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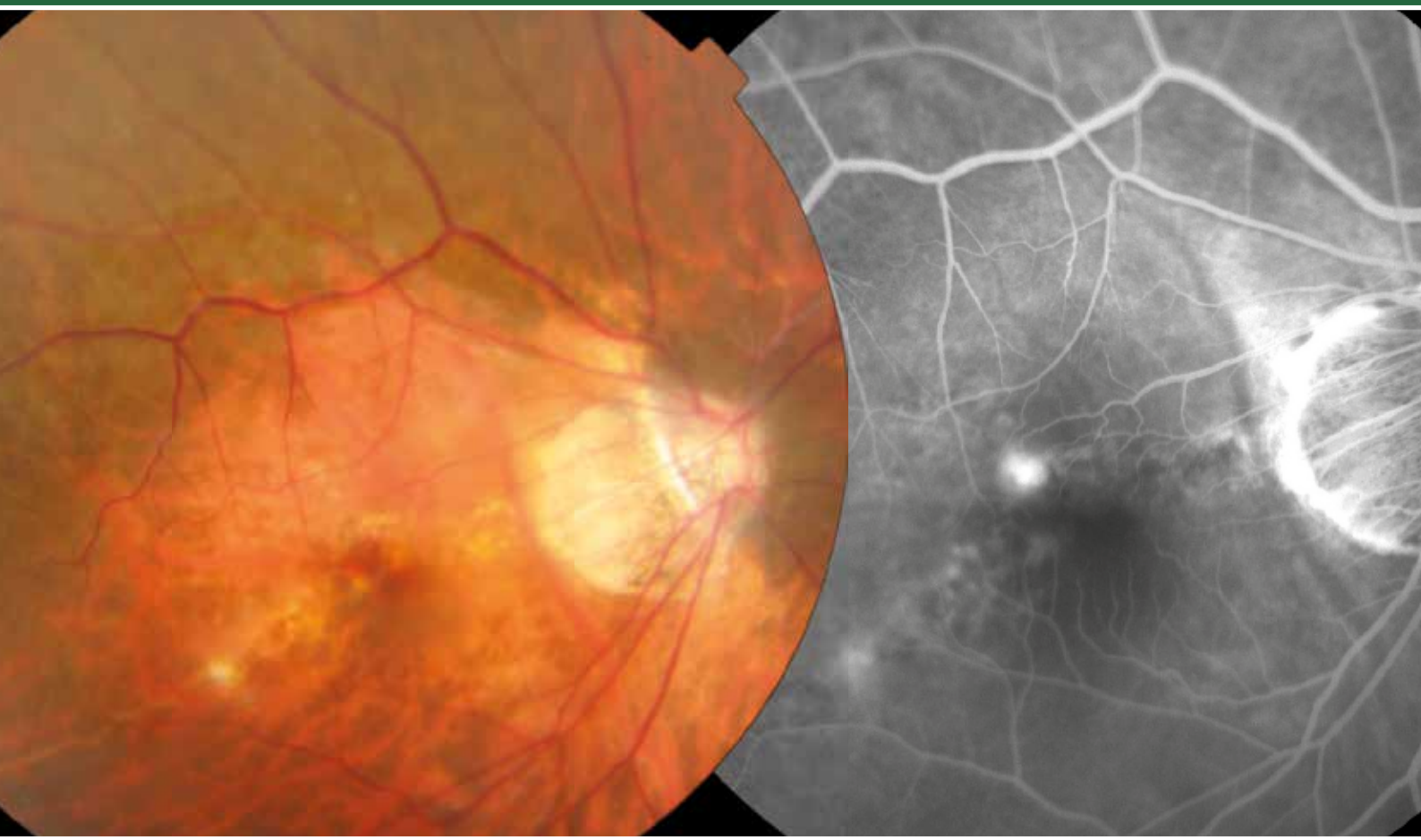

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The ROYAL COLLEGE of OPHTHALMOLOGISTS

EDITORIAL

社论:从亚洲视角看眼部疾病的发病特点

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亚洲是全球人口最密集的大洲，占世界人口的60%以上。由于各种遗传和环境因素，某些眼病在亚洲人群中发病率高且常见， 如高度近视、闭角型青光眼、脉络膜肥厚型眼病，例如中心性浆液性脉络膜视网膜病变和息肉状脉络膜血管病变(PCV)以及某些非感染性葡萄膜炎，如小柳原田病、结节病和白塞病。虽然亚洲的一些国家和地区城市人口发达，但较多地区仍处于相对不发达水平。由于这些欠发达地区缺乏良好的卫生条件、卫生标准，基础设施差，生活环境过于拥挤以及高降雨量和潮湿气候，使得因结核病和蚊子传播的疾病如登革热和基孔肯雅病等引起传染性葡萄膜炎在亚洲的这些地区更为常见。这些疾病在亚洲的高患病率为在该地区的临床医生和科学家提供了极好的机会调查与研究这些眼部疾病的流行病学、发病机理、诊断和治疗方法。在本期“亚洲视角特刊”中，，由亚洲及其他地区的专家共同撰写的评论文章，总结了该地区常见眼部疾病的关键要素。

脉络膜肥厚型眼病是一个相对较新的术语，用来描述由于脉络膜静脉扩张与脉络膜异常增厚引起的脉络膜毛细血管层的改变。[1]在Cheung等人的综述文章中，[2]讨论了各种脉络膜肥厚型疾病的临床特点、影像学特征和治疗注意事项。缺乏对脉络膜肥厚的统一定义是脉络膜特征研究中一个重要挑战。该文章作者强调，单一的中心凹下脉络膜厚度并不是定义脉络膜肥厚的关键特征。相反，提示内层脉络膜和脉络膜毛细血管层受压的形态学特征在认知过程中更重要。毫无疑问，影像学技术的进步将继续改善脉络膜体积测定的定性和定量方法，并识别其在三维空间结构中不同位置的变化。

在Yanagi等人的一篇相关文章中，[3]作者着重探讨了PCV和典型年龄相关性黄斑变性(AMD)的发病机制之间的差异。最近Spaide提出脉络膜厚度可能影响AMD的表型。[4]例如，脉络膜薄的患者有发展成为网状玻璃膜疣和3型新血管形成的倾向，而脉络膜厚的患者有发展成pachydrusen肥厚型玻璃膜疣和PCV的倾向。因此脉络膜厚度的变化可以解释AMD在不同人群间亚型的差异。然而，决定脉络膜厚度的因素尚不清楚，但已提出遗传和环境因素可能与其相关。

正如Wu医生等人在一篇关于近视和使用阿托品控制近视的评论文章[5]中强调的那样，近视发病率增加不再局限于东亚地区,全球范围内近视发病率都呈现迅速增长趋势。由于近视可出现黄斑萎缩、高度近视性脉络膜新生血管形成和牵拉性黄斑病变等威胁视力的并发症的发生[6]，因此近视已成为全球关注的流行病学问题。尽管在严格的随机对照试验中，低剂量阿托品被证明是控制近视发展安全有效的方法,但由于制药行业的经济利益的原因而导致目前尚无批准的低剂量阿托品制剂

进入市场，因此，其应用于预防近视方面仍有相当大的障碍。目前，欧洲国家低剂量阿托品在临床中的应用仍相当有限。现阶段针对欧洲儿童正在开展一些临床实验，旨在评估低剂量阿托品的有效性、安全性和耐受性。这些研究的结果将对低剂量阿托品用于患病人群的适用范围提供有价值的信息。因此，迫切需要全球共同努力，以应对近视日益严重的影响。

随着亚洲许多地区的快速城市化和社会经济发展，糖尿病发病率呈指数级增长。例如，2000年至2035年，南亚2型糖尿病的患病率预计将增加150%。[7]因此，对于糖尿病视网膜病变的筛查需求也将大大增加，同时也将给缺乏眼科医护人员的地区带来沉重负担。随着计算机和影像学技术的发展，人工智能在糖尿病视网膜病变筛查中的应用可能会为大规模糖尿病患者筛查提供一种经济有效的方法。在Raman等人的综述中[8]，作者比较并讨论了人工智能神经网络深度模型如何辅助糖尿病视网膜病变诊断。

未来有望将人工智能技术整合到现有的影像成像系统中，从而实现及早发现威胁视力的糖尿病视网膜病变，并迅速将患者转诊给眼科医生进行有效治疗。

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The ROYAL COLLEGE of OPHTHALMOLOGISTS

EDITORIAL

Asian perspective of eye diseases

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Asia is the world's most populated continent and contains over 60% of the world's population. Due to various genetic and environmental risk factors, certain eye diseases are particularly prevalent in Asian populations. These include high myopia, angle-closure glaucoma, pachychoroid eye diseases such as central serous chorioretinopathy and polypoidal choroidal vasculopathy (PCV), and certain non-infectious uveitis like Vogt–Koyanagi–Harada disease, sarcoidosis, and Behcet's disease. Although some Asian countries and regions are well-developed urban populations, many parts of Asia are still relatively underdeveloped. Due to the lack of good sanitation, poor hygiene standards, and infrastructure, an overcrowded living environment, together with high rainfall and humidity in these underdeveloped areas, infectious uveitis due to tuberculosis, and mosquito-borne diseases such as dengue and chikungunya are more commonly found in these parts of Asia. The higher prevalence of these conditions in Asia created excellent opportunities for clinicians and scientists in the region to investigate and study the epidemiology, pathogenesis, diagnosis, and treatment of these eye diseases. In this Special Asian Perspective Issue of *Eye*, review articles prepared by experts in Asia and beyond summarized key aspects of these eye conditions more commonly found in the region.

