Myopic Vitreopathy

II.B.

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Outline

Keywords
Myopia • Vitreous • Myopic vitreopathy • Posterior vitreous detachment • Anomalous PVD • Retinal detachment • Macular hole • Choroidal neovascularization • Vitreoretinal interface • Myopic foveoschisis

Key Concepts

1. Myopia is increasing rapidly in recent decades, associated with increasing education and urbanization of many populations. Elements of the modern environment such as prolonged reading and time spent indoors are disturbing the normal homeostasis of eye growth known as emmetropization.
2. Mutations of extracellular matrix proteins can result in both myopia and myopic vitreopathy, supporting the concept that vitreous is part of the myopic phenotype. Myopia is associated with increased liquefaction of vitreous, which resembles premature synchysis. This happens in younger myopes when vitreoretinal adhesion remains strong, thus creating anomalous posterior vitreous detachments with a full range of vitreoretinal complications.
3. All degrees of myopia have associated risks of blinding complications, including retinal detachment, maculopathy of various types, cataract, and glaucoma. Maculopathy and retinal detachment have direct connection to myopic vitreopathy. Prophylaxis for myopia and the various complications of myopic vitreopathy requires continued research.

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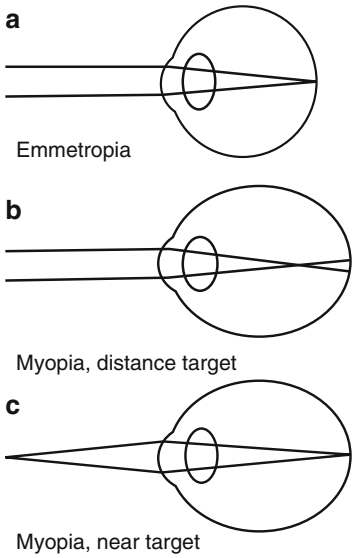

Figure II.B-1 (**a**) Schematic representation of emmetropia. Parallel light from the distance is brought to focus onto the fovea. (**b**) Schematic representation of myopia. Parallel light from the distance is brought to focus anterior to the retina in this elongated globe. This creates a blur circle on the retina. (**c**) Schematic representation of myopia. Divergent light from a near target is brought to focus on the fovea

I. Introduction

Myopia is gaining public health importance because it is a major cause of correctable blindness and visual impairment globally [1]. In some populations the complications of myopia are now the major cause of uncorrectable blindness [2, 3]. Historically, the mild phenotype of low myopia has been separated from the potentially blinding associations of pathological myopia with an arbitrary refractive error of −6.0D [4]. However it is becoming clear that there is no threshold effect and that common myopia of all levels contributes to risks of uncorrectable visual loss such as cataract, glaucoma, retinal detachment, and maculopathy [5, 6].

A. Definition of Myopia

Myopia, defined by refractive error, is the product of multiple optical variables in the eye. Parallel light from infinity is brought to focus anterior to the retina, and divergent light from near targets may focus at the retina, hence "nearsightedness" (Figure II.B-1). The anatomic substrate of this abnormality can be summarized as either an excessively powerful converging optical apparatus of the cornea and lens or an excessively long distance to the retina (axial length). There are many ways to classify or define myopia. At a population level, the main causes of myopia can be grouped as: (1) myopia with systemic associations or syndromes, (2) isolated ocular hereditary myopia, or (3) acquired myopia without associations (Table II.B-1). The first two groups have a clear genetic component. The first group demonstrates connections between the genetic causes of myopia, vitreous, and extracellular matrix in general. It is the third group, however, often known as school myopia or common myopia, which has more environmental causes and is becoming a major cause of correctable and uncorrectable vision loss worldwide.

Table II.B-1 Simple classification of myopia

1. *Syndromic myopia* with systemic associations; for example:
Stickler syndrome type 1 with clefting, arthropathy, vitreoretinal abnormalities, hearing loss, collagen 2A1 mutation
Marfan syndrome with long limbs, ectopia lentis, cardiac abnormalities, fibrillin mutation
2. *Nonsyndromic autosomal dominant myopia*
Isolated ocular hereditary myopia
E.g., early-onset high myopia with dominant inheritance and associated loci on genome-wide analysis
3. *Nonsyndromic myopia acquired in childhood*
Common myopia, school myopia

B. Emmetropization and Axial Length

The process by which the normal eye maintains emmetropia during growth and development is termed emmetropization. Myopia represents a failure of this process. Thus, common myopia may best be characterized as dysregulated eye growth [7]. A rich and expanding scientific literature has illuminated numerous elements of this emmetropization process, particularly through animal studies [8]. A positive lens over a developing chick eye will induce myopic defocus and corresponding shortening of the eye through reduced scleral growth and thickening of the choroid, while hyperopic focus or form deprivation will accelerate scleral growth and thin the choroid (Figure II.B-2). These changes are direction-specific, reversible, and can occur locally within the eye [8, 9]. There are important parallels between these animal findings and humans, as discussed below.

An implication of this understanding is that the failure of emmetropization that results in common myopia does so through an increased axial length. This can be observed in children developing myopia, with an increasing vitreous chamber [10]. Thus, axial length can be considered an important endophenotype of myopia, with greater sensitivity and specificity for the deranged emmetropization process than refractive error in general [11]. That is, the specific anatomic changes of myopia are most apparent in the measurement of the vitreous chamber. Whether cause or effect,

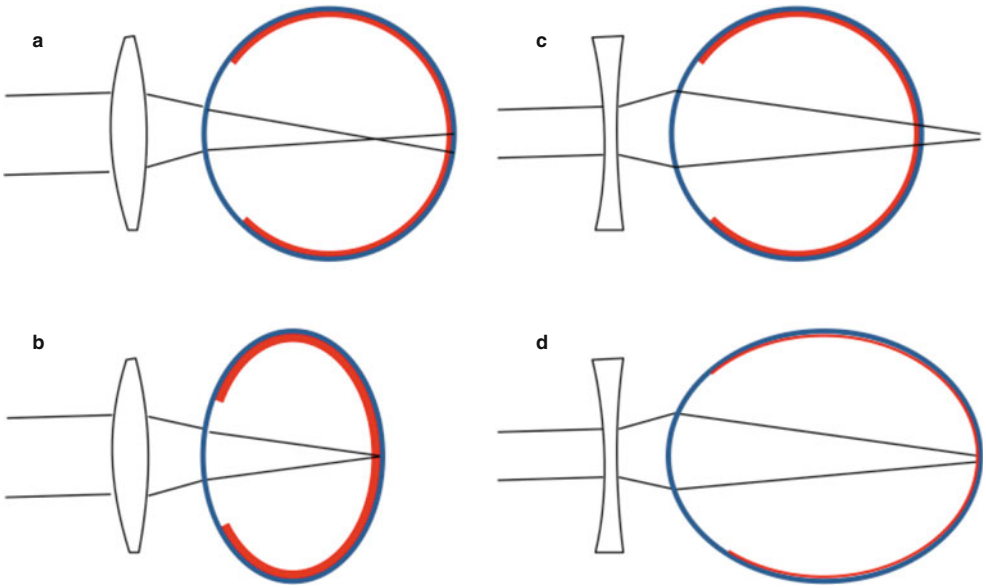

Figure II.B-2 Emmetropization in developing animals. (**a**) A positive lens will induce myopic defocus. (**b**) Axial growth will slow and the choroid will thicken, to bring the image into focus. (**c**) A negative lens will induce hyperopic defocus. (**d**) Axial growth accelerates and the choroid thins, to bring the image into focus

the associated changes within the vitreous constitute myopic vitreopathy. This chapter will discuss the various etiologic (both genetic and environmental) aspects of myopia, the effects on the vitreous that result in myopic vitreopathy, how this causes anomalous PVD, and its various clinical consequences.

II. Myopia

A. Epidemiology

Refractive error is the leading cause of correctable visual impairment worldwide and therefore a major international public health issue [1, 12]. Myopia is common, and prevalence varies between populations [13]. The complications of myopia are the major causes of uncorrectable blindness at a population level in European and Asian populations [2, 3].

