Myopic Maculopathy: A Review

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Key Words

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Abstract

Pathological myopia is a major cause of irreversible vision loss and is the fourth to ninth most frequent cause of blindness in the world. Choroidal neovascularization (CNV) secondary to pathological myopia is the leading cause of vision impairment in patients younger than 50 years. New scientific contributions have been made to the understanding of high myopia and associated CNV. New treatments have been used in recent years, and the results are still controversial. This paper is an updated review of pathological myopia – its definition and progression, epidemiology and genetics – and a review of myopic CNV including the natural history, epidemiology, risk factors, pathogenic mechanisms and treatment.

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Introduction

High myopia is a leading cause of visual loss, especially in younger populations, and a major cause of legal blindness in many developed countries [1–3]. Visual acu-

ity loss is associated with choroidal neovascularization (CNV) but also with progressive atrophic changes in the macula, usually by the fifth decade. In younger patients a rapid visual acuity loss is more common and associated with the development of CNV. These membranes may develop more frequently in the presence of lacquer cracks or patchy atrophy [4]. If left untreated, they show a poor visual outcome for a majority of patients. More recently antiangiogenic drugs have shown promising results in the treatment of myopic CNV.

This manuscript reviews myopic maculopathy with a special emphasis on clinical aspects and recent treatment modalities for myopic CNV.

Pathological Myopia

Definition of Pathological Myopia

By definition, pathological myopia is also known as high, degenerative or malignant myopia. It refers to a condition in which individuals have an axial length exceeding a certain threshold (typically ≥ 25.5 or 26.50 mm), a corresponding refractive error (of at least -5.0 dpt) and which is accompanied by characteristic pathological changes [5, 6]. Posterior pole abnormalities typical of pathological myopia include tessellated fundus, lacquer cracks, diffuse atrophy, patchy atrophy, CNV, macu-

lar atrophy, posterior staphyloma but also straightened and stretched vessels, temporal peripapillary atrophic crescent, hemorrhages and tilting of the optic disk [4, 7].

The limit of 25.5 mm of anteroposterior diameter of the eye is arbitrary and has been previously set as 25, 25.5 or 26.5 mm [8]. The superposition of the myopic and emmetropic populations occurs between 25 and 26.7 mm [9].

From a refractive point of view, pathological myopia is defined by a refractive error with an inferior limit of -6 to -10 dpt. In the clinical practice we may consider pathological myopia as a refractive error greater than -6 dpt, provided that the average refractive power of the cornea is $+43.5$ dpt, in the absence of spherophakia or nuclear cataract. The definition of pathological myopia as a refractive error of -6 dpt is clinically useful, though it may exclude a number of eyes.

Some authors have considered pathological myopia as refractive errors greater than -4 dpt in children less than 5 years of age [10]. Pathological myopia usually starts in childhood between 5 and 10 years of age and progresses until the third decade or even later. Tokoro [11] reported a prevalence of 0.1% in preschool children, 0.5% in high-school students and 1.5% in university students.

Progression of Myopic Maculopathy and Visual Acuity Impact

Progression of myopic maculopathy has been studied for a long time. Avila et al. [12] developed a classification of myopic maculopathy, 28 years ago. They graded myopic retinopathy of increasing severity from 0 to 5 as follows: M0, normal-appearing posterior pole; M1, choroidal pallor and tessellation (defined as the condition in which the choroidal vessels can be seen through the retina owing to reduced pigmentation or hypoplasia of the retinal pigment epithelium, RPE); M2, choroidal pallor and tessellation with posterior staphyloma; M3, choroidal pallor and tessellation with posterior staphyloma and lacquer cracks; M4, choroidal pallor and tessellation with lacquer cracks, posterior staphyloma, and focal areas of deep choroidal atrophy; M5, posterior pole with large geographic areas of deep chorioretinal atrophy and 'bare' sclera.

Hayashi et al. [4] found some problems with this scale, following a large number of highly myopic eyes during a mean time of 12.7 years. For these authors, lacquer cracks, placed into a relatively advanced group (M3), often develop at the early stage of myopic maculopathy, and they are often observed in young individuals without an obvious staphyloma or early atrophic changes of the retina.

They also showed evidence that a posterior staphyloma is the cause of the development of myopic maculopathy and not the reverse. They proposed a longitudinal progression pattern of myopic maculopathy from a tessellated fundus to macular atrophy. During the mean follow-up of 12.7 years, 40.6% of the 806 highly myopic eyes followed by Haiashi et al. showed progression of the myopic maculopathy. The most commonly observed patterns were from tessellated fundus to the development of diffuse atrophy and lacquer cracks, an increase in the width and progression to patchy atrophy in eyes with lacquer cracks, an enlargement of the diffuse atrophy, the development of patchy atrophy in eyes with diffuse atrophy, and an enlargement and fusion of patches of atrophic areas in eyes with patchy atrophy. Patients with tessellated fundus were less myopic and younger than any of the other groups. Progression to CNV was found in eyes with tessellated fundus, lacquer cracks, diffuse atrophy and patchy atrophy at the initial examination. Macular atrophy developed after CNV. The fusion of patchy atrophy, the development of CNV and macular atrophy all led to significant visual decreases. A posterior staphyloma was observed more frequently in eyes that showed progression from tessellated fundus, diffuse atrophy and patchy atrophy than in those without a progression.

Myopic maculopathy tends to progress more quickly after the stage of tessellated fundus. Only 13.4% of eyes with a tessellated fundus showed a progression of myopic maculopathy during the follow-up period, whereas 69.3% of eyes with lacquer cracks, 49.2% of eyes with diffuse atrophy, 70.3% of eyes with patchy atrophy and 90.1% of eyes with CNV showed a progression of the myopic atrophy. The incidence of progression to a CNV was higher in the eyes with lacquer cracks or patchy atrophy than from a tessellated fundus [4].

Submacular hemorrhage in a person with high myopia is usually small and not associated with CNV, especially in younger patients. It takes over 1–2 months to resolve spontaneously with preservation of good visual acuity. Lacquer cracks may appear in the area of the hemorrhage [12] and are better visualized with indocyanine green (ICG) angiography or fundus autofluorescence.

