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Parameters associated with papillomacular bundle defects in glaucoma *

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Abstract. To evaluate the relationship between the papillomacular bundle defect and glaucoma types, abnormalities of the optic disc, distance between the disc and foveola, and axial length, we examined one eye of 82 patients with normal tension glaucoma, 117 patients with chronic high tension glaucoma, and 102 controls. Two types (diffuse and focal types) were found in the papillomacular bundle defect, and the former predominated. Eyes with a long axial length ($P<0.01$), a diagnosis of normal tension glaucoma ($P<0.05$), or a large optic disc ($P<0.05$) tended to have diffuse-type papillomacular bundle defects, while eyes with a short axial length, a diagnosis of high tension glaucoma, or a large ovalness index are less likely to have it. Thus, a long axial length, a large optic disc, and normal tension glaucoma are risk factors for the diffuse-type papillomacular bundle defect.

Introduction

A diffuse loss of nerve fibers including the papillomacular bundle is common in patients with chronic high tension glaucoma [2]. Nevertheless, the papillomacular bundle is one of the last nerve fibers to become severely involved in patients with glaucoma. A papillomacular bundle defect which precedes a defect in another sector of the optic disc may be observed in severely myopic glaucoma patients [6, 10]. In severe myopia, the optic discs frequently have an abnormal shape. In this case, the risk of developing a papillomacular bundle defect in an individual case may be influenced by such local factors in the optic disc as an uneven distribution of the intercellular matrix or of the collagenous supporting tissue. Another risk factor for the papillomacular bundle defect may be the type of glaucoma. In a patient with normal tension glaucoma, the visual field defect may be close to fixation and have a steep slope [5]. As the abnormalities of the papillomacular bundle directly affects visual acuity, it is important clinically to know which parameters correlate with vulnerability of the papillomacular bundle.

In this study, the relationship between papillomacular bundle defect and parameters such as the type of glaucoma, shape or size of the optic disc, axial length, and distance between the disc and foveola was evaluated.

Patients and methods

Prospectively, we examined one eye of 199 glaucoma patients and of 102 control subjects. All were oriental in race and were seen consecutively as outpatients at Kyoto University. All patients gave informed consent prior to being examined. Of the glaucoma patients, 82 had normal tension glaucoma, and 117 had chronic high tension glaucoma. The relationship between the papillomacular bundle defect and the type of glaucoma, tilting of the disc, size of the disc, index of ovalness (quotient of long to short optic disc axes), distance between the disc and foveola, and axial length was analyzed.

The control subjects were normal outpatients who consecutively visited our department for the prescription of glasses or contact lenses and check-ups for ocular disease. The left or right eye was selected randomly for examination. Age of the control subjects was matched with that of the high tension glaucoma group (Table 1).

Table 1. Distribution of patients in each group by age

Patients' age (years)	NTG ($n=82$)	HTG ($n=117$)	Control ($n=102$)
0–20	2 (2%)	3 (3%)	8 (8%)
21–40	11 (13%)	23 (20%)	27 (26%)
41–60	35 (43%)	51 (44%)	44 (43%)
61–80	34 (41%)	40 (34%)	23 (23%)

NTG, Normal tension glaucoma; HTG, chronic high tension glaucoma

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Table 2. Visual field defects in each group

Mean defect	NTG (A) ($n=39$)	HTG (A) ($n=58$)	NTG (B) ($n=43$)	HTG (B) ($n=59$)
0–5 dB	7 (18%)	10 (17%)	8 (19%)	13 (22%)
5–10 dB	9 (23%)	14 (24%)	13 (30%)	16 (27%)
10–15 dB	19 (49%)	28 (48%)	21 (49%)	25 (42%)
15–17.5 dB	4 (10%)	6 (10%)	1 (2%)	5 (8%)

A, Eyes without deformation of the optic discs; B, eyes with deformation

All of the 199 glaucoma patients had detectable defects in the retinal nerve fiber layer. A diagnosis of normal tension glaucoma was based upon the findings of an open angle, glaucomatous visual field defects, glaucomatous cupping of the optic disc, untreated intraocular pressure less than 22 mmHg documented monthly on examination for more than 2 years, and no other possible cause of nerve fiber loss such as trauma, pigment dispersion, diabetes mellitus, neuro-opthalmological disease, or congenital anomaly. Arcuate scotomas and nasal steps were considered as glaucomatous field defects, and "glaucoma suspect" patients with atypical visual field defects were referred for an evaluation of the optic disc findings. Possible signs of glaucomatous optic atrophy included undermining of the cup, visualization of the laminar dots, and notches or diffuse loss of the neural rim.

