Long Term Transneuronal Retrograde Degeneration of the Retinal Ganglion Cells in Patients with Cerebral Infarction

Serebral İnfarkt Hastalarında Uzun Dönemde Retinal Ganglion Hücrelerinin Transnöronal Retrograde Dejenerasyonu

Ali Atakhan YILDIZ,[a]
Ayşegül MAVİ YILDIZ,[b]
Zeynep Ayşe ACAR,[c]
Dilek GÜVEN,[c]
Ali OLGUN,[c]
Selam Yekta ŞENDÜL[c]

[a]Clinic of Ophthalmology, Kelkit State Hospital,
[b]Clinic of Ophthalmology, Gümüşhane State Hospital, Gümüşhane
[c]Clinic of Ophthalmology Şişli Hamidiye Etfal Training and Research Hospital, İstanbul

Geliş Tarihi/*Received:* 22.11.2015
Kabul Tarihi/*Accepted:* 11.04.2016

This study was presented as an abstract at t he 15th ESASO Retina Academy Annual Meeting, 22-24 October 2015, Barcelona, Spain.

Yazışma Adresi/*Correspondence:*
Ali Atakhan YILDIZ
Kelkit State Hospital,
Clinic of Ophthalmology, Gümüşhane, TÜRKİYE/TURKEY
atoyildiz@hotmail.com

ABSTRACT Objective: The purpose of this study was to investigate the probable transneuronal retrograde degeneration (TRD) of the retinal ganglion cells (RGCs) in humans with cerebral infarction. In addition, the correlation between the laterality and severity of the retinal nerve fiber layer (RNFL) damage and other variables (laterality of hemispheric damage and arterial territory of the infarct) were analyzed. **Material and Methods:** Thirty consecutive patients were included. All of the subjects underwent complete ophthalmic examinations, including optical coherence tomography (OCT) and perimetry after diagnosis, and in the 6th and 12th months. The main outcome measures were the changes in the thicknesses of the RNFL, RGCs, and visual field (VF). The average thickness of the total macular RGCs and MD and PSD values analyzed in the perimetry (using the SITA Standard 24-2 Threshold Test) were taken into account. **Results:** The RNFL thicknesses were reduced significantly in all four quadrants in the contralateral eyes, and in the superior, inferior, and temporal quadrants in the ipsilateral eyes at 12 months. However, the reduction of the RGCs' average total thickness was not statistically significant for either the ipsilateral or contralateral groups ($p>0.05$). The loss of the VF considering the mean MD measurements was statistically significant in the contralateral group ($p=0.001$) unlike in the ipsilateral group. **Conclusions:** The RNFL thickness was reduced in both eyes at 12 months, providing evidence for TRD. The TRD was more pronounced in the nasal quadrant of the contralateral and temporal quadrant of the ipsilateral eye.

Key Words: Brain infarction; retrograde degeneration; optic nerve; retinal ganglion cells; visual field tests

ÖZET Amaç: Çalışmanın amacı serebral infarkt hastalarında retinal ganglion hücrelerinin (RGH) olası transnöronal retrograde dejenerasyonunu (TRD) araştırmaktır. Retinal sinir lifi (RNFL) hasarının ciddiyeti ve tarafı ile diğer değişkenlerin arasındaki ilişkinin yanı sıra hemisferik hasarın tarafı ve infarkta sebep olan arter bölgesi de analiz edildi. **Gereç ve Yöntemler:** Otuz ardışık hasta çalışmaya dahil edildi. Tüm hastalar tanı aldıktan sonra optik koherens tomografi (OKT) ve perimetriyi de içeren tam bir oftalmik muayeneden geçirildi ve tetkikler 6. ve 12. aylarda tekrarlandı. Çalışmanın ana amacı RSLT ve RGH tabakalarındaki kalınlık değişimleri ile görme alanındaki değişimleri değerlendirmekti. Ortalama total maküler RGH kalınlığı ve perimetri (SITA- Standart 24-2 eşik test) MD, PSD değerleri dikkate alındı. **Bulgular:** On ikinci ayda RSLT; kontralateral gözde dört kadranda; ipsilateral gözde ise superior, inferior ve temporal kadranlarda anlamlı derecede incelmiş idi. Ortalama total maküler RGH tabakasındaki incelme ipsilateral ve kontralateral göz için istatistiksel olarak anlamlı değildi ($p>0,05$). İpsilateral grubun aksine kontralateral gruptaki görme alanı kaybı MD değerleri göz önüne alındığında istatistiksel olarak anlamlı idi ($p=0,001$). **Sonuç:** Transnöronal retrograde dejenerasyonu destekler şekilde 12. ayda her iki gözde de RSLT incelmişti. Transnöronal retrograde dejenerasyon kontralateral gözün nazal; ipsilateral gözün ise temporal alanında daha belirgin idi.