Many large cross-sectional studies have found the prevalence of myopia > −0.5D in adults, to range from 15 % in older Australians [14] to 49 % in 44-year-old Britons [15]. In the United States, the overall prevalence has been measured around 25–35 % in adults [16–19] with lower prevalence in Black and Latino people [17, 18, 20, 21]. Asian populations, particularly those of Chinese ethnicity, appear to be mildly more susceptible to myopia [13, 22, 23].

In cross-sectional studies of adults, the prevalence of myopia is found to decline with age, which is due to two factors: the gradual hypermetropization during adulthood [24–26] and an increasing prevalence of myopia in recent generations [27, 28]. Initially noted in Inuit populations in the 1960s [29, 30] and then strikingly documented in Taiwan and Singapore [27, 31], the increasing prevalence of myopia in recent birth cohorts is now clear [28, 32–34]. In Taiwan, for example, the prevalence of myopia in 7-year-old children has increased from 6 % in 1983 to 21 % in 2000, and in those aged 16–18 years, the prevalence of myopia has increased from 74 to 84 % with doubled prevalence of high myopia > −6.0D from 11 % in 1983 to 21 % in 2000. Thus, myopia is beginning earlier and also increasing in severity, especially in young urban educated Asian people. This increase has occurred within three generations, highlighting aspects of the modern environment that are associated with this epidemic of myopia [34, 35].

B. Etiology

It is likely that myopia, like cardiovascular disease, for example, represents a complex interaction of genetic and environmental factors. The increasing prevalence of myopia associated with ethnicity, urbanization, and education highlights the multifactorial etiology, rather than simply nature versus nurture [36].

1. Genetic Factors

Human myopia is etiologically heterogenous at a genetic level, with more than 300 associations identified. As briefly summarized in Table II.B-1, several syndromes of ocular and systemic abnormality can include high myopia, such as Marfan, Weill-Marchesani (both fibrillin mutations), Stickler types 1 and 2 (collagen II and XI mutations), Ehlers-Danlos (type 4, collagen III mutation), Knobloch (collagen XVIII mutation), and congenital stationary night blindness syndromes [37]. These syndromes often include abnormalities

of the vitreous and relate to mutations of the extracellular matrix [see chapter I.C. Hereditary vitreo-retinopathies].

There are also isolated ocular forms of familial high myopia, which is often early-onset and severe [37]. In general, high myopia may have a stronger genetic component [38]. These familial forms of myopia (e.g., associated with chromosomes 18p or 12q) do not seem to relate to the common school myopia, which has a greater environmental component [39, 40].

The heritability of myopia appears to diminish between generations. Children of myopic parents have a higher prevalence of myopia, but in China this relationship has changed dramatically in two generations [35]. For the parents' generation, being born to myopic parents resulted in an odds ratio (OR) of 6.71 for developing myopia, but for their children's generation, myopic parents only conveyed an OR of 1.85 [35]. This indicates the genetic risk has been diluted by the environmental risks. In general, the heritability estimates that are derived from correlations of refractive error are greater from sibling to sibling correlations than parent–child correlations (particularly in times of intergenerational change), indicating shared environments are a large part of these correlations [37, 38].

Eye size is heritable, but this does not seem relevant to myopia. Children of myopic parents were found to have larger eyes before they developed myopia and after controlling for near work and education [41]. However, eye size and axial length are poor predictors of myopia because the process of emmetropization adjusts ocular growth to match focal length [42]. There is scant evidence to suggest that larger eyes are more vulnerable to derangement of emmetropization [37, 40]. The implication of this is that the larger eyes in children of myopes may simply reflect shared environmental factors or irrelevant covariates such as height, rather than a genetic determinant of myopia. On the other hand, some carefully controlled observational studies find parental myopia far more strongly associated with myopia than environmental factors in multivariate models that adjust for both [40].

Twin studies are a powerful method for testing heritability, and several early results showed extremely high estimates of heritability (summarized and tabulated in Guggenheim et al. [38]). The assumptions concerning twins sharing environments have been challenged, and these studies will consistently overestimate heritability at a population level [37].

Genome-wide association studies provide a powerful method to establish genetic causes of the disease and understand pathophysiology. Hammond et al. [43] performed a linkage analysis in 280 dizygotic twins (with any type of myopia), revealing the 11p13 locus overlying PAX6 as a possible association, as well as other loci of interest at 3q26, 8p23, and 4q12. Genetic investigation of dizygotic twins shares the power of twin studies by controlling environments to a large degree. Stambolian et al. [44] were the first to perform genome-wide analysis exclusively for the common school myopia, with methods designed to increase the likelihood of linkage, and identified one locus at 22q12 for further study. In recent years, a rapidly growing number of genome-wide association studies have established a growing number of loci of interest, though differences in populations and differences in the types of myopia that are included can make interpretation difficult. Now, very large consortia have examined the entire genome of many thousands of participants for associations with myopia [45–49]. Fan et al. [45] identified a locus of interest in 1q41 among three large Singapore genome-wide studies. Verhoeven et al. [46] validated an association of myopia with 15q14 (GDJ2) among many cohorts across Europe and Asia and also commented on a gene for Connexin36 and actin proteins that could have relevance to retinal signaling or scleral remodeling. Cheng et al. [49] limited their analysis to loci associated with axial length, as this is a suitable endophenotype for myopia, and tested over 12,000 Europeans and 8,000 Asians, then validated the findings in another independent group of over 23,000. They found nine loci common to both European and Asian cohorts to be associated with myopia, including 1q41 (ZC3H11B) and 15q14 (GJD2), as well as laminin alpha-2 subunit (LAMA2) on chromosome 6. Two other loci were associated with Wnt signaling pathways. Verhoeven et al. [47] performed a similar large consortium-derived genome-wide analysis of refractive error in many thousands of participants in multiple continents. They identified 24 loci, including GDJ2 and LAMA2 again but also candidate genes with functions in neurotransmission (GRIA4), ion transport (KCNQ5), retinoic acid metabolism (RDH5), and eye development (SIX6 and PRSS56). Kiefer et al. [48] found 22 loci associated with myopia in another large genome-wide study of Europeans, including LAMA2 and candidate genes involved in photopigment regeneration and retinal development and signaling. These powerful studies and enticing findings require considerable follow-up investigation to understand the relevant genetic and molecular pathways in common myopia.

The genetic associations of myopia can be summarized by stating that mutations of extracellular matrix proteins commonly result in both myopia and vitreopathy, supporting the concept that vitreopathy is part of the myopic phenotype. Common myopia represents failure of the emmetropization process, and the genetic associations include signaling pathways and the LAMA2 subunit of laminin, an important extracellular protein in the vitreoretinal interface.

2. Environmental Factors

Animal studies, particularly with chicks, rodents, and nonhuman primates, have clearly shown that the homeostasis of ocular growth is guided by vision [5, 8]. Form deprivation

results in myopia in monkeys [50] and children [51] as well as other animals. In chicks as in other animals, a positive lens providing myopic defocus results in thickening of the choroid and slowing of scleral growth, while hyperopic defocus from a negative lens results in ocular elongation and choroidal thinning [52] (Figure II.B-2). These responses are partially preserved with optic nerve transection and can be generated locally in only half of one eye using partial lenses [9, 53–55], indicating that an important signal for eye growth is generated locally in the retina. Thus it appears that the developing retina can detect blur but can also detect the sign of the defocus, in order to slow or accelerate growth in the correct direction, which may be mediated by combining cues from chromatic and non-chromatic aberrations and from accommodation [8, 56]. These findings implicate a signaling pathway from the retina, through the choroid to the sclera. Although the pathways involved have not been clearly demonstrated, retinoic acid production in the choroid is likely to be involved because it is upregulated by myopic defocus and inhibits scleral proteoglycan synthesis and downregulated in hyperopic defocus when the sclera elongates and causes increased scleral proteoglycan synthesis [57]. The effector mechanism of emmetropization involves changes in fluid lacunae in the choroid [58] and changes in the scleral growth, with scleral thinning, remodeling, and increased viscoelasticity ("creep"). The abnormalities of myopic sclera are described below. Together these findings elucidate mechanisms by which environmental factors can affect the normal process of emmetropization.

