Update on the Pathology of Pathological Myopia

7

Alia Rashid and Hans E. Grossniklaus

7.1 Introduction

Pathological myopia is the leading cause of blindness in many developed countries, especially in Asia and the Middle East [1–3]. Pathological myopia has been defined in several different ways, but usually combines a high refractive error with degenerative changes. Duke-Elder defined it as a myopia occurring with (predominantly posterior lobe) degenerative changes [4]. In Japan, where pathological myopia affects between 6 and 18 % of the myopic population, a high refractive error of >−8 diopters (D) is used as the diagnostic criteria for pathological myopia [5]. High myopia is usually associated with enlargement or elongation of the globe. The mechanical stretching forces associated with this enlargement can lead to several different types of fundus changes which can result in variable amount of visual deterioration.

There have been a number of research studies that have documented the most common histopathological findings in myopic eyes. Most recently, a review of 308 eyes comprehensively delineated the histopathological findings in pathological myopia [6]. These include the tigroid fundus, lacquer cracks, geographic atrophy of RPE and choroid, posterior staphyloma, choroidal neovascularization also known as Fuchs spot, myopic configuration of the optic nerve head including peripapillary changes, macular holes and retinal holes or detachments, and vitreous, cobblestone, and lattice degeneration (see Table 7.1).

Studies have shown that both genetic and environmental factors both cause and affect the development of pathological myopia [7–10]. Recent studies investigating the genomics of this condition have successfully identified novel loci which may be responsible for the development of this pathological process. With the under acknowledged but significant impact of pathological myopia in patients, the importance of genomic profiling and early recognition of pathological changes in the myopic eye can potentially aid earlier intervention or appropriate alternative therapies to improve the quality of life of these patients. In recent years, various interventional techniques have been tried to control progression myopia in children, including the use of antimuscarinic or cycloplegic drops, bifocal lenses, RGPCLs, and intraocular pressure-lowering drugs. According to a recent Cochrane review, the most promising results were shown in trials using antimuscarinic topical medication. Bifocal lenses and lenses to reshape the corneal surface were deemed to also be promising but in need of further elucidation with clinical trials [11]. Understanding the histopathology of pathological myopia is an important step in being able to focus the future development of appropriate interventions on those tissues that may benefit the most.

7.2 Pathological Findings in Pathological Myopia

7.2.1 Lacquer Cracks

Lacquer cracks are a result of linear breaks forming in the Bruch's membrane. The breaks occur in the posterior pole and clinically appear as a crisscrossed, reticular pattern of subretinal yellowish-white fine irregular lines and are associated with retinal hemorrhage as well as subretinal neovascularization [12, 13]. Typically the overlying neuroretina appears normal. The presence of lacquer cracks may have some relation to the stress caused by mechanical forces acting on the ocular tissues from an enlarged eye as typically found in high myopia [6, 14]. Between 1.6 and 4.3 % of severely myopic eyes to have been shown to have lacquer crack formation pathologically [6, 15]. Curtin et al. noted that axial length showed some correlation with the presence

A. Rashid, MBChB (✉) • H.E. Grossniklaus, MD, MBA
L.F Montogomery Laboratory, Department of Ophthalmology,
Emory University School of Medicine,
1365 Clifton Road/ BT 428, Atlanta, GA 30322, USA
e-mail: arashi6@emory.edu; ophtheg@emory.edu

R.F. Spaide et al. (eds.), *Pathologic Myopia*,
DOI 10.1007/978-1-4614-8338-0_7, © Springer Science+Business Media New York 2014

Table 7.1 Histopathologic findings in 308 myopic eyes

Finding	Percent of total
Myopic configuration of optic nerve head	37.7
Staphyloma	35.4
Vitreous degeneration (liquefaction, detachment)	35.1
Cobblestone degeneration	14.3
Myopic degeneration of retina	11.4
Retinal detachment	11.4
Retinal pits, holes, or tears	8.1
Subretinal neovascularization	5.2
Lattice degeneration	4.9
Fuchs spot	3.2
Lacquer cracks	0.6

of lacquer cracks, finding that 4.3 % of eyes with an axial length greater than 26.5 mm exhibited lacquer cracks and eyes with an axial length of 31.5 mm or more had the highest incidence [16]. Klein et al. found a distinct correlation between the presence and extent of lacquer cracks and worsening visual acuity [15]. Histopathologically, lacquer cracks can be seen as distinct defects in Bruch's membrane, leading to capillary-like vessels extending internally, through the defect to the underlying retinal pigment epithelium. Sometimes these linear tears can be healed by retinal gliosis that fills in the area of the defect. Hyperplasia of the retinal pigment epithelium can also be seen to extend into the choroid through the defects. Clinically this hyperplasia of the RPE can be seen as pigmentary changes in the area of the lacquer cracks. The mechanical forces causing the stretching and hence breakage in the elastic lamina of Bruch's membrane can lead to the formation of choroidal neovascular membranes which may bleed, eventually causing scarring and atrophy of the RPE.

A study by Ohno-Matsui et al. found that subretinal bleeding in the absence of a myopic CNV heralded the development of lacquer cracks [17]. The study prospectively examined 22 highly myopic eyes in 19 patients that had exhibited subretinal bleeding. Ophthalmoscopy and fluorescein funduscopic angiography were used to evaluate the area of the subretinal bleed. 17 of the eyes (77 %) developed lacquer cracks in the following 2–6 months (mean 4 months) following the subretinal bleeds. Another study by the same team followed 66 eyes with lacquer cracks for an average of 73 months [18]. Progression of the lacquer cracks was seen in 37 eyes (56.1 %), and of these, 37 % showed an increase in the number of cracks, and evolved into other myopic fundus changes such as patchy atrophy, diffuse atrophy and Fuchs' spot, in 68 %. We know that lacquer cracks are formed when there is a break in Bruch's membrane through the RPE to the choriocapillaris. Laser photocoagulation, used to treat CNV as well as retinal holes/tears, can also cause fractions in this RPE-Bruch's-choriocapillaris complex. It then stands to reason that laser photocoagulation can lead to the formation of lacquer cracks. Johnson et al. reviewed 5 eyes treated for myopic CNV with laser photocoagulation and found that the existing lacquer cracks expanded from the laser scar between 10 days and 3 months after treatment [19]. Furthermore, the cracks acted as pathways for recurrence or progression of the myopic CNVs. Ohno-Matsui et al. evaluated 325 highly myopic eyes and found that of those that were noted to have lacquer cracks, 29.4 % went on to develop myopic CNV, showing that lacquer cracks are an important predisposing risk factor for the development of CNV [20].

7.2.2 Geographic Atrophy of RPE and Choroid (Diffuse vs. Patchy)

The degenerative changes that are found in high myopia cause early changes, primarily atrophy of the choriocapillaris and retinal pigment epithelium. The atrophy of the RPE and choriocapillaris leads to a reduction in nutritional support for the retina, and this subsequently also atrophies. The atrophy leads to increased visualization of the choroidal circulation, known as a "tessellated" or "tigroid" fundus appearance.

Chorioretinal degeneration is the most commonly reported clinical finding in pathological myopia [8]. The changes progress from the early findings of a tigroid fundus to lacquer crack and staphyloma formation and then diffuse followed by patchy choroidal atrophy and eventually leading to bare sclera [21, 22]. A study by Ohno-Matsui et al. reviewed 325 eyes with myopic fundus changes over a course of at least 3 years and found that choroidal neovascularization occurred in 3.7 % of eyes with diffuse chorioretinal atrophy and in 20 % of eyes with patchy atrophy [20].

Kobayashi et al. reviewed the fundus characteristics in children with high myopia and found that only mild chorioretinal atrophy was noted in 16.3 % of eyes, and this was located around the optic disc. None of the children exhibited signs of geographic atrophy, suggesting that aging, in addition to mechanical tension, may be an important factor in the development of myopic chorioretinal degeneration [23].

A long-term study (range 5–32 years, mean 12.7 years) of 806 highly myopic eyes in 429 patients found that myopic maculopathy – that is, a tessellated fundus, diffuse or patchy chorioretinal atrophy, CNV, and macular atrophy – was seen to progress in approximately 40 % of eyes over time [24]. Additionally, eyes that also had posterior staphyloma were more likely to show progression of maculopathy.

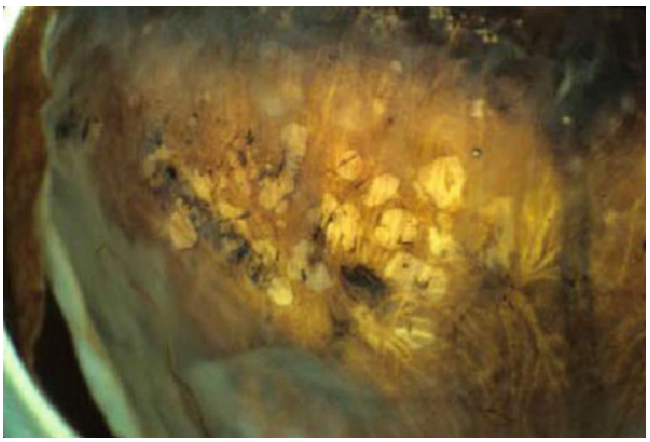

Fig. 7.1 Gross appearance of cobblestone degeneration. There is diffuse and patchy atrophy of the peripheral RPE and outer retina forming cobblestone degeneration