The progression of high myopia is also associated with visual acuity decline. In fact, myopic retinopathy is an important cause of visual impairment. It is often bilateral and irreversible, and it frequently affects individuals during their productive years. Of great importance is the severe reduction in corrected vision that is associated with the CNV [12–19]. However, the impact of myopic maculopathy on visual impairment is not only due to

CNV. Shih et al. [20] evaluated the visual outcomes for highly myopic patients aged 40 years and older with or without myopic maculopathy. In 92% of patients aged 40–49 years, the final visual acuity was better than 20/40 after 10 years of follow-up. However, it was less than 40% in those older than 60 years, and only 20% of those aged over 70 years showed a best corrected vision of 20/40. Moreover, around 26% of patients aged over 70 years had a best corrected vision worse than 20/200. For more than 50% of patients older than 40 years with maculopathy, their vision had decreased more than 2 lines in Snellen visual acuity after 10 years of follow-up, compared to only 4.3% of analogs without myopic maculopathy. Patchy atrophy and choroidal neovascularization showed poorer visual outcome than lacquer cracks. The fusion of areas with other patchy atrophy was the only progression pattern causing a significant decrease in vision other than the development of a CNV or macular atrophy [4]. Other prognostic factors of visual outcomes included myopic refraction, axial length, and ageing. An apparent visual acuity ceiling effect is observed with age in highly myopic eyes and is not only due to CNV. Shih et al. [20] noted that the incidence of cases ‘without maculopathy’ decreased with the age while the incidence of cases ‘with maculopathy’ increased. Obviously, ageing is not only an important factor of visual acuity loss but also an important factor in the development of maculopathy. Older patients tend to have severer myopic maculopathy and poorer visual acuity outcome. Moreover, ageing may affect RPE function. Older patients with high myopia are expected to have more widespread RPE dysfunction than younger subjects [20, 21]. Pathological myopia even without any chorioretinal degeneration has been shown to be associated with an early functional impairment of the outer retina when studied by electrophysiological and psychophysiological methods [22–24]. Also, RPE dysfunction has been described in highly myopic eyes [25–27].

Prevalence of Pathological Myopia

The Blue Mountain Eye Study reported a prevalence of 1.2% for myopic retinopathy in a population of 3,654 Australian residents, aged 49 years or older, and Fuchs spots were observed in 0.1% [28].

However, ethnic origin seems to influence the likelihood of developing pathological myopia. The prevalence is higher in Asian populations and lower in African and Pacific island groups [29].

There is a wide variation in the prevalence in different ethnic groups: 0.2% in Egypt, 1% in Czechoslovakia, 2% in the USA, 8% in Japan or 9.6% in Spain were document-

ed, with most countries having a prevalence of approximately 1–4% [3, 30, 31].

Genetic Factors of Pathological Myopia

It is well known that there is a higher prevalence of high myopia in Asian populations and a lower prevalence in African and Pacific island groups [32–38]. Myopia is a complex disease affected by both environmental and genetic factors [39, 40].

Determination of the genetic factors that predispose a person to myopia is challenging because myopia is a multigenetic condition involving several overlapping signaling pathways, each of which is associated with a group of distinct genetic profiles [41].

High myopia most commonly appears as a complex disease caused by a combination of genetic and environmental factors working together. However, it sometimes presents as one of the features in a wide variety of genetic disorders. Genes responsible for these syndromic genetic disorders with myopia as a consistent clinical finding have been identified: collagen 2A1 and 11A1 for Stickler syndromes type 1 and 2, respectively [42, 43], lysyl-procollagen hydroxylase for type 4 Ehler-Danlos syndrome, [44], collagen 18A1 for Knobloch syndrome [45], and fibrillin for Marfan syndrome [46, 47].

Each of these genes is expressed in the sclera, demonstrating how knowledge of gene expression in the scleral wall is critical to our understanding of eye expansion and myopia [48].

Family studies in both Asian [49–52] and Caucasian populations [49, 53–57] have demonstrated that the parental refractive status plays an important role in the refractive status of their offspring.

Large twin studies support the evidence that genetic factors play a critical role in the development of myopia, especially high myopia. High heritabilities of 84–86% [58], 89–94% [40] and 75–88% [59] were found.

Myopia can be inherited as a complex trait or in a monogenic form. For the complex form, myopia appears to be the result of an interaction of multiple genes and environmental factors. Several loci have been identified by genome-wide association study as being responsible for complex myopia [60–63].

There is substantive evidence that genetic factors play a significant role in the development of nonsyndromic high myopia. It may be inherited in a monogenic form, in an autosomal dominant, autosomal recessive and X-linked recessive manner [64].

One of the first myopia loci to be mapped was on chromosome Xq28 (named MYP1) from a family with the X-

linked recessive form of myopia. The syndrome was later renamed as the Bornholm eye disease, and includes myopia, lazy eyes and red-green color blindness in its diagnosis [65].

Three autosomal dominant loci by linkage analysis were mapped in multiple independent families with non-syndromic dominant high myopia (over -6 dpt): myopia-2 locus (MYP2) localized to chromosome 18p11.31, myopia-3 locus (MYP3) localized to chromosome 12q23.1-q24, myopia locus to chromosome 17q21-q22 [48].

Several other genetic loci (MYP1-12) have been linked with myopia. These include the loci at 2q37.1 (MYP12) [66], 4q22-27 (MYP11) [67] and 7q36 (MYP4) [60, 68], which are linked to high myopia (SphE -6.00 dpt). Zhu et al. [69] have shown that axial length, a major endophenotype for refractive error, is highly heritable and is likely to be influenced by one or more genes on the long arm of chromosome 5. In addition, low/moderate (common) myopia (SphE -0.50 to -5.99 dpt) has been linked to 22q12 (MYP6) [70], 11p13 (MYP7), 3q36 (MYP8), 4q12 (MYP9) and 8q23 (MYP10) [71].

There is now evidence to show that the high-myopia loci are heterogeneous [66, 72, 73], and it has been speculated that some high-myopia loci may contribute to all degrees of myopia [74, 75]. However, studies that have attempted to achieve this have so far failed to replicate high-myopia loci (MYP2 and MYP3) when using the phenotype of common myopia (-1.00 or -0.75 dpt in each meridian) [74, 75].