Pachychoroid eye disease is a relatively new term describing changes in the choriocapillaris due to dilated choroidal veins associated with abnormal thickening of the choroid [1]. In a review article by Cheung et al., [2] the clinical characteristics, imaging features, and management considerations of various pachychoroid conditions will be discussed. A notable challenge in the study of choroidal features is the lack of unified definition of pachychoroid. The authors of the review highlighted that subfoveal choroidal thickness alone is not the key defining feature of pachychoroid. Rather, morphological features which suggest compression of the inner choroid and choriocapillaris are more important to be recognized. Advances in imaging will no doubt continue to improve both qualitative and quantitative measures of the choroid in a volumetric manner and recognize variations in different locations of this three-dimensional structure.

In a related article by Yanagi et al., [3] the authors highlighted and explored the differences in the basic pathogenic mechanisms of PCV and typical age-related macular degeneration (AMD). Recently, Spaide proposed that choroidal thickness may influence the expression of AMD[4]. For example, patients with thin choroid have a propensity to develop reticular pseudodrusen and type 3 neovascularization, whereas patients with thick choroid are predisposed to develop pachydrusen and PCV. Thus, variations in choroidal thickness may explain some of the differences in the sub-phenotypes of AMD between different populations. The factors that determine choroidal thickness however, are not well understood yet, but both genetic and environmental factors have been proposed.

As highlighted by Wu et al. in their review article on myopia and the use of atropine for myopia control, [5] the condition is no longer a problem limited to East Asia as the prevalence of myopia is increasing rapidly worldwide. With the potential development of sight-threatening complications including macular atrophy, myopic choroidal neovascularization, and myopic traction maculopathy arising from high myopia, [6] it has thus become a major epidemiological problem globally. Despite low-dose atropine being proven as an effective and safe method in controlling myopia progression in well-designed randomized controlled trials, the lack of approved licensed preparation of low-dose

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atropine due to insufficient financial interest from the pharmaceutical industry has led to a considerable barrier in its uptake in the prevention of myopia. The clinical implementation of low-dose atropine in European countries is still rather limited at present. Randomized clinical trials to evaluate the efficacy, safety, and tolerability of low-dose atropine in children of European descent are currently ongoing. The results of these studies will be valuable to inform on the applicability of low-dose atropine in these patient populations. A global concerted effort to tackle the increasing impact of myopia is thus urgently needed.

With the rapid urbanization and socioeconomic changes occurring in many parts of Asia, the incidence of diabetes mellitus is growing exponentially. For example, the prevalence of type 2 diabetes mellitus in South Asia is expected to increase by 150% between 2000 and 2035 [7]. The demand for screening of diabetic retinopathy will therefore also increase tremendously and will put substantial burden in areas already having insufficient eye care providers. With the recent advancements in computing and imaging technologies, the use of artificial intelligence in the detection of diabetic retinopathy might provide a solution in providing a cost-effective method in screening a large population of diabetic patients. In the review by Raman et al., [8] the authors compared and discussed how deep learning models with artificial intelligence neural networks can help in the diagnosis of diabetic retinopathy. Future integration of artificial intelligence technology into existing imaging systems will hopefully allow early detection of sight-threatening diabetic retinopathy so that prompt referral of patients to ophthalmologists can be offered for effective treatment.

Compliance with ethical standards

Conflict of interest Dr. Lai has received honoraria for consultancy, lecture fee, and grant support from Allergan, Bayer, Roche, and Novartis. Dr. Cheung has received honoraria for consultancy, lecture fee, and grant support from Allergan, Bayer, Novartis, Roche, Samsung, and Topcon. The authors declare that they have no conflict of interest.

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REVIEW ARTICLE

关于控制近视及阿托品治疗策略的研究进展

摘要

全球近视的患病率正在急剧上升，且近视的并发症消耗巨大的社会和财政支出。人们认为，成年后的高度近视由学龄期发生的近视而来。因此，实施近视控制的有效措施至关重要，措施包括预防近视产生以及延缓学龄儿童的近视发展。目前，然而关于近视的致病机制仍然知之甚少。一些证据表明Bruch膜的过度扩张，可能引起了周边远视离焦，并且它可能是导致眼球发生不可控制的眼轴伸长的机制之一。阿托品是目前控制近视最有效的方法。最近的临床试验表明，与高浓度制剂相比，低剂量阿托品滴眼液如0.01%可以延缓近视发展，副作用明显减少。然而，仍然有一部分患者的反应较差，其中最佳处理仍不明确。已提出的临床策略包括逐步增加阿托品给药频率，以及低剂量阿托品结合增加室外活动时间。本综述将重点介绍目前近视在流行病学、病理生理学中的研究进展，以及最近在学龄儿童中使用阿托品的临床试验和临床实施的远视、近视前期、近视儿童的治疗策略。

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The ROYAL COLLEGE of OPHTHALMOLOGISTS

REVIEW ARTICLE

Update in myopia and treatment strategy of atropine use in myopia control

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Abstract

The prevalence of myopia is increasing globally. Complications of myopia are associated with huge economic and social costs. It is believed that high myopia in adulthood can be traced back to school age onset myopia. Therefore, it is crucial and urgent to implement effective measures of myopia control, which may include preventing myopia onset as well as retarding myopia progression in school age children. The mechanism of myopia is still poorly understood. There are some evidences to suggest excessive expansion of Bruch's membrane, possibly in response to peripheral hyperopic defocus, and it may be one of the mechanisms leading to the uncontrolled axial elongation of the globe. Atropine is currently the most effective therapy for myopia control. Recent clinical trials demonstrated low-dose atropine eye drops such as 0.01% resulted in retardation of myopia progression, with significantly less side effects compared to higher concentration preparation. However, there remain a proportion of patients who are poor responders, in whom the optimal management remains unclear. Proposed strategies include stepwise increase of atropine dosing, and a combination of low-dose atropine with increase outdoor time. This review will focus on the current understanding of epidemiology, pathophysiology in myopia and highlight recent clinical trials using atropine in the school-aged children, as well as the treatment strategy in clinical implementation in hyperopic, pre-myopic and myopic children.

Myopia is the most common eye disorder worldwide, but it is often misregarded as merely a refractive error that can simply be corrected by spectacles, contact lenses, or refractive surgery. As a matter of fact, high myopia is often associated with an increased risk of a range of serious ocular complications, which may result in irreversible vision loss. The World Health Organization (WHO) recently defined "high myopia" as −5 Diopter (D) or greater, which is associated with increased risk of blindness [1]. Eyes with high myopia that develop degenerative changes in the macula, optic nerve and peripheral retina are considered as having pathologic myopia, and are at the highest risk of developing potentially blinding complications such as retinal detachments, myopic choroidal neovascularization (CNV), myopic macular degeneration, foveoschisis, glaucoma, and cataract [2, 3]. Myopia has become a major public health issue because of its rapid increase of prevalence, especially in the East Asia, and its link to potential irreversible blindness.

Significant racial differences in the prevalence of myopia have been reported. The prevalence of high myopia is estimated to range between 2 and 5% in white populations and between 5 and 10% in Asian populations [4], while the prevalence of pathologic myopia is estimated to be ~1% in white populations and ~1–3% in Asians [5]. Regardless of these racial differences, there is evidence to suggest that the

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prevalence of myopia is increasing globally. A recent review estimated that 22.9% of the world population has myopia and 2.7% has high myopia in 2000, but by 2050, these figures will increase to 49.7% and 9.8%, respectively. In other words, almost 1 billion people will have high myopia [6], suggesting an alarming increase of prevalence globally.

