Controversies in the association of parapapillary atrophy with glaucoma

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Abstract:
Parapapillary atrophy is a condition which is seen in around 70% of normal individuals. Classically divided into zone alpha and beta, recently, it has been further categorized into zone gamma and delta. Some of these zones of parapapillary atrophy are more prevalent and larger in size in glaucoma patients. Studies have also found the rate of progression of glaucomatous change to be faster in patients with this anomaly. This condition is of clinical significance in glaucoma suspects, as it could be another pointer indicating potential risk of converting to glaucoma. On the contrary, there are other studies which question the relevance of these clinical features in glaucoma patients. In the light of these conflicting reports, it becomes an interesting exercise to explore this controversial area further. This review attempts to determine the role of parapapillary atrophy and its relevance with glaucoma. With this purpose, an online search for this term was conducted on search engines such as PubMed, Google Scholar, and others.

Keywords:
Glaucoma, optic disc, peripapillary atrophy

Introduction
The area surrounding the optic nerve head (ONH) usually appears uniform in pigmentation with a distinct differentiation between the retina and optic nerve.[1] The vascular supply of this region, which comprises of the distal part of the optic nerve and peripapillary retina, is through the circle of Zinn–Haller. In addition, the prelaminar and laminar regions of the nerve receive their main blood supply through the peripapillary choroid through branches of short posterior ciliary arteries.[2] Due to heredity, aging or disease there can be decreased coverage of the Bruch’s membrane by the choriocapillaris. This results in progressive retinal pigmentary epithelium (RPE) degeneration and atrophy. In such situations, the ONH often appears surrounded by different zones of atrophic-like changes occurring in the retina and choroid. These zones may vary in width, circumference, or pigmentation. Since the atrophy usually is adjacent to but does not surround the optic nerve completely, the term “parapapillary” (beside the optic nerve) is preferred to “peripapillary atrophy” (surrounding the optic nerve). However, these terms are often used interchangeably in literature.

Parapapillary atrophy (PPA) is defined as the thinning, misalignment, irregularity, and degeneration of the RPE, choriocapillaris, choroid, and sclera just adjacent to the outer border of the optic disc.[3] It can occur as a congenital anomaly, in which the neurosensory retina is found to terminate short of the optic disc or acquired in association with a number of ocular diseases.[1,4]

The first mention of parapapillary atrophic changes in glaucoma is ascribed to Elschnig who termed them “halo glaucomatosus.”[5] Primrose noted these changes appear in more than half of glaucomatous eyes, as well as “many fellow eyes as yet free...
from cupping.”[6] Anderson mentioned “that the conformation of peripapillary tissues. Help determine… which portion of the optic disc and visual field (VF) will be most affected.”[7] Wilensky and Kolker graded these changes in nonglaucomatous and glaucomatous eyes and noted this condition was more common in bilateral rather than unilateral glaucoma.[8]

However, the aforementioned reports were not clear in their description of PPA and consequently no relationship with glaucoma could be derived. According to some authors, it remains debatable whether PPA is an epiphenomenon or causally related to glaucomatous optic neuropathy (GON).[9] It is also not clear whether PPA is present before the onset of glaucoma and predisposes the eye to glaucomatous optic nerve damage, or whether it develops later, in association with glaucoma and progresses along with GON.[10] Due to the conflicting reports regarding PPA, it remains to be seen how these findings can be appropriately used in clinical practice.

Zones of Parapapillary Atrophy

The normal anatomic architecture of the peripapillary region is characterized by the retinal cell layers organized in a parallel fashion, ending at the edge of the ONH, with the topmost retinal nerve fiber layer (RNFL) increasing in thickness before diving into the disc.[11] PPA is a form of outer retinal atrophy that abuts the optic disc and was conventionally divided into two zones, namely “alpha” and “beta,” based on their location and appearance.[12] However, recently, Jonas has described two other zones, which he termed “zone gamma” and “zone delta.” Zone alpha is located circumferentially away from the nerve. In this zone, there is irregular arrangement and partial atrophy of RPE cells, resulting in both hypo- and hyper-pigmentation.[13-14] Zone beta is located closest to the ONH. There is marked atrophy of RPE, choriocapillaris and most of the photoreceptors in this area. There is also thinning of the chorioretinal tissue so that the sclera and large choroidal vessels become visible.[15-17] The region between the outer margin of the optic nerve (covered by pia mater) and the end of Bruch’s membrane (if the end of Bruch’s membrane did not overhang into the region of the ONH) is the “gamma zone,” as described by Jonas. The central part of the gamma zone, in which blood vessels of at least 50 µm diameter were not detected and which had a minimal length of 300 µm was termed “delta zone.” This zone was associated with axial length (P = 0.001) and scleral flange length (P < 0.001) but not with glaucoma (P = 0.73). Delta zone was seen only in eyes with axial length >27 mm (myopic eyes) and eyes with a scleral flange of >80 mm. Gamma zone was not significantly associated with age or gender. In glaucomatous and nonglaucomatous groups, the size of gamma zone did not vary significantly.

