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CLINICAL STUDY

Retinal ganglion cell and axonal loss in optic neuritis: risk factors and visual functions

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Abstract

Purpose **The peripapillary retinal nerve fiber layer (pRNFL) and the macular ganglion cell-inner plexiform layer (GCIPL) are important predictive factors for the prognosis of optic neuritis (ON). We investigated the risk factors for pRNFL and GCIPL thinning in ON and its relationship with visual function.**

Patients and methods **We analyzed 33 eyes of 33 patients with a first attack of unilateral ON. Patients were divided into two groups according to pRNFL and GCIPL thinning, using spectral-domain optical coherence tomography. We evaluated patients' age, sex, color vision, visual acuity (VA), optic nerve findings on MRI, elapsed period from onset of visual symptoms to steroid treatment, visual field (VF) mean deviation (MD), average pRNFL thickness, and GCIPL thickness.**

Results **There was no patient with residual VF defect in the groups without pRNFL or GCIPL thinning. Significant correlations were found between pRNFL (some sectors) and GCIPL (all sectors) thickness and BCVA and VF MD ($P<0.03$ for all). Multivariate logistic regression analysis revealed that only worse initial VF MD was a significant risk factor of pRFNL and GCIPL thinning after ON (OR, 0.841; 95% CI, 0.730–0.970; $P=0.017$ and OR, 0.871; 95% CI, 0.761–0.998; $P=0.046$, respectively).**

Conclusion **Retinal ganglion cell and axonal losses occurred in ON cases showing severe initial VF loss. Therefore, it is necessary to pay more attention to the degree of initial VF loss in ON while considering the possibility of residual VF loss accompanying pRNFL and GCIPL thinning.**

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Introduction

Optic neuritis (ON) is an acute inflammatory condition that affects the optic nerve. ON is a common clinical manifestation of multiple sclerosis (MS) and is characterized by an acute onset of visual acuity (VA) loss and often accompanied by visual field (VF) loss, color desaturation, and pain upon eye movement. Significant axonal loss occurs following the acute inflammatory process that eventually results in retinal ganglion cell neuronal loss through retrograde degeneration.[1–5] The macular ganglion cell layer (GCL) gives rise to the retinal nerve fiber layer (RNFL) and can be affected by axonal inflammation.[6]

Previously, the RNFL around the optic disc, which is composed of axons originating from retinal ganglion cell neurons, was used to assess eye damage instead of the GCL, because the GCL could not be analyzed separately *in vivo*. The recent development in spectral-domain optical coherence tomography (SD-OCT) enables faster imaging and higher resolution.[7] SD-OCT can demonstrate both peripapillary retinal nerve fiber layer (pRNFL) and retinal GCL thinning in optic nerve injuries.[5,8]

The RNFL contains the retinal ganglion cell axons that comprise the optic nerve. It represents a unique region of the central nervous system because it lacks myelin. Changes in the RNFL thickness after ON have been interpreted as reflecting initial axoplasmic flow stasis and subsequent attrition caused by inflammation in the anterior visual pathway. Recent studies have shown that OCT-measured RNFL values are reduced after ON and that the extent of the RNFL atrophy correlates with diminished visual and neurological function scores.[9–13] Another study has reported that neuronal loss in the macular retinal ganglion cell-inner plexiform layer (GCIPL) is strongly related to visual function and vision-related quality of life in MS patients, and is observed with and without a history of acute ON.[4] A recent study reported that quantifying GCL thickness after acute ON provides

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opportunities for monitoring early axonal loss and ON-to-MS progression in early ON.[14]

GCIPL and pRNFL thinning are important predictive factors for the prognosis of ON. An analysis of associated risk factors would be a very meaningful investigation. To the best of our knowledge, an analysis of risk factors for pRNFL and GCIPL thinning after ON has not been reported yet. We aimed to investigate the risk factors and their relationship with visual functions of pRNFL or GCIPL thinning by using SD-OCT after ON.

Materials and methods

This retrospective study was approved by the institutional review board of Chonnam National University Hospital (Gwangju, South Korea). It was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from each subject enrolled in the study. We reviewed the medical records of patients who attended the Neuro-ophthalmic Clinic in the Department of Ophthalmology at Chonnam National University Hospital and were diagnosed with ON between October 2011 and June 2014.

