Neurological Sciences
https://doi.org/10.1007/s10072-023-06675-2

ORIGINAL ARTICLE

Quantification of retinal ganglion cell loss in patients with homonymous visual field defect due to stroke

Stefania Bianchi Marzoli[1] · **Lisa Melzi**[1] · **Paola Ciasca**[1] · **Alberto Raggi**[2] · **Anna Bersano**[3] · **Carlotta Casati**[4] · **Nadia Bolognini**[4,5]

Received: 2 December 2022 / Accepted: 8 February 2023

Abstract

Background To quantify the degree of ganglion cell degeneration through spectral domain optical coherence tomography (SD-OCT) in adult patients with post-stroke homonymous visual field defect.

Methods Fifty patients with acquired visual field defect due to stroke (mean age = 61 years) and thirty healthy controls (mean age = 58 years) were included. Mean deviation (MD) and pattern standard deviation (PSD), average peripapillary retinal nerve fibre layer thickness (pRNLF-AVG), average ganglion cell complex thickness (GCC-AVG), global loss volume (GLV) and focal loss volume (FLV) were measured. Patients were divided according to the damaged vascular territories (occipital vs. parieto-occipital) and stroke type (ischaemic vs. haemorrhagic). Group analysis was conducted with ANOVA and multiple regressions.

Results pRNFL-AVG was significantly decreased among patients with lesions in parieto-occipital territories compared to controls and to patients with lesions in occipital territories ($p = .04$), with no differences with respect to stroke type. GCC-AVG, GLV and FLV differed in stroke patients and controls, regardless of stroke type and involved vascular territories. Age and elapsed time from stroke had a significant effect on pRNFL-AVG and GCC-AVG ($p < .01$), but not on MD and PSD.

Conclusions Reduction of SD-OCT parameters occurs following both ischaemic and haemorrhagic occipital stroke, but it is larger when the injury extends to parietal territories and increases as time since stroke increases. The size of visual field defect is unrelated to SD-OCT measurements. Macular GCC thinning appeared to be more sensitive than pRNFL in detecting retrograde retinal ganglion cell degeneration and its retinotopic pattern in stroke.

Keywords Stroke · Retinal ganglion cell degeneration · Visual field defect · Peripapillary retinal nerve fibre layer thickness · Ganglion cell complex thickness · Spectral domain optical coherence tomography

Introduction

Trans-synaptic retrograde retinal ganglion cell (RGC) degeneration takes place in the retinal projections to the lateral geniculate nucleus. It has been observed after the death of the neurons that synapse with these cells and, in the human visual system, in patients with both congenital and acquired occipital lobe lesions [1–4]. Optic tract and RGC degeneration have been shown experimentally in macaque monkeys after occipital lobectomy [5–7], in humans through post-mortem histological examinations [7], and in vivo by magnetic resonance imaging (MRI) [8]. Addressing the nature of the acquired lesion, either cortical alone or related to the retina-cortical projections, enables hypothesizing on the likelihood of exploiting neural plasticity for recovery purposes.

✉ Stefania Bianchi Marzoli
s.bianchimarzoli@auxologico.it

✉ Nadia Bolognini
nadia.bolognini@unimib.it

1 Neuro-Ophthalmology Center and Ocular Electrophysiology Laboratory, Scientific Institute Capitanio Hospital, IRCCS Istituto Auxologico Italiano, Milan, Italy

2 Neurology, Public Health and Disability Unit, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy

3 Cerebrovascular Unit, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy

4 Department of Psychology, University of Milano-Bicocca, Piazza dell'Ateneo Nuovo 1, 20126 Milan, Italy

5 Laboratory of Neuropsychology, IRCCS Istituto Auxologico Italiano, Milan, Italy

Published online: 11 March 2023

An important issue pertains to the occurrence, in the human visual system, of trans-synaptic acquired retrograde degeneration following damage to the human post-geniculate visual pathway. Preliminary evidences from clinical observation originally suggested that retrograde trans-synaptic degeneration occurred only in subjects with a prenatal damage to the post-geniculate pathway [9, 10]. Recently, this type of degeneration was observed also in the patients with occipital lobe/optic radiation damage due to stroke, as detected by optical coherence tomography [11–14]. With spectral domain optical coherence tomography (SD-OCT), it has been shown that thinning of the peripapillary retinal nerve fibre layer (pRNFL) can occur in association with both congenital and acquired homonymous visual field defects (quadrantanopia or hemianopia) [11, 15, 16]. Changes in pRNFL following an acquired occipital stroke have been detected both within the first year post-stroke, and then slowly progress over a period of several years [12, 13, 17]. A recent study by de Vries-Knoppert and colleagues on patients with white matter damage following surgical partial temporal lobe resection showed a linear association between brain tissue volume loss and inner retinal layer atrophy, with area of atrophy determined by the size of damage to the retina-cortical projections. Importantly, results from this study suggest the existence of different potential patterns of inner retinal layer atrophy. Acquired retrograde trans-synaptic axonal degeneration secondary to small-size lesion is slow, restricted to the damaged area of its retina-cortical projections and the atrophy rate slows within a 3-month period. On the contrary, degeneration due to large lesions continues for a prolonged time and might radiate out of the area of immediate damage [18]. Thus, in large lesions, the prolonged period of time might give room to intervene with early visual rehabilitation interventions.