A diagnosis of chronic high tension glaucoma was based on documentation of a high intraocular pressure (IOP) of 26 mmHg or more on at least two consecutive monthly examinations, an open angle, and a glaucomatous cupping of the disc and/or visual field loss. In this study, a deformed disc was defined as having at least one of the following clinical features: large disc area (exceeding the emmetropic or hyperopic control optic discs by one standard deviation), a tilting of the disc (nasal slope of the cup is invisible and the temporal slope visible), a large ovalness index (exceeding 1.16, a level which was exceeded by less than 32% of normal optic discs). Axial length was classified into 3 subgroups: short (less than 23.79 mm), medium (23.79–25.32 mm) and long (25.32 mm or more). The axial lengths of 23.79 and 25.32 mm corresponded to a refractive error of -0.5 and -5 D following the single linear regression equation of $y=-0.34\,x+23.62$ ($y=$ axial length, $x=$ diopters) in control eyes. Excluded from this study were eyes with a cloudy media, a large myopic conus exceeding 1.5 disc diameters, myopic macular degeneration, severe retinochoroidal thinning, and localized staphylomas. Patients with burnt-out glaucoma, prior steroid therapy, or a major hemodynamic crisis were also excluded from this study. The visual field was studied by program G1 or 32 of the Octopus 201 and 500EZ after a complete correction of the refractive error. The visual field defect was classified by the mean defect of the G1 program into 0–5, 5–10, 10–15, and 15–17.5 dB. Eyes with normal and high tension glaucoma had similar degrees of visual field defect (Table 2). Defects in the retinal nerve fiber layer were photographed on black and white film (ISO 100, Neopan SS, Fuji Film Co., Tokyo) under a red free light using a fundus camera (CZ 60U; Canon, Tokyo, or TRC-SS, Topcon, Tokyo). Photographs were magnified five times. The green filter used was a Wratan 58 (Kodak, Rochester, N.Y.). The optic disc was covered with black paper, and the nerve fiber layer defect was assessed in a masked fashion. The location of the nerve fiber layer defect was expressed using the 14 sectors described by Airaksinen [6] (Fig. 1).

In this study, a papillomacular bundle defect was defined according to two criteria. First, the defect had to be found in sectors 4 and 5 in a photograph obtained under red-free light and had to be equal to or more severe than those in other sectors if present (Fig. 2a, b). Second, the mean retinal sensitivity of the central 10° of the static perimeter had to be less than that at 10°–20° or 20°–30° (Fig. 2c). The focality of the defects was assessed by the detectability of the boundary of the defects.

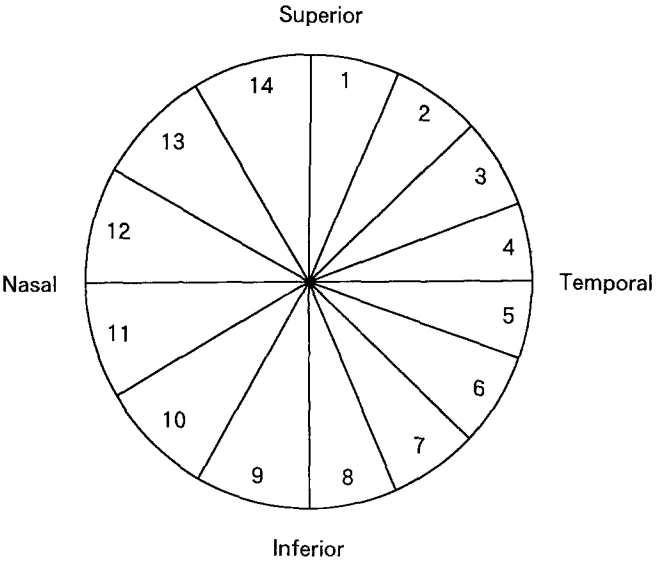

Fig. 1. A schema for sectioning the optic disc and the peripapillary area [6]. The nasal part of the disc was divided evenly into 6 sectors of 30°; the papillomacular bundle was divided into 20° superior and inferior sectors each, with the remainder evenly divided into 3 sectors every 23.3°. Each sector was numbered from 1–14 from the superior-temporal to the inferior and superior-nasal sector