Diagnosis of ON

All patients were definitively diagnosed with ON by an experienced neuro-ophthalmologist (HH). ON was diagnosed on the basis of the following clinical symptoms and signs: acute loss of VA or VF, ocular pain on eye movement, presence of relative afferent pupillary defect (RAPD), signs of abnormal optic nerve thickening or enhancement on magnetic resonance imaging (MRI) with contrast, abnormal color vision, and a compatible fundus examination. Patients presenting with a first attack of acute unilateral ON and visual symptoms of $\leq$15-days of duration were included. All patients were admitted and received intravenous methylprednisolone (250 mg every 6 h for 3 days) followed by oral prednisolone (1 mg/kg) for 11 days.[15] Patients with any of the following conditions were excluded from the study: a known history of MS or other demyelinating events, bilateral ON, recurrent ON, age <20 or >65 years, refractive error of <-6.0 diopters or $>+3.0$ diopters (spherical equivalent), media opacities, intracranial lesion or neurologic disorder, systemic medication that may induce optic neuropathy, a history of ocular surgery, and other ocular pathology that may affect OCT measurements including glaucoma and retinal disease. Patients who underwent any treatment before the visit to our clinic and who had a previous history of visual loss or other ocular abnormalities that cause visual loss were also excluded.

Study measurements

Patient characteristics, including age, gender, medical history, elapsed period from onset of visual symptoms to steroid treatment (onset was defined as onset of visual dysfunction), and the presence of abnormal optic nerve thickening or enhancement on MRI were investigated. The best-corrected visual acuity (BCVA), VF testing, color function testing, fundus examination, and SD-OCT (Cirrus HD-OCT, Carl Zeiss Meditec Inc., Dublin, CA, USA) were performed during the initial visit and at each follow-up visit. Intereye pRNFL and GCIPL asymmetry values were calculated by subtracting the pRNFL and GCIPL thickness values of the eye without ON from those of the ON eye. The mean BCVAs were calculated after conversion to a logarithm of the minimal angle of resolution (logMAR). The VF was tested using a Swedish interactive threshold algorithm (SITA) 30-2 perimetry with a Humphrey Field Analyzer (Carl Zeiss Meditec Inc.). Only reliable VFs were considered ($\leq$33% false positives, false negatives; fixation losses $<$20%) and the mean deviation (MD) was recorded. We examined color abnormalities using a Hardy–Rand–Rittler (HRR) color plate. Fundus photography (TRC-NW6 fundus camera, Topcon Corp., Tokyo, Japan) was performed. To distinguish ON from a nonarteritic anterior ischemic optic neuropathy (NAION), fluorescein angiography (FAG) was also performed and disc nonperfusion was ruled out.

Data analysis

The Cirrus HD-OCT GCIPL and RNFL significance maps use the same three-level color coding system to determine whether the measurement is within the normal (green) or borderline (yellow) range or outside the normal range (red). Green, yellow, and red indicate that the measurements have 5–95%, 1–5%, and <1% probability, respectively, to be within the normal range for an age-matched normal population. For the RNFL analysis, the average thickness map with yellow or red color codes and the quadrant and clock-hour maps with ≥ 1 yellow- or red-colored sectors defined thinning. For ganglion cell analysis, the yellow or red color-coded average and minimum thickness map and a sector map with ≥ 1 yellow or red-colored sectors defined thinning.[16]

A VF is definitely normal if all locations are within normal limits on the total deviation plot. An abnormal VF at the final follow-up visit was defined as meeting any of the following criteria:[17] (1) a Glaucoma Hemifield Test result outside the normal limits, (2) a corrected pattern standard deviation (PSD) or PSD at $P<5$%, (3) a single point worse than the 0.5% probability level on the total and/or pattern deviation probability plots, (4) two adjacent points (cluster) beyond the normal limits

($P<5\%$) and at least one point worse than the $P<1\%$ on the total and/or pattern deviation probability plot (a cluster is defined as ≥ 2 horizontally or vertically, not diagonally, contiguous abnormal points at $P<5\%$), or (5) three or more clustered points worse than the $P<5\%$ level on the total and/or pattern deviation probability plot.

