Glaucoma in Myopia

19

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19.1 Introduction

Over the past few decades, the prevalence of myopia and possibly pathological myopia has been increasing rapidly worldwide, especially in East Asia [1–3]. Increasing prevalence of myopia has a huge public health impact because of the concomitant increase in potentially blinding diseases associated with myopia. This chapter focuses on glaucoma among the many myopia-associated pathological conditions.

Glaucoma is a progressive optic neuropathy characterized by a specific pattern of optic nerve head and visual field damage. Various imaging modalities are widely used to evaluate the optic disc for glaucoma diagnosis and monitoring. Myopia adds significant complexity to the diagnosis, monitoring, and treatment of glaucoma. These glaucoma diagnostic and therapeutic challenges in the myopic eye stem from similarities between the glaucomatous optic disc and the myopic optic disc and between glaucomatous visual field defects and those that can be associated with myopia. Results of these imaging tests should be interpreted carefully not only because the normative data of imaging devices do not represent myopic population but also because myopic eyes often cause imaging artifacts and reduced test reliability (increased false positives and false negatives). Diagnosis of glaucoma becomes more difficult when myopic optic nerve changes progress over time. Therapeutic challenges in glaucoma with myopia result mostly from thin sclera associated with axial elongation of the globe. Lastly, myopia increases the risk of open-angle glaucoma (OAG) independently of other risk factors including intraocular pressure (IOP) [4, 5], although the pathophysiologic mechanism underlying this association is unclear.

Understanding the structural characteristics of myopic optic discs and sclera and the effects of myopia on ocular imaging and visual field tests is crucial for accurate diagnosis of glaucoma and proper treatment.

19.2 Myopia as a Risk Factor for Open-Angle Glaucoma

Myopia is a risk factor for OAG, increasing the risk of developing the disease approximately by two- to threefold [4, 5]. In a meta-analysis of 11 population-based cross-sectional studies [4], the pooled odds ratio (OR) of the association between any myopia and OAG was 1.92 (95 % confidence interval [CI], 1.54–2.38). There was a moderate dose–response relationship between the degree of myopia and glaucoma with a pooled OR of 2.46 (95 % CI, 1.93–3.15) for high myopia and 1.77 (95 % CI, 1.41–2.23) for low myopia, with a cutoff value of approximately −3.00 diopters (D). However, the range of refractive error (severity of myopia) that is important for OAG is unclear. In the 11 studies analyzed in this meta-analysis, the cutoff point between emmetropia and (low) myopia varied between −0.01 and −1.5 D (−0.5 or −1 D in most studies).

The pathophysiologic mechanism underlying the association between myopia and OAG remains unclear, although several hypotheses have been made [6, 7]. IOP-induced stress and strain within the lamina cribrosa and peripapillary sclera may cause structural, cellular, and/or molecular changes in the connective tissue [8]. IOP-induced stress and strain may also impair blood flow in the

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laminar region, decreasing the delivery of oxygen and nutrients to the retinal ganglion cell axons [8]. Compared to non-myopic eyes, myopic eyes have greater peripapillary scleral tension making them more susceptible to glaucomatous optic neuropathy [9]. The lamina cribrosa is thinner in myopic eyes than in non-myopic eyes, contributing to a steeper translaminar pressure gradient [10, 11] which also increases the susceptibility to glaucomatous damage [12–14]. IOP was similar between myopic and non-myopic eyes in one population-based study [15], but other studies found significantly greater IOP in myopic eyes than in non-myopic eyes, making them more prone to glaucoma onset and progression [16, 17]. Additionally, ocular blood flow, which appears to play an important role in the pathophysiology of glaucoma, is decreased in myopia [18, 19], possibly leading to an increased vulnerability to the effects of IOP on the optic nerve head complex (optic nerve and peripapillary structures). Optic disc tilting is one of the features of myopic eyes [20–22]. A greater degree of disc tilting correlates with greater myopia and longer axial length [23]. The path of some retinal ganglion cell axons may be disturbed in tilted discs, interfering with axonal transport and contributing to the association between myopia and glaucoma [24].

Central corneal thickness (CCT) is a powerful predictor for the development of primary open-angle glaucoma [25] and a strong risk factor for advanced glaucomatous damage at the initial examination [26]. Axial elongation of the eyeball is a hallmark of myopia, but thinning of the outer ocular layer (cornea, sclera, and lamina cribrosa) occurs mainly in the posterior part of the eye [27, 28]. Previous studies demonstrated that CCT did not increase or decrease significantly with increasing axial length or myopic refractive error [29–32]. Similar studies on Korean and Indian populations reported a positive correlation between CCT and axial length, indicating a thicker cornea in more myopic subjects [33, 34]. These results suggest that corneal architecture and thickness may not contribute to the association between myopia and glaucoma.

