Japanese Journal of Ophthalmology (2019) 63:7–25
https://doi.org/10.1007/s10384-018-0641-2

THE OFFICIAL INTERNATIONAL JOURNAL OF THE JAPANESE OPHTHALMOLOGICAL SOCIETY

REVIEW

The impact of disc hemorrhage studies on our understanding of glaucoma: a systematic review 50 years after the rediscovery of disc hemorrhage

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Received: 10 September 2018 / Accepted: 19 October 2018 / Published online: 21 November 2018
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Abstract

Purpose of review To trace the influence of disc hemorrhage studies on our understanding of glaucoma.

Sources Major articles published during the last 50 years since the rediscovery of disc hemorrhage were identified. A total of 196 articles were selected from 435 articles retrieved using the keywords *glaucoma* and *disc hemorrhage* as of August 9 2018 from PubMed.

Recent findings The main characteristics of disc hemorrhage, including its morphology, recurrence rate, duration, increased incidence in glaucoma, and role in the progression of normal tension glaucoma was well understood by the year 2000. Since then, studies have focused on more sophisticated and accurate methods of elucidating both structural and functional progression, with special attention to the role of the lamina cribrosa. Nevertheless, both the mechanism of disc hemorrhage development and its fuller relationship with glaucoma remain unclear.

Summary Disc hemorrhage research requires careful study of glaucomatous optic neuropathy. This has been facilitated by recent advances in optical coherence tomography (OCT) angiography and other OCT technologies. Furthermore, animal studies of disc hemorrhage promise new insights into glaucomatous optic neuropathy.

Keywords Disc hemorrhage · Glaucoma · Normal tension glaucoma · Optic nerve head · Open angle glaucoma

Introduction

Description of disc hemorrhage (DH) first appeared in the 19th century literature. In 1858, Eduard Jaeger, a German ophthalmologist, described a condition called cerebral amaurosis, in which splinter hemorrhages could be present on the optic disc [1, 2]. The disc was usually shallowly excavated and the intraocular pressure (IOP) was elevated in such cases. In 1889, Jannik Peterson Bjerrum, a Danish ophthalmologist best known for his campimetry studies, presented 3 cases of glaucoma with retinal hemorrhages [1]. In 1 case, the hemorrhages were located at and on the superior margin of the optic disc. Unfortunately, these findings on the association of DH with glaucoma remained relatively obscure until 1969 when Feldman, Sweeney, and Drance rediscovered it [3]. Thus, the year 2019 marks the 50th anniversary of the rediscovery of the role of DH in glaucoma (Fig. 1).

Here, the author systematically reviewed articles published over the last 50 years on DH in glaucoma. Of the 435 studies reviewed, 196 were selected. All the articles were retrieved from a PubMed (US National Library of Medicine) search using 2 keywords: *glaucoma* and *disc hemorrhage*. The review is current as of August 9, 2018. The author classified the papers into the following categories: pathogenesis, prevalence and incidence, change in incidence after glaucoma treatment, morphology and topography, risk factors/relationship with systemic diseases, detection/difficulty in detection, relationship with the lamina cribrosa, glaucoma progression (structure), glaucoma progression (function), glaucoma progression (both structure and function), optical coherence tomography (OCT) angiographic studies, and miscellaneous topics. After they had been briefly summarized, the articles were listed according to the publication year. The author reworded some basic terminology to

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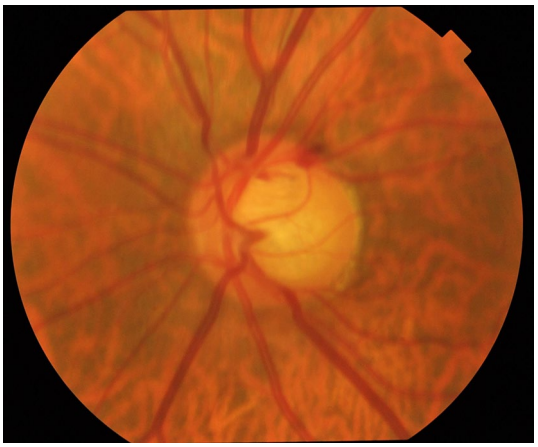

Fig. 1 A disc hemorrhage in an eye with normal tension glaucoma

maintain clarity; for example, the term normal pressure glaucoma was updated to normal tension glaucoma.

The following abbreviations are used: disc hemorrhage (DH), normal tension glaucoma (NTG), primary open angle glaucoma (POAG), intraocular pressure (IOP), visual field (VF), retinal nerve fiber layer (RNFL), and optical coherence tomography (OCT).

Chronology of key publications on DH: before 2000

1969: Feldman et al [4] described a glaucoma case with high myopia and a small linear hemorrhage on the disc in a cerebrovascular study of 58 cases. This publication was taken to mark the rediscovery of DH.

1970: Drance and Begg [5] observed a fresh scotoma in a POAG patient with a DH, which remained after the DH disappeared.

1971: Begg et al [6] reported progression or development of glaucomatous VF after a DH.

1972: Drance [7] observed the presence of DH in 20% of NTG patients.

1976: Kottler and Drance [8] surveyed systemic conditions including hypertension and cardiac abnormalities in patients with and without a DH. They were unable to confirm any significant difference between these cases, except a significant positive correlation between systemic hypertension and DH.

Chumbley and Brubaker [9] reported splinter-shaped DH in 10% of the affected eyes from 45 NTG cases.

1977: Drance et al [10] investigated the VF progression in open-angle glaucoma and ocular hypertension and found a positive correlation between the progression and DH.

1978: Susanna et al [11] assessed risks of VF defects in the fellow normal eyes of unilateral open-angle glaucoma. Development of new VF defects was positively correlated with a higher cup-to-disc ratio, DH, and elevated IOP in the fellow eye.

1981: Bengtsson et al [12] described the features of DH based on 51 cases [10] and found a positive correlation between DH and VF progression, although the relationship was not immediately recognized. DH was considered to be a "forerunner" of the glaucomatous process, and the possibility that DH occurs in all cases of glaucoma was not rejected.

Using multivariate analysis, Airaksinen [13] found a positive correlation between DH and neural rim notching and a negative correlation between DH and exfoliation glaucoma.

Bengtsson [14] found that 8 of 10 elderly glaucoma patients developed DH.

Gloster [15] investigated the incidence of DH in open-angle glaucoma and ocular hypertension using a series of photographs and observed the presence of DH in about one-third of glaucoma patients. Further, DH was observed more frequently in NTG than in POAG.

Airaksinen et al [16] studied the basic characteristics of DH in 112 cases of glaucoma or suspected glaucoma in which optic disc stereophotographs had been taken. They reported the frequency and location, relationship with IOP, and other characteristics of DH. For example, they found a high rate of DH in the presence of rim notching and a higher incidence in NTG.

Airaksinen et al [17] reported out that DH preceded RNFL defects and VF abnormality in ocular hypertension. They also found that the location of DH accurately predicted the location of RNFL defects.

1982: Shihab et al [18] reported a higher incidence of VF deterioration in eyes with a DH compared with those without a DH in bilateral open-angle glaucoma.

1983: Airaksinen and Heijl [19] observed early glaucomatous VF loss using a static perimeter in 9 of 10 eyes with photographically demonstrable RNFL defects after DH.

Airaksinen and Alanko [20] studied 29 cases with ocular hypertension with DH using stereophotographs over a mean follow-up period of 5.2 years. Early structural glaucoma damage developed in 12 eyes of 11 cases during the follow-up period

1984: Airaksinen [21] observed 1506 cases with glaucoma or suspected glaucoma by optic disc stereo photography with special attention to DH and identified 2 groups of patients: those with DH and those without DH. He suggested that they represented distinct glaucoma populations.

1986: Bengtsson [22] found a close relationship between DH and glaucoma using data from 2 population surveys and a review of clinical records.

Kitazawa et al [23] studied the characteristics of DH in a prospective fashion and found that DH was most prevalent (20.5%) in NTG. In a study of 58 NTG patients examined every 1 to 4 weeks for 6 to 32 months, they determined the

incidence of DH to be 24.8%. Recurrences were seen in 64% of the eyes in these cases. The DH lasted at least 4 weeks in 92% of the cases (Fig. 2). They hypothesized that NTG arises in 2 distinct forms: one that develops recurrent DH and one that is very unlikely to bleed throughout its course.

Heijl [24] studied the detectability of DH and, on the basis of a series of photographs examined in chronological order, found that they were often too small, before disappearing, to be detected.

Sonnsjö [25] performed fundus photography at an interval of 1 to 2 weeks on 2 glaucoma cases with DHs and observed that DHs developed several times at the same location.

Poinoosawmy et al [26] studied 120 POAG cases and found that DH was evident at some point in 62 of those cases. Furthermore, patients with a DH had a higher incidence of abnormal glucose tolerance and lower IOP than did those without a DH.

1987: Miller and Quigley [27] compared the morphologic features of the optic disc of POAG and NTG and found no difference between the 2 groups in terms of the presence or absence of DH.

1988: Sonnsjö et al [28] presented basic statistics on DH and glaucoma in a general ophthalmic practice. The detection rate of DH among glaucoma patients was low but consistent. No correlation between DH and general hypertension or diabetes mellitus was found.

1989: Bengtsson [29] reported a 33% prevalence of DH at the time of detection of a VF defect in manifest glaucoma. She also stated that 80% of manifest glaucoma cases had had at least 1 DH during its course.

1990: Diehl et al [30] reported the frequency of DH in normal eyes, suspected glaucoma, and glaucoma eyes and showed that DH was significantly higher in glaucoma.

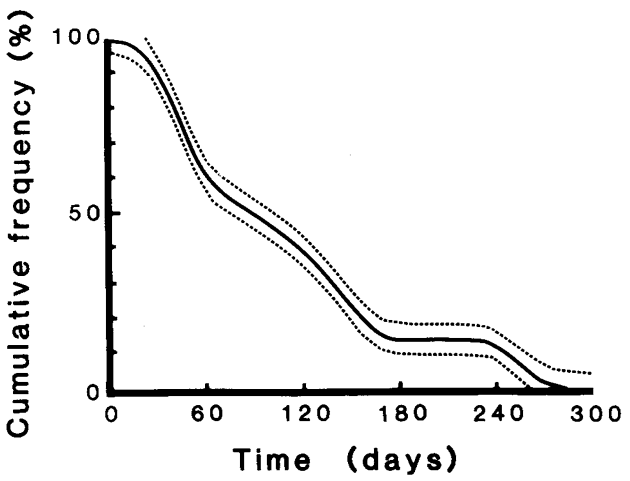

Fig. 2 Cumulative frequency of the duration of disc hemorrhages. The solid line represents the mean and the dotted lines indicate the 95% confidence interval. Reprinted from reference 23, with permission

They also noted that suspected glaucoma cases with DH tended to convert to glaucoma. However, they emphasized that the simple presence of DH was insufficient for use as a glaucoma screen owing to its low prevalence.

Bengtsson [31] reported on DH in the Dalby population study and noted that 5 of 12 cases showed no manifest glaucoma with DH, with a follow-up period over 6 years. The period between the detection of the DH and the development of a VF defect was 2, 3, 5, 6, and 7 years, respectively.

Using a nonmydriatic fundus camera, Tuulonen et al [32] screened 183 first-degree relatives of glaucoma patients and found a DH in 5 of the screened individuals.

Geijssen and Greve [33] documented DH in 46% of cases of focal ischemic-type NTG, whereas no DH was found in cases of high-tension glaucoma.

1991: Sonnsjö et al [34] compared the frequency of DH between cases treated with pilocarpine or timolol and those without treatment and found no difference in the frequency of DH.

1992: Hoyng et al [35] found a higher prevalence of platelet aggregation in POAG with VF deterioration than in cases without it or in cases of suspected glaucoma. They found no correlation between spontaneous platelet aggregation and DH.

Sonnsjö [36] studied DH and retinal vein occlusion in glaucoma in 999 patients and found 179 cases of DH and 95 cases of retinal vein occlusion.

Klein et al [37], in a report from the Beaver Dam Eye Study, reported DH in 46 patients, of whom only two had glaucoma.

Susanna and Basseto [38] investigated neurosensorial dysacousia in glaucoma and found a positive correlation between DH in glaucoma and neurosensorial dysacousia, suggesting a possible causal relationship between the 2 pathologic conditions.

1994: Jonas and Schiro [39] evaluated wedge-shaped localized RNFL defects with red-free wide-angle photography and found a positive correlation between localized RNFL defects and DH.

Hendrickx et al [40] reported on the fundamental characteristics of DH in a longitudinal study of 68 cases of POAG, 34 cases of NTG, and 125 cases of suspected glaucoma, with a mean follow-up of 7.3 years. They found cumulative incidences of DH of 35.3%, 10.3%, and 10.4%, respectively. In the DH-positive group, recurrent DH was observed in 67% of the NTG, 29% of the POAG, and 54% of the suspected glaucoma cases. Therapy had no effect on the incidence of DH in NTG but had a significant effect in the suspected glaucoma cases. They suggested the existence of 2 distinct populations within the NTG group: one with DH and one with no history of DH. However, no such distinction was made for the POAG or suspected glaucoma group.