Statistical analysis

SPSS version 18.0 (SPSS Institute Inc., Chicago, IL, USA) was used for statistical analyses. The normality of the variable distribution was verified by the Kolmogorov–Smirnov test. The Mann–Whitney and χ^2 or Fisher's exact tests were used to compare variables between groups. Linear regressions were used to search for correlations between the thickness parameters and BCVA or VF MD, introducing age and spherical equivalent refractive error as covariates. A multiple logistic regression analysis was used to evaluate the risk factors for pRNFL and GCIPL thinning in ON patients. Each variable was first analyzed in a univariate model. Subsequently, all variables with a significance level (P) of <0.10 were included in the multivariate model. Statistical significance was considered when $P<0.05$. The role of each variable is expressed as the odds ratio (OR) and its 95% confidence interval (CI).

Results

The characteristics of patients with ON are summarized in Table 1. Thirty-three eyes (33 patients) were included. The mean age of the patients was 45.88 ± 17.06 years (range, 20–64 years). There were 12 men and 21 women. The initial mean logMAR BCVA of the affected eyes was 1.13 ± 1.17. The mean initial VF MD was -17.60 ± 10.05 dB.

Table 1 Characteristics of patients with optic neuritis

Variable	*Data*
Age (years)	45.88 ± 17.06
Female, no. (%)	21 (64)
Laterality, left, no. (%)	21 (64)
Pain on eyeball movement, no. (%)	27 (82)
Initial color vision abnormality, no. (%)	23 (70)
Abnormal optic nerve thickening or enhancement on MRI, no. (%)	21 (64)
Initial visual acuity (logMAR)	1.13 ± 1.17
Initial visual field (MD)	-17.60 ± 10.05
Initial average pRNFL thickness (μm)	156.24 ± 58.10
Initial average GCIPL thickness	79.30 ± 5.06
pRNFL thinning, no. (%)	21 (64)
GCIPL thinning, no. (%)	25 (76)

Abbreviations: MRI, magnetic resonance imaging; logMAR, logarithm of the minimum angle of resolution; MD, mean deviation; pRNFL, peripapillary retinal nerve fiber layer; GCIPL, ganglion cell-inner plexiform layer.

Initial color vision abnormalities were identified in 70% of the patients and abnormal optic nerve thickening or enhancement on MRI was observed in 64% of the patients. The number of patients with pRNFL and GCIPL thinning was 21 and 25, respectively.

The comparison of eyes with and without pRNFL thinning in ON patients is summarized in Table 2. Eyes with pRNFL thinning had a worse initial VA ($P=0.019$). They also had a worse initial and final VF MD ($P=0.011$ and $P=0.030$, respectively). There was a significant difference in the presence of an abnormal VF between the groups at the 6-month follow-up visit ($P=0.002$). A significant reduction in the pRNFL and GCIPL thicknesses was seen in eyes with pRNFL thinning at the 6-months follow-up visit ($P<0.001$ and $P=0.004$, respectively). No patients in the group without pRNFL thinning had residual VF defects. However, 11 of 21 patients (52%) remained with VF defects in the group with pRNFL thinning.

The comparison of eyes with and without GCIPL thinning in ON patients is summarized in Table 3. There was a significant difference in the initial VF MD between the two groups ($P=0.025$). The eyes with GCIPL thinning showed significantly thinner pRNFL and GCIPL at the 6-month follow-up visit (all for $P<0.001$). There was a difference in the presence of abnormal VF between the groups at the 6-month follow-up visit, but it was not significant ($P=0.071$). No patient had residual VF defects in the group without GCIPL thinning. However, 10 of 25 patients (40%) remained with VF defects in the group with GCIPL thinning.

The correlations between the pRNFL thickness and BCVA, and VF MD in the eyes with ON at the 6-month follow-up visit are summarized in Table 4. Significant correlations were found between the BCVA and the inferior pRNFL thickness ($P=0.003$). VF MD was correlated with average ($P=0.011$), superior ($P=0.007$), and inferior pRNFL thickness ($P<0.001$). There were significant correlations among all sectors of GCIPL thickness and BCVA, and VF MD (all for $P<0.01$).

