ORIGINAL ARTICLE

Macular Ganglion Cell Layer and Peripapillary Retinal Nerve Fibre Layer Thickness in Patients with Unilateral Posterior Cerebral Artery Ischaemic Lesion: An Optical Coherence Tomography Study

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ABSTRACT

The purpose of this study is to evaluate the macular ganglion cell layer (GCL) and peripapillary retinal nerve fibre layer (RNFL) thickness in patients with unilateral posterior cerebral artery (PCA) ischaemic lesions using spectral-domain optical coherence tomography (SD-OCT). A prospective, case-control study of patients with unilateral PCA lesion was conducted in the neuro-ophthalmology clinic of Centro Hospitalar Lisboa Central. Macular and peripapillary SD-OCT scans were performed in both eyes of each patient. Twelve patients with PCA lesions (stroke group) and 12 healthy normal controls were included in this study. Peripapillary RNFL comparison between both eyes of the same subject in the stroke group found a thinning in the superior-temporal ($p = 0.008$) and inferior-temporal ($p = 0.023$) sectors of the ipsilateral eye and nasal sector ($p = 0.003$) of the contralateral eye. Macular GCL thickness comparison showed a reduction temporally in the ipsilateral eye ($p = 0.004$) and nasally in the contralateral eye ($p = 0.002$). Peripapillary RNFL thickness was significantly reduced in both eyes of patients with PCA compared with controls, affecting all sectors in the contralateral eye and predominantly temporal sectors in the ipsilateral eye. A statistically significant decrease in macular GCL thickness was found in both hemiretinas of both eyes of stroke patients when compared with controls ($p < 0.05$). This study shows that TRD may play a role in the physiopathology of lesions of the posterior visual pathway.

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Introduction

Neurodegeneration is a complex process that can result from a direct insult to cells or from disruption of their connections. The loss of input (anterograde) or output (retrograde) of synapsing neurons can result in transneural degeneration. Transneural retrograde degeneration (TRD) occurs in presynaptic neurons after loss of postsynaptic target.^{1,2} In the visual system, degeneration of retinal ganglion cells (RGCs) (second-order neurons) would follow a posterior cortical damage (third-order neurons).¹

According to classical teaching, patients with acquired damage to the postgeniculate region show no fundoscopic abnormality. However, in congenital lesions, it is described as a typical pattern of optic nerve atrophy similar to the one found in optic tract pathology.³ In the eye

contralateral to the lesion, there is loss of crossing fibres that relate to the nasal hemiretina. These fibres enter the optic disc at the nasal and temporal equatorial poles, resulting in a pattern known as “band atrophy” or “bowtie atrophy”. In the eye ipsilateral to the lesion, there is general optic disc pallor due to loss of non-crossing fibres that relate to the temporal hemiretina and travel to the disc in the arcuate bundles.⁴

In the past years, evidence of TRD in the human visual system has been emerging.¹ Newer imaging methods such as spectral-domain optical coherence tomography (SD-OCT) provide an easy in vivo visualization of the retinal ganglion cell layer (GCL) and retinal nerve fibre layer (RNFL). Peripapillary RNFL measurements have been used to characterise ganglion cell changes in posterior lesions.^{4–6} Even though retinotopic mapping

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investigation has already described the fibre entry order in the optic disc,⁷ retinal GCL analyses could provide an equally easy and non-invasive but more precise method for neural degeneration characterization. SD-OCT analysis of the GCL is expanding in the neuro-ophthalmological field,⁸ with the study of diseases such as non-arteritic ischaemic optic neuropathy,^{9,10} optic neuritis,^{11–14} papilloedema due to idiopathic intracranial hypertension¹⁵ and toxic and nutritional optic neuropathy.¹⁶

The purpose of this study is to evaluate the macular GCL and peripapillary RNFL thickness in patients with unilateral posterior cerebral artery (PCA) ischaemic lesions.

