(74)

Ophthalmoscopic Evaluation of the Parapapillary Region of the Optic Nerve Head

Oftalmoskopowa ocena okołotarczowego obszaru tarczy nerwu wzrokowego

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Summary: Neuropatiom wzrokowym towarzyszą morfologiczne zmiany występujące w okołotarczowym obszarze tarczy nerwu wzrokowego. Dla wczesnego wykrywania jaskrowego uszkodzenia nerwu wzrokowego w oczach z wysokim ciśnieniem wewnątrzgałkowym, jeszcze przed rozwojem ubytków perymetrycznych, istotnymi zmianami są: uogólnione lub segmentowe zmniejszenie widoczności warstwy włókien nerwowych siatkówki, występowanie zlokalizowanych ubytków tej warstwy oraz obecność krwotoczków na tarczy nerwu wzrokowego. Okołotarczowy zanik naczyniówkowo-siatkówkowy zwykle nie występuje w oczach z niejaskrowym uszkodzeniem nerwu wzrokowego, co jest pomocne w różnicowaniu jaskrowej i niejaskrowej neuropatii nerwu wzrokowego. Zarówno w jaskrowej, jak i niejaskrowej neuropatii wzrokowej dochodzi do zmniejszenia widoczności warstwy włókien nerwowych siatkówki i zmniejszenia średnicy tętniczek siatkówkowych wraz z ogniskowym zwężeniem tych naczyń.

Aksony komórek zwojowych siatkówki opuszczają oko przez tarczę nerwu wzrokowego, będącą wąskim gardłem wstępującej drogi wzrokowej. Wszystkie informacje wzrokowe powstające na przestrzeni tysiąca milimetrów kwadratowych siatkówki (111) skupiają się na obszarze 2-3 mm kwadratowych (58) tarczy nerwu wzrokowego. Daje to wyobrażenie o znaczeniu tarczy nerwu wzrokowego dla morfologicznej diagnostyki jego chorób i anomalii, które prowadzą do zmian w regionie okołotarczowym i na samej tarczy.

Metodyka doboru piśmiennictwa: Wykorzystywaną bazą danych był MedLine. Przeanalizowano literaturę z lat 1970-1997. Kryteriami włączenia czy wykluczenia artykułu z tego przeglądu były: oryginalność, znaczenie dla oftalmoskopowej oceny tarczy nerwu wzrokowego z pominięciem zaawansowanych metod badania, nowe doniesienia dotyczące anatomii czy patomorfologii tarczy nerwu wzrokowego z klinicznymi i/lub patogenetycznymi implikacjami. Opis nowych metod badania nie był wystarczającą przyczyną uwzględnienia artykułu w tym opracowaniu.

Typowe dla jaskrowego uszkodzenia tarczy nerwu wzrokowego są płomykowate krwotoczki (34,35). Diagnostyczne znaczenie krwotoczków tarczy oparte jest na ich wysokiej specyficzności, gdyż są one rzadko spotykane w oczach prawidłowych. Wskazują zwykle na obecność jaskry, gdy brak jeszcze zauważalnych ubytków w polu widzenia (2-5,19,99,148).

Okołotarczowy zanik naczyniówkowo–siatkówkowy jest jedną spośród innych morfologicznych zmian występujących w jaskrowych nieprawidłowościach tarczy nerwu wzrokowego. Pod względem przydatności w wykrywaniu jaskrowego uszkodzenia nerwu wzrokowego jest to cecha drugorzędna. Stanowi ona jeden z parametrów użytecznych w różnicowaniu poszczególnych typów pierwotnej i wtórnej jaskry otwartego kąta oraz w diagnostyce różnicowej jaskrowego i niejaskrowego uszkodzenia nerwu wzrokowego.

Uogólnione i ogniskowe zwężenie naczyń siatkówkowych występuje zarówno w jaskrowych, jak i w niejaskrowych neuropatiach wzrokowych (43,70,71,78,79). Jest ono typowe dla uszkodzenia nerwu wzrokowego, ale nie jest patognomiczne dla jaskry.

Zgodnie z definicją, jaskrowy zanik nerwu wzrokowego jest związany z utratą wzrokowych włókien nerwowych, a zatem zmniejszoną widocznością RNFL. Utrata włókien nerwowych może występować w formie zlokalizowanych ubytków bądź też w formie uogólnionej. Warstwa włókien nerwowych siatkówki powinna być oceniana podczas każdego rutynowego badania oftalmoskopowego. Dotyczy to zwłaszcza pacjentów z wczesnym uszkodzeniem nerwu wzrokowego. Kolejne badania kliniczne potwierdzają znaczenie oceny RNFL, umożliwiającej wcześniejsze wykrycie jaskrowego uszkodzenia nerwu wzrokowego niż w konwencjonalnej perymetrii komputerowej.

Słowa kluczowe: tarcza nerwu wzrokowego, pierścień neuroretinalny, zagłębienie wzrokowe, przytarczowy pierścień twardówki, zanik okołotarczowy i morfometria tarczy nerwu wzrokowego.

Key words: optic disc, peripapillary region, glaucomatous optic disc damage.