19.3 Diagnosis and Monitoring of Glaucoma in Myopia: Optic Nerve Structure

For the diagnosis and monitoring of glaucoma, clinicians evaluate optic disc and peripapillary structures. Compared to non-myopic eyes, myopic eyes tend to have more frequent tilted discs [20–22, 35, 36], greater cup-to-disc ratio [7], larger disc area [35, 37, 38], and larger beta zone parapapillary atrophy (PPA) [21, 22, 37, 39, 40]. Because of these characteristics, accurate diagnosis and monitoring of glaucoma in myopic eyes is challenging.

When the optic disc is evaluated using ophthalmoscopy or stereo disc photography for glaucoma, the integrity of the neuroretinal rim is assessed among other parameters. Localized or diffuse neuroretinal rim narrowing is a characteristic feature of glaucoma, and progressive rim narrowing indicates disease progression. However, in myopic eyes, accurate evaluation of rim width is more difficult than in non-myopic eyes. Tilted discs in myopic eyes have a more gradually sloped rim surface in the area adjacent to the PPA (Fig. 19.1). Therefore it is more difficult to delineate the rim margin in stereo disc photographs. Additionally, larger optic discs and greater cup-to-disc ratio in myopic eyes can mimic glaucomatous optic neuropathy and result in an errant diagnosis of glaucoma and unnecessary treatment. Because evaluation of static rim structure is challenging, assessment of rim structure change over time to determine glaucoma progression is also problematic.

A retinal nerve fiber layer (RNFL) defect, in which the parapapillary RNFL is thinner than the adjacent areas, appears as a dark stripe or a wedge during clinical examination. RNFL defects are more easily identified in eyes with darker retinal pigment epithelium (RPE), for example, in Asian eyes than in Caucasian eyes. Myopic eyes have less pigmentation in the fundus, and therefore it is more difficult to detect RNFL defects in those eyes. Circumpapillary RNFL thickness measurement using optical coherence tomography (OCT) is commonly used to diagnose and monitor glaucoma. RNFL thickness profile and RNFL thickness sector maps (e.g., quadrant or clock-hour maps) are compared with those of normative database to detect significant RNFL thinning. Because RNFL measured by OCT is thinner in myopic eyes than in non-myopic eyes [41–45], myopic eyes are more likely to have false-positive RNFL thickness measurements, results that mimic glaucomatous optic neuropathy [46].

Correct OCT RNFL scan circle placement is important because the scan circle location affects the RNFL thickness profile and RNFL thickness measurements in sector maps. The RNFL thickness profile is more comparable to the normative database when the scan circle is placed based on the contour of the neural canal opening, rather than based on the optic disc [47]. In non-myopic eyes with a non-tilted disc, the optic disc forms almost concentric circles or ellipses with the neural canal opening (Bruch's membrane opening). Therefore, the RNFL scan circle can be placed concentrically on the optic disc in eyes with a non-tilted disc. However, in myopic eyes, the tilted disc forms eccentric circles or ellipses with the neural canal opening. Consequently, for example, in a myopic eye with a temporally tilted disc, the temporal RNFL thickness will be overestimated, and nasal RNFL thickness will be underestimated if the scan circle is centered on the optic disc.

The typical OCT RNFL thickness profile has two peaks, at the superotemporal and inferotemporal RNFL bundles.

