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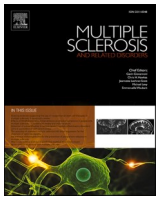

Associations between cortical lesions, optic nerve damage, and disability at the onset of multiple sclerosis: insights into neurodegenerative processes.

Kyriakoula Varmpompiti [a], Geoffrey Chow [b], Michael Foster [a], Srikirti Kodali [a], Ferran Prados [a,b,c], Marios C. Yiannakas [a], Baris Kanber [a,b], Ailbhe Burke [d], Lola Ogunbowale [d], Indran Davagnanam [e], Ahmed T Toosy [a], Sara Collorone [a,*]

[a] NMR Research Unit, Queen Square MS Centre, Department of Neuroinflammation, UCL Queen Square Institute of Neurology, Faculty of Brain Sciences, University College London, London, UK
[b] Centre for Medical Image Computing (CMIC), Department of Medical Physics and Biomedical Engineering, University College London, London, UK
[c] eHealth Center, Universitat Oberta de Catalunya, Barcelona, Spain
[d] Moorfields Eye Hospital, City Road, London, UK
[e] Department of Brain Repair and Rehabilitation, University College London Institute of Neurology, Faculty of Brain Sciences, UCL, London, UK

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ABSTRACT

Background: Multiple sclerosis cortical lesions are areas of demyelination and neuroaxonal loss. Retinal layer thickness, measured with optical coherence tomography (OCT), is an emerging biomarker of neuroaxonal loss. Studies have reported correlations between cortical lesions and retinal layer thinning in established multiple sclerosis, suggesting a shared pathophysiological process. Here, we assessed the correlation between cortical lesions and OCT metrics at the onset of multiple sclerosis, examining, for the first time, associations with physical or cognitive disability.

Objective: To examine the relationship between cortical lesions, optic nerve and retinal layer thicknesses, and physical and cognitive disability at the first demyelinating event.

Methods: Thirty-nine patients and 22 controls underwent 3T-MRI, optical coherence tomography, and clinical tests. We identified cortical lesions on phase-sensitive inversion recovery sequences, including occipital cortex lesions. We measured the estimated total intracranial volume and the white matter lesion volume. OCT metrics included peripapillary retinal nerve fibre layer (pRNFL), ganglion cell and inner plexiform layer (GCIPL) and inner nuclear layer (INL) thicknesses.

Results: Higher total cortical and leukocortical lesion volumes correlated with thinner pRNFL (B = -0.0005, 95 % CI -0.0008 to -0.0001, $p = 0.01$; B = -0.0005, 95 % CI -0.0008 to -0.0001, p = 0.01, respectively). Leukocortical lesion number correlated with colour vision deficits (B = 0.58, 95 %CI 0.039 to 1,11, $p = 0.036$). Thinner GCIPL correlated with a higher Expanded Disability Status Scale (B = -0.06, 95 % CI -1.1 to -0.008, p = 0.026). MS diagnosis ($n = 18$) correlated with higher cortical and leukocortical lesion numbers (p = 0.004 and p = 0.003), thinner GCIPL ($p = 0.029$) and INL ($p = 0.041$).

Conclusion: The association between cortical lesions and axonal damage in the optic nerve reinforces the role of neurodegenerative processes in MS pathogenesis at onset.

1. Background

Cortical lesions (CLs) are a pathological hallmark of multiple sclerosis (MS) and an integral part of the diagnostic criteria. (Thompson et al., 2018) CLs also possess prognostic value since they are associated with conversion to progressive disease (Haider et al., 2021), physical disability (Haider et al., 2021) and cognitive impairment. (Todea et al., 2020) Conversely, white matter lesions only moderately correlate with disability.(Fisniku et al., 2008)

Histopathologically, CLs represent areas of extensive demyelination and neuroaxonal loss in the cortex. (Calabrese et al., 2010) Compared with white matter lesions, they have distinctive histopathological

* Corresponding author at: UCL Queen Square Institute of Neurology, Queen Square Multiple Sclerosis Centre, 1st Floor, Russell Square House 10-12 Russell Square ,WC1B 5EH London.
E-mail address: s.collorone@ucl.ac.uk (S. Collorone).

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features with different degrees and types of inflammation. (Calabrese et al., 2010)

An emerging biomarker of neuroaxonal loss in MS is the retinal layer thickness, especially the peripapillary retinal nerve fibre layer (pRNFL) and combined macular ganglion cell and inner plexiform layer (GCIPL), as quantified by optical coherence tomography (OCT). (Graves et al., 2022) Retinal thinning, irrespective of optic neuritis (ON) (Ratchford et al., 2013), can reflect grey matter (GM) atrophy (Saidha et al., 2015) and correlate with a physical disability. (Behbehani et al., 2015; Birkeldh et al., 2019; Bsteh et al., 2019, 2023; Cellerino et al., 2021a, 2021b; Collorone et al., 2022; El Ayoubi et al., 2016; Martinez-Lapiscina et al., 2016; Toledo et al., 2008) Two studies have explored the relationship between CLs and retinal layer thickness in MS. (Mizell et al., 2022; Petracca et al., 2017) Petracca and colleagues found a correlation between CLs and GCIPL in a cohort of 25 people with primary-progressive MS (PPMS). Interestingly, they did not find an association between the CLs in the occipital lobe and OCT metrics, thereby not supporting a direct relationship between CLs and retrograde trans-synaptic degeneration.(Petracca et al., 2017) Mizell and colleagues examined a larger cohort of people with MS – most of whom had relapsing-remitting MS (RRMS) – confirming the correlation between CLs and GCIPL. (Mizell et al., 2022) Both studies suggested a shared pathophysiological process behind CLs and retinal thinning. However, none of the studies explored correlations with physical or cognitive disability. Furthermore, Petracca et al. focused on PPMS, which is characterised by different pathophysiological mechanisms than RRMS, while Mizell et al. included patients with varying durations of disease (mean 12.0 (SD 8.7) years), which may have influenced the degree of retinal thinning, and on different disease-modifying treatments, which might have differently affected the observed relationship between CLs and GCIPL.

