Effect of optic disc hemorrhage on glaucoma progression

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ABSTRACT

Optic disc evaluation is a valuable marker in the diagnosis and follow-up of patients with glaucoma. Detection of disc hemorrhages plays an important role in the prognosis of the disease, as it is a precursor of progressive functional visual field loss in glaucoma. During routine ophthalmological examination, optic disc hemorrhages can often be overlooked and confused with vascular structures. Ophthalmoscopic examination and stereophotography are the best methods to detect disc hemorrhages. In this review, optic disc hemorrhage, which has an important impact on the diagnosis and prognosis of glaucoma, is extensively discussed.

Keywords: Glaucoma, optic disc hemorrhage, visual field loss, progression.

INTRODUCTION

Glaucoma is an irreversible optic neuropathy associated with progressive morphologic changes in the optic nerve head and visual loss. There are many reports on the relationship between optic disc hemorrhage (ODH) and glaucomatous damage and progression.[1-4] Since disc hemorrhages are transient and subtle, there may be difficulties in their detection and follow-up due to differences in follow-up time and fixed scanning intervals. For these reasons, the reported prevalence of ODH may vary between studies. The prevalence of ODH in the normal population ranges from 0-1.4%, whereas it is 2-37% in primary open angle glaucoma (POAG), 11-42% in normotensive glaucoma (NTG), and 0.4-10% in ocular hypertension (OHT).[5,6] It has also been reported that ODH precedes the development and progression of retinal nerve fiber layer (RNFL) defects and leads to functional impairment in the visual field (VF).[4,7]

Optic disc hemorrhage may indicate the presence of glaucomatous damage even if visual field loss is not evident. Recent studies of long-term follow-up of preperimetric glaucoma (PPG) cases suggest that ODH is also an important risk factor for progression of PPG.[8] Optic disc hemorrhage is more common in early glaucoma cases and normal tension glaucoma cases than in high pressure glaucoma cases.[9]

The importance of investigating the presence of disc hemorrhage as an important biomarker of glaucoma damage in a group of patients with normal intraocular pressure (IOP) and no or early visual field loss in 1113 eyes of 562 patients with optic disc hemorrhage evaluated by stereophotography was emphasized.[10] Localized subclinical structural changes predispose to disc hemorrhages. Furthermore, while ODH is a marker of rapid glaucoma progression, recurrent optic disc hemorrhages may be associated with rapid structural progression of glaucomatous damage.

Pathogenesis

Although the pathogenesis of disc hemorrhage and its vascular origin (arteriole, venule or capillary) remain unclear, Chou et al. measured the geometric profiles and densitometry of POAG-associated disc hemorrhages and compared them with hemorrhages from retinal vein occlusions and retinal macroaneurysms, which have venous and arterial sources of hemorrhage, respectively, and suggested that POAG-associated ODH is arterial in origin.[11]

Underlying mechanisms such as structural changes at

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the level of the lamina cribrosa, microinfarction of the optic nerve head, retinal circulatory disorders, decreased capillary perfusion pressure in the optic nerve head and primary vascular dysregulation have been proposed to explain the pathogenesis of disc hemorrhage.[12-14]

Four biomechanical forces affecting the lamina cribrosa and surrounding tissue; IOP, cerebrospinal fluid pressure, arterial pressure and venous pressure are thought to contribute to the development of optic disc hemorrhage. Miyake et al. found that the incidence of disc hemorrhage decreased after trabeculectomy in both populations in their study of NTG and POAG groups. The incidence of disc hemorrhage decreased from 33% to 6% in POAG patients and from 42% to 23% in NTG patients.[15] POAG eyes with higher postoperative IOP than NTG patients had a much higher incidence of disc hemorrhage than the low postoperative IOP group. This may be considered as evidence that the development of disc hemorrhage is correlated with IOP. Furthermore, a recent review of the Ocular Hypertension Treatment Trial (OHTT) found that IOP reduction reduced the risk of disc hemorrhage and that there was a close association between IOP and optic disc hemorrhage.[16-17]

