB Software Library) tool has been previously used for assessing brain atrophy in MS using T1 images.[6,7] Rather than T2-weighted images, T1-weighted images were used for lesion segmentation as they represent more accurately axonal damage,[8] and recent studies demonstrated increased sensitivity of T1 magnetization-prepared rapid-acquisition gradient echo to detect white matter lesions.[9]

Statistical analysis. The study hypothesis was that primary retinal inflammation was associated with MS severity. Therefore, we compared the unadjusted means of clinical (EDSS score at baseline and after 12 months), MRI (lesion volume and brain volumes), and OCT (RNFL and MV) variables among patients with and without primary retinal inflammation with independent 2-sample *t* test. Then, the multivariable-adjusted means of these parameters and the differences among patients with RP and patients without primary retinal inflammation, were estimated using general linear models adjusting for sex, age at study, MS disease duration, and use of MS treatments. All *p* values were 2-tailed at the <0.05 level. Statistical analyses were performed with SPSS version 17.0 software (SPSS Inc., Chicago, IL).

Figure **Primary retinal inflammation in patients with multiple sclerosis**



(A, B) Retinal periphlebitis (RP). (C, D) Microcystic macular edema (MME). (A) Note the white sheathing around the vessel next to the dark pigment changes probably due to earlier inflammation of the same vessel (white arrow). (B) Active RP in another patient reflected by several small and subtle round hemorrhages (white arrows) in the peripheral retina. (C) Infrared imaging of the retina with corresponding Spectralis optical coherence tomography cross-sectional image in D (at the level of the highlighted green line). (D) MME is seen as small, round, and empty spaces in the inner nuclear layer: the red stars indicate the inner plexiform–retinal ganglion cell complex just above the cysts.

RESULTS Of the 100 patients with MS analyzed, 5 patients showed RP, 2 MME, and the retina was normal in the remaining 93 (figure). Four of the patients with RP had a history of ON (2 in the eye affected with RP and the other 2 in the fellow eye). Both patients with MME had a history of acute ON (one in the same eye affected with the edema and the other in both eyes). No patient had uveitis in the past.

Patients with primary retinal inflammation (71.4% women, aged 41.80 ± 5.86 years) had a mean MS duration of 15.94 ± 11.55 years, and 85.7% of patients received a disease-modifying treatment. Patients without primary retinal inflammation (68.8% women, aged 41.32 ± 9.78 years) had a mean MS duration of 8.51 ± 7.37 years, and 76.3% received a disease-modifying treatment (nonsignificant).

The unadjusted means of clinical, MRI, and OCT variables are shown in table 1. The differences

Table 1 Comparison of the unadjusted means of clinical and imaging markers of MS severity among MS patients with and without primary retinal inflammation[a]

	Retinopathy (n = 7)		No retinopathy (n = 93)	p Value
EDSS baseline	2.43 ± 1.13		1.83 ± 1.16	0.190
Median (range)	2.0 (1.5–4)		1.5 (0–7)	
	RP (n = 5)	MME (n = 2)		
	2.70 ± 1.25	1.75 ± 1.35		
EDSS progression after 1 y[b]	0.21 ± 0.57		0.13 ± 0.44	0.434
	RP (n = 5)	MME (n = 2)		
	0.30 ± 0.67	0		
T1 lesion volume, cm^3	19.3 ± 16.2		9.9 ± 10.6	0.033
	RP (n = 5)	MME (n = 2)		
	22.8 ± 18	10.6 ± 8.6		
T1 total brain volume, cm^3	1,469 ± 130		1,536 ± 94	0.081
	RP (n = 5)	MME (n = 2)		
	1,434 ± 142	1,555 ± 20		
T1 gray matter volume, cm^3	804 ± 56		774 ± 65	0.188
	RP (n = 5)	MME (n = 2)		
	756 ± 66	819 ± 44		
Average RNFL, μm	77.71 ± 13.70		93.27 ± 12.60	0.002
	RP (n = 5)	MME (n = 2)		
	76.0 ± 16.1	82.0 ± 5.6		
Macular volume, mm^3	8.53 ± 0.40		8.33 ± 0.40	0.216
	RP (n = 5)	MME (n = 2)		
	8.31 ± 0.49	8.37 ± 0.15		