Anahtar Kelimeler: Beyin infarktüsü; retrograd dejenerasyon; optik sinir; retinal gangliyon hücreleri; görme alanı testi

doi: 10.5336/ophthal.2015-47455

Turkiye Klinikleri J Ophthalmol 2016;25(3):164-73

Transneuronal degeneration is the damage of neurons resulting from the disruption of input from or output to other neurons.[1] It is an active excitotoxic process which occurs when a neuron is overstimulated by a neurotransmitter (most commonly glutamate), causing the dysfunction of that neuron which drives neighboring neurons into metabolic deficit, resulting in a rapid, widespread loss of neurons.[2] This can be either anterograde or retrograde, indicating the direction of the degeneration relative to the original site of damage. In the eye, an anterograde projection is from the retina to the primary visual cortex, and a retrograde projection is from the primary visual cortex to the retina. The atrophy seen in the cells of the mammalian lateral geniculate nucleus following the interruption of the optic nerve is a type of transneuronal anterograde degeneration (TAD); while the degeneration of retinal ganglion cells (RGC) after lesions of the visual cortex is a transneuronal retrograde degeneration (TRD).[3-6] Several studies in primate models of glaucoma and in glaucoma patients have demonstrated decreased neuronal density, and decreased biological activity in the visual pathway, primary visual cortex, or both.[7] On the other hand, despite completely different pathological mechanisms, the eventual loss of the RGC and the retinal nerve fiber layer (RNFL) may make it difficult to differentiate TRD from glaucoma.[8]

Both geniculate and retinal degeneration have been reported in primates after the removal of the striate cortex.[9] In human eyes, histological evidence of the TRD of the RGC has only been reported in patients with congenital malformations, or after a surgical lobectomy to remove a brain tumor.[10-12] However, a recent study using optical coherence tomography (OCT) demonstrated the TRD of the RNFL in patients with an acquired cerebral infarction.[13]

OBJECTIVE

1) Demonstrate the TRD of the RGC after a cerebral infarct using OCT and a visual field analyzer.

2) Investigate the relationship between the severity of the RNFL loss and arterial territory of the infarction, and between the severity of the RNFL loss and the laterality of the hemispheric damage.

3) Investigate the relationship between the severity of the visual field loss and the arterial territory of the infarction, and between the severity of the visual field loss and the laterality of the hemispheric damage.

MATERIAL AND METHODS

Thirty patients diagnosed with cerebral ischemic infarcts at the Neurology Clinic of the Şişli Hamidiye Etfal Training and Research Hospital, between August of 2013 and November of 2013, were included in this study. The patient records were reviewed prospectively, and the diagnosis of cerebral ischemic infarct was confirmed by the Neurology Clinic using magnetic resonance imaging (MRI) and computerized tomography (CT) angiography.

Both eyes of each patient were included in this study, and all of the patients were informed about their participation in the study, with written informed consent obtained. The study was approved by the Ethics Committee of the Şişli Hamidiye Etfal Training and Research Hospital, and was conducted according to the guidelines of the Declaration of Helsinki.

All of the patients were examined thoroughly, including the best corrected visual acuity, slit lamp biomicroscopy, Goldmann applanation tonometry measurements, dilated inspection of the optic nerve head and fundus, retinal nerve fiber and ganglion cell layer thickness measurements (RTVue Fourier-Domain Optical Coherence Tomography; Optovue, Fremont, CA), and automatized perimetry (Humphrey Visual Field Analyzer; Carl Zeiss Meditec, Inc., Dublin, CA). The MD and PSD values were analyzed in the perimetry, using the SITA Standard 24-2 Threshold Test after the diagnosis of a cerebral infarction, and at the 6th month and 12th month.

INCLUSION CRITERIA

1) Improved best visual acuity of 20/40 or above.

2) Spherical refractive impairment between -6.00 and +3.00 diopters (D) and cylindrical refractive impairment between -2.50D and +2.50D.

3) Normal anterior chamber depth upon slit lamp examination.

4) Reliable perimetry results (false positive/negative correlation below 15% and loss of fixation below 20%).

EXCLUSION CRITERIA

1) Presence of a diabetic retinal disease, including hypertensive retinopathy of grades 3 or 4.

2) History of an ophthalmological surgery other than cataract surgery without any complications, or a history of trauma to the eye.

3) History of glaucoma, optic neuropathy, or similar diseases that can affect the optic nerve.

4) History of a systemic or neurological disease that can affect the visual field, other than the cerebral infarct.

For each patient, the intraocular pressure measurement using Goldmann applanation tonometry was repeated for a minimum of 3 times. Those patients with one or more of these symptoms were also excluded from the study: abnormal glaucomatous optic disc appearance, visual field deficiency (possibly associated with glaucoma), and a corrected intraocular pressure of 21 mmHg or above in a random measurement. Focal or common thinning, an indentation of the neuroretinal rim, disc hemorrhage, or a vertical cup/disc proportion of 20% or higher, compared to the opposite eye, were accepted as an abnormal glaucomatous disc appearance.