Earlier age onset of myopia is a significant risk factor for high myopia in the future [7]. After adolescence, myopia progression gradually stabilizes for most individuals. The early onset of myopia in Asian schoolchildren is associated with longer duration to reach stability in refraction, and in some cases faster progression rate (-1 D per year) [8], which ultimately results in the higher prevalence of high myopia in Asian young adults, with risks to develop sequelae associated with high myopia and resulting in pathologic myopia [9]. Therefore, delaying myopia onset and retarding myopia progression in school-aged children is potentially the key to reduce high myopia later in life.

There are strong evidences to suggest environmental factors play a crucial role in the development of school age onset myopia [10], which include time spent outdoors [11], prolonged intense education [12], urbanization [10], near work [13], prenatal factors [14], and socioeconomic status [15]. Recently, outdoor activities and decreasing the duration of near work have been reported to be effective in delaying myopia onset [11, 16]. However, among the various interventions evaluated, atropine has been found to be one of the most consistently effective interventions in slowing down myopia progression[17, 18]. This review will cover recent understanding of pathogenesis of myopia, rationale, as well as clinical trial results of the use of atropine to retard myopia progression.

Epidemiology of school myopia

Most individuals develop myopia at childhood, particularly during the school years; children with younger age at the onset of myopia tend to have greater myopia progression subsequently. Generally myopia at school age or juvenile-onset myopia often refers to the children who develop myopia in the primary school or early secondary school years, with the exclusion of the early onset forms of high myopia which are associated with strong familial inheritance [10]. Similar to the prevalence of myopia in adulthood, the prevalence and incidence rates of myopia in children varies among different areas and countries; in China and Taiwan, the annual incidence of myopia in 7–12-year-old children has been reported to be 8–18% [11, 19]. In contrast, a much lower annual incidence rate of 2.2% has been reported in children of 12-year-old in Australia [20].

Over the past decades, a number of reports have demonstrated that prevalence of myopia and high myopia has been increasing dramatically in schoolchildren, especially in the East Asia [21, 22]. For example, from 1983 to 2000 the prevalence of myopia in the 7-year olds increased from 5.8% to 21.0% in Taiwan [21]. In urban areas of East Asia, up to 80–90% of children completing secondary school are now myopic, and approximately one fifth of those has high myopia [23]. It is thought that environmental factors play a crucial role in this trend, as prevalence of school age onset myopia has remained low in the rural areas, such as in rural Mongolia, where the prevalence reported in 2006 was 5.8% [24].

European populations have had an estimated prevalence of 30.6% and the prevalence is steadily increasing [25, 26]. An increasing trend for the prevalence of myopia has also been observed in North America and Australia. According to a review in the United States, the prevalence of myopia in schoolchildren aged 12–17 years increased from 12.0% (between 1971 and 1972) to 31.2% (between 1999 and 2004) [27]. Another meta-analysis of population-based, cross-sectional studies of myopia prevalence in Western and Northern Europe demonstrated that there was a trend of higher myopia prevalence in the younger adults with a more recent birth year, of whom approximately half were affected [26]. Even in Australia, where prevalence of myopia appears to be lower than Europe and North America; it has been estimated that there may have been a four-fold increase in the prevalence of myopia over the last century [28].

Current understanding of pathophysiology of myopia

The process of emmetropization is the adjustment of the length of the optical axis to the optical characteristics of the lens and cornea after the end of the second year of life. Myopization can be described as an overshooting of the process of emmetropization. In the first two years of life, the globe grows mostly spherically in all directions, increasing in sagittal diameter from about 17 mm at full-term birth to ~21 to 22 mm at the end of the second year of life. This eye growth is associated with an increase in the volume of the sclera and is thus probably accompanied by active formation of new scleral tissue [29]. Beyond the second year of life, further enlargement of the globe occurs predominantly in the axial direction, with 1 mm of axial elongation corresponding to a 0.5 mm increase in the horizontal and vertical diameters of the eye up to an axial length of 24 mm [30]. Beyond an axial length of 24 mm, the horizontal and vertical globe diameter increases by 0.2 mm or less for each mm of axial elongation. The axial elongation is associated

with thinning of the choroid and, to a lower degree in relative terms, of the sclera. Choroidal and scleral thinning is most pronounced at the posterior pole and less marked at the equator [31]. The axial elongation is also associated with thinning of the retina and reduced density of the retinal pigment epithelium cells (RPE) in the retro-equatorial region, while retinal thickness and RPE cell density in the macular region and the thickness of Bruch's membrane (BM) in any region are independent of axial length [32–34]. The axial elongation-associated increase in the fovea-optic disc distance is mainly due to the development and enlargement of parapapillary gamma zone defined as the BM free region around the optic disc [35, 36]. Subsequently, the length of BM in the macular region is not increased in axially elongated eyes, unless defects in BM in the macular region have developed [37]. The independence of the RPE cell density, retinal thickness, and length of the BM in the macular region fit with the observation that the best corrected visual acuity was independent of the axial length in axially elongated eyes without myopic maculopathy [38].

The process of emmetropization may occur in a feedback mechanism with an afferent, sensory part and an efferent part. Experimental studies in animals and clinical observations have suggested that the afferent sensory part may be located in the mid periphery of the fundus in the retro-equatorial region of the eye [39, 40]. This assumption is based on observations in animals that peripheral defocus leads to axial elongation of the eyes. In keeping with this hypothesis, patients with a congenital macular scar, e.g. due to a toxoplasmotic retinochoroiditis, usually do not develop axial elongation, while eyes with destruction of themed-peripheral retina, such as after laser photocoagulation for retinopathy of prematurity, can develop marked axial myopia. In contrast, eyes with retinopathy of prematurity treated by intravitreal application of anti-VEGF (vascular endothelial growth factor) drugs develop less axial myopia [41]. The notion of the mid-periphery fundus as the location of the sensory arm of the process of emmetropization is also supported by clinical trials on myopic children randomly assigned to wear single vision lenses or progressive addition lenses [42]. In contrast, understanding of the efferent arm of the proposed feedback mechanism has remained limited. The elusiveness includes the target tissue as well as the mode of communication between the afferent and efferent arms. A messenger molecule has been proposed to transfer the information from the afferent to the efferent arm. Proposed candidates include dopamine, levodopa, or a dopamine-like agonist that inhibited the axial elongation of occluded eyes with form-deprivation myopia in rabbits, guinea pigs or mice [43–45]. As a corollary, the intravitreal injection of apomorphine as a non-specific dopaminergic agonist resulted in an ocular growth inhibition in a lens-induced myopia model [46, 47]. However, contradictory findings have been reported in other animal models [48]. Another group of molecules proposed to be involved in the etiology of myopia were muscarinic antagonists. Studies revealed that pirenzepine, an anticholinergic agent with high muscarinic M1 receptor selectivity inhibited the axial elongation in guinea pigs, tree shrews, and in monkeys when applied intravitreally [49–51]. In guinea pigs, pirenzepine intraocularly applied increased the expression of tissue inhibitors of metalloproteinases (TIMP-2) and of tyrosine hydroxylase [51]. It fits with the results of clinical trials discussed later in this review, in which atropine applied topically in low concentrations of 0.01% was associated with a reduced progression of myopia in school-aged children. Another candidate molecule is the adenosine receptor antagonist, 7-methylxanthine [52].