Methods

A prospective, observational, cross-sectional study was performed in the ophthalmology department of Centro Hospitalar Lisboa Central. Stroke patients were consecutively recruited among outpatients who attended the neuro-ophthalmology clinic from March to September 2014 and included patients who suffered from posterior cerebral artery infarction that resulted in homonymous hemianopia. Scans were reviewed by a neuro-radiologist to confirm an isolated PCA ischaemic lesion that resulted only in occipital damage. Age- and sex-matched normal healthy controls were recruited from the general ophthalmology clinic while undergoing standard regular examination. Each participant had a systemic and ophthalmological history review and a complete ophthalmological assessment. Patients from the stroke group underwent visual field analysis with computerised static perimetry (CSP) using Octopus 900 (Haag-Streit, Koeniz, Switzerland) to confirm homonymous hemianopic visual loss. All patients were required to have age above 18 years; best-corrected visual acuity of 20/40 or better; refractive error inferior to 6 dioptres in sphere or 3 dioptres in cylinder; intraocular pressure (IOP) < 21 mm Hg; clear media; no history of retinal disease (diabetic retinopathy, macular degeneration, or hypertensive retinopathy); no optic nerve disease (glaucoma, optic nerve congenital abnormalities, inflammatory optic neuropathy, ischaemic optic neuropathy, compressive optic neuropathy, and other acquired optic

neuropathies); no previous history of trauma or ocular surgery; and no evidence of other neurological disease that could affect the visual fields or retinal/optic disc imaging.

This study follows the guidelines for experimental investigation in human subjects of the ethics committee in our institution and complies with the tenets of the Declaration of Helsinki. Written informed consent was obtained from each patient included in the study.

Imaging

SD-OCT scans were performed by a single experienced technician masked to the patient's information using the Heidelberg Spectralis (Heidelberg Instruments, Heidelberg, Germany). Patients were dilated using three drops of a tropicamide 1% and placed in a seated and resting position. No optical correction was used during the scans and 1 drop of artificial tear was used to increase image quality.

A 20° × 20° retinal region was scanned using a horizontal fast protocol (25 sections separated by 240 µm) centred on the fovea with an A-scan density of 1024. The peripapillary area was scanned by a circular scan with 12° in diameter centred in the optic disc with an A-scan density of 1536. Only images with a clear view of the different structures to be analysed and a minimum of 20-dB resolution were accepted for study inclusion. One image centred in the fovea and one centred in the optic disc were selected by the technician who performed the scans. Macular GCL segmentation was performed automatically using Heidelberg Eye Explorer software provided by the manufacturer, and corresponding data were obtained from the nasal and temporal sectors of the ring from 1 to 3 mm to the fovea (Figure 1). Automated peripapillary RNFL thickness measurements were generated using the Heidelberg Eye Explorer software provided by the manufacturer. Values of global RNFL thickness and nasal (N), superonasal (SN), inferonasal (IN), temporal (T), temporo-nasal (TN), and superonasal (SN) were collected.

Statistical analysis

The data were analysed using analytical commercial software (SPSS for Windows version

Figure 1. Macular GCL analysis in the contralateral eye of patient 9 in the stroke group.

22; SPSS IBM, Armonk, NY, USA), and results were presented as mean $\pm$ SD unless otherwise specified. For demographic data, Mann-Whitney test was used to find mean significance between groups and Fischer's exact test was used for categorical variables. Wilcoxon test was used to detect differences in GCL and RNFL thickness between eyes of the same subject in both groups. Mann-Whitney test was used to detect differences in GCL and RNFL thickness between eyes ipsilateral to the lesion and control eyes as

well as eyes contralateral to the lesion and control eyes. A probability value inferior to 0.05 was deemed statistically significant.

Results

Twenty stroke patients were screened, of whom only 12 fulfilled the inclusion criteria. The remaining 8 were excluded due to concomitant vascular events in other cerebral arteries (2), glaucoma (2), ischaemic optic nerve disease (1), lupus erythematosus (1), diabetic retinopathy (1), and high myopia (1). Twelve healthy individuals were included in the control group. Image quality was sufficient for at least one image in both eyes of all participants (24 eyes in the stroke group and 24 eyes in the control group).

Neither age nor gender was statistically different between groups (age: 66.6 ± 12.7 years in stroke group vs. 59.1 ± 13.36 years in control group, $p = 0.178$; gender: 7 males in stroke group vs. 3 males in control group, $p = 0.214$). Stroke group had 8 patients with a right PCA stroke, and there was a mean 50.6 ± 53.9 months (range: 3–156) gap from time of lesion to study imaging. Demographics of stroke group are described in Table 1.