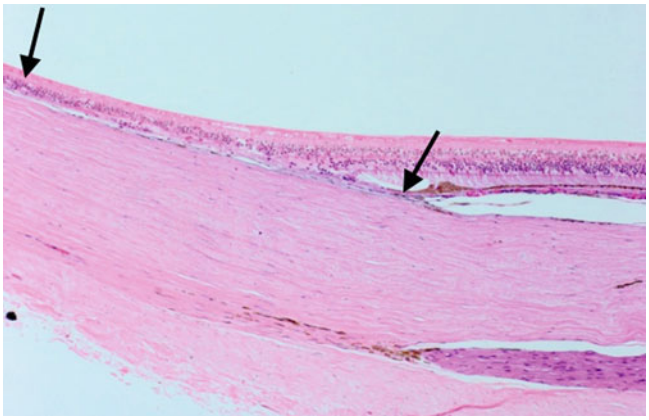

Fig. 7.3 Cobblestone degeneration. Outer retinal atrophy. There is atrophy of the outer retina and retinal pigment epithelium present (*between arrows*) *H&E 25×*

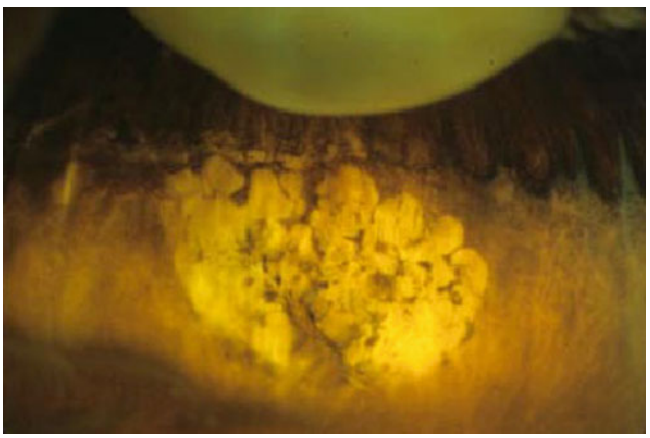

Fig. 7.2 Gross appearance of confluent cobblestone degeneration

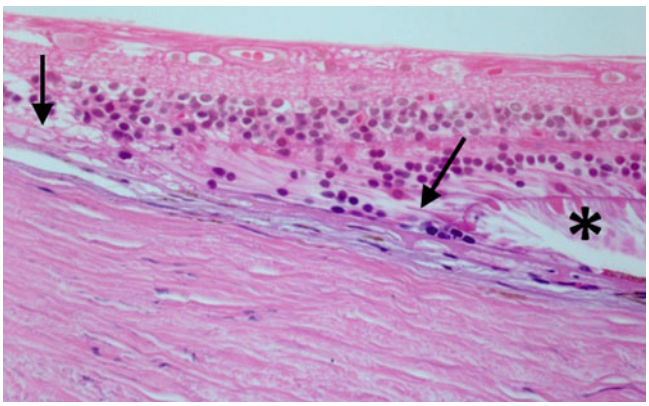

Fig. 7.4 Cobblestone degeneration. This area of cobblestone degeneration is composed of RPE atrophy and overlying atrophy of the outer retinal layers (*between arrows*). Adjacent to the cobblestone degeneration, the photoreceptor outer segments are intact (*asterisk*) *H&E 100×*

Histopathologically, the study by Grossniklaus et al. found that the RPE did indeed show substantial atrophy, and interestingly they also noted a loss of choroidal melanocytes in the area [6] (see Figs. 7.1, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, and 7.8). The choriocapillaris has been shown on ultramicroscopy to progressively thin with a graduated blockade of the choriocapillaris [25]. A study to evaluate macular choroidal thickness in eyes with myopic maculopathy found that a thinner macular choroidal thickness was related to more advanced stages of maculopathy and an increased likelihood of the presence of lacquer cracks and a lower BCVA [26]. This finding was confirmed by a recent comparative study of choroidal thickness in highly myopic eyes with emmetropic eyes [27]. Enhanced depth imaging optical coherence tomography (EDI-OCT) was performed on 25 highly myopic eyes and 25 normal eyes. The choroidal thickness in the macula was significantly smaller ($p<0.0001$) in the highly myopic group as compared to the normal group.

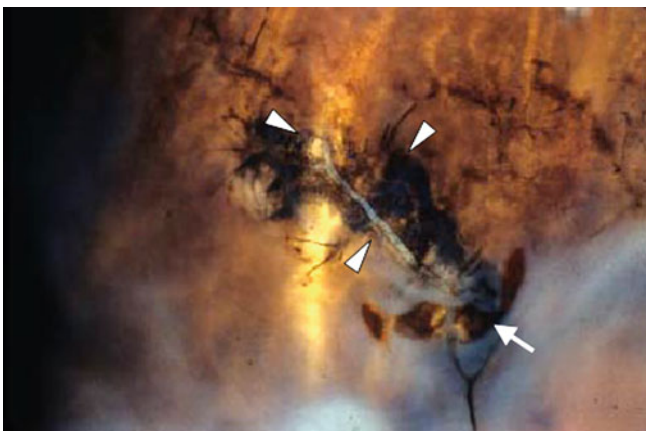

Fig. 7.5 Gross appearance of lattice degeneration. The area of lattice degeneration (*arrowheads*) has an associated retinal hole (*arrow*)

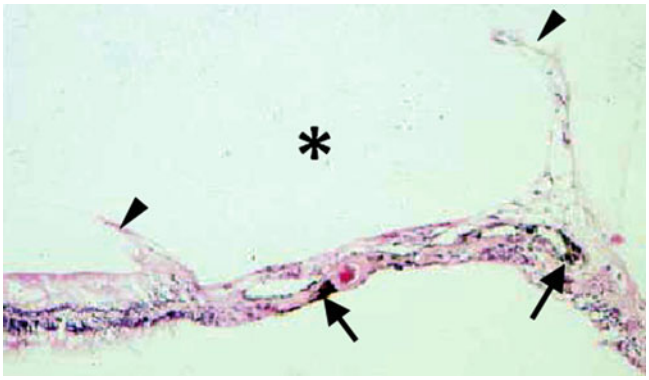

Fig. 7.6 Lattice degeneration. Lattice degeneration in this myopic eye is composed of inner layer atrophy with an overlying pocket of liquid vitreous (*asterisk*) surrounded by tufts of gliotic retina (*arrowheads*). There is RPE hypertrophy and hyperplasia present (*arrows*) and a sclerotic vessel is observed. *H&E 100×*

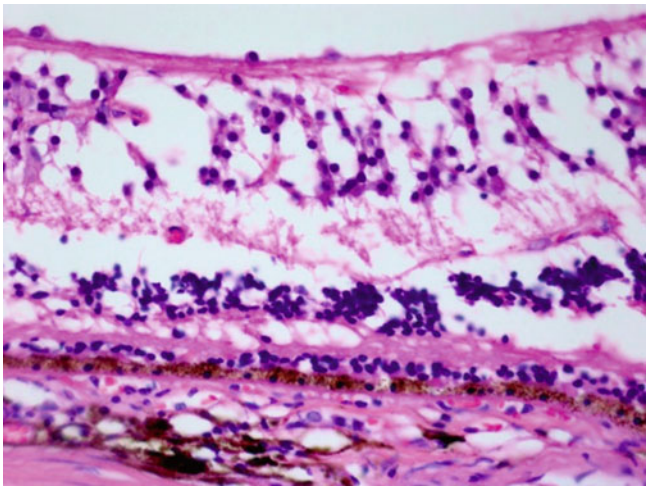

Fig. 7.8 Outer retinal atrophy. The outer retina is atrophic and only a thin portion of the outer nuclear layer remains. *H&E 100×*

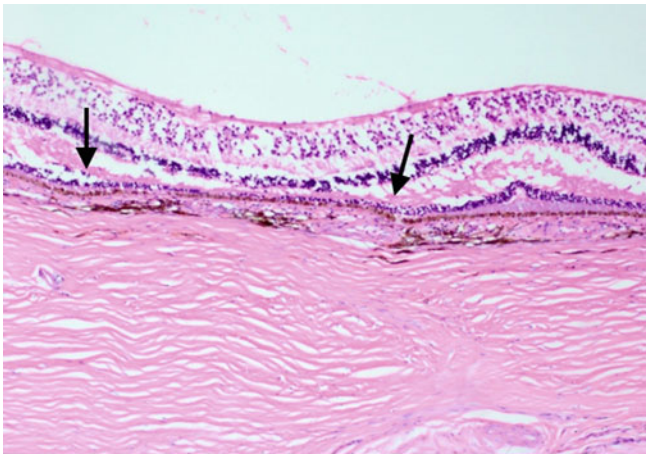

Fig. 7.7 Outer retinal atrophy. The outer retina is atrophic (*between arrows*) and only a thin portion of the outer nuclear layer remains. *H&E 25×*

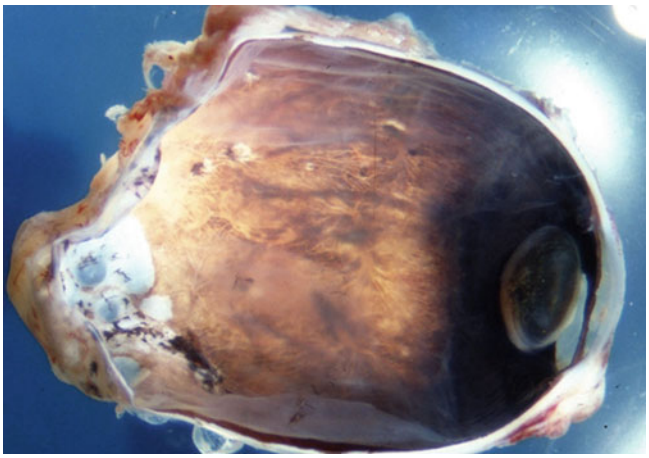

Fig. 7.9 Gross appearance of highly myopic eye with posterior staphyloma. This highly myopic eye exhibits a posterior staphyloma composed of an area of extremely thin sclera with underlying atrophy of the choroid, retinal pigment epithelium, and retina

At the edges of the atrophied areas, pigment clumping could be seen, a sign that can also be frequently noted on clinical examination. Animal models of myopia have shown that ultrastructural changes include a reduced density of the choroidal capillaries and irregular, attenuated intercapillary meshes [28].

