Myopic Choroidal Neovascularization

Myopia and pathologic myopia (PM) are among the leading causes of visual impairment in the world. One of the most feared complications of myopia or PM is the development of choroidal neovascularization (CNV). High myopia is defined as an axial length greater than 26.5 mm or refractive error greater than –6 D. Pathologic myopia is defined as the presence of structural changes due to axial elongation in eyes with high myopia. Other clinical findings associated with PM include posterior staphyloma, lacquer cracks, tessellated fundus, tilted optic disc, and straightened and attenuated vessels. It is now recognized that myopic CNV can occur in patients with any degree of myopia, even in the absence of characteristic degenerative retinal changes.[1]

Epidemiology

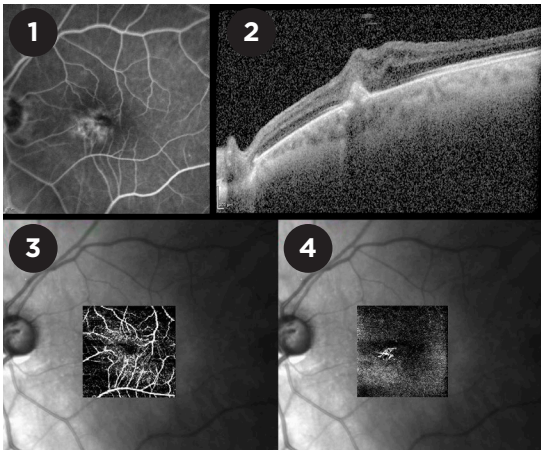
The reported prevalence of myopia and PM is highest in East Asian countries, with reported rates around 40%.[2] According to a comprehensive systematic literature review of English-language studies, PM is present in 3% of the global population.[2]

Myopic CNV has been reported in 5% to 11% of patients with PM. Notably, 62% of these patients developed CNV before the age of 50,[3] and a patient with a history of myopic CNV in one eye has an average risk of 34.8% for developing CNV in the fellow eye.[4]

The relationship between the degree of myopia and CNV is not fully understood; in one study, 5.2% of eyes with axial length greater than 26.5 mm were found to have CNV.[3]

Genetics

Although some information is available regarding the genetics of PM, the genetic factors specifically associated with the development and presentation of myopic CNV are not yet fully understood. One study found a correlation between the *COL8A1* gene and the presence of myopic CNV. Interestingly, this gene encodes chains of collagen type VIII, one of the major components of Bruch membrane and choroidal stroma. Mutations in this gene might lead to the structural changes frequently observed in patients with PM. Alterations in *SERPINF1*, the gene that encodes pigment epithelium–derived factor, may also be related to CNV progression.[5]



MYOPIC CNV. *(1) Early phase of FA shows hyperfluorescence due to leakage, suggestive of active type 2 (classic) CNV. (2) SD-OCT shows a highly reflective area above the RPE, corroborating type 2 CNV. (3, 4) OCTA with segmentation of the outer retinal layers shows an irregular, tangled CNV pattern.*

Pathophysiology

In addition to genetic factors, structural and hemodynamic mechanisms have been postulated to contribute to the development of myopic CNV. Excessive elongation of the globe is presumed to cause mechanical stress, with retinal damage and imbalance of proangiogenic and antiangiogenic factors resulting in CNV. The axial elongation promotes alteration in collagen proteins that subsequently leads to degenerative changes in the retina, choroid, and sclera. A chain of molecular and inflammatory events may occur as a consequence of this mechanical and structural stress. The amacrine cells in the retina are thought to play a part in this process.[6]

Compared to unaffected individuals, patients with PM had significantly higher levels of inflammatory factors such as high-sensitivity C-reactive protein and complement factors C3 and CH50; these findings strongly suggest that inflammation is involved in myo-

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pic CNV. Another hypothesis suggests that hemodynamic changes at the level of the choroid lead to choroidal thinning and hypoperfusion, predisposing to CNV development.[2]

Visual acuity (VA) can be impaired even in the absence of funduscopic changes typically associated with PM. This may be attributable to excessive stretching in the posterior pole, which alters the arrangement of photoreceptors. In high myopia, the cones in the nasal macula are aligned toward the optic nerve, while those in the temporal zone are aligned toward the center of the pupil. This displacement in directional sensitivity is known as the Stiles-Crawford effect of the first kind.[7] Specifically, light that enters the eye near the pupillary edge stimulates a lesser photoreceptor response compared with light of equal intensity that enters the eye near the center of the pupil.