Optic neuropathies are associated with morphologic changes occurring in the parapapillary region of the optic nerve head. These alterations can ophthalmoscopically be evaluated using the parameters presence and location of splinter-shaped hemorrhages, occurrence, size, configuration and location of parapapillary chorioretinal atrophy, diffuse and/or focal decrease of the diameter of the retinal arterioles, and visibility of the retinal nerve fiber layer. For the early detection of glaucomatous optic nerve damage in ocular hypertensive eyes prior to the development of perimetric defects, the most important parapapillary variables are diffusely or segmentally decreased visibility of the retinal nerve fiber layer, occurrence of localized retinal nerve fiber layer defects and presence of disc

hemorrhages. With parapapillary atrophy usually not occurring in eyes with nonglaucomatous optic nerve damage, it is helpful for the differentation of glaucomatous versus nonglaucomatous optic neuropathy. Glaucomatous and nonglaucomatous optic neuropathy have in common a reduced visibility of the retinal nerve fiber layer and a decreased diameter of the retinal arterioles including the occurrence of focal arteriole narrowing.

With all the retinal ganglion cell axons leaving the eye through the optic nerve head, the optic disc becomes the bottleneck of the afferent visual pathway. In the optic disc, all visual information gathered on around 1000 mm^2 of retina (111) is concentrated on an area of about 2 mm^2 to 3 mm^2 (58). It shows the importance of the optic nerve head for the morphologic diagnosis of optic nerve anomalies and diseases which lead to changes in the intrapapillary and parapapillary region of the optic disc.

Purpose of this study is to describe the ophthalmoscopic evaluation of the alterations occurring in the parapapillary region. These alterations include splinter-shaped hemorrhages at the optic disc border, parapapillary chorioretinal atrophy, diffuse and/or focal decrease of the diameters of the retinal arterioles, and diffuse and/or focally accentuated decrease in the visibility of the retinal nerve fiber layer. These variables can be assessed just by using a simple ophthalmoscope. Technically advanced examination methods such as confoal scanning laser tomography (100) and laser polarimetry for measurement of the retinal nerve fiber layer thickness (160) are not the major topic of this review.

I) Optic Disc Hemorrhages

IA) General findings

Splinter-shaped or flame-shaped hemorrhages at the border of the optic disc are a hallmark of glaucomatous optic nerve atrophy (34,35). Rarely or very rarely found in normal eyes (51,59,60,94,96,133), disc hemorrhages are detected in about 4% to 7% of eyes with glaucoma (1,18,36,47,54,95,98,138). Their frequency increases from an early stage of glaucoma to a medium advanced stage and decreases again towards a far advanced stage (59). One study suggested that disc hemorrhages are not found in disc regions or eyes without detectable neuroretinal rim (59). In early glaucoma, they are usually located in the inferotemporal or superotemporal disc regions. They are associated with localized retinal nerve fiber layer defects, neuroretinal rim notches and circumscribed perimetrical loss (1,36,52,59,61,147).

IB) Diagnostic importance

The diagnostic importance of disc hemorrhages is based on their high specificity, since they are only rarely found in normal eyes; that they usually indicate the presence of glaucomatous optic nerve damage, even if the visual field is unremarkable (2-5,19,99,148); and that they suggest progression of glaucoma (2-5,35,36,99,132,138,139,147). In two epidemiological studies, frequency of disc hemorrhages in non-glaucomatous eyes was about 1% (51,96). This high specificity of about 99% points towards a helpful role in the early diagnosis of glaucoma. Due to the low prevalence of disc hemorrhages in eyes with glaucoma (1,18,36,47,54,95,98,138) and thus low sensitivity, however, they are as single variable not at all sufficient to separate normal eyes and eyes with early glaucoma. Their low sensitivity also explains why disc hemorrhages are not a useful tool in screening examinations for glaucoma. About two months after the initial bleeding, often a localized defect of the retinal nerve fiber layer or a broadening of a localized retinal nerve fiber layer defect can be detected correlating with a circumscribed scotoma in the visual field (52).

IC) Differences between the various glaucoma types

Since frequency of optic disc hemorrhages differs between the various types of the open-angle glaucomas, assessment of disc bleedings can be helpful for classification of the glaucoma type. Disc hemorrhages were found most often in patients with focal normal-pressure glaucoma. Frequency of detected disc bleedings was lower in patients with juvenile-onset primary open-glaucoma, age-related atrophic primary open-angle glaucoma, and highly myopic primary open-angle glaucoma (25,36,45,59,62,63,63, 95,144). Disc hemorrhages, however, can be found in all types of the chronic open-angle glaucomas, suggesting that the pathomechanism associated with disc hemorrhages may be present in all these glaucoma types.

There are factors, however, which limit the practical importance of the reported differences in the frequencies of disc henmorrhages in the various types of the glaucomas. The differences between the groups were mostly not statistically significant. Since the selection of glaucoma patients in the hospital-based studies is partially dependent on the appearance of the optic disc, one cannot exclude with certainty that the frequency of the disc hemorrhages is arteficially high in the studies. It is possible that clinic-based glaucoma groups as used in many studies have a larger number of disc hemorrhages than a population-based sample because one way in which referral into the care system could occur is because a disc hemorrhage was detected. Those patients with normal-pressure glaucoma are likely to be under care because of optic disc abnormalities including hemorrhages since they would not have been identified through elevated intraocular pressure. This could result in a bias with normal-pressure glaucoma patients presenting with a false high frequency of disc hemorrhages compared to patients with high-pressure glaucoma. Some evidence for this hypothesis is presented in a longitudinal study of Diehl, Quigley and colleagues (33). This follow-up examination revealed fewer normal-pressure glaucoma patients developing disc hemorrhages than could be expected given the initial prevalence.