The target tissue as the primary driver of the axial elongation has remained elusive so far. In many studies, the sclera, and in some investigations the choroid, have been considered to be primarily responsible for the myopic enlargement of the eye [53, 54]. The sclera as the primary driver of axial elongation does not fit however with the anatomical finding of a marked thinning of the choroid, most marked at the posterior pole and being in relative terms considerably more pronounced than the thinning of the sclera [25]. If the sclera was the primary tissue governing the axial length of the eye, one would expect a widening of the choroidal space. An alternative model could be to consider BM as the primary structure expanding posteriorly and compressing the choroid, most markedly at the posterior pole, and distending secondarily the sclera. This hypothesis is supported by several anatomical observations: (1) the volume of the sclera (and choroid) is not enlarged in axially elongated eyes, suggesting re-arrangement of available tissue without active formation of new tissue; (2) the thickness of BM is independent of the axial length; and (3) the goal of the process of emmetropization is the adaption of the length of the optical axis that ends at the photoreceptor outer segments. The first firm structure located closest to the photoreceptor outer segments is BM while the sclera is separated from the photoreceptor outer segments by the spongy choroid, the thickness of which additionally shows a diurnal variation. The notion of BM as the primary driver is supported by a recent study in which the biomechanical strength of BM in relationship to its thickness was about 50–100 times stronger as compared to the strength of the sclera (Girard, personal communication). This hypothesis also fits with the observation that the RPE cell density and retinal thickness in the fundus mid-periphery decrease with longer axial length, perhaps due to the production of BM in that region leading to a mostly tube-like enlargement of the globe. If BM is the primary driver of axial elongation, the RPE producing BM as its basal membrane would be the target tissue. Interestingly, a

recent experimental study on lens-induced myopia in young guinea pigs revealed that amphiregulin antibody if applied intravitreally was associated with a dose-dependent reduction in axial elongation [55]. The RPE has receptors for the epidermal growth factor with amphiregulin being a member of the epidermal growth factor family.

Rationale for use of atropine

To date, atropine is the only medication that has been demonstrated to be consistently effective in slowing myopic progression [17, 18]. Once myopia has developed in a child, the rate of progression is estimated to be around −1 D per year in East Asians and around −0.5 D per year in Caucasians [8, 56]. Several years later, a significant proportion of these children will reach the definition of high myopia. Therefore, intervention to prevent myopia progression early on in myopic children is urgent and important. The higher concentrations of atropine such as 1% or 0.5% have been shown to be very effective in retarding myopia progression, but the high rate of photophobia side-effect (in up to 100%) has been associated with high dropout rate (16–58%) [57, 58]. In addition, there are concerns regarding potential long-term systemic or ocular side effects. Besides, rebound effect after atropine discontinuation has also been described, and is particularly notable in higher concentration of atropine. Recently, several publications from Asia have reported efficacy of 0.01% atropine in myopia control while having lower rates of side effects. As a result, there have been renewed interests in the clinical implementation of atropine for myopia control.

The exact mechanism of topical atropine is still not known, although the up- and downregulation of retinal and scleral muscarinic receptors with influence on the scleral matrix has been postulated [59, 60]. Moreover, atropine inhibits myopia induction in both mammalian and avian eyes [61, 62]. Different to the mammalian eye, the avian eye contains striated ciliary muscle innervated by nicotinic receptor rather than muscarinic receptors [63]. Therefore, atropine might have function at a relatively lower dose, through M1/M4 receptors in the retina, not via the accommodation system. On the other hand, a non-muscarinic and a direct influence of atropine on the scleral fibroblasts could also contribute to the effect [64].

Review of clinical trials

Refraction change of myopia

Anti-muscarinic agents was named as “the most likely effective treatment to slow myopia progression” in the Cochrane database systemic review of 2011. Among them, atropine is the most widely studied anti-muscarinic agents [17]. The randomized control trial in Taiwan, published by Yen et al. in 1989, reported that 1% atropine had better effect on controlling myopic progression in a year of follow-up visit when compared to 1% cyclopentolate and placebo [58]. The mean myopia progression was −0.22 ± 0.54 D per year in eyes receiving 1% atropine, which was lower compared to 1% cyclopentolate (−0.58 ± 0.49 D per year) or placebo groups (−0.91 ± 0.58 D per year). Shin et al. later published another randomized control trial [8]. Children aged 6–13 years received tropicamide and served as the control group, in comparison with those who had 0.5, 0.25, or 0.1% of atropine. After 2 years of follow-up, all the atropine groups showed a positive effect on reducing myopic progression. Sixty-one percent of children in the 0.5% atropine group had cessation of myopic progression, while 4% had rapid progression. A lower proportion of eyes had cessation of myopia progression was observed in the control compared with the atropine groups (49%, 42% and 8% in the 0.25% atropine, 0.1% atropine and control group, respectively). Concurrently, a higher percentage of children with rapid progression was observed in the control group compare with the atropine treated children (17%, 33% and 44% in the 0.25% atropine, 0.1% atropine, and control group, respectively).

Atropine for the treatment of childhood myopia (ATOM) 1 study enrolled 400 school-aged children with myopia (spherical equivalent −1.00 to −6.00 D) and low astigmatism (≤1.5 D) in a double-masked trial in which, half of the enrolled children received 1% atropine in one eye nightly, and the other half received vehicle eye drops as the placebo [65]. After 2 years, the mean progression of myopia was significant lower in the 1% atropine group (−0.28 ± 0.92 D), compared to the control group (−1.20 ± 0.69 D). Atropine was stopped after 2 years and the children were observed for a further 12 months. During this “wash-out year”, myopic rebound was observed, which was more marked in the atropine group (−1.14 ± 0.80 D) than the placebo group (−0.38 ± 0.39 D) [66]. Despite the rebound, the overall myopic progression was still less for the eyes treated with atropine than placebo, over the 3-year period. Ocular side effects included photophobia, glare, and loss of accommodation. The use of bifocal or multifocal glasses could be used to relieve the symptom of blurred vision at near, Use of sun glasses or photochromic tinted lenses helped to relieve the symptom of photophobia and minimize the risks of cataract and retinal phototoxicity by excess exposure of Ultraviolet light irradiating into the eye. In addition, the cycloplegic effect was found to recover upon cessation despite long-term chronic use of atropine eye drops [66].

ATOM 2 study recruited another 400 children in Singapore and randomized them in 2:2:1 ratio to receive 0.5%,

0.1%, and 0.01% atropine per night for 2 years, in order to clarify if atropine at lower concentration could have similar efficacy as 1% atropine dosing [67]. The mean progression in the first 24 month (phase 1) was −0.30 ± 0.60 D, −0.38 ± 0.60 D, and −0.49 ± 0.63 D in the 0.5%, 0.1%, and 0.01% atropine arms respectively (0.01% vs. 0.5%, p = 0.02; between other concentrations: p > 0.05). Atropine was stopped at the end of 2 years, and all participants were monitored for a year (phase 2) [68]. During this 'wash-out period', rebound progression of myopia was more prominent in the 0.5% atropine group (−0.87 ± 0.52 D), compared to the 0.1% (−0.68 ± 0.45 D) and 0.01% group (−0.28 ± 0.33 D, p < 0.001). The overall progression of myopia over the 36-month period was significant lowest in the 0.01% atropine group (−0.72 ± 0.72 D) followed by the 0.1% atropine group (−1.04 ± 0.83 D) and the highest progression was observed in children that were treated with 0.5% atropine group (−1.15 ± 0.81 D) (p = 0.0002). 192 children who had rapid progression of myopia (defined as more than -0.5D/ year) within the washout year of phase 2 went on to restart the 0.01% atropine for 2 future years (phase 3) [69]. At the end of this 5-year clinical trial, the overall progression of spherical equivalence myopia in the 0.01% atropine group (−1.38 ± 0.98 D) was significantly less compared to the 0.1% and 0.5% atropine 1.83 ± 1.16 D and −1.98 ± 1.10 D; $p < 0.05$).

Change in axial length

Excessive elongation of the globe is believed to contribute significantly to the degenerative changes of pathologic myopia [70], the biometric characteristics of myopia control is considered an important area to study. In 2001, 188 school-aged participants were treated with 0.5% atropine plus multi-focal spectacles vs. multi-focal glasses alone, or single-vision glasses alone, in a double-blind randomized control trial [71]. After regularly followed up at a single center in Taiwan for 18 months, the increase in the axial length in the atropine plus multi-focal glasses group was significantly less than the other two groups ($p = 0.0001$).

Atropine, particularly in higher concentrations, has been shown to have a positive effect in reducing the elongation of axial length in myopic eyes. The mean increase in axial length in ATOM 1 study was 0.02 ± 0.35 mm in the 1% atropine group, after 24 months of follow-up [65]. During the same period, a significantly more marked increase in axial length (0.38 ± 0.38 mm, $p < 0.001$) was observed in the placebo group, as well as the untreated fellow eyes of atropine group. This effect on the axial length in the atropine group was maintained until the end of the wash-out period. At the end of the third year, mean axial length increase was 0.29 ± 0.37 mm in the 1% atropine group, while the placebo-treated eyes experienced a mean increase of 0.52 ± 0.45 mm ($p < 0.0001$) [66]. To further understand the biometrical changes during atropine treatment, 313 subjects in ATOM 1 study completed biometric measurements including cycloplegic autorefraction, corneal curvature, anterior chamber depth, lens thickness, vitreous chamber depth, and axial length [72]. Eyes with myopic rebound at the end of the 3-year clinical trial were accompanied by a prominent increase in vitreous chamber depth and axial length (both had a p value < 0.001). It suggested that the main effect of atropine in tempering myopic progression was by slowing the growth of vitreous chamber depth and axial length.

