Intraocular Pressure–independent Risk Factors for Progression of Glaucoma

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Although intraocular pressure is the most widely studied risk factor for progression of open angle glaucoma, there is growing evidence that other factors may affect the prognosis of this disease. Among the intraocular pressure–independent risk factors, disc haemorrhage and peripapillary atrophy have been associated with progression of open angle glaucoma. There is a relationship between the location of the disc haemorrhage and the area of progression of visual field loss. Peripapillary atrophy occurs more frequently in eyes with glaucoma than in healthy eyes. This paper reviews the evidence suggesting that disc haemorrhage and peripapillary atrophy may be independent prognostic factors for progression of glaucoma.

Key Words: *Atrophy, Glaucoma, open angle, Hemorrhage, Optic disk, Prognosis, Risk Factors*

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Introduction

Intraocular pressure (IOP) is undoubtedly the most significant risk factor for the progression of optic disc damage and visual field defect in open angle glaucoma (OAG) and normal tension glaucoma (NTG). However, there is growing evidence that ocular factors other than IOP affect the prognosis of OAG. Ocular risk factors for glaucoma progression can therefore be divided into 2 groups of IOP-dependent and IOP-independent risk factors. Disc haemorrhage and peripapillary atrophy are the 2 most important IOP-independent risk factors for progression.

Features of Disc Haemorrhage

Disc haemorrhage is not uncommon in OAG, with a reported prevalence rate of 20% in NTG. In Japan, the prevalence rate of disc haemorrhage is reported to be 20.5% in NTG, 4.2% in OAG, and 0.4% in non-glaucomatous eyes (Table 1).[1] In this study, disc haemorrhage was not noted in eyes with angle closure glaucoma (ACG).

Disc haemorrhage is a transient condition, lasting for a few weeks to several months.[2] It is possible that the limited duration of each episode of disc haemorrhage contributes to underestimates of the prevalence rate. The probability of occurrence of disc haemorrhage is 38.4% for NTG and 16.9% for OAG in 11 and 14 years, respectively.[3]

It has been noted that disc haemorrhage occurs most frequently in the inferotemporal margin of the disc, with the inferonasal side of the disc being least involved.[2] The appearance of notching of the neuroretinal rim at the site of the disc haemorrhage has been observed.

Recurrence is another important characteristic of disc haemorrhage, and it occurs in 12% to 64% of patients with glaucoma.[1,2] Kitazawa et al noted that 18 of 28 eyes with disc haemorrhage (64%) had recurrent episodes.[1] The number of recurrences ranged from 1 to 7. In 13 eyes (72%), the recurrent haemorrhages occurred in the same quadrant of the optic disc where the previous haemorrhages had been present. This finding was also described by Shihab et al in 3 of 25 patients who had disc haemorrhage.[2] This is clinically important because disc haemorrhage tends to precede the deterioration of visual field and indicates an unfavourable prognosis.

Disc Haemorrhage as a Risk Factor for Progression

In 1998, Ishida et al reported that disc haemorrhage was a risk factor for the rate of visual field progression in NTG. In this study of 110 patients with NTG, several clinical factors were investigated to find a possible association with progression of glaucomatous visual field.[4] Change in the visual field was found to be significantly associated with treatment with calcium channel blockers, recovery rate from a cold recovery test, systolic blood pressure, disc haemorrhage, corrected pattern standard deviation, mean deviation, and diurnal fluctuation of IOP. These authors concluded that factors other than IOP are associated with visual field loss in NTG.

This conclusion was supported by the finding that the rate of visual field progression is significantly higher in eyes with NTG with disc haemorrhage than in

Table 1. Prevalence of disc haemorrhage in glaucoma in Japan.

Glaucoma type	Number of patients/Total (%)
Primary open angle glaucoma	8/192 (4.2)
Normal tension glaucoma	16/78 (20.5)
Primary angle closure glaucoma	0/113 (0)
Ocular hypertension	1/204 (0.5)
Healthy eyes	2/473 (0.4)

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Table 2. Progression of eyes with and without disc haemorrhage according to mean deviation definition and pointwise definition of progression.

	Eyes with disc haemorrhage (n = 32)	Eyes without disc haemorrhage (n = 38)	p Value
Mean deviation definition	17	4	0.0002
Pointwise definition	26	17	0.004

Table 3. Progression of eyes with and without recurrent disc haemorrhage according to mean deviation definition and pointwise definition of progression.

	Eyes with 1 disc haemorrhage (n = 9)	Eyes with ≥2 disc haemorrhages (n = 23)	p Value
Mean deviation definition	4	13	
Probability of no further visual field deterioration (%)	67 ± 16	27 ± 13	
Pointwise definition	3	23	0.0001
Probability of no further visual field deterioration (%)	42 ± 17	0 ± 0	

those without disc haemorrhage and that recurrent disc haemorrhage indicates a higher probability for the visual field to deteriorate.[5] Ishida et al investigated the relationship between disc haemorrhage in NTG and the progression of visual field defects in 70 eyes of 70 patients to determine the extent to which progression of visual field loss in NTG is affected by disc haemorrhage.[5] Disc haemorrhage, age, corrected-pattern standard deviation, systolic blood pressure, and pulse rate were found to be significant risk factors for visual field progression.