One can further raise the questions whether the different frequencies of the disc bleedings in the various glaucoma types are caused by a varying amount of blood per hemorrhage, and whether a different rate in the absorption of blood played a role. The disc hemorrhages are visible for about 8 days to 12 weeks after the initial bleeding (52). One cannot exclude the possibility that a high intraocular pressure may stop a bleeding relatively early resulting in a small disc hemorrhage in high-pressure glaucoma eyes, and that a low intraocular pressure may stop the bleeding relatively late leading to a large disc hemorrhage in eyes with normal-pressure glaucoma. This would favor a faster absorption of disc hemorrhages in eyes with high-pressure glaucoma than in eyes with normal-pressure glaucoma. If this holds true, the differences in intraocular pressure between the various types of the open-angle glaucomas will not be causative for a preferred development of disc hemorrhages in eyes with normal-pressure glaucoma but they will be responsible for a longer visibility of the bleedings and could mimic a higher incidence of the hemorrhages.

One also has to consider that the disc hemorrhages described in these and other studies might represent the extreme of large disc

ISSN 0023-2157 Index 362646

bleedings in a possible spectrum of hemorrhages including also microscopical bleedings undetectable upon ophthalmoscopy. This would mean that all figures concerning the frequencies of bleedings would relate to only a fraction of the whole of the disc hemorrhages.

ID) Pathogenetic aspects

Concerning the pathogenesis of disc hemorrhages, one could argue that the rapid movements of the lamina cribrosa tear the superficial blood vessels of the optic disc resulting in a break and subsequent circumscribed bleeding. This is contradicted by the clinical experience that eyes after a contusion with a very marked and short elevation of intraocular pressure normally do not show splinter-like or flame-shaped disc hemorrhages (97). The question arises whether disc hemorrhages have their origin in the arterioles, veinules, or the capillaries of the peripapillary radial network on the surface of the peripapillary retina (14). The commonly held believe that disc hemorrhages indicate an ischemic event may be contradicted by the fact that they are never associated with a cotton-wool spot which is the typical sign for an ischemic infarct in the retinal nerve fiber layer.

II) Parapapillary Chorioretinal Atrophy

IIA) Historical remarks

Around the beginning of the 20th century, ophthalmologists like Elschnig and Bücklers turned attention to an association between glaucoma and parapapillary chorioretinal atrophy (21,40,41). It was called "halo glaucomatosus" when it totally encircled the optic disc in eyes with end-stage glaucoma. Later, Primrose, Hayreh, Wilensky and Kolker, Anderson, Airaksinen and other investigators confirmed the observations describing the occurrence of parapapillary atrophy in eyes with glaucoma (6,15,24,42,46,48,49,53, 65-67, 93,103,109, 117-119, 130,134, 150-152,163). Heijl and Samander found a spatial correlation between the parapapillary chorioretinal atrophy and the location of the most marked visual field loss (53). Anderson described that the presence or extent of a crescent correlated with the glaucomatous disc damage (15).

IIB) Alpha zone and beta zone

Ophthalmoscopically, the parapapillary chorioretinal atrophy has been divided into a central beta zone and a peripheral alpha zone (65-67). A peripheral zone (alpha zone) is characterized by an irregular hypopigmentation and hyperpigmentation and intimated thinning of the chorioretinal tissue layer. On its outer side it is adjacent to the retina, and on its inner side it is in touch with a zone characterized by visible sclera and visible large choroidal vessels (beta zone), or with the peripapillary scleral ring, respectively. Features of the inner zone (beta zone) are marked atrophy of the retinal pigment epithelium and of the choriocapillaris, good visibility of the large choroidal vessels and the sclera, thinning of the chorioretinal tissues, and round bounds to the adjacent alpha zone on its peripheral side and to the peripapillary scleral ring on its central side. If both zones are present, beta zone is always closer to the optic disc than alpha zone.

In indirect and direct clinical-histologic comparisons, beta zone correlates with a complete loss of retinal pigment epithelium cells and a markedly diminished count of retinal photoreceptors (42,68,101). Corespondingly, the circle of Zinn-Haller can be visualized in some eyes in vivo in the area of parapapillary atrophy (114). Alpha zone is the equivalent of pigmentary irregularities in the retinal pigment epithelium. Correspondingly, beta zone corresponds psychophysically to an absolute scotoma, and alpha zone to a relative scotoma (69,105,146). It is unclear whether the observed thinning of the uvea in eyes with glaucoma (102,108) suggesting a decreased uveal blood flow is pathogenetically connected with the development of parapapillary chorioretinal atrophy in glaucoma eyes. Indocyanine green angiography showed areas of hypofluorescence in the peripapillary region in late-phase angiograms in about two third of eyes with glaucoma compared to 20% of control eyes. These hypofluorescent areas were discussed to be either the result of blockage of background fluorescence by pigment or caused by an absence of vascular tisse in the level of the choriocapillaris (110).