In the ATOM 2 study, the mean change in axial length after 2 years was 0.27 ± 0.25, 0.28 ± 0.28, and 0.41 ± 0.32 mm in the 0.5%, 0.1%, and 0.01% atropine treated group, respectively ($p < 0.001$when comparing 0.01% with 0.1% or 0.5%). However, the situation reversed after the 1-year washout period. At the end of the third year, eyes in the 0.01% atropine group experienced the least increase in axial length (0.19 ± 0.13 mm), compared to eyes in the 0.5% and 0.1% atropine group (0.35 ± 0.20 and 0.33 ± 0.18 mm respectively, $p < 0.001$). A slower increase in axial length continued to be observed in the 0.01% atropine group during phase 3 of the study (0.19 ± 0.18 mm), in comparison with 0.1% atropine (0.24 ± 0.21 mm, $p = 0.042$) and 0.5% atropine (0.26 ± 0.23 mm; $p = 0.013$) groups. However, at the end of the 5-year study, there was no significant difference in axial length increase between the three groups (0.75 ± 0.48, 0.85 ± 0.83, 0.87 ± 0.49 mm; $p = 0.185$) [69].

Response rate

Shih et al. found 10.6% of children did not respond to atropine 0.5% [71]. In another study, progressors (defined as >1 D increase of myopia /year) was found in 4% of the 0.5% atropine group, 17% of the 0.25% atropine group and 33% of the 0.1% atropine group, in comparison to 44% in control group [8]. In a retrospective cohort study, Wu et al. found 45% of children were "poor responders" to 0.05% atropine, and they continued to progress by >0.5 D over 6 months [73]. These poor responders were switched to 0.1% atropine and over the 4.5 years follow-up, around 20% progressed further by >0.5 D per year, although this rate was much lower than those without treatment (100% progressed by >0.5 D per year). Despite the encouraging overall results in ATOM 1 study, not all the participants had good responses to atropine. 12% of children treated with atropine 1% at 1 year continued to progress by >−0.5 D per year [74]. These "progressors" were more likely to be younger, more myopic or have 2 myopic parents. In ATOM 2, 4.3%, 6.4%, and 9.3% of children in the 0.5%, 0.1%, and 0.01% group, respectively, had myopia progression ≥−1.5 D over the initial 2-year of active treatment.

Side effects

Systemic side effects in the ocular use of atropine is uncommon, such as dry mouth, face flush, headache, increased blood pressure, constipation, difficulty in micturition, and central nervous system disturbances. The most frequent ocular side effects with atropine eye drops include photophobia, blurriness of near vision, and local allergic response. Among them, photophobia is the most common and its incidence is positively correlated with the concentration of atropine. All of the patients who received 1% atropine in the study of Yen et al. reported photophobia, and this was described as the major reason that led to over a half of subjects dropping out of the study [58]. In contrast, photophobia was reported in only 22% and 7% of participants who received 0.5% and 0.25% atropine, respectively. None of the participants in the 0.1% atropine group reported significant photophobia [8]. Similarly, photophobia was uncommon in children who received 0.01% atropine in ATOM 2 study, and only 7% of subjects requested photochromatic lenses.

Among the 34 participants (17%) who withdrew from ATOM 1 study, the reasons were hypersensitivity, glare, and poor near-visual acuity. As for ATOM 2, 4.1% children in 0.1% and 0.5% atropine group reported allergic conjunctivitis [7]. Reduction of near visual acuity was reported in the 0.1% and 0.5% groups, but completely recover by 26 months. Rarely, glaucoma may be induced by atropine. The incidence is as low as 1 in 20,000 [75]. One study reported 621 children treated with atropine for 3 year and none found ocular hypertension [76].

Clinical trials from non-Asian populations

Since the prevalence of myopia is much higher in Asian than in other areas, it is not surprising that majority of randomized trials in myopia control have been conducted in Asia. Nonetheless, several cohort studies about myopia in non-Asian population had been published. These studies are also important in addressing initial concerns for potential ocular side effects, particularly photophobia in patients with lightly pigment and light-colored iris.

The effectiveness of 1% atropine in myopic control had been demonstrated by Brodstein et al., in 1984, and Kennedy et al., in 2000 [77, 78]. They both recruited more than 200 children and teenagers in the United States, with the mean follow-up of around 4 years. Another smaller study in United States, included 15 myopic children treated with 1% atropine and the other 15 children as control. The mean annual myopic progression was decreased to 0.05 D compared to 0.84 D in the controls [79]. 0.5% atropine once daily was used in a study based in Rotterdam with a sample size of 77 children with progressive myopia (defined as spherical equivalent (SE) ≤ −3D and SE progression rate ≥1 D per year under cycloplegic conditions) [80]. The aim of this study was to determine whether 0.5% atropine was effective at slowing the myopia progression, as well as to study the adherence to therapy in a setting outside Asians. Half (50.6%) of the children were already highly myopic (SE > −6 D). Of adverse events reported, photophobia was common (72%), followed by reading problems (38%), and headaches (22%). More than half (60%; 36/60) of the children adhered to therapy. However, 17 stopped treatment, of whom 11 (64.7%) discontinued treatment within the first month. The progression of myopia was −1.0 D per year before treatment diminished substantially to −0.1 D per year after 1 year treatment in the continued treatment group. Children who completed the 12-month trial benefited more than those who stopped prematurely. The study concluded that atropine at 0.5% can be effective for treating progressive myopia in Europe and suggested that intervention with atropine could work irrespective of ethnicity.

Clark et al. performed a study using low concentration atropine on 60 school-aged children in California [56], and reported slowing of myopia progression rate in 0.01% atropine-treated eyes (−0.1 ± 0.6 D per year) compared to control eyes (−0.6 ± 0.4 D per year, $p = 0.001$). Only three subjects in the atropine group complained of intermittent blurred vision or light sensitivity. None discontinued the treatment due to the symptoms. A Spanish study used 0.01% atropine in 400 eyes of 200 children aged between age 9 and 12 years, randomized to treatment vs. no treatment [81]. The mean annual myopia progression of the treated group was −0.14 ± 0.35 D per year vs. −0.65 ± 0.54 D per year in the control group without treatment over a 5-year follow-up period. The authors concluded that 0.01% atropine can slow myopia progression. Only 2% of patients stop treatment due to side effects.

To determine the highest dose of atropine that can be well tolerated, 12 subjects, ages from 8 to 16 years old, were evaluated by Cooper et al. [82]. They found that accommodation becomes affected in atropine above 0.02%. In keeping with this report, 14 Caucasian participants aged above 18 years were given 0.01% atropine for 5 sequential days [83]. The treatment was well tolerated by all participants and none reported problems in near or distant vision.

Clinical implementation

Based on the results of randomized controlled trials, atropine treatment has been implemented in clinical practice in some countries, mostly in Asia. Currently, the clinical management of myopia in Europe is predominantly focused on refractive correction, as data from studies on European populations remain limited.

Initial assessment

Regardless of whether atropine treatment is available, the refractive error should be determined accurately in all children referred for refractive error at their first consultation. Cycloplegic refraction is the gold standard for clinical practice or research [84]. The accommodation amplitude could be >10 D in a 10-year-old child [85]. Due to this large range of accommodation, pseudo-myopia is commonly noted if only auto-refractometry examination is used. Short and mid-duration cycloplegic agents include tropicamide or cyclopentolate and long-duration cycloplegic agents such as atropine could be used for cycloplegic refraction in children [86, 87].

After cycloplegic refraction, spherical equivalent refractive error (SER) could be categorized as hyperopia, pre-myopia, and myopia. The definition of hyperopia is the SER > +0.5 D and the definition of myopia is SER ≤ −0.5 D. The definition of pre-myopia is SER ≤ +0.5 D and > -0.5 D [88].

Hyperopic children should be educated regarding good eye care, including encouragement for outdoor activities around 2 h every day and near work breaks [89–91]. Regular follow-up with cycloplegic refraction every half or 1 year to monitor the speed of myopic refraction shift until the end of adolescence is suggested. In the United Kingdom, the National Health Service offers optical vouchers which cover annual free eye test and spectacles for all children up to age 16 (and age 19 if in full time education). The eye test can be performed more frequently if there are new symptoms.