On the other hand, there are also publications that disc hemorrhage is not related to IOP.[1,6,9,18] In the studies by Healy et al. and Kitazawa et al. the prevalence of disc hemorrhage in ocular hypertension was similar to that in normotensive eyes in the general population.[5,9] Kitazawa et al. also compared glaucoma patients with and without ODH and found that although IOP decreased with anti-glaucoma treatment, especially among NTG patients, hemorrhage developed again in eyes with ODH.[9] The Early Detection Glaucoma Treatment Study also showed that optic disc hemorrhage did not change after IOP-lowering medication.[1]

There are studies showing that ODH can also occur in nonglaucomatous eyes.[9] In a study examining ODH in nonglaucomatous eyes, a decrease in peripapillary vascular density in the ODH region and progression of the VF defect corresponding to the ODH region were found in non-glaucomatous eyes at long-term follow-up. Retinal pigmentation with RNFL defects is a predictor for ODH, but RNFL did not change significantly. However, it has been stated that antiglaucomatous treatment may not prevent deterioration in visual function.[19]

In order to elucidate the biomechanical background of disc hemorrhage, the properties of the lamina cribrosa, an important structure, should also be examined in detail. The lamina cribrosa is known to act as a barrier that affects the translaminar pressure gradient between cerebrospinal fluid pressure and IOP. In a study conducted among NTG patients, the lamina cribrosa was significantly thinner in patients with disc hemorrhage than in patients without disc hemorrhage.[20] Thinner lamina cribrosa has been shown to provide less connective tissue support to axons, resulting in a higher translaminar pressure gradient and increased IOP-related stress on the optic nerve head. In addition, disc hemorrhage commonly develops in the upper and lower regions of the lamina cribrosa, which contain large pores and less connective tissue, more susceptible to mechanical damage. This suggests that disc hemorrhage is related to the mechanical properties of the optic disc rather than IOP. Kim and Park reported a higher rate of structural changes in the lamina cribrosa in POAG eyes with ODH compared to eyes without ODH.[21] This finding was recently reconfirmed in a prospective study.[22]

Grieshaber et al. investigated the underlying mechanism of optic disc hemorrhage and focused on vascular dysregulation and reported that increased blood flow resistance, decreased blood flow in extraocular vessels, low systemic blood pressure, and simultaneous high plasma levels of endothelin-1 and matrixmetalloproteinase may cause ODH.[14]

Systemic arterial pressure can also affect arterial pressure in the optic nerve head. Kim et al. showed that hypertension was a statistically significant ODH risk factor among NTG patients across several parameters, including IOP, diabetes and aspirin use.[23] On the other hand, in another study evaluating the risk factors for ODH, reported that the risk of ODH was higher in POAG patients with diabetes and aspirin users. It has been emphasized that aspirin may cause larger ODH with its effect on the coagulation cascade, may take longer to be absorbed and thus may be detected more frequently during periodic examinations.[24] Increased venous pressure from Valsalva or head-down posture, increased episcleral venous pressure and choroidal enlargement may increase the likelihood of disc hemorrhage.[25] In patients with microinfarction of the optic nerve head, retinal circulation was impaired and capillary perfusion pressure in the optic nerve head was decreased. The incidence of disc hemorrhage was high in patients with both branch retinal vein occlusion and NTG. This suggests that some cases of NTG, especially those involving disc hemorrhage, may share a common pathophysiology with branch retinal vein occlusion.[26-27]

Recently, several studies using optical coherence tomography angiography (OCTA) have revealed a regional relationship between microvascular density loss (MvD) in the deep peripapillary layer, RNFL defects and decreased peripapillary vascular density (VD) in glaucomatous eyes, suggesting that microvascular changes may influence the pathogenesis of glaucoma.

