Progress in Retinal and Eye Research 63 (2018) 92–106

Contents lists available at ScienceDirect

Progress in Retinal and Eye Research

journal homepage: www.elsevier.com/locate/preteyeres

Diagnosis and treatment guideline for myopic choroidal neovascularization due to pathologic myopia

Kyoko Ohno-Matsui[a,*], Yasushi Ikuno[b], Timothy Y.Y. Lai[c], Chui Ming Gemmy Cheung[d]

[a] Department of Ophthalmology and Visual Science, Tokyo Medical and Dental University, 1-5-45 Yushima, Bunkyo-ku, Tokyo 113 8510, Japan
[b] Ikuno Eye Center, 2-9-10-3F Juso-Higashi, Yodogawa-Ku, Osaka 532 0023, Japan
[c] Department of Ophthalmology & Visual Sciences, The Chinese University of Hong Kong, Hong Kong Eye Hospital, 147K Argyle Street, Kowloon, Hong Kong
[d] Singapore Eye Research Institutes, National University of Singapore, Singapore

ARTICLE INFO

Keywords:
Anti-VEGF therapy
Myopic choroidal neovascularization
Overview
Prognosis
Treatment recommendations

ABSTRACT

Pathologic myopia is a leading cause of visual impairment. Development of myopic choroidal neovascularization (CNV) is one of the most common complications that leads to central vision loss in patients with pathologic myopia. If left untreated, it can cause scarring with expanding macular atrophy leading to irreversible visual loss in a period as short as 5 years. Advancements in multimodal imaging technology have furthered our understanding of the condition; however, further studies are necessary to extend its utility in the diagnosis of myopic CNV. Intravitreal anti-vascular endothelial growth factor (anti-VEGF) therapy has become the standard-of-care and the recommended first-line treatment option for myopic CNV. Long-term studies have demonstrated that early treatment of confirmed myopic CNV cases with an intravitreal anti-VEGF agent is useful to avoid late-stage complications. This strategy has also been shown to achieve visual outcome improvements for up to 4 years and visual stabilization up to 6 years. This review article provides an overview of the current knowledge on myopic CNV and discusses recent updates in the diagnosis and management of the condition. Furthermore, treatment recommendations are provided based on the authors' expert opinions.

1. Introduction

Pathologic myopia is a major cause of blindness (best-corrected visual acuity [BCVA] < 0.1) worldwide (Wong et al., 2014). Wong et al. reported that the prevalence of visual impairment attributable to pathologic myopia ranged from 0.1% to 0.5% in European studies and from 0.2% to 1.4% in Asian studies (Wong et al., 2014). Indeed, up to 3% of the world's population is affected by pathologic myopia, which is among the top three most frequent causes of blindness, particularly in Asian countries (Wong et al., 2014). Blindness is currently defined as BCVA < 0.1 according to the World Health Organization (ICD-10; Version:2016). Severe visual loss develops in individuals with pathologic myopia because of alterations in the macula and optic nerve secondary to axial elongation and posterior ocular segment deformity, represented by the posterior staphyloma (Ohno-Matsui, 2014; Pruett, 1998).

Development of macular choroidal neovascularization (CNV) is one of the most frequent causes of central vision loss. Myopic CNV presents as a small, greyish membrane on slit-lamp biomicroscopy. It typically appears as a "classic" pattern on fluorescein angiography (FA), with well-defined hyperfluorescence in the early phases and fluorescein dye leakage in the late phases. It is classified as a type 2 CNV when the CNV grows over the retinal pigment epithelium (RPE), and is characterized by a highly reflective area above the RPE layer on optical coherence tomography (OCT). Unlike neovascular age-related macular degeneration (AMD), exudative changes are less obvious in myopic CNV. Although myopic CNV may be self-limiting in some patients as described by Avila et al. (1984), a long-term follow-up study conducted almost 20 years later showed that if left untreated, myopic CNV can cause scarring with expanding macular atrophy. Subsequently, these changes lead to irreversible visual loss in a period as short as 5 years and the mean BCVA becomes ≤0.1 in approximately 10 years (Yoshida et al., 2003).