For pre-myopic children, hyperopic refraction <+0.75 noted during the elementary school period has been reported to be a risk for subsequent myopia onset [92]. The overall evidence for the benefit of atropine treatment in the pre-myopic children is still limited. Fang et al. reported 24 of 50 pre-myopic children received 0.025% atropine at bedtime decreased the onset of myopia from 54% to 21% compared to the control group after 1 year [88]. However, larger studies with longer follow-up are needed to determine whether atropine should also be started in all pre-myopic children. Similarly the optimal dose will need to be evaluated. Monitoring the myopia shift every 3–6 months according to child's age and parent's myopia history is recommended. In the United Kingdom, children aged between 4- and 5-year old have visual screening performed at school, predominantly by orthoptists. Those that found to have suboptimal vision, amblyopia or abnormal eye movements are being monitored and refract accordingly in their local pediatric eye department. The older children, without ocular disease, are being monitored 6–12 monthly, in the community, outside the setting of hospital eye service.

Commencing atropine treatment

For myopic children, atropine treatment can be offered with the aim to slow down myopia progression. Before starting, the treatment aim and procedure, potential side effects, success criteria and rate should be discussed. It is important for parents and children to understand that atropine treatment works to slow down myopia progression but does not improve the vision as with orthokeratology. However, the risks associated with atropine treatment are relatively low and the benefits may last long term. The course of treatment is expected to be a minimum of 2 years initially, after which the child should be monitored to keep the low myopia status until the end of adolescence. Concurrent to atropine treatment, outdoor activities should continue to be encouraged [93]. The child's age, baseline refractive error, any evidence of recent progression, and refractive error of parents may help to predict the likelihood of progression. Starting treatment with the lowest concentration, such as 0.01% atropine, would be preferable as this is associated with the least ocular side effects. The dosing frequency is once daily at bed time. A small hyperopic shift is often noted 2–3 weeks after initiation of atropine, which may result from backward relaxation of ciliary body and lens zonular fiber becoming taut. Therefore, record of both the baseline without treatment and the post-atropine baseline refraction after 2–4 weeks later is useful. Thereafter, follow-up every 3 months with the cycloplegic refraction is recommended.

Assessment after starting atropine treatment

During the period of atropine treatment, the appropriate distance glasses should be prescribed if the child has difficulty in far vision, such as looking at blackboard in classroom or watching TV. It may be useful to explicitly explain to patients that while glasses improve vision, they have no clinical significant effect on myopia control [94, 95]. However, it is recommended that the child removes the distance glasses during near work, as distance glasses could induce hyeropic defocus during near-work and is believed to contribute to further myopia progression [96, 97]. In addition, distance glasses can aggravate symptom of near-blur in children on atropine treatment. Children who experience near-blurred symptom can also be offered bifocal or multi-focal glasses. Hat, photochromic, or sunglasses are recommended during outdoor activities to prevent photophobia symptoms. During the annual review, it is good clinical practice to check for side effects such as dry eye, allergic conjunctivitis, flushing, headache, heart, and urinary symptoms. The standard examinations include non-contact axial length, funduscopy to screen for myopic related peripheral retinal degeneration, e.g., lattice or breaks, and intraocular pressure measurement.

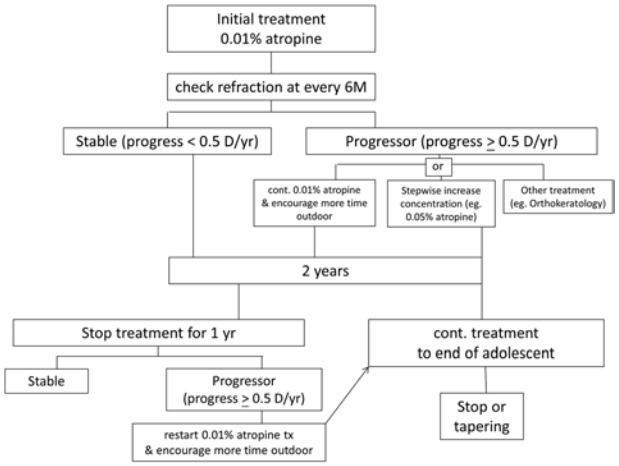

Fig. 1 The proposed strategy of atropine treatment for myopia control in clinical implementation

If myopia continues to progress by ≥0.5 D in Asian children after 6 months or in Caucasian children after 1 year, it indicates the efficacy of the current treatment dosing is probably not adequate. The management strategy in these suboptimal responders remains unclear. Alternative strategies include increasing the concentration of atropine, or continue the same concentration of atropine combined with more outdoors time, or, change to a different treatment modality, such as orthokeratology (Fig. 1). The evidence for better result with higher doses of atropine is, however, limited [69]. The higher rate of side effects and potentially higher discontinuation rate should also be considered. Wu et al. had reported the stepwise method for the myopic long-term control [73]. They recommended stepwise increase in the concentration of atropine according the effect of myopia control.

While most studies have reported active treatment period of 1–2 years, the optimal length of treatment is not known. One strategy is to adopt the ATOM 2 study approach with 2 years of initial treatment, followed by withholding treatment for 1 year, during which time any further progression is monitored. Children who progress after stopping treatment can be offered further treatment. Alternatively, some centers in Taiwan adopt the continuous treatment till late adolescent (around 15–18 years old), as myopia progression is known to slow down in the late adolescent period [98, 99]. Some investigators suggest tapering instead of abrupt stop to prevent possible rebound effect; however this has not been studied in detail.

A European perspective

In Europe, atropine eye drops 1% are commonly used in the treatment of amblyopia, but the adoption of atropine treatment for myopia retardation has been less widely practice than in Asia. This is likely due to a combination of factors, e.g., limitation of data from European studies, lack of availability of licensed preparation of atropine at ultra-low concentration, as well as cultural differences and attitudes towards side effects. Although there are good evidence to suggest atropine could be effective, more research is needed in European populations to propel the clinical application. In addition, there are logistic challenges. In the United Kingdom, the 0.01% atropine eye drop is not available as a licensed product. The "do-it-yourself" or self-dilution method is not endorsed, due to inaccurate dosing and potential issues with infection control. There are some motivated families manage to access the 0.01% atropine eye drops from south-east Asian countries, through personal connections.

There is also the anticipated barrier for children and their families to use atropine in the European population due to less acute awareness of myopic-related ocular complications and fundamental cultural differences, compared to the Asian populations. Parents and children may be more focused on the immediate potential side effects from atropine, particularly in those with lighter iris colors. The differences in the appearance of their pupil size compared with pre-treatment level could potentially attract unwanted attention from their peer groups, which could be interpreted as teasing or bullying. The negative psychosocial impact of appearance of more dilated pupils and possible photosensitivity could lead to a premature cessation of therapy.

The 0.01% atropine eye drops is not being used as a standard clinical treatment for myopia in the National Health Service at present, but its popularity is likely to surge when a licensed product become available.

In conclusion, results from research have demonstrated low concentration of atropine is useful in retarding myopia progression in a certain proportion of myopic schoolchildren. Atropine treatment has now been incorporated into clinical practice in some Asian countries. However, for optimal results, the motivation of parent and children is important, and long-term compliance and adherence with atropine treatment cannot be over-emphasized. Education regarding the consequences of high myopia and sharing the effect of myopia control to children and parents at each visit are helpful strategies to keep them motivated during the course of treatment. Individualized treatment protocol of atropine starting from low concentration seems practical. On top of atropine, good eye-care habits, enhancement of time outdoors and limiting near-work load should also not be overlooked. Though low-dose atropine treatment is promising in myopia control, there are still remaining areas of uncertainty such as treatment strategy and targeting population. Although the current prevalence of myopia in Europe is not as high as in Asia, the prevalence of myopia is steadily rising in Europe and US as well. The clinical and

economic burden will become significant with time, therefore further research on myopia prevention in European populations is important.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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The ROYAL COLLEGE of OPHTHALMOLOGISTS

REVIEW ARTICLE

肥厚型脉络膜疾病

摘要

肥厚型脉络膜疾病是近年来提出的新概念，其描述了一类特征为脉络膜毛细血管层的静脉扩张，并且与进行性视网膜色素上皮功能障碍和新生血管的形成有关的一类疾病。定义肥厚型脉络膜相关疾病的重点已经从简单的脉络膜厚度异常（脉络膜肥厚）转向影响功能的病理状态（“肥厚型脉络膜疾病”）的详细形态学定义，这将在本综述中详细讨论。属于肥厚型脉络膜疾病谱的疾病，包括中心性浆液性脉络膜视网膜病变，肥厚型脉络膜色素上皮病变，肥厚型脉络膜新生血管病变，息肉状脉络膜血管病变/1型动脉瘤新生血管，局灶性脉络膜凹陷，视盘周围毛细脉络膜肥厚综合症。这些病症都表现出特征性的脉络膜改变，并且被认为代表了常见致病过程的不同临床表现。