Diagnosis

Clinical findings. A diagnosis of myopic CNV should be considered for a middle-aged myope who presents with sudden vision loss, metamorphopsia, and typical funduscopic changes. Establishing a diagnosis in an elderly patient is more challenging because other conditions that can lead to CNV, such as age-related macular degeneration (AMD), may be present. Nevertheless, some clinical findings can help distinguish among the conditions.

Staging. In 1998, Tokoro[8] outlined three stages of myopic CNV: active, scar, and atrophic, defined according to funduscopic and other clinical findings.

Active. In the active stage, patients usually have sudden visual loss associated with a central scotoma or metamorphopsia; fundus changes include a small, slightly elevated, grayish lesion in the subfoveolar zone, although CNV may also be seen in the juxtafoveal zone. The neovascular membranes of myopic CNV are typically less than 1,000 µm in diameter, and sub–retinal pigment epithelium (RPE) fluid or exudates are uncommon. In contrast, AMD-associated CNV lesions are typically larger, are often associated with hemorrhage and drusen, and may be accompanied by sub-RPE fluid.

Scar. In the scar phase, the CNV regresses, and a characteristic hyperpigmented area known as a Fuchs spot forms around the prior lesion. In this phase, the patient experiences a period of stabilization or transient improvement in VA. Patients with AMD, however, usually do not have VA improvement without treatment, and the pigmentary changes seen in the fundus are associated mainly with drusen.

Atrophic. Finally, in the atrophic phase, further visual decline occurs. Patchy and, over time, diffuse atrophy may be present in the macula.[2] In AMD, the areas of atrophy are more prominent and confluent; additional findings including drusen, pigment epithelial detachment, and generalized pigmentary changes will be present, helping to differentiate AMD from myopic CNV.

Differential diagnosis. Inflammatory conditions such as multifocal choroiditis, presumed ocular histoplasmosis syndrome, recent hemorrhage from lacquer crack formation, idiopathic CNV, and various hereditary disorders including Best disease, reticular dystrophy, and retinitis pigmentosa should be considered. Blunt ocular trauma with choroidal rupture can also lead to CNV. As noted above, AMD should always be ruled out in elderly patients.

Imaging. Imaging studies can aid in the differential diagnosis and help avoid unnecessary treatment.

Fluorescein angiography (FA). On FA, myopic CNV typically shows a "classic" pattern, with hyperfluorescence in the early phase. Less than 10% of the membranes will leak beyond the borders in the late phase, and the amount of leakage is minimal compared with that seen in AMD. Some inactive membranes will stain only in the late frames.

However, because other conditions may present with similar staining on FA, other modalities such as indocyanine green angiography (ICGA), spectral-domain optical coherence tomography (SD-OCT), and OCT angiography (OCTA) may be useful.

ICGA. In patients with extensive hemorrhages, ICGA can provide better information than can FA about the choroidal circulation, particularly about the presence and status of lacquer cracks, and ICGA can help distinguish myopic CNV from AMD. In myopic CNV, ICGA generally shows an early small, hyperfluorescent area, surrounded by a hypopigmented halo, sometimes associated with lacquer cracks.

OCT. SD-OCT can delineate the retinal structure in different stages of myopic CNV and helps to differentiate it from conditions such as posterior staphyloma, retinoschisis, thinned choroid, posterior vitreous detachment, macular atrophy, macular hemorrhage, vitreomacular traction, or macular hole formation. It can also be helpful in identifying some inflammatory conditions such as multifocal choroiditis and panuveitis.

- *Choroid.* Myopes are known to have a significantly thinned choroid. This essential finding is usually associated with sporadic large choroidal vessels with defects at Bruch membrane.
- *CNV.* In the acute phase of myopic CNV, a highly reflective area above the RPE (CNV type 2) can typically be seen, without or with minimal subretinal fluid (SRF). However, the use of OCT alone may not be adequate in distinguishing subretinal hemorrhage caused by recent lacquer crack formation from that caused by myopic CNV, which could result in unnecessary treatment. Recent evidence shows that leakage and exudative changes associated with myopic CNV were identified on FA in up to 82% of cases, compared with 48.6% with use of SD-OCT alone. Thus, FA may be more reliable in confirming the diagnosis of acute CNV.[9]