In a study evaluating the relationship between ODH and intradisk VD in POAG eyes, intradisk VD measurements on Swept Source (SS) OCTA scans were significantly lower in the ODH group compared to the non-ODH group, whereas parapapillary choroidal VD values were similar between the two groups. Furthermore, the occurrence of ODH was significantly associated with a lower intra-disc VD based on multivariate analyses. These findings suggest that eyes with ODH may be associated with a loss of microvasculature in the optic nerve head region.[28]

Nishida et al. evaluated circumpapillary retinal nerve fibre layer (cpRNFL) thinning and capillary density loss in glaucomatous eyes with ODH, the mean vessel density loss rates between eyes with and without ODH were found to be different not only in the affected area but also in other regions. In contrast, a significant difference in cpRNFL thinning between the two groups was found only in the inferior temporal sector. ODH was found to be an independent predictor of faster vessel density loss in glaucoma suspects and POAG patients.[29]

Many studies investigating the relationship between optic disc hemorrhage and β-zone peripapillary atrophy (PPA) suggest that, β-zone PPA size is a predictive factor and have reported that disc hemorrhage tends to occur in areas of the eye with the largest β-zone PPA width.[30-32] Jonas et al. found that morphologic factors such as optic disc size and shape, α-zone PPA, retinal vessel diameter and cup depth were not associated with disc hemorrhage, but neuroretinal rim area and β-zone PPA were associated with ODH. In addition, a retrospective study investigating the relationship between the geographical pattern of peripapillary choroidal vessel density (pCVD) loss within the β-zone PPA and optic disc haemorrhage in POAG patients showed more severe regional pCVD loss in the area corresponding to the ODH location when POAG eyes with ODH were compared with non-ODH POAG eyes.[33]

They also examined interocular differences in morphologic parameters, VF loss and IOP measurements in patients with bilateral chronic open-angle glaucoma and unilateral disc hemorrhage and found no correlation between these differences and the onset of disc hemorrhage. This suggests that patients with unilateral disc hemorrhage are as likely to develop optic disc hemorrhage in the contralateral eye as in the affected eye.[32] Disc hemorrhage has also been strongly associated with rim notch, small neuroretinal rim and RNFL problems. Nitta et al. found that eyes with disc hemorrhage had a higher prevalence of localized RNFL defects on both NTG and POAG than eyes without disc hemorrhage. In their study, it was emphasized that RNFL thinning is an active site of damage and may cause optic disc hemorrhage with disruption in the capillary network.[34]

View and Location

Disc hemorrhages may occur adjacent to areas of previous damage such as the PPA, RNFL defect or rim notch (Figure 1-2). In two thirds of cases, they are located in the inferotemporal region of the optic disc, which is consistent with early glaucomatous optic disc finding.[35] The incidence of optic disc hemorrhage increases from early to intermediate stages of glaucoma and decreases in advanced glaucoma. Optic disc hemorrhage usually disappears within two months.[32]

In a study evaluating disc hemorrhage and optic disc morphology, 1113 optic disc views were examined and disc hemorrhage was most common in focal ischemic glaucomatous optic nerves (66.7%). Hemorrhage was less common in senile sclerotic (15.6%), myopic glaucomatous (13.3%) and concentric enlargement (4.4%) optic nerve

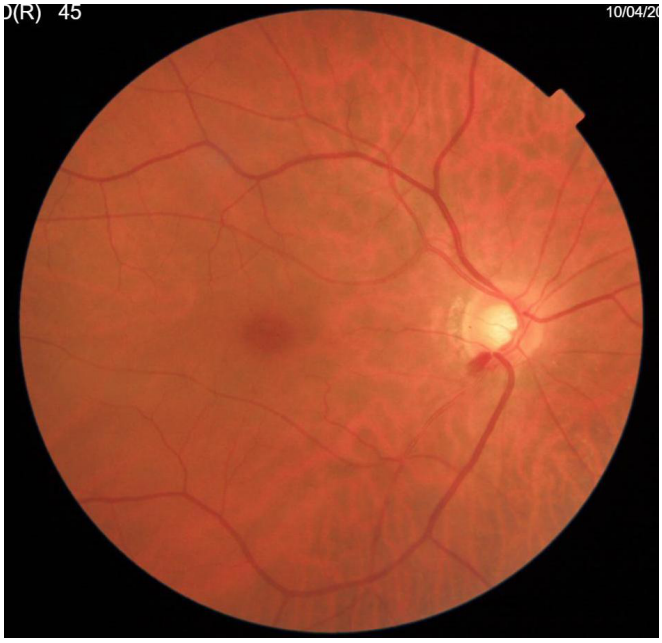

Figure 1: *Optic disc hemorrhage extending to the peripapillary retina inferotemporal to the optic disc.*