No difference was found in peripapillary RNFL thickness between both eyes of same subject in the control group (Table 2). When comparing both eyes of the same subject in the stroke group, peripapillary RNFL was thinner in the ST and IT sectors in the

Table 1. Demographic characteristics of patients in the stroke group depicting age, sex, laterality of ischaemic lesion, and time between ischaemic lesion and study imaging.

Patient	Age (years)	Sex	Lesion laterality	Study inclusion (months)
Patient 1	83	Male	Right	59
Patient 2	68	Male	Right	24
Patient 3	56	Female	Right	108
Patient 4	69	Male	Left	156
Patient 5	68	Male	Left	34
Patient 6	74	Male	Right	6
Patient 7	47	Female	Right	18
Patient 8	79	Female	Right	15
Patient 9	64	Male	Left	7
Patient 10	70	Female	Right	139
Patient 11	42	Male	Right	3
Patient 12	79	Female	Left	38

Table 2. Peripapillary retinal nerve fibre thickness in control and stroke groups.

Sector	Mean $\pm$ SD thickness (μ m)					
	Control group			Stroke group		
	Right eye (n = 12)	Left eye (n = 12)	p	Ipsilateral eye (n = 12)	Contralateral eye (n = 12)	p
Global	103.08 $\pm$ 10.33	102.08 $\pm$ 10.70	0.348	79.33 $\pm$ 13.54	81.08 $\pm$ 11.52	0.721
ST	138.00 $\pm$ 21.57	136.33 $\pm$ 20.38	0.327	95.58 $\pm$ 28.15	118.17 $\pm$ 21.78	0.008
T	75.58 $\pm$ 10.77	70.17 $\pm$ 7.63	0.065	52.42 $\pm$ 13.49	53.67 $\pm$ 16.78	0.409
IT	147.67 $\pm$ 19.24	150.33 $\pm$ 18.07	0.533	90.75 $\pm$ 27.60	122.67 $\pm$ 14.16	0.023
IN	116.58 $\pm$ 26.62	117.17 $\pm$ 17.82	0.814	95.25 $\pm$ 25.49	92.42 $\pm$ 21.53	0.638
N	82.00 $\pm$ 13.14	77.83 $\pm$ 13.48	0.272	75.17 $\pm$ 10.87	57.67 $\pm$ 19.96	0.003
SN	106.67 $\pm$ 20.97	116.58 $\pm$ 20.06	0.065	98.42 $\pm$ 15.25	92.00 $\pm$ 27.11	0.333

Note. ST = superotemporal; T = temporal; IT = inferotemporal; IN = inferonasal; N = nasal; SN = superonasal.

Table 3. Macular retinal ganglion cell thickness in control and stroke groups.

Sector	Mean $\pm$ SD thickness (μ m)					
	Control group			Stroke group		
	Right eye (n = 12)	Left eye (n = 12)	p	Ipsilateral eye (n = 12)	Contralateral eye (n = 12)	p
Nasal	52.08 $\pm$ 4.06	52.33 $\pm$ 4.77	0.516	45.08 $\pm$ 8.49	29.67 $\pm$ 12.96	0.002
Temporal	46.83 $\pm$ 4.61	47.67 $\pm$ 4.29	0.077	25.92 $\pm$ 12.73	41.5 $\pm$ 8.47	0.004

Table 4. Comparison of peripapillary retinal nerve fibre layer thickness in control eyes, stroke ipsilateral eyes, and stroke contralateral eyes.