2. Objective

In this observational cross-sectional study, we aimed to clarify the relationship between CLs (numbers and volume), optic nerve and retinal layer thinning, physical and cognitive disability, and McDonald 2017 RRMS diagnosis at presentation in individuals with their first episode of neurological symptoms suggestive of demyelination, clinically isolated syndrome (CIS) or RRMS. This can be crucial because one of the primary causes of permanent disability in patients with MS is neuroaxonal degeneration (Absinta et al., 2020), which is present in both the retina and CLs.

3. Methods

3.1. Study Design and Participants

This study was conducted at the University College London (UCL) Queen Square Institute of Neurology (Collorone et al., 2021) (UCL ethical committee approval: 13/LO/1762; 13/0231-CIS2013). We prospectively recruited patients at the onset of their first demyelinating episode from the National Hospital of Neurology and Neurosurgery and Moorfields Eye Hospital in London, United Kingdom. All subjects gave written informed consent. Inclusion criteria were: within three months from symptom onset; age between 18 and 65 years; able to provide written informed consent in English and to undergo magnetic resonance imaging (MRI). Exclusion criteria included known neurological disease (other than CIS or RRMS); the presence of antibodies against aquaporin-4 or myelin oligodendrocyte glycoprotein, routinely assessed in patients with ON; pregnancy or breastfeeding and the presence of magnetically sensitive or otherwise MRI incompatible implants. We also recruited age and sex-matched healthy controls (HCs), who underwent the same MRI and OCT protocol, to assess the presence of atrophy in the brain and retinal layers.

3.2. MRI acquisition

We used a 3T Achieva MRI scanner (Philips Medical Systems, Best, Netherlands) with a 32-channel head coil and a maximum gradient strength of 62 mT/m. All participants underwent structural MRI of the brain and spinal cord (see Table 1 in Supplementary Material for details). The brain MRI protocol included:

1. Axial proton density (PD)/T2-weighted imaging.
2. 3D T1-weighted magnetisation-prepared turbo field echo.
3. 3D fluid-attenuated inversion recovery (FLAIR).
4. Phase-sensitive inversion recovery (PSIR)).
5. For patients only, axial pre- and post-gadolinium T1-weighted turbo spin-echo sequences.

The spinal cord MRI protocol included the following sequences: (i) sagittal PD; (ii) sagittal T2-weighted; (iii) for patients only, pre- and post-gadolinium sagittal T1-weighted turbo spin-echo.

3.3. MRI analysis

In the cortex, two experienced raters (GC and ID) manually segmented lesions with cortical involvement on the PSIR sequence using 3D slicer software (version 4.6.2 https://www.slicer.org/) with a threshold of 3 mm in any direction. We categorised PSIR lesions into leukocortical and intracortical locations and defined the number and volume for each category. By registering the PSIR masks onto the

We outlined the T2-hyperintense lesions in the white matter of each participant on the 2D proton density/T2-weighted image using a semi-automated edge finding tool in JIM v6.0 (Xinapse systems; http://www.xinapse.com/).

We obtained the total intracranial volume using Geodesic Information Flows (GIF)(Cardoso et al., 2015) on the lesion-filled 3D-T1 scans.

By registering the PSIR masks into the 3D-T1, we obtained the CLs volume in the occipital cortex.

3.4. OCT acquisition

We used the eye-tracking function with the spectral domain OCT machine (Spectralis v.1.7.1.0, Heidelberg Engineering, Heidelberg, Germany). The examination was carried out in a dark room without pharmacological pupil dilatation. pRNFL scans were obtained with an automatic real-time (ART) of 100, using a 3.4 mm diameter circle manually centred on the head of the optic nerve. Three scans were obtained for the optic nerve, all acquisitions were screened with the OSCAR-IB criteria (Tewarie et al., 2012), and the scan with the highest quality was chosen for the analysis (in case of equal quality, a scan was

Table 1
Demographics and clinical characteristics of subjects.

Age	Patients (n = 39)	Controls (n=22)	p-value*
Mean (SD, Min-Max)	32 (6, 19–50)	33 (6, 22–49)	0.79
Gender			
Female, n (%)	29 (74)	20 (59)	0.22
Male, n (%)	10 (26)	24 (41)	
Diagnosis of MS, n (%)	18 (46.2)	-	
CIS type			
Brainstem, n (%)	4 (10.3)	-	
Hemisphere, n (%)	2 (5.1)	-	
Optic neuritis, n (%)	31 (79.5)	-	
Spinal Cord, n (%)	2 (5.1)	-	
Steroids, n (%)	18 (48.7)	-	
EDSS			
Median (Min-Max)	1 (0–3.5)	-	

Abbreviations: CIS: clinically isolated syndrome; EDSS: Expanded Disability Status Scale; MS: multiple sclerosis; SD: standard deviation.
* linear regression analysis

selected arbitrarily). We took the global average of the pRNFL thickness for the eye from these scans.