Several positional candidate genes were screened and found to be located at specific loci; these genes included *TGIF*, *EMLIN-2*, *MLCB* and *CLUL1*, and they map within the high-grade myopia-2 locus (MYP2) candidate interval [48] and on the dermatan sulfate proteoglycan 3, decorin and *LUM* genes located on MYP3 [73]. However, there is disagreement about the role of some of these candidate genes [41]. For example, *TGIF* was proposed as a possible gene for MYP2-associated high myopia because of its location and possible involvement in scleral growth [76], but this finding was questioned by Scavell et al. [77]. Polymorphism in the *LUM* gene was also found to be associated with high myopia [78].

Results of case-control studies indicated that the single-nucleotide polymorphism of the *LUM* gene may be a risk factor for the pathogenesis of high myopia in Han Chinese, English and Finnish populations [79] and also in the Taiwanese population [41].

Until now, genetic linkage studies have mapped two dozen loci, while association studies have implicated more than 25 different genes in refractive variation. Ac-

cording to Wojciechowski [80], many of these genes are involved in common biological pathways known to mediate extracellular matrix composition and regulate connective tissue remodeling. Other associated genomic regions suggest novel mechanisms in the etiology of human myopia, such as mitochondrial-mediated cell death or photoreceptor-mediated visual signal transmission. Taken together, observational and experimental studies have revealed the complex nature of human refractive variation, which likely involves variants in several genes and functional pathways. Multiway interactions between genes and/or environmental factors may also be important in determining individual risks of myopia, and may help explain the complex pattern of refractive error in human populations [81].

Instead of a simple 1-gene locus controlling the onset of myopia, a complex interaction of many mutated proteins acting in concert may be the cause. Instead of myopia being caused by a defect in a structural protein, defects in the control of these structural proteins might be the actual cause of myopia [81].

CNV in Pathological Myopia

Incidence and Prevalence of Myopic CNV

CNV was histopathologically observed in 5.2% of eyes with pathological myopia [7]. It was reported to affect 5.2% of the eyes with an axial length longer than 26.5 mm [5].

Two different studies with a large number of eyes (325 and 806, respectively) have shown that approximately 10-11% of highly myopic eyes may develop CNV in a course of 11-12 years [4, 82].

Myopic CNV may account for as much as 62% of CNV occurring in patients younger than 50 years of age [83].

Highly myopic eyes with lacquer cracks or patchy atrophy close to the fovea have a higher risk of developing CNV. Ohno-Matsui et al. [82] followed 325 highly myopic eyes during a mean follow-up of 130.2 months and found that CNV developed only in 3.7% of the eyes with chorioretinal atrophy but in 20% of the eyes with patchy atrophy and in 29.4% of the eyes with lacquer cracks.

The development of CNV in both eyes may be simultaneous but this is not the rule: one study of 33 patients found that only 4 patients (12%) had recently developed CNV in both eyes [15].

Fuchs spots represent late-stage myopic CNV, and histopathology has shown them to consist of an ingrowth of fibrovascular tissue [1, 9].

A study of 206 highly myopic eyes in 145 patients showed that 40–52% of patients had Fuchs spots in both eyes, and that the proportion with bilateral involvement increased over time with a mean time to bilateral involvement of 2.4 years, ranging from 0 to 8 years [13].

In a retrospective review of 218 patients (325 highly myopic eyes), Ohno-Matsui et al. [82] described an incidence of CNV of 34.8% in the fellow eye of patients with preexisting CNV in the other eye, but of only 6.1% in patients with no previous CNV.

Extrafoveal CNV may be located around the myopic conus and was named ‘periconus CNV’ by Nagaoka et al. [84]. They described this type of myopic CNV as representing only 4.2% of the eyes with a myopic CNV. It is more likely to develop in eyes with a large myopic conus, and apparently there is no significant association between the degree of myopia and the incidence of periconus CNV suggesting that the morphological characteristics of the eye are not the causes of the periconus CNV. An angiographic closure of the CNV can be easily attained with or without the treatment. However, the later development and progression of chorioretinal atrophy can impair vision [84].

Natural Course of Myopic CNV

The natural course of CNV in highly myopic eyes is variable. Reports to date have conflicting results. A moderately favorable result was reported by few authors. Fried et al. [13] followed the natural history of 55 highly myopic eyes with CNV for 36–180 months. In approximately 63% of the eyes, visual acuity was stabilized or improved without treatment during the follow-up. A visual acuity of 0.2 or more was maintained by 41.3% of the eyes. Avila et al. [12] followed 70 eyes with myopic CNV during an average of 40.9 months. In 96% of these eyes, the CNV remained stable or regressed, leaving an exudative scar, and visual acuity remained stable or improved in 54% of the eyes. However, final visual acuity was 20/200 or less in 60% of the eyes.

A poor or very poor visual acuity outcome for myopic CNV was reported in many other series. Hotchkiss and Fine [15] reported a series of 23 patients with myopic CNV who were observed for an average of 26 months with a final visual acuity of 20/200 or worse in 44%. Of these, however, 22% of 23 patients were treated with laser photocoagulation [15].

Hampton et al. [14] observed 42 eyes for 3 months to 2 years. The final visual acuity was 20/200 or worse in 60% of the eyes.

Tabandeh et al. [17] observed 22 eyes of patients aged 50 and over for a mean of 49 months. The final visual acuity was 20/200 or worse in 73%. All the lesions were reported as subfoveal or juxtafoveal.

Secretan et al. [16] followed the natural history of 50 eyes with extrafoveal (11%) or juxtafoveal (89%) CNV associated with high myopia. By 5 years of follow-up, all lesions were subfoveal, and the mean visual acuity was 20/160.

Yoshida et al. [19] reviewed the medical records of 27 eyes from 25 consecutive patients with high-myopia CNV and described an extremely poor long-term visual acuity outcome in this group of Asian patients. At the onset of CNV, 19 eyes (70.4%) had a visual acuity better than 20/200, and 6 eyes (22.2%) had a visual acuity better than 20/40. Three years after the onset of CNV, 15 eyes (55.5%) retained a visual acuity of better than 20/200. At 5 and 10 years after the onset, however, visual acuity dropped to 20/200 or less in 24 eyes (88.9%) and in 26 eyes (96.3%), respectively. The logarithm of the minimum angle of resolution (logMAR) visual acuity was significantly worse at 5 and 10 years after onset as compared with that at CNV onset. Chorioretinal atrophy developed around the regressed CNV in 26 eyes (96.3%) at 5 and 10 years after the onset of CNV.

Younger patients seem to have a better visual acuity outcome, compared with older patients. Tabandeh et al. [17] followed for a short period 22 patients older than 50 years with myopic CNV and reported that their visual prognosis was worse than in previous studies that included patients of all ages.