Education and urbanization are the two environmental factors that are closely associated with myopia at a population level. Common myopia correlates strongly with education across all major population groups of the world [37]. This association exists with the duration of education, intensity of study and final academic achievement, and professional training in law, medicine, or engineering. The progression of myopia may even occur in parallel with the school terms in some populations [59]. Similarly, in regions with very similar genetic background, people in urban centers have consistently higher prevalence of myopia than in rural areas, even after adjusting for education, affluence, and activities [37].

Near work is the environmental factor that is used to explain these associations mechanistically at an individual level. The mechanism here is not excessive accommodative effort, but accommodative lag or deficiency. Accommodation is driven by a blur-feedback loop, so there is a tendency to accommodate only to the point of acceptable blur, resulting in mild hyperopic defocus for near targets (accommodative lag). Myopes have more accommodative lag than emmetropes, but it is unclear whether this accommodative lag precedes myopia development and whether this lag is a specific defect in pre-myopes [60–63]. Thus, the association between near work and myopia is sometimes weak and difficult to quantify. Other factors such as the relative potency of different types of defocus for eye growth, peripheral refraction patterns, and the variations in defocus due to physical environments are all explanations for why these associations can be hard to measure [5].

A more recently revealed association between time spent outdoors and a reduced risk of myopia may also explain much of the associations of myopia with urbanization, population, and education [64–66]. This was hypothesized to be related to UV light stimulation of dopamine release from amacrine cells, a pathway that is shown to reduce eye growth and myopia in animal studies [33, 64].

In summary, the normal processes of emmetropization may be deranged or confused by aspects of the environment to create myopia. The retina has the central role in detecting not only the blur but also the direction of defocus and changing ocular growth to compensate. Near work could result in persistent low-grade hyperopic defocus to drive excessive ocular growth, although multiple optical considerations can make this association tenuous at a population level. Certainly, education and urbanization are strongly associated with myopia, and both near work and time spent outdoors might partially explain these associations. Clinical trials of outdoor education and optical interventions continue [33, 67].

3. Vitreous Factors

Curtin [68] and Seltner [69] proposed a role for the vitreous in the development of myopia, suggesting excessive vitreous formation was a cause for ocular enlargement. As mentioned, hereditary abnormalities of collagen can result in syndromic vitreopathy and myopia, linking the two with common causation [70]. In line with this concept, Wilkinson [71] correlated intraocular pressure with ocular growth in experimental chick models, and Quinn [72] showed a slightly increased IOP among myopic children. On the other hand, the rate of passive scleral creep in experimental situations is two orders of magnitude greater than the maximal rate of ocular elongation [73], and scleral remodeling appears to be an active cellular process rather than a passive stretching process [8]. Also in opposition to this theory of "overinflation," tree shrews showed scleral contraction in response to experimentally increased IOP [74]. It is hard to propose a complete model by which vitreous expansion could lead to axial growth, when the formation of the vitreous in the mature eye is not well understood.

C. Ocular Features of Myopia

1. Scleral Changes and Axial Length

The characteristic changes of myopia are seen in the size and shape of the globe. Axial length accounts for more than 40 %

of refractive error and is considered an important endophenotype of myopia [10, 49, 75, 76]. Axial length also correlates more closely with complications of myopia than does refractive state [77].

Myopic sclera is thin and distensible, particularly in the posterior globe, with good agreement between mammalian models and the limited human data reported [7, 78–81]. At a histological level, myopic sclera has thin collagen fibrils distributed uniformly through the scleral wall in a lamellar pattern, compared to normal sclera with thicker fibrils in the outer layers and greater interweaving [80, 82, 83]. In experimental myopia induced with hyperopic defocus or deprivation, the posterior scleral collagen fibers are lost first, and overall scleral dry weight decreases, implicating a remodeling process rather than stretching and redistribution of fibers [83, 84]. The viscoelastic stretching known as scleral creep is increased, particularly in the posterior sclera [73, 85, 86]. The posterior sclera matures later than the anterior sclera, and these changes of experimental myopia have been described as delayed maturation of the posterior sclera [8]. Corresponding to this, the sensitive period through which deprivation can induce myopia corresponds to the maturation of the sclera [87].

At a biochemical level, several changes can be detected in the elongating myopic sclera. Collagen content and collagen synthesis in the sclera are reduced in experimental myopia, and prevention of collagen cross-linking also worsened deprivation-induced myopia but did not affect the open contralateral eyes [88]. Specifically, collagen I synthesis is reduced, with increased proportions of collagen III and collagen V, which may explain the reduced collagen fibril diameters [89]. In mammalian models of deprivation myopia, in contrast to avian models, which have different scleral structure, glycosaminoglycans (GAG) synthesis is reduced [88, 90]. Scleral metalloproteinases are upregulated in experimental myopia, further reducing collagen content [91, 92], and there is differential expression of regulating proteins (TIMPs) which can further activate metalloproteinases [88, 93]. At a cellular level too, differentiation of dormant scleral fibroblasts into contractile myofibroblasts appears to have an important role in scleral biomechanics, but the exact relevance to myopic sclera has not been established [7].

In summary, signals from the retina lead to elongation of the globe and scleral thinning through changes in the sclera which include reduced collagen production, increased viscoelasticity, remodeling and thinning, and potentially changes in cellular activity.

2. Myopic Vitreopathy

The vitreous is particularly liquefied in myopic eyes [94, 95]. Nonspecific vitreous degeneration is observed in myopic eyes, but histology cannot differentiate specific myopic changes from age-related synchysis [96]. This myopic liquefaction could be because the vitreous chamber is of increased volume and production of gel components does not keep pace with the expanding chamber. In measuring the molecular components of myopic vitreous with early techniques, Berman and Michaelson [97] found reduced protein concentration, collagen content, and estimated hyaluronate concentrations in myopic vitreous compared to controls. Total protein of the vitreous was not directly measured.

In experimental deprivation myopia in chicks, it is relevant to understand the normal development: vitreous protein concentration declines during embryonic development, as a blood ocular barrier and vitreous macromolecules form, both of which exclude plasma proteins. By hatching, there is a formed gel vitreous anterior to a 20–30 % chamber of liquid vitreous posteriorly, which is surrounded by a thin cortical layer [98, 99]. This liquid component increases to 60 % volume by adulthood. When a diffuser is used to create deprivation myopia in one eye in the first days after hatching, the vitreous chamber expands and total volume increases, with the increase entirely due to liquid vitreous [69, 100]. The gel vitreous did not change in size or protein composition, but the myopic liquid vitreous had mildly reduced protein concentration (although not significantly) [100]. This implies that in aging of the chicken vitreous, or in experimental deprivation myopia, the liquid vitreous gains in size and reduces in protein concentration.

Together these findings imply that the production of vitreous gel occurs in the vascular and cellular embryonic vitreous and that myopic ocular growth during postnatal development is not matched by production of additional vitreous gel. Thus, the elongation of the globe is accompanied by increased liquid, low-protein vitreous.

As a result, myopic vitreous has a phenotype resembling premature synchysis, and posterior vitreous detachment (PVD) occurs earlier in highly myopic eyes [101, 102]. Akiba [101] found PVD occurred around 10 years earlier in myopia > −6.0D (compared to emmetropes). Indeed, 23 % of these myopes had PVD between age 30 and 40 years, with 100 % over 70 years, compared to no PVD among emmetropes under 40 years, with PVD in 74 % of those 70–80 years old. Morita [102] found PVD to occur closer to 20 years earlier in those with axial length >26.0 mm (myopia > −8.25D), compared to age-matched controls who were low myopes, emmetropes, or hypermetropes.

