Accurate Clinical Examination in Glaucoma is Key: Disc Features

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Intraocular pressure (IOP) is a crucial component in the diagnosis of Glaucoma, but as our understanding of Glaucoma has grown it has become evident that IOP is just one of the components in the diagnostic puzzle and great caution has to be exercised so that due focus is given to the other elements required to make a comprehensive diagnosis. Several population-based studies done in different parts of the world suggest that one-third or more of patients diagnosed with glaucoma in the community will present without elevated IOP levels[1,2,3]. In fact, in an epidemiological study published by Iwase et al in Tajimi, Japan the authors noted that IOP was 21 mmHg or less in 92 percent of patients identified with open angle glaucoma[3].

In a population-based cross-sectional study published by Wong et al titled "Detection of undiagnosed glaucoma by eye health professionals" the authors concluded that raised IOP should not be relied upon as the only triggering factor for glaucoma evaluation[4].

Apart from intraocular pressure, gonioscopy plays a very crucial role in the evaluation of a glaucoma patient. It has a role in the diagnosis and classification of a patient and also sheds some light into the prognostic aspect depending upon the gonioscopic findings.

Besides the above two crucial tests the optic nerve head (ONH) evaluation is perhaps the most important clinical test in the evaluation of a glaucoma patient. The ONH is composed of neural tissue, glial and collagenous supportive tissue and blood vessels. Glaucoma as it is understood today is an optic neuropathy characterized by progressive injury to retinal ganglion cells and their axons leading to changes in the intrapapillary and parapapillary regions of the optic disc (OD) and the surrounding retinal nerve fiber layer. Despite technological advances, clinical identification of optic nerve head and retinal nerve fiber layer changes remains one of the main tools in the diagnosis of glaucoma.

Careful examination of the disc parameters including disc shape, size, neuroretinal rim width, size of the optic cup in relation to the area of the disc, the cup -disc ratio , configuration and depth of the optic cup, presence and location of splinter hemorrhages, occurrence, size, configuration, and location of peripapillary chorioretinal atrophy, and changes in the retinal nerve fiber layer (RNFL) are important to differentiate between glaucomatous and nonglaucomatous optic neuropathy.

The evaluation of the optic disc (OD) is helpful in detecting glaucomatous ONH damage. Even cases of early rim thinning or notching can be picked up with the help of careful ONH evaluation. Once a case has been detected, periodical evaluation of the OD can be helpful to note any form of progressive damage. The careful evaluation of a glaucomatous disc may also help to differentiate certain types of glaucomas and it may also give us an idea about the prognosis of a particular patient.

NORMAL ANATOMY OF THE OPTIC NERVE

Ganglion cell axons make up the vast majority of the neuroretinal rim tissue of the optic disc. One to 1.5 million axons leave via the optic nerve head through the scleral canal, while the remainder of the neuroretinal rim is composed of capillaries and astrocytes[5,6].

There are four distinct layers of the optic nerve head, including the surface, prelaminar, laminar, and retrolaminar layers[6]. The surface layer is the anterior limit of the optic nerve and is the point of contact with the vitreous. Its peripheral edge is defined by the anterior limits of the scleral ring, and its posterior limit is where the axon bundles have completed a 90-degree turn from the plane of the retina and reached the level of the choroid[6]. The prelaminar optic nerve is an indistinct segment of axons surrounded by outer retina, choriocapillaris, and choroid. Within the laminar optic nerve, the ganglion cell axon bundles are wrapped in glial cells and confined in the rigid pores of the lamina cribrosa. The retrolaminar optic nerve thickness is doubled by the presence of myelinating oligodendrocytes[6].

The lamina cribrosa is a part of the scleral tissue through which ganglion cell axons exit as they leave the globe. It is composed of several sheets of connective tissue that is fenestrated to allow the passage of the nerve fiber bundles[7,8]. The superior and inferior poles have the largest pores, thus providing less structural support for the axon bundles leaving the nerve in these two areas[8,9]. This may explain why there is typically greater damage to the retinal ganglion cell axons in the superior and inferior poles of the optic nerve that we see clinically[7]. Furthermore, as ganglion cell axons are lost, the laminar dots become more exposed, which can also be visualized clinically. While laminar dots may certainly be present in healthy non-glaucomatous eyes, their presence should alert the clinician to look for other signs of glaucoma. The lamina is also susceptible to thinning and bowing backward due to effects of the intraocular pressure, which results in a clinically visible deeper cup in glaucomatous eyes[10].

The surface optic nerve receives its blood supply from small branches of the central retinal artery[6,7]. The pre-laminar optic nerve is supplied by the short posterior ciliary arteries (SPCA), and their integrity is responsible for the reddish hue that is observed clinically in healthy optic nerves[5,6,7]. The

laminar optic nerve is supplied by the Circle of Zinn-Haller, which is composed of anastomoses from adjacent SPCA's[6,7]. The retro-laminar optic nerve head is supplied by axial vasculature from the central retinal artery, the pial vascular plexus, and the SPCA's. Knowing the vasculature of the optic nerve is critical when evaluating the health and integrity of the neuroretinal rim as it is necessary to remember that glaucoma is cupping without pallor[10,11]. If pallor of the optic nerve is observed, it indicates insult to the prelaminar vasculature and should always alert the clinician that a different or an additional optic neuropathy is present.

Venous drainage of the optic nerve occurs via the central retinal vein[6,7]. In chronic glaucoma, optociliary shunt vessels may appear due to disturbed retinal circulation. These vessels are pre-existing venules that become more visible as they dilate to re-route blood around an area of obstruction[6]. They can be differentiated from neovascular vessels as optociliary shunt vessels will not leak on fluorescein angiography, while neovascular vessels will always leak fluorescein dye.

OD EVALUATION

The evaluation of the disc is to be done methodically with emphasis given to each and every point. The evaluation should be done under the following headings:

1. Disc size
2. Disc shape
3. The Neuroretinal Rim
4. Cup Disc ratio
5. Disc Haemorrhages
6. Retinal Nerve Fiber Layer changes
7. Peripapillary changes
8. Vascular changes

The early changes which can be detected on careful evaluation of the OD are focal or generalized loss of the neuroretinal rim (NRR) (cup enlargement), superficial splinter hemorrhages, nerve fibre layer (NFL) defects and thinning and translucency of the neuroretinal rim.

The glaucomatous changes of the ONH may present as one or a combination of the following - structural changes, contour changes and colour changes. The changes of the ONH in glaucoma can also be classified as either quantitative changes or qualitative changes. The quantitative changes include optic disc size, cup- disc ratio (vertical or horizontal) and the rim/disc ratio. The qualitative changes include changes in the contour of the NRR (thinning , notching etc.), OD haemorrhages, peripapillary changes, the baring of circumlinear vessels (BCLV) and RNFL defects.

For the proper evaluation of the OD a stereoscopic view with magnification for proper evaluation of the neuroretinal rim changes and an estimation of the optic nerve head size are extremely important. Stereoscopic view of the optic nerve head is best achieved with the help of a Volk or Ocular + 90D, + 78D,+60 D or a superfield NC lens. The +78D lens give a good magnified view of the disc and the peripapillary region and also provides a decent field of view and is preferred by a lot of glaucoma specialists but the 90D lens is also preferred by many as it has excellent optics and gives a great view of the disc and also gives a wider field of view. Some of the other methods which may be used to give a stereoscopic view of the disc are indirect ophthalmoscopy, Hruby lens and the central part of a goniolens. Apart from the OD assessment the RNFL assessment is also extremely important. A slit lamp with red free light along with any one of the above lenses may be used for this purpose.

It is better to evaluate the ONH through a dialated pupil. In a study done by Kirwan et al the authors found that there was better interobserver agreement in size determined through a dilated pupil[12]. Disc diameter can be measured by adjusting the slitlamp beam height to the edges of the disc while viewing the disc with a +60D lens. As a +60D lens has a correction factor of approximately x 1, it is the optimal lens for the measurement of optic disc size. A similar measurement of the vertical and horizontal disc diameter can be obtained with other lenses by multiplying the measured value with the appropriate magnification factor: Goldmann contact lens (1.26) and Volk superfield lens (1.5), Volk +90 D (1.33), Volk + 78D (1.2) and Volk + 60D (0.88)[13,14,15].