Risk factors for pRNFL thinning in the univariate analysis were sex (male, OR, 4.545; 95% CI, 0.795–25.976), abnormal optic nerve thickening or enhancement on MRI (OR, 4.480; 95% CI, 0.975–20.585), initial VA (OR, 4.032; 95% CI, 1.146–14.185), initial VF MD (OR, 0.870; 95% CI, 0.781–0.968), and final VF MD (OR, 0.666; 95% CI, 0.428–1.003). Multivariate analysis revealed an initial VF MD (OR, 0.841; 95% CI, 0.730–0.970) as significantly associated with pRNFL thinning in ON patients. For GCIPL thinning, the risk factors were age (OR, 0.943; 95% CI, 0.885–1.005), abnormal optic nerve thickening or enhancement on MRI (OR, 4.286; 95% CI, 0.801–22.917), and initial VF MD (OR, 0.878; 95% CI, 0.776–0.993) in the univariate analysis. In the multivariate analysis, an initial

Table 2 Comparison of eyes with and without pRNFL thinning in patients with optic neuritis

Variables	*Thinning (−) (n = 12)*	*Thinning (+) (n = 21)*	P-*value*
Age (year)	50.83 ± 16.22	43.05 ± 17.27	0.129
Sex (M/F)	2 : 10	10 : 11	0.133
Initial color vision abnormality, *n* (%)	7 (58)	15 (71)	0.471
Retrobulbar ON, *n* (%)	2 (17)	8 (38)	0.259
Abnormal optic nerve thickening or enhancement on MRI, *n* (%)	5 (42)	16 (76)	0.067
Elapsed period from onset of visual symptoms to steroid treatment (days)	8.73 ± 3.82	9.95 ± 7.17	0.829
Visual acuity (logMAR)			
Initial	0.41 ± 0.46	1.53 ± 1.26	0.019
Final	0.05 ± 0.06	0.31 ± 0.69	0.699
Visual field (MD)			
Initial	−11.05 ± 4.56	−21.35 ± 10.48	0.011
Final	−2.09 ± 1.51	−6.63 ± 9.18	0.030
Final visual field abnormality, *n* (%)	0 (0%)	11 (52%)	0.002
pRNFL (average)			
Initial	170.08 ± 58.05	148.33 ± 58.03	0.254
Intereye difference[a]	38.83 ± 27.27	42.86 ± 33.58	0.534
Final	101.25 ± 10.04	69.81 ± 10.88	<0.001
Intereye difference[a]	8.0 ± 11.73	−21.14 ± 16.39	0.045
GCIPL (average GCL+IPL)			
Initial	80.57 ± 5.56	78.75 ± 4.91	0.376
Intereye difference[a]	0 ± 7.32	−1.0 ± 4.90	0.534
Final	75.29 ± 6.78	63.14 ± 8.64	0.004
Intereye difference[a]	−7.5 ± 12.91	−17.0 ± 10.0	0.234

Abbreviations: pRNFL, peripapillary retinal nerve fiber layer; *n*, number; logMAR, logarithm of the minimum angle of resolution; MD, mean deviation; GCIPL, ganglion cell-inner plexiform layer; GCL, ganglion cell layer; IPL: inner plexiform layer. [a]The difference was calculated by subtracting the value of the eye without optic neuritis from that of the eye with optic neuritis.

VF MD (OR, 0.871; 95% CI, 0.761–0.998) was the only risk factor for GCIPL thinning (Table 5).

Discussion

Our study showed that the initial severity of VF loss is a risk factor for pRNFL and GCIPL thinning and that pRNFL and macular GCIPL thicknesses showed a strong correlation with visual functions 6 months after the attack in ON patients.

The retinal nerve fibers originate from retinal ganglion cells. Degeneration of the RNFL may lead to average macular thickness reductions, partly because of ganglion cell death resulting from retrograde axonal degeneration.[18] However, the presence of optic disc swelling in the acute phase of ON prevents accurate quantification of pRNFL atrophy. Therefore, quantification of the macular RGC layer thickness may be a more specific marker for neuronal damage than pRNFL thickness.[14] Previous studies have reported the timing of pRNFL and GCIPL thinning after the onset of ON.[14,19] Henderson *et al*[19] showed that RNFL thinning can be observed during the first 6 months following ON and that >90% of this fiber loss occurred by the end of the third month. Another study reported that RNFL thinning occurred gradually, up to 6–9 months after ON, and that GCL thinning occurred earlier than RNFL thinning, within a few weeks after acute ON.[14] Therefore, we defined the time of thinning based on the values of the pRNFL and GCIPL at the 6-month follow-up visit.