1996: Siegner and Netland [41] reported positive correlations between DH and glaucomatous progression in the optic disc and the VF in a retrospective study with a mean follow-up of 42 months among 91 patients with glaucoma or ocular hypertension.

Graham et al [42] measured activated protein C resistance, which was thought to be related to systemic venous thrombosis, in glaucoma cases with DH. They could not show positive activated protein C resistance in the cases and were skeptical of any correlation between DH and risk of systemic thrombosis.

Meyer et al [43] monitored 24-hour blood pressure changes in NTG cases and found no difference in this measure between focal ischemic-type NTG with a history of DH and other types of NTG.

Tezel et al [44] compared optic disc characteristics and peripapillary atrophy among eyes with ocular hypertension, POAG, and NTG [42]. They found that DH and arteriolar narrowing were more frequently seen in NTG. They could not observe any differences in the morphologic characteristics between NTG patients with and without serum abnormalities of humoral autoimmunity.

1997: Barry et al [45] reported on the frequency of DH in various types of glaucoma using photographs taken during 1 to 14 years of follow-up (mean: 2.9 years) [43]. The highest frequency of DH was found in NTG (37.5%), followed by 11% in POAG (11%).

Rasker et al [46] conducted a prospective study with a mean follow-up of 9 years on VF changes in POAG, NTG, and ocular hypertension. They observed that VF deterioration occurred in 32%, 32%, and 6% of these cases, respectively, without DH, but occurred in 80%, 89%, and 14% cases, respectively, in the presence of DH. The hazard ratio for DH cases to show VF progression was 5.4 and 3.6 for NTG and POAG, respectively. They also found that DH was only indicative of deterioration in ipsilateral eyes in patients with NTG.

Sugiyama et al [47] investigated the relationship of DH with RNFL defects and peripapillary atrophy in NTG and found a correlation between DH and both the RNFL defect location and the size of the peripapillary atrophy.

1998: Healey et al [48] reported on DH findings from the Blue Mountains Eye Study. The overall prevalence of DH was 1.4%, with 70% of the DH cases showing no signs of glaucoma, although there was a strong correlation between DH and open-angle glaucoma.

Oguri et al [49] studied IOP changes in NTG and found that higher maximum IOP during initial 24-hour phasing and DH development during follow-up were correlated with subsequent IOP elevation in NTG.

Daugeliene et al [50] investigated the efficacy of trabeculectomy with mitomycin C on the VF in NTG eyes. They found that the VF outcome was worse in cases not treated with calcium channel blockers and in cases with a history of DH when only cases with untreated diurnal IOP of less than 15 mmHg were included.

Jonas et al [51] evaluated the morphology of the optic disc in pigmentary glaucoma via stereophotography and found no difference in the incidence of DH between pigmentary glaucoma and POAG.

Hayakawa et al [52] investigated the correlations among peripapillary atrophy, optic disc cupping area, and DH in 6070 individuals who underwent ocular examination as part of a routine health examination. They concluded that peripapillary atrophy was positively correlated with both a higher degree of disc cupping and DH.

Ishida et al [53] studied the clinical factors associated with VF progression in NTG and found the following to be significant prognostic factors: treatment with calcium channel blockers, recovery rate from a cold recovery test, systolic blood pressure, DH, corrected pattern standard deviation, mean deviation, and IOP fluctuation. Eyes with DH tended to show higher VF progression.

1999: Daugeliene et al [54] investigated the risk factors for VF progression in NTG with a minimum follow-up of 5 years and found positive correlations between VF progression and nonuse of calcium channel blockers, peripapillary atrophy, and DH.

Sugiyama et al [55] estimated the prevalence of DH using a screening method and plain color fundus photographs of 12,140 eyes of 6070 participants [53]. DH was found in 0.6% of the eyes. The prevalence of DH was highest in women aged 60 years or older.

Sugiyama et al [56] investigated the topological relationship between DH and localized wedge-shaped RNFL defect using scanning laser ophthalmoscopy in NTG and POAG. They found that localized RNFL defect occurred significantly more in DH eyes than in non-DH eyes in both glaucoma subtypes. The majority of DH was found near the border between localized RNFL defects and relatively healthy-looking RNFL in both subtypes.

2000: Jonas and Budde [57] compared optic disc appearance between NTG and high-tension glaucoma. In NTG, they found that localized RNFL defects were significantly broader, that DH was both more common and significantly larger, and that rim notches were both more common and deeper. They speculated that the lower detection rate for DH might be due to its smaller size in high-tension glaucoma.

Oguri et al [58] studied IOP changes during the natural course of NTG and found instances of spontaneous IOP reduction in the absence of treatment. They also found a positive correlation between the absence of DH and IOP reduction in such cases.

Ishida et al [59] investigated correlations between DH and VF progression in NTG and found greater VF progression in the presence of DH (Fig. 3). All eyes that had at least 2

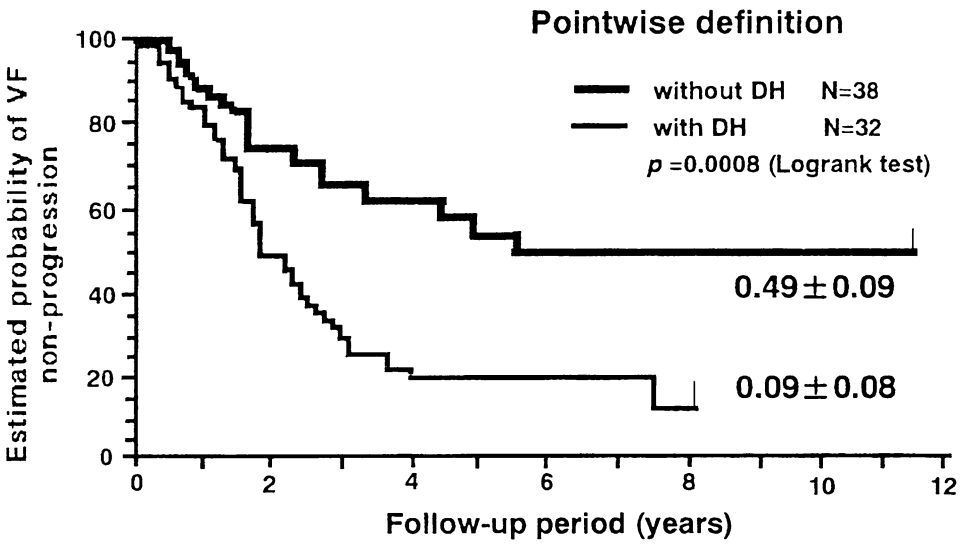

Fig. 3 Probability of visual field stability in normal tension glaucoma divided by presence/absence of disc hemorrhage. Visual field progression was determined by a pointwise definition. Reprinted from reference 59, with permission

occurrences of DH showed progression, whereas only 3 of 9 eyes showed progression in the nonrecurrent DH group. A significant positive correlation was found between DH location and the area of VF progression in 65.4% of cases of progressive NTG with DH.

Chronology of key publications on DH by subtopic: 2001 to the present

Pathogenesis

2001 to 2010

Sugiyama et al [60] reduced optic nerve head circulation in rabbits by applying electric stimulation to the optic chasm. Four weeks after the strong stimulation, cup enlargement was observed. DH developed in some rabbits after cup enlargement.

Sonnsjö et al [61] investigated correlations between open-angle glaucoma and DH and/or retinal vein occlusion based on their clinical experience. DH was seen in 20% of glaucoma cases and was a precursor of glaucoma changes. Retinal vein occlusions and DH behaved similarly with respect to glaucoma. They concluded that a vascular pathogenesis was possible in open-angle glaucoma.

2011 to the present

Yang et al [62] observed development of a splinter-like DH in 1 eye of 4 Rhesus monkeys that underwent implantation of a lumbar-peritoneal cerebrospinal fluid shunt to induce optic neuropathy by restricting cerebrospinal fluid pressure to approximately 40 mmH_2O. Two other monkeys in their study developed bilateral reduction in RNFL thickness.

Chung et al [63] tried to determine whether structural progression occurs before detection of DH by examining fundus photographs in 2 patient groups: those in which DH developed at follow-up and those in which DH was present at baseline. No significant changes were found in structural glaucomatous progression before or after the occurrence of DH, suggesting that DH may not be a discrete event leading to subsequent progression.

Park et al [64] conducted a fluorescein angiographic study in glaucoma cases with DH. Eyes with DH showed prolonged arteriovenous transit time and had frequent vessel filling defects or delayed filling that indicated blood flow stasis and thrombus formation at the DH site.

Kim et al [65] compared central retinal venous pressure measured by ophthalmodynamometry among NTG eyes with or without DH. No difference was found in central retinal venous pressure between eyes with DH and those without DH, indicating no correlation between increased central retinal venous resistance and DH.

Zhang et al [66] evaluated optic nerve head biomechanics based on scleral and lamina cribrosa collagen fiber organization. Scleral collagen fibers were circumferential and presented the highest alignment at 400 to 500 μm from the lamina cribrosa. This fiber arrangement yielded rings of low strain in the scleral region immediately adjacent to the lamina cribrosa in models. They concluded that heterogeneous collagen fiber organization in the peripapillary region may limit lamina cribrosa strain, resulting in lamina cribrosa disinsertion, focal lamina cribrosa defects, and DH in glaucoma.

Lee et al [67] sought to identify correlations among nailfold capillaroscopy, heart rate variability, and DH with the plasma matrix metalloproteinase-9 level in NTG. They found a positive correlation between nailfold capillaroscopy and the plasma matrix metalloproteinase-9 level. However,

no such correlation was found between DH and either heart rate variability or the plasma matrix metalloproteinase-9 level. Kosior-Jarecka et al [68] found positive correlations between abnormal nailfold videocapillaroscopy patterns and NTG in young controls. Microbleedings were also more frequent in NTG, and DH was more frequent in NTG with an abnormal nailfold videocapillaroscopy pattern.

Shim et al [69] investigated platelet function in NTG and suggested that delayed platelet aggregation may affect the detectability of DH.

Lorenz et al [70] investigated immunoreactivity (anti-adaptor protein 1 complex subunit mu-1 antibodies and anti-SPRY domain-containing SOCS box protein 3 antibodies) in POAG and found that autoimmune reactivities were more prominent in the sera of patients with concomitant DH.

Lee et al [71] presented a new theory of pathogenesis of DH in which a fibrous glial scar forms with proliferative reactive gliosis, the traction force induced by the scar formation disrupts capillaries at the border between the healthy and damaged RNFL, and a splinter-shaped DH then develops as a consequence. In addition to the glial scar formation, remodeling and deformation of the LC beams was hypothesized to insult the capillaries surrounding the pore of the lamina cribrosa, leading to development of a round-shaped DH.

Chou et al [72] analyzed DH in POAG by densitometry and measured the grey-scale pixel intensity of the hemorrhages and adjacent arterioles and venules over the same background tissue in eyes with DH, retinal macroaneurysm, or retinal vein occlusion. They found that DH had a comparable densitometry profile to macroaneurysms, but its profile differed from that of retinal vein occlusion, suggesting that DH has an arterial origin.

Prevalence and incidence

2001 to 2010

Gazzard et al [73] found a prevalence of DH in Singaporean glaucoma patients of 2.99% and discovered that it was more common in POAG than in primary angle-closure glaucoma.

Krupin et al [74] reported baseline data from 190 participants in the Low-pressure Glaucoma Treatment Study and documented a DH prevalence of 15% at baseline in 32 eyes of 29 patients.

Lan et al [75] found an incidence of DH in primary angle-closure glaucoma of 5.7% over 9 years of follow-up. They also found a positive correlation between DH and glaucoma progression.

Bengtsson et al [76] described the features of DH from the Early Manifest Glaucoma Trial (follow-up maximum, 11 years; median, 8 years) based mainly on a series of photographs. The presence of DH was identified in 55% of cases and was equally distributed between the treated and control groups: 51.2% versus 45.2%. Neither was there a difference in the frequency of DH over time between the 2 groups (8.4% versus 8.5%), although DH was positively correlated with time to progression.

Tomidokoro et al [77] reported on the prevalence of DH detected using fundus photography in the Tajimi Study, a population-based glaucoma survey. The prevalence was 1.2% in this Japanese population among those aged at least 40 years. Both glaucoma and older age were positively correlated with a higher prevalence of DH.

Hsieh et al [78] reported on the incidence of DH in POAG, NTG, and primary angle closure in a 9-year follow-up study in which NTG showed the highest incidence. They also found strong correlation between the presence of DH and glaucoma progression.

2011 to present

Suh and Park [79] used stereoscopic optic disc photography to identify period prevalence and incidence rates of DH of 33.3% and 0.46 ± 0.18 times/year in NTG and 17.6% and 0.34 ± 0.23 times/year in POAG, respectively.