Optic Disc size

There is a lot of inter individual variability when it comes to the size of the optic disc. In the various studies done on Indian eyes the results reflect this variability in the disc size. In the Andhra Pradesh Eye Disease Study (APEDS)[16], the mean optic disc area was 3.37 mm^2. This was larger than that found in the other studies. The Vellore Eye Study (VES)[17] showed a mean area of 2.58 mm^2. The Central India Eye and Medical study (CIEMS)[18] reported a mean optic disk area measured 2.25 ± 0.51 mm^2. As is evident from the figures above, there was a difference in the mean OD size which can be explained by the fact that different techniques were used to determine the disc size in the above studies.

The average vertical height of the healthy optic nerve ranges from 1.8 to 2.0 millimeters[19,20]. A small disc is referred to as one where the vertical diameter is equal to or less than 1.5 millimeters; similarly a disc is referred to as a large disc if the vertical diameter is greater than 2.2 millimeters[20].

The size of the OD/optic cup can vary due to the following factors

a) Hereditary factors: Individuals may have similar disc size(small or large) as their parents and/or siblings.
b) Age: Some studies have shown that although the disc size approximately remains the same there is an increase in the size of cup and pallor with increase in age[11,13].
c) Race: Individuals of African descent have larger disc size and thus larger cup disc ratios compared to whites[1,2].
d) Refractive errors: Myopes are more prone to develop primary open angle glaucoma (POAG). The disc size is highly variable in myopes ranging from very small optic discs to very large ones with extensive zones of peripapillary atrophy[18]. Hypermetropic eyes on the other hand present with small discs and these eyes are a risk factor for development of primary angle closure glaucoma(PACG).

The boundaries of the optic disc conform to the edges of the scleral canal, which appears as a whitish circular band. In the other words, the size of the scleral canal determines the optic disc size. Eyes with small scleral canals have small optic discs (high hyperopia) and eyes with large scleral canals have large discs (high myopia). The borders of the optic disc are defined as the innermost border of reflective tissue that is internal to any pigmented tissue and within which only neuroretinal tissue is present. It can be difficult to determine the borders of the optic disc in individuals with high myopia and eyes with significant PPA[10,21].

The ONH diameter can be calculated using the formula:

ONH diameter (mm) = (X/H) x D x C

(X = height of beam (mm); H = height

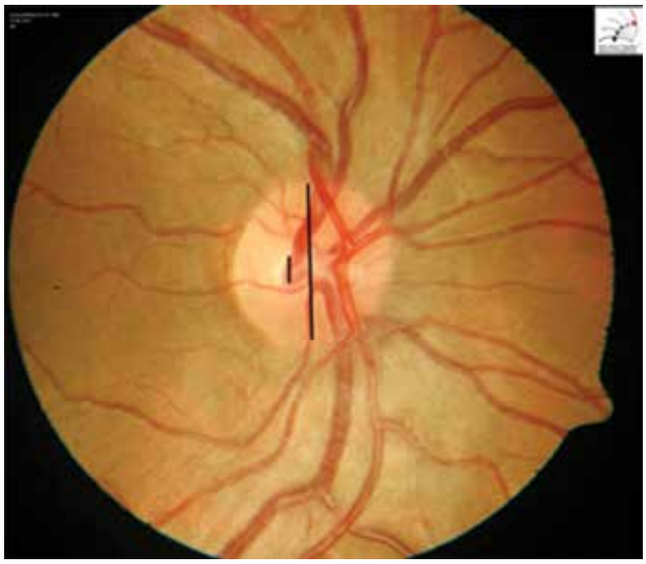

Figure 1a: *Normal small disc with a very small cup.*

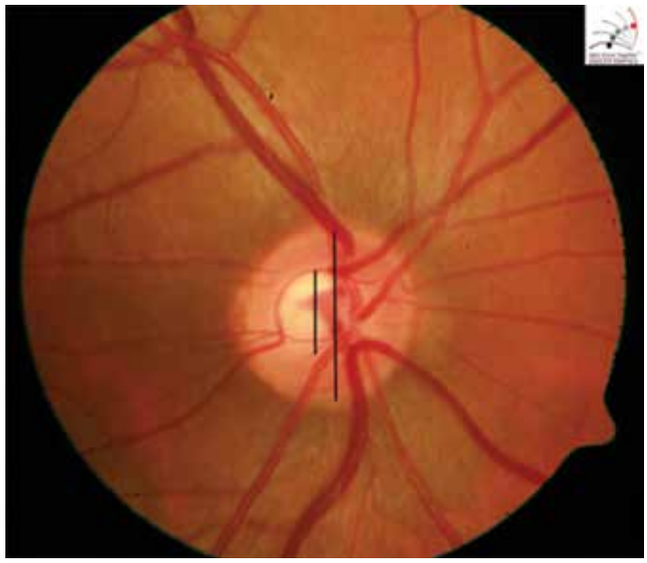

Figure 1b: *Normal small disc with a small cup.*

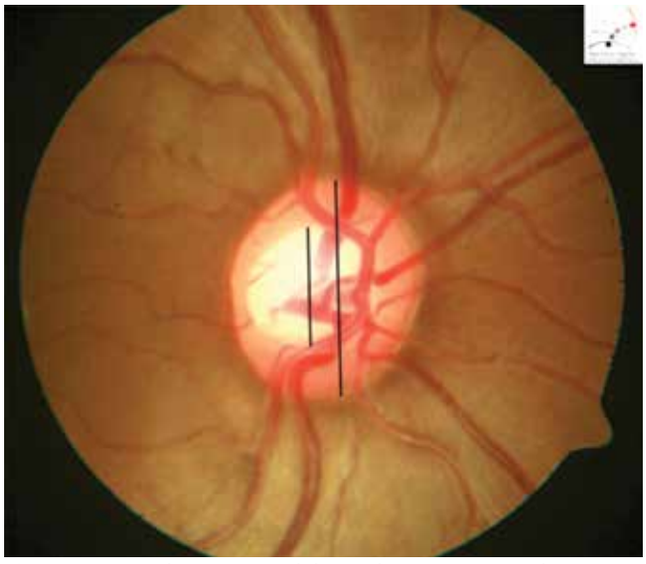

Figure 1c: *Normal average sized disc with an average sized cup.*

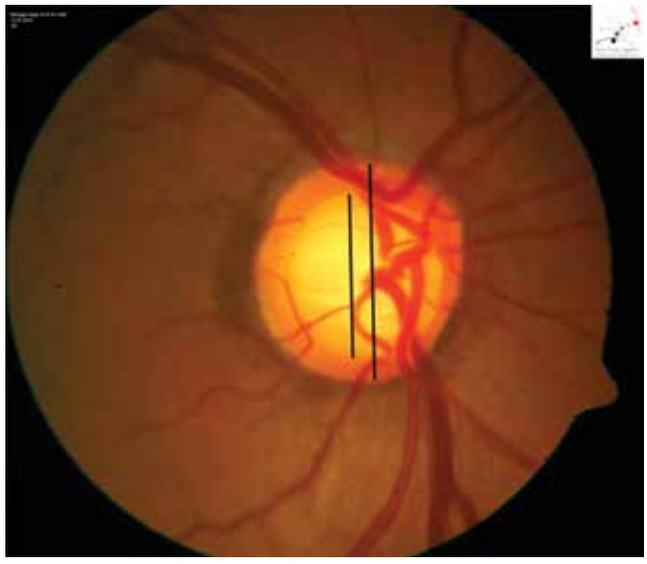

Figure 1d: *Normal large sized disc with a large cup.*

setting on the beam height indicator (mm); D = diameter of the optic disc measured by the beam height indicator (mm); C = correction factor)[19].

Additionally, the area of the ONH can be calculated using a modified formula: ONH area (mm): r/4 X horizontal disc diameter X vertical disc diameter (r = the correction factor based on used lens diopter)[19].

The distance between the optic disc and the fovea as disc diameters can be used for the evaluation of the optic disc size. This distance as measured from the temporal edge of the optic disc to the center of the fovea is approximately two to three disc diameters in eyes with normal size and axial length. A shorter distance indicates a larger disc, and a longer one signifies a smaller optic disc[21].

Clinical estimation of optic nerve head size is possible with a Welch Allyn Ophthalmoscope or with Volk 60D lens. The smallest white round spot of the Welch Allyn ophthalmoscope usually illuminates a cone angle of 5° and casts a light of 1.5 mm in diameter and an area of 1.77 mm^2 which is slightly smaller than the size of the average disc on the retina[22]. With this one can determine if the disc is small, average or large in size. This retinal spot size remains constant in phakic eyes with refractive errors between -5.00 D and + 4.00 D.