Thinning of the pRNFL, which corresponds to the crossed and uncrossed projections, implies a loss of RGC but it is not a direct measurement of cell atrophy. Interestingly, pRNFL thickness measurements vary in healthy population due to some confounding factors, including age, refractive error and ethnicity [19]. Objective measurements of macular layers, including RGC layer, can be achieved with retinal segmentation by means of SD-OCT analysis that have been demonstrated to correlate with visual field loss in glaucoma and other optic neuropathies [20–23]. SD-OCT analysis has been recently used in case series [10, 16, 24] and in one larger study [25] to demonstrate trans-synaptic retrograde degeneration caused by brain lesions of different aetiologies, particularly vascular and oncological injuries, in different locations from the chiasm to the primary visual cortex. The pattern of RGC loss showed the homonymous nature of the lesion, not evidenced by pRNFL thickness measurement alone, suggesting that trans-synaptic retrograde retinal degeneration could be better demonstrated by measuring the RGC layer thickness across the macula, rather than the projection of their axons in the peripapillary area. pRNFL and macular ganglion cell complex (GCC) thickness, as measured by SD-OCT, and visual filed defect, as measured by automated perimetry, are interrelated: the first ones shows the retinotopic pattern of retrograde retinal degeneration, thus describing the structural aspect of the damage; the second shows the part of visual field to which the patients cannot respond due to his/her impairment, thus describing the functional consequence of such damage.

Stroke is the second-leading cause of death and the third-leading cause of death and disability combined at the global level [26]. The observed decrease in incidence and improved survival has determined an increase in prevalence of stroke sequelae (estimated globally in 2019 at 1240/100,000), which is clearly larger than brain cancer prevalence (estimated globally in 2019 at 13.5/100,000) [27]. The retrograde trans-synaptic degeneration in stroke survivors may be misdiagnosed and is likely underrated, thus potentially leaving some patients without a complete appraisal of their sequelae and, as a consequence, limiting their access to tailored rehabilitation. In fact, as evidenced in a retrospective analysis [28], only a small minority of patients (9.6%) was referred to perimetry, and an even smaller one (2.3%) was submitted to visual function rehabilitation.

In this perspective, the present study aimed to quantify the degree of retrograde trans-synaptic degeneration of RGC and their axons at the peripapillary layer level assessed by means of SD-OCT in stroke survivors, considering the influence of the extension of damaged vascular territories (occipital vs. parieto-occipital) and type (ischaemic vs. haemorrhagic stroke), as well as the relationship between the extent of posterior visual pathway damage and the time elapsed from stroke and the age of the patients. Results will increase the understanding of the consequences of acquired brain lesion on visual functioning going beyond the impact on visual functioning that depends on direct cortical damage, with possible implication for vision restitution and its rehabilitation.

Methods

Participants

For the present study, we have analysed data of consecutive patients with radiologically confirmed ischaemic and haemorrhagic stroke, who underwent a neuro-ophthalmological examination at the Neuro-Ophthalmology Service of the IRCCS Istituto Auxologico Italiano between May 2012 and May 2014. Patients presenting visual field defects secondary to stroke involving the post-geniculate pathway (optic radiation or primary visual cortex) were included in the study. Exclusion criteria were as follows: cerebral lesions involving the optic tract or the lateral geniculate nuclei identified on a neuroradiological report and evidence of a relative afferent pupillary defect; history or evidence of retinal disease, retinal surgery, ocular trauma, optic neuropathies, including glaucoma and ocular hypertension; myopia equal to or greater than 6 diopters.

A control group of healthy volunteers was also recruited from general population, all with no history or evidence of neurological or ophthalmic disorders. All participants gave their informed consent prior to their inclusion in the study, and the study conforms to the World Medical Association Declaration of Helsinki. The study, both with regard the retrospective analysis on stroke patients and on the enrolment of control subjects, was approved by the Ethical Committee of the IRCCS Istituto Auxologico Italiano (protocol no. 2018_04_17_03).

Procedure

Patients and controls underwent a full neuro-ophthalmological examination that included visual field testing by the Humphrey field analyser Swedish Interactive Threshold Algorithm 30–2 (Carl Zeiss Meditec, Dublin, CA, USA) and SD-OCT imaging (RTVue-100 Version 5.1, Optovue Inc. Fremont, CA, USA). Visual field defects were quantified by mean deviation (MD, measured in dB) and pattern standard deviation (PSD, measured in dB).

SD-OCT imaging was used to measure the pRNFL and the macular ganglion cell complex (GCC) thickness. The pRNFL thickness was measured in both eyes of each subject by optic nerve head scan pattern protocol. This includes a 3-dimensional optic disc scan for the definition of the disc margin-based on computer-assisted determination of retinal pigment epithelium endpoints, an optic nerve head scan to measure the optic disc parameters and pRNFL thickness within an area of diameter 4 mm, cantered on the predefined disc. The measured average pRNFL (pRNFL-AVG, measured in µm) thickness is automatically given for the total circle.