Thinning of the innermost layers of the retina (RNFL and GCL) has been consistently reported in ON patients.[5,20–22] Syc *et al*[5] observed the average pRNFL and GCIPL thicknesses using SD-OCT in ON patients. They noted that the average pRNFL thickness was reduced by 21.63% and the GCIPL thickness by 12.17% after 6 months of follow-up. Another study reported that the pRNFL and GCIPL thicknesses were reduced by 45.3% and 11.3%, respectively, in ON patients after 6 months of follow-up.[23] In our study, however, the average pRNFL and GCIPL thickness reduced by 48.0% and 12.26%, respectively, after 6 months. We think that the discrepancy in the degree of RNFL reduction that is reported in various studies may be a result of the patient selection criteria, including ethnic differences and different rates of retrobulbar ON. According to previous studies, ON in Asian countries shows a higher rate of papillitis than that in Western countries.[24–26] As a result, an increase in

Table 3 Comparison of eyes with and without GCIPL thinning in patients with optic neuritis

Variables	*Thinning (−)* (n = *8)*	*Thinning (+)* (n = *25)*	P-*value*
Age (year)	54.75 ± 16.25	43.04 ± 16.64	0.055
Sex (M/F)	1 : 7	11 : 14	0.206
Initial color vision abnormality, *n* (%)	6 (75)	16 (64)	0.687
Retrobulbar ON, *n* (%)	2 (25)	8 (32)	1.000
Abnormal optic nerve thickening or enhancement on MRI, *n* (%)	3 (38)	18 (72)	0.106
Elapsed period from onset of visual symptoms to steroid treatment (days)	6.88 ± 2.23	10.45 ± 6.80	0.202
Visual acuity (logMAR)			
Initial	0.54 ± 0.52	1.31 ± 1.26	0.352
Final	0.06 ± 0.07	0.26 ± 0.64	0.984
Visual field (MD)			
Initial	− 10.53 ± 4.91	− 19.87 ± 10.28	0.025
Final	− 2.10 ± 2.04	− 5.81 ± 8.60	0.204
Final visual field abnormality, *n* (%)	0 (0%)	10 (40%)	0.071
pRNFL (average)			
Initial	171.38 ± 66.10	151.40 ± 55.90	0.522
Intereye difference[a]	33.67 ± 25.15	43.20 ± 27.33	0.217
Final	105.25 ± 10.15	73.56 ± 13.26	< 0.001
Intereye difference[a]	16.0 ± 26.15	− 15.0 ± 17.0	0.077
GCIPL (average GCL+IPL)			
Initial	83.67 ± 3.84	79.32 ± 4.27	0.108
Intereye difference[a]	6.0 ± 2.65	− 2.50 ± 3.10	0.287
Final	81.67 ± 4.28	64.32 ± 8.48	< 0.001
Intereye difference[a]	3.66 ± 2.52	− 17.0 ± 9.0	0.007

Abbreviations: GCIPL, ganglion cell-inner plexiform layer; *n*, number; logMAR, logarithm of the minimum angle of resolution; MD, mean deviation; pRNFL, peripapillary retinal nerve fiber layer; GCL, ganglion cell layer; IPL: inner plexiform layer. [a]The difference was calculated by subtracting the value of the eye without optic neuritis from that of the eye with optic neuritis.

Table 4 The correlation between pRNFL and GCIPL thickness, BCVA, and VF MD in optic neuritis patients at the 6-month follow-up visit