The location of the originating point of the light cone does not significantly affect the retinal spot size as long as it is ± 3mm from the anterior focal point of the patient's eye. Since 1.5 mm is the usual size of the optic nerve head, this can be used as a yard stick for measuring disc size. Simplistically, in eyes with large physiological cups due to large discs the area illuminated is less than the area occupied by the cup.

The thickness of the central retinal vein (CRV) can also be used to help estimate optic disc size. The average thickness or diameter of CRV is approximately 125 µm at the region where the CRV crosses the inferior NRR. If the optic disc has a width of about 12–14 CRV diameters, it can be considered that ONH is normal in size. A higher number of CRV diameters points out a larger ONH, whereas a smaller number of CRV diameters refers a smaller ONH[7,10].

At the onset it is very important to determine if the optic disc is of an average size, or it is smaller or larger than the average for the given population. The size of the disc is not a predictor of glaucoma by itself. A normal disc can be small, average or large in terms of size. However the size is relevant because it is the disc size which determines the cup disc

rato (CDR) (the vertical and horizontal cup/disc ratios), the neuroretinal rim thickness and the parameters like the cup/disc area ratio and the rim/disc area ratio. Thus a smaller disc is expected to have a smaller cup and a larger disc is expected to have a larger cup. This assessment becomes essential in order to avoid over-testing and over-diagnosis in large nerves due to the instantaneous reaction that any CDR greater than 0.4 is immediately suspicious for glaucoma. It is very important to examine a small disc very closely too as an early nothing or thinning may be missed due to the small size of the cup and the disc itself. Larger discs however may be more susceptible to glaucomatous damage. Jonas et al reported higher susceptibility of neuroretinal rim loss in area farthest from the exit of the central retinal vessel trunk, which is greater in a large disc[23] (Figures: 1a,1b,1c ,1d).

The disc size of the two eyes in the same individual are to be compared and any asymmetry is to be noted. If there is any asymmetry in the size of the disc between the two eyes of an individual then it is to be kept in mind that this may lead to an asymmetry in the other parameters like the thickness of the NRR and the CDR. However certain factors like a difference in the axial length between the two eyes or a difference in the refractive status of the eyes may lead to disc size asymmetry between the two eyes in the same individual.

OD shape

The shape of the optic disc is variable just like the size. However an optic disc is usually vertically oval with the vertical diameter being greater than the horizontal diameter. In the Vellore Eye Study (VES) done in a south Indian population the vertical diameter of the optic disc was found to be 6% longer than the horizontal one[17]. Infact in the VES, in 81.4% of the studied population the vertical diameter was longer than the horizontal one. In a study done by Jonas et al the authors reported the vertical optic disc diameter to be about 6%–10% longer than the horizontal one in whites[21]. However in quite a few glaucomatous patients as well as normal individuals the disc may be horizontally oval or round. In 14.3% of the eyes studied in the VES, the horizontal disc diameter was longer than the vertical and in 4.2% the vertical and horizontal diameters were equal[17].

In a study done by Jonas et al to assess the correlation between optic disc shape, corneal astigmatism and amblyopia the authors concluded that an abnormal optic disc shape is significantly correlated with corneal astigmatism[24]. The authors stated that if an abnormal optic disc shape is found on routine ophthalmoscopy, specially in children, refractometry should be performed to rule out corneal astigmatism and to prevent amblyopia. The study also suggested that the direction of the longest optic disc diameter could indicate the axis of corneal astigmatism[24].

The ISNT Rule

By analyzing the neuroretinal rim in disc photographs of normal subjects, Jonas and associates found that the rim width typically exhibited a specific pattern[25]. They used rim area measurements of normal eyes, calculated from projected optic disc photographs. Later, retinal nerve fiber layer thickness was measured at the optic disc borders histomorphometrically and was found to follow the same pattern[26]. They found that in normal individuals the neuroretinal rim was thickest inferiorly and thinnest temporally (Thickness of the NRR: Inferior >Superior > Nasal>Temporal). This specific neuroretinal rim pattern was later coined by Elliot Werner as the ''ISNT rule''[27].

Because neuroretinal rim loss is a hallmark feature of glaucoma, patients who deviate from the ISNT rule may need to be watched more closely for glaucoma. The RNFL, on the other hand, has also been shown in histologic studies in normal, nonglaucomatous eyes to exhibit a similar pattern of the inferior quadrant being the thickest, followed by the superior, nasal, and then temporal quadrant[26]. Because RNFL thinning, particularly in the superior and inferior quadrants, is also a characteristic structural change in glaucoma, deviation from the ISNT rule for RNFL thickness may also be an early indicator of glaucomatous structural change[28]. In a patient of glaucoma there occurs vertical thinning, with atrophy along the inferior and superior rims. Thus, when the optic nerve doesn't follow the ISNT rule, they may be undergoing glaucomatous damage.

In contrast, RNFL ISNT rule studies based on OCT findings are in uniform agreement, stating that the ISNT rule and its variants were not helpful in the diagnosis of glaucoma[29,30]. Some have hypothesized that the ISNT rule is not easily generalizable to the individual, because the initial studies were derived from mean values[25,26]. Therefore, some of the limitations of the ISNT rule may stem from the fact that it is unclear what percentage of individual normal eyes follow the ISNT rule. Other limitations may arise from the fact that perhaps other rules may be more common in the normal population.

In earlier studies based on disc photographs 52-79% of the individuals studied were found to obey the ISNT rule[31,32]. However later studies have revealed that the percentage of individuals obeying the ISNT rule was much lower. In a study done by Poon et al the percentage of individuals obeying the ISNT rule was found to be 37%[33]. One of the main reasons that the ISNT rule was not valid for a huge percentage of the population was because of considerable variation in the rim order of the nasal quadrant. In a large percentage of the population the rim width was wider nasally than inferiorly. In a normal population of 92 Chinese subjects, Wang and associates found that 9 out of 92 subjects (10%) had a nasal rim that was the widest compared to all the other rims, while Harizman and associates also reported in their study that 5 out of 66 normal subjects (7.6%) had a nasal rim that was thicker than the inferior rim[31,34].

A possible reason for the high variability in nasal rim order and hence the low fulfilment rate of the ISNT rule is that, although the central retinal vessel is not considered as part of the neuroretinal rim during disc assessments, there often is partial obscuration of the nasal rim by these large retinal vessels, which would make evaluation of the nasal rim width ranking more variable. Therefore, it is important to take into consideration the large variation that exists for the nasal rim order in the normal population when using the ISNT rule for determining whether a patient's optic nerve has glaucoma or not[31,33].

Thus our current understanding from various studies point to the fact that the ISNT rule may not be valid for a large percentage of the population and probably it is time to shift to a different rule or form of assessment. Some authors have stated that if the nasal quadrant is left out from the evaluation and the IST rule is followed or if both the nasal and the temporal quadrants are left out and the IS rule is followed then it would be more appropriate as more than 70% of

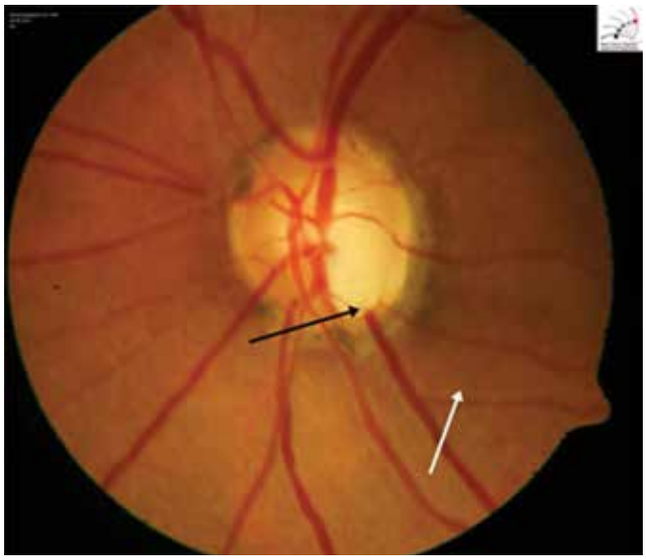

Figure 2a: *Figure showing a disc with a deep inferior notch (black arrow) with an NFLD (white arrow).*

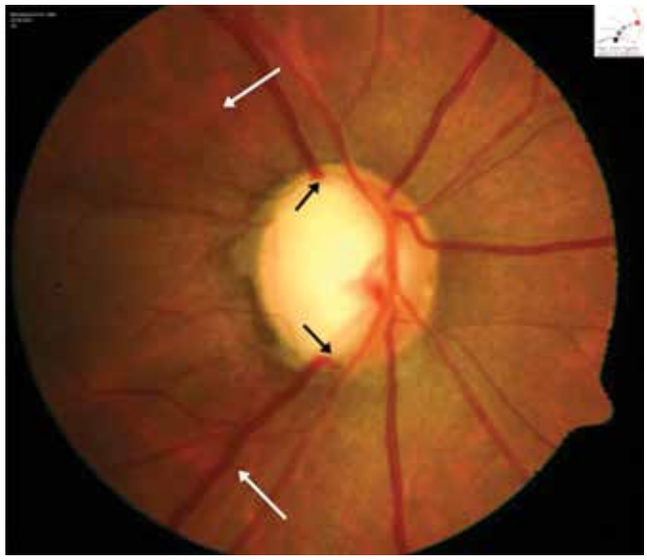

Figure 2b: *Figure showing a disc with bipolar notching with focal rim loss (black arrows) with NFLD (white arrows).*

normal eyes would follow the IST and the IS rule for both disc photographs and OCT RNFL thickness measurements[33].