OCTA. A study by Querques et al. analyzed the utility of OCTA in detecting CNV and its morphological patterns in eyes with PM. They found a sensitivity of 90.48% and specificity of 93.75% for detection of CNV in this group of patients. They also reported that the OCTA findings suggestive of myopic CNV disease activity were predominantly in a vascular network pattern described as "tangled" or "interlacing."[10]

Another study compared the effectiveness of OCTA to that of other imaging

methods for detecting CNV in patients with suspected AMD, chronic central serous retinopathy, or PM. It found that OCTA had an overall sensitivity of 71% and specificity of 81% compared with FA and was particularly sensitive in detecting type 2 CNV in AMD.[11]

Both studies noted that although OCTA was an excellent aid in situations of diagnostic uncertainty by FA or SD-OCT, it has limitations, including inability to show leakage, and should be considered an adjunct to those tests.[10,11]

Management

Anti-VEGF therapy is considered the first-line treatment for myopic CNV. Ranibizumab (Lucentis) is the only FDA-approved anti-VEGF agent for this indication, although bevacizumab (Avastin) and aflibercept (Eylea) are often used off label. Verteporfin photodynamic therapy (vPDT) may be considered for cases in which anti-VEGF is contraindicated.

Ranibizumab. Several studies propose a treatment regimen of a single 0.5-mg ranibizumab injection followed by additional injections as needed (1+PRN).[12] Other studies suggest starting with three monthly doses, followed by as-needed treatment (3+PRN).[13] However, the majority of clinical studies with 0.5 mg of ranibizumab showed consistent gains in best-corrected VA (BCVA), regardless of the anti-VEGF treatment regimen.[2]

The phase 2 REPAIR study (1+PRN)[12] showed that 86% of patients had improved BCVA, with 37% achieving a gain of more than 15 letters. Moreover, a marked decrease in central macular thickness (CMT) was seen at the 12-month follow-up.

Another pivotal study was the phase 3 RADIANCE trial, which compared the efficacy of ranibizumab (group 1: injection on day 1 and month 1+PRN; group 2: day 1+PRN) versus vPDT (PDT day 1+PDT or ranibizumab at investigator's discretion starting at month 3). Ranibizumab was superior in mean change in BCVA from baseline during 12 months of follow-up. In addition, between 63% and 65% of patients showed resolution of leakage from the CNV.[14]

Aflibercept. The phase 3 MYRROR study evaluated the safety and efficacy of 2.0 mg aflibercept for the treatment of myopic CNV. The dosing regimen in the treatment group was 1+PRN. After 24 weeks, 39% of the treated patients experienced a gain of more than 15 letters in BCVA and demonstrated a decrease in CMT. These changes were maintained for 48 weeks. The sham injection group received aflibercept for the first time at week 24; after that injection they had a modest gain in VA, substantially less than that in the treatment group. These results support early initiation of treatment to achieve optimal visual outcomes.[15]

Bevacizumab. Several studies have demonstrated the effectiveness of bevacizumab in treating myopic CNV. Although there is no standardized dosage, the use of 1.25 mg of bevacizumab has been reported to be safe in a 1+PRN or 3+PRN regimen, with no marked difference in efficacy between the two treatment regimens.[2]

A recent retrospective comparative study examined the efficacy of bevacizumab versus aflibercept. Both agents were administered on a 1+PRN basis. No significant differences were found in VA outcomes; however, significantly fewer injections were administered in the aflibercept group, suggesting that it has a more prolonged effect.[16]

Verteporfin photodynamic therapy (vPDT). The VIP study examined the effect of vPDT compared with placebo in maintaining or improving vision.[17] Although VIP yielded better visual outcomes for vPDT at 12 months, later studies suggest worsening after the second year; at five years, chorioretinal atrophy was seen in 83% of patients.[18] Currently, this treatment should be considered only if anti-VEGF therapy is contraindicated.[2]

Follow-up and Prognosis

In a 1+PRN regimen (the preferred approach in our clinic), the patient is monitored every month for the next three to six months with VA evaluation and ancillary tests such as FA, SD-OCT, or OCTA.[1] The criteria for retreatment are based on signs and symptoms of CNV activity, including visual loss and metamorphopsia, evidence of new leakage on FA, and persistent or increased intraretinal fluid on OCT. If there are no signs of active CNV, follow-up can be extended to every three months during the first year. Patients with myopic CNV usually respond rapidly to treatment, and recurrence is much less frequent than in other neovascular disorders such as AMD.

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