Parameters	*BCVA (logMAR)*			*VF MD*		
	B (SE)	*β*	P-*value*[a]	*B (SE)*	*β*	P-*value*[a]
pRNFL thickness, μm						
Average	− 0.010 (0.005)	− 0.333	0.067	0.189 (0.069)	0.456	**0.011**
Superior	− 0.007 (0.004)	− 0.322	0.068	0.135 (0.046)	0.466	**0.007**
Inferior	− 0.010 (0.003)	− 0.537	**0.003**	0.160 (0.039)	0.639	**< 0.001**
Nasal	− 0.003 (0.009)	0.070	0.704	0.018 (0.126)	0.027	0.885
Temporal	− 0.003 (0.007)	− 0.092	0.615	0.082 (0.093)	0.160	0.385
GCIPL thickness, μm						
Minimum	− 0.020 (0.006)	− 0.497	**0.003**	0.313 (0.084)	0.556	**0.001**
Average	− 0.024 (0.007)	− 0.521	**0.002**	0.360 (0.096)	0.569	**0.001**
Superonasal	− 0.019 (0.006)	− 0.484	**0.005**	0.285 (0.084)	0.533	**0.002**
Superior	− 0.019 (0.007)	− 0.454	**0.009**	0.284 (0.090)	0.499	**0.004**
Superotemporal	− 0.020 (0.007)	− 0.457	**0.008**	0.327 (0.093)	0.539	**0.001**
Inferotemporal	− 0.027 (0.007)	− 0.563	**0.001**	0.397 (0.100)	0.595	**< 0.001**
Inferior	− 0.028 (0.008)	− 0.560	**0.001**	0.400 (0.102)	0.589	**< 0.001**
Inferonasal	− 0.021 (0.007)	− 0.498	**0.004**	0.315 (0.091)	0.539	**0.002**

Abbreviations: pRNFL, peripapillary retinal nerve fiber layer; GCIPL, ganglion cell-inner plexiform layer; BCVA, best-corrected visual acuity; VF, visual field; MD, mean deviation; logMAR, logarithm of the minimum angle of resolution; B, unstandardized coefficient; *β*, standardized coefficient.
Factors with statistical significance are shown in bold. [a]Value for analysis of covariance after controlling for spherical equivalent refractive error and age.

Table 5 Factors associated with pRNFL and GCIPL thinning in optic neuritis patients

Variables	*Univariate analysis*		*Multivariate analysis*	
	Odd ratio (95% CI)	P-*value*	*Odd ratio (95% CI)*	P-*value*
pRNFL thinning				
Age	0.972 (0.930–1.016)	0.209		
Sex (male)	4.545 (0.795–25.976)	0.089	8.694 (0.854–88.507)	0.068
Initial color vision abnormality	1.786 (0.403–7.906)	0.445		
Abnormal optic nerve thickening or enhancement on MRI	4.480 (0.975–20.585)	0.054	1.497 (0.098–22.923)	0.772
Elapsed period from onset of visual symptoms to steroid treatment (day)	1.036 (0.909–1.181)	0.594		
Initial visual acuity (logMAR)	4.032 (1.146–14.185)	0.030	1.750 (0.329–9.303)	0.512
Initial visual field (MD)	0.870 (0.781–0.968)	0.011	0.841 (0.730–0.970)	**0.017**
Initial average pRNFL thickness (μm)	0.993 (0.981–1.006)	0.302		
Initial average GCIPL thickness (μm)	0.921 (0.754–1.126)	0.424		
Final visual acuity (logMAR)	15.490 (0.034–7022.247)	0.380		
Final visual field (MD)	0.666 (0.428–1.036)	0.071	0.630 (0.386–1.026)	0.063
Initial intereye average pRNFL asymmetry	0.997 (0.989–1.005)	0.507		
Initial intereye average GCIPL asymmetry	1.008 (0.987–1.029)	0.477		
GCIPL thinning				
Age	0.943 (0.885–1.005)	0.069	0.936(0.869–1.007)	0.077
Sex (male)	5.500 (0.586–51.620)	0.136		
Initial color vision abnormality	0.593 (0.098–3.573)	0.273		
Abnormal optic nerve thickening or enhancement on MRI	4.286 (0.801–22.197)	0.089	0.850 (0.078–9.263)	0.894
Elapsed period from onset of visual symptoms to steroid treatment (day)	1.143 (0.949–1.375)	0.159		
Initial visual acuity (logMAR)	2.234 (0.782–6.379)	0.133		
Initial visual field (MD)	0.878 (0.776–0.993)	0.039	0.871 (0.761–0.998)	**0.046**
Initial average pRNFL thickness (μm)	0.994 (0.981–1.008)	0.397		
Initial average GCIPL thickness (μm)	0.637 (0.337–1.206)	0.166		
Final visual acuity (logMAR)	4.953 (0.050–491.929)	0.495		
Final visual field (MD)	0.769 (0.510–1.160)	0.211		
Initial intereye average pRNFL asymmetry	0.997 (0.988–1.006)	0.484		
Initial intereye average GCIPL asymmetry	1.051 (0.968–1.140)	0.234		