Macular scans were performed using a macular volume protocol with a 20 × 20 degree field centred over the fovea with an ART 10–25. The individual macular layers were obtained with automated segmentation software (HRA/Spectralis Viewing Module version 5.6.4.0). We overlaid the 1–3-6 diameter mm circular grid, centred on the fovea. From these scans, we extracted the macular ganglion cell layer thicknesses, the inner plexiform layer, and the inner nuclear layer (INL). The sum of the ganglion cell layer and the inner plexiform layer was determined to obtain the GCIPL thickness. We considered the inner circle of the macular grid for our analyses. OCT methods and results are reported in agreement with consensus APOSTEL recommendations. (Cruz-Herranz et al., 2016)

3.5. Diagnosis of relapsing-remitting MS

The 2017 revisions of the McDonald diagnostic guidelines were used to diagnose study participants with RRMS if their baseline MRI scan fulfilled the criteria for dissemination in both time and space. (Thompson et al., 2018) In the case of CIS with dissemination in space but no dissemination in time, we offered a lumbar puncture to detect unmatched oligoclonal bands in the cerebrospinal fluid.

3.6. Disability Assessment

Physical disability was assessed with the Kurtzke Expanded Disability Status Scale (EDSS), (Kurtzke, 1983) lower-limb function with the timed 25-foot walk test (T25FWT), and upper-limb function with the 9-hole peg test (9HPT). (Fischer et al., 1999) Since people with MS with visual pathway damage typically perform worse in vision-dependent tests (Collorone et al., 2022), we used two vision-dependent tests: the Symbol Digit Modalities Test (SDMT) for visual information processing speed, and the Brief Visuospatial Memory Test – Revised (BVMT-R) for visuospatial memory. (Langdon et al., 2012)

For the T25FWT and 9HPT, z-scores were calculated according to the National Multiple Sclerosis Society Task Force guidelines (Fischer et al., 1999). For the SDMT and BVMT-R, we recorded the years of education for each patient and obtained z-scores from the Brief International Cognitive Assessment for MS initiative dataset. (Parmenter et al., 2010)

3.7. Visual tests

We assessed all visual tests with participants' habitual refractive correction. Lighting levels were consistent in the testing environment.

We assessed low contrast letter acuity (LCLA) (Balcer et al., 2017) using Sloan charts at 2.5 % and 1.25 % contrast levels for each eye separately. The LCLA score was the number of letters the participant could correctly identify at a specific contrast level. The maximum score is 70.

We examined colour vision using the Farnsworth Munsell 100 hue test. (Menage et al., 1993) Each eye was tested separately; the Farnsworth-Munsell square root error score was used for data analysis.

3.8. Statistical analysis

Statistical calculations were performed with IBM SPSS Statistics (Version 29). For participants with unilateral optic neuritis, the OCT metrics from the fellow eye were used as these would not be affected by changes due to ON. For patients without ON and HCs, we averaged the OCT metrics.

We compared total intracranial volume(eTiv) and OCT metrics between patients and HCs using linear regression analysis adjusted for age and sex.

We used linear regression analyses with age and sex as covariates to assess relationships between:

1. CLs (volume and number) and OCT metrics (pRNFL, GCIPL and INL thicknesses),
2. CLs (volume and number) and McDonald 2017 MS diagnosis and clinical measures,
3. OCT metrics (pRNFL, GCIPL and INL thicknesses) and McDonald 2017 MS diagnosis and clinical measures

We also assessed if the eTiv, CLs volume in the occipital lobe and white matter lesion volume were correlated to OCT metrics and clinical parameters in our cohort.

Statistically significant results met the threshold of $p<0.05$. The analyses of this study are considered exploratory. Therefore, multiple comparison correction was not performed, as there are no ideal methods for adjusting for multiple comparisons in this context.

3.9. Data availability

The data supporting this study's findings are available from the corresponding author upon reasonable request.

4. Results

We consecutively recruited 60 patients, of which 50 had acceptable PSIR scans. From these 50, we included in the study 39 subjects whose OCT scans survived our quality check. Most patients (N =31) presented with optic neuritis. Eighteen patients were diagnosed with McDonald 2017 MS. We also recruited 22 HCs. Demographic and clinical characteristics are reported in Table 1.

Patients had thinner pRNFL and GCIPL than HCs (B = -6.3 95 % Confidence Interval (CI) = -12.2 to -0.31, p=0.039; B =-12.7, 95 %CI = -16.1 to -9.18, $p < 0.000$, respectively) while eTiv was not statistically significantly different. Twelve patients (30 %) had intracortical lesions in the occipital cortex. Brain, retinal imaging characteristics and differences between patients and HCs are illustrated in Table 2.

Table 2
Imaging characteristics.

Imaging Finding	Patients (n = 39) Mean (SD, range)	HCs (n = 22) Mean (SD, range)	Unstandardised coeff. (CI) p-value*
Total cortical lesion count	2 (2, 0 – 9)	-	
Total cortical lesion volume (ml)	0.3 (1, 0 – 5)	-	
Intracortical lesion count	0 (0 – 5)	-	
Intracortical lesion volume (ml)	0.02 (0.04, 0 – 0.2)	-	
Leukocortical lesion count	0 (0 – 8)	-	
Leukocortical lesion volume (ml)	0.3 (1, 0 – 5)	-	
White matter lesion volume (ml)	14 (83, 0 – 642)	-	
Total intracranial volume	1329 (203, 831 -1723)	1428 (230, 1004–1861)	-43.2 (-127.4 to 40.9) 0.3
pRNFL mean global thickness (μm)	96 (11.3, 72 – 131)	101 (9.2, 82 - 117)	-6.3 (-12.2 to -0.31) 0.039**
GCIPL thickness 1–3 mm (μm)	84.9 (5.9, 72.3 – 96.3)	97 (6.4, 87.5 – 113)	-12.7 (-16.1 to -9.18) <0.0001**
INL average 1–3 mm thickness (μm)	37.8 (3, 31 – 43)	39.3 (3, 33 – 46)	-1.5 (-3.5 to 10.45) 0.13