Disc size was measured by tracing the inner margin of Elschnig's scleral ring with a computerized planimeter (Planix 5000, Tamaya, Tokyo). Axial length and corneal curvature were measured, and the data were corrected for magnification by Littmann's procedure [17]. The distance between the disc margin and foveola was also corrected for magnification. In patients with nondeformed optic discs, peripapillary chorioretinal atrophy was separated into zones alpha (hyper- and hypopigmentation) and beta (visible sclera and choroidal vessels) [14]. The 95% confidence interval of the numerical parameters was less than 3% of the mean.

Statistical methods

Data were analyzed with the commercially available program package of multivariate analysis "Quantification II" (Social Survey Research Information Co., Tokyo) and by Student's t-test and the χ^2 test with $P<0.05$ considered as significant. With the multivariate analysis "Quantification II", any correlation between the papillomacular bundle defect and each parameter was evaluated under the condition that the other parameters did not modify them. Partial correlation coefficients indicate the degree to which each parameter is associated with the papillomacular bundle defect. The degree of positive or negative participation by each category of the parameters in the development of the papillomacular bundle defect appears in the category score [11, 21]. The parameters studied by the multivariate analysis appear in Table 3.

Results

Patients with normal tension glaucoma and high tension glaucoma did not differ significantly with regard to sex or refractive error (Table 4). The prevalence of zone alpha in the nondeformed optic disc of patients with normal tension glaucoma (35/39, 90%) was higher than that in patients with high tension glaucoma (45/58, 71%; $P<0.05$). The prevalence of zone beta, however, did not