The GCC protocol was used to obtain measurements of all macular area, from the inner limiting membrane to the outer boundary of the inner plexiform layer by means of 1 horizontal line scan 7 mm in length (467 A scans) and 15 vertical line scans 7 mm in length (each 400 A scans) at 0.5 mm intervals; the centre of the GCC scan is shifted 0.75 mm temporally to improve sampling of the temporal periphery. One average and two pattern-based parameters related to GCC loss were automatically calculated: average GCC thickness (GCC-AVG, measured in µm); focal and global loss volume (GCC-FLV and -GLV, both measured in %). GCC-FLV is the total sum of statistically significant GCC volume loss divided by the GCC map area; GCC-GLV represents the sum of negative fractional deviation in the entire measurements area.

Neuroradiological exams were used to separate patients according to damaged vascular territories (occipital vs. parieto-occipital lobe) and to stroke type (ischaemic vs. haemorrhagic).

Statistical analysis

One-way analyses of variance (ANOVA) was used to test differences between stroke patients and controls for pRNFL and GCC parameters of the mean for right and left eye, i.e. pRNFL-AVG (µm), GCC-AVG (µm), GCC-FLV (%) and GCC-GLC (%). In order for the constant variance assumption to be satisfied, the ANOVAs were performed on the logarithm of the peripapillary retinal nerve fibre layer thickness in microns [10]. Two series of ANOVA were carried out, the first comparing healthy controls and patients by damaged vascular territory (i.e. occipital vs. parieto-occipital) and the second comparing healthy controls and patients by stroke type (ischaemic vs. haemorrhagic). Bonferroni's post hoc test was thus implemented when the group difference reached the significance level, set at 0.05.

Then, multiple regression analyses were performed to evaluate, among stroke patients, the relationship between pRNFL-AVG, GCC-AVG, GCC-FLV and GCC-GLV, and (1) the log elapsed time in years; (2) MD and PSD calculated on the Humphrey field analyser. In each analysis, linear age in years was used as a covariate since it is known that the pRNFL and GCC thickness declines with age. A third regression was performed to address the relationship between SD-OCT parameters and age among healthy controls. The logarithm of elapsed time was shown to provide a better fit to the data than a linear or square root relationship [12]. The assumptions underlying the multiple regression analyses were checked by the study of the residuals and found to be satisfied. A significance level of 0.05 was used throughout.

The Statistica Software (Statsoft, version 6.0) was used to analyse the data.

Results

The stroke sample included 50 participants: 32 of them were males (mean age = 61.1 ± 13.3 years, range = 34–86); the mean time elapsed from stroke was 34 ± 64 months (range = 1–348). Thirty-five patients (70%) presented with damage in the parieto-occipital vascular territories; they were approximately 8 years older and their distance from stroke was 22 months longer. Fourteen (28%) suffered from a haemorrhagic stroke and thirty-six (72%) from ischaemic stroke; they were approximately 4 years younger and their distance from acute event was almost 30 months longer. It has to be noted that all patients affected by haemorrhagic stroke reported damage in the parieto-occipital vascular territories.

Out of the 50 patients herein included, 33 had homonymous hemianopia and 28 of them had a complete one. The healthy control group comprised 30 participants (18 males; mean age 58.0 ± 13.9, range 25–78 years). Table 1 reports demographic and clinical data for healthy controls and stroke patients.

In stroke patients, mean MD was − 13.6 dB (± − 5.7; range = − 4.5 to − 18.5 dB), PSD was 14.3 dB (± 3.4; range = 3.1–17.2 dB); mean pRNFL-AVG was 95.6 µm (± 13.2; range = 63.7–126.8 µm); mean GCC-AVG was 87.5 µm (± 8.7; range = 63.2–106.1 µm); mean GCC-FLV was 3.1% (± 3.2; range = 0–14%) and GCC-GLV was 11.9% (± 7.4; range = 0.5–27.7%). Macular GCC thinning, which was localized to the hemiretina corresponding to the affected visual field defects, allowed to show the retinotopic pattern of retrograde retinal degeneration in stroke patients. Please see Supplementary material (Figs. 1 and 2) for an example of visual field and SD-OCT outputs of a case of post-stroke hemianopia.

Comparison between damages in occipital vs. parieto-occipital vascular territories

Results from the ANOVA addressing differences between controls and patients with damages in occipital or parieto-occipital vascular territories are reported in Table 1. The ANOVA showed a main effect of group for all parameters.

With regard to pRNFL-AVG, post hoc comparisons showed a significant difference between controls and patients with damage in parieto-occipital vascular territories ($p = 0.04$); no differences were detected between controls and patients with damages in occipital vascular territories and between the two subgroups of stroke patients. With regard to GCC-AVG, GCC-FLV and GCC-GLV, post hoc comparisons showed significant differences between controls and both the two subgroups of stroke patients, with no difference between the two last (p-values ≤ 0.003).

Comparison between damages due to ischaemic vs. haemorrhagic stroke

Results from the ANOVA addressing differences between controls and stroke patients who suffered ischaemic vs. haemorrhagic stroke are reported in Table 1. The ANOVA showed a main effect of group for all parameters. With regard to pRNFL-AVG, post hoc comparisons showed no difference. With regard to GCC-AVG, GCC-FLV and GCC-GLV, post hoc comparisons showed significant differences between controls and both the two subgroups of patients, with no difference between the two stroke groups (p-values ≤ 0.001).