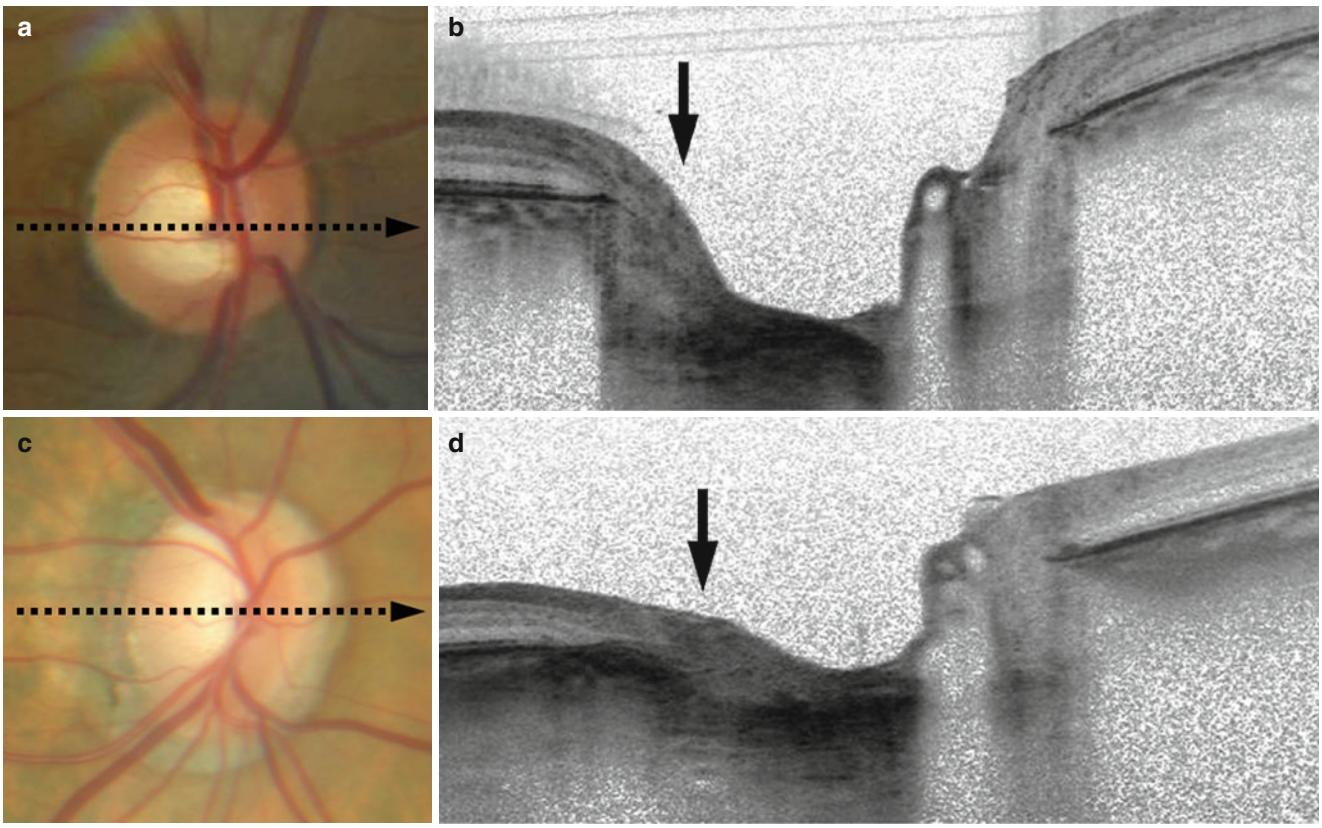

Fig. 19.1 Temporal neuroretinal rim surface (*black arrows*) is more gradually sloped in the myopic eye (**a**, **b**) than in the non-myopic eye (**c**, **d**). The *dotted lines* with *arrows* in (**a**) and (**c**) indicate the locations of the cross-sectional OCT scans in (**b**) and (**d**)

With increasing axial length, the angle bounded by the superotemporal and inferotemporal RNFL bundles decreases, which means these RNFL bundles become closer to the macula in myopic eyes than in non-myopic eyes [48–50]. Consequently, portions of the RNFL thickness profile may be statistically borderline (1–5 % of normative database) or abnormal (less than 1 % of normative database), and some circumpapillary sectors may also be coded similarly in myopic eyes without glaucoma (Fig. 19.2).

When part of the scan circle passes through the beta zone PPA area in myopic eyes, the quality of OCT RNFL image decreases locally. In this situation, the OCT RNFL segmentation algorithm often fails resulting in underestimation or overestimation of RNFL thickness and a false-positive or false-negative result (Fig. 19.3). An accurate RNFL thickness profile can be obtained after manual correction of the RNFL segmentation.

In myopic eyes, the raw RNFL scan has greater undulation than in non-myopic eyes. Therefore, myopic eyes are more likely have part of the RNFL scan located outside of the OCT scan range, which in turn also results in an erroneous RNFL thickness results (Fig. 19.4). Greater undulation of the raw RNFL scan also causes a focal area of poor quality, which also leads to erroneous RNFL thickness results.

PPA is a common anatomic feature of the optic nerve head. Based on clinical and histological characteristics, PPA is divided into alpha and beta zones. The alpha zone PPA is the outer area of the PPA distinguished by irregular hypo- and hyperpigmentation and thinning of the chorioretinal tissues, and the beta zone PPA is the whitish area between the alpha zone and the scleral ring characterized by atrophy of the RPE and choriocapillaris. Studies have revealed the presence of beta zone PPA to be associated with both the occurrence of glaucoma [51–54] and progression of functional damage in glaucomatous eyes [55–58]. The enlargement of beta zone PPA was also related to the disease progression [59, 60]. In myopic eyes, however, the current clinical definition of beta zone PPA often includes the area of externalized scleral canal wall associated with axial elongation of the globe [61]. The area of externalized scleral canal wall is not true atrophy because there is no RPE or choriocapillaris on the scleral canal wall embryologically. Therefore, evaluation of the presence, extent, size, and enlargement of beta zone PPA is often misleading in myopic eyes. Recently, the classic beta zone PPA has been further divided into a gamma zone and a (new) beta zone based on the presence or absence of Bruch's membrane (Fig. 19.5) [62, 63]. Gamma zone PPA was defined as the PPA area without Bruch's membrane or