The clinical significance of the shape also lies in the fact that it influences the distance between NRR at the disk border and the central retinal vessel trunk exit. It is important to document the shape of the disc if it is unusual as it is very difficult to assess the rim area in these discs. For these discs with unusual shapes it is very important to document them for future comparisons. Also the ISNT rule is not applicable in discs which are not vertically oval. It is very difficult to assess myopic discs because these discs may have may have a variation in disc shape, and they usually have a zone of peripapillary atrophy. Due to these it is very difficult to determine the margin of the disc. Careful attention should be paid while evaluating these discs as the unusual shape and the presence of a PPA may cause difficulty in the determination of the disc margin and thus the assessment of the disc as a whole.

The Neuroretinal Rim

The neuroretinal rim (NRR) is the intrapapillary equivalent of the optic nerve fibers. The NRR will reflect selective loss of the ganglion cell axons and is the primary location of pathologic changes seen in glaucoma[35]. Because the cup-disc ration ratio is often a poor indicator of early glaucoma, close attention should be paid to the width and health of the neuroretinal rim instead[36]. In fact the assessment of the NRR is probably the most important parameter in the optic disc evaluation of a patient. When assessing the neuroretinal rim tissue, its size, shape, and color must be taken into consideration[37]. As stated above the ISNT rule (or the IST or IS rule) should be kept in mind while evaluating the NRR as it correlates with the distribution of the nerve fiber bundles as they leave the scleral canal but there may be a huge percentage of anatomical variations which should also be kept in mind[33].

The mean NRR area was reported to be 1.97 ± 0.5 mm^2 by Jonas et al[21]. This study was done in a Caucasian subject population. Indian population based studies have however reported a larger disc area. The mean disc area was reported to be 2.8 ± 0.53 mm^2 in the participants of the Andhra Pradesh Eye Disease Study (APEDS) and 2.29 ± 0.39 mm^2 by the Chennai Glaucoma Study (CGS) group[38,39]. The Vellore Eye Study (VES) however reported a smaller rim area of 1.6 ± 0.37 mm^2, in a south Indian population[21].

The neuroretinal rim should be observed carefully to evaluate any thinning and notching of the rim tissue, which would indicate glaucomatous damage. The notch is defined as localized defect in the NRR on the cup side of the rim. The notch is usually a small defect and the circumferential extent of the notch occupies less than or equal to 60°, i.e. 2 contiguous clock hours (Figure 2a). If the area of damage is larger then it would be referred to as a thinning of the neuroretinal rim and as the thinning progresses it would be referred to as a focal rim loss (Figure 2b). A notch is usually associated with a nerve fiber layer defect. The cardinal feature of glaucomatous optic neuropathy is the loss of NRR from the inner edge of the rim. This loss can occur in all sections of the disc with regional preference depending on the stage of glaucoma[40]. The typical sequence of neuroretinal rim loss in glaucoma is loss of rim tissue at the infero-temporal and supero-temporal poles, followed by the temporal rim, and lastly the nasal rim[35].

The authors of the Chennai Glaucoma Study (CGS) stated a correlation between the rim area and the disc area. The study showed that the rim area had a strong positive correlation with the disc area. For every 1 mm^2 increase in disc area, the rim area increased by 0.5 mm^2 [39]. It has been observed that the larger is the optic nerve the larger is the NRR area and as the glaucoma progresses there is an increase in the cup area and thus correspondingly the NRR area decreases.

The changes which may be noted in the neuroretinal rim are:

Focal atrophy

a) This is due to focal loss of neural rim tissue in glaucoma that primarily occurs in the infero-temporal or supero-temporal region.
b) It begins as a small, discrete defect, referred as polar notching \ focal notching \ pit like change.
c) This defect enlarges and deepens, developing a sharp nasal margin referred to as sharpened polar nasal edge
d) As progression of glaucomatous atrophy continues, the local thinning reaches the neural rim of the disc margins, thus forming the sharpened

Figure 3: *Figure showing a deep inferior notch in the left eye of a patient. The "laminar dot" sign can be clearly seen in the picture (black arrow).*

Figure 4: *Figure showing the optic discs of the right and left eye of a subject. The right eye has an average sized disc with an average sized cup while the left eye shows a larger disc and hence a larger cup leading to a cup-disc ratio asymmetry between the two eyes.*

rim.

e) If the retinal vessels cross this sharpened rim, it bends sharply at the edge of the disc, termed as the bayoneting of the vessels at the disc edge.

Concentric Atrophy

This occurs less commonly, but when it occurs, it usually begins temporally and then progresses circumferentially towards the poles which is referred to as temporal unfolding.

Deepening of the cup

This is seen as glaucoma progresses and the following may be noted:

a) Over pass cupping – in which, vessels initially bridge the deepened cup and later collapse into it.

b) Laminar dot sign – which is owing to the exposure of underlying lamina cribrosa, by the deepened cup (Figure 3).

Pallor/ cup discrepancy

In early stages of glaucomatous optic atrophy, enlargement of the cup progresses ahead of the area of pallor. It may occur with diffuse/focal enlargement of the cup.

a) *Saucerisation:* It is the extension of diffuse shallow cupping towards the disc margin with retention of central pale cup and is an early sign of glaucoma.

b) *Focal saucerisation:* More localized shallow cup usually in the inferotemporal quadrant.

c) *Tinted hollow:* It is the retention of normal neural rim color in the area of focal saucerisation.

d) *Shadow sign:* Replacement of the tinted hollow by a greyish hue on progression of glaucomatous cup.

Advanced glaucomatous cupping

Occurs in the advanced stages of glaucoma leading to total loss of neural rim and bending of all vessels at the margin of the disc. It is sometimes also referred to as bean pot cupping.

Cup - Disc Ratio

Ganglion cells are scattered all over the retina, and their fibers converge on the optic nerve head. The layer of fibers gets quite thick just at the nerve head and then the fibers pile up and dive into the opening. The optic nerve head or the disc, is mostly filled with fibers. There is left over space in the middle of the nerve head called the cup, and the fibers are grouped around the cup in the rim. The size of the cup is determined by the size of the optic disc. There is a positive correlation between the size of the disc and the size of the cup. A large disc will have a large cup and a small disc will usually have a small cup or practically no cup at all.

The cup-disc ratio (CDR) is the value obtained by dividing the cup diameter by the disc diameter and is usually expressed in decimal values. Usually when the CDR is mentioned it is the vertical cup to disc ratio of that individual. The reason why the vertical CDR is important is that early neuroretinal rim loss occurs preferentially at the upper and lower poles of the disc. The direction or point of deviation of small blood vessels on the surface of the ONH is used to determine the size of the optic cup (contour method) but not the area of pallor in the center of the optic disc (colour contrast method[21].

A CDR asymmetry between two eyes with equal overall optic disc size may be suggestive of loss of neuroretinal rim tissue and should thus raise the suspicion of glaucoma (Figure 4). There is some inconsistency in the literature as to what cut offs to use for a small or large disc, but in general a disc can be considered small if ≤ 1.5 mm and large if ≥ 2.2 mm.[21] Mean area of the optic cup in Indian eyes as found in the Vellore Eye Study (VES) is 0.98 mm^2. The same study revealed that the area of the optic cup is independent of age, refractive error, and sex, axial length of the globe and depth of the anterior chamber[17]. The mean horizontal C:D diameter ratio is around 0.66 and the mean vertical C:D diameter ratio is 0.56. Thus the diagnosis of glaucoma should be considered if the vertical CDR is ≥0.7 (seen only in 10% of normal individuals) or the CDR asymmetry between the two eyes is more than 0.2 (seen only in 1% of normal individuals).