Table 1 Descriptive statistics and ANOVA with Bonferroni's post hoc comparing healthy controls, patients with occipital and parieto-occipital lesions, as well as healthy controls, patients with sequelae of ischaemic and haemorrhagic stroke

	Healthy controls	Stroke site				Stroke type			
		Occipital lesions	Parieto-occipital lesions	ANOVA F; p-value	Bonferroni's post hoc	Ischaemic stroke	Haemorrhagic stroke	ANOVA F; p-value	Bonferroni's post hoc
N	30	15	35			36	14		
Age (years)	58.0 ± 13.9	52.7 ± 14.9	60.5 ± 12.7			62.2 ± 12.5	58.4 ± 13.3		
Time from stroke (months)	–	19.6 ± 29.9	41.4 ± 79.7			26.8 ± 50.6	55.6 ± 102.2		
MD (dB)	–	− 16.6 ± − 7.5	− 12.4 ± − 4.1			− 14.3 ± − 6.0	− 11.8 ± − 4.0		
PSD (dB)	–	13.6 ± 3.4	14.5 ± 3.2			14.2 ± 3.2	14.3 ± 3.4		
pRNFL-AVG (µm)	102.6 ± 10.1	97.0 ± 12.1	94.8 ± 13.7	$F_{2,77} = 3.2$ $p = 0.05$	HC vs. P-Oc ($p = 0.04$)	96.0 ± 13.2	94.1 ± 13.4	$F_{2,77} = 3.2$ $p = 0.05$	None
GCC-AVG (µm)	97.3 ± 2.6	89.8 ± 7.2	86.7 ± 8.8	$F_{2,77} = 19.3$ $p < 0.001$	HC vs. Oc ($p < 0.001$) HC vs. P-Oc ($p = 0.003$)	88.3 ± 7.9	85.8 ± 9.9	$F_{2,77} = 18.6$ $p < 0.001$	HC vs. IS ($p < 0.001$) HC vs. HS ($p < 0.001$)
GCC-FLV (%)	0.6 ± 0.5	2.6 ± 2.5	3.5 ± 3.2	$F_{2,77} = 15.3$ $p < 0.001$	HC vs. Oc ($p = 0.001$) HC vs. P-Oc ($p < 0.0001$)	3.1 ± 3.0	3.7 ± 3.2	$F_{2,77} = 15.2$ $p < 0.001$	HC vs. IS ($p = 0.001$) HC vs. HS ($p = 0.001$)
GCC-GLV (%)	3.7 ± 1.8	9.7 ± 6.2	12.7 ± 7.4	$F_{2,77} = 16.2$ $p < 0.001$	HC vs. Oc ($p = 0.01$) HC vs. P-Oc ($p < 0.001$)	11.2 ± 6.5	13.5 ± 8.6	$F_{2,77} = 15.7$ $p < 0.001$	HC vs. IS ($p < 0.001$) HC vs. HS ($p < 0.001$)

MD, mean deviation; *PSD*, pattern standard deviation; *pRNFL-AVG*, average peripapillary retinal nerve fibre layer; *GCC-AVG*, average ganglion cell complex; *GCC-FLV*, focal loss volume of the GCC; *GCC-GLV*, global loss volume of the GCC; *HC*, healthy controls; *Oc*, occipital lobe lesion; *P-Oc*, parieto-occipital lobe lesion; *IS*, ischaemic stroke; *HS*, haemorrhagic stroke

Effect of elapsed time from stroke, age and visual field defect on pRNFL and GCC among stroke patients

Tables 2 and 3 report multiple regression analyses addressing, respectively, the joint effect of age and elapsed time from stroke on pRNFL and GCC parameters, and the age-adjusted effect of visual field defect on pRNFL and GCC parameters. Taken as a whole, the models show that the degree of optic nerve degeneration, as defined by pRNFL and GCC parameters, is predicted by chronological age and elapsed time from stroke (Table 2), but not by visual field defect, defined by both the MD and the PSD in both eyes (Table 3).

Effect of age on pRNFL and GCC among healthy controls

Finally, for the control group linear regressions were performed with age as an independent factor and the pRNFL and GCC parameters in both eyes as dependent variables (Table 4). These analyses show that in healthy individuals, the age is associated with pRNFL-AVG, but not with GCC-AVG, GCC-FLV or GCC-GLV.

Discussion

Acquired unilateral ischaemic or haemorrhagic damage following either a circumscribed occipital stroke or a stroke affecting both the occipital and the parietal vascular territories, responsible of a contralateral homonymous visual field loss, is associated with reduction of both pRNFL and macular GCC thickness as measured by different parameters derived by means of SD-OCT analysis. These results confirm, in a large cohort of patients with posterior visual pathway lesion due to stroke, the occurrence of thinning of macular GCC, which has

Table 3 Effect of visual field defect on pRNFL and GCC parameters in stroke patients