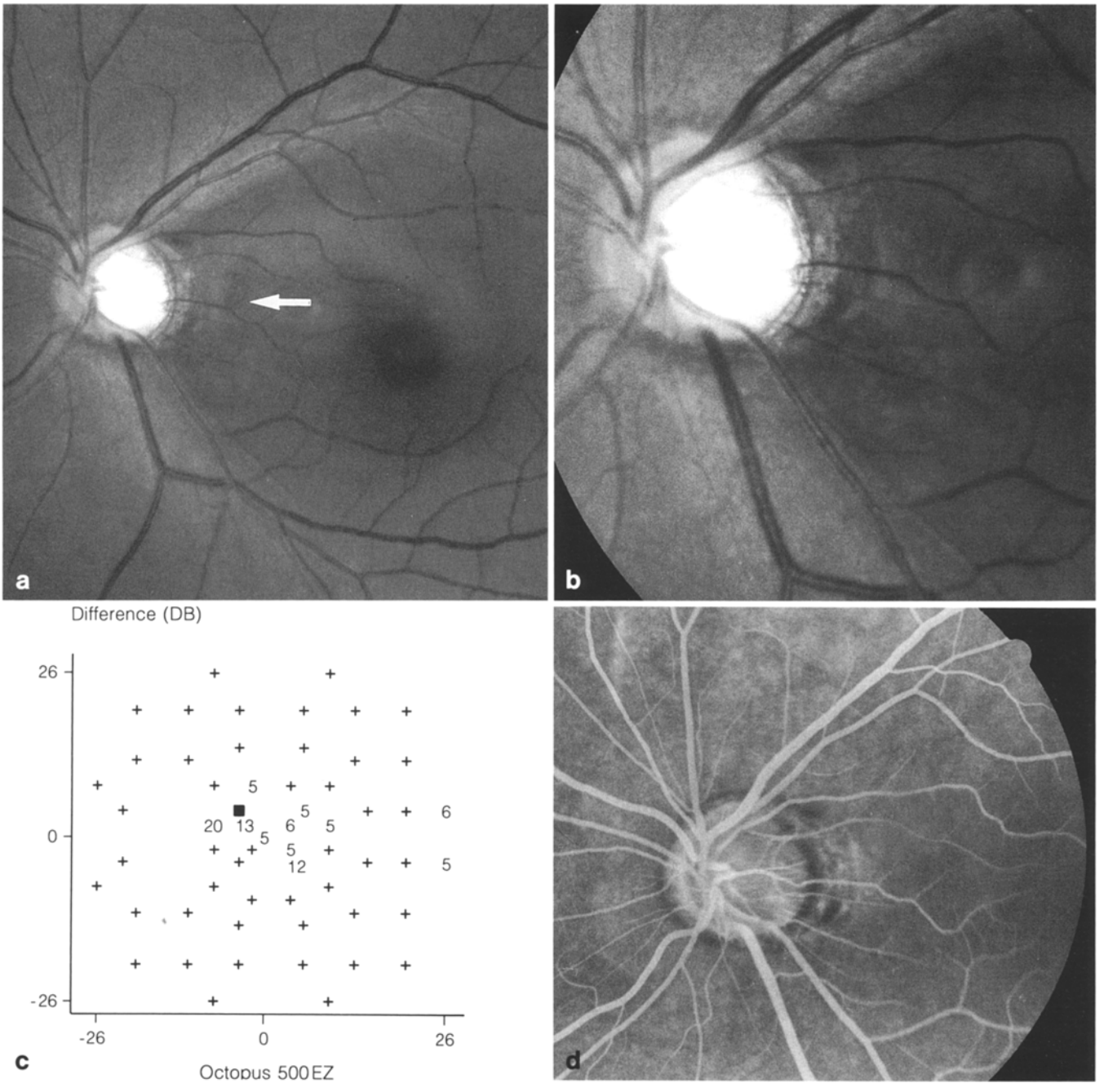

Fig. 2. a Involvement of the papillomacular bundle in a 50-year-old woman with normal tension glaucoma and a deformed optic disc (refractive error −8 D, disc area 3.13 mm^2). Note that the optic disc is enlarged at the inferior-temporal meridian (*arrow*). **b** Magnification of photograph in **a**. The diffuse and broad retinal nerve fiber layer defect in the papillomacular area contrasts with the relatively intact nerve fiber layer at the superior and inferior poles of the disc. The clinical features differ from those focal defects observed in the nondeformed optic discs of patients with normal tension glaucoma shown in Fig. 3. **c** Visual field of the same patient as shown by the Octopus 500EZ. The mean retinal sensitivity within 10° of fixation (22.2±9.0 dB) was less than that in the 10°–20° section (26.1±1.6 dB). **d** Fluorescein angiography of same patient. There was no vascular leakage from the optic disc or macula

differ significantly between those glaucoma groups (20/39, 51% and 24/58 41%, respectively). Differentiation of the myopic crescent from glaucomatous peripapillary choroidal atrophy was difficult to establish in some cases of severe myopia. Thus, we did not determine the prevalence of the peripapillary atrophy in patients with a deformed optic disc. The size of the optic disc and distance between the disc and foveola in emmetropic or hyperopic control eyes was 2.51±0.52 mm^2 and 3.78±0.37 mm (mean±standard deviation, $n=44$), respectively. Thus, the criteria for determining the optic disc deformity on the base of the optic disc size was set at 3.03 mm^2.

Glaucoma patients with a nondeformed optic disc were older than those with a deformed optic disc (Table 4). The prevalence of tilted disc and of a deformed optic disc in patients with normal tension glaucoma (17/82,

Table 3. Parameters subjected to multivariate analysis of risk for the papillomacular bundle defect (significance by the χ^2 test)

Parameter	Categories	Eyes with diffuse papillomacular bundle defect ($n=18$)
1. Type of glaucoma:		
a)	HTG ($n=117$)	6/117 (5%)
b)	NTG ($n=82$)	12/82 (15%)*
2. Oblique insertion of the optic disc:		
a)	Yes ($n=49$)	6/49 (12%)
b)	No ($n=150$)	12/150 (8%)
3. Size of optic disc:		
a)	<1.99 mm^2 ($n=33$)	4/33 (12%)
b)	1.99–3.03 mm^2 ($n=123$)	6/123 (5%)
c)	≤ 3.03 mm^2 ($n=43$)	8/43 (19%)*
4. Ovalness index:		
a)	<1.16 ($n=130$)	12/130 (9%)
b)	≥ 1.16 ($n=69$)	6/69 (9%)
5. Distance between disc and foveola:		
a)	<3.41 mm ($n=22$)	2/22 (9%)
b)	3.41–4.15 mm ($n3122$)	11/122 (9%)
c)	≥ 4.15 mm ($n=55$)	5/55 (9%)
6. Axial length:		
a)	<23.79 mm ($n=81$)	2/81 (2%)
b)	23.79–25.32 mm ($n=66$)	5/66 (8%)
c)	≥ 25.32 mm ($n=52$)	11/52 (21%)**