本综述基于目前已发表的文献和作者自身的临床经验以及最近在肥厚型脉络疾病的相关研究结果，重点强调了临床表现、影像学特征、治疗要点以及目前对这些疾病发病机制的探讨。

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The ROYAL COLLEGE of OPHTHALMOLOGISTS

REVIEW ARTICLE

Pachychoroid disease

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Abstract

Pachychoroid is a relatively novel concept describing a phenotype characterized by attenuation of the choriocapillaris overlying dilated choroidal veins, and associated with progressive retinal pigment epithelium dysfunction and neovascularization. The emphasis in defining pachychoroid-related disorders has shifted away from simply an abnormally thick choroid (pachychoroid) toward a detailed morphological definition of a pathologic state (pachychoroid disease) with functional implications, which will be discussed in this review. Several clinical manifestations have been described to reside within the pachychoroid disease spectrum, including central serous chorioretinopathy, pachychoroid pigment epitheliopathy, pachychoroid neovasculopathy, polypoidal choroidal vasculopathy/aneurysmal type 1 neovascularization, focal choroidal excavation, peripapillary pachychoroid syndrome. These conditions all exhibit the characteristic choroidal alterations and are believed to represent different manifestations of a common pathogenic process. This review is based on both the current literature and the clinical experience of our individual authors, with an emphasis on the clinical and imaging features, management considerations, as well as current understanding of pathogenesis of these disorders within the context of the recent findings related to pachychoroid disease.

Method

This comprehensive literature review was performed based on a search of peer-reviewed published papers relevant to the pachychoroid disease spectrum according to our current knowledge, up to January 2018, available on the PubMed database. This review will highlight clinical and imaging features, pathogenesis, and management options. Remaining areas of controversy will be discussed and how future research may clarify these.

Advances in imaging technology over the past decade have led to new insights and understanding of changes within the choroid in diseases previously identified predominantly by their retinal manifestations [1, 2]. Hyperpermeable and dilated choroidal vessels have been observed using indocyanine green angiography (ICGA) in eyes with central serous chorioretinopathy (CSC) and polypoidal choroidal vasculopathy (PCV) [3]. With the advent of enhanced-depth imaging optical coherence tomography (EDI-OCT) and subsequently swept-source optical coherence tomography (SS-OCT) [4, 5], increased choroidal thickness was also described. The terms pachychoroid and, subsequently, pachychoroid disease were introduced to describe a phenotype characterized by focal or diffuse increase in choroidal thickness, accounted for by dilated

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choroidal vessels in Haller's layer (pachyvessels), accompanied by thinning of the choriocapillaris and Sattler's layer with/without retinal pigment epithelium (RPE) abnormalities overlying the pachyvessels [6–10]. While a thick choroid is frequently seen, choroidal thickness per se is not the most important criterion for defining the pachychoroid disease phenotype. Instead, the presence of characteristic morphologic changes which implicate structural and functional choroidal alteration as key pathophysiologic mechanism is essential to diagnose pachychoroid disease [9]. These features will be discussed in detail in this review. Although the etiology of pachychoroid disease remains controversial, these choroidal changes are believed to play an important pathogenic role in the development of the following clinical manifestations which reside within the pachychoroid disease spectrum [6–10]:

i. Central serous chorioretinopathy (CSC).
ii. Pachychoroid pigment epitheliopathy (PPE).
iii. Pachychoroid neovasculopathy (PNV).
iv. Polypoidal choroidal vasculopathy (PCV)/aneurysmal type 1 neovascularization (AT1).
v. Focal choroidal excavation (FCE).
vi. Peripapillary pachychoroid syndrome (PPS).

These conditions are believed to represent different manifestations of a common pathogenic process, as overlapping features have been observed, and progression from one to another has been well described [11, 12].

Choroidal features common to pachychoroid disease entities

Focal or diffuse increase in choroidal thickness

Using EDI-OCT or SS-OCT, the choroid–scleral interface (CSI) can be delineated in most eyes, thus facilitating quantitative analysis of choroidal thickness (Fig. 1) [1]. Subfoveal choroidal thickness in normal subjects has been reported to be between 191–350 µm in previously studies [13], but choroidal thickness can be influenced by a variety of factors, including age, axial length, refractive error, blood pressure, as well as time of the day. Thus, a wide range of values have been reported even in normal subjects. Nonetheless, increased choroidal thickness was subsequently described in patients with CSC (345–505 µm) [13–15] and PCV (223–590 µm) [16–19]. In these patients, increased choroidal thickness in the contralateral eye was also commonly found [15]. In view of the wide range of choroidal thickness and the multiple factors which may influence this parameter, there is no definitive quantitative threshold for defining an eye as having abnormally thick choroid. However, many investigators may consider subfoveal choroidal thickness >300 µm as pathological [4, 20]. Regional variation of choroidal thickness has also been described, with studies showing the thickest region beneath the fovea and thinnest areas nasally [21]. Regional variations in choroidal profile can be evaluated in detail using SS-OCT, as the shorter acquisition time allows for dense scans which can produce choroidal volume maps. Eyes with pachychoroid disease may have normal subfoveal choroidal thickness, but exhibit an extrafoveal focus of increased choroidal thickness (defined as exceeding subfoveal choroidal thickness by 50 µm) [4]. The area of maximal choroidal thickness is likely to be of significance if it correlates spatially with the distribution of pachyvessels and with the disease focus [7].

Pachyvessels

Increased choroidal thickness is thought to result predominantly from dilatation of choroidal vessels in Haller's layer. Increased diameter of choroidal vessels has been observed as larger hyporeflective lumen in cross-sectional OCT in eyes with CSC, PCV, focal choroidal excavation (FCE), and PPS [22, 23]. In histological sections in eyes with PCV, dilated choroidal vessels with diameter of up to 300 µm have been observed. With en face OCT, detailed morphological changes within the intermediate and large choroidal vessels can be evaluated in a depth-specific manner. Pathologically dilated vessels in eyes with pachychoroid disease can be detected within the deep choroid [5]. In addition to increase in caliber, pachyvessels can also be distinguished from normal choroidal vessels as they do not taper toward the posterior pole, but retain their large caliber and terminate abruptly. This feature is best appreciated using en face OCT or ICGA. Pachyvessels may be present diffusely or focally (e.g., in 1 or 2 quadrants) [4]. When localized, they correlate spatially with the areas of maximal choroidal thickening, as well as disease focus within the RPE or retina [4]. Choriocapillaris thinning may be observed in areas overlying pachyvessels, as evidenced by inward displacement of large dilated choroidal vessels which become visible in a more superficial en face plane [4].

Attenuation of inner choroid

Thickened choroid per se may not necessarily have any pathologic consequences. Healthy eyes with abnormally thick choroids may be considered to have "pachychoroid" or "uncomplicated pachychoroid". Regardless of choroidal thickness, presence of morphological features of pathologic sequelae resulting from abnormally dilated choroid may be a more significant finding for diagnosing "pachychoroid disease" [9, 10]. A key feature is inner choroidal attenuation, characterized by focal or diffuse attenuation of the choriocapillaris and intermediate caliber vessels within