	Covariates	Slope (95% CI)	Beta	t, p-value
pRNFL-AVG	MD	−0.06 (−0.62 to 0.5)	−0.02	−0.21, p = 0.8
	PSD	0.17 (−0.80 to 1.15)	0.05	0.36, p = 0.7
GCC-AVG	MD	−0.05 (−0.42 to 0.32)	−0.03	−0.29, p = 0.7
	PSD	0.36 (−0.27 to 0.99)	0.13	1.16, p = 0.3
GCC-FLV	MD	−0.07 (−0.21 to 0.08)	−0.013	−0.97, p = 0.3
	PSD	0.11 (−0.14 to 0.37)	0.12	0.93, p = 0.4
GCC-GLV	MD	0.03 (−0.28 to 0.34)	0.03	0.22, p = 0.8
	PSD	−0.21 (−0.75 to 0.32)	−0.1	−0.82, p = 0.4

MD, mean deviation; *PSD*, pattern standard deviation; *pRNFL-AVG*, average peripapillary retinal nerve fibre layer; *GCC-AVG*, average ganglion cell complex; *GCC-FLV*, focal loss volume of the GCC; *GCC-GLV*, global loss volume of the GCC

Table 2 Effect of elapsed time from stroke and age on pRNFL and GCC parameters in stroke patients

	Covariates	Slope (95% CI)	Beta	t, p-value
pRNFL-AVG	Time elapsed since stroke (log years)	−8.17 (−12.40 to −3.94)	−0.42	−3.89, p = 0.0003
	Age (years)	−0.54 (−0.76 to −0.32)	−0.54	−4.99, p = 0.0001
GCC-AVG	Time elapsed since stroke (log years)	−3.51 (−6.24 to −0.77)	−0.28	−2.58, p = 0.01
	Age (years)	−0.39 (−0.53 to −0.25)	−0.62	−5.62, p = 0.0001
GCC-FLV	Time elapsed since stroke (log years)	1.60 (0.53 to 2.67)	0.36	3.01, p = 0.004
	Age (years)	0.11 (0.05 to 0.16)	0.47	4.01, p = 0.0002
GCC-GLV	Time elapsed since stroke (log years)	3.12 (0.83 to 5.42)	0.30	2.74, p = 0.01
	Age (years)	0.33 (0.21 to 0.45)	0.62	5.65, p = 0.0001

pRNFL-AVG, average peripapillary retinal nerve fibre layer; *GCC-AVG*, average ganglion cell complex; *GCC-FLV*, focal loss volume of the GCC; *GCC-GLV*, global loss volume of the GCC

Table 4 Effect of age on pRNFL and GCC parameters in healthy controls

	Covariates	Slope (95% CI)	Beta	*t*, *p*-value
pRNFL-AVG	Age (years)	−0.30 (−0.54 to −0.04)	−0.41	−2.37, $p=0.03$
GCC-AVG	Age (years)	−0.05 (−0.11 to 0.02)	−0.27	−1.47, $p=0.2$
GCC-FLV	Age (years)	−0.001 (−0.015 to 0.013)	−0.01	−0.06, $p=0.9$
GCC-GLV	Age (years)	−0.001 (−0.05 to 0.05)	−0.005	−0.01, $p=0.09$

pRNFL-AVG, average peripapillary retinal nerve fibre layer; *GCC-AVG*, average ganglion cell complex; *GCC-FLV*, focal loss volume of the GCC; *GCC-GLV*, global loss volume of the GCC

not systematically been addressed or observed in heterogeneous populations or in case series [10, 16, 17, 24, 25]. Macular GCC analysis appears to have higher ability in detecting retrograde trans-neuronal retinal degeneration than pRNFL, whose measurements varied in neurologically healthy individuals as an effect of ageing, as shown in the present study and also previously suggested by Kim and colleagues [19]. Thinning of all retinal parameters occurred independently of the type of stroke, ischaemic or haemorrhagic, and reduction of pRNFL was influenced by the affected vascular territory, being significantly reduced among patients with lesions in parieto-occipital vascular territories contrasted to healthy controls, but not among those with lesion confined to occipital vascular territory.

The GCC protocol was used to obtain the macular measurements of the inner retinal thickness which includes the nerve fibre layer, ganglion cell layer and inner plexiform layer generating one average and two pattern parameters. The average and pattern parameters did not differ between the two patients' subgroups (damaged vascular territories and stroke type).

Macular GCC thinning, which is localized to the portion of retina corresponding to the affected visual field defects, allows to show and quantify the retinotopic pattern of trans-synaptic retrograde degeneration in stroke patients. The findings of our study support the use of SD-OCT to measure macular GCC thickness as a reliable imaging marker of retrograde trans-synaptic degeneration in the visual pathway after stroke.

Our study also confirmed the existence of a negative relationship between every pRNFL and GCC indexes and the elapsed time since stroke (in log years), after adjusting for age. In line with previous evidence [12], pRNFL-AVG has a rate of decline of 8.17 µm per log year; the GCC-AVG decreases by 3.5 µm per log year. This decline differs from the rate of thinning found in healthy controls that showed a pRNFL decrease by ≈0.3 µm with each year of age but not significantly changes for GCC measurements. Such evidence is suggestive of a decelerating rate of loss in stroke patients, regardless of the stroke type and site, which differs from the rate of decline found with chronological age (see also [12]).