Premature vitreous liquefaction occurring in younger people who have strong vitreoretinal adhesion [103] creates the conditions for an anomalous PVD and pathological vitreoretinal interactions [104]. Stirpe and Heimann [105]

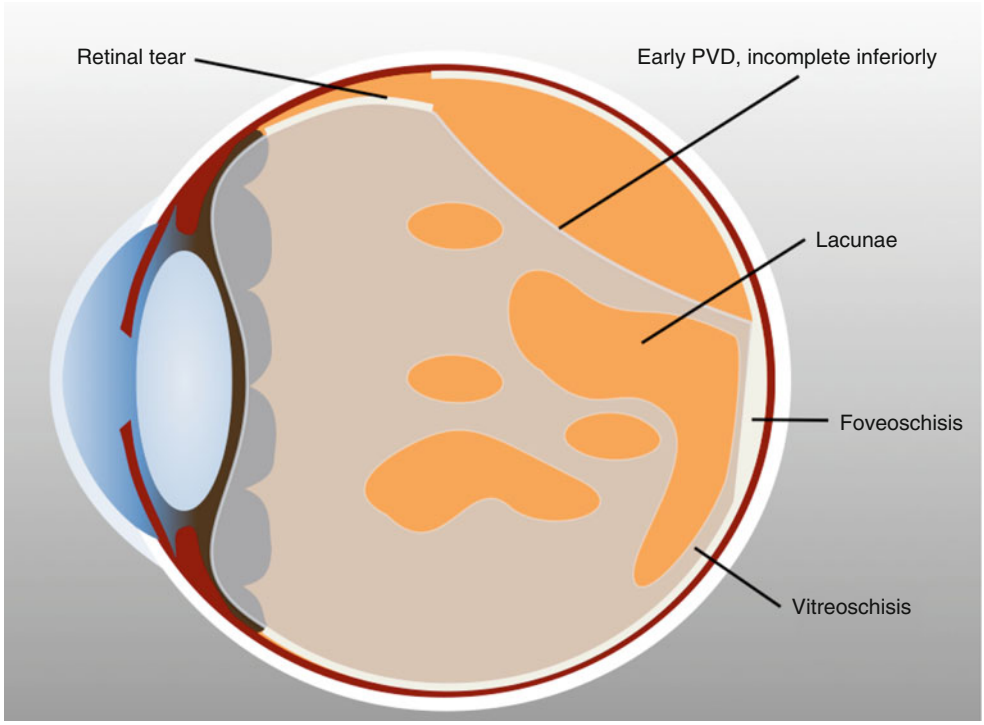

Figure II.B-3 Features of myopic vitreopathy. Increased liquefaction and early synchysis result in lacunae, vitreous collapse, and premature posterior vitreous detachment (PVD) when vitreoretinal adhesion persists. This may lead to an anomalous PVD, with risk of retinal tears or maculopathy such as foveoschisis

found that among 496 highly myopic eyes undergoing retinal detachment surgery, there were 17.5 % with prominent posterior vitreous lacunae overlying posterior staphyloma with a thin but strongly adherent vitreous cortex, and among these posterior retinal breaks such as macular holes were common. Forty-six of the 496 eyes had incomplete PVD inferiorly, with partial PVD and retinal breaks in the superior globe, and a tendency for delayed postoperative retinal tears inferiorly. Similarly, Sakaguchi and colleagues [106] found vitreoschisis, preretinal proliferation, and a firmly adherent ILM during vitrectomy in a 73-year-old highly myopic woman with macular hole, requiring three layers of membrane peeling [see chapter III.B. Anomalous PVD and vitreoschisis]. Thus, PVD and peripheral retinal breaks have an ominous prognosis in myopia, due to persistence of the normal vitreoretinal adhesion of youth. These changes are summarized in Figure II.B-3.

3. Retina and Choroid

Changes in the myopic retina have long been observed by clinicians. In humans and experimental models, the choroid is thinner, and may sometimes lack the choriocapillaris, with overlying retinal thinning that is presumed to be secondary [33, 80]. The clinical relevance of these changes in the retinal periphery has been hard to define precisely [107]. The vision-threatening manifestations of this chorioretinal thinning at the macula are discussed below.

a. Retinal Lattice

Retinal lattice (also called "lattice degeneration") is associated with myopia, particularly over −6.0D, and is of interest in this review of myopic vitreopathy because abnormal vitreoretinal adhesions are a key part of this pathology. As summarized by Saw [108], the evidence for an association between myopia and lattice is not strong because there are few prospective studies. In the United States, Karlin and Curtin [109] examined over 1,400 asymptomatic myopic eyes, and Pierro [110] examined 513 asymptomatic myopic patients and found an association between retinal lattice and axial length. On the other hand, Yura [111] examined 542 high myopes in Japan and did not find an association with axial length, while Celorio [112] even found the prevalence of lattice to be decreased in extreme myopia. In preoperative evaluations of 165 eyes in patients with pathological myopia (> − 8.0D or 26.0 mm axial length) undergoing clear lens extraction, retinal lattice was detected in 10 % of patients [113]. Histological evaluation of 308 eyes with pathological myopia revealed peripheral retinal degeneration in 31 %, cobblestone degeneration in 14 %, and retinal lattice in 5 % [114]. A variant of retinal lattice was present in an additional 11 %. A total of around 16 % was in agreement with another study of 436 eyes with myopia of > −6.0D, among patients with retinal detachments [115]. It is tempting to speculate that retinal lattice, as a feature most prominent in those with moderate and high myopia, represents a feature of common myopia (rather than the more severe isolated

heritable myopia). Another intriguing connection is with Stickler syndrome [see chapter I.C. Hereditary vitreo-retinopathies], where a mutation of collagen II results in vitreopathy, myopia, and widespread lattice. Because collagen II is predominant in the vitreous, this could suggest that lattice is a manifestation of a myopic vitreopathy. Prospective observation of lattice in child populations at high risk of myopia (e.g., urban Taiwan, Singapore) could establish the temporal connection between these peripheral retinal changes and the development of axial elongation.

D. The Pathologies of Myopic Vitreopathy

1. Retinal Detachment

As discussed above, myopia results in premature vitreous synchysis combined with vitreoschisis and firm vitreoretinal adhesion, creating the conditions for anomalous PVD and retinal tears with persistent vitreous traction. Retinal tears are common in myopia. Hyams and Neumann [116] found peripheral retinal breaks in 10.5 % of low myopes and 13 % of high myopes from a total of 332 asymptomatic myopes in the clinic. Consequently, there is a clear association between rhegmatogenous retinal detachment (RRD) and myopia. Two case–control studies found elevated odds ratio for myopia among those with RRD compared to controls [115, 117], and this was confirmed in a large multicenter case–control study [118]. Excluding pathological myopia, there was an odds ratio of 7.8 for myopia overall, increasing from 4.4 for myopia between −1.0D and −3.0D to almost ten-fold increased risk for those over −3.0D [118].

Prophylaxis for retinal detachment in myopia remains controversial [119]. While laser retinopexy is recommended for retinal tears under traction before cataract surgery, prospective evidence should be collected, and trials of pharmacologic vitreolysis or primary vitrectomy could be considered.

a. Retinal Detachment After Anterior Segment Surgery

Retinal detachment is an uncommon complication after cataract surgery, with incidence rates between 0.3 and 1.2 % in the general cataract population [120–124]. This incidence of RRD after cataract surgery presumably relates to surgical forces on the anterior vitreous cortex and postoperative inflammation, resulting in anomalous PVD and vitreoretinal traction [125]. The rate of RRD after cataract surgery in myopes is of particular interest to ophthalmologists, particularly as clear lens extraction gains popularity for refractive correction. Initial studies from the 1980s using predominantly extracapsular cataract extraction (ECCE) showed pseudophakic RRD incidence of 1.6 % in myopes > −6.0D (or 4.1 % in those with axial length >26.5 mm) [77]. With retrospective comparison Badr [126] found that intraocular lenses resulted in fewer RD among myopes, compared with aphakia. A population-based case–control study [127] comparing 291 cases of RD after cataract surgery to 870 matched uncomplicated cataract operations found that the odds ratio of RD increased by 0.92 for each diopter of myopia and by 1.21 for each millimeter of axial elongation, potentially supporting the concept that axial length predicts RRD risk better than refraction [77].