Park et al [80] compared glaucoma cases having initial parafoveal scotoma with those having initial nasal step. The scotoma group had a significantly lower maximum untreated IOP and a higher rate of DH detection (44% vs 17%). Furthermore, significant systemic risk factors included hypotension, migraine, the Raynaud phenomenon, and sleep apnea. Kang et al [81] conducted a similar study for NTG and found a significantly higher frequency of DH in patients with initial central scotoma.

Schor et al [82] compared glaucoma progression among 4 optic disc phenotypes: focal ischemic, myopic, senile sclerotic, and generalized enlargement. They found that VF progression was similar among the 4 phenotypes but that DH was more frequent in the focal ischemic and senile sclerotic subgroups.

Kim et al [83] compared various features of NTG between Western and Korean patients. Although some variables including cup shape, RNFL thickness, and central corneal thickness differed significantly, no differences were found in the frequency of DH.

Jonas et al [84] used population-based data from India to identify a prevalence of DH of 0.2% per eye (0.4% per participant) in Indians aged 30 years and older. Furthermore, DH showed a strong positive correlation with glaucoma.

Park et al [85] used fundus photography of over 160,000 cases from a health screening facility to identify a DH prevalence of 0.14%. They also found a positive correlation between DH and either older age or RNFL defects.

Kim et al [86] reviewed a large population-based database in Korea and documented a prevalence of DH of 0.42% and found a positive correlation of DH with age and glaucoma.

Cho et al [87] studied the prognosis of untreated initially nonglaucomatous fellow eyes of 50 cases of unilateral NTG and found that DH developed most frequently in the glaucomatous eye compared with the fellow eye [85].

Skaat et al [88] compared the frequency of DH and the prevalence of beta-zone peripapillary atrophy between individuals of African descent and European descent in a prospective, multicenter cohort. They found that the participants of European descent were at higher risk for DH, whereas those of African descent had greater prevalence of beta-zone peripapillary atrophy.

Budenz et al [89] used the Ocular Hypertension Treatment Study to identify an incidence of DH of 0.5% per year during an average of 13 years before the development of POAG and of 1.2% per year during an average of 6 years after the development of POAG. The cumulative incidences of POAG development were 25.6% and 12.9% in eyes with and without DH, respectively. DH increased the risk of developing POAG by 2.6 fold.

Change in incidence after glaucoma treatment

2001 to 2010

Miyake et al [90] studied changes in the incidence of DH after trabeculectomy in POAG and NTG. They used a life-table analysis to document final probabilities of detecting DH before and after surgery of 33.4% and 5.5%, respectively, in POAG, and of 42.1% and 23.1%, respectively, in NTG. They concluded that trabeculectomy significantly decreases the frequency of DH in open-angle glaucoma.

Morphology and topography

2001 to 2010

Liou et al [91] investigated the structural characteristics of NTG eyes with DH using scanning laser tomography and found prominent localized damage of the disc rim and RNFL at the inferotemporal sector in eyes with DH.

Jonas et al [92] compared optic disc morphology between glaucoma eyes with and without DH. They found a positive correlation between DH development and a smaller neuroretinal rim and, possibly, with a larger peripapillary beta zone. No correlations were found between DH and optic disc size or shape, optic cup depth, size of the alpha zone in peripapillary atrophy, or retinal vessel diameter. Jonas et al [93] also compared optic disc morphology in bilateral open angle glaucoma with unilateral DH and found no difference between eyes with DH and the contralateral eye without it in terms of the size and shape of the optic disc or neuroretinal rim, the optic cup depth, the size of the alpha or beta zone in peripapillary atrophy, or other factors.

Ahn et al [94] investigated the correlation between DH and peripapillary atrophy in glaucoma cases with a unilateral DH and found higher prevalence and significantly greater area and extent of peripapillary atrophy in eyes with DH than in their contralateral eyes.

Yamamoto et al [95] investigated the prevalence and topographical characteristics of DH in a large-scale (N = 13,965 cases), eye-disease screening project and documented a DH prevalence of 8.2% in glaucoma cases and 0.2% in nonglaucoma cases. Most instances of DH were observed in the inferotemporal and superotemporal regions.

Radcliffe et al [96] studied the anatomical relationship between DH and peripapillary atrophy using digital optic nerve stereophotography and found that 91.3% of eyes with DH showed beta zone peripapillary atrophy. They also documented an increased risk of DH development in eyes having wider peripapillary atrophy.

Jeoung et al [97] studied RNFL using OCT in cases presenting as normal RNFL, suspected normal RNFL (according to red-free fundus photography) with DH, preperimetric glaucoma, and perimetric glaucoma. They documented a significant increase in RNFL defects in eyes with DH and in those in suspected normal RNFL eyes.

2011 to present

Kim et al [98] classified DH into 4 types: lamina cribrosa-, cup margin-, disc rim-, and peripapillary-types, according to their location. They documented significantly higher rates of lamina cribrosa-type DH in the myopic group than in the nonmyopic group and speculated that the pathogenesis of DH may differ between myopic and nonmyopic eyes.

Kim et al [99] studied the topographic characteristics of DH and documented higher rates of DH in the inferotemporal sector, as well as DH with greater areas and lengths in NTG than in POAG.

Kim et al [100] studied the relationship among VF, DH, and OCT parameters and found a significant positive correlation among inner nuclear layer thickness, DH, and mean deviation.

Ozturker et al [101] described the basic features of DH including inferior predominance, close association with a notch, and higher incidence in eyes with normal IOP. They recommended careful examination of the optic disc to detect DH as an important biomarker of glaucoma.

Risk factors / Relationship with systemic diseases

2001 to 2010

Grødum et al [102] used population-based data in Sweden to investigate the relationship between DH and 4 different

groups of medications in common use for general vascular disease and diabetes mellitus, including platelet aggregation inhibitors, antihypertensive agents, cholesterol-lowering medication, and antidiabetic agents. They found that DH developed significantly more frequently in patients taking platelet aggregation inhibitors.

Soares et al [103] investigated both systemic and ocular factors correlated with DH development. This cohort study found a positive correlation between DH and both the presence of diabetes mellitus and the use of aspirin.

Kim et al [104] investigated correlations between DH and other conditions observed in NTG, conditions including diabetes mellitus, hypertension, hypotension, cardiac disease, stroke, cold hands, migraine, constipation, smoking, and the use of steroids, aspirin, anticoagulant, or gingko extract. They found a positive correlation between DH and systemic hypertension. They also noted that IOP range, diabetes mellitus, and use of aspirin tended to be associated.

2011 to present

Furlanetto et al [105] studied the risk factors for DH in the Low-Pressure Glaucoma Treatment Study. This cohort study identified migraine, baseline narrower neuroretinal rim width, low systolic blood pressure and mean arterial ocular perfusion pressure, and use of systemic beta-blockers as risk factors for DH.

Kwon et al [106] studied the associations among DH, 24-hour blood pressure monitoring, and glaucoma progression and found that overdippers showed higher rates of DH than did either dippers or nondippers. They also found that DH was a risk factor for VF progression.

Jeoung et al [107] studied polymorphisms of the endothelial NO synthase (eNOS) gene in NTG and found an association between DH and polymorphic genotypes of rs2070744. They speculated that the eNOS polymorphism may be a genetic risk factor in the development of DH in NTG.

Detection/Difficulty in detection

2001 to 2010

Budde et al [108] used confocal scanning laser tomography to document a detection rate for DH of only 32% and determined that this method was inadequate for either detection or documentation of DH.

O'Brien et al [109] studied the effect of mydriasis on the detectability of glaucomatous optic disc changes in plain photography. They found that pharmacological mydriasis was not essential for reproducible evaluation in patients with a sufficiently observable optic disc, although this was not the case for the detection of saucering, disc notching, or DH.

2011 to present

Kong et al [110] investigated the consistency of glaucoma evaluation in optic disc images in an internet-based study and found high interobserver agreement in the detection of DH ($a = 0.83$) but somewhat lower agreement for disc size, disc shape, cup-to-disc ratio, peripapillary atrophy, and cup shape (κuw) = 0.59–0.68).

Syed et al [111] studied the efficacy of new methods for evaluating serial images of the optic disc for the detection of DH and determined that the *automated alternation flicker* method was more sensitive than either side-by-side or single photograph evaluation.

Lee et al [112] compared spectral-domain OCT and photography as methods to track the progression of glaucoma and found that OCT was more sensitive in eyes with a diffuse RNFL defect, whereas photography was more sensitive in detecting DH and deepening of a RNFL defect.

O'Neill et al [113] quantified the difficulty of optic disc evaluations using a series of 42 monoscopic optic disc photographs of healthy and glaucomatous eyes presented to clinicians ranging from glaucoma specialists to ophthalmology trainees. The key factors that led to underestimation of glaucoma included DH, RNFL defects, the vertical cup-disc ratio, and the cup shape. They concluded that underestimation increased to almost 50% when all 4 parameters were incorrectly assessed.

Sandhu et al [114] compared the efficacy of detection of various characteristics of optic disc changes by 3-dimensional and 2-dimensional digital imaging. They concluded that both methods showed excellent reproducibility in evaluating the vertical cup-to-disc ratio, notching, and DH. Three-dimensional imaging was slightly more effective than 2-dimensional for evaluating DH, notching, and sloping.

Relationship with the lamina cribrosa

2001 to 2010

Healey and Mitchell [115] investigated optic disc pits found in the Blue Mountains Eye Study and found that optic pit was associated with high-pressure open-angle glaucoma, beta-peripapillary atrophy, and DH.

2011 to present

Park et al [116] studied the LC using the enhanced-depth imaging mode of spectral-domain OCT and observed significantly thinner areas in the mid-superior, central, and

mid-inferior regions of the LC in cases of NTG with DH than in those without DH.

Takayama et al [117] observed LC defects via 3-dimensional swept-source OCT and found a positive correlation between the presence of LC defects and both longer axial length and DH.

Park et al [118] conducted a multivariate logistic regression analysis to assess factors related to focal LC defects in glaucoma. They observed a positive correlation between the presence of a focal defect and DH, a diagnosis of NTG, and more advanced glaucoma.

Lee et al [119] investigated the topographical relationship between DH and the 1-year structural changes in peripheral LC using enhanced-depth imaging spectral-domain OCT. They observed structural alteration of the LC in 88.9% of the eyes in the DH group, but in only 11.1% of the eyes in the non-DH group. The maximum LC alteration was observed within 1 clock-hour of the DH location in all the eyes.

Faridi et al [120] studied the correlation between focal defects of the LC and VF progression in glaucoma and found a significant positive correlation between VF progression and focal LC defects, DH, higher mean follow-up IOP, and other factors.

Choi et al [121] studied the structural and clinical characteristics of the optic disc pit in POAG using spectral-domain OCT and found that LC alterations located at the far periphery were significantly positively correlated with DH and peripapillary retinoschisis.

Kim et al [122] studied the relationship between DH and focal LC defects in POAG using in vivo LC images obtained by swept-source OCT immediately following the detection of DH. They observed larger and more proximally located DH associated with focal LC defects compared with those without such defects and suggested that focal LC defects may affect the topographic characteristics of DH.

Sharpe et al [123] observed laminar disinsertions in glaucoma at a rate of 96% in the presence of DH and of 52% in the absence of DH. However, no spatial relationship between DH and laminar disinsertion was inferred because only 39% of the DH was located within a laminar disinsertion.

Kim and Park [124] studied focal defects of the LC in eyes with DH via swept-source OCT and found a positive correlation between the presence of focal defects of the LC and the frequency of DH. Because DH and LC defects were spatially correlated in many cases, they speculated that DH is associated with focal abnormalities of the lamina cribrosa.

Park et al [125] studied the relationship among DH, focal LC defects, and VF progression in open-angle glaucoma and found a positive correlation between VF progression and focal LC defects at the DH site. They also found a positive correlation between eyes with DH at the site of focal LC defects and a VF progression that was both more frequent and more rapid.

Glaucoma progression (structure)

2001 to 2010

Choi et al [126] studied DH and RNFL using OCT and found a positive correlation between DH and RNFL thinning and a negative correlation between recurrent DH and a thicker RNFL.

2011 to present

Nitta et al [127] studied changes in the RNFL in NTG and found a positive correlation between progressive RNFL defect and both DH and VF progression.

Kernstock et al [128] studied structural progression after DH using high-resolution OCT circular scans and found significantly less RNFL thinning in the affected quadrant after DH but not in the DH site itself in the majority of the cases.

Wang et al [129] studied risk factors for the progression of glaucomatous optic nerve changes in the Beijing Eye Study and found a significant positive correlation between DH and glaucoma progression, a larger beta zone, more frequent beta zone increase, and higher IOP.

Niles et al [130] studied macular thickness changes using time-domain OCT in glaucoma and suspected glaucoma and found a positive correlation between thickness change rate and the presence of DH in the nasal inner or temporal outer macular region.