Sector	Mean $\pm$ SD thickness (μ m)				
	Control eyes (n = 24)	Ipsilateral eye (n = 12)	Contralateral eye (n = 12)	p	
Global	102.58 $\pm$ 10.30	79.33 $\pm$ 13.54	81.08 $\pm$ 11.52	0.000*/0.000 [†]	
ST	137.17 $\pm$ 20.54	95.58 $\pm$ 28.15	118.17 $\pm$ 21.78	0.000*/0.027 [†]	
T	72.88 $\pm$ 9.53	52.42 $\pm$ 13.49	53.67 $\pm$ 16.78	0.000*/0.001 [†]	
IT	149.00 $\pm$ 18.30	90.75 $\pm$ 27.60	122.67 $\pm$ 14.16	0.000*/0.000 [†]	
IN	116.88 $\pm$ 22.16	95.25 $\pm$ 25.49	92.42 $\pm$ 21.53	0.033*/0.001 [†]	
N	79.92 $\pm$ 13.19	75.17 $\pm$ 10.87	57.67 $\pm$ 19.96	0.355*/0.002 [†]	
SN	111.63 $\pm$ 20.70	98.42 $\pm$ 15.25	92.00 $\pm$ 27.11	0.067*/0.042 [†]	

ST = superotemporal; T = temporal; IT = inferotemporal; IN = inferonasal; N = nasal; SN = superonasal.

*Comparison between control eyes and ipsilateral eyes with Mann-Whitney test.

[†]Comparison between control eyes and contralateral eyes with Mann-Whitney test.

ipsilateral eye and in the N sector of the contralateral eye (Table 2). There were no differences in macular GCL thickness between both eyes of same subject in the control group (Table 3). A GCL thinning of the temporal macular sector of ipsilateral eyes and the nasal macular sector of contralateral eye was found when comparing both eyes of the same subject in the stroke group (Table 3). Figure 2 shows the distribution of macular ganglion cell layer thickness by sectors in the stroke group.

Global peripapillary RNFL thickness was significantly reduced in both eyes of stroke patients compared with controls (Table 4). When compared with controls, there was a thinning of peripapillary RNFL in the ST, T, IT, and IN sectors in ipsilateral eyes and

all sectors of the contralateral eyes of stroke patients (Table 4). Both temporal and nasal macular GCL thickness was reduced in ipsilateral and contralateral eyes from stroke patients in comparison with controls (Table 5).

Discussion

Interest in human trans-neural degeneration dates back more than a century.¹⁷ Small case reports of histological demonstration of TRD in the humans visual system emerge in the early 1940s, most of them with confounding variables.^{18,19} New evidence rose to light with pattern-evoked electroretinogram studies in the 1990s that found

Figure 2. Distribution of macular ganglion cell layer thickness by sectors in the stroke group.

differences in signal strength between the two hemiretinas of homonymous hemianopic patients.^{20,21} More recently, resource to high-resolution magnetic resonance imaging revealed optic tract thinning in hemianopic patients.²² The development of OCT technology allowed for an easy and non-invasive analysis of the retina and the optic disc. RNFL analysis and more recently the study of RGC layers have been used as potential methods in TRD research. In 2005, Mehta and Plant²³ described a pattern of the RNFL loss and thinning as expected by the field defect in two cases of congenital/longstanding hemianopia. In a more extensive study, Jindahra et al.⁴ found a RNFL thinning in patients with congenital and acquired hemianopia that followed the known trajectories of the crossing and non-crossing axons entering the optic disc. In a subsequent study by this group,⁵ there was a detectable thinning of RNFL after 100 days of the insult, with greater loss occurring in the first 1–2 years. Only case reports^{3,24} and small-sample studies^{25–27} have reported a thinning of the RGC layer in the hemiretina of patients with either mixed posterior lesions or isolated PCA ischaemic events. To our knowledge, this is the first case-control study with patients with unilateral PCA ischaemic lesions.

Figure 3. Schematic representation of peripapillary retinal nerve fibre layer comparison in the stroke group superimposed in an illustration of a retinotopic map.

In our study, we found a peripapillary RNFL and a macular GCL thinning in both eyes of patients with PCA ischaemic lesion. Our results on peripapillary RNFL comparison from both eyes of the stroke group can be superimposed in the findings of retinotopic mapping studies by Naito,²⁸ Garway-Heath et al.,²⁹ and more recently Carreras et al.⁷ The nasal sector receives predominantly axons from ganglion cells of the nasal hemiretina (crossing fibres) and was accordingly thinner in the eye contralateral to the lesion (Table 2 and Figure 3). Superior temporal and inferior temporal sectors receive axons from the arcuate bundles that derivate mainly from the temporal hemiretina (non-crossing fibres) and were therefore significantly thinner in the eye ipsilateral to the lesion (Table 2 and Figure 3). The inferior nasal, superior nasal, and temporal sectors were not statistically different between both eyes in

Table 5. Comparison between macular retinal ganglion cell thickness in control eyes, stroke ipsilateral eyes, and stroke contralateral eyes.