A cerebral infarct is classified due to the localization of an arterial obstruction determined using magnetic resonance imaging (MRI) and computerize tomography (CT) angiography. The region of the anterior cerebral artery (ACA) contains the medial surface of the hemisphere to the superior and inferior sulcus, the anterior part of the frontal lobe, and the optic radiation. The region of the medial cerebral artery (MCA) contains the exterior surface of the hemisphere to the superior and inferior frontal sulcus and the lateral orbital gyrus. Ultimately, the region of the posterior cerebral artery contains the dorsal surface of the mid-brain and the inferomedial surface of the temporal and occipital lobes.[14]

The eye on the same side of the cerebral infarct, and expected to have nasal hemianopsia or quadranopsia corresponding to the non-decussating fibers, was defined as the ipsilateral eye. The eye on the opposite side of cerebral infarct, and expected to have temporal hemianopsia and quadranopsia due to the decussating fibers in the optic chiasm, was defined as the contralateral eye.

OPTICAL COHERENCE TOMOGRAPHY MEASUREMENTS

The retinal nerve fiber layer and ganglion cell complex were evaluated using optical coherence tomography (RTVue Fourier-Domain Optical Coherence Tomography; Optovue, Fremont, CA). The reliability of all of the imaging procedures (SSI) was greater than 50%, and all of the imaging procedures were done by the same physician. Moreover, the retinal nerve fiber layer measurements were evaluated as the common superior, inferior RNFL thickness, and 4-quadrant (nasal, temporal, superior, and inferior) RNFL thickness. The ganglion cell complex is composed of the three innermost retinal layers (nerve fiber layer, ganglion cell layer, and inner plexiform layer) containing the axons, cell bodies, and dendrites of the RGC. The macular GCC scan protocol using the SD-OCT iVue consists of 15,000 scan points in a 7 mm square area within 0.6 s, by using one horizontal line and 15 vertical lines at 0.5 mm intervals. The scans were centered 0.75 mm temporal to the fovea to improve the coverage of the temporal macula, and were processed automatically to provide a map of the GCC. In our study, the average of the total GCC (GCC av. total) was considered.

VISUAL FIELD ANALYSIS

All of the patients were subjected to a functional evaluation of the optic nerve by VF analysis using the SITA-Standard 24-2 on the Humphrey Field Analyzer II (Carl Zeiss Meditec, Inc.). Regarding

the VF analysis, the global indices Mean Deviation (MD) and Pattern Standard Deviation (PSD) were taken into account.

STATISTICAL ANALYSIS

The statistical analysis of this study was done using the Number Cruncher Statistical System (NCSS) 2007 Statistical Software (Utah, USA) packaged program. While evaluating the data, along with the definitive statistical methods (mean, standard deviation) in the repetitive measurements of the normally distributed variable groups, the repeated measures of variance analysis was used. In the subgroup comparison, the Newman Keuls multiple comparison test was used. The one-way analysis of variance was used in the intergroup comparison. In the comparison of the pairwise groups, the independent samples t-test was used. The Friedman test was used in the abnormally distributed groups. In the subgroup comparison, Dunn's multiple comparison test was used. The Kruskal Wallis test was used in the intergroup comparison, and finally, the Mann-Whitney U test was used in the comparison of the pairwise groups. The level of the statistical significance of the results was assumed to be $p<0.05$.

RESULTS

Thirty patients diagnosed with cerebral infarcts were included in this study. Eighteen of the patients (60%) were male, 12 (40%) were female, and the mean age of the patients was 52.83±10.82 years old (between 28 and 64). The mean of the best corrected visual acuity (BCVA) according to the Snellen chart was 0.96±0.09 (between 0.7-1.0), and the mean intraocular pressure (IOP) measured using Goldmann applanation tonometry was 12.97±1.81 (Table 1). Thirteen of the patients (43.3%) had an obstruction in the medial cerebral artery region, 9 of the patients (30%) had an obstruction in the anterior cerebral artery region, and 8 of the patients (26.7%) had an obstruction in the posterior cerebral artery region.

TABLE 1: Demographic characteristics of the patients.

	N	Mean±SD	Minimum	Maximum
Age (year)	30	52,83±10,82	28	64
Visual acuity	30	0,96±0,09	0,7	1
IOP	30	12,97±1,81	10	16

IDP: Intraocular pressure; SD: Standard deviation.

The RNFL, RGC, and VF measurements in the first week after the diagnosis of the cerebral infarct, and at the 6th month and 12th month were compared. A statistically significant change was observed in the initial, 6th, and 12th month mean RNFL superior quadrant measurements of both the ipsilateral (p=0.010) and contralateral (p=0.002) groups (Table 2). In addition, a statistically significant change was observed in the initial, 6th, and 12th month mean RNFL inferior quadrant measurements of both the ipsilateral (p=0.0001) and contralateral (p=0.037) groups. Moreover, a statistically significant change was observed in the initial, 6th, and 12th month mean RNFL temporal quadrant measurements of both the ipsilateral (p=0.0001) and contralateral (p=0.029) groups.

A statistically significant change was not observed between the initial, 6th, and 12th month RNFL nasal quadrant means of the ipsilateral group (p=0.189); however, a statistically significant change was observed in the initial, 6th, and 12th month RNFL nasal quadrant means of the contralateral group (p=0.012). The initial RNFL nasal quadrant means were statistically significantly increased when compared to the 12th month means (p=0.017), and the 6th month RNFL nasal quadrant means were statistically significantly increased when compared to the 12th month means (p=0.026), but a statistically significant change was not observed between the initial and 6th month RNFL nasal quadrant means (p=0.215).