An early study of 1,437 myopic eyes looked at the peripheral retinas and found a statistically significant association between axial length of the eye and white without pressure, pigmentary degeneration, paving stone (or cobblestone) degeneration, and lattice degeneration [29]. These findings have been supported by numerous other studies. Celorio et al. found that 33 % of highly myopic eyes had lattice degeneration; however, they found the greatest prevalence (40.9 %) in eyes between 26 and 26.9 mm in length and the least (7 %) in eyes with axial lengths greater than 32 mm [30]. A study from Japan found that independently of axial length, lattice degeneration was significantly more frequent in eyes that did not have posterior staphylomas, concluding that the type of axial elongation (staphyloma vs. no staphyloma) influenced the formation of lattice degeneration [31].

7.2.3 Posterior Staphyloma

Clinically, staphylomas have been noted in approximately 19 % of highly myopic eyes with axial lengths greater 26.5 mm [16] (see Figs. 7.9 and 7.10). In the study by Grossniklaus, the second most common histopathological finding was staphyloma, occurring in 33 % of the 369 eyes with pathological myopia [6], indicating that the presence of

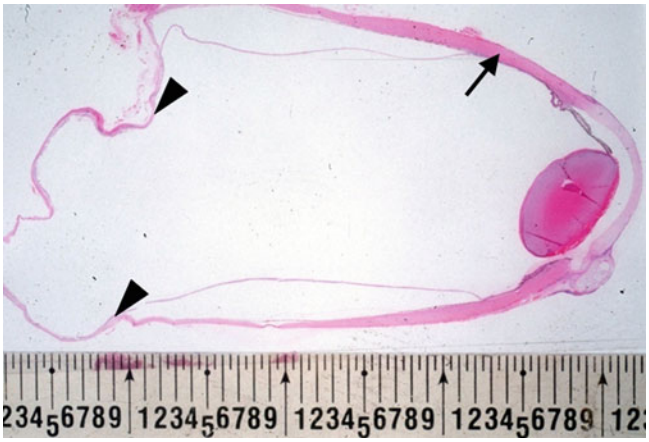

Fig. 7.10 Highly myopic eye with posterior staphyloma. This highly myopic eye is approximately 40 mm in anteroposterior dimension. There is normal sclera anteriorly (*arrow*) and a staphyloma posteriorly where the sclera has thinned and stretched (*between arrowheads*). *H&E 2×*

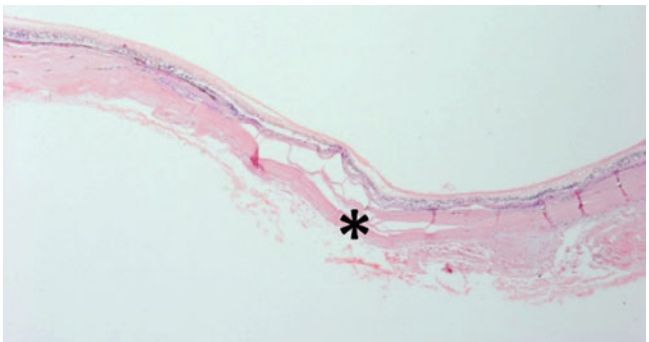

Fig. 7.11 Staphyloma. A staphyloma corresponds to an area of thinned sclera (*asterisk*). *H&E 10×*

staphyloma may be underestimated by clinical evaluation. Staphylomas occur most commonly in the posterior pole [32]. In pathological myopia, the sclera has been shown to be abnormal. Histopathologically, the collagen bundles in the sclera are found to be thinner, with fewer striations of collagen, and the lamellar structure of the sclera appears similar to the architecture of the corneal stroma [33] (see Figs. 7.6, 7.7, 7.8, 7.9, 7.10, and 7.11). Ultrastructural investigations have revealed that the scleral collagen in pathological myopia has a more lamellar fiber placement, as well as the appearance of star-shaped collagen fibrils, a decrease in the fibril caliber and number of fibrils, and increased interfibrillary separation [34]. Animal studies have indicated that these changes are due to accelerated collagen turnover and a decrease in the synthesis of collagen [35]. These ultrastructural alterations in the scleral tissue lead to a weaker, less rigid structure that is more susceptible to mechanical stresses and deformation. The histologic evaluation by Grossniklaus found that on gross examination, the mean anteroposterior measurement in pathologically myopic eyes was greater than either the horizontal or vertical measurements (26.5 mm vs. 25.5 mm and 25 mm, respectively), indicating that the eyes were "egg shaped" with the greatest mechanical forces/deformation occurring in the anteroposterior axis [6]. This finding is in keeping with the fact that the vast majority of staphylomas occur in the posterior pole, where these forces would have the greatest mechanical impact, leading to ectasia of the sclera and formation of a staphyloma.

In 1977, Curtin developed a grading system for posterior staphylomas, determined by the location, size, and severity of the staphyloma [36]. In total, ten types of staphyloma were identified. The primary staphylomas were type I–V, and compound staphylomas were type VI–X. A study by Hsiang et al. using ultrasound B-scans to evaluate posterior staphylomas looked at 209 eyes of 108 patients with pathological myopia [37]. By using ultrasound B-scans, they found that 90 % of the eyes had a staphyloma. The study found that the prevalence of staphyloma, as well as the severity, or grading, increased with increasing age. Type II staphylomas were the most common, occurring in 52.7 % of eyes, followed by Type I (23.4 %) and Type IX (17 %). Severe retinal degeneration was noted in 71.9 % of the Type IX eyes, in 50 % of both Type I and Type III eyes, and in 46.5 % of Type II staphyloma eyes. The difference between the Type II and Type IX eyes was statistically significant ($p=0.01$). Furthermore, when comparing Type II staphyloma eyes to Type IX eyes, the axial length was significantly greater for the latter group, as was the presence of lacquer cracks. These findings, of an increase in the prevalence of staphyloma and chorioretinal atrophy with increasing axial length and increasing age, have been confirmed by other studies [38].

Staphyloma formation in pathological myopia is part of a spectrum of myopic maculopathy, and a variety of features such as retinoschisis, retinal holes and detachments, CNV, and atrophy have been noted to occur in the presence of staphylomas [39–44]. A study by Henaine-Berra et al. has found that the prevalence of macular abnormalities in high myopia, such as foveoschisis, vascular traction, and epiretinal membrane formation, is significantly more frequent in the presence of a posterior staphyloma ($p=0.0001$) and that 53.65 % of eyes with posterior staphyloma were observed to have macular abnormalities [45]. Wu et al. found that foveoschisis and foveal detachment without macular hole were significantly associated with posterior staphyloma ($p=0.0003$) [46], a finding confirmed by Takano et al. [47]. The question of whether posterior staphyloma influenced the formation of macular holes and retinal detachments (MHRD) in highly myopic eyes was investigated by Oie et al., who found that the type of posterior staphyloma appeared to have some correlation [48]. They found that the percentage of eyes with staphyloma in the group of highly myopic eyes MHRD was significantly higher than in the highly myopic group without

MHRD ($p<0.001$), and furthermore, Type II staphylomas were significantly more prevalent in the MHRD group ($p=0.01$).

7.2.4 CNV/Fuchs Spot

Macular choroidal neovascularization (CNV), known as Fuchs spot in its later stages, has been reported in between 5 and 10 % of cases of pathological myopia [49]. It is the most common cause of vision loss in high myopia [12, 50]. One study found that in persons under the age of 50, myopia accounted for 62 % of CNV [51]. The CNV occurring in high myopia is associated with typical pathological findings such as lacquer cracks and patchy atrophy. Drusen, and pigment epithelium detachments, which are commonly found with age-related CNV, are rarely found in myopic CNV [52]. Myopic CNV tend to be smaller in dimension and with a smaller extent of leakage when compared to the age-related form of CNV. Subsequently, the areas of atrophy that develop over these CNV locations in myopia will initially be smaller. Later on, however, there is a well-documented tendency for areas of atrophy and scarring in myopic eyes to increase in size, a phenomenon known as "atrophic creep." This phenomenon is especially well recognized as a sequela of laser treatment in eyes with pathological myopia with several studies showing that >90 % of myopic eyes treated with laser of varying wavelengths will suffer from laser scar expansion [53–56]. An explanation for this phenomenon is that of mechanical stretching of the chorioretinal complex, which has been noted to occur in highly myopic eyes. The combination of thinning of the chorioretinal complex, along with the likely concomitant presence of a staphyloma, can often make the task of early detection of a myopic CNV a difficult one [52]. Chorioretinal atrophy itself is very common in the areas around a regressed CNV, with one study quoting the frequency as high as 96 % at 5–10 years after onset of the CNV [57].

CNV may occur more frequently in the presence of chorioretinal atrophy and lacquer cracks [24, 58, 59]. A study by Ohno-Matsui et al. found that of those eyes with chorioretinal atrophy, only 3.7 % progressed to CNV formation. This increased dramatically with patchy atrophy – with 20 % of those eyes developing CNV – and in the eyes with lacquer cracks, 29.4 % developed CNV [20].