Hayashi et al. [85] studied prospectively 57 eyes with myopic CNV during a minimum follow-up of 5 years after the onset of CNV. Only 14% had a visual acuity better than 20/40 in the final visit compared with 65% of the eyes with a final visual acuity worse than 20/200. Patients with a final visual acuity greater than 20/40 were significantly younger, had significantly smaller CNV, significantly better initial visual acuity and juxtafoveal CNV was more frequently observed in this group. Yoshida et al. [18] followed, for more than 3 years, 63 consecutive patients (73 eyes) with myopic CNV. They divided patients into two groups according to their ages (≤ 40 and > 40 years old) and found that half of the patients who were younger than 40 years old at the onset retained a final visual acuity of better than 20/40, and no significant change occurred in the logMAR during the follow-up period. However, in the patients who were more than 40 years old at the onset of CNV, there was a significant worsening of logMAR during the follow-up period, and

more than half of the patients in this group had a final visual acuity of less than 20/200.

These studies indicated that younger patients might be able to retain good vision for a while. However, after a long period, most of the patients with myopic CNV eventually have a poor visual prognosis regardless of their age at onset.

Additionally, eyes in the atrophic stage of myopic CNV have a higher risk of developing a macular hole at the edge of the CNV [86].

Risk Factors of Myopic CNV

Highly myopic eyes with lacquer cracks or patchy atrophy have a greater risk of developing CNV than with tessellated fundus or macular atrophy [4, 82].

Hayashi et al. [85] found that the most frequent pattern of progression of lacquer cracks was the evolution to patchy atrophy (42.7% of eyes). The other progression patterns included the development of CNV (13.3%). They also found that the patients who developed CNV or patchy (diffuse) atrophy were significantly older than those without progression.

Older age ($p < 0.001$), the presence of a choroidal filling delay ($p < 0.001$) and reduced choroidal thickness ($p = 0.003$) were significantly associated with myopic CNV on univariate analysis. The most important of these three factors associated with myopic CNV, in order of importance, were the choroidal filling delay (OR¼ 41.5, $p < 0.001$) and choroidal thickness (per 1 mm, OR¼ 0.97, $p < 0.01$). Older age was significantly associated with both choroidal filling delay (per 1 year, OR¼ 1.16, $p < 0.001$) and choroidal thinning ($p < 0.001$) [87].

Myopic CNV is predominant in females (67%) who may reflect estrogen receptor expression in CNV and the external influence of estrogen [88].

Environmental factors, particularly increases in intraocular pressure, have been suggested as risk factors for the development of CNV secondary to pathological myopia [89].

However, there is little evidence supporting this association. Ikuno et al. [90] described that choroidal thinning, but not axial length, intraocular pressure or refractive error, was a risk factor for unilateral CNV in highly myopic eyes.

An increased risk of myopic CNV in the unaffected fellow eyes was reported in patients with newly developed myopic CNV. The incidence of CNV was 34.6% in the fellow eyes of patients with preexisting CNV in the other eye, compared with 6.1% in patients with no previous CNV [82].

The contralateral eyes of patients with preexisting membranes may be an ideal group. However, an accurate analysis should adjust for other factors that may affect the progression to myopic CNV including the presence of myopic changes like lacquer cracks or patchy atrophy [90].

Pathogenic Mechanisms of Myopic CNV

The mechanism of myopic CNV is still controversial. Lacquer cracks are often present, and an association has been documented in clinical and angiographic studies [82, 91]. The incidence of lacquer cracks in eyes with myopic CNV ranged between 75 and 94%.

Other long-term natural history studies confirmed this association [4, 20] and included also patchy atrophy as a higher risk factor of developing myopic CNV.

However, the details of the association are not clearly understood. Curtin and Karlin [5] reported the incidence of various myopia-related diseases based on axial length. They observed that the incidence of temporal crescents, posterior staphyloma and chorioretinal atrophy increased along with axial length elongation, but not the lacquer cracks or Fuchs' spot (myopic CNV).

In that study, myopic CNV did not develop in eyes with an axial length exceeding 33 mm. Based on these facts, Ikuno et al. [90] hypothesized that axial length elongation alone does not cause myopic CNV and that there may be other latent factors. They confirmed that the axial length and refractive error did not differ between the affected eyes and the fellow eyes, indicating that these factors were not the major risk factors of myopic CNV and they found that in eyes with myopic CNV the subfoveal and inferior choroid was significantly thinner than in the fellow eyes. It is unclear how this can promote CNV formation. One possible explanation is that the choroidal vessels supply retinal oxygen to the outer retina. The outer retina is believed to be a major source of vascular endothelial growth factor (VEGF), and the choroidal thinning at the fovea may lead to outer retinal hypoxic changes via factors such as hypoxia-inducible factor [92].

However, VEGF secretion is stimulated at the RPE level by mechanical stretching in vitro [93].

The inferior choroidal thinning, the primary contributor to the development of myopic CNV, the extent of the RPE curve, and posterior staphyloma protrusion seem to be closely related. Ikuno et al. [90] also found that the posterior staphyloma was steeper in eyes with myopic CNV explaining the greater choroidal thinning caused by more mechanical stress related to stretching at the macula.

Histopathological and angiographic studies have demonstrated choroidal atrophy with pronounced thinning and disappearance of the lamina of small choroidal vessels in highly myopic eyes allied to disappearance of large vessels, disappearance or disturbance of RPE, consequent loss of photoreceptors and outer retinal layers [94–98].

Laser Doppler velocimetry and color Doppler ultrasonography studies in humans and animals suggest that choroidal blood flow is disturbed in highly myopic eyes [94, 99].

Ischemically induced growth factor expression caused by decreased choroidal perfusion may be related to the development of myopic CNV. Kobayashi and Iku-no [87] found that a choroidal filling delay (evaluated with ICG angiography), was the most significant factor, and choroidal thinning (evaluated with spectral-domain optical coherence tomography, SD-OCT) was the second strongest factor associated with myopic CNV, but age was not a factor. However, age was selected as a significant factor for both a choroidal filling delay and choroidal thickness around the macula. The filling delay was most prominently nasal [87]. Choroidal filling delays are observed in other CNV-associated disorders [100–102].