In the comparison of the ACA, MCA, and PCA groups, no statistically significant change was observed in the ipsilateral or contralateral groups between the initial, 6th, and 12th month RNFL thickness means in any quadrant (p>0.05) (Tables 3 and 4).

A statistically significant change was not observed between the initial, 6th, and 12th month average total RGC thicknesses of the ipsilateral or

TABLE 2: RNFL thickness of superior, inferior, temporal and nasal quadrant means of the ipsilateral and contrateral group.

		Ipsilateral	Contralateral	p*
RNFL superior quadrant	Initial	131,97±14,09	135,83±13,2	0,277
	6 thmonth	127,13±12,29	132,37±15,14	0,147
	12 th month	127,67±15,67	132,37±15,14	0,629
	p+	0,010	0,002	
RNFL inferior quadrant	Initial	143,27±14,47	142,93±17,13	0,935
	6 thmonth	140,53±13,13	140,73±16,84	0,959
	12 th month	136,43±15,21	137,97±21,18	0,749
	p+	0,0001	0,037	
RNFL temporal quadrant	Initial	86,53±12,64	82,33±14,37	0,234
	6 thmonth	84,27±11,56	81,53±15,37	0,439
	12 th month	79,33±12,95	78,57±16,83	0,844
	p+	0,0007	0,029	
RNFL temporal quadrant	Initial	80,73±16,55	83,6±18,95	0,535
	6 thmonth	79,8±16,93	81,37±18,21	0,731
	12 th month	77,27±15,09	777,93±18,98	0,0881
	p+	0,189	0,012	

*independent samples t-test + Matched pairs one-way analysis of variance.

TABLE 3: Assessment of general mean superior and inferior RNFL thicknesses of the ipsilateral eye according to the months and arterial territory; anterior cerebral artery (ACA), middle cerebral artery (MCA), posterior cerebral artery (PCA).

		İpsilateral			
		ACA n:9	MCA n:13	PCA n:8	p*
General mean superior RNFL thickness	Initial	103,56±35,15	98,69±31,05	101,38±36,15	0,945
	Month 6	110,44±10,5	103,15±10,01	109,13±4,67	0,152
	Month 12	110,33±10,99	99,54±10,52	109,13±8,94	0,239
General mean inferior RNFL thickness	Initial	109,33±10,95	110,92±9,14	115,13±8,87	0,454
	Month 6	109,22±8,7	105,69±7,8	112,13±9,34	0,247
	Month 12	107,78±11,24	102,69±9,46	108,5±9,58	0,352

One=way analysis of variance.

TABLE 4: Assessment of general mean superior and inferior RNFL thicknesses of the contralateral eye according to the months and arterial territory; anterior cerebral artery (ACA), middle cerebral artery (MCA), posterior cerebral artery (PCA).

		Contralateral			
		ACA n:9	MCA n:13	PCA n:8	p*
General mean superior RNFL thickness	Initial	111,22±9,04	109,69±9,6	113,63±10,18	0,664
	Month 6	109±9,54	107±8,13	111,13±16,68	0,720
	Month 12	106,44±9,14	103,46±9,95	107±18,75	0,783
General mean inferior RNFL thickness	Initial	112,22±14,77	110,54±10,61	114,75±12,01	0,751
	Month 6	108,89±8,22	108,23±11,97	111,88±16,33	0,799
	Month 12	104,78±11,64	104,92±13,28	110,13±19,57	0,692

One=way analysis of variance.

TABLE 5: Initial month 6 and month 12 mean RGC (retinal ganglion cell) thicknesses of ipsilateral and contralateral eyes.

RGC	İpsilateral	Contralateral	p*
Initial	97,91±8,16	99,18±9,39	0,577
Month 6	97,77±7,99	98,79±9,07	0,643
Month 12	97,13±7,56	98,72±8,94	0,460
p+	0,534	0,716	

*Independent t-test + Matched pairs one-way analysis of variance.

contralateral groups (Table 5). When the ipsilateral and contralateral groups were compared with each other in the means of the initial, 6th, and 12th month RGC values, a statistically significant change was not observed (p>0.05). Moreover, a statistically significant change was not observed between the initial, 6th, and 12th month average total RGC thicknesses of either the ipsilateral or contralateral ACA, MCA, or PCA groups (p>0.05).

A statistically significant change was not observed between the initial, 6th, and 12th month VF MD means of the ipsilateral group (p=0.107) (Figure 1); however, a statistically significant change was observed between the initial, 6th, and 12th month VF MD means of the contralateral group (p=0.001). The initial VF MD means were significantly lower when compared to the 6th and 12th month means (p=0.004 and p=0.022, respectively), whereas a statistically significant change was not observed between the 6th and 12th month VF MD means (p=0.230) (Table 6).