Abbreviations: HCs: healthy controls; GCIPL: ganglion cell and inner plexiform layer; INL: inner nuclear layer; pRNFL: peripapillary retinal nerve fiber layer.
* Linear regression analysis adjusted for age and sex
** Indicates significant results

4.1. Associations between CLs, retinal and optic nerve measures

A higher total cortical and leukocortical lesion volume was associated with a thinner pRNFL (B = -0.0005, 95 % CI -0.0008 to -0.0001, p = 0.01; B = -0.0005, 95 % CI -0.0008 to -0.0001, p = 0.01, respectively). Retinal and optic nerve measures did not correlate with occipital CL volume in patients with occipital CLs. Fig. 1 shows CLs, retinal and optic nerve metrics in one of the patients.

Fig. 1 illustrates cortical lesions and retinal and optic nerve metrics from a patient.

The relationships between cortical lesions, retinal and optic nerve measures are shown in Table 3.

4.2. Associations between CLs, retina and optic nerve measures, and MS diagnosis

MS diagnosis correlated with leukocortical and total cortical lesion numbers (B = 0.13, 95 % CI 0.05 to 0.22, p = 0.003 and B = 0.11, 95 %

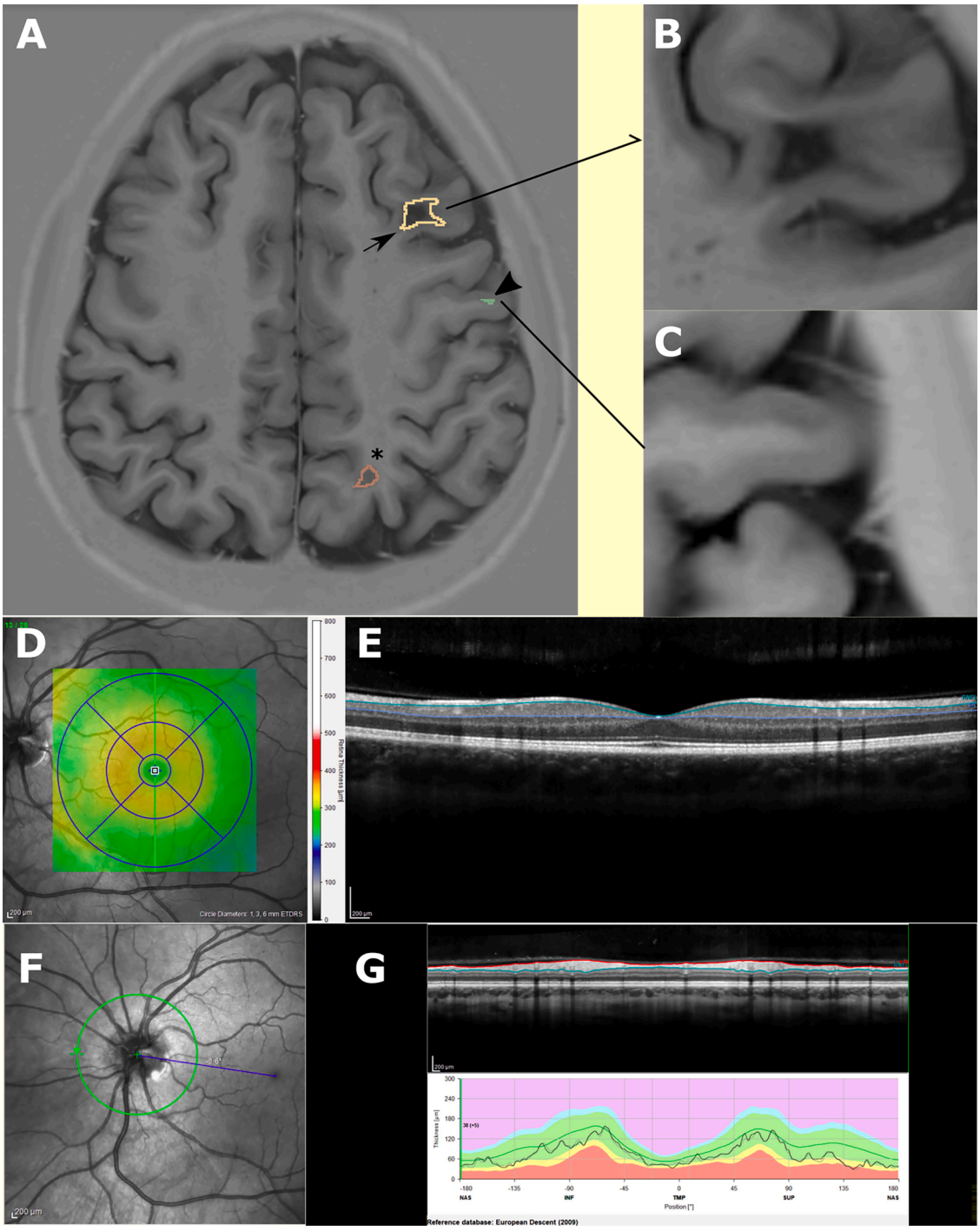

Fig. 1. Example of cortical lesions and retinal and optic nerve metrics from a patient A: axial phase-sensitive inversion recovery image with leukocortical lesion (arrow), intracortical lesion (arrowhead), and white matter lesion (asterisk); B: zoom on the leukocortical lesion; C: zoom on the intracortical lesion; D: macular thickness map of the non-affected eye; E: ganglion cell and inner plexiform layer segmentation; F: optic nerve scan; G: peripapillary retinal nerve fiber layer segmentation and thickness vs. a reference database.