* $P<0.05$; ** $P<0.001$

Table 4. Characteristics of 199 glaucoma patients and control subjects with and without deformation of optic disc (mean $\pm$ SD or %)

Parameter	Glaucoma (A)		Glaucoma (B)	
	NTG (A) ($n=39$)	HTG (A) ($n=58$)	NTG (B) ($n=43$)	HTG (B) ($n=59$)
Mean age (years)	61.1 ± 10.6[a]	56.6 ± 11.4[b]	53.9 ± 14.4	51.2 ± 16.4
Male/total	17/39 (44%)	31/58 (53%)	19/43 (44%)	30/59 (51%)
Refractive error	-0.43 ± 2.28	-1.06 ± 2.76	-3.66 ± 3.26	-4.78 ± 4.52
Size of optic disc (mm^2)	2.31 ± 0.45	2.36 ± 0.47	2.94 ± 0.85***	$2.87 \pm 0.0.87$***
Distance between disc and foveola (mm)				
	3.79 ± 0.37	3.80 ± 0.40	4.00 ± 0.47*	4.05 ± 0.52**
Ovalness index	1.09 ± 0.08	1.09 ± 0.07	1.18 ± 0.13***	1.20 ± 0.20***
Oblique insertion of disc	0/39	0/58	17/43 (40%)	32/59 (54%)

[a] Significantly older than NTG (B) ($P<0.05$) and HTG (B) ($P<0.01$)

[b] Significantly older than HTG (B) ($P<0.05$)

* $P<0.05$, ** $P<0.01$, *** $P<0.001$ in comparisons between nondeformed (A) and deformed (B) optic discs by Student's t-test

21% and 43/82, 52%) was not significantly greater than in patients with high tension glaucoma (32/117, 27% and 59/117, 50%, respectively; Table 4). Discrete, slitlike defects in the nerve fiber layer were found in 2 of 102 (2%) controls.

A papillomacular bundle defect was found in 22 of 199 glaucomatous eyes. Two types of papillomacular bundle defect were observed: In one, the defect was focal and narrow (Fig. 3), and in another, the defect was diffuse and broad (Fig. 2a, b). In this study, 4 eyes had the focal-type papillomacular bundle defect. The disc size and axial length in these eyes (2.33 ± 0.90 mm^2 and 23.70 ± 0.65 mm, mean $\pm$ SD, respectively) were smaller than in those eyes without a focal-type papillomacular

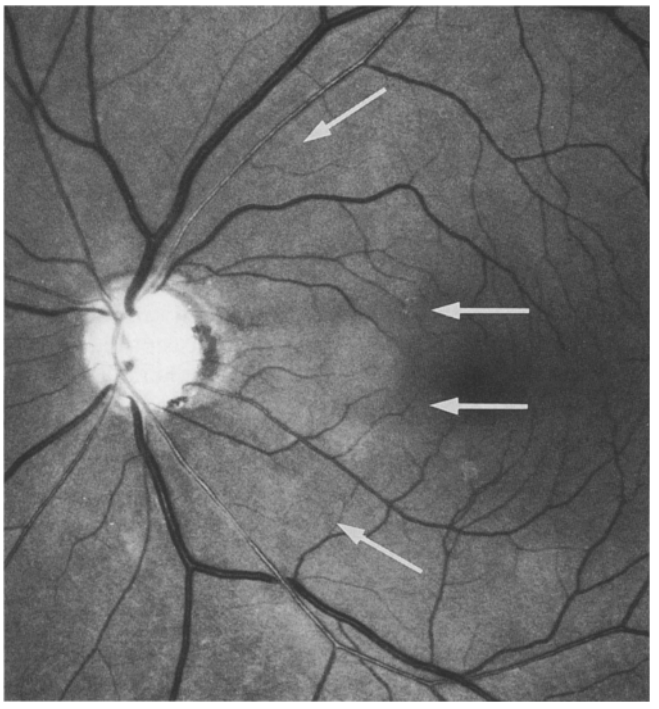

Fig. 3. Focal retinal nerve fiber layer defects involving the papillomacular bundle area in a 49-year-old man with normal tension glaucoma and a nondeformed optic disc (refractive error +0.75 D, optic disc size 2.13 mm^2). There are multiple focal and narrow retinal nerve fiber layer defects and peripapillary choroidal atrophy (*arrows*)