A statistically significant change was not observed between the initial, 6th, and 12th month VF PSD means of the ipsilateral group (p=0.079), but a significant change was observed between the initial, 6th, and 12th month VF PSD means of the con-

TABLE 6: Initial, month 6 and 12 mean deviation (MD) and pattern standard deviation (PSD) measurements in visual field analysis (VF) of both ipsilateral and contralateral eyes.

		İpsilateral	Contralateral	p*
VF MD	Initial	-3,76±3,81	-4,69±5,11	0,767
	Month 6	-3,33±4,24	-3,79±5,82	0,773
	Month 12	-3,33±5,52	-3,63±6,34	0,836
	p+	0,107	**0,001**	
VF PSD	Initial	4,21±2,83	4,44±3,65	0,728
	Month 6	3,71±2,59	3,93±3,09	0,853
	Month 12	4,03±3,5	3,80±3,09	0,813
	p+	0,079	**0,002**	

*Mann Whitney U test +Friedman test.

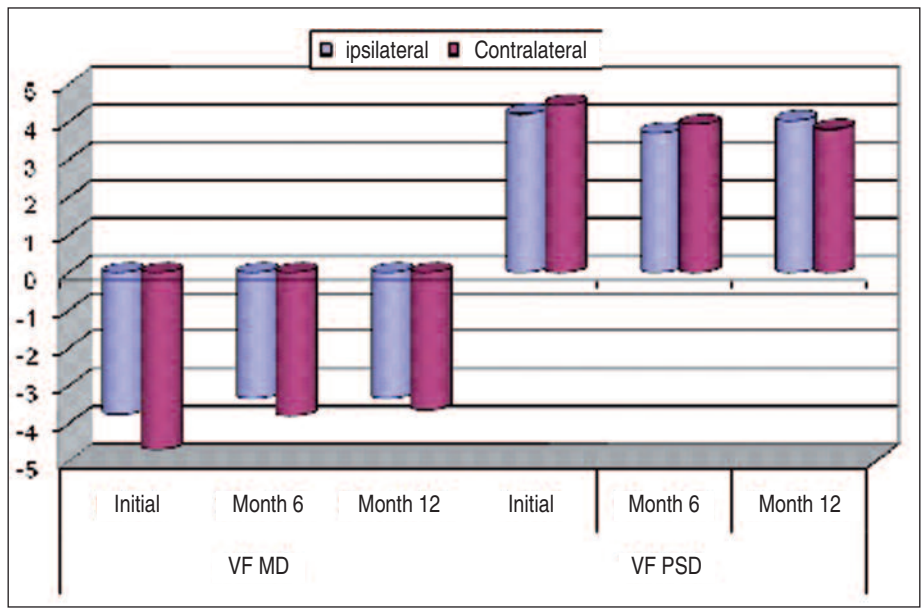

FIGURE 1: Initial, month 6 and month12 mean MD (Mean Deviation) and PSD (Pattern Standard Deviation) measure of both ipsilaterial and contralateral eyes.
(See color figure at http://www.turkiyeklinikleri.com/journal/oftalmoloji-ozel-dergisi/1308-111X/)

tralateral group (p=0.002). Additionally, the initial VF PSD means were significantly higher when compared to the 12th month means (p=0.037), whereas a significant change was not observed between the other time intervals (p>0.05). Overall, a statistically significant change was not observed between the initial, 6th, and 12th month visual field MD and PSD means of the ipsilateral or contralateral ACA, MCA, or PCA groups (p>0.05).

Twenty patients (66.6%) had visual field defects at the first visit: 2 (6.6%) had temporal hemianopsia, 1 (3.3%) had central sparing scotoma, 3 (10%) had arcuate scotoma, and 14 (46.6%) had constricted visual fields. Ten (33.3%) of the patients' visual field analyses were within normal limits at the first visit. Of the patients with visual field defects, 6 (20%) showed full recovery, 3 (10%) showed partial improvement, and 11 (36.6%) showed no improvement within 6 months of the onset of stroke.

DISCUSSION

In this study, we aimed to determine the TRD of the RNFL and the RGC by OCT in patients with acute cerebral infarction. We aimed to detect any relationship between the RNFL or RGC damage, and any eventual visual field defect occurrence, using optical coherence tomography and Humphrey perimetry, respectively. The ACA, MCA, and PCA territory infarctions together cover most regions of the brain, including the frontal, parietal, temporal, and occipital lobes. These regions of the brain may give projections to the visual pathways, and thus, lesions would result in the TRD of the RGC.

Central nervous system injury spreads from one population of neurons to another along the anatomical and functional connections in several neurodegenerative diseases. This process, which is called trans-synaptic or transneuronal degeneration, is a critical component of the disease progression in many neurological disorders.[14-18] Transneuronal anterograde degeneration is the degeneration of a target neuron after the death of the presynaptic neuron or loss of the presynaptic input.[3-6] However, the TRD occurs when neurons degenerate after the removal of their postsynaptic target. In the eye, transneuronal retrograde degeneration occurs in the RGC, which projects to the lateral geniculate nucleus (LGN), after the death of the neurons in the visual pathway that have synapses with the RGC.