Table 3
Relationship between GCIPL and pRNFL thickness and cortical lesion characteristics.
Linear regression analysis was performed with dependent variable the retinal thicknesses and predictors the cortical lesion number and volumes. All correlations are adjusted for covariates of sex and age.

	pRNFL				GCIPL				INL			
	Unst. Coef. (B)	P-value	95 % CI	R^2	Unst. Coef. (B)	p-value	95 % CI	R^2	Unst. Coef. (B)	p-value	95 % CI	R^2
ICL N	0.11	0.95	-3.54, 3.76	8.8 %	0.57	0.56	-1.40, 2.54	7.6 %	0.59	0.23	-0.0379, 1.556	6.9 %
LCL N	-1.3	0.23	-3.41, 0.85	12.5 %	-0.72	0.22	-1.87, 0.43	7.6 %	- 0.51	0.07	-1.072, 0.50	11.5 %
TCL N	-0.9	0.32	-2.73, 0.92	11.3 %	-0.38	0.45	-1.37,0.62	5 %	- 0.22	0.37	-0.717, 0.276	5 %
ICL vol	0.002	0.96	-0.10, 0.10	8.8 %	0.03	0.37	-0.003,0.008	5.7 %	0.001	0.35	-0.001, 0.004	5.3 %
LCL vol	-0.005	0.01**	-0.001,-0.0001	24.6 %	-0.002	0.07	-0.0004, 0.00002	12.1 %	-0.00007	0.19	-0.0002, 0.00003	7.6 %
TCL vol	-0.005	0.01**	-0.001,-0.0001	24.6 %	-0.002	0.08	-0.0004, 0.00002	11.8 %	-0.00006	0.20	-0.0002, 0.00004	7.3 %

Abbreviations: Coef.: coefficient; CI: confidence interval; GCIPL: ganglion cell and inner plexiform layer; ICL: intracortical lesions; INL: inner nuclear layer; LCL: leukocortical lesions; pRNFL: peripapillary retinal nerve fiber layer TCL: total cortical lesions; Unst.: unstandardized
** Indicates significant p-values

CI 0.04 to 0.18, p = 0.004, respectively) and volumes (B = 0.000016, 95 % CI 0.0.0000003 to 0.00003, p = 0.045 and B = 0.000016, 95 % CI 0.000008 to 0.00003, p = 0.040, respectively).

Patients diagnosed with RRMS had a thinner GCIPL (B = -0.029, 95 % CI = -0.06 to -0.003, p = 0.029) and INL (B = -0.055, 95 % CI -0.11 to -0.002, p = 0.041).

Fig. 2 shows the differences between CIS and MS patients in total cortical lesion number, GCIPL and INL.

4.3. Associations between CLs, retinal and optic nerve measures, and clinical parameters

The leukocortical lesion number correlated with the Farnsworth error square score (B = 0.58, 95 % CI 0.04 to1.1, p = 0.036)

The relationships between CLs and clinical parameters are shown in Table 4.

A thinner GCIPL layer was associated with a greater EDSS score (B = -0.06, 95 % CI -1.1 to -0.008, p = 0.026). A thinner pRNFL was associated with a longer time to complete the T25FW test (B = 0.026, 95 % CI 0.004 to 0.05, p = 0.023). A thicker INL was associated with higher scores at the LCLA 2.5 % (B = 1.5, 95 % CI 1.7 to 27.6, p = 0.028) and