The evaluation of CDR in normal subjects, subjects with physiological cup, and glaucoma patients is difficult. The application of the evaluation rules of CDR is not appropriate for subjects with an optic nerve or disc anomaly (tilted, hypoplasic, dysplasic optic discs). It is to be kept in mind that the size of the optic cup always seems smaller in monoscopic examination than in stereoscopic examination[21].

Disc Haemorrhages

Jannik P. Bjerrum was the first to publish a report of optic disc hemorrhage (DH) in 1889. He observed that a number of glaucoma patients whose eyes had elevated intraocular pressure (IOP) also had bleeding within the optic nerve head. However it was Dr. Stephen Drance and Dr. Ian Begg who suggested that DH was an important marker of glaucomatous damage in 1970. Thus the disc haemorrhages are sometimes referred to Drance haemorrhages. DH has been reported to be a risk factor for the onset and progression of glaucomatous optic neuropathy[41,42,43].

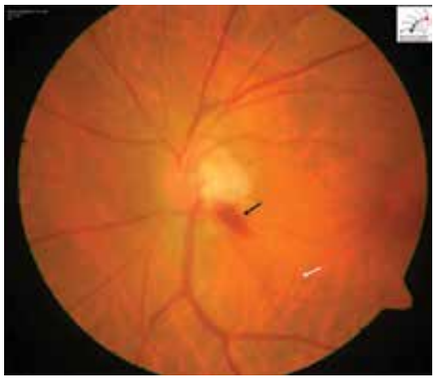

Figure 5a: *Figure showing a disc with a large disc haemorrhage in the infero - temporal aspect of the disc (black arrow). It is a typical flame shaped haemorrhage with feathered edges. An NFLD is also evident (white arrow).*

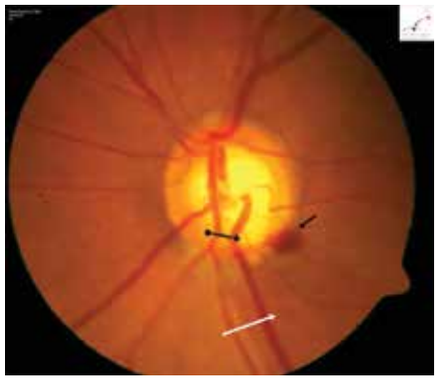

Figure 5b: *Figure showing a disc with a large disc haemorrhage in the infero - temporal aspect of the disc (black arrow) There is a deep inferior notch(black arrow with bulb) and a broad based nerve fiber layer defect(white arrow).*

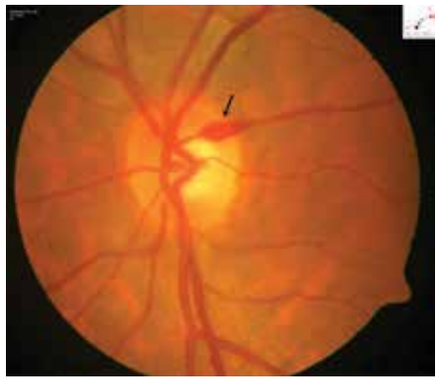

Figure 5c: *Figure showing why disc haemorrhages can be easily missed.Here the disc haemorrhage(black arrow) is present over the underlying vessel and can be easily overlooked.*

However there is some controversy as to whether disc haemorrhages are pathognomonic of glaucoma as it is still a poorly understood phenomenon and its exact etiology is still unknown. Most researchers would agree, however, that a DH in a glaucomatous eye is a negative prognostic factor and, in most cases, indicates advancing damage to the retinal nerve fiber layer (RNFL)[41-44].

A disc hemorrhage is a splinter or flame-shaped haemorrhage (and is sometimes referred to as such), with feathered edges, oriented radially and perpendicular to the disc margin (Figure 5a). The most common location of DH is at the temporal aspect of the disc. Disc hemorrhages tend to be small (but at times may be large) and extend from within the RNFL of the optic disc into the peripapillary region. is often associated with notching and structural change in the optic disc rim, focal defects of the RNFL, progressive defects of the visual field (VF), and beta zone peripapillary atrophy (β PPA) (Figure 5b). Sometimes the disc haemorrhages may be very small or subtle and may be mistaken for a blood vessel or just overlooked if the clinician is not specifically looking for it (Figure 5c). DHs are rarely found in normal eyes, but they are detected in approximately 4 to 7 percent of eyes with glaucoma[45]. It is located within one disc diameter from the optic disk border and one should rule out presence of optic disc edema, papillitis, diabetic retinopathy, central or branch retinal vein occlusion, or any other retinal disease associated with hemorrhage.

The prevalence of disc hemorrhage ranges from 0.6 to 1.4% in the normal population and from 1.9 to 16.9% in subjects with glaucoma[46]. The cumulative incidence of optic disc hemorrhages is reported as 0.5% per year in ocular hypertensives and 2.5% per year in eyes after the development of primary open angle glaucoma (POAG)[41]. In the Indian scenario the APEDS reported an incidence of 9.8% in the POAG group[38]. In the PACG group the reported incidence is around 5.4 % over a follow up of 9 years[47].

The ocular hypertension treatment study (OHTS) showed that optic disc hemorrhages are a predictive factor for the development of POAG in patients with OHT[48]. In the Collaborative Normal Tension Glaucoma Study (CNTGS) and the Early Manifest Glaucoma Trial (EMGT), glaucomatous eyes with disc hemorrhages experienced significantly more visual field progression during follow-up than eyes without hemorrhages[49,50]. Thus in glaucoma patients, the presence of a disc haemorrhage is indicative of disease progression and is also an indicator that more aggressive therapy should be instituted.

Retinal Nerve Fiber Layer

Discussion of the optic nerve in relation to glaucoma would be incomplete without mentioning the RNFL, which is composed of retinal ganglion cell axons which are covered by astrocytes and bundled by Muller cell processes[10]. The RNFL is seen as bright fine striations fanning off the optic disc. In normal eyes, the retinal nerve fiber layer (RNFL) is usually best visible in the inferior temporal part of the fundus, followed by the superior temporal region, the nasal superior region and the nasal inferior region[17]. The RNFL is least visible in the nasal sector. Histologically also it has been seen that the RNFL thickness is more superiorly and inferiorly compared to the nasal and temporal regions. This distribution correlates with the configuration of the neuroretinal rim, the diameter of the retinal arterioles, the location of the foveola, and the lamina cribrosa morphology. With increasing age, the RNFL visibility decreases diffusely without preferring special fundus regions and without the development of localized defects[9]. With all optic nerve diseases, the visibility of the RNFL is decreased in addition to the age-related loss, in a diffuse and/or a localized manner. Defects within the RNFL appear as darker zones in areas of expected brightness. This will cause retinal vessels to appear redder and darker, and will allow small vessels to become more visible.

To examine the RNFL it is always advisable to dilate the patient. A stereoscopic view of the fundus is achieved with a slitlamp and a non-contact lens. A lens which gives lesser magnification but a wider field of view is preferred. First the fundus is examined under normal conditions and any subtle changes in the RNFL are to be looked for (Figure 6a). Then red free illumination is used to visualize the fundus again (Figure 6b). The normal pattern of the fiber bundles can be detected as bright striations in the retinal reflex. If during fundus evaluation the RNFL is markedly better detectable in one sector then the examiner should carefully observe the other sectors to compare the visibility of the RNFL in those sectors. The retinal vessels are normally embedded in the retinal nerve fibers and thus do not look very bright and have a matt or dull look. When there is diffuse RNFL loss the vessels are covered only by the thin inner limiting membrane so are better visible and look brighter[9] (Figure 6c).