There are differences between myopic CNV in patients depending on age – younger patients (<55 years) have been shown to develop significantly smaller lesions than older patients ($p<0.05$) [60]. In younger patients, myopic CNVs tend to occur close to the fovea, and one study revealed that 83 % of myopic CNVs appear to be smaller "classic" lesions [61]. Extrafoveal locations for myopic CNV are less common, with a study by Yoshida et al. finding that about 20 % were not located in the foveal region [62]. Older patients tend to form more extensive and exudative myopic CNVs which can subsequently form large disciform scars which can easily be mistaken for those of neovascular age-related macular degeneration [62]. Histopathologically, the differences between the two processes can be determined more easily: in the majority of cases, myopic CNV is located between the neurosensory retina and the RPE, making it a Type 2 CNV, whereas the vast majority of AMD-related CNV are classified as Type 1 CNV, as they are sub-RPE lesions [63]. Myopic CNV is also characterized by several unique features: Bruch's membrane typically does not display diffuse thickening, the RPE and inner collagenous layer of Bruch's membrane tend not to cleave apart resulting in the formation of pigment epithelial detachments, and widespread deposits of extraneous extracellular matrix are not present [64]. Retinal hemorrhages are less common and neurosensory detachments are typically shallower than those found in AMD-related CNV and are also much shallower in depth. Subretinal and intraretinal fluid accumulation is very limited and usually insignificant [64]. Once the myopic CNV starts to regress, there may be some hyperpigmentation visible, and eventually this leads to fibrotic tissue scarring and subsequently thinning and atrophy of the chorioretinal complex. In the very end stages, the atrophy may be so severe as to result in exposure of bare sclera.

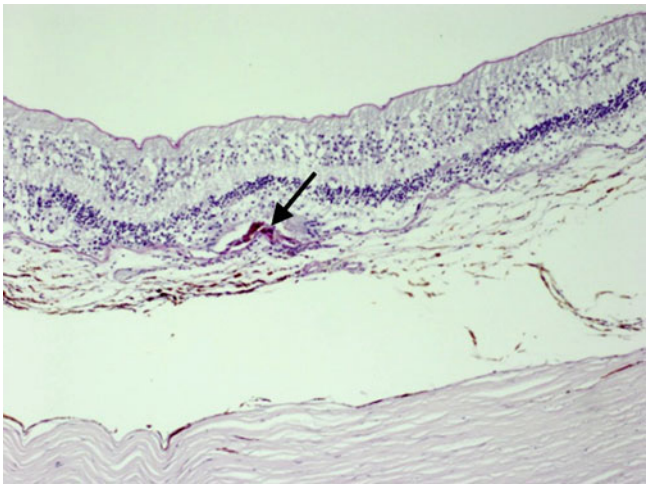

Fig. 7.12 Fuchs spot. The Fuchs spot is composed of a focal area of choroidal neovascularization surrounded by hyperplastic retinal pigment epithelium (*arrow*). *PAS 25×*

Light microscopy of a myopic CNV will show a thin fibrovascular membrane overlying RPE. The membrane may show small collagen bundles, fibroblasts, and nonuniformly distributed small blood vessels in a homogeneous matrix. Typically there is no evidence of inflammatory cells or thrombotic vessels [65] (see Figs. 7.12 and 7.13).

An interesting subtype of myopic CNV is the periconus CNV – that is, an extrafoveal CNV located next to a myopic

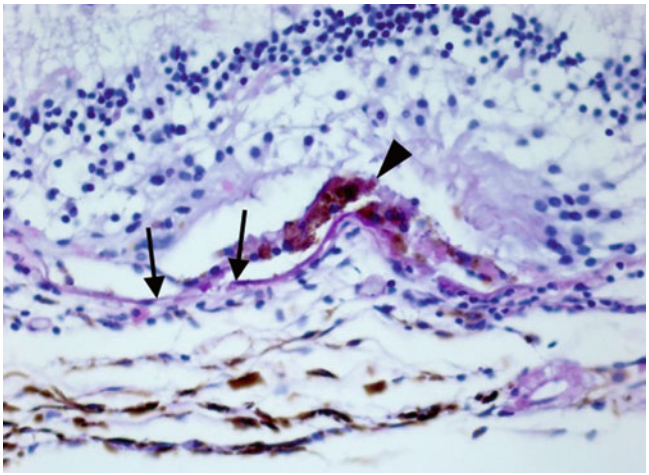

Fig. 7.13 Fuchs spot. There is a break in Bruch's membrane (*between arrows*) and a choroidal neovascular membrane surrounded by retinal pigment epithelium which extends through the break (*arrowhead*). *PAS 100×*

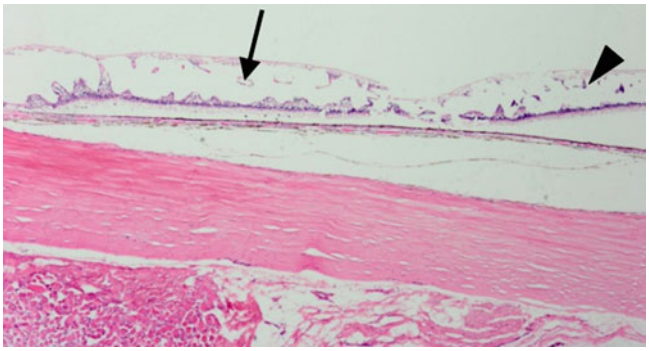

Fig. 7.14 Retinoschisis. An area of retinoschisis (*arrow*) is seen adjacent to an area of typical peripheral cystoid degeneration (*arrowhead*). *H&E 10×*

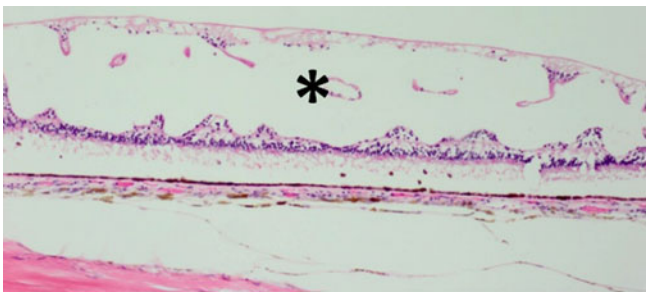

Fig. 7.15 Retinoschisis. Higher magnification shows the area of retinoschisis (*asterisk*) formed where there are interruptions of the bridges of Müller cells. *H&E 25×*

conus. Nagaoka et al. looked at 260 eyes with myopic CNV and found only 4.2 % exhibited a periconus CNV [66]. They found that this subtype was more likely to occur in eyes that had a large myopic conus, and furthermore, the eyes with a periconus CNV had a significantly larger conus than those eyes that had subfoveal CNV. Axial length and degree of myopia were not associated with the formation of a periconus CNV, suggesting the spatial characteristics of the eye did not have any effect on the formation of CNV in this location. The study also found that just under half of the patients with periconus CNV experienced sudden regression, and the rest resolved after a single treatment to the CNV. Chorioretinal atrophy developed in 3 eyes (27 %).

7.2.5 Retinal and Macular Hole/Schisis/Detachment

Changes in the vitreoretinal interface at the posterior pole can manifest as a macular hole, which can subsequently lead to retinal detachment in highly myopic eyes. Vector forces from axial elongation or staphyloma formation in highly myopic eyes, increased vitreous liquefaction, and atrophy of the chorioretinal complex which is common in pathological myopia may combine to form the perfect storm of which the unfortunate outcome is the formation of a macular hole.

A study by Gass looking at the mechanism of formation of macular hole in non-myopic eyes found that the posterior vitreous cortex would pull on the connections at the vitreoretinal interface, with the ensuing traction resulting in a hole being torn in the macula as the vitreous was pulled away [67]. It is easy to hypothesize that the space formed by the retraction of the vitreous from the retinal surface would cause a negative pressure space into which the liquefied vitreous could move, coursing through the newly formed macular hole and under the retina and inducing a retinal detachment.

There are several stages of foveal or macular change in this process: epiretinal membrane; macular schisis; partial and full-thickness macular hole, with or without PVD; and posterior macular retinal detachments (see Figs. 7.14, 7.15, 7.16, and 7.17). One study looked at 214 eyes with pathological myopia and staphyloma and noted there to be vitreoretinal abnormalities in 56.8 % of those patients [68].

Myopic foveoschisis was assessed using FD-OCT by Sayanagi et al. to evaluate the pathological features in this condition [69]. They found that defects in the inner and outer photoreceptor segments of foveal detachment type were seen in 3 of 6 eyes (50 %), and IS/OS (foveoschisis type) was seen in 2 of 11 eyes (18 %). Diffuse atrophy with the myopic foveoschisis was seen in 24 % and patchy atrophy was also observed in 24 %.

A study by Takano et al. looked at 32 eyes of 19 patients with severe myopia and posterior staphyloma [47]. Using OCT they found 11/32 eyes (34 %) to have

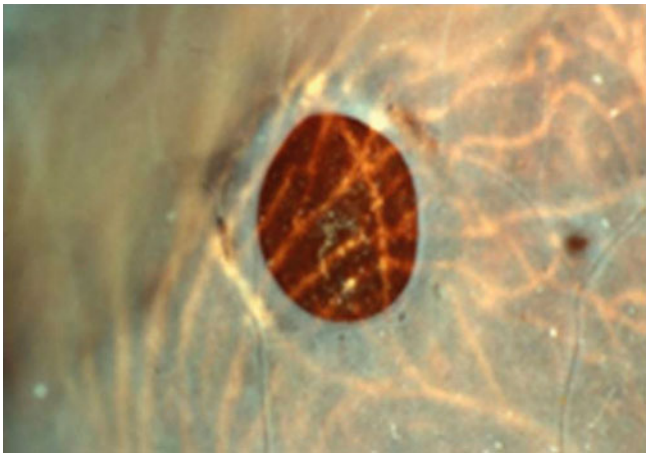

Fig. 7.16 Gross appearance of a full-thickness myopic retinal hole

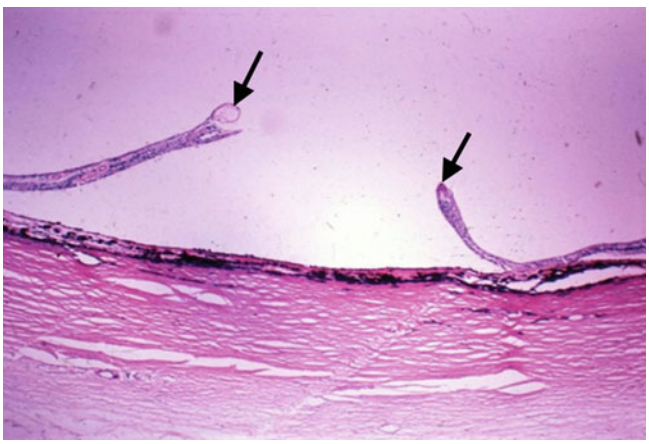

Fig. 7.17 Retinal hole. The full-thickness hole exhibits rounded edges of the surrounding retina (*arrows*). *H&E 100×*

foveal retinoschisis or detachment. Of these 8/32 eyes had foveal retinoschisis and retinal detachment, and 1/32 had only a foveal retinal detachment without schisis formation. 2/32 had only retinoschisis. The remaining 21/32 eyes with neither retinoschisis nor retinal detachment were all found to have macular thinning using OCT measurements of about 100–150 μm at the fovea. The results of this study suggest that a macular hole is not a prerequisite for retinoschisis or retinal detachment formation in severely myopic eyes that have a posterior staphyloma. It is possible that the tractional forces from the posterior staphyloma may cause a "stretch retinoschisis," leading to foveal detachment instead, followed by macular hole formation as these posteriorly located forces continue to act, pulling the macular retina away from the vitreous cortex.