In normal eyes, both alpha zone and beta zone are largest and most frequently located in the temporal horizontal sector, followed by the inferior temporal area and the superior temporal region (65,67). They are smallest and most rarely found in the nasal parapapillary area. Alpha zone is present in almost all normal eyes and is thus more common than beta zone (mean frequency in normal eyes: about 15%-20%) (65-67). Alpha zone and beta zone have to be differentiated from the myopic scleral crescent in eyes with high myopia and from the inferior scleral crescent in eyes with "tilted optic discs". The myopic scleral crescent present in highly myopic eyes differs histologically from the glaucomatous beta zone in non-highly myopic eyes. In the region of the myopic crescent, only the inner limiting membrane and underlying retinal nerve fiber layer or its remnants cover the sclera (31) while in the glaucomatous beta zone, Bruch`s membrane and the choroid is interposed between the remnants of the retina and the sclera (68,101).

IIC) Parapapillary atrophy in glaucomatous and non-glaucomatous optic nerve damage

Size, shape and frequency of both zones do not differ significantly between normal eyes and eyes with nonglaucomatous optic nerve atrophy (70,71). Both zones are significantly larger and beta zone occurs more often in eyes with glaucomatous optic nerve atrophy than in normal eyes (65-67,152). Size of both zones and frequency of beta zone are significantly correlated with variables indicating the severity of the glaucomatous optic nerve damage such as neuroretinal rim loss, decrease of retinal vessel diameter, reduced visibility of the retinal nerve fiber bundles, and perimetric defects. A large beta zone, also called "halo glaucomatosus" when encircling the optic disc, is often associated with a marked degree of fundus tessellation, a shallow glaucomatous disc cupping, a relatively low frequency of disc hemorrhages and detectable localized defects of the retinal nerve fiber layer, a mostly concentric loss of neuroretinal rim, and normal or almost normal intraocular pressure measurements (62,67). The location of parapapillary chorioretinal atrophy is spatially correlated with the neuroretinal rim loss in the intrapapillary region (66,67). It is larger in that sector with the more marked loss of neuroretinal rim. Accordingly, it is relatively largest in that quadrant that has the longest distance to the exit of the central retinal vessel trunk on the lamina cribrosa (72).

The general opinion about the association between parapapillary atrophy and glaucoma, however, has not completely been undivided (30,109,126). Derick and coworkers reported that, in monkeys with experimental glaucoma, parapapillary atrophy did not markedly enlarge after intraocular pressure had been elevated, and that the presence of peripapillary crescent was not significantly associated

with the development of glaucomatous optic disc cup enlargement (30). It is in contrast to the results of a recent investigation in which parapapillary atrophy, especially beta zone, was significantly larger and beta zone occurred significantly more often in monkey eyes after increase of intraocular pressure than before induced elevation of intraocular pressure (50). One possible reason for the discrepancy between these two studies on experimental glaucoma may be that the follow-up time in the investigation by Derick and colleagues was considerably shorter than in the other study, so that in Derick`s study, parapapillary atrophy may not have had enough time to develop.

In clinical studies as well as in investigations on experimental high-pressure glaucoma in monkeys, side differences in parapapillary atrophy were significantly correlated with side differences in neuroretinal rim area and mean visual field defect (67). In unilateral glaucoma, parapapillary atrophy was significantly larger and beta zone was found significantly more often in the affected eyes than in the contralateral nonglaucomatous eyes. Eliminating the effect of systemic parameters such as age, artherosclerosis and arterial blood pressure in these intraindividual inter-eye comparisons, these correlations suggest an association between parapapillary chorioretinal atrophy and the degree of glaucomatous optic nerve atrophy (67). It agrees with significant correlations of increasing frequency and enlarging area of parapapillary atrophy with decreasing area of neuroretinal rim (66,67,120,157,152), diminishing visibility of retinal nerve fiber layer (73), increasing visual field defect (15,16,66,67,92,115), decreased temporal contrast sensitivity as determined by a full-field flicker test (55), and decreasing diameter of the retrobulbar part of the optic nerve as measured sonographocally (32). In recent follow-up studies by Tezel and colleagues, progression of parapapillary atrophy, especially beta zone, was described as an early glaucomatous finding in some patients with ocular hypertension (150). Accordingly, presence and size of parapapillary atrophy were related to the development of subsequent optic disc or visual field damage in ocular hypertensive patients (145,151). In a study on patients with normal-pressure glaucoma, disc hemorrhages were associated closely associated with the size of parapapillary atrophy underlining the importance of parapapillary atrophy in the morphologic diagnosis of glaucomatous optic neuropathy (147).

In contrast to glaucomatous optic neuropathy, non-glaucomatous optic nerve damage does not lead to an enlargement of parapapillary atrophy (70,71). It indicates that parapapillary atrophy is one among other optic disc variables to differentiate between glaucomatous versus non-glaucomatous optic nerve damage.

IID) Parapapillary atrophy in the various types of the open-angle glaucomas

Parapapillary chorioretinal atrophy is helpful for the papillo-morphologic differentiation of various types of the open-angle glaucomas. The open-angle glaucomas are a heterogenous group of diseases which vary in the level of intraocular pressure, age of the patients, prevalence of arterial hypotension, refractive error, and atrophic appearance of the posterior fundus. These forms of the open-angle glaucomas differ in the appearance of the optic disc including the presence and area of parapapillary chorioretinal atrophy.