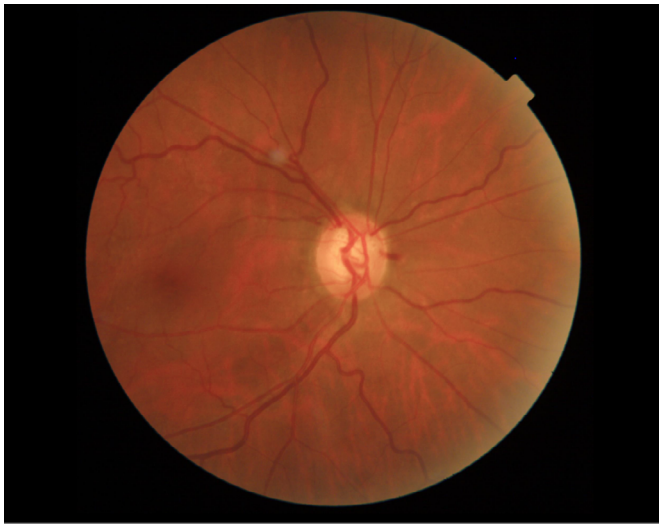

Figure 2: *Optic disc hemorrhage extending to the peripapillary retina nasal to the optic disc.*

phenotypes. The majority of ODH were flame and splinter-shaped (70.6%) and within or superficial to the RNFL (72.5%). Spot or spot hemorrhages (23.5%) and diffuse hemorrhages (5.9%) were less common. It was also stated that hemorrhages were most frequently localized in the inferior temporal region (60.8%).[10]

In this study, 4018 optic disc images were examined and the most common optic disc features were focal neural rim notch (36%), thin curved rim (42%), peripapillary atrophy (79%) and superior-inferior rim asymmetry (73%). In all eyes with a prior focal rim notch, disc hemorrhages were found on or adjacent to the notch.[36] The findings strengthen the theory that structural changes in the notching areas are effective in the formation of disc hemorrhage.

Optic disc hemorrhages may be located on the optic disc tissue or extend beyond the optic disc border into the peripapillary retina. Disc hemorrhages are typically splinter-shaped and located perpendicular to the disc margin. When extravasation is excessive, flame or fan-shaped bleeding may be observed. This typical bleeding pattern is the result of the orientation of RNFL axons and is usually associated with RNFL defects. The presence of hemorrhage at the level of the lamina cribrosa correlates with the location of the lamina cribrosa pores and changes in pore morphology as a result of tissue remodeling. A recent study showed that disc hemorrhage above the lamina cribrosa was significantly more frequent in myopic eyes.[37]

Although the cause of disc haemorrhage remains unclear, many related factors have been identified. First of all, it is known that not all eyes at risk for glaucoma develop ODH and the development of ODH is not correlated with IOP level. While the highest incidence is reported in patients with normal tension glaucoma, these patients are more likely to have both bilateral and recurrent disc hemorrhages. Furthermore, the rate of glaucoma development and progression is higher in eyes with recurrent disc hemorrhages.[35]

Jonas et al. evaluated patients with chronic open angle glaucoma and reported that a small neuroretinal margin and a large area of peripapillary beta atrophy were predictive of ODH, but other factors such as disc size and shape, alpha peripapillary atrophy, retinal vessel diameter and optic cup depth were not.[32]

They found that the development of disc hemorrhage was not related to differences in morphologic parameters, intraocular pressure measurements, or visual field loss in patients with bilateral chronic open-angle glaucoma and unilateral ODH.[38] In addition, corneal thickness does not seem to affect the development of ODH in patients with chronic open angle glaucoma. Choi et al. reported that disc hemorrhages were associated with RNFL thinning measured by optical coherence tomography and there was a negative correlation between recurrent hemorrhages and RNFL thickness.[39] IOP tends to be lower in eyes with temporal disc hemorrhage than in eyes with nasal disc hemorrhage. This is explained by the fact that the nerve tissue on the temporal side of the disc is more sensitive to vascular and mechanical trauma and that this injury occurs with lower intraocular pressure in susceptible eyes.