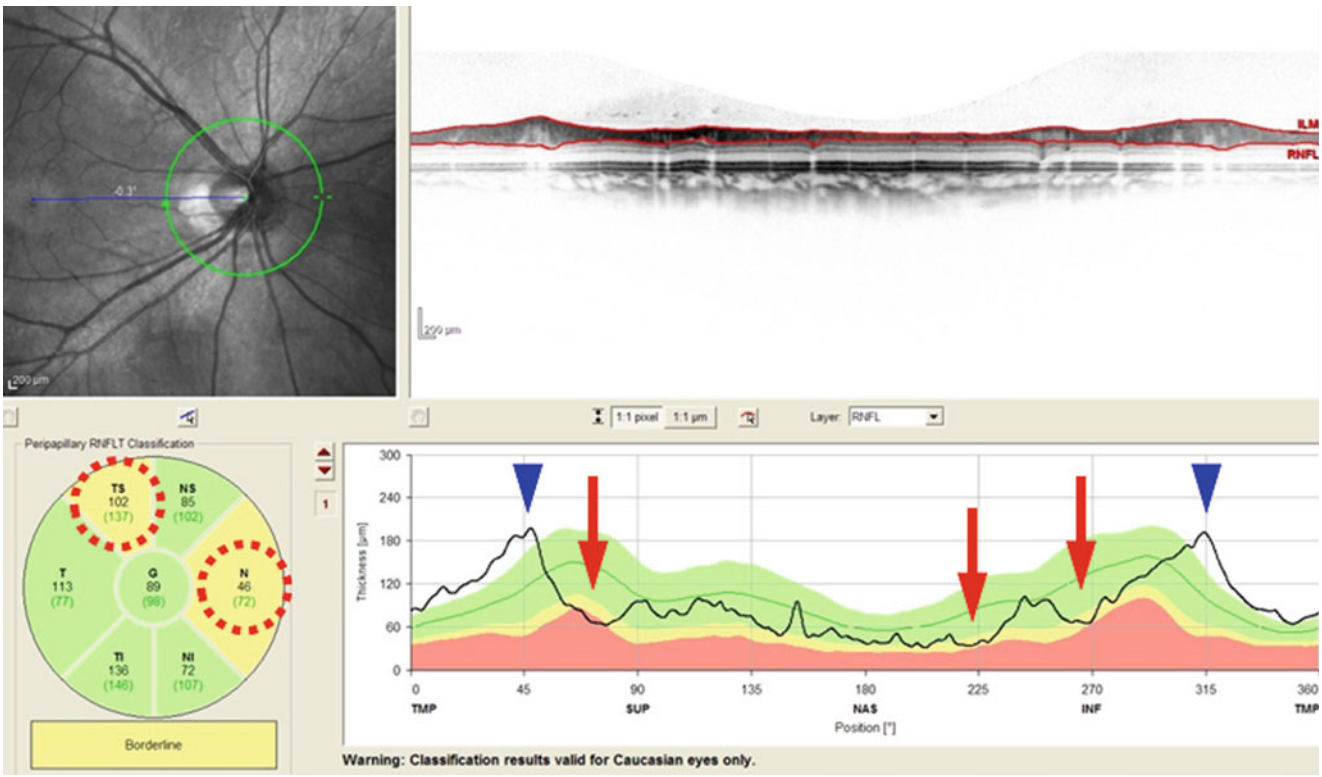

Fig. 19.2 Retinal nerve fiber layer (RNFL) thickness profile in a highly myopic eye. Note that the superotemporal and inferotemporal RNFL bundles (*blue arrowheads*) are closer to the line connecting the disc center and the fovea than those in normative data. *Red arrows* and *dotted circles* indicate the areas with borderline or abnormal RNFL thickness

RPE and was associated with axial length, but not with glaucoma. The revised beta zone PPA was defined as the PPA area with an intact Bruch's membrane but no RPE and was associated with glaucoma, but not with axial length [62, 63]. These findings suggest that the newly defined beta zone PPA is specifically related to glaucoma and should be evaluated in clinical practice. However, the new beta zone PPA is not readily identifiable ophthalmoscopically or in disc photographs and needs imaging technology such as spectral domain OCT for accurate identification.