However, the size of gamma zone significantly increased with axial length in a nonlinear manner.[18]

Myopic thinning of the sclera in the parapapillary region could be a risk factor which significantly contributes to the development of glaucoma in highly myopic eyes.[19] In a study conducted at the Tokyo High Myopia Clinic, it was found that the prevalence of GON increased from 12.2% in eyes with an axial length of <26.5 mm to 28.5% in eyes >26.5 mm, 32.6% in eyes >28 mm, 36% in eyes ≥29 mm and the prevalence of GON increased to 42.1% in eyes with axial length of >30 mm. Higher GON prevalence was associated with larger zone delta diameter, longer axial length, and older age. The authors concluded that if a highly myopic patient is found to have a large zone delta and/or large optic disc, the risk for this patient to have glaucoma may be higher compared to a highly myopic patient without zone delta and/or with a normal-sized optic disc.[20]

Vianna et al., in their study of zones-beta and -gamma in myopic eyes with and without glaucoma, found the prevalence of beta-PPA area to be larger in glaucoma patients in comparison to controls (0.66–1.53 mm² vs. 0.50–1.38 mm², respectively). Conversely, gamma PPA was smaller in glaucoma patients when compared to controls (0.14–0.50 mm² vs. 0.17–0.74 mm²). However, the distribution of beta- and gamma-PPA in the myopic glaucomatous versus myopic nonglaucomatous eyes overlapped extensively, such that any practical utility for discrimination between the two groups became insignificant. This was also reflected in the low areas under the receiver operating characteristic curve and sensitivity values between beta- and gamma-PPA.[21]

A biochemical basis for the development of PPA and its association with glaucoma has been suggested. Sullivan-Mee et al., in their study, found an increase in the magnitude of beta PPA with age. According to them, there is excessive leakage of catecholamines from the juxtapapillary choroidal vessels which may result in the development and progressive enlargement of beta PPA with aging. The released catecholamine is probably responsible for the severe vasoconstriction of the regional peripapillary vasculature leading to the appearance of PPA.[22] It has also been suggested that the complete loss of RPE cells in the beta zone and partial survival of retinal photoreceptors in this area suggests that choriocapillaris may play a role in the development of PPA. The absence or even obliteration of the centripetal branches in the area of the PPA probably results in an environment conducive for vascular insufficiency to develop in that segment of the ONH.[2] The RPE forms the outer blood-retinal barrier and its absence in the area of PPA exposes the inner retinal layers to vasoactive substances such as angiotensin. These biochemicals induce vasospasm and
ischemia in the ONH vessels. As the peripapillary region is a watershed zone for vascular supply, it is especially vulnerable for ischemic insults. This could contribute to ONH damage and glaucoma progression.\[^{10,23}\]

Not surprisingly, like in other anatomic changes such as myelinated nerve fibers at the optic disc which produce enlargement in the size of the blind spot, VF defects in eyes with PPA have been demonstrated. VF analysis of eyes with PPA have shown psychophysically beta zone corresponding to an absolute scotoma and alpha zone to a relative scotoma.\[^{24}\] Histologically, the relative scotoma produced by zone alpha has been explained by the presence of irregularities in RPE cells, whereas the absolute scotoma of zone beta is based on the loss of photoreceptors and RPE cells.\[^{10}\]

Based on the studies mentioned above, it is now obvious that there are at least four zones present in the area of PPA. These are called zone-alpha, zone-beta, zone-gamma, zone-delta. What is not clear is the association of PPA with age, myopia, or optic disc appearance.