Similarly, studies of myopic traction maculopathy using OCT have found that macular traction seems to be associated with a schisis, suggesting that the etiology of macular schisis may be a result of pre- or extraretinal traction due to the stretching forces experienced by an enlarged highly myopic eye [70, 71]. Following on from this finding, another study reviewed the prevalence of macular holes in highly myopic eyes and found that the macular holes were present in 6.26 % of the eyes [72]. The most frequent vitreoretinal abnormalities associated with the macular holes was a schisis, found in 75 % of that subgroup. 20.8 % of the eyes with macular hole showed progression over a mean follow-up time of 30.2 months, in the form of enlargement of the hole, or a posterior retinal detachment.

In the study by Grossniklaus et al., the prevalence of retinal pits, holes, or tears seen on histologic section in the 369 eyes evaluated was 8.4 % [6]. Previous studies have shown a link between myopic eyes and an increased risk for retinal hole formation [73, 74] and a significant correlation between retinal detachment and high myopia [75]. Retinal detachments were seen in 12.2 % of eyes in the Grossniklaus study; however, the authors also considered the fact that a number of eyes in the study had at some point undergone a retinal detachment repair procedure, which increased the prevalence of retinal detachment occurrence in the study population of highly myopic eyes to 20 %. One study found several factors that were associated with myopia and the formation of retinal detachments, including lattice degeneration, asymptomatic retinal breaks, increased frequency of posterior vitreous detachment, and vitreous liquefaction [76].

A large Scottish study of 1,202 cases of retinal detachment found that 18.7 % of the eyes exhibited lattice degeneration [77]. Of these, retinal hole-related RD was significantly more common (35.7 %) than horseshoe-tear RD (19.3 %) and occurred mostly in more myopic patients. Furthermore, >85 % of the RD were associated with PVD and related tractional abnormalities. These results are similar to another British study which found that retinal hole-related RD were more common in younger patients (median age 28.9 years) with a high degree of myopia (−5.5 D, range −1 to −18 D), and about 50 % of the cases exhibited lattice degeneration [78].

7.2.6 Myopic Configuration of the Optic Nerve Head, Including Peripapillary Changes

In the American histopathological study of highly myopic eyes by Grossniklaus, the most common finding was of myopic configuration of the optic nerve head, found in 40 % of the eyes [6]. A clinical study of pathological myopia fundus changes from Singapore found that peripapillary atrophy was the most common finding by far, in 81.2 % of eyes, followed by disc tilt, found in 57.4 % of eyes, and furthermore

Fig. 7.18 Gross appearance of myopic degeneration of the optic nerve head. There is a myopic conus present surrounding the optic nerve. This is manifested by peripapillary atrophy and thinning of the sclera

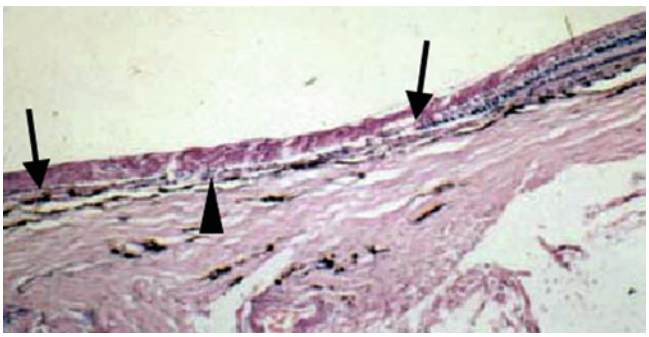

Fig. 7.19 Myopic degeneration. The peripapillary myopic conus corresponds to where the retina is reduced to a thin gliotic band (*between arrows*), and there is underlying atrophy of the retinal pigment epithelium and choroid (*arrowhead*). *H&E 100×*

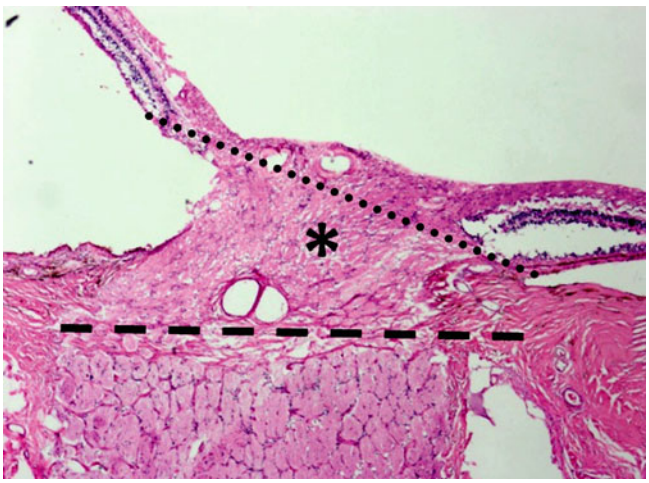

Fig. 7.20 Oblique optic nerve head. The optic nerve head (*asterisk*) enters the eye at an oblique angle (*dotted line*) compared to the lamina cribrosa (*dashed line*). *H&E 10×*

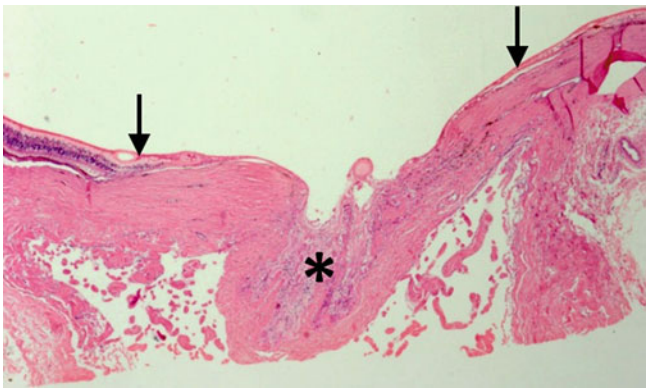

Fig. 7.21 Myopic conus. There is extensive peripapillary atrophy and thinning (*arrows*) which corresponds to a myopic conus. The bare sclera is seen surrounding an atrophic optic nerve (*asterisk*). *H&E 10×*

was found to be more common in teenaged high-myopes than in adults and those of Chinese descent [38]. Clinically, this myopic configuration appears as a tilted disc with the retina, RPE, and choroid extending over the disc nasally and the retina falling short of the optic disc on the temporal side. This combination gives rise to the appearance of a temporal crescent at the optic disc, although it can occasionally be seen nasally, or inferiorly, or in about 10 % of cases surrounding the disc completely [22, 79]. These findings can all be seen clearly on histopathological examination, and in addition, the peripapillary sclera is often found to be stretched with a widening of the vaginal space between the subdural and subarachnoid spaces (see Figs. 7.18, 7.19, 7.20, 7.21, and 7.22). In addition, they found that when the optic nerve head was involved in the area of a staphyloma, it was typically enlarged.

A study by Jonas et al. compared the optic discs of highly myopic eyes to those of normal eyes [79]. They found that highly myopic eyes had significantly ($p<0.000001$) larger

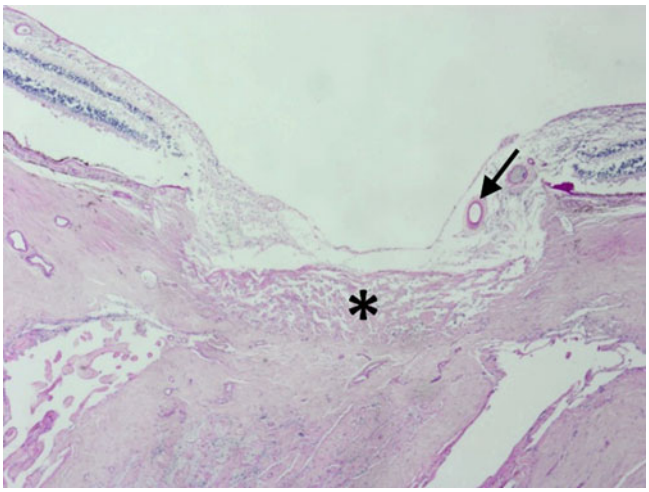

Fig. 7.22 Optic nerve degeneration. There is optic nerve atrophy down to the lamina cribrosa (*asterisk*) and only a vestigial blood vessel remains (*arrow*) in the atrophic tissue. *PAS 5×*

and more oval shaped optic discs than normal eyes and suggested that highly myopic optic discs could be regarded as secondary acquired macrodiscs, whereby the size of the disc could be correlated with refractive error and age.