Macular ganglion cell layer thickness analysis using OCT is a promising method that may improve the diagnostic accuracy of glaucoma in high myopia. Macular ganglion cell layer is usually measured together with inner plexiform layer as "ganglion cell complex (GCC)" because it is difficult to separate those two layers accurately. When compared to circumpapillary RNFL thickness, GCC thickness had comparable [64, 65] or better [66, 67] diagnostic ability to detect glaucoma in high myopia. Although both GCC and RNFL are derived from the same structure (retinal ganglion cell), they may be used as mutually complementary parameters for glaucoma diagnosis and monitoring.

Optic disc and peripapillary structure assessment is limited in myopic eyes. Clinicians should know the structural characteristics of myopic optic discs and how to correct false-positive or false-negative imaging test results. Nonetheless, clinicians would better able to confirm the diagnosis of glaucoma and make therapeutic decisions based on careful longitudinal follow-up in myopic eyes. Further investigation is warranted on new modalities and/or algorithms that can confirm the diagnosis and progression of glaucoma in myopic eyes with a shorter period of follow-up.

19.4 Diagnosis and Monitoring of Glaucoma in Myopia: Optic Nerve Function

Automated perimetry is the most commonly used modality to evaluate visual function of glaucoma suspects or patients. Eyes with early glaucoma do not necessarily have detectable visual field defects (e.g., preperimetric glaucoma), but the presence of visual field defects corresponding to neuroretinal rim or RNFL loss adds confidence to the diagnosis of glaucoma. When structural tests for glaucoma (optic disc photography or imaging tests) are inconclusive in myopic eyes, visual field testing becomes more important in the diagnosis and monitoring of glaucoma. However, it is often difficult to interpret the perimetric test results accurately in myopic eyes because many of them have a tilted optic disc that can lead to