Miyake et al. found that POAG and NTG eyes behaved differently to different IOP levels after trabeculectomy. POAG eyes with higher postoperative IOP exhibited a much higher incidence of disc hemorrhage than the low postoperative IOP group, whereas NTG eyes with higher postoperative IOP exhibited a much lower incidence of disc hemorrhage than NTG eyes with lower postoperative IOP.[15]

Clinical factors other than IOP may be important determinants for the development and prognostic impact of disc hemorrhages in different patients. Disc hemorrhages are also associated with advanced age, female gender and vascular disease. Systemic hypertension, diabetes, migraine, migraine, pseudoexfoliation, aspirin use and use of platelet aggregation inhibitors are other possible factors with reported associations.[5,24,40-42] Optic disc hemorrhage can be caused not only by ischemic microinfarcts in the optic disc, but also by mechanical tearing of small blood

vessels resulting from structural changes at the level of the lamina cribrosa. Microvascular disease may be associated with optic disc hemorrhage in NTG patients, as systemic hypertension and diabetes-related vasculopathy can cause microinfarcts and ischemic changes in optic disc vessels, making them vulnerable to mechanical tearing.

Differential Diagnosis

Although disc hemorrhages are considered a sign of glaucomatous progression, they can also occur in normal eyes at very low rates (0-0.04%).[9]

ODH can also occur in conditions such as posterior vitreous detachment, optic disc drusen, vascular occlusive diseases of the retina and non-glaucomatous optic neuropathies. Systemic conditions such as diabetes, hypertension, leukemia and systemic lupus erythematosus are also associated with disc hemorrhage. Glaucomatous disc hemorrhage can be distinguished from hemorrhages associated with other ocular or systemic conditions by the absence of any signs of papillitis and vitreoretinal pathology.

Diagnostic methods

Disc hemorrhage is usually transient and can be mistaken for blood vessels and therefore easily missed during examination. Commonly used digital imaging devices such as optical coherence tomography, scanning laser ophthalmoscopy and scanning laser polarimetry are inadequate in detecting disc hemorrhages. Direct evaluation and photography of the optic disc remains the gold standard for the detection of ODH.

Optic disc photography provides both qualitative and quantitative information about the optic nerve head in glaucoma and can detect subtle hemorrhages. Studies show that disc hemorrhage is better detected by stereoscopic disc photography than by clinical examination.[(40)] While the Ocular Hypertension Treatment Study reported that ODH was four times more likely to be detected in disc photographs than in standard disc examinations, several studies, including the Early Detection Glaucoma Treatment Study, found no statistically significant difference between clinical and photographic detection.[1,43-44] The present results show that while disc hemorrhages are more easily detected photographically, they can be found in similar numbers with frequent and careful clinical examinations.

Glaucoma Progression and Optic Disc Hemorrhage

Disc hemorrhages may be a marker of rapid glaucoma progression, but their role in the cause of progression is not clear. There are many studies with different results regarding the correlation between IOP reduction and glaucoma progression in eyes with optic disc hemorrhage. The underestimation of subtle changes in optic disc, RNFL and VF results may be the reason for the delayed detection of functional damage after ODH in early to moderate glaucoma cases. In a study by Akagi et al. investigating the relationship between ODH and RNFL, they showed that intensification of glaucoma treatment may have a beneficial effect in reducing the RNFL thinning rate in the ODH quadrant worsened after ODH.[45]