Abbreviations: EDSS = Expanded Disability Status Scale; MME = microcystic macular edema; MS = multiple sclerosis; RNFL = retinal nerve fiber layer; RP = retinal periphlebitis.
[a] The results are expressed as the mean and SD.
[b] Eighty-seven patients.

between MS patients with and without primary retinal inflammation were mainly attributable to the RP group. Because we have only identified 2 patients with MME, and our study was underpowered to evaluate MME as a possible biomarker of MS severity, we performed the multivariate analyses comparing patients with RP and patients without primary retinal inflammation (table 2). Patients with MS who had RP tended toward a higher mean EDSS score at baseline and progression of the disability after 12 months. Patients with RP had a significantly higher lesion load and lower total brain volume. Although not significant, an association with gray matter deserves to be mentioned because it correlates better with disability than other volumetric metrics. These patients also had a lower RNFL thickness and a trend to lower MV.

DISCUSSION RP has been related to a more active disease.[1] Previous studies have shown that patients with stronger disease activity develop more severe disability and brain atrophy.[10] Thus, our findings support the notion that primary retinal inflammation parallels the inflammatory processes within the CNS that contribute to brain damage. Based on these studies, focal retinal inflammation may be part of the overall brain inflammatory activity.

At the clinical level, RP may become an objectively measurable biomarker of disease severity. Several disease-modifying drugs with different risk-benefit profiles are available. The presence of RP might favor the election of a more effective drug, even assuming a greater risk of side effects. Also, identification of disease-severity biomarkers is critical for assessing the efficacy of neuroprotective drugs. Additionally, RP may be a good model to improve our understanding of the role and dynamics of inflammation in MS. However, the similarities between the prototypical demyelinating lesions of

Table 2 Comparison of the adjusted means of clinical and imaging markers of MS severity among MS patients with and without retinal periphlebitis[a]

	Retinal periphlebitis (n = 5)			No retinopathy (n = 93)	
	Mean	95% CI	*p* Value	Mean	95% CI
EDSS	2.38	1.44–3.32		1.87	1.61–2.12
Adjusted difference	+0.52	−0.43 to 1.45	0.285	—	
Change in EDSS by 1 y[b]	0.34	−0.08 to −0.75		0.17	0.05–0.29
Adjusted difference	0.16	−0.25 to 0.58	0.439	—	
T1 lesion volume, cm^3	19.0	9.3–28.8		8.6	6.0–11.3
Adjusted difference	10.4	0.6–20.2	0.038	—	
T1 total brain volume, cm^3	1,481	1,410–1,552		1,550	1,530–1,569
Adjusted difference	−68	−139 to 2	0.059	—	
T1 gray matter volume, cm^3	772	733–811		806	796–817
Adjusted difference	−34	−73 to 4	0.085	—	
Average RNFL, μm	79.2	68.2–90.2		92.6	89.6–95.5
Adjusted difference	−13.4	−24.4 to −2.3	0.018	—	
Macular volume, mm^3	8.43	8.07–8.80		8.55	8.45–8.64
Adjusted difference	−0.11	−0.48 to 0.26	0.563	—	

Abbreviations: CI = confidence interval; EDSS = Expanded Disability Status Scale; MS = multiple sclerosis; RNFL = retinal nerve fiber layer.
[a] General linear models adjusted by sex, age, disease duration, and use of MS treatment.
[b] Eighty-seven patients.

the white matter and the vasculitis in nonmyelinated retina remain unclear.

Our study has several limitations. The prevalence of RP and MME is lower in our study than in previous reports.[1,2] This could be attributable to the higher frequency of disease-modifying therapies in our cohort compared with previous studies, which may have influenced the ongoing retinal inflammation. This may have limited the power to detect statistical differences of some associations. The longitudinal follow-up was limited to a subgroup of 87 patients and for a period of 1 year. It is well established from clinical trials that a follow-up of more than 2 years is required to observe significant differences in disability progression. Finally, we did not use retinal fluorescein angiography, although we have shown previously that this technique would not improve our ability to detect RP in patients.[1] Confidence in our results is strengthened by the following factors: first, the neurologic and ophthalmologic evaluations were assessed with standardized tools; and second, potential confounders were carefully recorded and controlled for in the analyses.