The size of visual field loss, as indexed by MD and PSD, did not predict the pRNFL and GCC thickness. This result could indicate that the amount of RGC degeneration is influenced by the occurrence of the damage in occipital vascular territory, whereas the additional involvement of the parietal one had no impact. Another explanation could be that the visual field defects in our series were all very similar with a larger number of complete homonymous hemianopia compared to localized defect (homonymous quadrantanopia or scotoma). In fact, 33 out of 50 patients herein included had homonymous hemianopia, of whom 28 had complete ones. Furthermore, in contrast to the study of Keller and colleagues [16], which showed the correspondence between visual field quadrant parameters and areas of macular atrophy in a small cases series of eight patients (of whom, five with stroke sequelae), our study included a tenfold larger group of stroke patients.

It has been suggested that stroke patients with small field defects due to acquired occipital lesions had less amount of retinal nerve fibre layer thinning and tended to have stable results and to show greater visual recovery [12]. These can be due to less sensitivity of pRNFL analysis to detect some small changes of magnitude. Our data suggest that retrograde trans-neuronal degeneration can be better demonstrated by measuring the RGC layer thickness across the macula, rather than the projection of their axons within the pRNFL. Mapping between lesions in the posterior visual pathway and their retinal projection can be used to justify a possible mechanism that helps explain functional consequences and permanent visual impairment. In cases with lesions circumscribed to the retrogeniculate pathway, among factors contributing to variability in the amount of retinal degeneration, it could also be implicated that there is a protective mechanism mediated by surviving neurons in spared regions of the visual pathway.

Visual field defects adversely affect daily life activities, such as reading and driving. Visual field testing must therefore be performed in all patients with lesions of the visual pathway, and early testing is of paramount importance in order to plan rehabilitation of visual function. In fact, the recovery of visual functions after injury occurring in adulthood is scarce but possible, in particular in the first few weeks after the insult, with 10% to 50% of patients achieving at least a partial recovery [29, 30]. In addition to this, the results of Schneider and colleagues [31] showed that residual visual cortex activity in response to blind field stimulation in the acute phase post-stroke predicts the degree of retinal GCC thinning 6 months later. These findings indicate an activity-dependent survival of retinal ganglion cells after ischaemic damage to the geniculostriate pathway, thus opening to possible therapeutic interventions.

Current approaches for post-stroke visual rehabilitation are still unsatisfactory. For instance, a retrospective analysis showed that only 9.6% of patients with stroke sequelae were referred to perimetry, and very few patients (2.3%) were submitted to visual function rehabilitation [28]. However, as shown in a prospective study, 46.7% of the patients who underwent a visual rehabilitation showed at least a partial improvement over a period of time comprised between 2 and 12 weeks [32]. Such a study included patients who received a variety of treatments (including visual search training, visual awareness, typoscopes, substitutive prisms, low vision aids, refraction and occlusive patches). In this context, the present findings are of relevance showing the need of an in-depth neuro-ophthalmological examination of post-stroke visual field defect, in order to address a so far neglected issue, namely the potential impact of retinal degeneration to functional adaptation to visual field loss and responses to different type of treatments.

Our study presents some limitations. First, the inputs on the effect of age and of distance from acute event have also been taken with caution due to the cross-sectional design. Second, the sample was entirely drawn from a single centre, with a specific expertise in the diagnosis of complex neuro-ophthalmological conditions. The degree to which the features of this sample is comparable to that of patients showing visual field defects due to stroke cannot be ascertained. Third, we did not have specific information on the main risk factors for stroke (e.g. hypertension, cigarette smoking, excessive alcohol consumption, inadequate diet and physical activity or diabetes) [33]. Moreover, it is unclear whether known risk factors, which account up to 90% of the population-attributable risk of stroke [34], might exert any role on retrograde retinal ganglion cell degeneration. A specific study is needed to ascertain the presence of such a relationship and whether risk factors impact only the development of degeneration, only on its progression, or whether they might impact on both development and progression of retrograde retinal ganglion cell degeneration. Fourth, we have no information on thrombolytic therapy implemented in the acute phase for those patients who attended emergeny department: thus, we cannot explore its potential impact on visual outcome. The influence of thrombolytic therapy on visual field recovery and retinal degeneration deserves attention in future studies.

Conclusions

In conclusion, the results of this study show that thinning of SD-OCT parameters occurs independently of the type of stroke, it is influenced by the extend of the cortical injury and it is related to time elapsed from the acute event. Macular GCC thinning appeared to be more sensitive than pRNFL in detecting retrograde retinal ganglion cell degeneration and its retinotopic pattern in stroke.

These results are of importance in relation to the early detection and monitoring of visual field defects in stroke survivors. Early treatments might prevent, or at least circumscribed, retinal degeneration, in turn improving visual restitution. So far, there is no evidence on whether and how visual rehabilitation could impact also on retinal functioning, and in turn the role of retina integrity in visual field recovery. Post-stroke rehabilitation of visual functions is of great importance to generate and test hypotheses about therapeutic interventions. For instance, addressing the potential role of risk factors for stroke on retrograde retinal ganglion cell degeneration will be of relevance to test new neuroplasticity-enhancing drugs.

Supplementary information The online version contains supplementary material available at https://doi.org/10.1007/s10072-023-06675-2.

Acknowledgements Research funded by the Italian Ministry of Health to Nadia Bolognini (Grant number: GR-2016-02362497) and Stefania Bianchi Marzoli.

Data availability Data analysed in present study are available on the Open Science Framework (OSF) repository (https://osf.io/4vkwb/).