In conclusion, the mechanism of CNV formation in myopic CNV is still unclear. A possible explanation includes, certainly, the induced hypoxia in the outer retina, which is a large source of VEGF secretion. Chorioretinal stretching, lacquer crack formation, choroidal thinning, choroidal flow disturbance with reduced flow, choroidal filling delay, RPE and overlying retina atrophy, loss of photoreceptors, all of them can be involved in growth factor release and myopic CNV formation. The role of each of these features and the interconnections between them remain unclear.

Clinical Findings in Myopic CNV

The biomicroscopic findings of CNV associated with high myopia typically show a small (<1 disk area), flat, grayish subretinal membrane with hyperpigmented borders. These membranes are typically less than 1,000 μm in diameter [14]. They are located in the subretinal space, as opposed to the sub-RPE space in age-related macular degeneration (AMD) and subretinal or sub-RPE fluid, hemorrhage or exudates are uncommon [1].

The location of CNV was reported to be subfoveal in 58% of the cases, juxtafoveal in 23% and extrafoveal in 19% [14].

Angiography

Fluorescein angiography (FA) and ICG angiography are both useful for studying degenerative changes associated with myopic CNV. FA is still the main tool for diagnosing myopic CNV and has been used in all randomized clinical trials for evaluating whether any therapy is indicated for CNV due to pathological myopia. Almost 90% of myopic CNV demonstrates mild hyperfluorescence confined to the early phase of the fluorescein angiography. Most membranes will hyperfluoresce in the transit phase, but contrasting with AMD, only a minimal leakage beyond the borders of the lesion is observed in the late phases [6].

Some membranes may be inactive and stain only in the late frames. Avila et al. [12] found that less than 10% of myopic CNV leak beyond the borders in the late phases. This finding was associated with worse prognosis.

The visualization of myopic CNV may be complicated by several factors, including reduced leakage, presence of staining associated with lacquer cracks, and subretinal hemorrhage [6]. Even with limitations, FA is able to detect the myopic CNV in most of the cases. However, when large hemorrhages are present, ICG angiography may better identify the CNV as a faint hyperfluorescence spot or area often surrounded by a hypopigmented halo. ICG also allows a better definition of lacquer cracks than FA [103, 104]. This was confirmed by Axer-Siegel et al. [105] showing that ICG angiography was able to identify lacquer cracks in 89% of eyes with pathological myopia, compared with 28% using FA. In the same study, FA and ICG angiography detected CNV in a similar number of cases [105]. ICG may also allow a more precise CNV localization and feeder vessel detection [104–106].

Both FA and ICG angiography may complement the study of myopic CNV allied to optical coherent tomography (OCT).

Optical Coherent Tomography

OCT appears to be useful in evaluating the stage and activity of myopic CNV. Baba et al. [107] described the morphological changes in different stages. In the active stage, time domain OCT clearly displayed a neovascular membrane as a highly reflective dome-like elevation above the RPE with no apparent subretinal fluid accumulation around the CNV. In the scar stage, only the surface of the CNV showed high reflectivity, which was markedly attenuated below the surface. In the atrophic stage the CNV became totally flat and chorioretinal atrophy around the regressed CNV showed high reflectivity [107].

OCT can provide supplementary information while making treatment decisions by demonstrating various stages and activities of myopic CNV [107].

SD-OCT is a powerful modality for investigating the retinal/choroidal structure of highly myopic eyes. The low signal-to-noise ratio and higher scanning speed allow for images with higher resolution and a higher scan density than conventional time domain OCT. This advantage enables us to observe choroidal changes in high-myopia-specific disease [108].

It is extremely useful for evaluating the CNV but also associated features like posterior staphyloma, retinoschisis, thinned choroid, posterior vitreous detachment, macular atrophy, macular hemorrhage, retinal traction or macular hole formation.

A thinned choroid is a common feature in highly myopic eyes. It was described in histological studies [7] and in animal models of myopia [109]. 'In vivo' studies using ICG angiography [98, 110] and color Doppler ultrasonography [99] also have shown that choroidal circulation is decreased in myopic eyes. But a thinned choroid was also described using SD-OCT [111].

Myopic CNV appears in SD-OCT as a type 2 (subretinal) neovascular membrane associated with a very thin choroid [112].

A method called 'enhanced depth imaging' SD-OCT has been developed that enables in vivo cross-sectional imaging of the choroid [113]. Using this method, choroidal thickness was studied in normal eyes and was shown to be thickest underneath the fovea and to be inversely proportional to age [114]. The enhanced depth imaging SD-OCT has demonstrated that the choroid in highly myopic eyes is very thin and undergoes further thinning with increasing age and degree of myopia [115]. The chorioretinal atrophy adjacent to a myopic CNV can be well documented with SD-OCT. It increases the risk of developing a macular hole, and a periodic OCT is recommended [116].

Choroidal thinning seems to be a hallmark of high myopia. Ikuno et al. [90] found that choroidal thinning is more prominent in eyes with myopic CNV when compared with myopic eyes without CNV. It is unknown how choroidal thinning is associated with the development of myopic CNV. One mechanism is that the choroidal vessels supply retinal oxygen to the outer retina. The outer retina is believed to be a major source of VEGF, and the choroidal thinning at the fovea may lead to outer retinal hypoxic changes via factors such as hypoxia-inducible factor, resulting in VEGF secretion at the fovea [90].

SD-OCT is also recommended for the evaluation of posterior staphyloma. Ikuno et al. [90] reported that the

absolute value of the nasal posterior staphyloma height from the fovea was significantly greater in eyes with myopic CNV than in myopic eyes without CNV.

However, OCT alone may have poor sensitivity in diagnosing recurrence. In fact, myopic CNV can often have minimal leakage and the choroid is usually thin. In fact, in some cases, the extent of perfusion of the CNV in pathological myopia may be difficult to evaluate without FA.

Treatment of Myopic CNV

Because of the poor natural history of myopic CNV, several procedures have been tried to treat it, for example thermal laser photocoagulation [117], photodynamic therapy (PDT) with Visudyne [118], transpupillary thermotherapy (TTT), intravitreal bevacizumab (Avastin; Genentech, South San Francisco, Calif., USA), a recombinant humanized monoclonal anti-VEGF antibody [119, 120], intravitreal ranibizumab, surgery and combined treatments.