The RNFL defects which are initially

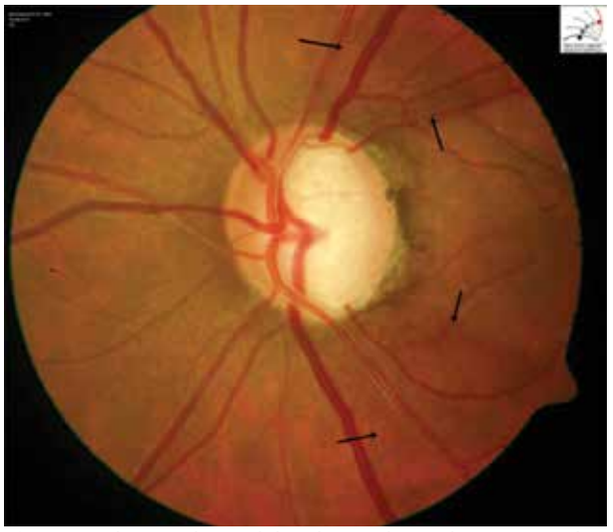

Figure 6a: *Shows a disc with bipolar notching. The corresponding large broad based NFL defects (black arrows) in the super-temporal and infero-temporal aspects can be seen.*

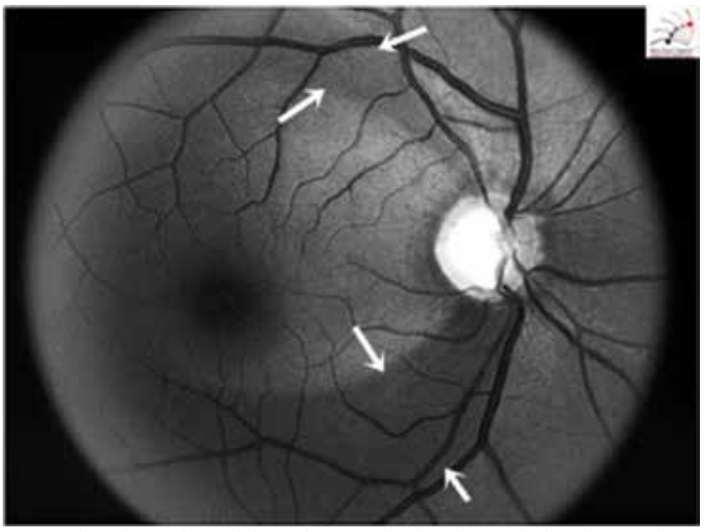

Figure 6b: *Shows the red free photograph of a disc with bipolar notching. The corresponding large broad based NFL defect can be seen in the infero-temporal aspect and a smaller typical RNFL defect can be visualized in the supero-temporal aspect (white arrows).*

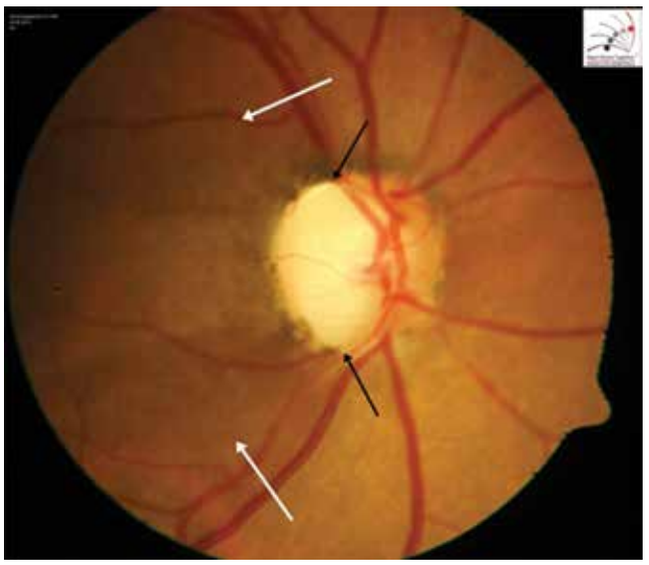

Figure 6c: *Shows a disc with bipolar rim loss (black arrows). The corresponding large broad based NFL defects in the super-temporal and infero-temporal aspects can be seen (white arrows). Note the better visibility of the retinal vessels which are sharper and clearly defined.*

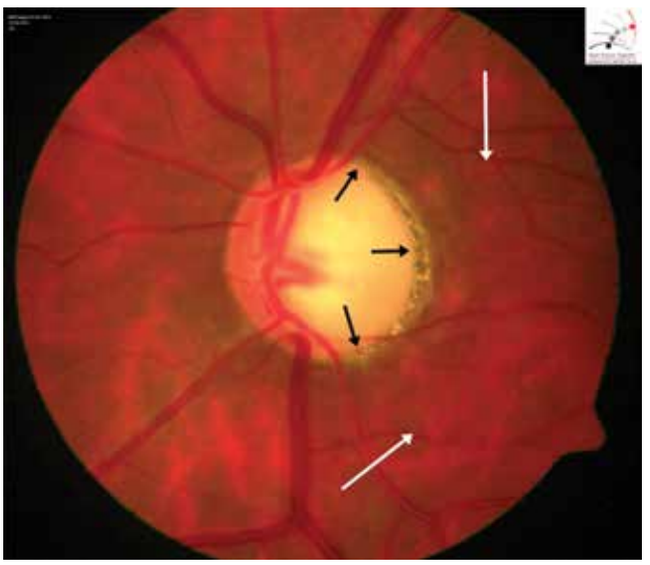

Figure 6d: *Shows a disc with bipolar rim loss (black arrows). The RNFL loss here is diffuse and is difficult to visualize (white arrows) but increased sharpness and prominence of peripapillary vessels, and clearer visualization of the underlying choroid can be appreciated.*

seen in early glaucoma are the localized defects. The localized defects are wedge-shaped and not spindle-like defects, running toward or touching the optic disc border. A localized defect is defined as a wedge-shaped defect running toward or touching the optic disc border occupying not more than 60° of the circumference of the disc[51]. This has to be differentiated from a pseudodefect which may be a spindle shaped area of RNFL defect away from the disc and not approaching or touching the disc. The number of localized defects are more in early and moderate glaucoma. As the glaucoma progresses the RNFL loss becomes more diffuse and it becomes more difficult to visualize it[51]. Diffuse RNFL defects are the most difficult to detect. The clinician should compare the striations between the superior and inferior bundles of the same eye, as well as the striations between the right and left eyes and look for any loss of brightness, increased sharpness and prominence of peripapillary vessels, and clearer visualization of the underlying choroid (Figure 6d).

While examining a patient of glaucoma along with the disc evaluation very careful assessment of the peripapillary region and the nerve fiber layer is extremely important. There may be subtle changes visible clinically in the RNFL during a fundus evaluation even before the disc changes like a notch or a thinning become evident. Quigley et al described these RNFL changes to be sensitive indicators of early optic nerve damage seen earlier than optic disc changes[52]. On the other hand if a notch or a thinning is evident, then close examination of the RNFL surrounding the disc may reveal the characteristic RNFL changes and that will help to establish the diagnosis of glaucoma. RNFL defects occur in about 20% of all glaucomatous eyes but they are not pathognomonic of glaucoma since they can also be found in other ocular diseases, such as optic disc drusen, toxoplasmotic retinochoroidal scars, longstanding papilloedema or

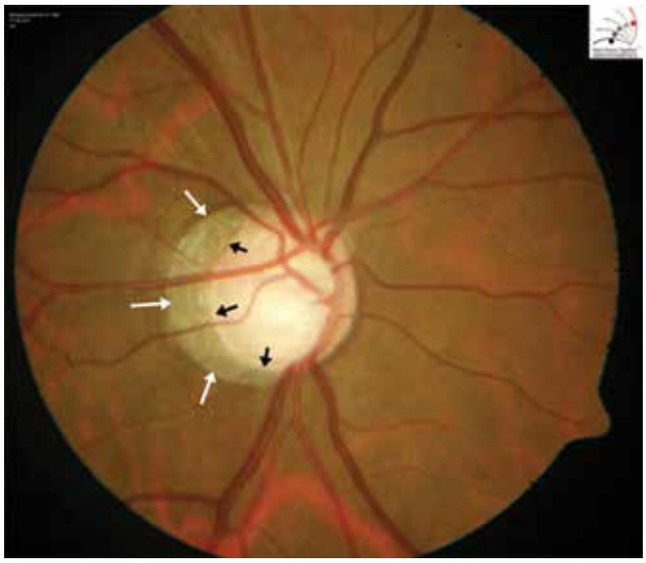

Figure 7a: *Shows peripapillary atrophy (white arrows) with corresponding thinning of the neuroretinal rim (black arrows).*