However, as phacoemulsification technology improves, cataract surgery appears to be getting safer for myopes. In a large retrospective cohort of 2,356 eyes (1,519 patients) all with >27.0 mm axial length, the incidence of pseudophakic RRD after phacoemulsification was 1.5–2.2 % (the minimum value excluding RRD that could be attributed to other causes) [128]. Across a range of similar retrospective cohorts, the incidence of RRD among high myopes after phacoemulsification ranges from 0 to 8.1 % depending on the age, indication, and severity of myopia [129–134].

Clear lens extraction for myopia may have an even greater risk of RRD, simply because it is offered to younger patients with stronger vitreoretinal adhesion. In young patients receiving clear lens extraction for high myopia, some of the greatest rates of pseudophakic RD have been reported, for example, 8.1 % [129], 7.3 % with ECCE [113], and 8.0 % with very high myopia >−15.0D. However, some argue that these rates are not greatly higher than the incidence of spontaneous RRD among cohorts of similar severe myopia [128].

Refractive corneal surgery such as laser-assisted in-situ keratomileusis (LASIK) induces PVD in some high myopes due to physical forces from the suction ring [135]. However, LASIK appears to have a lower incidence of RRD than lens extraction, estimated 0.19 % at 10 years postoperatively among 11,594 myopes <−10.0D [136]. Other posterior segment complications of LASIK for myopia also appear to be rare [137].

2. Myopic Maculopathy

Myopic maculopathy encompasses a range of vision-threatening pathologies [4, 138], many of which bear direct connection to myopic vitreopathy. The regular presence of vitreoschisis, large lacunae, and anomalous PVD results in specific myopic maculopathies such as foveoschisis and macular hole with extensive retinal detachment. There are also some indications that CNV can relate to the vitreoretinal interface [see chapter III.G. Vitreous in age-related macular degeneration], although this has not been shown in myopia [139]. Anomalous PVD with vitreomacular traction can be different in myopia than emmetropia (Video II.B-1). Pharmacologic vitreolysis [see chapter VI.A. Pharmacologic vitreolysis] and dye-assisted chromodissection [see chapter V.A.3. Chromodissection in vitreoretinal surgery] to remove vitreoschisis layers during surgery will likely assist greatly in management [140].

a. Myopic Macular Degeneration

There are two types of atrophic degenerations in high myopia: patchy atrophy is seen as a whitish lesion and well demarcated

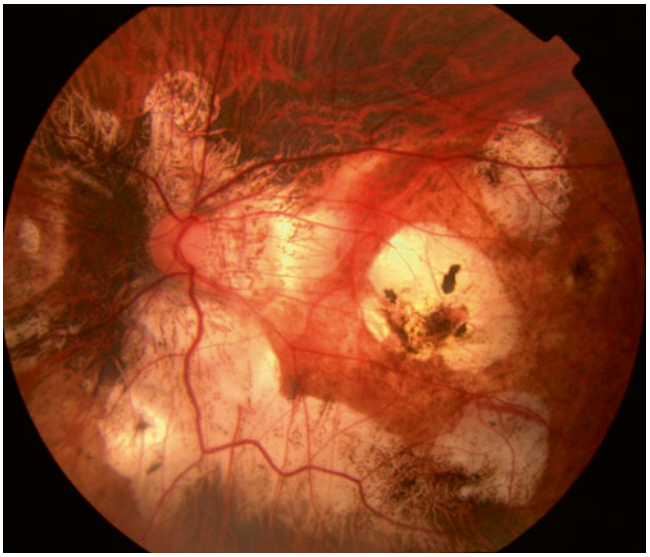

Figure II.B-4 Patchy chorioretinal atrophy. Several whitish lesions with well-identifiable margins are typically seen at the posterior pole

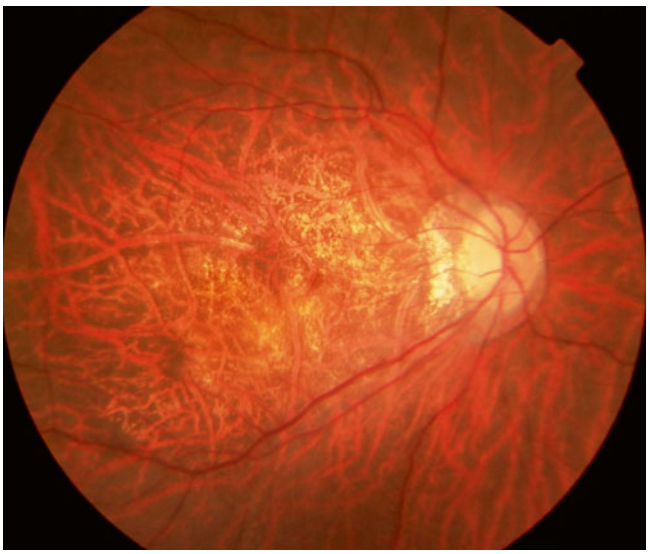

Figure II.B-5 Diffuse atrophy. The area inside the posterior staphyloma is yellowish-white, and the margin is ill-defined

(Figure II.B-4), and diffuse atrophy is yellowish-white and harder to demarcate or identify (Figure II.B-5). Lacquer cracks are whitish linear or crisscrossing lesions that sometimes are accompanied by a myopic subretinal hemorrhage. These atrophic changes appear to relate to loss of underlying choriocapillaris and splits in Bruch's membrane (lacquer cracks). The presence of lacquer cracks implies that stretching and redistribution of the scleral collagen and the underlying mechanical stretching and thinning of the choroid are part of the pathological process in myopic development. No treatment currently exists for these changes, and there are no prospective data to quantify the risk of vision loss, which can be severe.

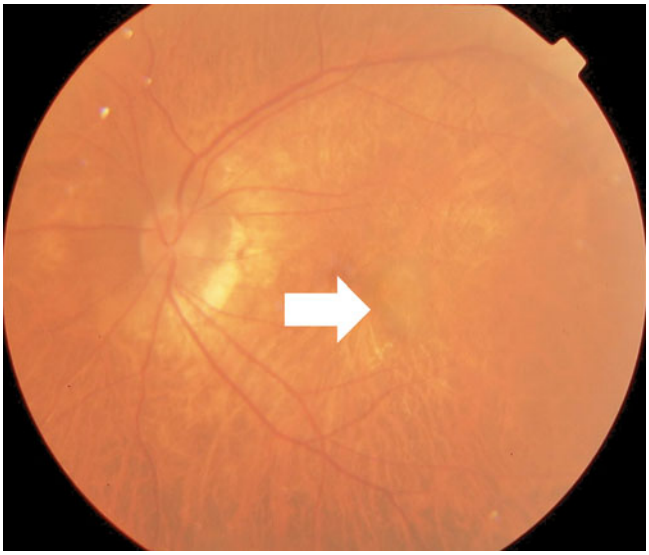

Figure II.B-6 Representative case of choroidal neovascularization (CNV) from pathological myopia. A small, grayish round lesion can be seen (*arrow*)

i. Choroidal Neovascularization

Choroidal neovascularization (CNV) is the main complication of degenerative myopic maculopathy and lacquer cracks [138]. Myopia is the second leading cause of CNV after age-related macular degeneration and the most common predisposing factor in younger patients [4]. The CNV in myopia is also referred to as a Forster-Fuchs' spot and commonly presents as a mound-shaped, grayish, small, and round lesion (Figure II.B-6). The incidence is unknown; however, Curtin and Karlin [141] reported it in 5.2 % of postmortem eyes with axial lengths exceeding 26.5 mm. Unfortunately, prospective clinical data are lacking [108]. The etiology is not fully understood, but lacquer crack formation and consequent upregulation of vascular endothelial growth factor (VEGF) may play critical roles. As in the case in AMD [see chapter III.G. Vitreous in age-related macular degeneration], the vitreous may play a role in the pathophysiology of myopic CNV, but this has yet to be investigated. While a range of treatments have been successfully offered for myopic CNV, anti-VEGF therapy currently appears to have the best risk-benefit profile with excellent visual outcomes [138].

b. Myopic Foveoschisis

Prior to the widespread use of optical coherence tomography (OCT), myopic foveoschisis was potentially mislabeled as a retinal detachment of the macula overlying a posterior staphyloma, without a macular hole [142, 143]. The term foveoschisis includes a variety of pathologies: a foveal cyst in 47 %, a lamellar hole in 29 %, and a foveal detachment in 29 % [144]. The inner retina is often split from the outer retina by traction that includes residual adherent vitreous cortex, with or without vitreoschisis [see chapter III.B.