Direct Thermal Laser Photocoagulation for Myopic CNV

Laser treatment was the only treatment for juxtafoveal and extrafoveal myopic CNV during many years and with very limited benefit [16, 121–124]. Jalkh et al. [121] described the results of 19 eyes with extrafoveal CNV treated with thermal laser photocoagulation. All had a dry atrophic photocoagulation scar at a mean of 29.2 months after direct thermal laser with 11% having visual improvement [121]. No visual improvement was described by Steidl and Pruett [122], in another study with laser photocoagulation for myopic CNV resulting in complete closure of myopic CNV but with visual acuity deterioration in all the studied eyes at the end of follow-up. Secretan et al. [16] compared natural history with laser photocoagulation and found a significant benefit at 2 years. However, at 5 years no significant difference was found between treated and untreated eyes.

Juxtafoveal CNV treated with laser photocoagulation showed no benefit at 3 years in another study [125]. The expansion of a laser scar is responsible for the loss of initial gain [126]. This late failure is seen in 92–100% of the treated eyes [16, 121–124]. Recurrence [16] of CNV, occurring in up to 72% of the treated eyes (with half of them being subfoveal), is also responsible for the bad prognosis. Most recurrences occur in the first year after treatment and at a declining rate in each subsequent year, with 69% of recurrences occurring at the foveal edge of the laser

scar [123, 125, 127]. Laser photocoagulation itself may be associated with the formation of lacquer cracks and an increased incidence of recurrences [128].

Considering the results of these previous studies in myopic CNV, laser photocoagulation is no more an alternative for subfoveal or juxtafoveal lesions. The available data for extrafoveal lesions is insufficient. Considering the new available treatments, a careful evaluation of potential progression of the membrane and of the laser scar needs to be weighted before laser photocoagulation is carried out.

Transpupillary Thermotherapy for Myopic CNV

Few reports on the effect of TTT on myopic CNV have been published in the ophthalmic literature. TTT uses a low-energy, longer-exposure diode (810 nm) laser that gently heats up the CNV leading to closure of abnormal neovasculature apparently sparing the overlying neurosensory retina. In a retrospective analysis, Ozdek et al. [129] reported, a stabilization of myopic CNV, both clinically and as revealed by angiography.

Wu et al. [130] reported that subthreshold TTT in Chinese patients with pathological myopia and subfoveal or juxtafoveal CNV was able to maintain vision at the 1- and 2-year follow-up. Considering the available therapeutic alternatives, TTT is no longer an option to be considered.

Surgical Treatment of CNV

Surgical treatments for subfoveal CNV were tried before PDT or antiangiogenic drugs were introduced. Thomas et al. [131] reported visual acuity stabilization or improvement in selected cases of subfoveal CNV of different pathologies, including 10 eyes with myopic CNV, treated with surgical removal.

Surgical approaches for myopic CNV include submacular surgery and macular translocation. Controversial results were reported in submacular surgery for myopic CNV [132–134] ranging from no change [134] to an improvement of 2 lines in 45% of the eyes [132, 135]. Two techniques of macular translocation – limited macular translocation and macular translocation with 360-degree (MT360) retinotomy – have been performed in the last decade also with controversial results [136–139]. Better results were reported for limited macular translocation than for surgical removal [137] but with a high rate of recurrences.

Better visual acuity results were also reported in myopic CNV than in exudative AMD with limited macular translocation [136].

A retrospective, nonrandomized study reported better visual acuity results at 2 years with limited macular translocation than with PDT, in subfoveal myopic CNV [140]. The prognosis for visual acuity was affected by the smaller foveal displacement, the lower rate of recurrence and retinal detachment, and the younger age.

Retinal detachment, CNV recurrence and expansion of chorioretinal atrophy may occur after limited macular translocation [6] affecting the final visual acuity.

MT360 for myopic eyes has been performed by some authors, but the results of this approach are still controversial and complications may include retinal detachment, macular hole, torsional diplopia and proliferative vitreoretinopathy [138, 139].

Yamada et al. [139] reported the results of 5 eyes with myopic CNV at least 5 years after MT360. The mean visual acuity was maintained, and these results were better than those observed in 27 exudative AMD eyes, treated with 360-degree macular translocation and evaluated in the same study. The only prognostic factor for better visual acuity after macular translocation in myopic CNV was younger age. They proposed MT360 for selected cases of myopic CNV with foveal fibrosis or high activity in which PDT or anti-VEGF therapy is ineffective. However, we must stress that postoperative complications in these 5 eyes included, within 1 year after the operation, epiretinal membrane, glaucoma, CNV recurrence and ischemic optic neuropathy in 1 eye each. Foveal atrophy was observed in 3 eyes 5 years or more after surgery.

In conclusion, the surgical treatment of myopic CNV including CNV removal, limited macular translocation or MT360 is controversial. The existence of only small case series published in the literature, the possible complications associated with the procedures, the lack of reports with significant and persistent visual acuity improvement and the availability of other alternatives such as photodynamic therapy and antiangiogenic drugs make surgery an option not valid for myopic CNV.

Treatment of Myopic CNV with PDT with Verteporfin

PDT with verteporfin (Visudyne; QLT Inc., Vancouver, B.C., Canada) is a well-established treatment for CNV associated with various diseases, including myopic CNV. The Verteporfin in Photodynamic Therapy (VIP) study of patients with subfoveal CNV secondary to pathological myopia reported that PDT with verteporfin stabilized the visual acuity in 72% of the patients for 1 year [141]. The visual outcome following PDT was significantly better than the placebo at 3 and 12 months, but 57% of eyes had persistent leakage at 12 months. Only 28% (n =

23) of the 81 eyes treated with PDT with verteporfin lost 8 or more letters of visual acuity at the 12-month examination, compared with 56% (n = 22) of the 39 eyes given placebo (p = 0.01).

However, the significant benefit was lost at 2 years. In fact, despite the gain of ≥ 3 lines in 12% of the treated eyes, 26% lost ≥ 3 lines, and no statistically significant difference with sham regarding the primary outcome (< 8 letters lost) was achieved. The 24-month data showed no statistical significance in benefit on visual acuity for either the percentage of eyes losing at least 8 letters (verteporfin 36%, placebo 51%, p = 0.11) or the percentage losing at least 15 letters (verteporfin 21%, placebo 28%, p = 0.38). A mean gain of 1 letter was achieved after 5.1 treatments [118].

Many other studies have reported favorable outcomes for PDT for subfoveal or juxtafoveal myopic CNV [142–152].