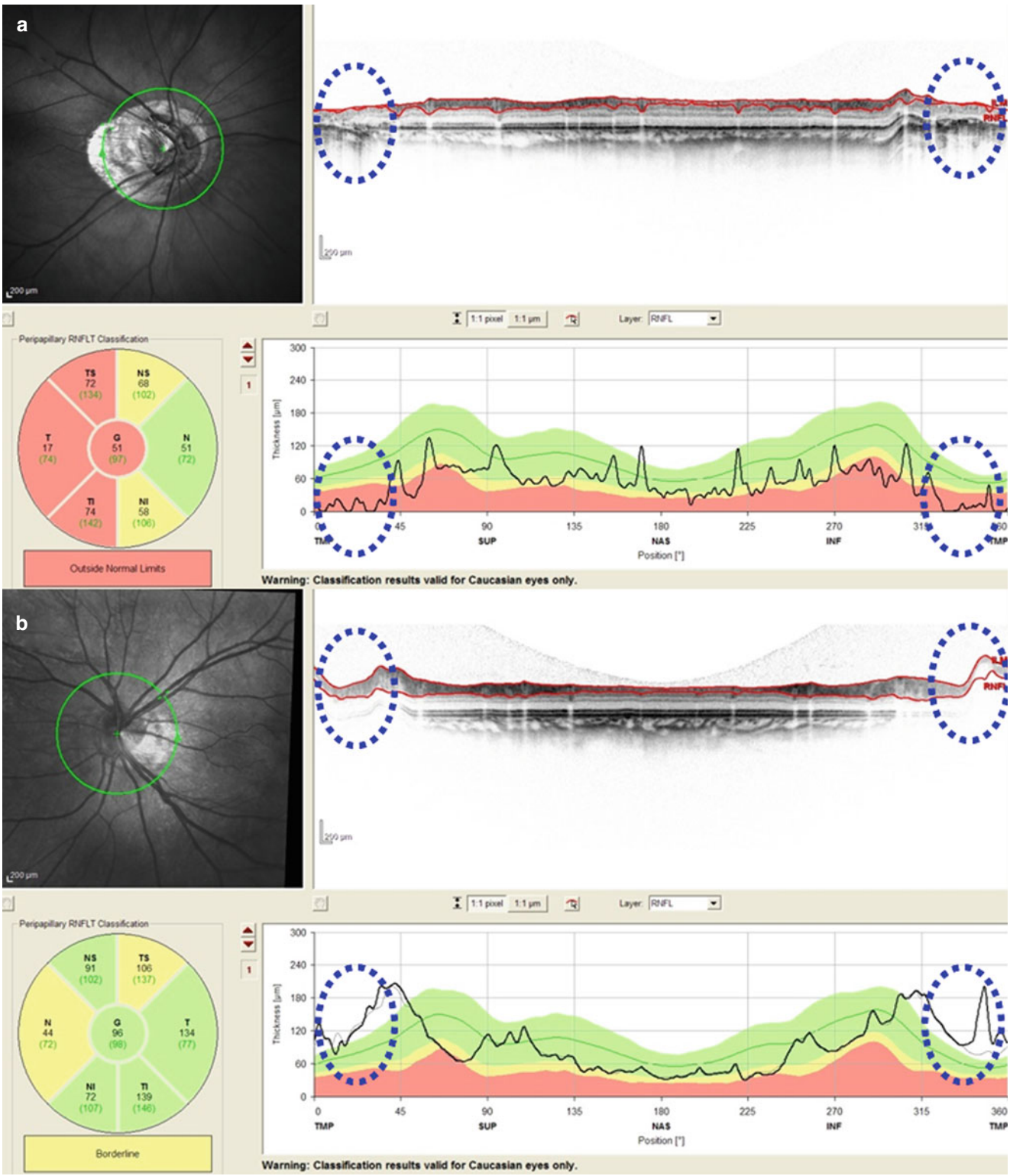

Fig. 19.3 Retinal nerve fiber layer (RNFL) thickness profile of two eyes with high myopia and large beta zone parapapillary atrophy. *Dotted ellipses* indicate the areas where RNFL segmentation algorithm failed resulting in underestimation (**a**) or overestimation (**b**) of RNFL thickness

visual field defects mimicking glaucoma. Eyes with greater myopia with a longer axial length tend to have greater disc tilting [23].

There is conflicting evidence regarding visual field defects in eyes with a tilted disc and myopia. In the Blue Mountains Eye Study, a population-based study conducted