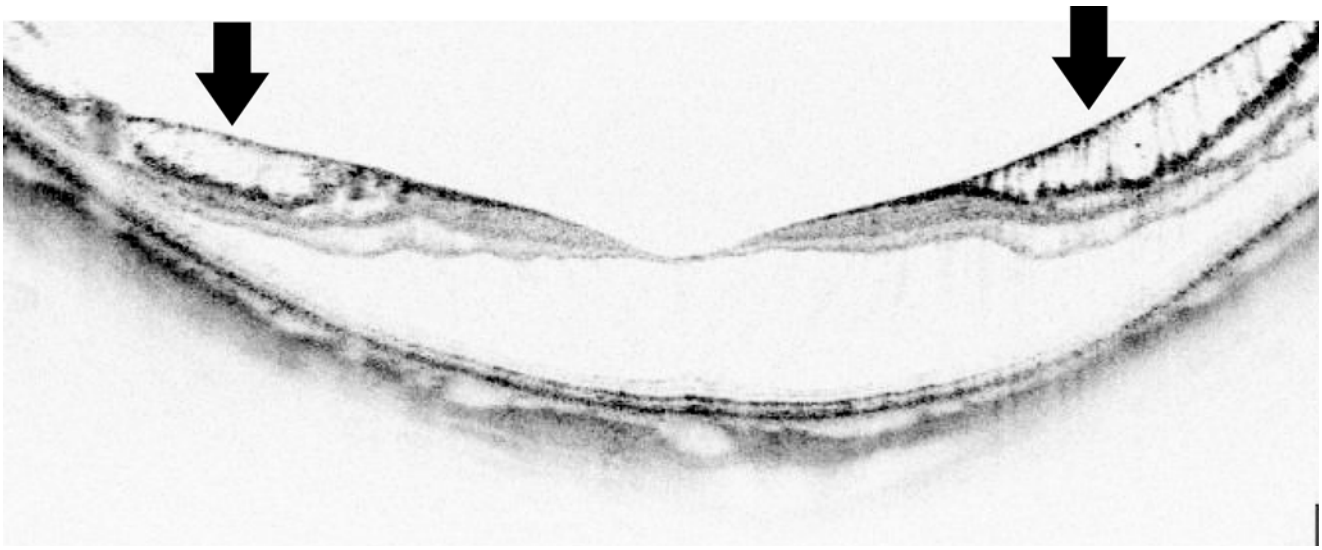

Figure II.B-7 Optical coherence tomography (OCT) appearance of an inner limiting membrane (ILM) detachment in myopic foveoschisis (*arrows*). A thin sheet is separated from the other retinal layers. Columns bridge the split between the layers

Figure II.B-8 Typical optical coherence tomography (OCT) image of retinal microfolds from retinal vascular traction (*arrows*). A tentlike lesion can be seen with retinal arterioles on the top

Anomalous PVD and vitreoschisis], and a rigid inner limiting membrane (ILM). The foveoschisis sometimes leads to macular hole formation and consequent retinal detachment [145]. The so-called ILM detachment is observed and is an indicator of the tractional force upon the ILM (Figure II.B-7) [146]. A tentlike peak of the inner retina is seen on OCT images coincident with retinal vessels and the so-called retinal microfolds (Figure II.B-8) [147]. The inner segment/outer segment (IS/OS) junction of the photoreceptors sometimes disappears in the area of the retinal detachment [148]; however, the IS/OS line is typically well preserved in the area of the retinoschisis, suggesting that the photoreceptor function is not affected in this subtype. Retinoschisis has two stages before macular hole formation [149]. The first is the retinoschisis type, in which only retinoschisis and not a retinal detachment is present (Figure II.B-9). A retinal detachment later begins from the fovea. The next stage is the foveal detachment type (Figure II.B-10). After a while, the inner retina above the detachment is stretched and torn (Figure II.B-11). This is the appearance of a macular hole as a result of retinoschisis with a retinal detachment. The OCT images from these myopic eyes led to the hypothesis that the inner retina is less flexible than the outer retina because the vitreous cortex adheres to the retina [149]. The pattern

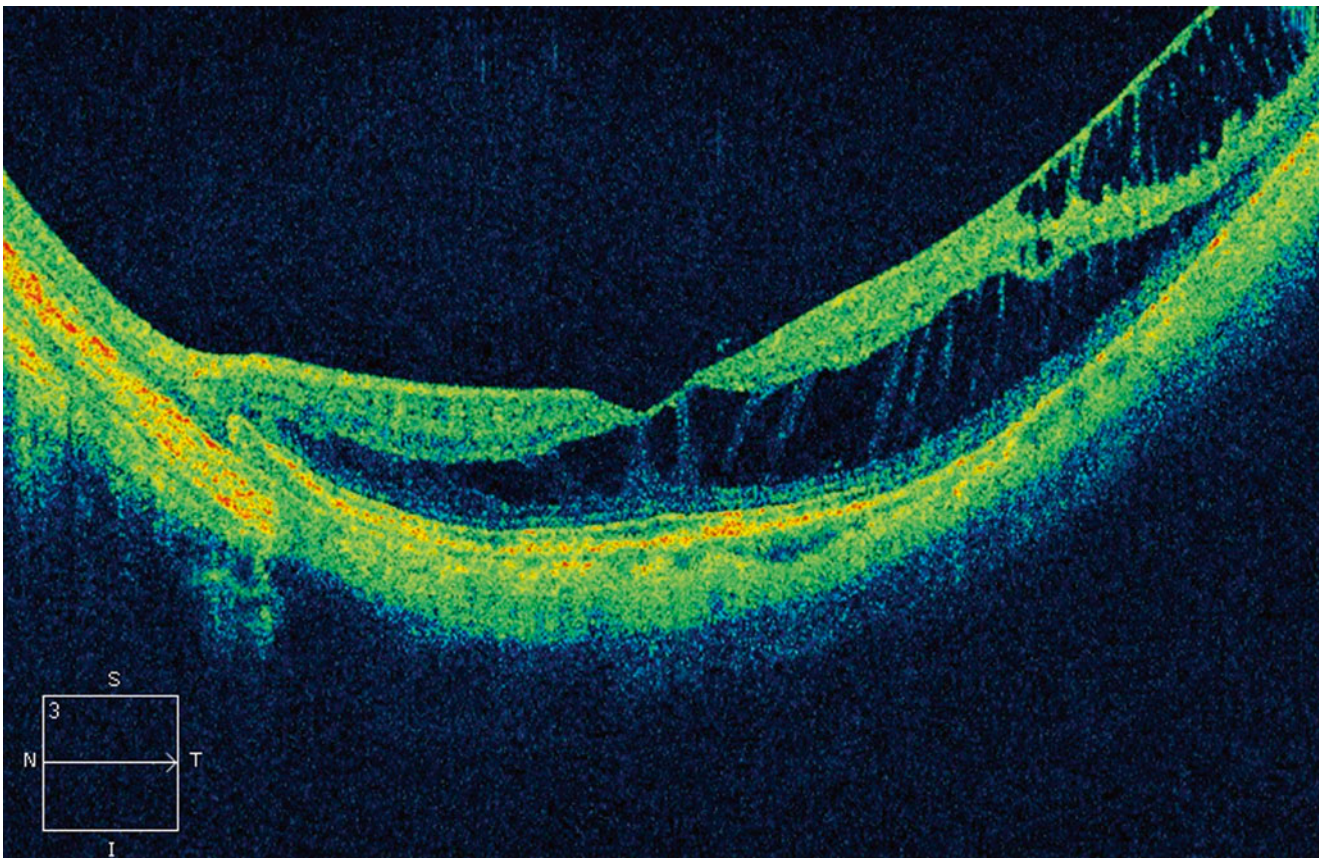

Figure II.B-9 Optical coherence tomography (OCT) image of retinoschisis type of myopic foveoschisis. The inner and outer retina is split and connected by columns. The photoreceptors are still attached to the retinal pigment epithelium (RPE)

of ILM detachments illustrates the underlying traction from the ILM, which is anchored at blood vessels on the retinal surface (Figure II.B-7) [146, 147]. An OCT study of over 200 highly myopic eyes reported ILM detachments in 6 %, retinoschisis in 13.5 %, and retinal vascular microfolds in 20 % [150].