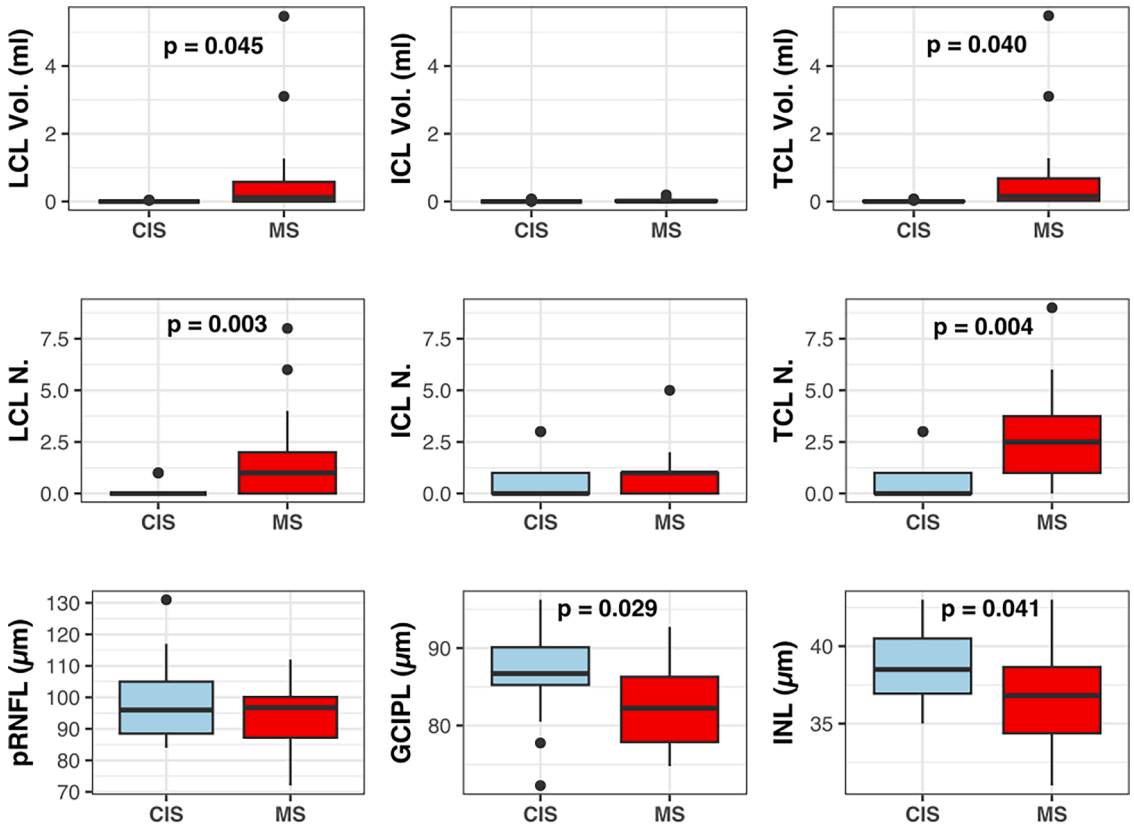

Fig. 2. Cortical lesions numbers (top), cortical lesions volumes (middle), and retinal and optic nerve metrics (bottom) in CIS and MS patients.
Abbreviations: CIS: clinically isolated syndrome; GCIPL: ganglion cell and inner plexiform layer; INL: inner nuclear layer; MS: multiple sclerosis; pRNFL: peripapillary retinal nerve fiber layer.

Table 4
Association between CLs and clinical parameters.
Linear regression analysis was performed with dependent variable the clinical measures and predictors and CLs characteristics. All correlations are adjusted for covariates of sex and age.

	EDSS				BVMT-R				SDMT				T25FW			
	Unst. Coef. (B)	P-value	95 % CI	R^2	Unst. Coef. (B)	P-value	95 % CI	R^2	Unst. Coef. (B)	P-value	95 % CI	R^2	Unst. Coef. (B)	P-value	95 % CI	R^2
ICL N	-0.18	0.28	-0.5, 0.15	0.1 %	-1.07	0.32	-3.24, 1.101	12.6 %	-0.76	0.69	-4.5, 3.02	24.3 %	-0.03	0.82	-0.28, 0.22	4.9 %
LCL N	-0.05	0.58	-0.25, 0.14	5.7 %	-0.79	0.22	-2.07, 0.49	139.9 %	0.34	0.76	-1.91, 2.59	24.1 %	-0.06	0.42	-0.21, 0.08	6.6 %
TCL N	-0.09	0.31	-0.25, 0.08	7.7 %	-0.86	0.12	-1.93, 0.22	16.2 %	0.05	0.96	-1.87, 1.97	23.9 %	-0.05	0.42	-0.18, 0.07	6.6 %
ICL vol	-0.006	0.2	-0.001, 0.0003	9.2 %	-0.05	0.08	-0.11, 0.007	17.5 %	-0.004	0.48	-0.014,0.006	25 %	-0.000018	0.96	-0.00073, 0.00069	4.8 %
LCL vol	0.0001	0.4	-0.0001, 0.0004	6.7 %	0.0001	0.92	-0.00021, 0.00023	10.1 %	-0.001	0.64	-0.00047, 0.00029	24.4 %	-0.0000051	0.69	-0.00003, 0.00002	5.2 %
TCL vol	0.0001	0.43	-0.0002, 0.0004	6.5 %	0.00004	0.97	-0.000006, 0.0000012	10 %.1	-0.001	0.62	-0.00048, 0.00029	24.5 %	-0.00005	0.69	-0.0000005, 0.0000003	5.2 %
	9HPT				FM ES				LCLA 2.5 %				LCLA 1.25 %			
	Unst. Coef. (B)	P-value	95 %CI	R^2	Unst. Coef. (B)	P-value	95 % CI	R^2	Unst. Coef. (B)	P-value	95 % CI	R^2	Unst. Coef. (B)	P-value	95 % CI	R^2
ICL N	0.06	0.884	-0.78, 0.91	14.8 %	0.1	0.84	-0.86, 1.05	11.7 %	1.6	0.41	-2.36, 5.58	2.6 %	2.9	0.14	-0.96, 6.71	7.6 %
LCL N	-0.16	0.518	-0.66, 0.34	15.8 %	0.58	0.036**	0.039, 1,11	22.1 %	-1.19	0.31	-3.54, 1.16	3.6 %	-1.2	0.305	-3.51, 1,13	4.5 %
TCL N	-0.1	0.633	-0.53, 0.32	15.3 %	0.44	0.059	-0.018, 0.9	20.2 %	-0.45	0.65	-2.48, 1.57	1.3 %	-0.13	0.9	-2.13, 1.88	1.6 %
ICL vol	0.04	0.728	-0.00196, 0.00278	15 %	0.001	0.35	-0.0014, 0.0038	13.8 %	0.007	0.24	-0.0044, 0.017	4.6 %	0.008	0.13	0.0024, 0.018	7.9 %
LCL vol	-0.00007	0.069	-0.00015, 0.0000062	22.5 %	0.000036	0.48	-0.00006, 0.00013	12.8 %	-0.0003	0.18	-0.00067, 0.00013	5.8 %	-0.002	0.215	-0.00064, 0.00014	5.8 %
TCL vol	-0.000076	0.071	-0.00015, 0.0000069	22.4 %	0.000036	0.456	-0.000061, 0.00013	13 %	-0.0003	0.19	-0.00066, 0.00013	5.4 %	-0.002	0.24	-0.00063, 0.00016	5.4 %

Abbreviations: BVMT-R: Brief Visuospatial Memory Test – Revised; CI: confidence interval; Coef.: coefficient; EDSS: Expanded Disability Status Scale; FM ES: Farnsworth Munsell 100 hue error score; ICL: intracortical lesions; LCL: leuko-cortical lesions; LCLA: low-contrast letter acuity; SDMT: Symbol Digit Modality Test; TCL: total cortical lesions; T25FW: timed 25-foot walk; Unst.: unstandardised;; 9HPT: 9-hole peg test
** Indicates significant p-values

LCLA 1.25 % (B = 2.1, 95 % CI 0.9 to 3.3, $p < 0.001$).