Our results support the role of RP as a suitable biomarker of MS severity. New prospective and multicenter studies are required to define the diagnostic accuracy of these findings as biomarkers of MS disease activity.

AUTHOR CONTRIBUTIONS

Santiago Ortiz-Pérez and Elena Martínez-Lapiscina: drafting and revision of the manuscript content, including medical content, study concept and design, statistical analysis, and interpretation of the data. Iñigo Gabilondo: drafting and revision of the manuscript content, including medical content, and analysis and interpretation of the data. Elena Fraga-Pumar: data collection, and analysis and interpretation of the data. Eloy Martínez-Heras: data collection and analysis and interpretation of the data. Albert Saiz: drafting and revision of the manuscript content, including medical content. Bernardo Sanchez-Dalmau: analysis and interpretation of the data, drafting and revision of the manuscript content, including medical content. Pablo Villoslada: drafting and revision of the manuscript content, including medical content, study concept and design, and analysis and interpretation of the data.

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DISCLOSURE

S. Ortiz-Pérez has received consultancy fees from Novartis. E. Martínez-Lapiscina has received travel and accommodation expenses from Novartis, Biogen, Teva, Sanofi-Aventis, Lundbeck, and Bayer for national and international congresses. I. Gabilondo has received travel and accommodation expenses from Novartis for national and international congresses. E. Fraga-Pumar and E. Martínez-Heras have no conflicts of interest to disclosure. A. Saiz has received remuneration for consulting services and for giving lectures from Bayer-Schering, Merck-Serono, Biogen-Idec, Sanofi-Aventis, Teva Pharmaceutical Industries Ltd., and Novartis. B. Sanchez-Dalmau has received travel and accommodation expenses from Novartis for national and international congresses. P. Villoslada has received consultancy fees from Roche, Novartis, MedImmune, TFS, Heidelberg Engineering, Digna

Biotech, and Neurotec Pharma and is a shareholder in Bionure Farma. Go to Neurology.org for full disclosures.

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REFERENCES

1. Sepulcre J, Murie-Fernandez M, Salinas-Alaman A, Garcia-Layana A, Bejarano B, Villoslada P. Diagnostic accuracy of retinal abnormalities in predicting disease activity in MS. Neurology 2007;68:1488–1494.
2. Gelfand JM, Nolan R, Schwartz DM, Graves J, Green AJ. Microcystic macular oedema in multiple sclerosis is associated with disease severity. Brain 2012;135:1786–1793.
3. Toledo J, Sepulcre J, Salinas-Alaman A, et al. Retinal nerve fiber layer atrophy is associated with physical and cognitive disability in multiple sclerosis. Mult Scler 2008;14: 906–912.
4. Petzold A, de Boer JF, Schippling S, et al. Optical coherence tomography in multiple sclerosis: a systematic review and meta-analysis. Lancet Neurol 2010;9:921–932.
5. Villoslada P, Cuneo A, Gelfand J, Hauser SL, Green A. Color vision is strongly associated with retinal thinning in multiple sclerosis. Mult Scler 2012;18:991–999.
6. Dorr J, Wernecke KD, Bock M, et al. Association of retinal and macular damage with brain atrophy in multiple sclerosis. PloS One 2011;6:e18132.
7. Neacsu V, Jasperse B, Korteweg T, et al. Agreement between different input image types in brain atrophy measurement in multiple sclerosis using SIENAX and SIENA. J Magn Reson Imaging 2008;28:559–565.
8. Comi G, Rovaris M, Leocani L, Martinelli V, Filippi M. Assessment of the damage of the cerebral hemispheres in MS using neuroimaging techniques. J Neurol Sci 2000; 172(suppl 1):S63–S66.
9. Mistry N, Tallantyre EC, Dixon JE, et al. Focal multiple sclerosis lesions abound in 'normal appearing white matter.' Mult Scler 2011;17:1313–1323.
10. Barkhof F, Calabresi PA, Miller DH, Reingold SC. Imaging outcomes for neuroprotection and repair in multiple sclerosis trials. Nat Rev Neurol 2009;5:256–266.