A similar study by Fulk et al. attempted to correlate optic disc crescents with axial length and refractive error [80]. The study found that crescent size was significantly associated with both parameters ($p=0.02$). For crescents ≥0.2 mm in width, each millimeter increase in axial length correlated to an average 1.26 D increase in myopic shift, but for those with <0.2 mm of crescent, each millimeter increase in axial length only correlated to about 0.66 D of myopic shift. The results also suggested that male gender and refractive error were directly associated with a large optic nerve crescent.

Nakazawa et al. did a long-term study to assess changes in optic nerve crescents in myopic eyes [81] and found that the degree of disc deviation correlated significantly to myopic progression ($p<0.0001$). The optic discs observed were noted to deviate nasally in most cases as the myopia progressed, with subsequent formation of a peripapillary crescent on the temporal side of the disc.

The lamina cribrosa is known to be affected by myopic degeneration [82, 83]. Both high myopia and glaucomatous change are independently significantly correlated with thinning of the lamina cribrosa [82]. In addition, numerous studies have shown that the peripapillary retinal nerve fiber layer is changed in highly myopic eyes [84–86]. OCT has been used to image the optic nerve and peripapillary regions of highly myopic eyes to reveal that the RNFL is typically thickened temporally and thinned nasally in eyes with tilted nerves [86]. Additionally, a thicker mean RNFL significantly correlated with both a lower degree of myopia and greater optic nerve disc and rim areas [85]. Superior and inferior RNFL thickness was not found to be significantly different between myopic and emmetropic eyes [84].

A histologic review of the peripapillary area in highly myopic eyes by Jonas et al. revealed that the distance between the border of the optic nerve and the dura mater, also known as the scleral flange, showed a significant increase with increasing axial length and decrease in length relative to the thickness of the flange area [87]. Furthermore, they discovered that 42 % of the highly myopic eyes had a space >0.5 mm between the border of the optic nerve and the start of Bruch's membrane, where the flange was both elongated and thinned and a retrobulbar cerebrospinal fluid space was found to extend into the retroparapapillary region. Notably, the parapapillary region in these eyes only contained the RNFL or its remnants, with no detectable Bruch's membrane or choroid.

The peripapillary region in highly myopic eyes also exhibits other changes such as cavitations or pits. Wei et al. used OCT to evaluate these peripapillary intrachoroidal cavitations which appear as elevated, patchy, yellowish lesions on fundoscopic examination [88]. OCT revealed these lesions to be intrachoroidal spaces located below the RPE. About half of the cases showed evidence of communicating channels leading from the vitreous to the intrachoroidal cavitation, and one quarter also revealed intrachoroidal splitting. Wei et al. hypothesized that these peripapillary lesions could represent either a cavitation or choroidal schisis, with the possibility that they could both be part of a spectrum of the same pathological process.

Another finding in the optic nerve and peripapillary region of highly myopic eyes is that of pitlike structures. One study found that pits were found at the optic nerve border or peripapillary area in 16.2 % of highly myopic eyes and that these eyes also were more highly myopic and had significantly larger optic discs and longer axial lengths than highly myopic eyes that did not have any pits [89]. In about a third of cases, the pits were located at the optic disc, where they were present at either the superior or inferior border, and in two-thirds the pits were located in the peripapillary conus. The conus pits were associated with Type IX staphyloma, and the pitting was evident in between the optic nerve border and the scleral ridge and appeared to have developed from a staphyloma-induced schisis.

7.2.7 Vitreous Degeneration

It is known that vitreous syneresis occurs earlier in myopia and, additionally, is more extensive and increases as the myopia worsens [90]. Both vitreous liquefaction and posterior vitreous detachment are common clinical findings with pathological myopia as the increased intraocular volume of an enlarged myopic eye contributes to the development of vitreous degeneration [91]. In the study by Grossniklaus, central vitreous liquefaction was found on histopathological examination in all the myopic eyes examined and posterior vitreous detachment in 33 % of the eyes [6]. In most cases, only the cortical vitreous remained intact (see Fig. 7.23). In several cases they also noted that the posterior vitreous traction had caused retinal holes, cystic degeneration, and retinoschisis. Although increased age is known to be a risk factor for the formation of posterior vitreous detachment, one study compared 224 eyes with high myopia (−6 D or greater) with emmetropic eyes, and found that the prevalence of PVD was higher in the myopic group at every age group [92].

Animal models have found that faulty proteins encoding for the inner limiting membrane (ILM) and vitreous body lead to a 50 % increase in eye size within 4 days, a process which was only slowed by reconstituting the ILM [93]. The results indicate that congenital high myopia can be affected by the integrity of the vitreoretinal border. A study by Chuo et al. found a significant association between myopic

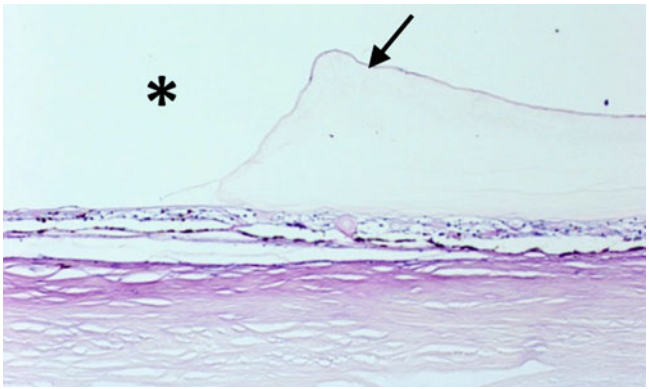

Fig. 7.23 Posterior vitreous detachment. The posterior vitreous is liquefied (*asterisk*) and the anterior vitreous has been dragged forward (*arrow*). *PAS 100×*

refraction and the formation of a posterior vitreous detachment (OR = 4.32, $p < 0.0005$) [94].

A study by Stirpe et al. looked at 496 highly myopic eyes that underwent surgical treatment for retinal detachments [95]. They noticed five characteristic appearances for the vitreous and retina: (1) uniform PVD (21.8 %), (2) PVD spreading to upper quadrants (46.5 %), (3) extensive liquefaction and condensations of the vitreous base (10.2 %), (4) posterior vitreous lacuna (17.5 %), and (5) very limited PVD (3.8 %). The group with posterior vitreous lacuna was found to have a higher degree of myopia as well as more pronounced staphylomas.

Conclusion

The histopathology of pathological myopia plays an important role in understanding the mechanisms by which this condition can affect vision. There have been several excellent and extensive histopathological studies of highly myopic eyes, but in recent years, the use of other imaging modalities such as OCT, fluorescein angiograms, and ICG has become more commonplace in trying to elucidate the nature of the pathological processes. It is important to be able to use these imaging studies in combination with the histopathological descriptions in order to be able to better understand the disease processes and spectrum.

References

1. Foster PJ. Myopia in Asia. Br J Ophthalmol. 2004;88(4):443–4. PubMed PMID: 15031147. Pubmed Central PMCID: 1772076.
2. Ghafour IM, Allan D, Foulds WS. Common causes of blindness and visual handicap in the west of Scotland. Br J Ophthalmol. 1983;67(4):209–13. PubMed PMID: 6830738. Pubmed Central PMCID: 1040020.
3. Sperduto RD, Seigel D, Roberts J, Rowland M. Prevalence of myopia in the United States. Arch Ophthalmol. 1983;101(3):405–7. PubMed PMID: 6830491.
4. Duke Elder S. Pathological refractive errors. In: Ophthalmic optics and refraction, System of ophthalmology, vol. V. St. Louis: Mosby; 1970. p. 297–373.
5. Tokoro T. On the definition of pathologic myopia in group studies. Acta Ophthalmol Suppl. 1988;185:107–8. PubMed PMID: 2853512.
6. Grossniklaus HE, Green WR. Pathologic findings in pathologic myopia. Retina. 1992;12(2):127–33. PubMed PMID: 1439243. Epub 1992/01/01.
7. Curtin BJ. The etiology of myopia. In: The myopias: basic science and clinical management. Philadelphia: Harper and Row; 1985. p. 61–113.
8. Curtin BJ. Physiologic vs pathologic myopia: genetics vs environment. Ophthalmology. 1979;86(5):681–91. PubMed PMID: 397448.
9. Zejmo M, Forminska-Kapuscik M, Pieczara E, Filipek E, Mrukwa-Kominek E, Samochowiec-Donocik E, et al. Etiopathogenesis and management of high myopia. Part II. Med Sci Monit. 2009;15(11):RA252–5. PubMed PMID: 19865068.
10. Zejmo M, Forminska-Kapuscik M, Pieczara E, Filipek E, Mrukwa-Kominek E, Samochowiec-Donocik E, et al. Etiopathogenesis and management of high-degree myopia. Part I. Med Sci Monit. 2009;15(9):RA199–202. PubMed PMID: 19721411.
11. Walline JJ, Lindsley K, Vedula SS, Cotter SA, Mutti DO, Twelker JD. Interventions to slow progression of myopia in children. Cochrane Database Syst Rev. 2011(12):CD004916. PubMed PMID: 22161388.
12. Avila MP, Weiter JJ, Jalkh AE, Trempe CL, Pruett RC, Schepens CL. Natural history of choroidal neovascularization in degenerative myopia. Ophthalmology. 1984;91(12):1573–81. PubMed PMID: 6084222.
13. Klein RM, Green S. The development of lacquer cracks in pathologic myopia. Am J Ophthalmol. 1988;106(3):282–5. PubMed PMID: 3421288.
14. Pruett RC, Weiter JJ, Goldstein RB. Myopic cracks, angioid streaks, and traumatic tears in Bruch's membrane. Am J Ophthalmol. 1987;103(4):537–43. PubMed PMID: 3565514.
15. Klein RM, Curtin BJ. Lacquer crack lesions in pathologic myopia. Am J Ophthalmol. 1975;79(3):386–92. PubMed PMID: 1121996.
16. Curtin BJ, Karlin DB. Axial length measurements and fundus changes of the myopic eye. Am J Ophthalmol. 1971;71(1 Pt 1):42–53. PubMed PMID: 5099937.
17. Ohno-Matsui K, Ito M, Tokoro T. Subretinal bleeding without choroidal neovascularization in pathologic myopia. A sign of new lacquer crack formation. Retina. 1996;16(3):196–202. PubMed PMID: 8789857. Epub 1996/01/01.
18. Ohno-Matsui K, Tokoro T. The progression of lacquer cracks in pathologic myopia. Retina. 1996;16(1):29–37. PubMed PMID: 8927806. Epub 1996/01/01.
19. Johnson DA, Yannuzzi LA, Shakin JL, Lightman DA. Lacquer cracks following laser treatment of choroidal neovascularization in pathologic myopia. Retina. 1998;18(2):118–24. PubMed PMID: 9564691. Epub 1998/06/27.
20. Ohno-Matsui K, Yoshida T, Futagami S, Yasuzumi K, Shimada N, Kojima A, et al. Patchy atrophy and lacquer cracks predispose to the development of choroidal neovascularisation in pathological myopia. Br J Ophthalmol. 2003;87(5):570–3. PubMed PMID: 12714395. Pubmed Central PMCID: 1771643. Epub 2003/04/26.
21. Noble KG, Carr RE. Pathologic myopia. Ophthalmology. 1982;89(9):1099–100. PubMed PMID: 7177575.
22. Rabb MF, Garoon I, LaFranco FP. Myopic macular degeneration. Int Ophthalmol Clin. 1981 Fall;21(3):51–69. PubMed PMID: 6169677.