This study examined patients with various cerebral infarctions using spectral-domain OCT and Humphrey perimetry; however, we did not find any statistically significant differences between the baseline, 6th, and 12th month RGC thicknesses. This result may be associated with the limited follow up time, or the evaluation of only the overall average thicknesses of the RGC, instead of the other quantifiable aspects of the RGC, such as the superior and inferior quadrant measurements and the percentage of focal loss volume (FLV%) and global loss volume (GLV%). Furthermore, there may be isolated pockets of thinning in the GCC associated with the TRD.

In a study using OCT by Park et al., the pattern of thinning in the RNFL differed between the eye on the same side and the eye on the opposite side of the infarction.[13] The nasal and temporal peripapillary retina does not correspond to the retinotopic map of the visual cortex, and both crossed and uncrossed fibers may pass through the superior, inferior, and temporal peripapillary retina to the optic disc. However, the nasal peripapillary retina contains a preponderance of crossed axons, and the temporal peripapillary retina contains a preponderance of uncrossed axons.[19] The results of this study showed that the superior, inferior, and nasal peripapillary retina in the contralateral eye was affected by the TRD of the RGC where the crossed fibers are located. Additionally, the superior, inferior, and temporal peripapillary retina in the ipsilateral eye was affected by the TRD of the RGC where the uncrossed fibers are located. The nasal regions were found to be affected mainly in the contralateral eye and temporal regions in the ipsilateral eye. In the same study, Park et al. reported that the RNFL thickness reduction was greater in those patients with PCA infarctions (n=17), followed by MCA (n=21) and ACA infarctions (n=8), respectively.

However, in our study, no statistically significant change was observed in the RNFL thickness means of the ACA (n=9), MCA (n=13), and PCA (n=8) groups between the initial, 6th, and 12th months ($p>0.05$). This result may be associated with the limited number of subjects in our study.

Naito showed that the projection of crossing fibers from the nasal retina exclusively makes up a larger sector on the nasal than on the temporal side of the optic disc. This region has considerably greater intermingling of crossed and uncrossed fibers.[20] Theoretically, the superior and inferior peripapillary retina may contain crossed fibers, uncrossed fibers, or both from the more temporally located papillomacular bundle. An RNFL thickness change in the superior and inferior peripapillary retina was observed in both the contralateral and ipsilateral eyes in the study by Naito. In our study, the first and 12th month superior average RNFL thicknesses of the ipsilateral eye did not differ from each other statistically. However, the superior average RNFL thickness of the contralateral eye in the 12th month was apparently lower than in the beginning. Furthermore, the 6th and 12th month examinations showed a statistically significant decrease in the RNFL thicknesses in the superior, inferior, and temporal sectors when compared with the baseline thicknesses in both the contralateral and ipsilateral eyes. The first, 6th, and 12th month nasal RNFL thicknesses differed significantly in only the contralateral eyes, and these findings are accordance with the results of Park, Jindahra, and Naito et al.[13,20]

Visual field loss following stroke has been largely attributed to cortical strokes in which the visual pathway is damaged. Following a stroke, the loss of the visual field is usually more peripheral in nature. The most common type of visual field loss is that of homonymous hemianopia, in which there is a loss of the same half of the visual field in both eyes, and which occurs in approximately two-thirds of those patients with visual field losses.[21-23] Other types of visual field losses may include inferior and superior quadrantanopia, constricted visual fields, scotomas, and altitudinal defects.[24-28] Pambakian and Kennard reported visual field losses due to an occipital lobe lesion in 40%, a parietal lobe lesion in 30%, a temporal lobe lesion in 25%, and 5% with damage to the optic tract and lateral geniculate nucleus.[29] Zhang et al. reported the area of stroke as the occipital lobe in 54%, optic radiations in 33%, the tract in 6%, lateral geniculate nucleus in 1%, and 5% with multiple pathway segment involvement.[30] Further reports state that most stroke related visual field loss is related to an occipital infarct.[31-33]

One previous study showed that the removal of the striate cortex in a monkey resulted in the nearly complete loss of projection neurons in the corresponding region of the LGN within 12 weeks.[33] The subsequent TRD of the RGC occurred after the degeneration of the projection neurons of the LGN. In addition, shrinkage of the optic tract was pronounced through the first 1 to 2 years, and the TRD of the RGC occurred after 3 years. As in animal studies, the degeneration of the RGC in humans has been shown to be progressive in the first years after the lesion, becoming relatively stable or progressing slowly in later years.

Rowe et al. reported that the type of visual field loss was predominantly homonymous hemianopia, which occurred as a complete or partial loss (with or without macular sparing) (73.5%).[34] Other types of visual field loss included inferior and superior quadrantanopia (15.2%), constricted visual fields (9.2%), scotomas (5.1%), and altitudinal defects. When considering the type of field loss and location of the stroke lesion, homonymous hemianopia was more prevalent in the occipital lobe and middle or posterior cerebral artery strokes. Moreover, quadrantic defects were more prevalent in occipital, parietal, and temporal lobe strokes, while homonymous scotomas, altitudinal defects, and temporal crescent defects were associated with occipital lobe strokes.