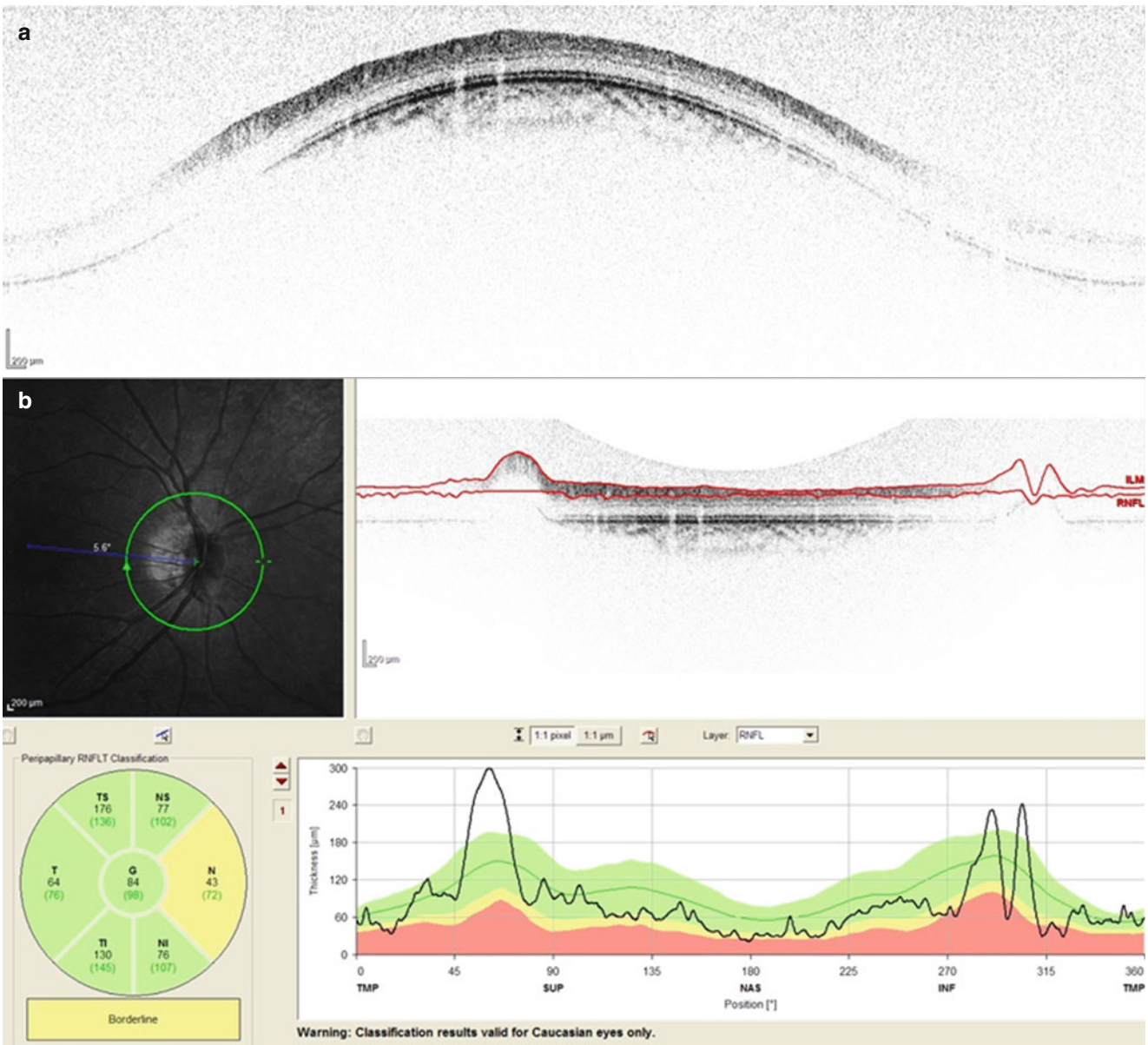

Fig. 19.4 Greater undulation of the raw retinal nerve fiber layer (RNFL) scan (**a**) in a highly myopic eye resulted in areas of poor image quality at both ends, which lead to erroneous RNFL thickness profile (**b**)

Fig. 19.5 The classic beta zone parapapillary atrophy (between *arrows 1* and *3*) can be divided into a gamma zone (between *arrows 1* and *2*) and a new beta zone (between *arrows 2* and *3*) based on the presence or absence of Bruch's membrane. The *dotted line* with an *arrow* in (**a**) indicates the location of the cross-sectional OCT scans in (**b**)

in Australia, 12 of 62 eyes with a tilted disc (19.4 %) had visual field defects, most commonly in the superotemporal quadrant of visual field [36]. This study only looked for inferiorly, inferonasally, nasally, or superonasally tilted discs. Therefore, many of the eyes likely had tilted disc syndrome. Also, when 41 eyes with a tilted disc were examined after a mean period of 61 months, 11 had glaucoma or myopic retinopathy [36]. In a prospective study on 137 young men aged 19–24 years with myopia, 40.2 % of subjects had tilted discs with a disc ovality index (a ratio of shortest disc diameter to longest disc diameter) of 0.8 or less [23]. In this study, only one subject had a reproducible visual field defect with both trial lens and contact lens optical correction. The subject had myopia of −8.00 D and disc ovality index of 0.83, which does not fall in the category of tilted discs based on the authors' definition. Four subjects had visual field defects with the trial lens but not with the contact lens. In a study on 38 eyes with tilted disc syndrome, small additional myopic correction improved visual field test results [68]. After initial visual field testing using Goldmann perimetry, the defective isopters in 35 eyes were tested again with gradually increasing myopic correction until no further change was noted. The visual field defect partly or totally disappeared with increased myopic correction of 3.1 ± 1.5 D. A retrospective case series reported 16 patients with refractive error ranging from −11.25 to +0.25 D who had optic disc cupping and visual field defects stable for 7 years [24]. A tilted disc was present in 75 %, but there was no detailed definition of tilted disc. In another retrospective study on 492 highly myopic eyes with a mean follow-up period of 11.6 years, visual field defects were newly developed in 13.2 % of the eyes [69]. The incidence of visual field defects was significantly higher in eyes with an oval disc than in eyes with a round disc. Based on the high proportion of temporal visual field defects, the authors of this study claimed that the visual field defects in highly myopic eyes most likely were not caused by the same mechanisms that caused glaucomatous visual field defects. However, about one-third of the eyes had nasal visual field defects only [69].

Peripapillary intrachoroidal cavitation, which was previously known as peripapillary detachment in pathologic myopia, is associated with visual field defects. It appears clinically as a yellowish-orange lesion around the optic disc myopic conus [70]. OCT revealed an intrachoroidal cavity separating the RPE from the sclera [71]. In a study on 127 highly myopic eyes, glaucoma-like visual field defects were detected more frequently in eyes with peripapillary intrachoroidal cavitation than in eyes without (64.3 % vs. 19.5 %) [72]. Additionally, one-quarter of eyes with peripapillary intrachoroidal cavitation may have defects in the retina (and therefore the RNFL) which may cause visual field defects that mimic those found in glaucoma [73].

Another problem in interpreting visual field tests in myopic eyes is that visual field sensitivity decreases with an increasing degree of myopia in eyes with moderate to high myopia [74]. In 99 young myopic male soldiers with refractive error worse than −4 D, the visual field mean deviation decreased significantly as axial length increased and as refractive error became more myopic. This result was consistent when two methods of refractive error correction (trial lens and contact lens) were used. The authors postulated that the reduced sensitivity in greater myopia may be attributed to ectasia of the fundus, structural changes in the retina and choroid, axial elongation of the eye with increased spacing or distortion of retinal photoreceptor matrix, and minification/distortion of the stimulus by the negative prescription of the lenses.