Pece et al. [146] could not find any statistically significant changes (p = 0.854) in best-corrected visual acuity (BCVA) at 2 years in 52 patients. In the 20 eyes receiving PDT reported by Krebs et al. [144], the mean value of BCVA remained nearly unchanged at 3 years.

In the study of Lam et al. [145], BCVA of 22 eyes was maintained at the baseline level over a 24-month follow-up period.

Patients who completed the 24-month examination of the VIP trial and met the inclusion/exclusion criteria of the VIP extension could receive verteporfin treatment in either their study eye or their fellow eye at 3-month follow-up visits for an additional 36 months, up to a total of 60 months. The results of the first 12 months of this extension study showed that in verteporfin-treated patients with subfoveal CNV due to pathological myopia, visual acuity outcomes remained relatively stable from 24 to 36 months after therapy was initiated. Patients with vision improvement maintained this improved vision, and few patients required treatment during the extension. No additional safety concerns were observed [153].

Many other case series studies reported similar results in different countries and ethnicities with a significant visual acuity gain in the first 6 and/or 12 months which was not maintained after that. This was described in Indian populations [154] but also in Asian populations [145, 152, 155] and in Caucasians [144, 146, 156].

Pece et al. [146] reported a stabilization or improvement of visual acuity in 68% of the eyes with patients younger than 55 years of age obtaining a significantly better visual acuity outcome. Similar results were reported at 4 years by Ruiz-Moreno et al. [148] with 72% of eyes showing stabilization or visual acuity improvement.

Coutinho et al. [157] followed prospectively, during 5 years, 45 myopic CNV eyes treated with PDT. A mean gain of 4 letters was obtained and visual acuity stabilized or improved in 65% of the eyes. A visual acuity stabilization was reported after 24 months with no significant visual acuity change between month 24 and month 60. A visual acuity gain of ≥ 3 lines occurred in 32.6% of the eyes, and a visual acuity decrease of ≥ 3 lines was registered in 20.9% of the cases at 5 years. This visual acuity gain was mainly observed in younger patients. In fact, significantly more patients younger than 55 years of age gained vision between 2 and 5 years of follow-up, and younger age was shown to have a predictive value for a better visual acuity outcome [157]. The number of treatments decreased after the 12 months of follow-up, with a mean of 3.1 during the first year, 1.1 in the second year, 0.5 in the third year, 0.07 in the 4th year and zero in the fifth year [157].

PDT with verteporfin may also have been shown to be beneficial in eyes with juxtafoveal CNV due to pathological myopia [147, 149, 158]. Pece et al. [147] found that visual acuity was stabilized in patients with juxtafoveal CNV, while Virgili et al. [149] registered a positive outcome from the use of PDT in a retrospective study on a large series of patients with nonsubfoveal myopic CNV [147, 149].

Treatment of Myopic CNV with Antiangiogenic Drugs Treatment with Bevacizumab

The first report of myopic CNV treated with bevacizumab was published in 2005 in a small series of 9 patients with AMD who were treated with systemic bevacizumab [159]. Also in 2005, Nguyen et al. [160] reported the use of systemic bevacizumab in eyes with subfoveal myopic CNV. Intravitreal bevacizumab was tested with no apparent retinal toxicity [161].

Following that, Yamamoto et al. [162], Sakaguchi et al. [163] and Laud et al. [164] reported the off-label use of intravitreal bevacizumab in eyes with subfoveal myopic CNV, with promising short-term results and no ocular or systemic side effects in small case series.

Many prospective and retrospective studies evaluating safety and efficacy of bevacizumab in myopic CNV eyes have been published in the last few years, showing results at 1 year [165–170] and at 2 years [119, 155, 171–174].

Even so all of the investigators reported that the statistically significant visual improvement of two lines or more was sustained at 12 months, the same did not occur at 24 months. In fact, some studies reported that the initial statistically significant visual acuity gain was not maintained at 2 years [171, 172].

In conclusion, due to the lack of large randomized trials, it is not possible, at present, to have a conclusion regarding the long-term efficacy of intravitreal bevacizumab in foveal myopic CNV.

The anatomical changes evaluated with OCT in different reports are not coincident either. A statistically significant reduction of mean central foveal thickness was not registered in some of the studies [175, 176].

However, a functional improvement was registered performing microperimetry studies at 6 and 12 months [177, 178].

Treatment with Ranibizumab

Intravitreal ranibizumab has been used off label and showed apparently superior results when compared with PDT for juxtafoveal and subfoveal myopic CNV. Silva et al. [179] reported the first results of ranibizumab for myopic CNV following a PRN (pro re nata) regimen since the first injection. The short-term result of 26 eyes treated with intravitreal ranibizumab was promising a 3 and 6 months. At 3 months after intravitreal ranibizumab injection, visual acuity improved by 1 or more lines in 65% of eyes and all eyes had stable or improved vision at 3 months. These short-term results seemed to be similar with those of other studies using intravitreal bevacizumab for myopic CNV [163, 168, 180, 181].

Lai et al. [182] reported a mean visual acuity improvement at 12 months of 3.0 lines, 75.0% of the eyes had improvement of 2 or more lines with angiographic closure occurring at 3 months in 93.8% of the eyes. All eyes were treatment naïve and a loading dose of 3 initial injections was used. In a prospective case series study of 32 eyes of 32 patients affected with myopic CNV and treated with intravitreal ranibizumab, the BCVA improved by 3 lines in 15 of 32 eyes (46.8%) with a median number of 3 injections and a median follow-up of 17 months. Silva et al. [183] reported, at 12 months, a mean visual acuity improvement of 8 letters with all the eyes losing less than 15 letters and 24% improving 3 or more lines. A mean of 3.6 treatments was performed during the 12-month follow-up.

Treatment regimens with and without loading dose were evaluated in different studies. Lai et al. [182] obtained a significant visual acuity gain at 1 year using a loading dose of 3 monthly injections in their protocol, with 75% of the 16 patients gaining vision and with only 1 patient needing retreatment.

In a prospective study, Mones et al. [184] treated 23 patients with a single injection followed by PRN retreatments. Almost 70% of the patients gained at least 1 line of vision, and the average number of injections was 1.5.

Other authors also reported similar results, in prospective studies with a nonloading dose, and a significant BCVA improvement from baseline [185–187].