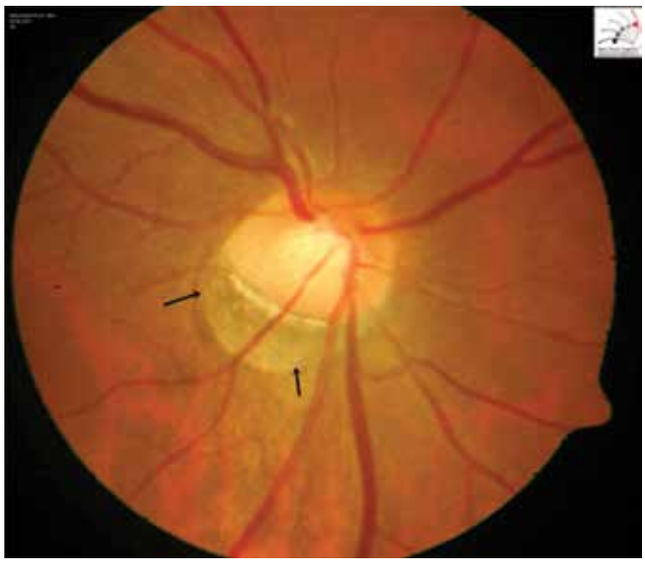

Figure 7c: *Shows peripapillary atrophy (black arrows) associated with a "tilted optic disc".*

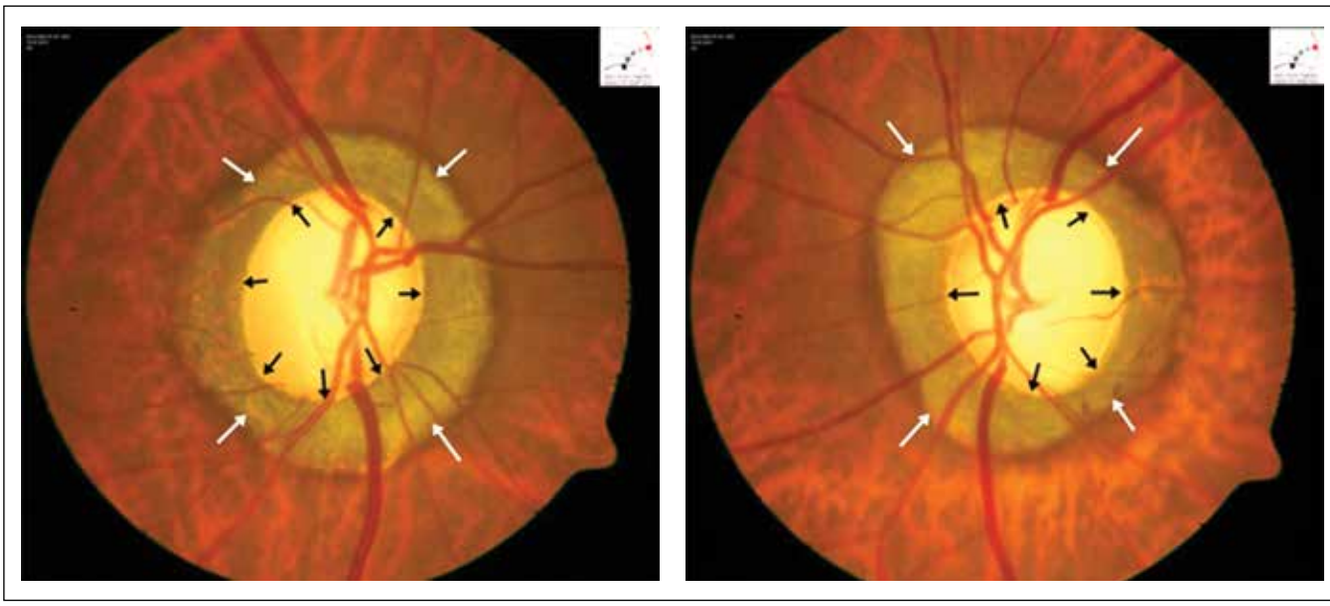

Figure 7b: *Shows peripapillary atrophy (white arrows) with corresponding advanced thinning of the neuroretinal rim in both eyes of the same individual (black arrows).*

optic neuritis[51]. Since they are not present in normal eyes, they almost always signify an abnormality but it may not specifically be glaucoma. RNFL evaluation is especially helpful for early glaucoma diagnosis and in glaucoma eyes with small optic discs. RNFL defects are found more commonly in normal tension glaucoma followed by primary open angle glaucoma and then secondary open angle glaucomas. In advanced optic nerve atrophy, other examination techniques, such as perimetry, may be more helpful for following optic nerve damage.

Considering its great importance in the assessment of optic nerve anomalies and diseases and taking into account the feasibility of its ophthalmoscopic evaluation using green light, the retinal nerve fiber layer should be examined during any routine ophthalmoscopy.

Peripapillary Changes

Irregular pigmentation around the optic nerve is a non-specific finding that can be seen in many healthy eyes. However the presence of peripapillary atrophy should raise a suspicion for glaucoma, specially if additional risk factors are identified in the patient. The atrophy in the peripapillary region differs from normal peripapillary variants in the respect that the atrophy is typically irregular and patchy, whereas crescents are typically very uniform in colour and shape. The clinical appearance of PPA is a moth-eaten pattern of the RPE temporal to the optic nerve head; if truly associated with glaucoma, there is typically neuro-retinal rim thinning adjacent to the area of atrophy[37,53,54,55].

Ophthalmoscopically and histopathologically, parapapillary atrophy may be divided into a peripheral alpha zone and a central beta zone. The alpha zone is characterized by an irregular hypopigmentation and hyperpigmentation of the retinal pigment epithelium and slight thinning of the chorioretinal tissue layer. Nasally it is always separated from the neuro-retinal rim by either zone beta if present, or by the scleral ring if zone beta is absent, and temporally it is bounded by normal retina. There is thinning of the chorioretinal layer above this region. Zone alpha is a non-specific finding that is present in both normal and glaucomatous eyes[10,11,54,55].

The beta zone is characterized by a complete loss of the retinal pigment epithelium, marked atrophy of the retinal photoreceptor layer and the

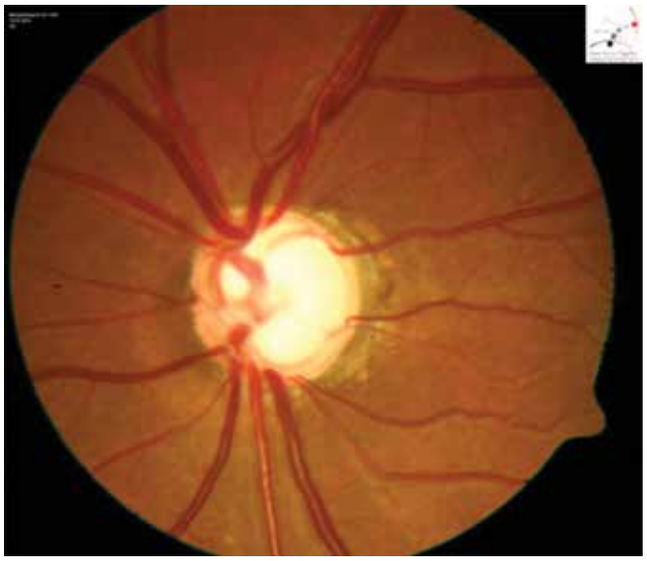

Figure 8: *Figure showing the bayoneting of the blood vessels in a case of advanced glaucomatous cupping.*

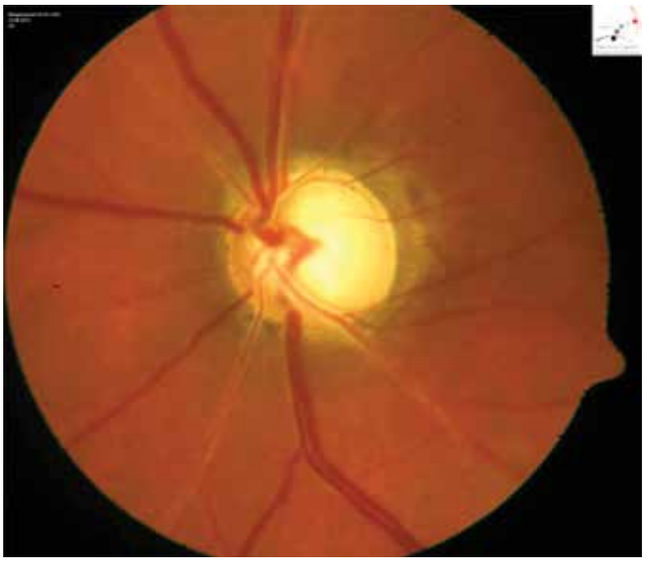

Figure 9: *Figure showing the nasalization of the blood vessels in a case of advanced glaucomatous cupping.*

choriocapillaris, clear visibility of the large choroidal vessels and sclera, and round boundaries to the adjacent alpha zone on its peripheral side and to the peripapillary scleral ring on its central side. It is thought to be caused by poor perfusion of the peripapillary area, and though it may also be present in normal eyes, it is much more common in glaucomatous eyes[11,54,55].