Declarations

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Conflict of interest The authors declare no competing interest.

References

1. Hoyt WF, Rios-Montenegro EN, Behrens MM, Eckelhoff RJ (1972) Homonymous hemioptic hypoplasia. Fundoscopic features in standard and red-free illumination in three patients with congenital hemiplegia. Br J Ophthalmol 56:537–545. https://doi.org/10.1136/bjo.56.7.537
2. Beatty RM, Sadun AA, Smith L, Vonsattel JP, Richardson EP Jr (1982) Direct demonstration of transsynaptic degeneration in the human visual system: a comparison of retrograde and anterograde changes. J Neurol Neurosurg Psychiatry 45:143–146. https://doi.org/10.1136/jnnp.45.2.143
3. Mehta JS, Plant GT (2005) Optical coherence tomography (OCT) findings in congenital/long-standing homonymous hemianopia. Am J Ophthalmol 140:727–729. https://doi.org/10.1016/j.ajo.2005.03.059
4. Yamashita T, Miki A, Goto K, Araki S, Takizawa G, Ieki Y, Kiryu J, Tabuchi A, Iguchi Y, Kimura K, Yagita Y (2019) Evaluation of significance maps and the analysis of the longitudinal time course of the macular ganglion cell complex thicknesses in acquired occipital homonymous hemianopia using spectral-domain optical coherence tomography. Neuroophthalmology 44:236–245. https://doi.org/10.1080/01658107.2019.1686764

