·Letter to the Editor·

Microperimetry and spectral domain optical coherence tomography in myelinated retinal nerve fibers

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Dear Sir,

I write to present the correlation between microperimetric (MP) values and the density of myelinated retinal nerve fibers (MNFs) in optical coherence tomography (OCT) imaging.

MNFs appear as white or gray-white striated patches that correspond in shape to the distribution of retinal nerve fibers and demonstrate frayed borders[1]. Visual system myelination normally begins at the optic tracts at 7mo of gestational age and progresses anteriorly, finishing within 3mo after birth and stopping at the lamina cribrosa. However, this process may progress beyond this level and cause retinal nerve fibers to become myelinated [2-4]. The incidence of MNFs in a large series of examined eyes at autopsy was 0.54%[1,5].

Conventional visual field testing often reveals a defect in the area corresponding to the affected retina [6]. MNFs remaining in the nerve fiber layer might interrupt the penetration of light. Therefore, it becomes difficult for light to reach the photoreceptor layers beneath the lesion, and the patient may perceive a relative scotoma from the MNFs. In other words, the degree of the scotoma might be partly dependent on the degree of light penetration. This could be correlated to the ability of the OCT light to penetrate the underlying tissue, which could be manifested as the degree of image formation of outer retina. However, if OCT image does not correspond with MP value, or if all MP values are equally low, MNFs could accompany other dysfunctions of visual cells or abnormalities of the visual tracts.

We wanted to determine retinal sensitivity in the MNF lesions and to measure the correlation between the MP value and the degree of reflectivity of the outer layers [photoreceptor and retinal pigment epithelium (RPE)] in the OCT image at the MNFs.

This study evaluated the eyes with localized MNF layers who underwent simultaneous spectral domain-OCT (SD-OCT) and MP testing (Optos OCT SLO, Optos, Scotland, UK) at the Department of Ophthalmology, Korea University Ansan Hospital from June 2011 to May 2014. The pupil was dilated and the patient was dark-adapted for at least 15min. Threshold fundus perimetry was performed on the MNFs using an individually customized pattern in which the number of stimulus points was individualized according to the condition of the patient (range, 13 to 49). Any test spot overlying a vessel was discarded because blood vessels reduce retinal sensitivity. OCT was performed with a topography map consisting of 250 horizontal A-scans and 250 vertical lines across a 5×5-mm^2 area. The OCT image at the MP test point was graded according to the visibility of the underlying retinal layers. The degree of visibility the retinal structure in the each OCT image was graded subjectively (grade 1-3; Figure 1), and independently by two retina specialists (Lee KH and Kim SW). Because the signal strength of the RPE line is stronger than that of the photoreceptor inner and outer segment (IS/OS) junction, the RPE line persisted better than the IS/OS junction when the OCT signal became weak due to the highly reflective structure. Based on this observation, the grading of visibility was determined as follows: grade 1, when the reflective line integrity of the IS/OS junction was noticeable; grade 2, when the IS/OS junction was invisible but the RPE line was visible; grade 3, when both the IS/OS junction and the RPE line were invisible. If there was a difference between the two grades, the final grade was decided by consensus after discussion between the graders.

Cohen's kappa measure was calculated to test agreement between the evaluations of the two observers. The kappa measure was considered to be strong if the coefficient was greater than 0.8. A linear mixed model (LMM) was used to test the linear trend by regressing MP on the OCT grade. Statistical analyses were conducted with use of the R software environment, version 2.15.2 (R Foundation for Statistical Computing, Vienna, Austria) with the use of PSYCH and NLME packages. All statistics were two-tailed, and P-values <0.05 were considered statistically significant.