Sector	Mean $\pm$ SD thickness (μ m)			<i>p</i>
	Control eyes (<i>n</i> = 24)	Ipsilateral eye (<i>n</i> = 12)	Contralateral eye (<i>n</i> = 12)	
Nasal	52.21 $\pm$ 4.33	45.08 $\pm$ 8.49	29.67 $\pm$ 12.96	0.003*/0.000 [†]
Temporal	47.25 $\pm$ 4.38	25.92 $\pm$ 12.73	41.5 $\pm$ 8.47	0.000*/0.013 [†]

*Comparison between control eyes and ipsilateral eyes with Mann-Whitney test.

[†]Comparison between control eyes and contralateral eyes with Mann-Whitney test.

the stroke group, as there is a more even portion of crossing and non-crossing fibres (Figure 3). These results are in accordance with previously published RNFL studies in hemianopic patients by Jindahra et al.⁴ and Park et al.⁶ Comparison of eyes from the stroke group with normal control eyes showed a sparing of RNFL thinning in nasal sectors of the ipsilateral eye as already described in the literature.^{4,6} The general thinning of peripapillary RNFL in contralateral eyes in comparison with control eyes differs from the findings of Jindahra et al.⁴ and Park et al.,⁶ but may be justified by our division in 6 sectors instead of 12 sectors, which may have overlooked more subtle differences.

Macular GCL thickness was statistically different between both eyes of patients from the stroke group, with a thinning of the temporal side of the ipsilateral eye and the nasal side of the contralateral eye (Table 3 and Figure 2). These findings support our hypothesis of TRD after a posterior lesion, with degeneration of ganglion cells from the hemiretina related to the affected side.⁴ When comparing macular GCL between stroke patient's eyes and normal control eyes, we found a reduced thickness in the nasal and temporal sectors of eyes both ipsilateral and contralateral to the lesion. This phenomenon was already described previously by Yamashita et al.,³ and it was purposed that the nerve fibres of a particular retinal area were not necessarily originated from that area. Characterization of the retina-cortical projections in the midline has been in the core of research concerning the foveal-sparing phenomenon in hemianopic patients.³⁰ It has been hypothesised that there is a difference in the anatomic location of the ganglion cell bodies and the location of receptive fields and the existence of a region in the vertical midline where an intermingling of ganglion cells projects ipsilaterally and contralaterally.^{30–32} Validation of these findings is important to understand the mechanisms behind neuronal degeneration and bring implications for the management of these patients: GCL analysis could bring a direct correlation to visual field loss, a better understanding of disease mechanisms, and provide novel targets for therapy in these patients. As neuro-rehabilitation techniques are being developed, a deeper knowledge of mechanisms

behind the human visual system TRD could prevent the death of ganglion cells connecting to spared cortical areas.¹

Our study presents several limitations. The sample is small and heterogeneous in terms of time gap between the vascular event and study inclusion. Although care was taken to exclude patients with other lesions besides a unilateral PCA ischaemic stroke, our patients had several co-morbidities that could translate in minor infarctions or others lesions not detected by computed tomography (CT) scan or clinical evaluation as well as a generalised white matter ischaemic disease that was not quantified. Each scan was reviewed by our neuro-radiology department to confirm an isolated PCA ischaemic lesion that resulted solely on posterior damage, but we cannot exclude lateral geniculate nucleus damage that could result in direct neural degeneration.

In conclusion, our study shows that TRD may play a role in the physiopathology of lesions of the posterior visual pathway. There is a reduction in peripapillary RNFL and macular RGC in both hemiretinas of eyes ipsilateral and contralateral to the lesion. Macular GCL analysis with SD-OCT may be a relevant tool in TDR research and a potential new method for the management of patients with this disease.

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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