Table 4 (continued)

Parameter	Control (A) ($n=53$)	Control (B) ($n=49$)
Mean age	50.3±14.2	49.6±15.6
Male/total	27/53 (51%)	26/49 (53%)
Refractive error	−0.61±2.45	−5.77±6.82
Size of the optic disc (mm^2)	2.47±0.44	2.86±0.79**
Distance between the disc and foveola (mm)	3.89±0.40	4.11±0.65*
Ovalness index	1.07±0.05	1.23±0.16***
Oblique insertion of the disc	0/53	27/49 (55%)

bundle defect (2.64±0.77 mm^2 and 24.54±1.56 mm, respectively). This difference, however, was not statistically significant. The diffuse type of papillomacular bundle defect was found in 18 of 199 glaucoma eyes. Fluorescein angiography revealed no degeneration in the macular area (Fig. 2d). In these 18 eyes, the mean retinal sensitivity within the central 10° (10.67±9.7 dB) was less than that between 10°–20° (13.79±8.14 dB) or that between 20°–30° (15.71±6.52 dB; Fig. 2c). The disc size and axial length (3.04±1.02 mm^2 and 25.88±1.47 mm, respectively) were significantly greater than in those eyes without a diffuse-type papillomacular bundle defect

Table 5. Optic disc size and axial length of eyes with and without papillomacular bundle defect (mean±standard deviation)

Type of the NFLD	Disc size (mm^2)	Axial length (mm)
Eyes with a diffuse-type papillomacular bundle defect ($n=18$)	3.04±1.02*	25.88±1.47**
Eyes without a diffuse-type papillomacular bundle defect ($n=181$)	2.59±0.72	24.46±1.59

* $P<0.02$, ** $P<0.001$, Student's t-test
NFLD, Nerve fiber layer defect

Table 6. Risk factors for the diffuse-type papillomacular bundle defect

Parameter	P value (χ^2 test)	Partial correlation coefficient (multivariate analysis)
Type of glaucoma	0.0203*	0.1913
Tilting of disc	0.6280	0.0166
Disc size	0.0205*	0.1336
Ovalness index	0.8957	0.1009
Distance disc-foveola	0.9996	0.0335
Axial length	0.0015**	0.2675

P value was determined by the χ^2 test and partial correlation coefficient by the multivariate analysis "Quantification II" * $P<0.05$, ** $P<0.01$

($P<0.02$ and $P<0.001$, respectively; Table 5). Three of 97 (3%) glaucomatous eyes without deformation of the disc and 15 of 102 (15%) glaucomatous eyes with deformation of the disc had the diffuse-type papillomacular bundle defect. Thus, deformation of the disc correlated significantly with the diffuse-type papillomacular bundle defect ($\chi^2=4.52$, $P<0.05$).

When correlations between the parameters in Table 3 and the diffuse-type papillomacular bundle defect were studied by the χ^2 test, the risk factors which correlated significantly with the diffuse-type papillomacular bundle defect were axial length ($P<0.01$), type of glaucoma ($P<0.05$), and optic disc size ($P<0.05$; Tables 3, 6). The three main risk factors for the diffuse-type papillomacular bundle defect determined by multivariate analysis were: the type of glaucoma, axial length, and disc size. These parameters were also found to be risk factors by the χ^2 test; however, they ranked differently in importance (Table 6). In a more detailed study based upon category scores, the positive risk factors for diffuse-type papillomacular bundle defects were found to be longer axial length, diagnosis of normal tension glaucoma, and the large size of the optic disc (category scores of 0.1483, 0.0633, and 0.0577, respectively). On the other hand, eyes with a short axial length, diagnosis of high tension glaucoma, and large ovalness index were less likely to have the diffuse-type papillomacular bundle defect (category scores of −0.0852, −0.0444, and −0.0440, respectively; Table 7). The tilting of the disc and the distance