**Studies in Favor of Association of PPA with Glaucoma**

According to one school of thought, structural damage in glaucoma precedes irreversible functional decay.\[^{25,26}\] Probably as many as 20% of the retinal ganglion cells (RGCs) are dysfunctional before VF defects start appearing. Thus, detection of structural changes is imperative for early diagnosis of glaucoma. Beta PPA can serve as a biomarker for juxtapapillary choroidal atrophy.\[^{25}\] Beta PPA has also been suggested as a risk factor for the development of GON.\[^{22,24}\] It is also regarded as an independent risk factor and an important morphologic indicator for the progression of glaucoma when an end point was defined as loss of neuroretinal rim (NRR).\[^{9,27}\]

Jonas *et al.* have performed a study to evaluate the frequency of PPA in nonglaucomatous optic nerve damage versus in normal eyes. According to the study, the results did not differ significantly in nonglaucomatous and normal eyes. However, in glaucomatous eyes, both zones alpha and beta were significantly larger and occurred more frequently.\[^{28}\]

Jonas has reported beta PPA to occur in 20% of normal individuals and in 2/3 of glaucoma patients.\[^{29}\] In a study performed by Coombs *et al.*, glaucoma patients had significantly more clock hours of beta PPA and the size of maximum beta PPA in glaucomatous eyes was found to be significantly larger in comparison to normal eyes (8.7 vs. 4.9 clock hours; \(P < 0.05\) and 387 vs. 280 \(\mu \text{V}; P < 0.05\)).\[^{30,31}\] Jonas *et al.* have also reported that PPA as a whole and both zones alpha and beta were significantly \((P < 0.00001)\) larger and zone beta was significantly \((P < 0.00001)\) more frequent in the glaucoma group than in normal individuals. The size and frequency of PPA were significantly correlated \((P < 0.0001)\) with the glaucoma stage.\[^{27}\] Uhm *et al.* have reported the area, width, and angular extent of zones alpha and beta were significantly increased with the advancement in the stage of glaucoma. There was also a significant increase in the frequency of zone beta detected.\[^{10}\]

PPA appears more common in patients with normal tension glaucoma (NTG) in comparison to normal or ocular hypertension (OHT) patients.\[^{28,29}\] In NTG, the PPA is usually located inferior to the optic disc.\[^{31}\] Buus and Anderson, as well as Geijssen and Greve have also reported a higher prevalence of PPA in patients with NTG.\[^{32,33}\] Park *et al.* have reported in patients with PPA and NTG the area and extent of zone beta increased significantly with increasing VF defects expressed in terms of mean deviation (MD), corrected pattern standard deviation (CPSD), central VF defects within 5° of fixation and superior hemifield defects. The angular extent of zone beta represented localized VF defects better than diffuse field defects and significantly correlated with ONH topography. The location of VF defects also correlated significantly with the location of PPA.\[^{34}\]

Not only are glaucomatous changes more frequently observed in eyes with PPA but also the velocity of progression in these eyes is also found to be higher than eyes without PPA. Seidenstecker *et al.* have analyzed beta PPA in patients with advanced glaucoma utilizing spectral domain optical coherence tomography (OCT), scanning laser ophthalmoscopy and fundus auto-fluorescence. The researchers reported more rapid VF progression in eyes with PPA than those without it.\[^{23}\] Similarly, Na mentioned that an increase in PPA area can be an indicator of glaucoma progression.\[^{26}\] Healey has pointed out that the occurrence of beta PPA is associated with increased prevalence and progression of primary open-angle glaucoma (POAG). The presence of beta PPA and its subsequent enlargement over time have been reported to precede and predict the onset of glaucoma in ocular hypertensive eyes.\[^{35}\] Uhm in their study found the area of zone alpha to enlarge with the increase in the stage of glaucoma. The enlargement was most marked in the nasal sector, where the increase in frequency from 9.3% in the normal group to 25.7% in the glaucoma group was statistically significant. Zone beta was also found to increase significantly in area, frequency, width, and angular extent with advancing glaucoma. The authors noted areas of zone alpha and beta to increase significantly with decreasing rim area, rim/disc area ratio, MD, increasing vertical cup-to-disc...
Lee et al. have reported eyes with beta PPA (46 of 144) to have a significantly faster rate of RNFL thinning than eyes without (7 of 58; \( P < 0.001 \)). Faster rate of RNFL thinning was associated with risk factors such as beta zone PPA and percentage increase in PDR (beta zone PPA area-to-disc area ratio). The study showed that simply the presence of beta PPA, rather than baseline area was a stronger predictor of future VF progression.\(^{37}\) Yamada et al. have demonstrated the importance of microstructure of PPA in glaucoma progression. They reported that beta PPA in the presence of Bruch’s membrane is associated with faster VF progression and faster MD slope. Conversely, eyes with the absence of Bruch’s membrane had a slower MD slope.\(^{38}\)