The Early Detection Glaucoma Treatment Study reported that optic disc hemorrhage is an independent predictor of glaucoma progression and that the risk increases with increasing frequency of hemorrhage. Post-treatment IOP lowering showed very similar disc hemorrhage rates in the treatment and control groups, and no correlation was found between the amount of IOP lowering and hemorrhage rate in the treated group. Although the Early Detection Glaucoma Treatment Study found that lowering IOP generally slowed glaucoma progression, eyes with ODH showed faster progression despite a similar IOP reduction.[46] On the other hand, there are studies suggesting that intervention to lower IOP after ODH reduces the rate of glaucoma progression and the rate of ODH. Hendrickx et al. followed open angle glaucoma patients and reported that an IOP reduction of 5 mmHg also decreased the rate of ODH, whereas in a group of normotensive glaucoma patients with a mean IOP reduction of 2 mmHg, there was no reduction in the rate of ODH.[6] In Miyake et al.'s study of disc hemorrhage rates before and after IOP lowering in 99 glaucoma patients undergoing trabeculectomy, the cumulative probability of disc hemorrhage decreased from 42% to 23% in eyes with normotensive glaucoma with an IOP reduction of 30%, and from 33% to 6% in eyes with a higher initial IOP with a mean IOP reduction of 50%.[15]

It is reported that ODH is a sign of active disease process and VF progression develops after ODH.[7,40] In a study by Rasker et al. evaluating nine-year follow-up of glaucoma patients with ODH, VF progression was found in 89% of POAG patients and 32% of patients without ODH.[47] Another clinical study of 348 glaucoma patients followed for an average of 8.2 years reported twice the rate of visual field progression in eyes with disc hemorrhage at any time during follow-up.[48] Medeiros et al. noted that IOP reduction had a beneficial effect in slowing the rate of progression of visual field loss in eyes with ODH. They reported that the difference in visual field loss rates before

and after hemorrhage was significantly associated with a decrease in IOP in the post-hemorrhage period, with each 1 mm Hg change in IOP changing the rate of visual field index progression by 0.31% per year.[48] In addition, Prata et al. argue that IOP reduction should not be included as a significant risk factor for visual field progression after disc hemorrhage in glaucomatous eyes, but initial mean visual field deviation and older age should be included. The present results are explained by the fact that the study of Medeiros et al. had a longer mean follow-up period (8.2 years vs 3.8 years) and a higher degree of IOP reduction (5.6 mmHg vs 2 mmHg) than that of Prata et al.[49] Therefore, it can be hypothesized that progression of glaucoma after disc hemorrhage can be halted with higher IOP reduction and longer follow-up intervals. Patients with ODH may be considered to be at risk and should be followed up more frequently and the efficacy of treatment should be re-evaluated.

In studies evaluating recurrent ODH, Ishida et al. reported that recurrent ODH showed more progressive VF changes than single ODH.[7] Regarding glaucoma progression in VF, Siegner and Netland reported no difference in the rate of progression of optic disc changes or VF defects between recurrent and single disc hemorrhages.[39,43] De Beaufort HC et al. emphasize that recurrent ODH is not seen as an indicator of increased VF progression compared to ODH detected alone.[50]

The Ocular Hypertension Treatment Study also reported a fourfold increase in the risk of glaucoma in eyes with disc hemorrhage.[43] The overall probability of ODH in eyes with normotensive glaucoma was reported to be 45.5%, compared to about half that in eyes with higher intraocular pressure. Approximately half of all disc hemorrhages were observed in the first year of patient follow-up, while about three quarters were detected at 3 years. However, after 5 years, the incidence of ODH plateaued, with very few initial hemorrhages.[51] However, eyes with recurrent ODH were found to have progressive RNFL thinning compared to eyes with non-recurrent ODH, and progressive RNFL thinning after ODH was interpreted as being due to ongoing structural damage that caused the initial ODH.[49]

CONCLUSION

The relationship between optic disc hemorrhage and glaucoma has been investigated for many years. Although the mechanism of optic disc hemorrhage and its relationship to glaucoma progression remains unclear, its occurrence is a sign of glaucoma progression.

Although not pathognomonic, disc hemorrhages are specific for glaucoma. The presence of ODH in glaucoma patients has been found to be closely associated with glaucoma progression, VF progression and RNFL thinning in many studies. Therefore, in detecting ODH, more careful optic disc examination with pupil dilation is required at every check-up, if possible. It would be appropriate to increase the frequency of follow-up and evaluate the effectiveness of treatment in cases with ODH. Further studies with more frequent monitoring intervals and longer follow-up periods are needed to understand the pathogenesis of ODH.

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