Beta zone of parapapillary atrophy is significantly larger in eyes with highly myopic primary open-angle glaucoma (63) than in eyes with age-related atrophic primary open-angle glaucoma (62), in which beta zone is significantly larger than in eyes with secondary open-angle glaucoma due to pseudoexfoliation of the lens (pseudoexfoliative glaucoma) (74), primary melanin dispersion syndrome (pigmentary glaucoma) (75), and non-highly myopic primary open-angle glaucoma. Beta zone is significantly the smallest in juvenile-onset primary open-angle glaucoma (64).

The findings in patients with focal normal-pressure glaucoma are contradictory. Some studies suggested that parapapillary atrophy is larger in size in normal-pressure glaucoma than in primary open-angle glaucoma (152), other investigations found that eyes with normal-pressure glaucoma and eyes with primary open-angle glaucoma do not markedly differ in parapapillary atrophy (76,152). In a recent study in which eyes with the focal type of normal-pressure glaucoma were separated from other glaucoma eyes with normal intraocular pressure, beta zone was significantly smaller in eyes with focal type of normal-pressure glaucoma than in eyes with primary open-angle glaucoma and elevated intraocular pressure (77). In the same study, eyes with focal normal-pressure glaucoma and eyes with juvenile-onset primary open-angle glaucoma did not vary significantly in beta zone, despite marked differences in intraocular pressure. Taking all glaucoma types examined in this study, except focal normal-pressure glaucoma, beta zone increased significantly with decreasing mean intraocular pressure.

IIE) Conclusion

In conclusion, parapapillary chorioretinal atrophy is one among other morphologic variables to detect glaucomatous abnormalities in the optic nerve head. In a ranking list of optic disc variables for the detection of glaucomatous optic nerve damage, it is a variable of second order. As one among other parameters, it is useful for the differentiation of the various types of the primary and secondary open-angle glaucomas. In contrast to glaucomatous eyes, eyes with nonglaucomatous optic nerve atrophy including eyes after nonarteritic anterior ischemic optic neuropathy have a normal parapapillary atrophy (70,71). Evaluation of the parapapillary atrophy can, therefore, be helpful in the differential diagnosis of glaucomatous versus nonglaucomatous optic nerve damage.

III) Diameter of Retinal Arterioles

IIIA) Diffuse arteriole narowing

Diffuse narrowing of the retinal vessels has been described for glaucomatous and nonglaucomatous optic neuropathies (43,70,71,78,79). In glaucoma, the vessel diameter reduces with decreasing area of the neuroretinal rim, diminishing visibility of the retinal nerve fiber layer and increasing visual field defects (78). Since the reduction of the vessel caliber is also found in eyes with nonglaucomatous optic nerve damage such as descending optic nerve atrophy (43,70) and nonarteritic anterior ischemic optic neuropathy (71), one infered that a generalized reduction of the vessel diameter is typical for optic nerve damage but not characteristic for glaucoma. From a pathogenetical point of view, it suggested that vessel reduction was not causative for glaucomatous optic nerve fiber loss but, at least partially, secondary to a reduced demand in the superficial layers of the retina.

IIIB) Focal arteriole narowing

Rader, Feuer and Anderson have recently drawn attention to focal narrowing of the retinal arterioles in the intrapapillary and

ISSN 0023-2157 Index 362646

peripapillary region of eyes with glaucoma or nonarteritic anterior ischemic optic neuropathy (127). Similar observations were made by Rankin and Drance (131) and others (112). The degree of focal narrowing of the retinal arterioles increased significantly with age in the normal eyes (84). Corrected for age, it was significantly higher in the eyes with an optic nerve atrophy than in the normal eyes. The eyes with glaucoma and the eyes with nonglaucomatous optic nerve damage did not vary significantly in the severity of focal narrowing. Focal arteriole narrowing was slightly more pronounced in the eyes with normal-pressure glaucoma and the eyes with nonarteritic anterior ischemic optic neuropathy than in the other groups (112). These differences, however, were not marked. In the glaucoma group, the degree of focal narowing of the retinal arterioles was significantly more pronounced if the optic nerve damage was more advanced. A recent study comparing fundus photographs and fluorescein angiograms with each other showed that focal narrowing of the retinal arterioles in the parapapillary region of eyes with optic neuropathies represents a real stenosis of the vessel lumen and is not due to an ophthalmoscopic artifact (113). Taking into account that in focal arteriole narrowing the vessel diameter can be reduced by 50% or more, considerable hemodynamic changes may occur.

The finding that focal arteriole narrowing was mostly independent of parapapillary atrophy (112) points against the hypothesis that vasoconstrictive factors in the parapapillary region could lead to a focal vasospasm in the retina and simultanously to atrophic changes in the deep retinal layers, retinal pigment epithelium and the choroid. The finding that focal vessel attenuation was observed in glaucomatous eyes and in eyes with nonglaucomatous optic nerve atrophy makes one infer that focal narrowing of the retinal arterioles is part of a panoply of changes characteristic for any optic nerve damage. Its occurrence in both groups indicates that focal vessel narrowing is not specific for glaucoma and that it does not play a major specific role in the pathogenesis of the disease. This hypothesis is further favored by the fact that a reduced blood perfusion as in central retinal artery occlusion or nonarteritic anterior ischemic optic neuropathy (70,71) does not markedly decrease the neuroretinal rim area. In glaucoma, however, the neuroretinal rim area is reduced (7,20). This finding points against a deficiency of retinal blood perfusion as reason of the glaucomatous loss of neuroretinal rim and optic nerve fibers.