The importance of the alpha zone and the beta zone is to help the clinician differentiate between glaucomatous and non-glaucomatous optic nerves, particularly when additional anatomic changes suggest the presence of early glaucoma damage (Figure 7a). Additionally, because progression of beta zone is associated with progression of glaucoma, it may be a subtle yet important indication to alert the clinician that more aggressive glaucoma therapy may be necessary in a patient already diagnosed with the disease[11,54,55]. Some authors state that progressive changes in the beta zone are IOP independent. This is supported by the fact that pronounced alterations in the peripapillary region are seen in normal tension glaucoma[56] (Figure 7b).

Clinicians must differentiate the alpha and beta zones from the myopic scleral crescent in eyes with high myopia and from the inferior scleral crescent in eyes with "tilted optic discs"[57] (Figure 7c). In the region of the myopic crescent, only the inner limiting membrane and the underlying retinal nerve fiber layer or its remnants cover the sclera. In contrast, in the glaucomatous beta zone, Bruch's membrane and the choroid are interposed between the remnants of the retina and the sclera[58,59,60]. The alpha and beta zones may also be present in an eye with high myopia. Both zones are significantly larger in highly myopic eyes with glaucoma than in glaucomatous eyes that are not severely nearsighted[61].

Vascular Changes

Apart from optic disc haemorrhages which has been mentioned previously in this article several vascular changes can be observed in glaucomatous eyes. These include baring of circumlinear vessels, bayoneting, nasalization of vessels, optic nerve shunts, and retinal artery attenuation.

Baring of circumlinear vessels occurs in areas where neuroretinal rim tissue has been lost, thus the structural support for the vessels leaving the optic nerve is no longer present and is clinically seen as vessels "hanging" across the optic nerve cup without adjacent support of neuroretinal rim[20]. It is a subtle change to look for carefully in order to aid in the diagnosis of glaucoma.

Bayoneting of vessels is seen in areas of significant neuroretinal rim tissue loss, whereby visualization of the course of a particular blood vessel is temporarily lost as it makes its way along the excavated nerve borders and re-emerges at the edge of the rim from the deeply excavated cup[20] (Figure 8). It is typically seen in advanced cupping or in nerves with localized notching of the neuroretinal rim.

Nasalization of blood vessels occurs in very advanced glaucoma whereby the only structural support remains along the nasal rim due to severe loss of superior, inferior, and temporal rim tissue[20] (Figure 9). It is easily observable in advanced cupping and will not be present in early disease. Retinal artery attenuation can also occur in glaucomatous eyes, but is typically a subtler finding than the aforementioned vascular changes. It likely results due to decreased metabolic demand from an increasingly thinner rim tissue[10,11]. It is a very subtle but important change to look for in helping the clinician determine the level of suspicion for early glaucoma.

THE FIVE RULES OF ONH AND RNFL EVALUATION

Fingeret et al published an article in 2005 where they enumerated five rules to evaluate the optic disc and retinal nerve fiber layer for glaucoma[37]. This is a small but very helpful checklist to go through while examining a patient. The authors concluded that optic disc and RNFL assessment could be performed according to 5 rules that include the following:

a. Evaluation of optic disc size
b. Rim shape and area
c. Presence of RNFL loss
d. PPA, and
e. Retinal or optic disc hemorrhages.

The authors stated that by following these 5 rules, a thorough and systematic review of the optic disc and RNFL could be done and that would improve the ability to diagnose and manage glaucoma[37].

DIFFERENTIAL DIAGNOSIS OF GLAUCOMATOUS CUPPING

- OD Coloboma (Figure 10)
- Optic Disc pit
- Morning glory syndrome (Figure 11)

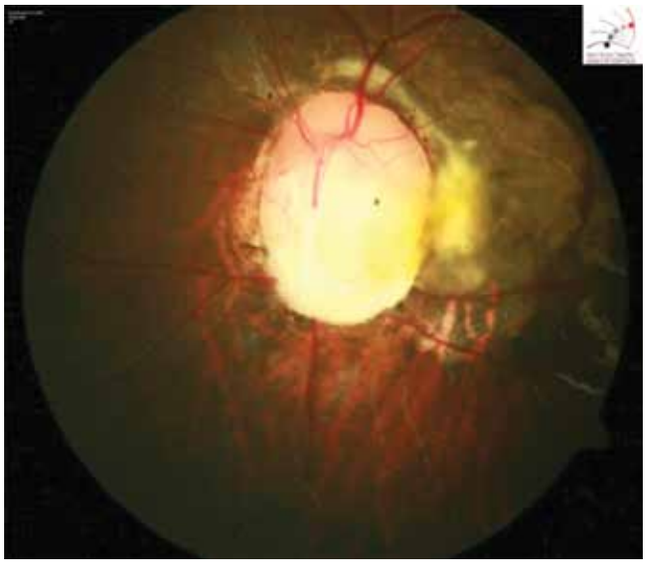

Figure 10: *Figure showing an optic disc coloboma.*

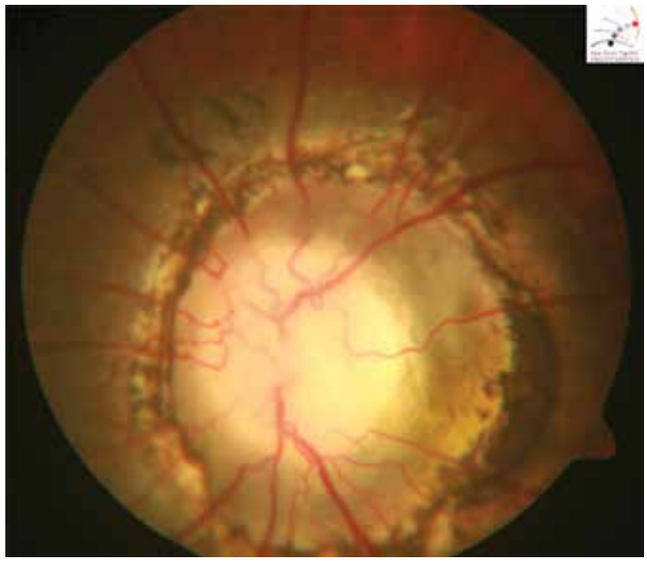

Figure 11: *Figure showing a Morning Glory disc.*

- AION (Anterior Ischaemic Optic Neuropathy)
- Sellar lesions
- Methyl alcohol poisoning
- Myopic disc
- Tilted disc

CHECKLIST FOR OPTIC NERVE EVALUATION

- *Disc Size:* Measure the vertical size of the OD at the slit lamp through dilated pupils.
- *CDR:* Determine the vertical CD ratio and consider it carefully in relation to the size of the disc.
- *NRR:* Evaluate the integrity of the NRR, and look specifically for early changes or alterations like thinning, notching or pallor.
- *Vascular changes:* Evaluate for the presence of any vascular changes: Disc hemorrhages, nasalization of vessels, baring of circumlinear vessels and optociliary shunt vessels.
- *RNFL:* Evaluate the integrity of the RNFL with a red-free filter.
- *PPA:* Evaluate for the presence and extent of peripapillary atrophy.

CONCLUSION

Evaluation of the optic nerve head is crucial for the early diagnosis and management of glaucoma. Clinicians must keep in mind that the cup-disc ratio is not the only factor to consider when evaluating the optic nerve, and due importance should be given to the neuroretinal rim and its surrounding peripapillary tissue and vasculature. Clinicians must also remember that glaucoma usually causes cupping without much pallor, therefore the presence of pallor of the neuroretinal rim must prompt the clinician to investigate for a different or additional optic neuropathy. Once the characteristic changes which suggest glaucoma - in terms of the NRR changes, the vascular changes, the peripapillary changes etc. have taken place it is fairly straightforward to make a diagnosis of glaucoma. The challenge lies in the early diagnosis of glaucoma. Very careful assessment of the optic disc, the vasculature and the peripapillary region to diagnose the subtle signs of glaucoma is pivotal for the early diagnosis prior to development of significant structural and functional damage. By following the steps outlined in this article one should be able to become proficient in this evaluation over time in order to prevent under-diagnosis, delayed diagnosis, as well as over-diagnosis of this disease.

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