Suh et al [131] studied structural progression after DH using time-domain OCT and found that 72.7% of eyes in the DH group showed progression within approximately 3 years, while only 27.3% did so in the fellow eyes.

Radcliffe et al [132] studied positional shifts in retinal blood vessels in open-angle glaucoma using stereophotography and found a positive correlation between such shifts and functionally progressive glaucoma, neuroretinal rim loss, and DH.

Hwang et al [133] studied longitudinal changes in RNFL by spectral-domain OCT after DH development in glaucomatous eyes. They observed a decrease in RNFL thickness in 38.5% and 58.5% of eyes at 1 and 2 years after DH detection, respectively. They also found a positive correlation between significant RNFL thinning and both recurrent DH and greater baseline RNFL thickness.

Lee et al [134] studied RNFL thinning in POAG with an optic disc pit using swept-source OCT and found a positive correlation between optic disc pit and both global and focal RNFL thinning. They also identified DH as a risk factor of progression, in addition to other factors such as higher untreated IOP.

Akagi et al [135] studied the longitudinal temporal and spatial associations between DH and rates of RNFL thinning before and after the onset of DH. They studied 40 eyes of

37 patients with a history of DH from the Diagnostic Innovations in Glaucoma Study and the African Descent and Glaucoma Evaluation Study. They concluded that glaucoma treatment may reduce the rate of RNFL thinning, but this rate increases in the DH quadrant after resolution of the DH.

Lee et al [136] studied ganglion cell-inner plexiform layer thickness in early-stage open angle glaucoma in a prospective manner and found a significant positive correlation between the thinning rate and DH in the same eye compared with those in the normal fellow eye. They also found a positive correlation between faster thinning and DH as compared with thinning rates in control glaucoma cases without DH.

Lee et al [137] studied topographical relationships between DH and RNFL progression in glaucoma eyes. DH was most frequently located in the temporal margin of an inferotemporal RNFL defect. The most frequent pattern of RNFL change was temporal widening.

Glaucoma progression (function)

2001 to 2010

Pereira et al [138] studied VF progression in POAG and found a positive correlation between asymmetric VF progression and DH.

Kono et al [139] studied the characteristics of VF progression in NTG eyes with DH and found that NTG with DH was associated with more VF progression in areas within 10 degrees, whereas no significant differences were found in the other clusters or in the whole field.

Leung et al [140] studied silent cerebral infarct in NTG using Cox proportional hazards regression analysis and found positive correlations between VF progression and DH, silent cerebral infarct, systemic hypertension, and central corneal thickness.

De Moraes et al [141] studied VF progression before and after detection of DH and found that the VF sector with the fastest progression predicted the location of the future DH in 85% of cases. The same VF sector maintained the fastest progression rate in almost all the eyes after the detection of DH. They hypothesized that rapid, localized disease progression is a risk factor for DH and that progressive VF loss reflects ongoing damage at or adjacent to the DH.

Leung et al [142] studied the effect of simvastatin use on VF stabilization in a cohort of 256 NTG cases and identified DH as a risk factor for VF progression, with a relative risk of 3.26.

De Beaufort et al [143] compared VF progression between glaucoma eyes with recurrent DH and those with single DH with a mean follow-up after the initial DH of 4.6 years. They found no correlation between recurrent DH and a faster rate of VF progression as compared with cases of a single DH.

Medeiros et al [144] studied the rate of VF deterioration in eyes with DH in the Diagnostic Innovations in Glaucoma Study, an observational cohort study, with a mean follow-up of 8.2 years. They observed a significantly faster VF index change in eyes with DH than in eyes without DH. The difference in rates of VF progression before and after DH was related to the reduction of IOP in the post-DH period compared with the pre-DH period. Each 1 mmHg of IOP reduction was associated with a VF index change of 0.31%/year.

2011 to the present

De Moraes et al [145] studied risk factors for VF progression in the Glaucoma Progression Study and identified both IOP-related and IOP-unrelated risk factors including peak IOP, thinner central cornea, DH, and the presence of beta-zone peripapillary atrophy.

Graham et al [146] studied arterial waveforms in glaucoma and found a positive correlation between VF progression and both DH and loss of spontaneous venous pulsation.

Sakata et al [147] identified factors related to VF progression in NTG treated with topical antiglaucoma medications and found a significant positive correlation between the extent of myopia and VF progression in the upper paracentral subfield for non-high-myopic eyes with NTG. No such correlation was found between DH and VF progression.

Hayamizu et al [148] sought to identify the prognostic factors for NTG using a Cox proportional hazards model and found a positive correlation between poor VF outcome and a larger optic disc area, presence of DH, and a lower IOP reduction ratio.

Lee et al [149] divided NTG into 2 groups on the basis of untreated IOP of 15 mmHg and found a positive correlation between VF progression and DH in cases of untreated IOP of $\leq$15 mmHg. The mean IOP was correlated with VF progression in cases with an untreated IOP of >15 mmHg.

Kim et al [150] identified the fast and slow rate components of VF decay in a retrospective longitudinal study and sought a relationship between the presence of DH and these components. They found a positive correlation for the fast rate component only.

Komori et al [151] studied the long-term outcome of NTG receiving medical therapy in a study with a mean follow-up of 18.3 years and found that DH was present in 38.5% of the cases. The mean VF progression rate was -0.38 $\pm$ 0.30 dB/year in the DH group. Multiple logistic regression analysis identified DH and IOP fluctuation during follow-up as risk factors.

Park et al [152] investigated the relationship between DH recurrence and VF progression in 147 cases with open-angle glaucoma. A single DH was found in 52.4% of the cases and recurrent DH was found in the remaining 47.6%. As for

the progression rate, the effect of recurrent DH at the same location (-0.32 dB/year) did not differ significantly from that of single DH. However, the DH group with recurrence at different locations (-1.07 dB/year) showed worse VF change when compared with the DH group with recurrence at the same location.

Park et al [153] studied glaucoma progression based on VF deterioration with special attention to the influences of myopia and age. Only the presence of DH showed a significant positive correlation to the rate of change in the mean deviation in the nonmyopic group, whereas age and baseline untreated IOP were correlated in the myopic group.

Sung et al [154] studied the factors associated with VF deterioration in myopic NTG and found a positive correlation between VF deterioration and DH, percentage IOP reduction in IOP, and optic disc rotation-VF defect correspondence. The hazards ratio for the presence of DH was calculated to be 2.623.

Kim and Sung [155] studied progressive visual loss in NTG and identified myopia and DH as risk factors for progressive loss of visual function in NTG patients aged younger than 64 years.

Kim et al [156] studied the development of VF abnormality in preperimetric glaucoma and documented a significantly shorter median time interval between the diagnosis of preperimetric glaucoma and the development of VF abnormality in cases of preperimetric glaucoma with DH. The VF abnormality developed 37.8 months (mean) after the first-detected DH.

Lee et al [157] studied the associations among endothelin-1, macrophage chemoattractant protein-1 (MCP-1) levels, and VF progression in NTG and found a positive correlation between VF progression and both systemic MCP-1 levels and DH in NTG.

Chan et al [158] studied VF progression in glaucoma and identified differences between rapid progressors, defined by mean deviation deterioration of at least 1 dB/year, and nonrapid progressors. Progressive factors included DH, older age, lower central corneal thickness, lower baseline IOP, and pseudoexfoliation.

Jin and Noh [159] studied the long-term VF outcome in NTG with a mean follow-up of 21.2 years. The mean MD progression rate was -0.28 ± 0.24 dB/year. A univariate model, but not a multivariate model, identified DH as a risk factor for progression. The multivariate model yielded a significant positive correlation between VF progression and both IOP reduction and mean ocular perfusion pressure.

Sawada et al [160] studied the long-term clinical course of 130 eyes of normotensive preperimetric glaucoma and found that 54.6% of the eyes developed a glaucomatous VF defect during the follow-up period of at least 5 years. The eyes with DH had a greater probability of developing a VF defect (Fig. 4). A Cox proportional hazards model yielded a positive correlation between DH and progression, a greater initial pattern standard deviation, and higher mean IOP.

Dias et al [161] sought correlations between DH and factors associated with parafoveal scotoma in glaucoma eyes in a case-control study. They found a significant positive

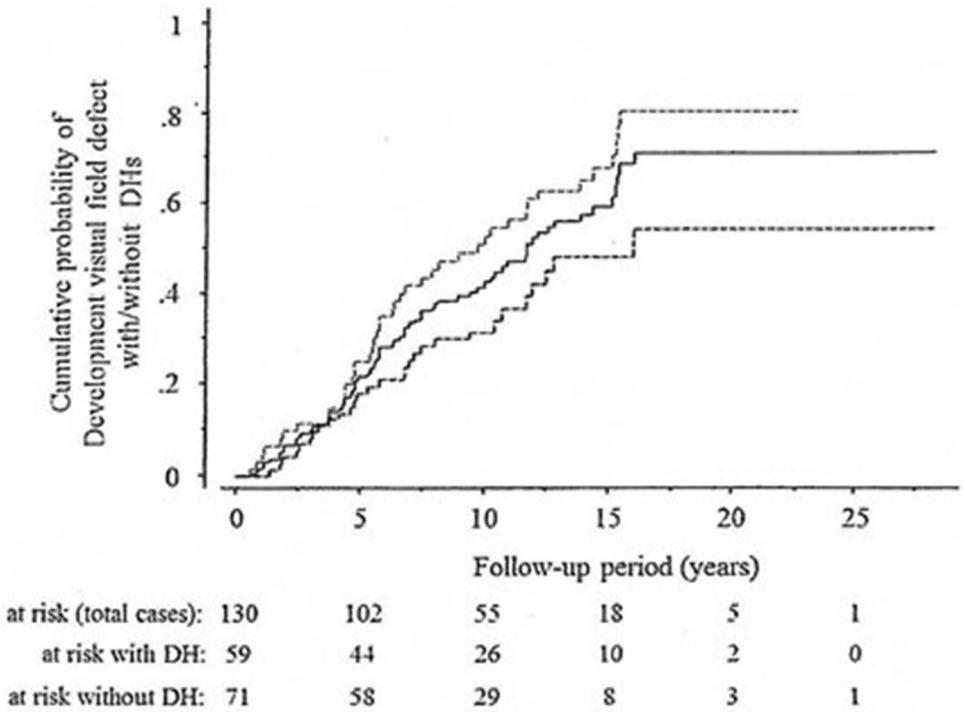

Fig. 4 Kaplan-Meier curve for probability of developing a visual field defect in eyes with initially preperimetric normal tension glaucoma. Solid line: total cases. Grey and black dotted lines: eyes with and without disc hemorrhages, respectively. The eyes with disc hemorrhages had greater probability of developing a visual field defect. Reprinted from reference 160, with permission

correlation between the presence of parafoveal scotoma in glaucoma eyes with DH and both white ethnicity and the presence and magnitude of myopia.

Glaucoma progression (both structure and function)

2001 to 2010

Leske et al [162] studied the factors associated with glaucoma progression in the Early Manifest Glaucoma Trial. Whilst the main factor was the magnitude of initial IOP reduction, a significant correlation was also found for frequent DH during follow-up, higher baseline IOP, exfoliation, bilaterality, worse mean deviation, and older age. Four years later, Leske et al [163] conducted a similar study in the same trial and confirmed the same correlations in addition to influences from some newly identified factors including lower systolic perfusion pressure, lower systolic blood pressure, and cardiovascular disease history.

Kim and Park [164] compared the progression in the optic disc and/or the RNFL and VF in eyes with single and recurrent DH. No significant correlations were found between VF progression and either recurrent or single-incidence DH, although there was a significant correlation between optic disc, including the RNFL, progression, and recurrent DH.

Keltner [165] studied prognostic factors for functional and structural progression in the Ocular Hypertension Treatment Study and found a positive correlation between the VF endpoint and DH, rim thinning, and enlargement of the horizontal cup-to-disc ratio.

Budenz et al [166] studied the characteristics associated with DH in the Ocular Hypertension Treatment Study and found that stereophotographs were more sensitive than clinical examination for detecting DH. They also found a positive correlation between ocular hypertension with DH and an increased risk of developing glaucoma. However, most eyes (86.7%) with a DH did not progress to glaucoma.

Hsieh and Lan [167] followed 3 cases of primary angle-closure glaucoma with DH for 10 years and found a positive correlation between the DH site and both cupping enlargement and VF deterioration.

2011 to present

Holló et al [168] studied prognostic factors for exfoliation glaucoma and identified the presence of DH as an independent risk factor for progression.

Araie et al [169] studied prognostic factors for NTG under treatment with a topical beta-blocker in a prospective fashion and identified DH and less-extensive myopia as risk factors for progression of NTG.

De Moraes et al [170] studied the relationship between structural and functional progression of glaucoma with a follow-up of over 10 years and identified DH as the single most significant predictor for VF worsening among all structural progression indicators.