Table 7. Risk factors for diffuse-type papillomacular bundle defect ranked by category score (by multivariate analysis "Quantification II")

Risk factor	Category score for diffuse-type papillomacular bundle defect
1. Long axial length ($\geq$25.32 mm)	0.1483
2. Diagnosis of normal tension glaucoma	0.0633
3. Large optic disc ($\geq$3.03 mm^2)	0.0577
4. Small disc size ($<$1.99 mm^2)	0.0311
5. Small ovalness index ($<$1.16)	0.0233
6. Short disc-foveolar distance ($<$3.41 mm)	0.0074
7. Moderate disc-foveolar distance (3.41–4.15 mm)	0.0059
8. No tilting of disc	0.0032
9. Tilting of disc	−0.0097
10. Moderate axial length (23.79–25.32 mm)	−0.0122
11. Long papillomacular bundle ($\geq$4.15 mm)	−0.0160
12. Moderate disc size (1.99–3.03 mm^2)	−0.0285
13. Large ovalness index ($\geq$1.16)	−0.0440
14. Diagnosis of high tension glaucoma	−0.0444
15. Short axial length ($<$23.79 mm)	−0.0852

between the disc and foveola did not correlate significantly with the diffuse-type papillomacular bundle defect (Tables 6, 7).

Discussion

In the present study, the optic disc size was greater than in some previous reports [7], but it was similar to the results obtained using a planimeter [15]. Different methodologies in tracing the margin of the optic disc by the planimeter or by a computerized disc analyzer may be a cause of the variations. Another explanation may be a variation of the optic disc size in connection with race. For example, the optic disc in black people is larger than that in white people [7, 20].

Large disc size was associated with a high risk of developing a diffuse-type papillomacular bundle defect (Tables 5–7). Meanwhile, eyes with a focal-type papillomacular bundle defect were more likely to have a small disc. Small discs are prone to vascular accidents [3] and multiple retinal nerve fiber layer defects in glaucoma [8] and tend to have focal-type papillomacular bundle defects. Thus, the pathogenesis of nerve damage in small discs may differ from that in large discs. However, the small sample size of the focal-type papillomacular bundle defect does not allow statistical analysis.

There are some explanations for the vulnerability of the papillomacular bundle in myopic and glaucomatous eyes. Large discs are common in myopic eyes, and they may suffer greater displacement by the pressure [7]. There are controversial reports on the correlation between disc size and susceptibility of nerve fibers to glaucomatous damage [7, 12, 13]. In this study, high myopes were not excluded, and the collagen or intercellular matrix in myopic exes may have been weak to begin with [9]. The laminar pore number is relatively constant regardless of the size of the choroidal lamina [18], and the total pore area increases as the size of the disc increases [16]. An increase in the size of the laminar pores of a large disc may predispose to the susceptibility of nerve fibers to glaucomatous damage in myopia [19]. If the enlargement of the optic disc occurs in the papillomacular bundle area as seen in Fig. 2, it may weaken the supportive connective tissue or impede the vascular supply and make the papillomacular bundle vulnerable to glaucomatous damage. Other explanations may imply that (1) the nerve fibers become more susceptible to glaucomatous damage by a distortion of the lamina cribrosa as the axial length increases, (2) the retinal nerve fiber layer in high myopia is thin to begin with, and the atrophy may become obvious with progression of the diffuse type defect, (3) the nerve fiber layer may become atrophic following the myopic macular degeneration. However, the last two possibilities are less probable because the visual field was selectively impaired at the macular area and there was no myopic degeneration upon fluorescein angiography (Fig. 2d). A papillomacular bundle defect was common in normal tension glaucoma. If mechanical damage was the main pathogenetic factor for the nerve damage in normal tension glaucoma, the prevalence of deformed optic disc in normal tension glaucoma may be expected to be high. However, this was not the case (Table 4). The nerve could be damaged by ischemia, which may occur in any sector of the disc. Eyes with a nondeformed optic disc and normal tension glaucoma had a high prevalence of peripapillary choroidal atrophy, confirming the findings described in a previous report [4]. A poor vascular supply in the temporal part of the optic disc may participate in the development of papillomacular bundle defects. However, the relationship between peripapillary choroidal atrophy and the presence of diffuse or focal-type papillomacular bundle defects is not clearly defined and may be clarified by studying a larger patient population.

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