Varano et al. [188] performed microperimetry studies and showed an improvement in retinal sensitivity at 36 weeks after ranibizumab.

Franqueira et al. [189] published the 3-year follow-up of a prospective study including 40 eyes of 39 patients with myopic CNV, 15 with previous PDT and 25 naïve eyes. The mean visual acuity improved from 55.4 ETDRS letters at baseline to 59.7 letters at 12 months ($p = 0.07$), 61.8 letters at 24 months ($p = 0.008$) and 63.4 letters at 36 months ($p = 0.039$). Twenty-five percent of the patients gained ≥ 15 letters (3 lines) at 12 months, 30% at 24 months and 35% at 36 months. There was a mean reduction of 90 μm in central foveal thickness ($p < 0.001$). A mean of 4.1 injections was used in the first year, 2.4 in the second year and 1.1 in the third year. Fifty-three percent of the eyes had no need for treatment during the third year of follow-up. No statistically significant difference ($p > 0.05$) was found between patients previously treated with PDT and naïve patients regarding efficacy and number of treatments [189].

Treatment of Juxtafoveal Myopic CNV

About one fourth to one half of eyes had nonsubfoveal location at presentation, and the natural history of juxtafoveal CNV is not well known [190].

In fact, the great majority of studies have included both subfoveal and juxtafoveal myopic CNV patients. Only one study reported the efficacy of intravitreal bevacizumab at 12 months in patients with only subfoveal CNV [175].

To date, no particular treatment has a precise indication for nonsubfoveal CNV as it is still not known whether treatment can alter its natural course.

When compared with intravitreal bevacizumab and laser photocoagulation, PDT was shown to be less effective for juxtafoveal CNV, at 2 years, in a small, prospective, uncontrolled study [191].

Comparing Treatment with PDT, Bevacizumab and Ranibizumab

Gharbiya et al. [192] enrolled 32 patients in a randomized trial, comparing ranibizumab and bevacizumab, and reported no statistically significant difference at 6 months between the two drugs regarding the improvement of BCVA, as well as reduction in central foveal thickness measured by OCT, and the resolution of fluorescein leakage on angiography.

Intravitreal anti-VEGF injection showed to be superior to PDT alone or a combination of PDT with anti-VEGF for treating myopic CNV [193]. One hundred and forty-two eyes of 128 consecutive patients treated with anti-VEGF (ranibizumab or bevacizumab) and/or PDT for myopic CNV were retrospectively reviewed. Patients were categorized into 3 groups: PDT (51 eyes), anti-VEGF (63 eyes) and a combination group (PDT with anti-VEGF; 28 eyes). The anti-VEGF group showed significant post-operative improvement in visual acuity compared with the PDT and combination groups [193].

Hayashi et al. [176] studied 42 eyes treated with PDT, 43 eyes with intravitreal bevacizumab and 74 control eyes. Intravitreal bevacizumab-treated patients had significantly better BCVA than PDT-treated and control eyes at 1 year.

Ikuno et al. [143] did not find significant improvement of BCVA in both PDT- and intravitreal bevacizumab-treated women aged 50 years or older at 24 months. However, the intravitreal bevacizumab group had significantly better BCVA values at 12 and 24 months than the PDT group.

Nevertheless, despite these small studies, optimal treatment for myopic CNV is still unclear to date because of a lack of randomized clinical trials.

A large, randomized, multicenter, clinical trial is now comparing PDT with ranibizumab (<http://clinicaltrials.gov/ct2/show/NCT01217944>). This study is designed to evaluate the efficacy and safety of two different dosing regimens of 0.5 mg ranibizumab given as intravitreal injection in comparison to verteporfin PDT in patients with visual impairment due to CNV secondary to pathological myopia.

The Influence of Age, Previous PDT, Dose and Frequency of Treatments

Younger patients with myopic CNV have been referred to show a better visual acuity outcome when comparing them to older patients, with and without treatment. In fact, the natural history of myopic CNV seems to be associated with a better prognosis in patients younger than 50 years [18, 19, 85, 194].

Also, treatment with PDT has been shown to be less effective in older patients [142, 195].

Conflicting results have been presented regarding the efficacy of bevacizumab in younger and older patients. Arias et al. [196] found no significant differences between the two groups. In contrast, Ruiz-Moreno et al. [165] and Gharbiya et al. [169] found better visual acuity outcomes in patients younger than 50 years. These apparently contradictory results may be associated with study designs

and sample sizes. However, the natural progression of myopic maculopathy may also be responsible for the lower visual acuity outcomes in older patients. However, the limit of 50 years of age is always theoretical. In fact, split into two age groups, above and below 50, does not have biological support. Vision of patients is not stable over time until a certain age, where it deteriorates rapidly to be stable again afterwards [197].

Many reports comparing results of ranibizumab and bevacizumab with and without previous PDT were published with conflicting conclusions. A more limited visual outcome was described by Chan et al. [168], Gharbiya et al. [169] and Ruiz-Moreno et al. [175].

In another study, Ruiz-Moreno et al. [165] found that previous PDT treatment did not have a significant difference in visual outcome compared with treatment-naïve eyes after bevacizumab in a series of 107 eyes.

Silva et al. [183], at 12 months, and Franqueira et al. [189], at 3 years, did not find a significant difference in visual acuity outcome, in patients treated with and without previous PDT.

The frequency of injections of anti-VEGF drugs is also subject of debate. Treatment regimens with a loading dose of 3 injections followed by PRN therapy have shown apparently the same results of one single injection followed by PRN therapy, with either ranibizumab or with bevacizumab.

Myopic CNV differs from AMD CNV due to the role of the RPE and the release of different VEGF-related factors [198]. Moreover, myopic patients are younger, with a healthier RPE, and a smaller dose of anti-VEGF may be effective.

Different doses of bevacizumab have been tested in pilot studies [166–170]. A single dose injection like with ranibizumab, may constitute a better option in an off-label therapy and avoid unnecessary risks and expenses from extra intravitreal injections [188, 197].

Future Investigations

The better treatment of myopic CNV is still unknown. A clinical trial comparing PDT and ranibizumab is ongoing (<http://clinicaltrials.gov/ct2/show/NCT01217944>).

Promising investigations that are being made in AMD could be extrapolated to the treatment of myopic CNV or be studied in myopic patients, and may include antiangiogenic molecules of greater duration of action, slow-release devices, RPE transplantation or human embryonic stem cell treatments.

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