Kim et al [171] studied prognostic factors in NTG with a mean follow-up of 12.2 years using a multivariate Cox proportional hazards model and found a significant correlation between progression and both DH and IOP reduction.

Jeong et al [172] studied risk factors for the progression of normotensive preperimetric glaucoma in a retrospective study and identified both DH and IOP reductions of <20% from the baseline as significant risk factors for progression.

Gracitelli et al [173] studied the relationship between DH and the change rate of estimated retinal ganglion cell number in the Diagnostic Innovations Glaucoma Study cohort and found that eyes with DH showed faster rates of loss of retinal ganglion cell number than did eyes without DH.

Kim et al [174] studied the rate of VF loss and associated factors for structural or functional progression in preperimetric open-angle glaucoma and found a significant positive correlation between progression and both the percent reduction in IOP and the presence of DH.

Erdem et al [175] studied the prognostic factors for NTG in 19 cases with a mean follow-up of 9.3 years using a retrospective chart review. They identified high peak IOP as a significant risk factor for progression, but could not show DH ($P = .098$) or thinner corneal thickness ($P = .085$) as significant factors.

Chin et al [176] compared structural and functional changes in glaucoma cases with unilateral DH and found more advanced glaucomatous change in eyes with DH than in eyes without DH.

Lee et al [177] studied progression of NTG and found a strong positive correlation between DH and progression in NTG cases having an IOP of ≤15 mmHg. They also identified baseline IOP as a significant risk factor for progression in POAG having an IOP of >21 mmHg.

Seol et al [178] studied the risk factors for functional and structural progression in myopic NTG and documented progression in 45.0% of cases during a mean follow-up of 7.55 years. The Cox proportional hazards model identified the presence of DH as a risk factor for progression, with a hazards ratio of 3.664.

Ha et al [179] studied the effect of DH on the progression of glaucoma in POAG eyes with mild-to-moderate myopia and found a positive correlation between structural progression, determined by optic disc and RNFL changes, and the presence of DH, as compared with eyes without DH. However, they could not show any differences in VF progression between the 2 subgroups.

Moon et al [180] compared progression factors between POAG and exfoliation glaucoma and found a positive

correlation between progression in POAG and both the number of glaucoma medications and DH. They also found a positive correlation between exfoliation glaucoma and higher baseline IOP, a lower IOP reduction, a greater number of glaucoma medications, and a worse baseline VF.

Optical coherence tomography angiographic studies

2011 to present

Using OCT angiography, Rao et al [181] studied the vessel density of the optic nerve head, and the peripapillary and macular regions in POAG eyes with and without DH and found few differences in the vessel density or structural measurements in POAG eyes with and without DH. Thus, they questioned the hypothesis that DH is caused by vascular abnormality in POAG.

Park et al [182] studied peripapillary choroidal microvasculature dropout using OCT angiography in open-angle glaucoma with DH and documented dropout in 46.3% of eyes with DH at the prior DH site, as compared with 29.4% of eyes without DH. They also found that microvasculature dropout was more common in progressive eyes.

Miscellaneous topics

2001 to 2010

Kurvinen et al [183] studied changes in peripapillary retinal blood flow after DH using scanning laser Doppler flowmetry and documented reduced flow at the time of DH and increased flow after its resorption.

2011 to present

Nangia [184] studied the prevalence of glaucoma and related factors in a population-based study and found that DH was strongly correlated with glaucoma.

Yusuf et al [185] reported the case of a 27-year-old with NTG and suspected that low cerebrospinal fluid pressure may have played a role in the pathology of the NTG. In this case, DH was noted 3 times during an 18-month follow-up.

Lopilly Park et al [186] studied glaucoma progression in eyes that developed unilateral branch retinal vein occlusion in the fellow eye and found a significantly greater frequency of DH in glaucoma cases with branch retinal vein occlusion in the fellow eye (35.0%).

Nitta et al [187] studied VF progression in NTG eyes with high myopia and proposed a novel theory of the pathogenesis of glaucoma, suggesting that highly myopic POAG arises from the combined influences of myopic optic neuropathy and glaucomatous optic neuropathy. They concluded that frequent DH and more progressive VF loss occurs when glaucomatous optic neuropathy is predominant and that less DH and less progressive VF loss develops when myopic optic neuropathy is predominant.

Nitta et al [188] studied glaucomatous VF progression using a large-scale, longitudinal and retrospective study. They adopted *presence or absence of DH during the follow-up period* as source of variance in the formula.

Chronology of review articles on DH

Pre-2000

Drance, the rediscoverer of DH, wrote a review of DH studies in 1989 [189]. Twenty years after the rediscovery of DH, he highlighted the characteristics of DH, including frequency, location, bilaterality, recurrence rate, appearance of the optic nerve head, duration, presence of other diseases, and the relationship with IOP. He also considered the significance of DH and its possible mechanisms of action.

Sonnsjö and Krakau used their clinical experience to hypothesize that DH and retinal vein occlusions are evidence of vascular abnormality in the optic nerve resulting in glaucomatous optic neuropathy [190].

2001 to 2010

Anderson [191] discussed VF progression and its risk factors in the Collaborative Normal Tension Glaucoma Study. He suggested that faster progression was associated with female gender, migraine headache, and the presence of DH.

Leske et al [192] reviewed prognostic factors in the Early Manifest Glaucoma Trial and suggested that frequent DH at follow-up increases the risk of progression.

Uhler and Piltz-Seymour [193] reviewed the research on DH and highlighted the difficulty of detecting DH and the importance of identifying DH as a negative prognostic indicator.

2011 to present

De Moraes et al [194] reviewed studies on DH and beta-zone peripapillary atrophy and emphasized the importance of DH as a predictive factor of glaucoma progression.

Ernest et al [195] studied the prognostic factors for glaucomatous VF progression based on a review of 85 articles and ranked DH as a strong prognostic factor, especially in cases of NTG.

Hollands et al [196] reviewed studies of POAG and found positive correlations between POAG and DH, increased cup-to-disc ratio, cup-to-disc ratio asymmetry, elevated IOP, and other factors.

Table 1 Change in focus of disc hemorrhage studies over the past 50 years. The author arbitrarily put each article into 1 category

Study category	Publication year			Total
	1969-2000	2001-2010	2011-2018	
Pathogenesis	6	2	11	19
Prevalence/incidence	19	7	11	37
Morphology/topology	10	7	4	21
Lamina cribrosa	0	1	10	11
Glaucoma progression	16	14	41	71
OCT angiography	0	0	2	2
Other fields	5	6	13	25
Total	56	37	92	185

Numbers indicate number of original articles published

Konieczka et al [197] introduced the term Flammer syndrome to describe a syndrome involving primary vascular dysregulation associated with a cluster of symptoms and signs including NTG. They noted an increased frequency of DH in this syndrome.

Suh and Park [198] discussed the pathogenesis and clinical implications of DH in glaucoma and concluded that DH may be a marker of rapid glaucoma progression.

Kim and Park [199] reviewed recent studies on the pathophysiology and clinical significance of DH in glaucoma and concluded that the underlying mechanism of DH is relatively complex.

Conclusions

The author has here reviewed and drawn up a chronology of major studies related to DH in glaucoma that were published during the last 50 years since the rediscovery of DH. Table 1 indicates changes in the focus of DH studies by presenting the number of original articles sorted by publication year and study category. Several major points were made evident by this review, which may be helpful in guiding further research in this area.

After the rediscovery of DH, researchers focused primarily on its basic characteristics during the 20th century. By 2000, its morphology, recurrence rate, duration, elevated incidence in glaucoma (especially in NTG), and relationship with glaucoma progression were well documented. Follow-up studies largely confirmed these findings into the 21st century.

However, after 2000 there began a new trend in the research, motivated in part by the availability of longitudinal clinical data, the use of static perimetry, and technological advances such as swept-source OCT. These advances allowed more sophisticated and accurate findings regarding progression, both structural and functional, to be incorporated into the new studies. Additionally, the involvement of the lamina cribrosa is more often included in recent studies. Another recent trend is the application of OCT angiography to the study of DH.

Nevertheless, and despite these many advances, the basic mechanism of development of DH and the nature of its intimate relationship to glaucomatous optic neuropathy remain elusive. This is most likely a reflection of the complex mechanisms involved.

It is the author's hope and expectation that ongoing lamina cribrosa research, driven by advances in OCT technology, as well as peripapillary vessel research, driven by advances in OCT angiography, will define the next generation of discoveries in this field. These will be further enhanced by animal studies, using either induced or naturally arising DH, to further advance our understanding of glaucomatous optic neuropathy.

None of the present possibilities would be possible without the pioneering discoveries of the above-cited researchers, and especially the work of Stephen M. Drance. Thanks to their care, creativity, and effort, we have greatly expanded our appreciation of the significance of DH in glaucoma.

Acknowledgements The author thanks the editorial board of the *Japanese Journal of Ophthalmology* for the opportunity to publish this systematic review.

Conflicts of interest T. Yamamoto, Co-Editor-in-Chief of the *Japanese Journal of Ophthalmology*, Grant (Alcon Japan, Alcon Pharma, Otsuka, Pfizer, Santen, Senju), Consultant/Advisor (Alcon Japan, Alcon Pharma, Astellas Pharma, Glaukos Japan, Inotek, Kowa, Otsuka, Pfizer, pH Pharma, Rohto, Santen, Seed, Senju), Lecture fees (Alcon Japan, Alcon Pharma, AMO Japan, CREWT Medical Systems, Glaukos Japan, Johnson & Johnson, Kowa, Novartis, Otsuka, Pfizer, Santen, Senju).

References

1. Jaeger E. Über Glaucom [in German]. Ztschr Ges Aerzte Wien. 1858;14:465–74.
2. Blanchard DL. Jaeger, about glaucoma. Doc Ophthalmol. 1995;89:185–91.
3. Bjerrum JP. Om en teillfojelse til den saedvanliga synsfeltsundersogelse samt om synsfelt ved glaukom [in Danish]. Nord Ophthalmol Tidskr (Copenh). 1889;2:141–85.
4. Feldman F, Sweeney VP, Drance SM. Cerebro-vascular studies in chronic simple glaucoma. Can J Ophthalmol. 1969;4:358–64.
5. Drance SM, Begg IS. Sector haemorrhage: a probable acute ischaemic disc change in chronic simple glaucoma. Can J Ophthalmol. 1970;5:137–41.
6. Begg IS, Drance SM, Sweeney VP. Ischaemic optic neuropathy in chronic simple glaucoma. Br J Ophthalmol. 1971;55:73–90.
7. Drance SM. Some factors in the production of low tension glaucoma. Br J Ophthalmol. 1972;56:229–42.
8. Kottler MS, Drance SM. Studies of hemorrhage on the optic disc. Can J Ophthalmol. 1976;11:102–5.