Zhang et al. found that scotomas and macular sparing could not be localized to only occipital lesions, but could occur in other locations of the visual pathway; a statement with which we concur.[30] Visual fields can recover spontaneously following damage to the geniculostriate pathway after cerebral

infarction and, generally, patients with homonymous field defects from vascular disease seem to have a poor prognosis for spontaneous recovery.

Pambakian and Kennard reported that less than 10% fully recover, and up to 50% show partial improvement of varying extents.[29] Zhang et al. reported that of those diagnosed with visual field loss within one month of stroke onset, 55% showed improvement of the field.[30] In addition, Gray et al. reported that most recovery occurred in the first 10 days, which is supported by Cassidy et al.[35,36] However, further recovery is negligible after 10-12 weeks.[35-37] More importantly, no patient, lesion, or visual field type was found to correlate with the outcome. Rowe et al. reported that 8% of their patients had achieved full recovery of their visual field loss within the first 2 weeks of stroke onset. Subsequently, a further 39% showed partial improvement within 3 months of stroke onset; however, 52% showed no improvement, and a very small number showed further deterioration.[34]

We preferred to use the mean deviation and pattern standard deviation scores for the statistical analysis of the visual field results. According to the MD score, no statistically significant difference was determined between the first, 6th month, and 12th month follow ups in the ipsilateral eye. In the contralateral eye, the MD score obtained at the first examination was significantly lower than the 6th and 12th month scores, while the MD score stabilized significantly after the 6th month. As a result, a statistically significant improvement in the visual field between the first and 6th month visit is in accordance with the present literature. The 6th month scores of both the MD and PSD did not differ significantly from the scores of the 12th month. Moreover, no territory of infarction was found to correlate with the scores of the MD and PSD in both the ipsilateral and contralateral eyes.

This result may be explained using 3 theories; for example, the patients underwent the first VF assessments in the first week of the acute cerebral infarction. Therefore, patient co-operation in the visual field test may have been poorer in the first examination when compared with the following examinations. The second theory is that in most of the optic neuropathies, functional damage (VF defects) becomes subsequent to the anatomical damage (RNFL loss); therefore, significant visual field loss may be detected in a longer follow up time. The last theory is about the VF testing procedure; since we used the 24-2 Humphrey testing, we might have overlooked the more peripheral VF defects.

To the best of our knowledge, this is the first clinical study to consider VF analysis and the thicknesses of the RGC complex and RNFL simultaneously after cerebral infarction. The RGC thickness was not found to be affected due to suspected transneuronal retrograde degeneration and cell loss. We believe that the follow up time should be longer, and sub-groups of the RGC thickness measurements should be considered in order to detect any changes in the ganglion cell complex thickness.

REFERENCES

1. Parker RS. Primary brain damage and concussion. Concussive Brain Trauma: Neurobehavioral Impairment and Maladaptation. 1st ed. New York: CRC Press LLC; 2000. p.107-8.
2. Garden GA, La Spada AR. Intercellular (mis)communication in neurodegenerative disease. Neuron 2012;73(5):886-901.
3. Yücel YH, Zhang Q, Weinreb RN, Kaufman PL, Gupta N. Effects of retinal ganglion cell loss on magno-, parvo-, koniocellular pathways in the lateral geniculate nucleus and visual cortex in glaucoma. Prog Retin Eye Res 2003;22(4):465-81.
4. Ito Y, Shimazawa M, Chen YN, Tsuruma K, Yamashima T, Araie M, et al. Morphological changes in the visual pathway induced by experimental glaucoma in Japanese monkeys. Exp Eye Res 2009;89(2):246-55.
5. Gupta N, Greenberg G, de Tilly LN, Gray B, Polemidiotis M, Yücel YH. Atrophy of the lateral geniculate nucleus in human glaucoma detected by magnetic resonance imaging. Br J Ophthalmol 2009;93(1):56-60.
6. Jindahra P, Petrie A, Plant GT. Retrograde trans-synaptic retinal ganglion cell loss identified by optical coherence tomography. Brain 2009;132(Pt 3):628-34.
7. Graham SL, Klistorner AI, Grigg JR, Billson FA. Objective VEP perimetry in glaucoma: asymmetry analysis to identify early deficits. J Glaucoma 2000;9(1):10-9.
8. Shon K, Sung KR. Assessment of macular ganglion cell loss patterns in neurologic lesions that mimic glaucoma. Korean J Ophthalmol 2014;28(4):314-22.
9. Cowey A, Stoerig P, Williams C. Variance in transneuronal retrograde ganglion cell degeneration in monkeys after removal of striate cortex: effects of size of the cortical lesion. Vision Res 1999;39(21):3642-52.