23. Kobayashi K, Ohno-Matsui K, Kojima A, Shimada N, Yasuzumi K, Yoshida T, et al. Fundus characteristics of high myopia in children. Jpn J Ophthalmol. 2005;49(4):306–11. PubMed PMID: 16075331.
24. Hayashi K, Ohno-Matsui K, Shimada N, Moriyama M, Kojima A, Hayashi W, et al. Long-term pattern of progression of myopic maculopathy: a natural history study. Ophthalmology. 2010;117(8): 1595–611, 611.e1–4. PubMed PMID: 20207005.
25. Okabe S, Matsuo N, Okamoto S, Kataoka H. Electron microscopic studies on retinochoroidal atrophy in the human eye. Acta Med Okayama. 1982;36(1):11–21. PubMed PMID: 7064730.
26. Wang NK, Lai CC, Chu HY, Chen YP, Chen KJ, Wu WC, et al. Classification of early dry-type myopic maculopathy with macular choroidal thickness. Am J Ophthalmol. 2012;153(4):669–77, 77. e1–2. PubMed PMID: 22071232.
27. Ohsugi H, Ikuno Y, Oshima K, Tabuchi H. 3-D choroidal thickness maps from EDI-OCT in highly myopic eyes. Optom Vis Sci. 2013;90:599–606. PubMed PMID: 23604298.
28. Hirata A, Negi A. Morphological changes of choriocapillaris in experimentally induced chick myopia. Graefes Arch Clin Exp Ophthalmol. 1998;236(2):132–7. PubMed PMID: 9498124.
29. Karlin DB, Curtin BJ. Peripheral chorioretinal lesions and axial length of the myopic eye. Am J Ophthalmol. 1976;81(5):625–35. PubMed PMID: 1275043.
30. Celorio JM, Pruett RC. Prevalence of lattice degeneration and its relation to axial length in severe myopia. Am J Ophthalmol. 1991;111(1):20–3. PubMed PMID: 1985485.
31. Yura T. The relationship between the types of axial elongation and the prevalence of lattice degeneration of the retina. Acta Ophthalmol Scand. 1998;76(1):90–5. PubMed PMID: 9541442.
32. Curtin BJ. Posterior staphyloma development in pathologic myopia. Ann Ophthalmol. 1982;14(7):655–8. PubMed PMID: 6982020.
33. Curtin BJ, Teng CC. Scleral changes in pathological myopia. Trans Am Acad Ophthalmol Otolaryngol. 1958;62(6):777–88; discussion 88–90. PubMed PMID: 13625324.
34. Curtin BJ, Iwamoto T, Renaldo DP. Normal and staphylomatous sclera of high myopia. An electron microscopic study. Arch Ophthalmol. 1979;97(5):912–5. PubMed PMID: 444126.
35. Gentle A, Liu Y, Martin JE, Conti GL, McBrien NA. Collagen gene expression and the altered accumulation of scleral collagen during the development of high myopia. J Biol Chem. 2003;278(19):16587–94. PubMed PMID: 12606541.
36. Curtin BJ. The posterior staphyloma of pathologic myopia. Trans Am Ophthalmol Soc. 1977;75:67–86. PubMed PMID: 613534. Pubmed Central PMCID: 1311542.
37. Hsiang HW, Ohno-Matsui K, Shimada N, Hayashi K, Moriyama M, Yoshida T, et al. Clinical characteristics of posterior staphyloma in eyes with pathologic myopia. Am J Ophthalmol. 2008;146(1):102–10. PubMed PMID: 18455142.
38. Chang L, Pan CW, Ohno-Matsui K, Lin X, Cheung GC, Gazzard G, et al. Myopia-related fundus changes in Singapore adults with high myopia. Am J Ophthalmol. 2013;155:991–999.e1. PubMed PMID: 23499368.
39. Moriyama M, Ohno-Matsui K, Futagami S, Yoshida T, Hayashi K, Shimada N, et al. Morphology and long-term changes of choroidal vascular structure in highly myopic eyes with and without posterior staphyloma. Ophthalmology. 2007;114(9):1755–62. PubMed PMID: 17368542.
40. Quaranta M, Brindeau C, Coscas G, Soubrane G. Multiple choroidal neovascularizations at the border of a myopic posterior macular staphyloma. Graefes Arch Clin Exp Ophthalmol. 2000;238(1):101–3. PubMed PMID: 10664062.
41. Mehta P, Dinakaran S, Squirrell D, Talbot J. Retinal pigment epithelial changes and choroidal neovascularisation at the edge of posterior staphylomas; a case series and review of the literature. Eye. 2006;20(2):150–3. PubMed PMID: 15776012.
42. Ohno-Matsui K, Akiba M, Moriyama M, Ishibashi T, Hirakata A, Tokoro T. Intrachoroidal cavitation in macular area of eyes with pathologic myopia. Am J Ophthalmol. 2012;154(2):382–93. PubMed PMID: 22541655.
43. Leys AM, Cohen SY. Subretinal leakage in myopic eyes with a posterior staphyloma or tilted disk syndrome. Retina. 2002;22(5): 659–65. PubMed PMID: 12441740.
44. Gaucher D, Erginay A, Lecleire-Collet A, Haouchine B, Puech M, Cohen SY, et al. Dome-shaped macula in eyes with myopic posterior staphyloma. Am J Ophthalmol. 2008;145(5):909–14. PubMed PMID: 18342827.
45. Henaine-Berra A, Zand-Hadas IM, Fromow-Guerra J, Garcia-Aguirre G. Prevalence of macular anatomic abnormalities in high myopia. Ophthalmic Surg Lasers Imaging Retina. 2013;44(2): 140–4. PubMed PMID: 23438042.
46. Wu PC, Chen YJ, Chen YH, Chen CH, Shin SJ, Tsai CL, et al. Factors associated with foveoschisis and foveal detachment without macular hole in high myopia. Eye. 2009;23(2):356–61. PubMed PMID: 18064059.
47. Takano M, Kishi S. Foveal retinoschisis and retinal detachment in severely myopic eyes with posterior staphyloma. Am J Ophthalmol. 1999;128(4):472–6. PubMed PMID: 10577588.
48. Oie Y, Ikuno Y, Fujikado T, Tano Y. Relation of posterior staphyloma in highly myopic eyes with macular hole and retinal detachment. Jpn J Ophthalmol. 2005;49(6):530–2. PubMed PMID: 16365803.
49. Tano Y. Pathologic myopia: where are we now? Am J Ophthalmol. 2002;134(5):645–60. PubMed PMID: 12429239.
50. Neelam K, Cheung CM, Ohno-Matsui K, Lai TY, Wong TY. Choroidal neovascularization in pathological myopia. Prog Retin Eye Res. 2012;31(5):495–525. PubMed PMID: 22569156.
51. Cohen SY, Laroche A, Leguen Y, Soubrane G, Coscas GJ. Etiology of choroidal neovascularization in young patients. Ophthalmology. 1996;103(8):1241–4. PubMed PMID: 8764794.
52. Inhoffen W, Ziemssen F. Morphological features of myopic choroidal neovascularization: differences to neovascular age-related macular degeneration. Ophthalmologe. 2012;109(8):749–57. PubMed PMID: 22911352. Morphologische Charakteristika der myopen choroidalen Neovaskularisation: Unterschiede zur neovaskularen altersabhangigen Makuladegeneration.
53. Jalkh AE, Weiter JJ, Trempe CL, Pruett RC, Schepens CL. Choroidal neovascularization in degenerative myopia: role of laser photocoagulation. Ophthalmic Surg. 1987;18(10):721–5. PubMed PMID: 2448722.
54. Brancato R, Pece A, Avanza P, Radrizzani E. Photocoagulation scar expansion after laser therapy for choroidal neovascularization in degenerative myopia. Retina. 1990;10(4):239–43. PubMed PMID: 1708513.
55. Pece A, Brancato R, Avanza P, Camesasca F, Galli L. Laser photocoagulation of choroidal neovascularization in pathologic myopia: long-term results. Int Ophthalmol. 1994;18(6):339–44. PubMed PMID: 7543889.
56. Morgan CM, Schatz H. Atrophic creep of the retinal pigment epithelium after focal macular photocoagulation. Ophthalmology. 1989;96(1):96–103. PubMed PMID: 2919053.
57. Yoshida T, Ohno-Matsui K, Yasuzumi K, Kojima A, Shimada N, Futagami S, et al. Myopic choroidal neovascularization: a 10-year follow-up. Ophthalmology. 2003;110(7):1297–305. PubMed PMID: 12867382.
58. Kim YM, Yoon JU, Koh HJ. The analysis of lacquer crack in the assessment of myopic choroidal neovascularization. Eye. 2011;25(7):937–46. PubMed PMID: 21527958. Pubmed Central PMCID: 3178161.
59. Ikuno Y, Sayanagi K, Soga K, Sawa M, Gomi F, Tsujikawa M, et al. Lacquer crack formation and choroidal neovascularization in