9. Chumbley LC, Brubaker RF. Low-tension glaucoma. Am J Ophthalmol. 1976;81:761–7.
10. Drance SM, Fairclough M, Butler DM, Kottler MS. The importance of disc hemorrhage in the prognosis of chronic open angle glaucoma. Arch Ophthalmol. 1977;95:226–8.
11. Susanna R, Drance SM, Douglas GR. The visual prognosis of the fellow eye in uniocular chronic open-angle glaucoma. Br J Ophthalmol. 1978;62:327–9.
12. Bengtsson B, Holmin C, Krakau CE. Disc haemorrhage and glaucoma. Acta Ophthalmol (Copenh). 1981;59:1–14.
13. Airaksinen PJ. Fellow eyes of glaucomatous patients with unioocular optic disc haemorrhage. Acta Ophthalmol (Copenh). 1981;59:231–6.
14. Bengtsson B. Manifest glaucoma in the aged II: cases detected by ophthalmoscopy. Acta Ophthalmol (Copenh). 1981;59:332–5.
15. Gloster J. Incidence of optic disc haemorrhages in chronic simple glaucoma and ocular hypertension. Br J Ophthalmol. 1981;65:452–6.
16. Airaksinen PJ, Mustonen E, Alanko HI. Optic disc hemorrhages: analysis of stereophotographs and clinical data of 112 patients. Arch Ophthalmol. 1981;99:1795–801.
17. Airaksinen PJ, Mustonen E, Alanko HI. Optic disc haemorrhages precede retinal nerve fibre layer defects in ocular hypertension. Acta Ophthalmol (Copenh). 1981;59:627–41.
18. Shihab ZM, Lee PF, Hay P. The significance of disc hemorrhage in open-angle glaucoma. Ophthalmology. 1982;89:211–3.
19. Airaksinen PJ, Heijl A. Visual field and retinal nerve fibre layer in early glaucoma after optic disc haemorrhage. Acta Ophthalmol (Copenh). 1983;61:186–94.
20. Airaksinen PJ, Alanko HI. Effect of retinal nerve fibre loss on the optic nerve head configuration in early glaucoma. Graefes Arch Clin Exp Ophthalmol. 1983;220:193–6.
21. Airaksinen PJ. Are optic disc haemorrhages a common finding in all glaucoma patients? Acta Ophthalmol (Copenh). 1984;62:193–6.
22. Bengtsson B. Chronic glaucoma and symptomatic vitreous detachment. Acta Ophthalmol (Copenh). 1986;64:152–6.
23. Kitazawa Y, Shirato S, Yamamoto T. Optic disc hemorrhage in low-tension glaucoma. Ophthalmology. 1986;93:853–7.
24. Heijl A. Frequent disc photography and computerized perimetry in eyes with optic disc haemorrhage: a pilot study. Acta Ophthalmol (Copenh). 1986;64:274–81.
25. Sonnsjö B. Glaucomatous disc haemorrhages photographed at short intervals. Acta Ophthalmol (Copenh). 1986;64:263–6.
26. Poinoosawmy D, Gloster J, Nagasubramanian S, Hitchings RA. Association between optic disc haemorrhages in glaucoma and abnormal glucose tolerance. Br J Ophthalmol. 1986;70:599–602.
27. Miller KM, Quigley HA. Comparison of optic disc features in low-tension and typical open-angle glaucoma. Ophthalmic Surg. 1987;18:882–9.
28. Sonnsjö B, Krakau CE, Bengtsson B. Disc haemorrhages and glaucoma in a general ophthalmic practice. Acta Ophthalmol (Copenh). 1988;66:174–9.
29. Bengtsson B. Characteristics of manifest glaucoma at early stages. Graefes Arch Clin Exp Ophthalmol. 1989;227:241–3.
30. Diehl DL, Quigley HA, Miller NR, Sommer A, Burney EN. Prevalence and significance of optic disc hemorrhage in a longitudinal study of glaucoma. Arch Ophthalmol. 1990;108:545–50.
31. Bengtsson B. Optic disc haemorrhages preceding manifest glaucoma. Acta Ophthalmol (Copenh). 1990;68:450–4.
32. Tuulonen A, Airaksinen PJ, Montagna A, Nieminen H. Screening for glaucoma with a non-mydriatic fundus camera. Acta Ophthalmol (Copenh). 1990;68:445–9.
33. Geijssen HC, Greve EL. Focal ischaemic normal pressure glaucoma versus high pressure glaucoma. Doc Ophthalmol. 1990;75:291–301.
34. Sonnsjö B, Holmin C, Krakau CE. Occurrence of disc haemorrhages in open-angle glaucoma treated with pilocarpine or timolol. Acta Ophthalmol (Copenh). 1991;69:217–24.
35. Hoyng PF, de Jong N, Oosting H, Stilma J. Platelet aggregation, disc haemorrhage and progressive loss of visual fields in glaucoma: a seven year follow-up study on glaucoma. Int Ophthalmol. 1992;16:65–73.
36. Sonnsjö B. Similarities between disc haemorrhages and thromboses of the retinal veins. Int Ophthalmol. 1992;16:235–8.
37. Klein BE, Klein R, Sponsel WE, Franke T, Cantor LB, Martone J, et al. Prevalence of glaucoma: the Beaver Dam Eye Study. Ophthalmology. 1992;99:1499–504.
38. Susanna R, Basseto FL. Hemorrhage of the optic disc and neurosensorial dysacousia. J Glaucoma. 1992;1:248–53.
39. Jonas JB, Schiro D. Localised wedge shaped defects of the retinal nerve fibre layer in glaucoma. Br J Ophthalmol. 1994;78:285–90.
40. Hendrickx KH, van den Enden A, Rasker MT, Hoyng PF. Cumulative incidence of patients with disc hemorrhages in glaucoma and the effect of therapy. Ophthalmology. 1994;101:1165–72.
41. Siegner SW, Netland PA. Optic disc hemorrhages and progression of glaucoma. Ophthalmology. 1996;103:1014–24.
42. Graham SL, Goldberg I, Murray B, Beaumont P, Chong BH. Activated protein C resistance: low incidence in glaucomatous optic disc haemorrhage and central retinal vein occlusion. Aust N Z J Ophthalmol. 1996;24:199–205.
43. Meyer JH, Brandi-Dohrn J, Funk J. Twenty four hour blood pressure monitoring in normal tension glaucoma. Br J Ophthalmol. 1996;80:864–7.
44. Tezel G, Kass MA, Kolker AE, Wax MB. Comparative optic disc analysis in normal pressure glaucoma, primary open-angle glaucoma, and ocular hypertension. Ophthalmology. 1996;103:2105–13.
45. Barry CJ, Cooper RL, Eikelboom RH. Optic disc haemorrhages and vascular abnormalities in a glaucoma population. Aust N Z J Ophthalmol. 1997;25:137–44.
46. Rasker MT, van den Enden A, Bakker D, Hoyng PF. Deterioration of visual fields in patients with glaucoma with and without optic disc hemorrhages. Arch Ophthalmol. 1997;115:1257–62.
47. Sugiyama K, Tomita G, Kitazawa Y, Onda E, Shinohara H, Park KH. The associations of optic disc hemorrhage with retinal nerve fiber layer defect and peripapillary atrophy in normal-tension glaucoma. Ophthalmology. 1997;104:1926–33.
48. Healey PR, Mitchell P, Smith W, Wang JJ. Optic disc hemorrhages in a population with and without signs of glaucoma. Ophthalmology. 1998;105:216–23.
49. Oguri A, Sogano S, Yamamoto T, Kitazawa Y. Incidence of elevation of intraocular pressure over time and associated factors in normal-tension glaucoma. J Glaucoma. 1998;7:117–20.
50. Daugeliene L, Yamamoto T, Kitazawa Y. Effect of trabeculectomy on visual field in progressive normal-tension glaucoma. Jpn J Ophthalmol. 1998;42:286–92.
51. Jonas JB, Dichtl A, Budde WM, Lang P. Optic disc morphology in pigmentary glaucoma. Br J Ophthalmol. 1998;82:875–9.
52. Hayakawa T, Sugiyama K, Tomita G, Kawase K, Onda E, Shinohara H, et al. Correlation of the peripapillary atrophy area with optic disc cupping and disc hemorrhage. J Glaucoma. 1998;7:306–11.
53. Ishida K, Yamamoto T, Kitazawa Y. Clinical factors associated with progression of normal-tension glaucoma. J Glaucoma. 1998;7:372–7.
54. Daugeliene L, Yamamoto T, Kitazawa Y. Risk factors for visual field damage progression in normal-tension glaucoma eyes. Graefes Arch Clin Exp Ophthalmol. 1999;237:105–8.

55. Sugiyama K, Tomita G, Kawase K, Onda E, Shinohara H, Hayakawa T, et al. Disc hemorrhage and peripapillary atrophy in apparently healthy subjects. Acta Ophthalmol Scand. 1999;77:139–42.
56. Sugiyama K, Uchida H, Tomita G, Sato Y, Iwase A, Kitazawa Y. Localized wedge-shaped defects of retinal nerve fiber layer and disc hemorrhage in glaucoma. Ophthalmology. 1999;106:1762–7.
57. Jonas JB, Budde WM. Optic nerve head appearance in juvenile-onset chronic high-pressure glaucoma and normal-pressure glaucoma. Ophthalmology. 2000;107:704–11.
58. Oguri A, Yamamoto T, Kitazawa Y. Spontaneous intraocular pressure reduction in normal-tension glaucoma and associated clinical factors. Jpn J Ophthalmol. 2000;44:263–7.
59. Ishida K, Yamamoto T, Sugiyama K, Kitazawa Y. Disk hemorrhage is a significantly negative prognostic factor in normal-tension glaucoma. Am J Ophthalmol. 2000;129:707–14.
60. Sugiyama T, Hara H, Oku H, Nakatsuji S, Okuno T, Sasaoka M, et al. Optic cup enlargement followed by reduced optic nerve head circulation after optic nerve stimulation. Invest Ophthalmol Vis Sci. 2001;42:2843–8.
61. Sonnsjö B, Dokmo Y, Krakau T. Disc haemorrhages, precursors of open angle glaucoma. Prog Retin Eye Res. 2002;21:35–56.
62. Yang D, Fu J, Hou R, Liu K, Jonas JB, Wang H, et al. Optic neuropathy induced by experimentally reduced cerebrospinal fluid pressure in monkeys. Invest Ophthalmol Vis Sci. 2014;55:3067–73.
63. Chung E, Demetriades AM, Christos PJ, Radcliffe NM. Structural glaucomatous progression before and after occurrence of an optic disc haemorrhage. Br J Ophthalmol. 2015;99:21–5.
64. Park HY, Jeong HJ, Kim YH, Park CK. Optic disc hemorrhage is related to various hemodynamic findings by disc angiography. PLoS One. 2015;10:e0120000.
65. Kim KE, Kim DM, Flammer J, Kim KN. Central retinal venous pressure in eyes of normal-tension glaucoma patients with optic disc hemorrhage. PLoS One. 2015;10:e0127920.
66. Zhang L, Albon J, Jones H, Gouget CL, Ethier CR, Goh JC, et al. Collagen microstructural factors influencing optic nerve head biomechanics. Invest Ophthalmol Vis Sci. 2015;56:2031–42.
67. Lee NY, Park HY, Park SH, Park CK. The association of nailfold capillaroscopy with systemic matrix metalloproteinase-9 concentration in normal-tension glaucoma. Curr Eye Res. 2015;40:1001–7.
68. Kosior-Jarecka E, Bartosińska J, Łukasik U, Wróbel-Dudzińska D, Krasowska D, Chodorowska G, et al. Results of nailfold capillaroscopy in patients with normal-tension glaucoma. Curr Eye Res. 2018;43:747–53.
69. Shim SH, Kim JM, Woo HY, Shin KU, Koh JW, Park KH. Association between platelet function and disc hemorrhage in patients with normal-tension glaucoma: a prospective cross-sectional study. Am J Ophthalmol. 2015;160:1191–9.
70. Lorenz K, Beck S, Keilani MM, Wasielica-Poslednik J, Pfeiffer N, Grus FH. Longitudinal analysis of serum autoantibody-reactivities in patients with primary open angle glaucoma and optic disc hemorrhage. PLoS One. 2016;11:e0166813.
71. Lee EJ, Han JC, Kee C. A novel hypothesis for the pathogenesis of glaucomatous disc hemorrhage. Prog Retin Eye Res. 2017;60:20–43.
72. Chou JC, Cousins CC, Miller JB, Song BJ, Shen LQ, Kass MA, et al. Fundus densitometry findings suggest optic disc hemorrhages in primary open-angle glaucoma have an arterial origin. Am J Ophthalmol. 2018;187:108–16.
73. Gazzard G, Morgan W, Devereux J, Foster P, Oen F, Seah S, et al. Optic disc hemorrhage in Asian glaucoma patients. J Glaucoma. 2003;12:226–31.
74. Krupin T, Liebmann JM, Greenfield DS, Rosenberg LF, Ritch R, Yang JW. The Low-pressure Glaucoma Treatment Study (LoGTS) study design and baseline characteristics of enrolled patients. Ophthalmology. 2005;112:376–85.
75. Lan YW, Wang IJ, Hsiao YC, Sun FJ, Hsieh JW. Characteristics of disc hemorrhage in primary angle-closure glaucoma. Ophthalmology. 2008;115:1328–33.
76. Bengtsson B, Leske MC, Yang Z, Heijl A. Disc hemorrhages and treatment in the early manifest glaucoma trial. Ophthalmology. 2008;115:2044–8.
77. Tomidokoro A, Iwase A, Araie M, Yamamoto T, Kitazawa Y. Population-based prevalence of optic disc haemorrhages in elderly Japanese. Eye (Lond). 2009;23:1032–7.
78. Hsieh JW, Lan YW, Wang IJ, Sun FJ. Clinical characteristics and prognostic significance of disc hemorrhage in open-angle and angle-closure glaucoma. J Glaucoma. 2010;19:483–7.
79. Suh MH, Park KH. Period prevalence and incidence of optic disc haemorrhage in normal tension glaucoma and primary open-angle glaucoma. Clin Exp Ophthalmol. 2011;39:513–9.
80. Park SC, De Moraes CG, Teng CC, Tello C, Liebmann JM, Ritch R. Initial parafoveal versus peripheral scotomas in glaucoma: risk factors and visual field characteristics. Ophthalmology. 2011;118:1782–9.
81. Kang JW, Park B, Cho BJ. Comparison of risk factors for initial central scotoma versus initial peripheral scotoma in normal-tension glaucoma. Korean J Ophthalmol. 2015;29:102–8.
82. Schor KS, De Moraes CG, Teng CC, Tello C, Liebmann JM, Ritch R. Rates of visual field progression in distinct optic disc phenotypes. Clin Exp Ophthalmol. 2012;40:706–12.
83. Kim JM, Jeoung JW, Bitrian E, Supawavej C, Mock D, Park KH, et al. Comparison of clinical characteristics between Korean and Western normal-tension glaucoma patients. Am J Ophthalmol. 2013;155:852–7.
84. Jonas JB, Nangia V, Khare A, Kulkarni M, Matin A, Sinha A, et al. Prevalence of optic disc hemorrhages in rural central India: the Central Indian Eye and Medical Study. PLoS One. 2013;8:e76154.
85. Park HS, Yoo C, Kim JM, Sung KC, Shim SH, Bae JH, et al. Disc hemorrhages and their risk factors in an urban South Korean population. Optom Vis Sci. 2015;92:700–6.
86. Kim DW, Kim YK, Jeoung JW, Kim DM, Park KH. Prevalence of optic disc hemorrhage in Korea: the Korea National Health and Nutrition Examination Survey. Invest Ophthalmol Vis Sci. 2015;56:3666–72.
87. Cho HK, Suh W, Kee C. Visual and structural prognosis of the untreated fellow eyes of unilateral normal tension glaucoma patients. Graefes Arch Clin Exp Ophthalmol. 2015;253:1547–55.
88. Skaat A, De Moraes CG, Bowd C, Sample PA, Girkin CA, Medeiros FA, et al. African Descent and Glaucoma Evaluation Study (ADAGES): racial differences in optic disc hemorrhage and beta-zone parapapillary atrophy. Ophthalmology. 2016;123:1476–83.
89. Budenz DL, Huecker JB, Gedde SJ, Gordon M, Kass M. Thirteen-year follow-up of optic disc hemorrhages in the Ocular Hypertension Treatment Study. Am J Ophthalmol. 2017;174:126–33.
90. Miyake T, Sawada A, Yamamoto T, Miyake K, Sugiyama K, Kitazawa Y. Incidence of disc hemorrhages in open-angle glaucoma before and after trabeculectomy. J Glaucoma. 2006;15:164–71.
91. Liou SY, Sugiyama K, Uchida H, Gu ZB, Yamamoto T, Tomita G, et al. Morphometric characteristics of optic disk with disk hemorrhage in normal-tension glaucoma. Am J Ophthalmol. 2001;132:618–25.