The incidence and prevalence of myopic CNV varies in different geographic regions and may be underestimated, partly because of a limited understanding of its pathophysiology, lack of uniform diagnostic criteria, and, until recently, an absence of highly accurate imaging methods. The growing interest in myopic CNV has led to an increased understanding of its pathogenesis and the subsequent development of promising treatment options. In particular, the efficacy and safety of anti-vascular endothelial growth factor (VEGF) therapy has been shown in both short- and long-term studies (Franqueira et al.,

* Corresponding author. Department of Ophthalmology and Visual Science, Tokyo Medical and Dental University, 1-5-45 Yushima, Bunkyo-ku, Tokyo 113-8510, Japan.
E-mail address: k.ohno.oph@med.tmd.ac.jp (K. Ohno-Matsui).

https://doi.org/10.1016/j.preteyeres.2017.10.005
Received 26 June 2017; Received in revised form 18 October 2017; Accepted 25 October 2017
Available online 28 October 2017
1350-9462/

2012; Tufail et al., 2013; Wolf et al., 2014; Kasahara et al., 2016).

Several treatment approaches have been studied for myopic CNV, including focal thermal laser photocoagulation, verteporfin photodynamic therapy, surgical management, and intravitreal anti-VEGF therapy. However, these approaches are limited by myopic CNV recurrence, complications, suboptimal response, or acceptable results in only subsets of patients. As emerging evidence suggests that newer strategies are more efficacious in treating myopic CNV, some of these approaches have been discontinued. Currently, intravitreal anti-VEGF therapy is the "gold standard treatment" for myopic CNV (El Matri et al., 2015). Reports of both anatomical and functional improvements of myopic CNV achieved with the off-label use of anti-VEGF agents date as far back as 2007. Ranibizumab, an anti-VEGF agent specifically designed for intraocular use, was approved for the treatment of myopic CNV in 2014. In addition, aflibercept has been approved for the treatment of myopic CNV in some European and Asian countries.

This review article aims to provide an overview of the current knowledge on myopic CNV, as well as to discuss recent updates in management and provide treatment recommendations based on the authors' expert opinions.

2. Disease overview

2.1. Incidence and prevalence

The reported incidence and prevalence of myopic CNV varies widely because, until recently, the definition and classification were not uniform. A recent systematic review summarized the epidemiology of CNV based on 39 reports (Wong et al., 2014) and reported that the prevalence of CNV in individuals with pathologic myopia ranged between 5.2% and 11.3%, and was bilateral in approximately 15% of patients. Moreover, they found that, in individuals with myopic CNV (disease duration ranging from less than 3 months to 21.5 years), BCVA deterioration was observed over time. However, the reported incidence and prevalence of myopic CNV may be underestimated because in patients with pathologic myopia, other complications, such as myopic traction maculopathy (MTM) and optic nerve damage, often co-exist (Nagaoka et al., 2015; Ohno-Matsui et al., 2012; Shimada et al., 2007). In such cases, vision is already impaired by these co-existing pathologies, and patients tend not to report additional or new symptoms.

2.2. Definition

Myopic CNV is defined as CNV that occurs in pathologic myopia. Therefore, we first need to define pathologic myopia. Previously, studies have defined pathologic myopia based on a variety of biometric criteria and/or fundoscopic findings (for example, levels of refractive error, axial length, and/or BCVA score); thus, the definition is not uniform. For comparison, definitions of pathologic myopia and myopic CNV used in previous studies are presented in Table 1. In the REPAIR study of intravitreal ranibizumab, patients with active CNV in the presence of high myopia with a spherical equivalent of at least −6 diopters were enrolled (Tufail et al., 2013). The definitions used in the RADIANCE study were more stringent. Patients were included if active CNV was present together with high myopia of at least −6 D, anteroposterior elongation ≥26 mm, and fundus changes compatible with pathologic myopia (Wolf et al., 2014). A similar definition was used in the MYRROR study (Ikuno et al., 2015), which evaluated the efficacy of intravitreal aflibercept in patients with high myopia (more myopic than −6.0 D or an axial length of ≥26.5 mm), active CNV, and a BCVA of 73–35 letters (0.58–0.1; ETDRS Equivalent Snellen Fraction; Gregori et al., 2010).