Tezel et al. in their study of PPA in patients with OHT reported that PPA, higher PPA area-disc area, zone beta area-disc area, and PPA length-disc circumference ratios at the baseline examination were associated with conversion to glaucoma. Intraocular pressure (IOP) (relative risk 1.19), NRR area (NRA)-disc area ratio (relative risk 0.72), and zone beta area-disc area ratio (relative risk 1.32) were found to be associated with the development of optic disc damage, VF damage, or both.\(^{39}\) Tezel et al. also reported in a study that PPA was already present in 48 (49%) of 98 eyes diagnosed with OHT which converted to glaucoma.\(^{40}\) The same group also reported that the extent of progressive changes of PPA detected during the OHT period correlated with the extent of changes in the VF parameters, including CPSD and MD measured after the development of glaucomatous changes. The VF abnormalities occurred in the corresponding quadrants of the progressive PPA.\(^{41}\)

Dai et al. have performed their study using enhanced depth imaging OCT (EDI-OCT) to show that beta zone (mean area: 0.85 ± 0.60 mm\(^2\)) was associated with longer axial length (\( P < 0.001 \)) and the presence of glaucoma (\( P < 0.001 \)). Conversely, gamma zone was related to the absence of glaucoma in these patients.\(^{42}\) EDI has also been used to obtain choroidal thickness measurements directly adjacent to the ONH. 172 patients with POAG, OHT, and normal eyes were consecutively imaged. The results of this study showed that beta PPA was disproportionately present, being significantly more common and extensive in patients with POAG compared to the other two groups. The total juxtapapillary choroidal volume was significantly reduced (\( n = 80 \)) in eyes with POAG only when beta PPA was present (POAG vs. normal eyes = 0.957 vs. 1.196 \( \mu \)l, \( P = 0.02 \)). In eyes without beta PPA (\( n = 61 \)), no differences in the choroidal volume were detected between the diagnostic groups.\(^{43}\) Enface swept source three-dimensional OCT of the region has shown the average ± SD area of zone-beta and -gamma to be 0.64 ± 0.79 and 0.16 ± 0.30 mm\(^2\), respectively. In multivariate models, the gamma zone significantly correlated with axial length and degree of myopia (\( P = 0.001 \)) but not with glaucoma (\( P = 0.944 \)). However, beta zone significantly correlated with age (\( P = 0.0249 \)) and glaucoma (\( P = 0.014 \)).\(^{44}\) OCT studies by Kim et al. in glaucomatous myopic eyes have shown transverse separation of inner nuclear layer from outer nuclear layer in the parapapillary region. This separation was associated with worsening of glaucomatous parameters on VF analysis and RNFL measurements.\(^{45}\)

**Studies against Association of PPA with Glaucoma**

While there have been a number of reports indicating a significant association of PPA, especially beta PPA with glaucoma, there are others which refute such a correlation. See et al. have compared the rates of global and sectoral NRA and peripapillary atrophy area (PPAA) change in open-angle glaucoma (OAG) patients and normal controls and to determine the relationship between rates of NRA and PPAA change. The global rates of PPAA change were not significantly higher in OAG patients compared with controls (12.66 \( \times 10^{-3} \) mm\(^2\)/year and 9.43 \( \times 10^{-3} \) mm\(^2\)/year, respectively, \( P = 0.173 \)). There was a high correlation between ranked sectors of NRA change in patients and controls (\( P = 0.001 \)), indicating similar patterns of NRA decline in patients and controls; however, this was not the case for rates of PPAA change. These findings indicate an age-related regional susceptibility of the optic disc that may be accelerated in glaucoma. The poor relationship between rates of NRA and PPAA change suggests their temporal dynamics are uncoupled.\(^{45}\)

Ehrlich and Radcliffe in their study concluded that “while PPA variables on their own were significantly predictive of the odds of OAG, this association was greatly attenuated by adjustment for four variables that comprise part of a typical glaucoma evaluation: age, central corneal thickness, IOP, and cup:disc ratio. Furthermore, when values of these covariates were already known, modeling of the odds of OAG was not greatly improved by the consideration of PPA variables. This suggests that in clinically evaluating and diagnosing glaucoma there may be little incremental value to assessing PPA. Therefore, PPA may be more useful for evaluating progression than for detecting glaucoma.”\(^{12}\)