IV) Evaluation of the Retinal Nerve Fiber Layer

IVA) Ophthalmoscopic evaluation

The retinal nerve fiber layer (RNFL) contains the retinal ganglion cell axons covered by astrocytes and bundled by processes of Müller cells. It can be assessed ophthalmoscopically (158,159), on wide-angle red-free photographs (8,9,140), or by using sophisticated techniques such as scanner laser tomography or laser polarimetry (135,153,160,161,162). For its ophthalmoscopical evaluation, it is helpful to use green light. In eyes with opaque media, a yellow lens coloration, and a low degree of pigmentation of the retinal pigment epithelium, the RNFL is less visible than in eyes with clear media and deeply pigmented retinal pigment epithelium.

The retinal nerve fibers or better the retinal nerve fiber bundles are ophthalmoscopically detectable as bright and fine striations in the inner retinal layer fanning off the optic disc to the retinal periphery (8,9,56,57,80,140,158,159). According to electron microscopical studies (128), these fine striations represent tissue canals in which processes of the Müller cells gather the axons together into bundles with a diameter of about 20 microns. In the temporal and nasal parapapillary region, the striations are finer and consist of one fiber bundle per stripe only. In the temporal inferior and temporal superior fundus regions, the striations are broader and have several bundles per stripe (128). The bright stripes lying inbetween the dark lines are formed by the processes of the Müller cells with other optical properties than the retinal nerve fibers themselves. The retinal nerve fibers have only a small tendency to leave their bundle.

Upon ophthalmoscopy, the RNFL can be examined through a dilated pupil using green light. The use of a Goldmann contact lens provides a better detectability of the RNFL than an indirect ophthalmoscope. Examining eyes with clear optical media and a normal fundus pigmentation, most wedge-shaped RNFL-defects can be detected. Minor defects are better seen on RNFL-photographs, especially in patients who do not cooperate well. In juvenile subjects, the evaluation of the RNFL is more difficult than in medium-aged individuals because the reflectivity of the inner limiting membrane is considerably higher in young subjects than in older patients.

Several techniques for the clinical evaluation of the retinal nerve fiber layer in glaucoma have been reported. Among them are red-free ophthalmoscopy (158,159), nerve fiber layer photography with a black and white film (9,141), computerized images to measure the relative height of the peripapilllary nerve fiber layer surface (26,27), polarimetric determinations of the retinal nerve fiber layer thickness (135,153,160-162), a densitometry of the reflectance of the retinal nerve fiber layer (39), photogrammetric measurements of the retinal nerve fiber layer thickness (116,136,149), and measurement of the retinal nerve fiber layer contour in the peripapillary region by confocal laser scanning tomography systems (22,23), to cite only some studies. Sommer (142) described that adding polarized light can improve the visualization of the RNFL. Airaksinen emphasized the use of a wide-angle fundus camera, using high-resolution, fine-grain, black-and white films with a blue monochromatic interference filter (wavelength 495 nm) (8,9). The same filter and camera can be used for conventional fundus fluorescein angiography. Recently, Tuulonen, Airaksinen and coworkers showed that the RNFL can also be evaluated on photographs taken with a non-mydriatic fundus camera (154). With only color fundus photographs available, the RNFL detectibility can be improved by reproducing the color slides through a green filter on a black-and-white film as reported by Hoyt (56,57) and Frisén (44). Due to the higher resolving power of a low-sensitive, black-and-white film as compared to a color film, the detectibility of the RNFL is inferior on reproduced color fundus photographs than on photographs taken by the method described by Airaksinen.

IVB) Clinical findings in normal eyes

In normal eyes, visibility of the RNFL is regionally unevenly distributed. Dividing the fundus into eight regions, the nerve fiber bundles are most visible in the temporal inferior sector, followed by the temporal superior area, the nasal superior region and finally the nasal inferior sector (81,82). It is least visible in the superior, inferior, temporal horizontal and nasal horizontal regions. Correspondingly, the diameters of the retinal arterioles are significantly widest at the temporal inferior disc border, followed the temporal superior disc region, the nasal superior area and finally the nasal inferior disc region (82). It is in agreement with the location of the foveola below a horizontal line drawn through the center of the optic disc (81), and

with configuration of the neuroretinal rim that is broadest at the temporal inferior disc border, followed the temporal superior disc region (58). The sectors' sequence concerning the best visibility of the RNFL correlates with the sectors' sequence in respect to rim configuration and retinal artery caliber. Physiologically, it points towards an anatomical and nutritional relationship. Visibility of the RNFL decreases with age (81,82). It correlates with an age-related reduction of the optic nerve fiber count with an annual loss of about 4,000 to 5,0000 fibers/year out of an original population of presumably 1.4 million optic nerve fibers (17,83,106). These features of the normal RNFL are important for diagnosis of RNFL changes secondary to optic nerve damage in the diseased eye.