Important features of pathologic myopia include the presence of myopic maculopathy and/or posterior staphyloma (Ohno-Matsui, 2016; Ohno-Matsui et al., 2016). Recently, a new uniform classification system for myopic maculopathy (META-PM classification) was developed by a panel of experts based on the existing literature (Ohno-Matsui et al., 2015). The key aspects of the META-PM classification are shown in Table 2. Briefly, myopic maculopathy lesions are classified into five categories (0–4). Three additional features (lacquer cracks, myopic CNV, and Fuchs' spots) that can develop from, or coexist, in eyes with any of the myopic maculopathy categories and lead to central vision loss were added to these categories as plus signs. This META-PM classification was established based on fundus photos. However, OCT is now widely used, and pathologies that are diagnosed with OCT (such as myopic traction maculopathy, retinoschisis, and macular holes) should be added to the classification in further studies.

Pathologic myopia is currently defined as the presence of chorioretinal atrophy equal to or more severe than diffuse atrophy (category 2) (Ohno-Matsui, 2016). Ohno-Matsui proposed that the definition of pathologic myopia should also include the feature of structural eye deformity. Specifically, the presence of posterior staphyloma strongly suggests the presence of pathologic myopia (Ohno-Matsui, 2016).

2.3. Natural history

During the natural course of myopic CNV, three stages are associated with vision loss (Fig. 1) (Ohno-Matsui et al., 2015; Ohno-Matsui and Yoshida, 2004; Yoshida et al., 2003): the active phase characterized by hemorrhage and/or serous retinal detachment; the scar phase with development of fibrous scars, which, in some cases, become pigmented and are known as "Fuchs' spot"; and the atrophic phase with development of macular chorioretinal atrophy around the regressed CNV (myopic CNV-related macular atrophy), characterized by the formation of a hole in Bruch's membrane (Ohno-Matsui and Yoshida, 2004). This macular atrophy is not a progression of pre-existing myopic chorioretinal atrophy, but rather it occurs specifically after the development of myopic CNV.

In general, the long-term outcome of CNV is extremely poor without treatment. This was confirmed in the 10-year follow-up study of 25 patients with myopic CNV by Yoshida et al. (2003). They showed that, if myopic CNV was left untreated, visual acuity deteriorated to 20/200 or worse in approximately 89% and 96% of eyes in 5 years and 10 years, respectively. Reportedly, in patients with pre-existing myopic CNV, 35% of patients developed CNV in the fellow eye, and the mean period between development of CNV in the first eye and development of CNV in the second eye was 8 years (Ohno-Matsui et al., 2003).

Several East Asian studies have reported a high prevalence of pathologic myopia in this region, suggesting a significant socio-economic impact of myopic CNV (Yoshida et al., 2003; Chan et al., 2016; Wong et al., 2014). The factors associated with worse visual outcomes are older age (> 40 years), subfoveal CNV location, larger baseline lesion size (> 400 μm), and lower BCVA at baseline (Wong et al., 2014, 2015).

2.4. Pathogenesis

The pathogenesis of myopic CNV is not well understood. Several theories, such as the mechanical theory and the heredodegenerative theory (which suggests that errors in myopic refraction are genetically predetermined) have been proposed to explain the development of myopic CNV (Wong et al., 2015). The precursor lesions of myopic CNV are large myopic conus and patchy atrophy (originating from lacquer cracks) (Ohno-Matsui et al., 2003). Lacquer cracks are thought to represent fissures in the RPE–Bruch's membrane–choriocapillaris complex caused by the elongation of myopic eyes. The presence of lacquer cracks has been associated with a higher risk of individuals developing myopic CNV. Despite the hypothesis that lacquer cracks are precursors of CNV, the development of CNV at the site of pre-existing lacquer cracks has not been demonstrated. In a longitudinal follow-up study, the incidence of myopic CNV was higher in eyes with lacquer cracks (29.4%) than in eyes with other types of myopic maculopathy (Ohno-Matsui et al.,