The relationships between retinal and optic nerve measures and clinical parameters are shown in Table 5.

4.4. Associations between white matter lesion volume, retinal and optic nerve measures, and clinical parameters

The total intracranial and white matter lesion volumes did not correlate with other parameters (see Table 2-4 in Supplementary Material).

5. Conclusion

This study aimed to examine the relationship between CL characteristics, retinal and optic nerve thickness and disability in patients at their first demyelinating event suggestive of MS. Our results support a relationship between these aspects of MS pathobiology.

Our main finding is the relationship between total CL volume and pRNFL thinning. These results are novel and crucial in understanding the processes behind CLs. The onset of the disease offers a valuable model since cortical demyelination occurs independently of white matter demyelination, which may influence cortical pathology in the progressive stages of the disease. (Fisher et al., 2008) Unmyelinated pRNFL axons represent neurodegeneration markers in the afferent visual pathway. (Graves et al., 2022)Therefore, the correlation between CL volume and axonal damage, as shown by pRNFL thickness, may indicate a shared pathological background characterised by neurodegeneration. The fact that the leukocortical component of CLs drove the observed relationships between CL volume and pRNFL thickness may further support our hypothesis. Leukocortical lesions seem to have a higher degree of neuro-axonal loss than the other CL subtypes, as seen in histopathological studies (Wegner et al., 2006) and animal models. (Pomeroy et al., 2010)However, leukocortical lesions were more numerous than intracortical lesions in our cohort, which may have also influenced our results.

In other MS cohorts (Mizell et al., 2022; Petracca et al., 2017), authors did not find any association between CLs and pRNFL, but only between CLs and GCIPL, that we could not replicate here, even if patients had a thinner GCIPL than controls. These discrepancies may suggest differences in the pathophysiological processes occurring in early-stage MS compared to later stages. On the one hand, in patients with longer disease duration, the pRNFL may have already reached a plateau causing a "ceiling effect": severe RNFL atrophy, corresponding to the lowest values of the OCT, may continue to deteriorate, but the OCT. would not capture the continued decrease (Rao et al., 2015) This would have affected the chances of finding correlations with CLs. On the other hand, it is possible that other factors, such as neuroinflammatory processes or secondary neurodegeneration, might play a more significant role in GCIPL thinning in the later stages of MS. These considerations do not rule out the influence of other factors, such as the fact that most patients in our cohort had ON, which may have contributed to changes in the contralateral eye (Petzold et al., 2017), and differences in the populations analysed by different studies.

Patients diagnosed with RRMS at onset had more CLs and more significant thinning of the GCIPL and INL. As far as cortical lesions are concerned, this study supports the specificity of this marker for RRMS, incorporated in the latest revision of diagnostic criteria. (Thompson et al., 2018) In our patients, we diagnosed RRMS according to the spatial dissemination of enhancing and non-enhancing lesions, hence new and old MS lesions. Similarly, thinner retinal layers in RRMS patients may signal a longer subclinical disease duration than in CIS. This would support using OCT in the study of MS prodromal stages. For the first time, we have studied the relationship between CLs, retinal and optic nerve measures, and disability.

The CL burden did not correlate with disability. Few studies have investigated the correlation between CLs and disability in CIS.(Diker

Table 5
Relationships between retinal measures and clinical parameters.
Linear Regression analysis was performed with dependent variable the clinical measurements and predictors the GCIPL thickness, total volume, INL thickness and the pRNFL thickness. All correlations are adjusted for covariates of sex and age.

	EDSS				BVMT-R				SDMT				T25FW			
	Unst.Coef. (B)	P-value	95 % CI	R^2	Unst. Coef. (B)	P-value	95 % CI	R^2	Unst. Coef. (B)	P-value	95 % CI	R^2	Unst. Coef. (B)	P-value	95 % CI	R^2
pRNFL	-0.02	0.209	-0.05, 0.011	9.1 %	-0.06	0.59	-0.26, 0.15	10.8 %	-0.047	0.79	-0.4, 0.3	24.1 %	0.026	0.023**	0.0038, 0.048	18.1 %
GCIPL (1–3 mm)	-0.06	0.026*	-0.11, -0.0077	17.5 %	0.11	0.57	-0.27, 0.48	10.9 %	0.27	0.39	-0.37, 0.92	25.5 %	0.007	0.75	-0.037, 0.051	5.1 %
INL (1–3 mm)	-0.07	0.22	-0.18, 0.044	8.8 %	-0.2	0.59	-0.96, 0.56	10.8 %	-0.29	0.66	-1.60, 1.02	24.4 %	0.015	0.74	-0.074, 0.10	5.1 %
	9-HPT				FM ES				LCLA 2.5 %				LCLA 1.25 %			
	Unst. Coef. (B)	P-value	R^2	95 % CI	Unst. Coef. (B)	P-value	95 % CI	R^2	Unst. Coef. (B)	P-value	95 % CI	R^2	Unst. Coef. (B)	P-value	95 % CI	R^2
pRNFL	-0.02	-0.038	0.33	17 %	-0.11, 0.04	-0.003	0.94	-0.093, 0.086	11.6 %	0.02	0.9	-0.35, 0.39	0.7 %	0.08	0.67	-0.29, 0.45
GCIPL (1–3 mm)	-0.06	-0.06	0.404	16.4 %	-0.20, 0.08	-0.087	0.28	-0.25, 0.076	14.4	0.097	0.77	-0.59, 0.79	0.9 %	0.41	0.22	-0.26, 1.08
INL (1–3 mm)	-0.07	0.05	0.693	15.1 %	-0.23, 0.35	-0.004	0.79	-0.37, 0.28	11.7 %	1.5	0.028**	0.17–2.76	13.7 %	2.09	<0.001**	0.92, 3.27