IVC) Clinical findings in glaucomatous eyes

By definition, glaucomatous optic nerve atrophy is associated with an optic nerve fiber loss and thus decreased visibility of the RNFL. This nerve fiber loss can occur in a diffuse way or in form of localized defects.

IVC1) Localized RNFL-Defects

In 1973, Hoyt, Frisén and coworkers (56,57) were the first to report on the significance of localized RNFL-defects in glaucomatous eyes. Localized defects of the RNFL are defined as wedge-shaped and not spindle-like defects, running towards or touching the optic disc border. If they are pronounced, they can have a broad basis at the temporal raphe of the fundus. Typically occurring in about 20% of all glaucoma eyes (61), they can also be found in eyes with an atrophy of the optic nerve due to other reasons such as optic disc drusen, toxoplasmotic retinochoroidal scars, ischemic retinopathies with cotton-wool spots of the retina, after longstanding papilledema or optic neuritis due to multiple sclerosis, to mention some examples (28,84). Since the localized RNFL defects are not present in normal eyes, they almost always signify a pathological abnormality (61). This is important for subjects with ocular hypertension in which a localized RNFL-defect points to an optic nerve damage even in the absence of perimetric abnormalities (2,85,107,121,143). One has to take into account however that localized RNFL defects are not pathognomonic for glaucoma since they occur also in other types of optic nerve atrophy (28,84). Due to their relatively low frequency in eyes with an optic nerve damage, their sensitivity to indicate an optic nerve atrophy is not very high.

In glaucomatous eyes, the frequency of localized RNFL-defects increases significantly from an "early" glaucoma stage to a stage with medium advanced glaucomatous damage and decreases again to a stage with very marked glaucomatous changes (61). In eyes with very advanced optic nerve damage they are usually no longer detectable due to the pronounced loss of nerve fiber fibers in all fundus sectors. Localized RNFL defects occur more often in eyes with the focal type of normal-pressure glaucoma than in eyes with the age-related atrophic type of open-angle glaucoma, the highly myopic type of open-angle glaucoma, and the juvenile-onset type of primary open-angle glaucoma (61-64). In their vicinity at the optic disc border, one often finds notches of the neuroretinal rim, sometimes an optic disc hemorrhage, and a parapapillary chorioretinal atrophy which is more marked in that sector than in other sectors (2,59,61). Localized RNFL-defects are often found six to eight weeks after an optic disc bleeding (2). They point towards a localized type of optic nerve damage.

With respect to different sectors of the fundus, localized RNFL defects are most often found in the temporal inferior sector followed by the temporal superior sector (61). In the nasal fundus region, localized RNFL defects are only rarely seen (61). This may be due to the fact that the RNFL in normal eyes is less detectable in the nasal fundus than in the temporal inferior and temporal superior fundus areas (81,82). In fundus areas, in which the RNFL physiologically is thin, also localized defects are harder to be found than in areas with a thick RNFL. It is unclear whether also the morphology of the lamina cribrosa with larger pores in the inferior and superior sectors and smaller pores in the temporal and nasal regions plays a role for the development of localized RNFL defects (86,122,129).

The importance of localized defects of the RNFL for the diagnosis of glaucoma have been shown in many studies. Airaksinen (2) described clearly detectable wedge-shaped defects of the RNFL in eyes with increased intraocular pressure and normal visual field. These eyes showed later localized perimetric changes when the area of concern was especially examined (10).

Experimental studies have shown (123), that localized RNFL defects can ophthalmoscopically be detected if more than 50% of the thickness of the retinal nerve fiber layer is lost. This can be explained by the "sandwich" arrangement of the retinal nerve fiber bundles in the RNFL. The first glaucomatous defects concern mainly retinal ganglion cells close at the temporal raphe of the retina. Their axons are located in the deep and middle layer of the RNFL. If these axons are lost, the configuration of the surface of the RNFL is only slightly changed because the axons over the lost fibers still cover the defect under them. The localized RNFL-defects have to be differentiated from slitlike or groovelike (pseudo-)defects that often do not extend to the optic disc border and that do not have a broad base close at the temporal raphe of the fundus. This includes a socalled cleavage of the RNFL that can mimic a true defect of the RNFL especially in high myopia (29).

IVC2) Diffuse loss

Besides localized RNFL-defects, a diffuse loss of retinal nerve fibers occurs in eyes with a damage of the optic nerve. It leads to a decreased visibility of the RNFL. After sectioning of the optic nerve in the orbit of monkeys, Quigley (124) observed a disappearing of the visibility of the RNFL starting one month after the operation, and being complete four weeks later. Ophthalmoscopically, the diffuse RNFL loss is more difficult to detect than a localized defect. It is helpful to use the variable "sequence of fundus sectors concerning the best RNFL visibility" (73,81,82,87). If one detects that in an eye without fundus irregularities the RNFL is markedly better detectable in the temporal superior fundus region than in the temporal inferior sector, it points towards a loss of RNFL mainly in the temporal inferior fundus region. This variable can be examined upon ophthalmoscopy without applying sophisticated techniques. It is also helpful to evaluate whether the retinal vessels are clearly and sharply detectable. The retinal vessels are normally embedded in the RNFL. In eyes with a diffuse RNFL loss, the retinal vessels are covered only by the inner limiting membrane resulting in a better visibility and a sharper image of the large retinal vessels. This is an important variable in the diagnosis of an optic nerve damage.