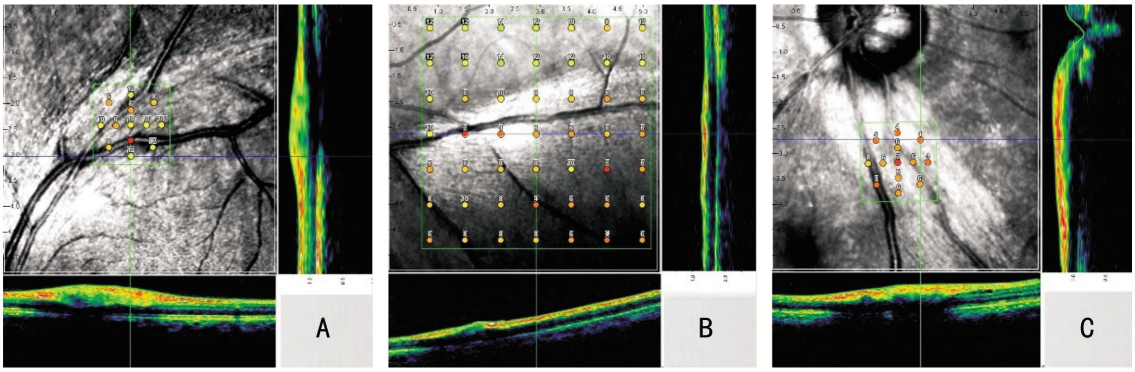

Figure 1 Representative images of OCT grading at the MP test point A: Grade 1 was when the reflective line integrity of the photoreceptor inner and outer segment junction (IS/OS) was noticeable; B: Grade 2 was when the IS/OS line was invisible but the RPE line was visible; C: Grade 3 was when both the IS/OS line and RPE line were invisible.

Table 1 Baseline characteristics of patients

Patients	Sex	Age(a)	OD/OS	Total MP test points	No. of MP test points at MNFs	Mean of MP values at MNFs	BCVA	Location
1	M	73	OS	13	11	4.91	0.8	Juxtapapillary, inferior
2	M	75	OD	13	9	2.67	0.32	ITRV, 3rd branch
3	M	78	OD	25	5	3.60	1.0	Juxtapapillary, inferior
3	M	78	OS	49	21	7.14	1.0	ITRV, 3rd branch
4	F	77	OS	13	7	8.00	0.63	STRV, 2nd branch
5	M	49	OS	40	10	9.00	1.0	Juxtapapillary, inferior
6	F	56	OD	25	19	0.95	1.0	INRV, 2nd branch
7	M	23	OS	13	12	9.17	1.0	Juxtapapillary, superior
8	M	10	OD	49	37	2.76	1.0	Juxtapapillary
9	F	43	OD	25	12	7.83	1.0	INRV, 1st branch
10	M	54	OD	49	3	4.00	0.8	Juxtapapillary, inferior
10	M	54	OS	49	5	6.00	1.0	Juxtapapillary, inferior
11	M	37	OS	13	5	0.00	1.0	Juxtapapillary, superior
12	M	51	OD	25	4	2.00	1.0	Juxtapapillary, inferior

ITRV: Inferotemporal retinal vein; STRV: Superotemporal retinal vein; INRV: Inferonasal retinal vein.

Fourteen eyes from 12 patients with MNFs were included in this study (Table 1). The patients included nine men and three women, whose ages ranged from 10 to 78y (mean, 52.18y). The total number of MP test points was 401. Among them, 165 test points outside MNF layers lesion were excluded. Seventy-six test points were not used in the analysis because they corresponded to the optic nerve or retina vessels. Finally, the 160 MP test points at MNFs were included for the study. The number of test points at MNFs in each eye ranged from 3 to 37. The mean of total MP values at the MNFs was 4.86±4.21 dB and the MP value of each test point ranged from 0 dB to 16 dB. The mean MP value in each eye ranged from 0.00 dB to 9.17 dB. The number of test points with each OCT image grades was 28 for grade 1, 65 for grade 2, and 67 for grade 3.

Inter-observer reliability between the two graders for the grading of OCT (grades 1-3) was statistically significant: κ =0.929 (P<0.0001). The MNF areas of the grade 1 OCT images showed the most sensitive MP values, and the grade 3 OCT images showed the least sensitivity (grade 1: 8.34±3.55 dB; grade 2: 6.61±4.14 dB; grade 3: 2.42±2.71 dB) (Figure 2).

Table 2 The estimated MP value according to the OCT grade (a mixed linear model with the SAS Proc mixed procedure)

Grade	Estimate	Standard error	DF	t	$P_r > \|t\|$
1	8.3367	0.9366	143	8.90	<0.0001
2	6.6092	0.8069	143	8.19	<0.0001
3	2.5231	0.8215	143	3.07	0.0026

Grade least squares means.

The estimated MP value according to the OCT grade was 8.34 dB (grade 1), 6.61 dB (grade 2), and 2.52 dB (grade 3), which indicated a decreasing trend of MP values as the OCT grade increased (P<0.0001) (Table 2; Figure 3). When the mean MP values according to OCT grade were compared using a post-hoc test with the Bonferroni method, there were clinically significant differences between each group [grade 1 and grade 2 (P<0.0001), grade 2 and grade 3 (P<0.0001) and grade 1 and grade 3 (P<0.0001)].