c. Premacular Membranes

Premacular membrane (PMM) formation and retinal thickening are common in highly myopic eyes. The membrane is often difficult to find without OCT. A PMM sometimes causes retinoschisis with retinal wrinkling or macular lamellar holes (i.e., distorted foveal contour without full thickness macular hole) [144]. Histological membrane specimens from macular holes and myopic foveoschisis revealed a thin collagenous vitreoschisis and a fibroblast PMM in many myopic eyes [106, 151].

d. Macular Hole

Macular holes may develop more frequently in highly myopic eyes, and while vitrectomy appears to be successful, it can be difficult to judge closure clinically on an atrophic myopic macula [152]. OCT has indicated that the presence of schisis in the retina surrounding the macular hole is of poor prognosis [153].

i. Macular Hole with Retinal Detachment

Retinal detachments from the macular hole are a typical finding in high myopia and uncommon in other settings besides trauma (see Figure II.B-12). Residual adherent vitreous cortex (vitreoschisis) on the retinal surface around the hole causes tangential traction that generates an anterior vector in a deep staphyloma [154]. Releasing the retinal traction is critical to anatomic success, and vitrectomy with vitreous cortex and membrane removal is the most common treatment.

e. Paravascular Retinal Microholes

A paravascular microhole and consequent retinal detachment are specific to high myopia. They are typically small, round, or oval, and sometimes there are multiple retinal

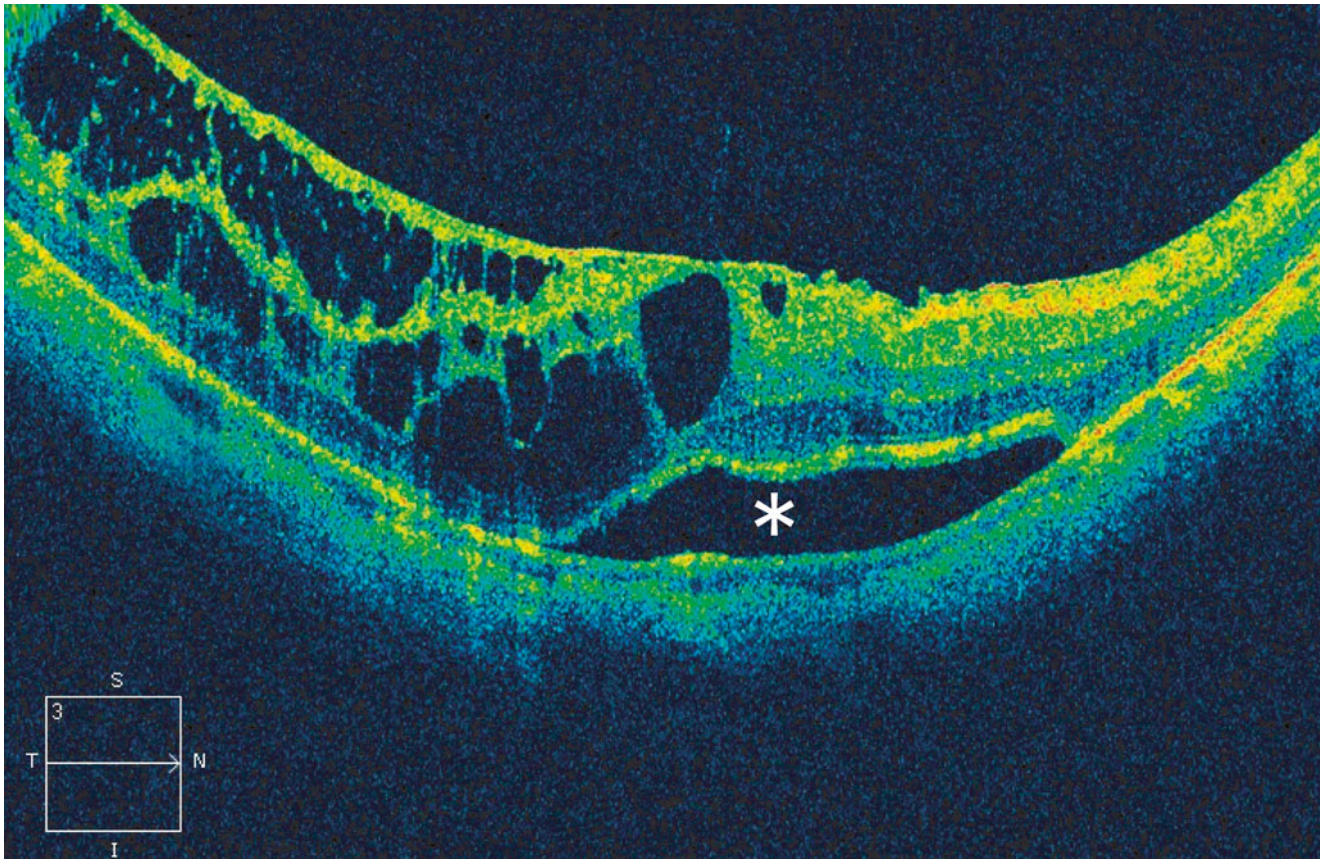

Figure II.B-10 Typical appearance of the foveal detachment type of myopic foveoschisis. The photoreceptors detach from the retinal pigment epithelium (RPE) (*asterisk*)

holes adjacent to posterior major vessels [155]. An OCT study of highly myopic eyes reported that the incidence rates of retinal cysts and paravascular holes were 50 % and 27 %, respectively. The vitreoretinal adhesion is normally strong at the paravascular site, and traction from the vitreous is believed to be the main cause [156]. Paravascular microholes often co-localize with vascular microfolds and retinoschisis, indicating a common pathology.

3. Cataract

The effect of myopia on cataract is relevant to this discussion of vitreopathy because some cataracts may be accelerated by vitreous liquefaction and because the increased risks of cataract are not confined to pathological or high myopia.

Some of the major population-based cross-sectional and cohort studies of eye disease have addressed the connection between myopia and cataract [6]. Early case–control studies showed no meaningful association [157]. In the Blue Mountains Eye Study of Australia, a cross-sectional study of 3,654 people found that increasing severity of early-onset myopia was associated with increasing odds ratio of posterior subcapsular (PSC) cataracts [158]. This same study found an increased risk of incident cataract over 5 years, particularly PSC, associated with myopia [159]. Another Australian cross-sectional study found increased risk of both nuclear and PSC cataracts among myopes [160]. In the prospective Barbados Eye Study, myopia was associated with an odds ratio of 2.8 for developing a nuclear opacity over 4 years [161] but not PSC or cortical cataract [162]. In the United States, the Beaver Dam Eye Study reported that myopia was associated with prevalent nuclear cataract, but not the 5-year incidence of cataract [163], although the incidence of cataract surgery was higher in myopes [164] by an OR of 1.89.

To summarize, cataracts and myopia may be associated because nuclear sclerosis causes myopia; however, the prospective cohort studies also indicate that cataract development is accelerated in those with longstanding myopia. It is possible that an increasingly liquefied vitreous in myopic vitreopathy is a mechanism by which retinal oxygenation can affect the lens more in myopia, accelerating cataract development [see chapter IV.B. Oxygen in vitreoretinal physiology and pathology].