92. Jonas JB, Martus P, Budde WM, Hayler J. Morphologic predictive factors for development of optic disc hemorrhages in glaucoma. Invest Ophthalmol Vis Sci. 2002;43:2956–61.
93. Jonas JB, Martus P, Budde WM. Inter-eye differences in chronic open-angle glaucoma patients with unilateral disc hemorrhages. Ophthalmology. 2002;109:2078–83.
94. Ahn JK, Kang JH, Park KH. Correlation between a disc hemorrhage and peripapillary atrophy in glaucoma patients with a unilateral disc hemorrhage. J Glaucoma. 2004;13:9–14.
95. Yamamoto T, Iwase A, Kawase K, Sawada A, Ishida K. Optic disc hemorrhages detected in a large-scale eye disease screening project. J Glaucoma. 2004;13:356–60.
96. Radcliffe NM, Liebmann JM, Rozenbaum I, Sbeity Z, Sandler SF, Tello C, et al. Anatomic relationships between disc hemorrhage and parapapillary atrophy. Am J Ophthalmol. 2008;146:735–40.
97. Jeoung JW, Park KH, Kim JM, Kang SH, Kang JH, Kim TW, et al. Optic disc hemorrhage may be associated with retinal nerve fiber loss in otherwise normal eyes. Ophthalmology. 2008;115:2132–40.
98. Kim HS, Park KH, Jeoung JW, Park J. Comparison of myopic and nonmyopic disc hemorrhage in primary open-angle glaucoma. Jpn J Ophthalmol. 2013;57:166–71.
99. Kim YK, Park KH, Yoo BW, Kim HC. Topographic characteristics of optic disc hemorrhage in primary open-angle glaucoma. Invest Ophthalmol Vis Sci. 2014;55:169–76.
100. Kim EK, Park HL, Park CK. Relationship between retinal inner nuclear layer thickness and severity of visual field loss in glaucoma. Sci Rep. 2017;7:5543.
101. Ozturker ZK, Munro K, Gupta N. Optic disc hemorrhages in glaucoma and common clinical features. Can J Ophthalmol. 2017;52:583–91.
102. Grødum K, Heijl A, Bengtsson B. Optic disc hemorrhages and generalized vascular disease. J Glaucoma. 2002;11:226–30.
103. Soares AS, Artes PH, Andreou P, Leblanc RP, Chauhan BC, Nicolela MT. Factors associated with optic disc hemorrhages in glaucoma. Ophthalmology. 2004;111:1653–7.
104. Kim YD, Han SB, Park KH, Kim SH, Kim SJ, Seong M, et al. Risk factors associated with optic disc haemorrhage in patients with normal tension glaucoma. Eye (Lond). 2010;24:567–72.
105. Furlanetto RL, De Moraes CG, Teng CC, Liebmann JM, Greenfield DS, Gardiner SK, et al. Risk factors for optic disc hemorrhage in the low-pressure glaucoma treatment study. Am J Ophthalmol. 2014;157:945–52.
106. Kwon J, Lee J, Choi J, Jeong D, Kook MS. Association between nocturnal blood pressure dips and optic disc hemorrhage in patients with normal-tension glaucoma. Am J Ophthalmol. 2017;176:87–101.
107. Jeoung JW, Kim DM, Oh S, Lee JS, Park SS, Kim JY. The relation between endothelial nitric oxide synthase polymorphisms and normal tension glaucoma. J Glaucoma. 2017;26:1030–5.
108. Budde WM, Mardin CY, Jonas JB. Glaucomatous optic disc hemorrhages on confocal scanning laser tomographic images. J Glaucoma. 2003;12:470–4.
109. O'Brien PD, Bogdan AJ, Fitzpatrick P, Beatty S. The influence of pharmacological mydriasis on biomicroscopic evaluation of the glaucomatous optic nerve head. Eye (Lond). 2005;19:1194–9.
110. Kong YX, Coote MA, O'Neill EC, Gurria LU, Xie J, Garway-Heath D, et al. Glaucomatous optic neuropathy evaluation project: a standardized internet system for assessing skills in optic disc examination. Clin Exp Ophthalmol. 2011;39:308–17.
111. Syed ZA, Radcliffe NM, De Moraes CG, Smith SD, Liebmann JM, Ritch R. Automated alternation flicker for the detection of optic disc haemorrhages. Acta Ophthalmol. 2012;90:645–50.
112. Lee JR, Sung KR, Na JH, Shon K, Lee KS. Discrepancy between optic disc and nerve fiber layer assessment and optical coherence tomography in detecting glaucomatous progression. Jpn J Ophthalmol. 2013;57:546–52.
113. O'Neill EC, Gurria LU, Pandav SS, Kong YX, Brennan JF, Xie J, et al. Glaucomatous optic neuropathy evaluation project: factors associated with underestimation of glaucoma likelihood. JAMA Ophthalmol. 2014;132:560–6.
114. Sandhu S, Rudnisky C, Arora S, Kassam F, Douglas G, Edwards MC, et al. Compressed 3D and 2D digital images versus standard 3D slide film for the evaluation of glaucomatous optic nerve features. Br J Ophthalmol. 2018;102:364–8.
115. Healey PR, Mitchell P. The prevalence of optic disc pits and their relationship to glaucoma. J Glaucoma. 2008;17:11–4.
116. Park HY, Jeon SH, Park CK. Enhanced depth imaging detects lamina cribrosa thickness differences in normal tension glaucoma and primary open-angle glaucoma. Ophthalmology. 2012;119:10–20.
117. Takayama K, Hangai M, Kimura Y, Morooka S, Nukada M, Akagi T, et al. Three-dimensional imaging of lamina cribrosa defects in glaucoma using swept-source optical coherence tomography. Invest Ophthalmol Vis Sci. 2013;54:4798–807.
118. Park SC, Hsu AT, Su D, Simonson JL, Al-Jumayli M, Liu Y, et al. Factors associated with focal lamina cribrosa defects in glaucoma. Invest Ophthalmol Vis Sci. 2013;54:8401–7.
119. Lee EJ, Kim TW, Kim M, Girard MJ, Mari JM, Weinreb RN. Recent structural alteration of the peripheral lamina cribrosa near the location of disc hemorrhage in glaucoma. Invest Ophthalmol Vis Sci. 2014;55:2805–15.
120. Faridi OS, Park SC, Kabadi R, Su D, De Moraes CG, Liebmann JM, et al. Effect of focal lamina cribrosa defect on glaucomatous visual field progression. Ophthalmology. 2014;121:1524–30.
121. Choi YJ, Lee EJ, Kim BH, Kim TW. Microstructure of the optic disc pit in open-angle glaucoma. Ophthalmology. 2014;121:2098–106.
122. Kim YK, Jeoung JW, Park KH. Effect of focal lamina cribrosa defect on disc hemorrhage area in glaucoma. Invest Ophthalmol Vis Sci. 2016;57:899–907.
123. Sharpe GP, Danthurebandara VM, Vianna JR, Alotaibi N, Hutchison DM, Belliveau AC, et al. Optic disc hemorrhages and laminar disinsertions in glaucoma. Ophthalmology. 2016;123:1949–56.
124. Kim YK, Park KH. Lamina cribrosa defects in eyes with glaucomatous disc haemorrhage. Acta Ophthalmol. 2016;94:e468–73.
125. Park HL, Lee J, Jung Y, Park CK. Optic disc hemorrhage and lamina cribrosa defects in glaucoma progression. Sci Rep. 2017;7:3489.
126. Choi F, Park KH, Kim DM, Kim TW. Retinal nerve fiber layer thickness evaluation using optical coherence tomography in eyes with optic disc hemorrhage. Ophthalmic Surg Lasers Imaging. 2007;38:118–25.
127. Nitta K, Sugiyama K, Higashide T, Ohkubo S, Tanahashi T, Kitazawa Y. Does the enlargement of retinal nerve fiber layer defects relate to disc hemorrhage or progressive visual field loss in normal-tension glaucoma? J Glaucoma. 2011;20:189–95.
128. Kernstock C, Dietzsch J, Januschowski K, Schiefer U, Fischer MD. Optical coherence tomography shows progressive local nerve fiber loss after disc hemorrhages in glaucoma patients. Graefes Arch Clin Exp Ophthalmol. 2012;250:583–7.
129. Wang YX, Hu LN, Yang H, Jonas JB, Xu L. Frequency and associated factors of structural progression of open-angle glaucoma in the Beijing Eye Study. Br J Ophthalmol. 2012;96:811–5.
130. Niles PI, Greenfield DS, Sehi M, Bhardwaj N, Iverson SM, Chung YS. Detection of progressive macular thickness loss using optical coherence tomography in glaucoma suspect and glaucomatous eyes. Eye (Lond). 2012;26:983–91.
131. Suh MH, Park KH, Kim H, Kim TW, Kim SW, Kim SY, et al. Glaucoma progression after the first-detected optic disc