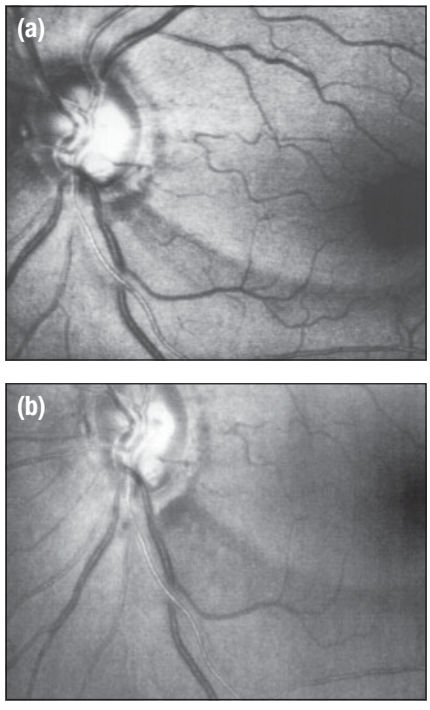
When eyes were divided into 2 subgroups according to the presence or absence of disc haemorrhage, significantly more eyes with disc haemorrhage progressed than eyes without disc haemorrhage (Table 2). Similarly, progression was shown in more eyes with recurrent disc haemorrhage (≥2 occurrences) than in eyes with only 1 disc haemorrhage (Table 3). In addition, there was a significant relationship between the location of the disc haemorrhage and the area of progression of visual field loss in 65.4% of patients with disc haemorrhage who progressed. These findings suggest that disc haemorrhage is a significant negative prognostic factor for patients with NTG and may be a sign of progressive damage of the retinal nerve fibre layer (RNFL), leading to functional deterioration of the visual field.

In 2001, Drance et al clearly demonstrated a higher rate of visual field progression in eyes with disc haemorrhage than in eyes without disc haemorrhage.[6] Visual field data from 160 eyes of 160 patients enrolled in the Collaborative Normal Tension Glaucoma Study showed that the presence of disc haemorrhage affected the subsequent course of visual field deterioration.[6] The mean time to demonstrable progression for eyes without an initial disc haemorrhage was 2159 ± 109 days compared with 1187 ± 196 days for eyes with a baseline disc haemorrhage (p = 0.0034). The adjusted odds ratio for the presence of a baseline disc haemorrhage was 2.72 (95% confidence interval, 1.39-5.32). The presence of disc haemorrhage signifies an additional risk factor for progression.

Disc haemorrhage often occurs at, or close to, the border of the retinal nerve fibre layer defect (RNFLD). In a study of the topographic correlation between optic disc haemorrhage and RNFLD, Sugiyama et al evaluated the relationship between the precise locations of disc haemorrhage and RNFLD in 42 patients with NTG.[7] Sixty four disc haemorrhages were noted in 48 eyes of 42 patients and RNFLDs were observed in 47 of the 48 eyes. Of the 64 disc haemorrhages, 51 coincided with the location of RNFLDs, in that the 51 disc haemorrhages were present on the border or adjacent to the border between the RNFLD and the apparently healthy-looking RNFL. The clinical significance of this finding is that disc haemorrhage might indicate the location of an RNFLD even in patients in whom such a defect may be difficult to discern by ophthalmoscopy. Figure 1 demonstrates an RNFLD 5 years after a disc haemorrhage.

A later study in which Sugiyama et al evaluated the frequency of localised wedge-shaped defects of the RNFL in 83 eyes with NTG and in 20 eyes with OAG with and without disc haemorrhage confirmed this finding.[8] Localised wedge-shaped defects of the RNFL occurred significantly more often among patients with disc haemorrhage than among those without disc

Figure 1. Enlargement of cupping and retinal nerve fibre layer defect during a 5-year period. (a) A small splinter haemorrhage is present at the 5-o'clock position in December 1995; and (b) the retinal nerve fibre layer defect is widened in August 2000. Photograph courtesy of Dr Kazuhisa Sugiyama.



haemorrhage in both NTG ($p < 0.0001$) and OAG ($p < 0.05$). Most disc haemorrhages were present in the vicinity of the border between the localised RNFLDs and relatively healthy-looking RNFL in eyes with POAG and those with NTG.

While IOP is the most extensively studied intrinsic ocular factor, the aetiology of disc haemorrhage remains to be elucidated. However, studies have shown that disc haemorrhage is more likely to develop at a relatively lower IOP during therapy with ocular hypotensive agents.[9] The reason for this phenomenon may be that IOP reduction causes anterior displacement of the lamina cribrosa, thereby increasing venous resistance; an increase in the pressure difference across the vascular wall; and changes in haemodynamic factors, possibly leading to haemorrhage.