5. Van Buren JM (1963) Trans-synaptic retrograde degeneration in the visual system of primates. J Neurol Neurosurg Psychiatry 26:402–429. https://doi.org/10.1136/jnnp.26.5.402
6. Cowey A (1974) Atrophy of retinal ganglion cells after removal of striate cortex in a rhesus monkey. Perception 3:257–260. https://doi.org/10.1068/p030257
7. Cowey A, Alexander I, Stoerig P (2011) Transneuronal retrograde degeneration of retinal ganglion cells and optic tract in hemianopic monkeys and humans. Brain 134:2149–2157. https://doi.org/10.1093/brain/awr125
8. Bridge H, Jindahra P, Barbur J, Plant GT (2011) Imaging reveals optic tract degeneration in hemianopia. Invest Ophthalmol Vis Sci 52:382–388. https://doi.org/10.1167/iovs.10-5708
9. Miller NR, Newman NJ (1995) Walsh and Hoyt's clinical neuro-ophthalmology. 5th edn. The Williams & Wilkin Company, Baltimore
10. Yamashita T, Miki A, Iguchi Y, Kimura K, Maeda F, Kiryu J (2012) Reduced retinal ganglion cell complex thickness in patients with posterior cerebral artery infarction detected using spectral-domain optical coherence tomography. Jpn J Ophthalmol 56:502–510. https://doi.org/10.1007/s10384-012-0146-3
11. Park HYL, Park YG, Cho AH, Park CK (2013) Transneuronal retrograde degeneration of the retinal ganglion cells in patients with cerebral infarction. Ophthalmology 120:1292–1299. https://doi.org/10.1016/j.ophtha.2012.11.021
12. Jindahra P, Petrie A, Plant GT (2012) The time course of retrograde trans-synaptic degeneration following occipital lobe damage in humans. Brain 135:534–541. https://doi.org/10.1093/brain/awr324
13. Goto K, Miki A, Yamashita T, Araki S, Takizawa G, Nakagawa M, Ieki Y, Kiryu J (2016) Sectoral analysis of the retinal nerve fiber layer thinning and its association with visual field loss in homonymous hemianopia caused by post-geniculate lesions using spectral-domain optical coherence tomography. Graefes Arch Clin Exp Ophthalmol 254:745–756. https://doi.org/10.1007/s00417-015-3181-1
14. Schwartz SG, Monroig A, Flynn HW (2017) Progression of transsynaptic retinal degeneration with spectral-domain optical coherence tomography. Am J Ophthalmol 5:67–72
15. Jindahra P, Petrie A, Plant GT (2009) Retrograde trans-synaptic retinal ganglion cell loss identified by optical coherence tomography. Brain 132:628–634. https://doi.org/10.1093/brain/awp001
16. Keller J, Sanchez-Dalmau BF, Villoslada P (2014) Lesions in the posterior visual pathway promote trans-synaptic degeneration of retinal ganglion cells. PLoS One 9:e97444. https://doi.org/10.1371/journal.pone.0097444
17. Yamashita T, Miki A, Goto K, Araki S, Takizawa G, Ieki Y, Kiryu J, Tabuchi A, Iguchi Y, Kimura K, Yagita Y (2016) Retinal ganglion cell atrophy in homonymous memianopia due to acquired occipital lesions observed using cirrus high-definition-OCT. J Ophthalmol 2016:2394957. https://doi.org/10.1155/2016/2394957
18. de Vries-Knoppert WA, Baaijen JC, Petzold A (2019) Patterns of retrograde axonal degeneration in the visual system. Brain 142:2775–2786
19. Kim YJ, Kang MH, Cho HY, Lim HW, Seong M (2014) Comparative study of macular ganglion cell complex thickness measured by spectral-domain optical coherence tomography in healthy eyes, eyes with preperimetric glaucoma, and eyes with early glaucoma. Jpn J Ophthalmol 58:244–251. https://doi.org/10.1007/s10384-014-0315-7
20. Tan O, Chopra V, Lu AT, Schuman JS, Ishikawa H, Wollstein G, Varma R, Huang D (2009) Detection of macular ganglion cell loss in glaucoma by Fourier-domain optical coherence tomography. Ophthalmology 116:2305–2314. https://doi.org/10.1016/j.ophtha.2009.05.025
21. Seong M, Sung KR, Choi EH, Kang SY, Cho JW, Um TW, Kim YJ, Park SB, Hong HE, Kook MS (2010) Macular and peripapillary retinal nerve fiber layer measurements by spectral domain optical coherence tomography in normal-tension glaucoma. Invest Ophthalmol Vis Sci 51:1446–1452. https://doi.org/10.1167/iovs.09-4258
22. Kardon RH (2011) Role of the macular optical coherence tomography scan in neuro-ophthalmology. J Neuroophthalmol 31:353–361. https://doi.org/10.1097/WNO.0b013e318238b9cb
23. Le PV, Tan O, Chopra V, Francis BA, Ragab O, Varma R, Huang D (2013) Regional correlation among ganglion cell complex, nerve fiber layer, and visual field loss in glaucoma. Invest Ophthalmol Vis Sci 54:4287–4295. https://doi.org/10.1167/iovs.12-11388
24. Meier PG, Maeder P, Kardon RH, Borruat FX (2015) Homonymous ganglion cell layer thinning after isolated occipital lesion: macular OCT demonstrates transsynaptic retrograde retinal degeneration. J Neuroophthalmol 35:112–116. https://doi.org/10.1097/WNO.0000000000000182
25. Moon H, Yoon JY, Lim HT, Sung KR (2015) Ganglion cell and inner plexiform layer thickness determined by spectral domain optical coherence tomography in patients with brain lesions. Br J Ophthalmol 99:329–335. https://doi.org/10.1136/bjophthalmol-2014-305361
26. GBD 2019 Stroke Collaborators (2021) Global, regional, and national burden of stroke and its risk factors, 1990–2019: a systematic analysis for the global burden of disease study 2019. Lancet Neurol 20:795–820. https://doi.org/10.1016/S1474-4422(21)00252-0
27. GBD 2019 Diseases and Injuries Collaborators (2020) Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the global burden of disease study 2019. Lancet 396:1204–1222. https://doi.org/10.1016/S0140-6736(20)30925-9
28. Sand KM, Thomassen L, Næss H, Rødahl E, Hoff JM (2012) Diagnosis and rehabilitation of visual field defects in stroke patients: a retrospective audit. Cerebrovasc Dis Extra 2:17–23. https://doi.org/10.1159/000337016
29. Grasso PA, Gallina J, Bertini C (2020) Shaping the visual system: cortical and subcortical plasticity in the intact and the lesioned brain. Neuropsychologia. 142:107464. https://doi.org/10.1016/j.neuropsychologia.2020.107464
30. Tiel K, Kolmel HW (1991) Patterns of recovery from homonymous hemianopia subsequent to infarction in the distribution of the posterior cerebral artery. Neuroophthalmology 11:33–39. https://doi.org/10.3109/01658109109009640
31. Schneider CL, Prentiss EK, Busza A, Matmati K, Matmati N, Williams ZR, Sahin B, Mahon BZ (2019) Survival of retinal ganglion cells after damage to the occipital lobe in humans is activity dependent. Proc Biol Sci 286:20182733. https://doi.org/10.1098/rspb.2018.2733
32. Rowe FJ, Wright D, Brand D, Jackson C, Harrison S, Maan T, Scott C, Vogwell L, Peel S, Akerman N, Dodridge C, Howard C, Shipman T, Sperring U, Macdiarmid S, Freeman C (2013) A prospective profile of visual field loss following stroke: prevalence, type, rehabilitation, and outcome. Biomed Res Int 2013:719096. https://doi.org/10.1155/2013/719096
33. Hankey GJ (2017) Stroke. Lancet 389:641–654. https://doi.org/10.1016/S0140-6736(16)30962-X
34. O'Donnell MJ, Chin SL, Rangarajan S, Xavier D, Liu L, Zhang H, Rao-Melacini P, Zhang X, Pais P, Agapay S, Lopez-Jaramillo P, Damasceno A, Langhorne P, McQueen MJ, Rosengren A, Dehghan M, Hankey GJ, Dans AL, Elsayed A, Avezum A, Mondo C, Diener HC, Ryglewicz D, Czlonkowska A, Pogosova N, Weimar C, Iqbal R, Diaz R, Yusoff K, Yusufali A, Oguz A, Wang X, Penaherrera E, Lanas F, Ogah OS, Ogunniyi A, Iversen HK, Malaga G, Rumboldt Z, Oveisgharan S, Al Hussain F, Magazi D, Nilanont Y, Ferguson J, Pare G, Yusuf S; INTERSTROKE investigators (2016) Global and regional effects of potentially modifiable risk factors associated with acute stroke in 32 countries (INTERSTROKE): a case-control study. Lancet. 388:761-75. https://doi.org/10.1016/S0140-6736(16)30506-2