Abbreviations: pRNFL, peripapillary retinal nerve fiber layer; GCIPL, ganglion cell-inner plexiform layer; CI, confidence interval; logMAR, logarithm of the minimum angle of resolution; MD, mean deviation.
Factors with statistical significance are shown in bold.

pRNFL thickness can be observed more frequently in Asians than in other ethnic groups. Therefore, the decrease in pRNFL is possibly higher in this study than that in other studies. However, the GCIPL thickness decrease in this study was similar to that in previous studies. These results show that the GCIPL thickness is less affected by optic disc edema, thereby supporting the results of a previous study regarding GCL thickness as a factor for monitoring the retinal ganglion cell status after acute ON.[14]

Previous studies have reported a significant correlation among RNFL thickness, VA, and VF.[10,14] Trip *et al*[10] reported that there were significant relationships among RNFL thickness and VA, VF, color vision, and the visual-evoked potential (VEP) amplitude. Walter *et al*[4] demonstrated that GCIPL thinning is most significantly correlated with visual function in MS patients with and without a history of acute ON and may serve as a useful structural marker of the disease. Our study also investigated the correlation between pRNFL or macular GCIPL thickness and visual function, including VA and VF. The correlations between pRNFL thickness and visual parameters in this study were consistent with the findings of a previous study to some extent.[27] The GCIPL thickness and visual parameters had significant correlations with all sectors as well as with the average thickness. Consequently, we found that compared with pRNFL thickness in ON, GCIPL thickness showed a strong correlation with VA and VF. Our results also showed that there were no residual VF defects in the groups without pRNFL or GCIPL thinning. We found that if there were no reductions in pRNFL and GCIPL thicknesses, all patients with ON had a normal VF.

In the ONTT, there was a 35% recurrence of ON at 10 years (14% in the original eye, 12% in the other eye, and 9% in both eyes).[28] Intravenous megadose steroids help early recovery of vision and offer some advantage in preventing a recurrence and development of multiple sclerosis in the first year.[29] The previous study investigated the critical timing for the use of corticosteroids to prevent the RGC loss in mice with experimental ON.[30] The results showed that ON could be suppressed and prevented with a steroid treatment before

the occurrence of optic nerve inflammation, and therefore chronic immunomodulation therapy may prevent RGC damage as well as ON recurrence. In this study, we revealed that a worse initial VF resulted in a reduction of RGC and axons in ON patients. We think that the poor initial VF signifies a more severe optic nerve inflammation and intensive axonal damage. In this case, we expect further reduction of the RGC in ON at follow-up periods. Based on the previous results, we believe that a more aggressive chronic immunomodulation treatment could prevent additional RGC loss in ON patients with severe VF loss; however, further studies are necessary to confirm this.

This study had several limitations. The sample size was small and we used a retrospective design. The study was performed using data from the same ethnic group; thus, results may not be applicable to other ethnic groups. We hypothesized that an initial VF loss could be a risk factor for thinning of the pRNFL and GCIPL in ON patients, but our study did not establish the cutoff values. The amplitude of VEPs is believed to reflect the number of functional optic nerve fibers that is determined by a combination of the severity of inflammation along the visual pathway and axonal degeneration.[31] However, our study did not include the VEP results as risk factors. In addition, although the most sensitive clinical measurement of ON is low contrast visual acuity, we did not routinely measure this parameter.[32] Nevertheless, it is meaningful, in that this is the first study to analyze risk factors related to pRNFL and GCIPL thinning after ON.

In conclusion, as initial VF loss was severe, retinal ganglion cell and axonal losses were observed in ON patients during follow-up visits. Therefore, it is necessary to pay more attention to the degree of the initial VF loss in patients with ON as well as to consider the possibility of residual VF loss associated with pRNFL and GCIPL thinning.

Summary

What was known before

- Thinning of peripapillary retinal nerve fiber layer (pRNFL) and macular ganglion cell-inner plexiform layer (GCIPL) was an important predictive factor for the prognosis of optic neuritis (ON).
- However, an analysis of risk factors for pRNFL and GCIPL thinning after ON has not been reported.

What this study adds

- The severe initial visual field loss is a risk factor for thinning of pRNFL and GCIPL in eyes with ON.

Conflict of interest

The authors declare no conflict of interest.

Author contributions

All authors had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analyses.

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