The presence of disc haemorrhage is thought to indicate an ongoing, active process that damages the optic disc in OAG.[1] Therefore, disc haemorrhage may be a useful and reliable indicator to distinguish patients who have progressive visual field loss from those who are less likely to progress, and may thus be clinically helpful for developing a management plan for patients with OAG.[5]

Peripapillary Atrophy as a Risk Factor for Progression

Peripapillary atrophy is also believed to be an IOP-independent risk factor for progression of glaucoma. It is widely accepted that peripapillary atrophy is more frequent and more extensive in patients with glaucoma than in healthy individuals.[10] Associations have been detected between the extent of peripapillary atrophy and the amount of optic disc damage, and between the location of peripapillary atrophy and the location of both optic disc damage and visual field defects.

In OAG, both structural and functional disc changes are closely related to the size of peripapillary atrophy.[10] In a study to determine the incidence and degree of progression of peripapillary atrophy in 75 eyes with progressive and non-progressive glaucoma, Uchida et al found that 28 eyes (37%) showed progression of peripapillary atrophy.[10] Thirty three eyes (44%) showed progressive optic disc damage. Twenty one of the 33 eyes with progressive disc damage (64%) showed progression of peripapillary atrophy compared with 7 of 42 eyes without progressive disc damage (17%) [$p < 0.01$].

Table 4. Optic disc progression and visual field progression in patients with and without progressive peripapillary atrophy.

	Progressive peripapillary atrophy	Non-progressive peripapillary atrophy
Optic disc progression	75%	26%
Visual field progression	54%	11%

Optic disc progression and visual field progression were both significantly more frequent among patients with progression of peripapillary atrophy than among those without progression of peripapillary atrophy ($p < 0.01$; Table 4). No correlation was found between progression of peripapillary atrophy and mean IOP. These findings suggest that progression of peripapillary atrophy is associated with progressive optic disc damage and progressive visual field loss in glaucoma and may be a useful marker for progressive glaucomatous damage.

The size of peripapillary atrophy relative to that of the disc and the cup-disc ratio is significantly greater in eyes with disc haemorrhage than in those without disc haemorrhage.[11] Peripapillary atrophy therefore appears to be associated with a higher degree of cupping of the optic disc and disc haemorrhage.

Hayakawa et al investigated the association of the peripapillary atrophy area with disc cupping area and disc haemorrhage in 8842 eyes of 4421 people undergoing a routine health examination.[11] The ratio of cup area to disc area was significantly greater in eyes with peripapillary atrophy (0.36 + 0.09) than in eyes without peripapillary atrophy (0.34 + 0.07), and the ratio of peripapillary atrophy area to disc area was significantly greater in eyes with disc haemorrhage (0.26 + 0.34) than in those without disc haemorrhage (0.09 + 0.18). Moreover, in eyes with peripapillary atrophy, the ratio of cup area to disc area was significantly larger in eyes with disc haemorrhage (0.48 + 0.08) than in those without disc haemorrhage (0.36 + 0.09). These results suggest an association between peripapillary atrophy and glaucomatous optic neuropathy.

Sugiyama et al studied the association of peripapillary atrophy and disc haemorrhage in patients with NTG.[7] These authors found that 39 of 40 eyes (97.5%) with disc haemorrhage had peripapillary atrophy compared with 42 of 51 eyes (82.4%) with no disc haemorrhage ($p = 0.0385$). The area, angular extent, and ratio of peripapillary atrophy area to disc area were significantly greater in eyes with disc haemorrhage than in eyes without disc haemorrhage ($p = 0.0446$, $p = 0.0263$, and $p = 0.0246$, respectively). These findings suggest a significant association between disc haemorrhage and peripapillary atrophy in NTG.

Uchida et al noted different peripapillary atrophy characteristics between eyes with ACG and eyes with OAG, suggesting different pathological processes of glaucomatous change for the 2 types of glaucoma.[12] Eight of 21 eyes with ACG (38%) and 21 of 31 eyes with OAG (68%) had peripapillary atrophy ($p = 0.048$). The ratio of peripapillary atrophy area to disc area of eyes with OAG was significantly larger than

that of eyes with ACG ($p = 0.005$). There was no significant correlation between the ratio of peripapillary atrophy area to disc area and the ratio of cup area to disc area or visual field mean deviation in eyes with ACG. However, there was a significant correlation between the peripapillary atrophy area to disc area and the ratio of cup area to disc area ($p = 0.003$) and the visual field mean deviation ($p < 0.001$) in the eyes with OAG.

Although little is known about the pathogenesis of peripapillary atrophy, and further study is required, progression of peripapillary atrophy is associated with progressive glaucomatous damage and may provide clinically relevant information about the status of glaucomatous optic nerve damage.

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