Savatovsky et al. reported zone beta to increase in size (\( P < 0.0010 \)) in eyes with incident POAG as well as...
matched controls. The increase in size did not change between over a mean follow-up period of 12.3 years. The results did not show a difference in size of the beta zone at baseline between eyes that went on to develop glaucoma and those that did not. Moreover, the beta zone enlarged equally in case and control eyes during follow-up. This shows a poor correlation between glaucoma and enlargement of PPA.\[46\]

Airaksinen et al. found only a weak correlation between the increase in areas of PPA and decrease in NRA among glaucomatous, OHT, and normal eyes. They concluded that the value of PPA in monitoring for progression of glaucoma is of little clinical significance.\[47\]

Jonas and Naumann have reported the frequency difference between glaucomatous and control groups for beta PPA to have a sensitivity of 53% and specificity of 90%. These values were too low and the correlation between decreased NRA and increase in the extent of zone beta cannot be used as a sole marker for glaucoma and thus to serve as a useful clinical parameter.\[48\] Tuulonen et al. also reported beta zone as the most reproducible parameter for measurement of PPA in glaucoma. However, they are of the opinion that this parameter is of limited usefulness in the management of glaucoma.\[49\] Uhm is of the opinion that the interpretation of the significance of PPA in the diagnosis and follow-up of glaucoma is not uniform. Furthermore, the interpretations of the results, rather than the results themselves, differ among clinicians leading to a decreased significance of this factor in the analysis of glaucoma.\[50\]

Nevarez et al. have compared peripapillary scleral and choroidal crescents between the two eyes in patients with unilateral glaucoma. They found that in most cases, the three tissue layers (RPE, choroid, and sclera) encircling the ONH in glaucomatous as well as nonglaucomatous eyes superimposed exactly on each other without any difference between the two groups. They opined that the PPA and scleral rim were more conspicuous in glaucomatous eyes due to thinning of RPE and not due to anatomic variations in the area.\[51\]

These studies show a disassociation between PPA and glaucomatous changes. The prevalence, conversion to glaucoma in suspects, enlargement of PPA with increase in IOP, have all been refuted in a number of observations and studies.

Differential Diagnosis of PPA

The clinical description of PPA should be distinguished from the physiological grey crescent that surrounds the optic nerve. The grey crescent represents a localized deposition of pigmentation demarcating the edge of the optic disc. In the Reykjavik Eye Study, the prevalence of grey crescent was determined to be 22%. No difference in prevalence rates were found between glaucomatous and nonglaucomatous eyes.\[52\] Other crescents that can be noted around the optic nerve include the myopic crescent which is a white sharply demarcated crescent to the temporal side of the optic disc, usually seen bilaterally and generally associated with axial myopia. This type of crescent does not show pigment mottling that is typically associated with PPA.\[1\]

Apart from physiological gray crescents, tilted or malinseted nerves could also prompt a diagnosis of PPA. Malinsertion may add to the glaucomatous appearance of the nerve. A number of ocular diseases have also been associated with PPA. These include conditions such as: Stargardt’s disease, helicoid PPA (Sveinsson chorioretinal atrophy), Vogt-Koyanagi-Harada disease, idiopathic multifocal choroiditis, multiple evanescent white dot syndrome, serpiginous choroiditis, toxoplasmosis, histoplasmosis, X-linked retinitis pigmentosa, sympathetic ophthalmia, angioid streaks, and autosomal dominant optic atrophy gene 1 (OPA1).\[1\]

Conclusion

PPA can occur in both normal and glaucomatous eyes, either congenitally or as an acquired condition. It is divided into four zones as follows: alpha, beta, gamma, and delta. Zone beta is more frequent and extensive in glaucomatous eyes. There appears to be a strong heritable component in the occurrence of zone beta. Zone delta is associated with glaucoma in myopic eyes. Functional deficits in glaucoma appear late and the appearance of PPA can be a subtle sign of structural damage. The velocity of progression of glaucoma is faster in eyes with PPA compared to those without. PPA is reportedly more significantly associated with OHT and NTG. However, some authors are of the opinion that this parameter is of limited usefulness denoting dissociation between PPA and glaucomatous changes. Therefore, PPA is a controversial factor and it is imperative to further analyze it in order to conclusively ascertain the role, if any, played by this clinical feature in the diagnosis and management of glaucoma.

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Conflicts of interest
The authors declare that there are no conflicts of interests of this paper.

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