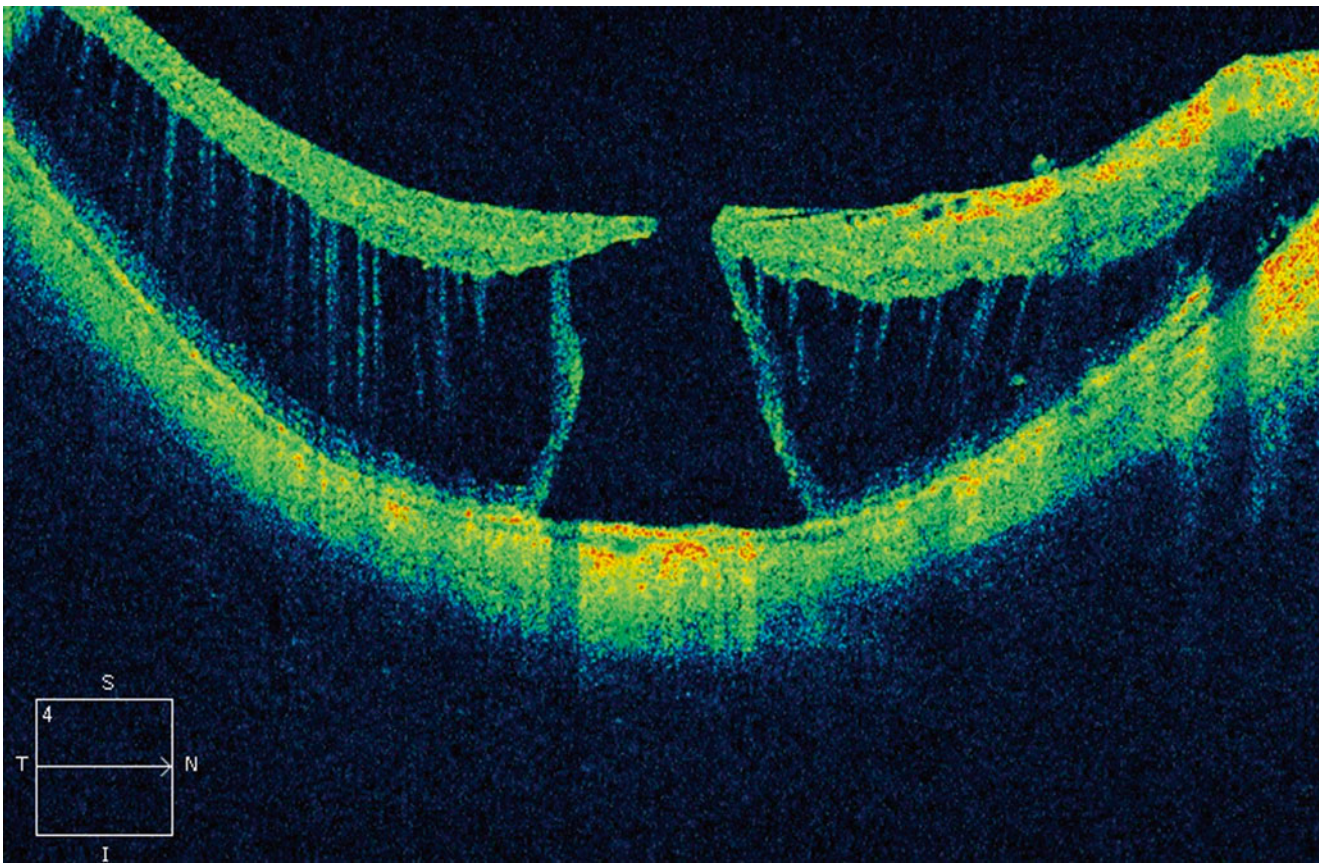

Figure II.B-11 A macular hole surrounded by retinoschisis. This type often occurs after myopic foveoschisis and with underlying traction. This type is at high risk for retinal detachment

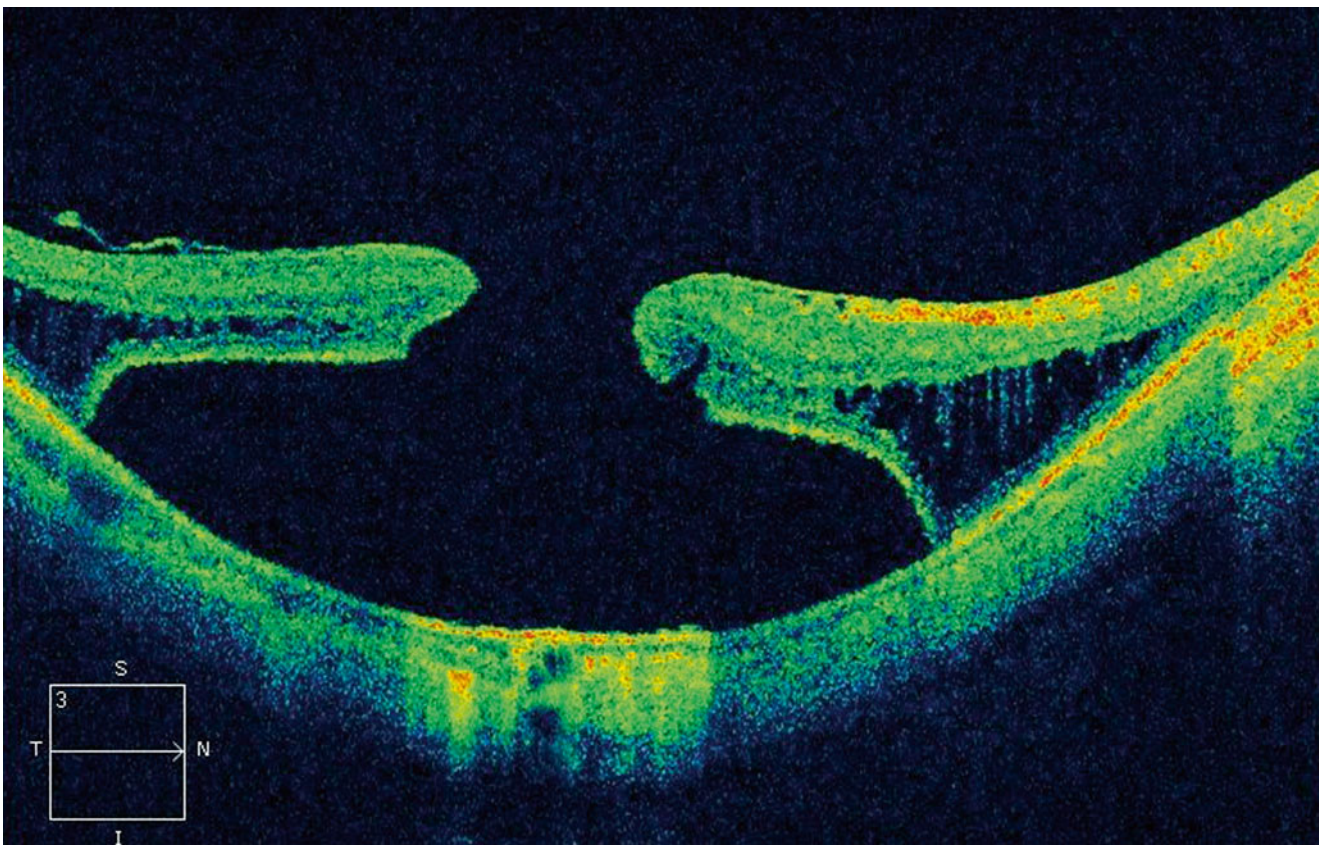

Figure II.B-12 Optical coherence tomograph (OCT) of a myopic staphyloma with full thickness macular hole and central retinal detachment

Abbreviations

CNV	Choroidal neovascularization
ECCE	Extracapsular cataract extraction
GAG	Glycosaminoglycans
ILM	Inner limiting membrane
IOP	Intraocular pressure
IS/OS	Inner segment/outer segment (junction of photoreceptors)
LAMA2	Laminin alpha-2 subunit gene
LASIK	Laser-assisted in-situ keratomileusis
OCT	Optical coherence tomography
OR	Odds ratio
PMM	Premacular (formerly "epiretinal") membrane
PSC	Posterior subcapsular cataract
PVD	Posterior vitreous detachment
RD	Retinal detachment
RRD	Rhegmatogenous retinal detachment
TIMPs	Tissue inhibitors of metalloproteases
UV	Ultraviolet
VEGF	Vascular endothelial growth

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