Gharai *et al*[6] reported OCT images of MNFs in two patients with high myopia and small optic nerves and showed a reduced retinal thickness with the same distribution as the myelination. Shelton *et al* [7] suggested two possible

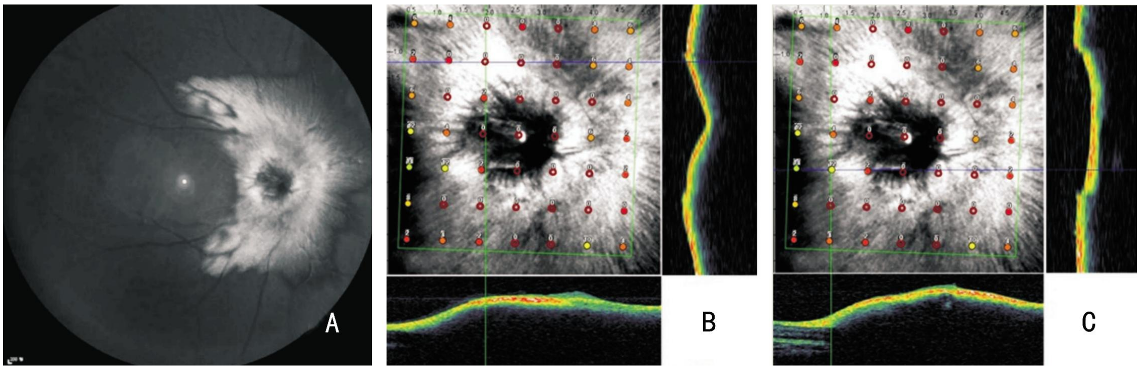

Figure 2 Right eye of patient 8 with MNFs A: The MNF area was noted in the juxtapapillary area in the fundus photograph; B: OCT scan corresponding to the point of the 0 dB MP value showing that the IS/OS and RPE lines have nearly disappeared (grade 3); C: In the OCT scan corresponding to the point of the 12 dB MP value, the signal of the IS/OS has nearly disappeared while the RPE signal persists (grade 2).

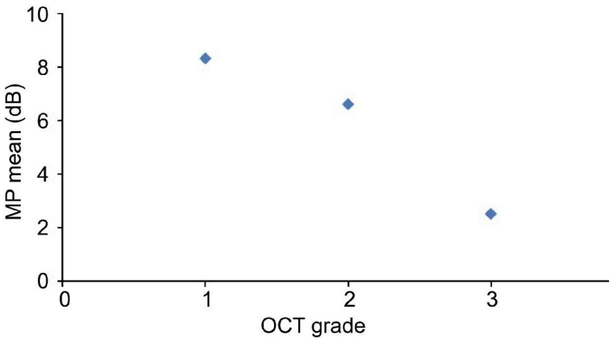

Figure 3 Graph of the estimated MP value according to the OCT grade The estimated MP value was 9.43 dB for grade 1, 5.52 dB for grade 2, and 3.41 dB for grade 3, which indicated a decreasing trend of the MP value as the OCT grade increased (P<0.0001).

interpretations regarding MNF lesion based on OCT images; myelination creates bulk around the axon or axon itself gets larger within MNFs.

In the present study, MP was decreased at the MNF lesions, and the MP value decreased as the degree by which the highly refractive MNFs obscured the OCT image increased. Although Nourinia *et al* [8] reported that retinal layers behind the MNFs were not visible due to the inability of the laser beam to pass through the MNFs, to be more precise, visibility of retinal layer behind MNFs depends on the degree of laser penetration through MNFs. Other authors reported a case series using electrophysiological tests and showed that the pattern of electroretinography (ERG) in eyes with MNFs showed both a reduction in amplitude and an increase in latency of the P50 and N95 waves. These abnormal findings were mainly localized and not extensive [9-10]. It is known that MNFs are caused by myelin sheaths of the retinal nerve fibers composed of concentric lipoprotein lamellae, but other components of the sensory retina are morphologically normal[4,11]. These findings support those of the present study, and suggest that blockage of a stimulus from the MNFs might play a more important role than possible associated functional disturbances in the retina.

In conclusion, MP values were correlated with the OCT image status, and relative scotoma seemed to be associated with the degree of light blockage by MNFs.

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