Pathogenetically, it is yet unclear whether the localized defects and the diffuse loss of the RNFL represent two pathomechanisms or whether they are two extremes of the same process (37). The contrast

ISSN 0023-2157 Index 362646

between localized and diffuse RNFL-loss, the varying frequencies of localized RNFL-defects in different types of glaucoma (61-64), and the association between localized RNFL-defects and optic disc hemorrhages (2,59,61) however makes one infer different types of glaucomatous optic nerve damage. It is also unknown whether all nerve fibers within a nerve fiber bundle get lost simultaneously or whether there is a gradual loss of fibers within a bundle resulting in a progressive thinning of the nerve fiber bundle.

For glaucoma, many studies have shown that disturbances of the RNFL are correlated with various other variables indicating the degree of glaucomatous optic nerve damage (11,12,13,38,88,104, 125,137,155,156).

Considering its great importance in the assessment of anomalies and diseases of the optic nerve and taking into account the feasibility of its ophthalmoscopical evaluation, the retinal nerve fiber layer should be examined during every routine ophthalmoscopy. This holds true especially for patients with an early damage of the optic nerve. The importance to evaluate the RNFL is further examplified in studies in which a glaucomatous damage of the optic nerve could earlier be detected by examination of the RNFL than by conventional computerized perimetry. It is of utmost importance for the detection of glaucoma in eyes with a pseudonormal but glaucomatous minicup in minidiscs (89), and it is useful to classify an eye with a pseudoglaucomatous but normal large cup in a large disc as normal (90,91). In eyes with advanced optic nerve atrophy, other examination techniques such as perimetry may be more helpful for the follow-up of the optic nerve damage.

Evaluation of the RNFL is also very useful in eyes with a nonglaucomatous optic nerve damage. The combination of a decreased visibility of the RNFL, a reduced caliber of the retinal arterioles and an increased pallor of the optic disc with an unremarkable size and shape of the optic disc, neuroretinal rim and parapapillary atrophy characterizes the nonglaucomatous optic nerve atrophy and distinguishes it from the glaucomatous type of optic nerve damage.

V) Early diagnosis of glaucomatous optic nerve damage and differentiation glaucomatous versus nonglaucomatous optic nerve damage

For the early detection of glaucomatous optic nerve damage in ocular hypertensive eyes prior to the development of perimetric defects, the most important parapapillary variables are diffusely or segmentally decreased visibility of the retinal nerve fiber layer, and occurrence of localized retinal nerve fiber layer defects and disc hemorrhages. With parapapillary atrophy usually not occurring in eyes with nonglaucomatous optic nerve damage, it is helpful for the differentation of glaucomatous versus nonglaucomatous optic neuropathy. Glaucomatous and nonglaucomatous optic neuropathy have in common a decreased diameter of the retinal arterioles including the occurrence of focal arteriole narrowing, and a reduced visibility of the retinal nerve fiber layer.

Methods of Literature Search

Used database was MedLine. Searchwords were optic disc, neuroretinal rim, optic cup, peripapillary scleral ring, parapapillary atrophy, and optic disc morphometry. Years covered were 1997 to 1970. Additional sources were other articles cited in the reference list of other articles. Criteria for inclusion or exclusion of articles from this review were originality, importance for the ophthalmoscopic evaluation of the optic nerve head without using sophisticated examination techniques, and new findings in the anatomy and pathomorphology of the optic disc with clinical and/or pathogenetic implications. Description of new examination techniques was not sufficient reason for the article to be considered for this review.

Questions-and-Answers

1) Is focal narrowing of retinal arterioles pathognomonic for focal normal-pressure glaucoma?

No, focal arteriole narrowing can also be found in other types of the glaucomas and in eyes with non-glaucomatous optic nerve atrophy.

2) Optic disc hemorrhage are associated with which other variables?

They are often associated with notches of the neuroretinal rim, localized retinal nerve fiber layer defects, and circumscribed deep scotomata in the visual field.

3) Does parapapillary atrophy have a psychophysical correlate?

Yes. Alpha zone represents a relative scotoma, and beta zone is the equivalent of an absolute scotoma.

4) Are localized defects of the retinal nerve fiber layer pathognomonic of glaucoma?

No. Localized retinal nerve fiber layer defects are almost never observed in normal eyes. They can occur, however, in many diseases affecting the optic nerve, such as nonarteritic anterior ischemic optic neuropathy and optic disc drusen.

5) Is assessment of parapapillary atrophy in the front line of the morphologic diagnosis of the glaucomas?

No. Parapapillary atrophy is an optic disc variable of second order to detect glaucomatous optic nerve damage. It is helpful for the differentiation of the various types of the chronic open-angle glaucomas.

6) Is parapapillary atrophy enlarged in eyes with non-glaucomatous optic neuropathy?

No. Consequently, parapapillary atrophy is helpful for the differentiation of glaucomatous versus non-glaucomatous optic neuropathy.

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Supported by Deutsche Forschungsgemeinschaft (SFB 539).
Praca wpłynęła 23.02.2004 r. (451).

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Publication: **Survey of ophthalmology, 43 (4): 293-320, Jost: "Ophthalmoscopic evaluation of the Parapapillary Region of the Optic Nerve Head".**