hemorrhage by optical coherence tomography. J Glaucoma. 2012;21:358–66.
132. Radcliffe NM, Smith SD, Syed ZA, Park SC, Ehrlich JR, De Moraes CG, et al. Retinal blood vessel positional shifts and glaucoma progression. Ophthalmology. 2014;121:842–8.
133. Hwang YH, Kim YY, Kim HK, Sohn YH. Changes in retinal nerve fiber layer thickness after optic disc hemorrhage in glaucomatous eyes. J Glaucoma. 2014;23:547–52.
134. Lee SH, Lee EJ, Kim TW. Structural characteristics of the acquired optic disc pit and the rate of progressive retinal nerve fiber layer thinning in primary open-angle glaucoma. JAMA Ophthalmol. 2015;133:1151–8.
135. Akagi T, Zangwill LM, Saunders LJ, Yarmohammadi A, Manalastas PIC, Suh MH, et al. Rates of local retinal nerve fiber layer thinning before and after disc hemorrhage in glaucoma. Ophthalmology. 2017;124:1403–11.
136. Lee WJ, Kim YK, Park KH, Jeoung JW. Evaluation of ganglion cell-inner plexiform layer thinning in eyes with optic disc hemorrhage: a trend-based progression analysis. Invest Ophthalmol Vis Sci. 2017;58:6449–56.
137. Lee EJ, Han JC, Kee C. Location of disc hemorrhage and direction of progression in glaucomatous retinal nerve fiber layer defects. J Glaucoma. 2018;27:504–10.
138. Pereira ML, Kim CS, Zimmerman MB, Alward WL, Hayreh SS, Kwon YH. Rate and pattern of visual field decline in primary open-angle glaucoma. Ophthalmology. 2002;109:2232–40.
139. Kono Y, Sugiyama K, Ishida K, Yamamoto T, Kitazawa Y. Characteristics of visual field progression in patients with normal-tension glaucoma with optic disk hemorrhages. Am J Ophthalmol. 2003;135:499–503.
140. Leung DY, Tham CC, Li FC, Kwong YY, Chi SC, Lam DS. Silent cerebral infarct and visual field progression in newly diagnosed normal-tension glaucoma: a cohort study. Ophthalmology. 2009;116:1250–6.
141. De Moraes CG, Prata TS, Liebmann CA, Tello C, Ritch R, Liebmann JM. Spatially consistent, localized visual field loss before and after disc hemorrhage. Invest Ophthalmol Vis Sci. 2009;50:4727–33.
142. Leung DY, Li FC, Kwong YY, Tham CC, Chi SC, Lam DS. Simvastatin and disease stabilization in normal tension glaucoma: a cohort study. Ophthalmology. 2010;117:471–6.
143. de Beaufort HC, De Moraes CG, Teng CC, Prata TS, Tello C, Ritch R, et al. Recurrent disc hemorrhage does not increase the rate of visual field progression. Graefes Arch Clin Exp Ophthalmol. 2010;248:839–44.
144. Medeiros FA, Alencar LM, Sample PA, Zangwill LM, Susanna R Jr, Weinreb RN. The relationship between intraocular pressure reduction and rates of progressive visual field loss in eyes with optic disc hemorrhage. Ophthalmology. 2010;117:2061–6.
145. De Moraes CG, Juthani VJ, Liebmann JM, Teng CC, Tello C, Susanna R Jr, et al. Risk factors for visual field progression in treated glaucoma. Arch Ophthalmol. 2011;129:562–8.
146. Graham SL, Butlin M, Lee M, Avolio AP. Central blood pressure, arterial waveform analysis, and vascular risk factors in glaucoma. J Glaucoma. 2013;22:98–103.
147. Sakata R, Aihara M, Murata H, Mayama C, Tomidokoro A, Iwase A, et al. Contributing factors for progression of visual field loss in normal-tension glaucoma patients with medical treatment. J Glaucoma. 2013;22:250–4.
148. Hayamizu F, Yamazaki Y, Nakagami T, Mizuki K. Optic disc size and progression of visual field damage in patients with normal-tension glaucoma. Clin Ophthalmol. 2013;7:807–13.
149. Lee J, Kong M, Kim J, Kee C. Comparison of visual field progression between relatively low and high intraocular pressure groups in normal tension glaucoma patients. J Glaucoma. 2014;23:553–60.
150. Kim JM, Kyung H, Azarbod P, Lee JM, Caprioli J. Disc haemorrhage is associated with the fast component, but not the slow component, of visual field decay rate in glaucoma. Br J Ophthalmol. 2014;98:1555–9.
151. Komori S, Ishida K, Yamamoto T. Results of long-term monitoring of normal-tension glaucoma patients receiving medical therapy: results of an 18-year follow-up. Graefes Arch Clin Exp Ophthalmol. 2014;252:1963–70.
152. Park HY, Kim EK, Park CK. Clinical significance of the location of recurrent optic disc hemorrhage in glaucoma. Invest Ophthalmol Vis Sci. 2015;56:7524–34.
153. Park HY, Hong KE, Park CK. Impact of age and myopia on the rate of visual field progression in glaucoma patients. Medicine (Baltimore). 2016;95:e3500.
154. Sung MS, Kang YS, Heo H, Park SW. Optic disc rotation as a clue for predicting visual field progression in myopic normal-tension glaucoma. Ophthalmology. 2016;123:1484–93.
155. Kim S, Sung KR. Factors associated with loss of visual function in medically treated advanced normal tension glaucoma. Curr Eye Res. 2017;42:429–35.
156. Kim HJ, Song YJ, Kim YK, Jeoung JW, Park KH. Development of visual field defect after first-detected optic disc hemorrhage in preperimetric open-angle glaucoma. Jpn J Ophthalmol. 2017;61:307–13.
157. Lee NY, Kim MH, Park CK. Visual field progression is associated with systemic concentration of macrophage chemoattractant protein-1 in normal-tension glaucoma. Curr Eye Res. 2017;42:1002–6.
158. Chan TCW, Bala C, Siu A, Wan F, White A. Risk factors for rapid glaucoma disease progression. Am J Ophthalmol. 2017;180:151–7.
159. Jin SW, Noh SY. Long-term clinical course of normal-tension glaucoma: 20 years of experience. J Ophthalmol. 2017;2017:2651645.
160. Sawada A, Manabe Y, Yamamoto T, Nagata C. Long-term clinical course of normotensive preperimetric glaucoma. Br J Ophthalmol. 2017;101:1649–53.
161. Dias DT, Almeida I, Sassaki AM, Juncal VR, Ushida M, Lopes FS, et al. Factors associated with the presence of parafoveal scotoma in glaucomatous eyes with optic disc hemorrhages. Eye (Lond). 2018;32:1669–74. https://doi.org/10.1038/s41433-018-0159-3.
162. Leske MC, Heijl A, Hussein M, Bengtsson B, Hyman L, Komaroff E. Factors for glaucoma progression and the effect of treatment: the Early Manifest Glaucoma Trial. Arch Ophthalmol. 2003;121:48–56.
163. Leske MC, Heijl A, Hyman L, Bengtsson B, Dong L, Yang Z. Predictors of long-term progression in the Early Manifest Glaucoma Trial. Ophthalmology. 2007;114:1965–72.
164. Kim SH, Park KH. The relationship between recurrent optic disc hemorrhage and glaucoma progression. Ophthalmology. 2006;113:598–602.
165. Keltner JL, Johnson CA, Anderson DR, Levine RA, Fan J, Cello KE, et al. The association between glaucomatous visual fields and optic nerve head features in the Ocular Hypertension Treatment Study. Ophthalmology. 2006;113:1603–12.
166. Budenz DL, Anderson DR, Feuer WJ, Beiser JA, Schiffman J, Parrish RK 2nd, et al. Detection and prognostic significance of optic disc hemorrhages during the Ocular Hypertension Treatment Study. Ophthalmology. 2006;113:2137–43.
167. Hsieh JW, Lan YW. Progression of optic neuropathy after disc hemorrhage in primary angle-closure glaucoma. Jpn J Ophthalmol. 2009;53:380–3.
168. Holló G, Quaranta L, Cvenkel B, Astakhov YS, Teus MA, Kóthy P, et al. Risk factors associated with progression in exfoliative glaucoma patients. Ophthalmic Res. 2012;47:208–13.

169. Araie M, Shirato S, Yamazaki Y, Matsumoto C, Kitazawa Y, Ohashi Y. Risk factors for progression of normal-tension glaucoma under β-blocker monotherapy. Acta Ophthalmol. 2012;90:e337–43.
170. De Moraes CG, Liebmann JM, Park SC, Teng CC, Nemiroff J, Tello C, et al. Optic disc progression and rates of visual field change in treated glaucoma. Acta Ophthalmol. 2013;91:e86–91.
171. Kim M, Kim DM, Park KH, Kim TW, Jeoung JW, Kim SH. Intraocular pressure reduction with topical medications and progression of normal-tension glaucoma: a 12-year mean follow-up study. Acta Ophthalmol. 2013;91:e270–5.
172. Jeong JH, Park KH, Jeoung JW, Kim DM. Preperimetric normal tension glaucoma study: long-term clinical course and effect of therapeutic lowering of intraocular pressure. Acta Ophthalmol. 2014;92:e185–93.
173. Gracitelli CP, Tatham AJ, Zangwill LM, Weinreb RN, Liu T, Medeiros FA. Estimated rates of retinal ganglion cell loss in glaucomatous eyes with and without optic disc hemorrhages. PLoS One. 2014;9:e105611.
174. Kim KE, Jeoung JW, Kim DM, Ahn SJ, Park KH, Kim SH. Long-term follow-up in preperimetric open-angle glaucoma: progression rates and associated factors. Am J Ophthalmol. 2015;159:160–8.
175. Erdem E, Williams A, Kuchar SD, Waisbourd M, Spaeth GL. Long-term (>8 years) evaluation of progression in patients with low-pressure glaucoma. Eur J Ophthalmol. 2015;25:490–5.
176. Chin YC, Perera SA, Tun TA, Teh GH, Cheung CY, Aung T, et al. Structural differences in the optic nerve head of glaucoma patients with and without disc hemorrhages. J Glaucoma. 2016;25:e76–81.
177. Lee JY, Sung KR, Lee JY. Comparison of the progression of high- and low-tension glaucoma as determined by two different criteria. Korean J Ophthalmol. 2016;30:40–7.
178. Seol BR, Kim S, Kim DM, Park KH, Jeoung JW, Kim SH. Influence of intraocular pressure reduction on progression of normal-tension glaucoma with myopic tilted disc and associated risk factors. Jpn J Ophthalmol. 2017;61:230–6.
179. Ha A, Kim YK, Jeoung JW, Park KH. Impact of optic disc hemorrhage on subsequent glaucoma progression in mild-to-moderate myopia. PLoS One. 2017;12:e0189706.
180. Moon Y, Sung KR, Kim JM, Shim SH, Yoo C, Park JH. Risk factors associated with glaucomatous progression in pseudoexfoliation patients. J Glaucoma. 2017;26:1107–13.
181. Rao HL, Pradhan ZS, Weinreb RN, Dasari S, Riyazuddin M, Venugopal JP, et al. Optical coherence tomography angiography vessel density measurements in eyes with primary open-angle glaucoma and disc hemorrhage. J Glaucoma. 2017;26:888–95.
182. Park HL, Kim JW, Park CK. Choroidal microvasculature dropout is associated with progressive retinal nerve fiber layer thinning in glaucoma with disc hemorrhage. Ophthalmology. 2018;125:1003–13.
183. Kurvinen L, Harju M, Saari J, Vesti E. Altered temporal peripapillary retinal flow in patients with disc hemorrhages. Graefes Arch Clin Exp Ophthalmol. 2010;248:1771–5.
184. Nangia V, Jonas JB, Matin A, Bhojwani K, Sinha A, Kulkarni M, et al. Prevalence and associated factors of glaucoma in rural central India: the Central India Eye and Medical Study. PLoS One. 2013;8:e76434.
185. Yusuf IH, Ratnarajan G, Kerr RS, Salmon JF. Juvenile-onset normal tension glaucoma from chronic, recurrent low cerebrospinal fluid pressure. J Glaucoma. 2016;25:e738–40.
186. Lopilly Park HY, Jeon S, Lee MY, Park CK. Glaucoma progression in the unaffected fellow eye of glaucoma patients who developed unilateral branch retinal vein occlusion. Am J Ophthalmol. 2017;175:194–200.
187. Nitta K, Sugiyama K, Wajima R, Tachibana G. Is high myopia a risk factor for visual field progression or disk hemorrhage in primary open-angle glaucoma? Clin Ophthalmol. 2017;11:599–604.
188. Nitta K, Wajima R, Tachibana G, Inoue S, Ohigashi T, Otsuka N, et al. Prediction of visual field progression in patients with primary open-angle glaucoma, mainly including normal tension glaucoma. Sci Rep. 2017;7:15048.
189. Drance SM. Disc hemorrhages in the glaucomas. Surv Ophthalmol. 1989;33:331–7.
190. Sonnsjö B, Krakau CE. Arguments for a vascular glaucoma etiology. Acta Ophthalmol (Copenh). 1993;71:433–44.
191. Anderson DR. Collaborative normal tension glaucoma study. Curr Opin Ophthalmol. 2003;14:86–90.
192. Leske MC, Heijl A, Hyman L, Bengtsson B, Komaroff E. Factors for progression and glaucoma treatment: the Early Manifest Glaucoma Trial. Curr Opin Ophthalmol. 2004;15:102–6.
193. Uhler TA, Piltz-Seymour J. Optic disc hemorrhages in glaucoma and ocular hypertension: implications and recommendations. Curr Opin Ophthalmol. 2008;19:89–94.
194. De Moraes CG, Liebmann JM, Ritch R. Predictive factors within the optic nerve complex for glaucoma progression: disc hemorrhage and parapapillary atrophy. Asia Pac J Ophthalmol (Phila). 2012;1:105–12.
195. Ernest PJ, Schouten JS, Beckers HJ, Hendrikse F, Prins MH, Webers CA. An evidence-based review of prognostic factors for glaucomatous visual field progression. Ophthalmology. 2013;120:512–9.
196. Hollands H, Johnson D, Hollands S, Simel DL, Jinapriya D, Sharma S. Do findings on routine examination identify patients at risk for primary open-angle glaucoma? The rational clinical examination systematic review. JAMA. 2013;309:2035–42.
197. Konieczka K, Ritch R, Traverso CE, Kim DM, Kook MS, Gallino A, et al. Flammer syndrome. EPMA J. 2014;5:11.
198. Suh MH, Park KH. Pathogenesis and clinical implications of optic disk hemorrhage in glaucoma. Surv Ophthalmol. 2014;59:19–29.
199. Kim KE, Park KH. Optic disc hemorrhage in glaucoma: pathophysiology and prognostic significance. Curr Opin Ophthalmol. 2017;28:105–12.