Abbreviations: BVMT-R: Brief Visuospatial Memory Test-Revised; CI: confidence interval; Coeff.: Coefficient; EDSS: Expanded Disability Status Scale; FM ES: Farnsworth Munsell 100 hue error score; LCLA: low- contrast letter acuity; SDMT: Symbol Digit Modality Test; T25FW: timed 25-foot walk; 9-HPT: 9-hole Peg Test;; Unst.: Unstandardised
** Indicates significant p-values

et al., 2016; Nielsen et al., 2013; Papadopoulou et al., 2013) While studies at 3T did not find any correlations with cognitive disability so early in the disease (Diker et al., 2016; Papadopoulou et al., 2013), a study at 7T highlighted a relationship between subpial CL and EDSS. (Nielsen et al., 2013) It is possible that in early disease, functional adaptations may compensate for brain damage, masking correlations with cognition. (Collorone et al., 2020) Alternatively, excluding subpial lesions, only visible at 7T, may have affected our results. We only found a correlation between CLs and errors in the colour vision test. This is just a preliminary study, and the small size of our cohort may cause incidental findings. If the result is confirmed in a larger cohort, the next step will be to investigate if this might be related to visual pathways lesions, including occipital lobe CLs.

Finally, GCIPL thickness, but not pRNFL, was associated with EDSS in our study. This is in keeping with the literature showing an association of GCIPL thickness with physical and cognitive decline in RRMS patients cross-sectionally (Behbehani et al., 2015; Bsteh, Berek, et al., 2021; Bsteh et al., 2019) and longitudinally (Britze et al., 2017; Britze & Frederiksen, 2018; Bsteh et al., 2023; Bsteh, Hegen, et al., 2021; Cellerino et al., 2021a) This could be explained by differences between the GCIPL and the pRNFL. More specifically, GCIPL thinning is more specific for MS-associated neuroaxonal damage, displays superior structure–function correlation, and is less prone to be influenced by concomitant swelling from acute clinical or subclinical ON.(Petzold et al., 2017) However, in some studies, pRNFL has been associated with cognitive decline (Toledo et al., 2008) and disability in patients with RRMS (Bsteh et al., 2019), and progressive disease. (Jankowska-Lech et al., 2019) In our study, pRNFL was only correlated with the T25FW test. Our findings confirm similar results in larger cohorts (Birkeldh et al., 2019; Bsteh et al., 2023; Martinez-Lapiscina et al., 2016; Petzold et al., 2017; Pihl-Jensen et al., 2021) supporting the suitability of OCT as a marker of neurodegeneration from the earliest stages of the disease, even in patients with not yet measurable brain atrophy.

Furthermore, INL thinning was significantly associated with worse LCLA scores. This is a novel finding because previous studies did not show any associations between INL and visual outcomes. (Pisa et al., 2021) However, our results need to be taken with caution as we included patients with both acute (less than one month from onset) and subacute (more than one month) ON, and some of them had had steroids (Table 1). This variability may have affected the INL, which can be thicker in the subacute phase of ON and thinner in patients having steroids. (Pisa et al., 2021)

There are several limitations to this study. This is a preliminary study with a relatively small sample size, which limited the ability to find subtle relationships. Secondly, due to the study's cross-sectional nature, we could show an association but did not establish a causal relationship between measures of retinal and brain damage. Longitudinal studies with the segmentation of retinal layers in a larger sample will further clarify the relationship of retinal thinning irrespective of ON with CL and its link to disability and progression. Finally, even if the measurements were irrespective of ON, we could not entirely exclude the presence of subclinical episodes in the non-affected eyes used for this study.

In conclusion, this study supports a relationship between CLs and axonal damage in the optic nerve at the onset of the disease, suggesting a shared pathological process behind these alterations. The association between more significant retinal damage and disability confirms the role of GCIPL as a possible biomarker of neurodegeneration, even at this early stage of the disease.

Data Statement

The data supporting this study's findings are available from the corresponding author upon reasonable request.

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CRediT authorship contribution statement

Kyriakoula Varmpompiti: Data curation, Formal analysis, Writing – original draft, Investigation. **Geoffrey Chow:** Formal analysis, Methodology, Investigation. **Michael Foster:** Data curation, Writing – review & editing. **Srikirti Kodali:** Writing – review & editing. **Ferran Prados:** Methodology, Writing – review & editing. **Marios C. Yiannakas:** Data curation, Writing – review & editing. **Baris Kanber:** Methodology, Writing – review & editing, Software. **Ailbhe Burke:** Data curation, Writing – review & editing. **Lola Ogunbowale:** Data curation, Writing – review & editing. **Indran Davagnanam:** Methodology, Supervision, Validation. **Ahmed T Toosy:** Funding acquisition, Supervision, Validation, Writing – review & editing. **Sara Collorone:** Conceptualization, Formal analysis, Funding acquisition, Investigation, Supervision, Visualization, Writing – original draft, Writing – review & editing.

Declaration of competing interest

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2023.105413.

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