pathologic myopia. Retina. 2008;28(8):1124–31. PubMed PMID: 18779719.
60. Leveziel N, Caillaux V, Bastuji-Garin S, Zmuda M, Souied EH. Angiographic and optical coherence tomography characteristics of recent myopic choroidal neovascularization. Am J Ophthalmol. 2013;155(5):913–9 e1. PubMed PMID: 23352343.
61. Verteporfin in Photodynamic Therapy Study Group. Photodynamic therapy of subfoveal choroidal neovascularization in pathologic myopia with verteporfin. 1-year results of a randomized clinical trial – VIP report no. 1. Ophthalmology. 2001;108(5):841–52. PubMed PMID: 11320011.
62. Yoshida T, Ohno-Matsui K, Ohtake Y, Takashima T, Futagami S, Baba T, et al. Long-term visual prognosis of choroidal neovascularization in high myopia: a comparison between age groups. Ophthalmology. 2002;109(4):712–9. PubMed PMID: 11927428.
63. Grossniklaus HE, Gass JD. Clinicopathologic correlations of surgically excised type 1 and type 2 submacular choroidal neovascular membranes. Am J Ophthalmol. 1998;126(1):59–69. PubMed PMID: 9683150.
64. Baba T, Ohno-Matsui K, Yoshida T, Yasuzumi K, Futagami S, Tokoro T, et al. Optical coherence tomography of choroidal neovascularization in high myopia. Acta Ophthalmol Scand. 2002;80(1):82–7. PubMed PMID: 11906310.
65. Scupola A, Ventura L, Tiberti AC, D'Andrea D, Balestrazzi E. Histological findings of a surgically excised myopic choroidal neovascular membrane after photodynamic therapy. A case report. Graefes Arch Clin Exp Ophthalmol. 2004;242(7):605–10. PubMed PMID: 14986008.
66. Nagaoka N, Shimada N, Hayashi W, Hayashi K, Moriyama M, Yoshida T, et al. Characteristics of periconus choroidal neovascularization in pathologic myopia. Am J Ophthalmol. 2011;152(3): 420–7 e1. PubMed PMID: 21696698.
67. Gass JD. Idiopathic senile macular hole: its early stages and pathogenesis. 1988. Retina. 2003;23(6 Suppl):629–39.
68. Ripandelli G, Rossi T, Scarinci F, Scassa C, Parisi V, Stirpe M. Macular vitreoretinal interface abnormalities in highly myopic eyes with posterior staphyloma: 5-year follow-up. Retina. 2012;32(8): 1531–8. PubMed PMID: 22614742.
69. Sayanagi K, Ikuno Y, Soga K, Tano Y. Photoreceptor inner and outer segment defects in myopic foveoschisis. Am J Ophthalmol. 2008;145(5):902–8. PubMed PMID: 18342829.
70. Robichaud JL, Besada E, Basler L, Frauens BJ. Spectral domain optical coherence tomography of myopic traction maculopathy. Optometry. 2011;82(10):607–13. PubMed PMID: 21840263.
71. Konidaris V, Androudi S, Brazitikos P. Myopic traction maculopathy: study with spectral domain optical coherence tomography and review of the literature. Hippokratia. 2009;13(2):110–3. PubMed PMID: 19561782. Pubmed Central PMCID: 2683149.
72. Coppe AM, Ripandelli G, Parisi V, Varano M, Stirpe M. Prevalence of asymptomatic macular holes in highly myopic eyes. Ophthalmology. 2005;112(12):2103–9. PubMed PMID: 16225922.
73. Ripandelli G, Coppe AM, Parisi V, Stirpe M. Fellow eye findings of highly myopic subjects operated for retinal detachment associated with a macular hole. Ophthalmology. 2008;115(9):1489–93. PubMed PMID: 18439680.
74. Tsujikawa A, Kikuchi M, Ishida K, Nonaka A, Yamashiro K, Kurimoto Y. Fellow eye of patients with retinal detachment associated with macular hole and bilateral high myopia. Clin Exp Ophthalmol. 2006;34(5):430–3. PubMed PMID: 16872338.
75. Tornquist R, Stenkula S, Tornquist P. Retinal detachment. A study of a population-based patient material in Sweden 1971–1981. I. Epidemiology. Acta Ophthalmol (Copenh). 1987;65(2):213–22.
76. Michels RG, Wilkinson CP, Rice TA. Retinal detachment. St. Louis: Mosby; 1990. p. 76–84.
77. Mitry D, Singh J, Yorston D, Siddiqui MA, Wright A, Fleck BW, et al. The predisposing pathology and clinical characteristics in the Scottish retinal detachment study. Ophthalmology. 2011;118(7):1429–34. PubMed PMID: 21561662.
78. Williams KM, Dogramaci M, Williamson TH. Retrospective study of rhegmatogenous retinal detachments secondary to round retinal holes. Eur J Ophthalmol. 2012;22(4):635–40. PubMed PMID: 22081671.
79. Jonas JB, Gusek GC, Naumann GO. Optic disk morphometry in high myopia. Graefes Arch Clin Exp Ophthalmol. 1988;226(6):587–90. PubMed PMID: 3209086.
80. Fulk GW, Goss DA, Christensen MT, Cline KB, Herrin-Lawson GA. Optic nerve crescents and refractive error. Optom Vis Sci. 1992;69(3):208–13. PubMed PMID: 1565418.
81. Nakazawa M, Kurotaki J, Ruike H. Long term findings in peripapillary crescent formation in eyes with mild or moderate myopia. Acta Ophthalmol. 2008;86(6):626–9. PubMed PMID: 18577184.
82. Jonas JB, Berenshtein E, Holbach L. Lamina cribrosa thickness and spatial relationships between intraocular space and cerebrospinal fluid space in highly myopic eyes. Invest Ophthalmol Vis Sci. 2004;45(8):2660–5. PubMed PMID: 15277489.
83. Kubena K, Rehak S. Collagen architecture of the lamina cribrosa of the human eye in glaucoma and severe myopia. Cesk Oftalmol. 1984;40(2–3):73–8. PubMed PMID: 6488366. Kolagenni architektura lamina cribrosa lidskeho oka pri glaukomu a tezke myopii.
84. Hsu SY, Chang MS, Ko ML, Harnod T. Retinal nerve fibre layer thickness and optic nerve head size measured in high myopes by optical coherence tomography. Clin Exp Optom. 2013;96:373–8. PubMed PMID: 23561012.
85. Hwang YH, Kim YY. Correlation between optic nerve head parameters and retinal nerve fibre layer thickness measured by spectral-domain optical coherence tomography in myopic eyes. Clin Exp Ophthalmol. 2012;40(7):713–20. PubMed PMID: 22429807.
86. Hwang YH, Yoo C, Kim YY. Characteristics of peripapillary retinal nerve fiber layer thickness in eyes with myopic optic disc tilt and rotation. J Glaucoma. 2012;21(6):394–400. PubMed PMID: 21946540.
87. Jonas JB, Jonas SB, Jonas RA, Holbach L, Panda-Jonas S. Histology of the parapapillary region in high myopia. Am J Ophthalmol. 2011;152(6):1021–9. PubMed PMID: 21821229.
88. Wei YH, Yang CM, Chen MS, Shih YF, Ho TC. Peripapillary intrachoroidal cavitation in high myopia: reappraisal. Eye. 2009;23(1):141–4. PubMed PMID: 17721499.
89. Ohno-Matsui K, Akiba M, Moriyama M, Shimada N, Ishibashi T, Tokoro T, et al. Acquired optic nerve and peripapillary pits in pathologic myopia. Ophthalmology. 2012;119(8):1685–92. PubMed PMID: 22494632.
90. Soubrane G, Coscas G, Kuhn D. Myopia. In: Retina-vitreous-macula [internet]. Philadelphia: WB Saunders Co; 1999. p. 189–205.
91. Curtin BJ. Pathology. In: The myopias: basic science and clinical management [internet]. Philadelphia: Harper and Row; 1985. p. 247–67.
92. Akiba J. Prevalence of posterior vitreous detachment in high myopia. Ophthalmology. 1993;100(9):1384–8. PubMed PMID: 8371928.
93. Halfter W, Winzen U, Bishop PN, Eller A. Regulation of eye size by the retinal basement membrane and vitreous body. Invest Ophthalmol Vis Sci. 2006;47(8):3586–94. PubMed PMID: 16877433. Epub 2006/08/01.
94. Chuo JY, Lee TY, Hollands H, Morris AH, Reyes RC, Rossiter JD, et al. Risk factors for posterior vitreous detachment: a case–control study. Am J Ophthalmol. 2006;142(6):931–7. PubMed PMID: 17157578. Epub 2006/12/13.
95. Stirpe M, Heimann K. Vitreous changes and retinal detachment in highly myopic eyes. Eur J Ophthalmol. 1996;6(1):50–8. PubMed PMID: 8744851. Epub 1996/01/01.