Considering these results, interpretation of visual field defects in myopic eyes remains a clinical dilemma. Visual field defects (relative scotomata) in myopic eyes may disappear with a proper correction of refractive error, be associated with tilted disc syndrome, be present with glaucoma-like disc cupping but stable for many years, and develop by glaucomatous damage. All of these features should be taken into consideration in the interpretation of visual fields of myopic patients. Follow-up visual field tests and confirmation of visual field progression corresponding to structural progression will confirm the diagnosis of glaucoma as the cause of visual dysfunction. Nonetheless, future studies are needed to see if the pathophysiologic mechanism(s) of visual field progression in some myopic eyes is different from glaucomatous process as well as to develop better functional tests or visual field algorithms that can confirm the diagnosis and progression of glaucoma in myopic eyes more easily.

19.5 Treatment of Glaucoma in Myopia

Miotic (parasympathomimetics, cholinergic agents) eyedrops help to open the trabecular meshwork and increase the aqueous outflow facility. These drugs may cause a variety of side effects and rarely result in retinal detachment. Because patients with high myopia are more prone to retinal detachment, thorough dilated fundus examination for peripheral retinal evaluation should be performed before prescribing miotics. Additionally, induced myopia is a common side effect of miotics. Myopic patients should be informed that they may become more nearsighted during the period of miotic use. The use of other classes of drug for treatment of glaucoma is similar for myopic and non-myopic eyes.

Myopia is a more important factor to consider during surgical treatment of glaucoma than during medical treatment. Highly myopic eyes have a greater risk of ocular trauma and globe perforation during retrobulbar anesthesia [75]. Preoperative measurement of axial length is helpful in estimating the size of globe and managing the angle

of the retrobulbar needle during anesthesia. For extremely long eyes, other types of anesthesia are recommended. We typically use topical or parabulbar anesthesia for glaucoma surgery in almost all patients.

Myopia is one of the risk factors for hypotony and choroidal detachment after glaucoma filtering surgery [76, 77]. Because of thinner-than-normal sclera [27, 28], myopic eyes can partially collapse and lose its original shape more easily than non-myopic eyes when they have intraocular surgery or penetrating trauma. Thinner sclera also makes it difficult to make an adequate partial-thickness scleral flap and suture during trabeculectomy, which is a guarded filtering procedure. Meticulous conjunctival closure to prevent wound leak, larger scleral flap and tighter scleral flap sutures to prevent overfiltration, and less exposure to antifibrotic agents will reduce the risk of hypotony in myopic eyes. Extra care should be taken in young male patients because they have a higher risk of hypotony maculopathy. Myopia is also one of the risk factors for intraoperative or postoperative suprachoroidal hemorrhage. In addition to the aforementioned procedures to prevent hypotony, control of blood pressure, maximal medical reduction of preoperative IOP, slow reduction of intraoperative IOP, and maintenance of the anterior chamber during surgery should be considered. Additionally, myopic eyes are more prone to have complications such as scleral thinning or perforation and endophthalmitis associated with the use of adjunctive antifibrosis chemotherapy. This is another reason for less exposure to antifibrotic agents during filtering surgery in myopic eyes. Non-penetrating glaucoma surgery, which uses no or less antimetabolites and decreases IOP slowly during the entire surgical procedure, may be beneficial for highly myopic eyes in terms of reducing complications, but the IOP outcome may not be satisfactory [78]. Myopic eyes with prior ocular surgery may have localized areas with extreme scleral thinning, which warrants careful preoperative and intraoperative surveillance.

Conclusions

Although myopia may complicate the diagnosis and treatment of glaucoma, many of these challenges can be overcome with the knowledge of the structural characteristics of myopic discs and correct interpretation of ocular imaging and visual field test results. Considering that a large proportion of myopic eyes may have clinical and diagnostic feature compatible with glaucoma but never progress (i.e., no change over time in the appearance of the optic nerve and RNFL and visual function), a more conservative approach with closer surveillance (more frequent follow-up visits) rather than early treatment may be beneficial in myopic patients to avoid treating non-glaucomatous eyes. Since established glaucoma progresses more rapidly in myopic eyes compared to non-myopic eyes, initial treatment may need to be more aggressive and surveillance be more frequent in eyes with myopia than in those without it, particularly until the rate of visual field progression has been assessed and found to be acceptable. Because the rising rate of myopia will increase the burden of difficult glaucoma cases, diagnostic and therapeutic guidelines for glaucoma in myopia should be established.

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