10. Vanburen JM. Trans-synaptic retrograde degeneration in the visual system of primates. J Neurol Neurosurg Psychiatry 1963;26(5):402-9.
11. Cowey A. Atrophy of retinal ganglion cells after removal of striate cortex in a rhesus monkey. Perception 1974;3(3):257-60.
12. Beatty RM, Sadun AA, Smith L, Vonsattel JP, Richardson EP Jr. Direct demonstration of transsynaptic degeneration in the human visual system: a comparison of retrograde and anterograde changes. J Neurol Neurosurg Psychiatry 1982;45(2):143-6.
13. Park HY, Park YG, Cho AH, Park CK. Transneuronal retrograde degeneration of the retinal ganglion cells in patients with cerebral infarction. Ophthalmology 2013;120(6):1292-9.
14. Saper CB, Wainer BH, German DC. Axonal and transneuronal transport in the transmission of neurological disease: potential role in system degenerations, including Alzheimer's disease. Neuroscience 1987;23(2):389-98.
15. Kume A, Takahashi A, Hashizume Y. Neuronal cell loss of the striatonigral system in multiple system atrophy. J Neurol Sci 1993;117(1-2):33-40.
16. Su JH, Deng G, Cotman CW. Transneuronal degeneration in the spread of Alzheimer's disease pathology: immunohistochemical evidence for the transmission of tau hyperphosphorylation. Neurobiol Dis 1997;4(5):365-75.
17. Suzuki H, Oyanagi K, Takahashi H, Ikuta F. Evidence for transneuronal degeneration in the spinal cord in man: a quantitative investigation of neurons in the intermediate zone after long-term amputation of the unilateral upper arm. Acta Neuropathol 1995;89(5):464-70.
18. Goldby F. A note on transneuronal atrophy in the human lateral geniculate body. J Neurol Neurosurg Psychiatry 1957;20(3):202-7.
19. Falke P, Abela BM Jr, Krakau CE, Lilja B, Lindgärde F, Maly P, et al. High frequency of asymptomatic visual field defects in subjects with transient ischaemic attacks or minor strokes. J Intern Med 1991;229(6):521-5.
20. Naito J. Retinogeniculate projection fibers in the monkey optic nerve: a demonstration of the fiber pathways by retrograde axonal transport of WGA-HRP. J Comp Neurol 1989; 284(2):174-86.
21. Rowe F, Brand D, Jackson CA, Price A, Walker L, Harrison S, et al. Visual impairment following stroke: do stroke patients require vision assessment? Age Ageing 2009;38(2): 188-93.
22. Pambakian AL, Wooding DS, Patel N, Morland AB, Kennard C, Mannan SK. Scanning the visual world: a study of patients with homonymous hemianopia. J Neurol Neurosurg Psychiatry 2000;69(6):751-9.
23. Zhang X, Kedar S, Lynn MJ, Newman NJ, Biousse V. Natural history of homonymous hemianopia. Neurology 2006;66(6):901-5.
24. Zihl J. Visual scanning behavior in patients with homonymous hemianopia. Neuropsychologia 1995;33(3):287-303.
25. Han SW, Sohn YH, Lee PH, Suh BC, Choi IS. Pure homonymous hemianopia due to anterior choroidal artery territory infarction. Eur Neurol 2000;43(1):35-8.
26. Holt LJ, Anderson SF. Bilateral occipital lobe stroke with inferior altitudinal defects. Optometry 2000;71(11):690-702.
27. Wein F, Miller NR. An unusual homonymous visual field defect. Survey Ophthalmol 2000;44(4):324-8.
28. Isa K, Miyashita K, Yanagimoto S, Nagatsuka K, Naritomi H. Homonymous defect of macular vision in ischemic stroke. Eur Neurol 2001;46(3):126-30.
29. Pambakian AL, Kennard C. Can visual function be restored in patients with homonymous hemianopia? Br J Ophthalmol 1997;81(4):324-8.
30. Zhang X, Kedar S, Lynn MJ, Newman NJ, Biousse V. Homonymous hemianopias: clinical-anatomic correlations in 904 cases. Neurology 2006;66(6):906-10.
31. Smith JL. Homonymous hemianopia. A review of one hundred cases. Am J Ophthalmol 1962;54(4):616-23.
32. Trobe JD, Lorber ML, Schlezinger NS. Isolated homonymous hemianopia. A review of 104 cases. Arch Ophthalmol 1973;89(5):377-81.
33. Fujino T, Kigazawa KI, Yamada R. Homonymous hemianopia: a retrospective study of 140 cases. J Neuroophthalmology 1986;6(1): 17-21.
34. Rowe FJ, Wright D, Brand D, Jackson C, Harrison S, Maan T, et al. A prospective profile of visual field loss following stroke: prevalence, type, rehabilitation, and outcome. Biomed Res Int 2013;2013:719096.
35. Gray CS, French JM, Bates D, Cartlidge NE, Venables GS, James OF. Recovery of visual fields in acute stroke: homonymous hemianopia associated with adverse prognosis. Age Ageing 1989;18(6):419-21.
36. Cassidy TP, Bruce DW, Lewis S, Gray CS. The association of visual field deficits and visuo-spatial neglect in acute right-hemisphere stroke patients. Age Ageing 1999;28(3):257-60.
37. Tiel K, Kolmel HW. Patterns of recovery from homonymous hemianopia subsequent to infarction in the distribution of the posterior cerebral artery. Neuro-Ophthalmology 1991;11(1): 33-9.