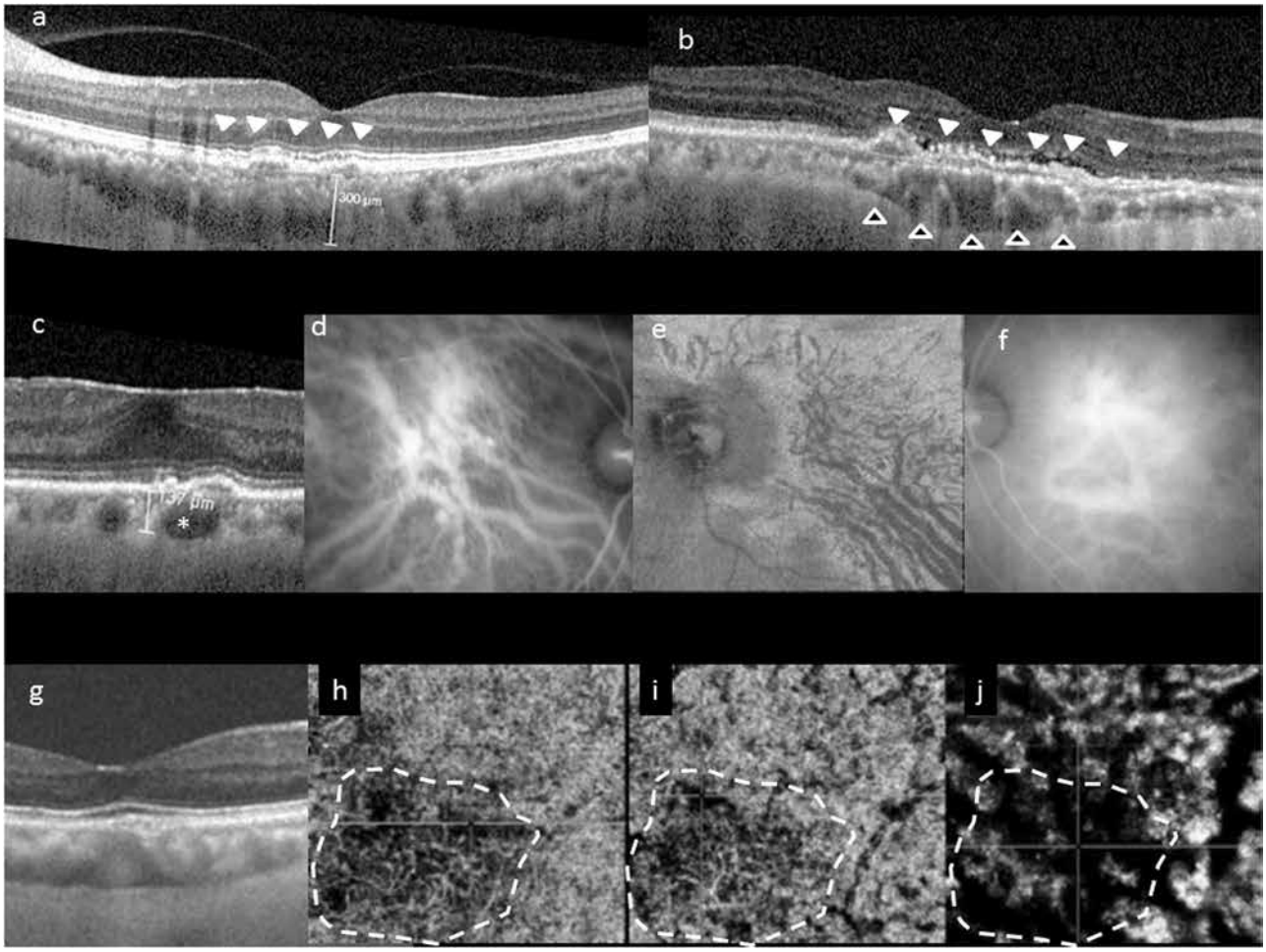

Fig. 1 Choroidal features common to pachychoroid phenotype. Typical choroidal features in the pachychoroid disease phenotype include diffuse or focal increase in choroidal thickness, which is typically associated with abnormally dilated Haller layer vessels (pachyvessels) and attenuation of the inner choroid (Sattler's layer and choriocapillaris). Choroidal thickness can be readily evaluated in cross-sectional optical coherence tomography (OCT), which may show diffuse thickening and increased subfoveal choroidal thickness (**a**), or focal thickening (**b**, hollow arrowheads). In some eyes, an irregular elevation of the retinal pigment epithelium (RPE) can be seen to overlie these choroidal abnormalities (white arrowheads). Pachyvessels can be identified as a choroidal vessel with enlarged caliber (**c**, *) which can occupy almost the entire thickness of the choroid. Pachyvessels can also be seen as dilated submacular vessels which do not taper toward the posterior pole on ICGA (**d**) or on en face OCT (**e**). These pachyvessels may be distributed in a diffuse (**d**) or patchy manner (**e**). Pachyvessels usually exhibit choroidal vascular hyperpermeability with indocyanine green angiography (ICGA) (**f**) which may suggest choriocapillaris ischemia. Using OCT angiography (OCTA), the spatial correlation between choriocapillaris blood flow and pachyvessels can be evaluated in a depth-resolved manner. In **g**–**j**, choroidal thickening and choriocapillaris attenuation seen in cross-sectional OCT (**g**) can be correlated with OCTA findings showing attenuation of flow signal (dash white outline) within the choriocapillaris (**h**) and inner choroid (**i**) which directly overlie areas with dilated outer choroidal vessels (**j**)

Sattler's layer in areas overlying abnormally dilated Haller's layer vessel [4]. In severe cases, the Haller's layer vessel may occupy the full extent of the choroidal thickness. If the luminal volume increase in the outer choroidal vessel is offset by a reduction in inner choroidal volume resulting from atrophy of the latter, it is possible for an eye to have normal or even subnormal choroidal thickness but still exhibit the pachychoroid disease phenotype [9]. Therefore, in addition to evaluating choroidal thickness, detailed examination of the morphology of the choroid is also required to determine if any eye exhibits pachychoroid disease. To facilitate this, automated software based on binarized OCT or ICGA images have been developed to quantify the ratio between choroidal vascular luminal area to total choroidal area [24], and some have reported increased choroidal vascularity in eyes with pachychoroid disease [24–26]. However, challenges remain in optimizing such algorithms as signal strength within the choroid may be affected by blood, subretinal fluid (SRF), and pigment epithelial detachment (PED), particularly in eyes with PCV, CSC, and pachychoroid neovasculopathy (PNV) [19]. In addition to attenuation of the inner choroid, thinning of outer nuclear layer (ONL) has also been observed in eyes with pachychoroid disease. Interestingly, the ONL was

thinner in eyes with pachychoroid pigment epitheliopathy (PPE) than in eyes with uncomplicated pachychoroid in one study, suggesting that degeneration of photoreceptors and/or RPE may also occur, even in the absence of SRF [20].

Choroidal vascular hyperpermeability

On ICGA, pachyvessels appear as a cluster of relatively straight and dilated choroidal vessels. In addition to choroidal venous dilatation, choroidal filling defects, delayed arterial filling in the early phase, and focal or punctate hyperfluorescence have been observed in eyes with CSC, PCV, and FCE, suggestive of possible choroidal ischemia [27–30]. In the mid to late phase, patchy areas of ICGA hyperfluorescence can be seen corresponding to the leakage and staining sites observed on fluorescein angiography (FA) [27–30]. Choroidal hyperpermeability is believed to result from increased extravasation of fluid and lipoprotein-bound ICGA from the choriocapillaris or the larger choroidal vessels into the surrounding choroidal stroma. Previous studies have reported choroidal hyperpermeability to be present in >90% of eyes with PPE and CSC [27], and in 10–50% of eyes with PCV [2, 18]. Punctate hyperfluorescence spots have also been observed in the mid to late phase of ICGA in eyes with CSC and PCV [18, 31]. Both diffuse and punctate hyperfluorescent spots have been frequently observed in contralateral eyes of patients with CSC and PCV without overt pathology [27, 30]. These ICGA findings characteristically persist in eyes with CSC even after resolution of SRF [30]. These observations support the hypothesis that the choroidal changes are likely the primary etiology in these disease entities. Eyes with choroidal hyperpermeability usually have increased choroidal thickness, but not all eyes with thick choroids exhibit choroidal hyperpermeability [32]. Interestingly, choroidal hyperpermeability was reported to be more common in eyes with CSC and PPE than in eyes with uncomplicated pachychoroid [27]. As choroidal hyperpermeability may indicate structural choriocapillaris damage producing relative ischemia, this finding suggests functional implications of the pachychoroid phenotype beyond increased choroidal thickness.

Clinical and imaging features of specific conditions

Central serous chorioretinopathy

CSC is a common disorder characterized by serous retinal detachment with or without serous PED (Table 1, Fig. 2). CSC occurs mainly in young to middle-aged men with emmetropic or hyperopic eyes, but this gender predilection decreases with age [33]. Maumenee was the first to describe leaks at the level of the RPE seen with FA in eyes with CSC [34], and later ICGA confirmed choroidal vascular congestion as being involved in the pathogenesis of CSC [28, 30, 35]. Although the precise etiology and pathogenesis of CSC remain unknown, systemic use of corticosteroids and sympathomimetics are well-known major risk factors. Patients with CSC usually complain of decreased or distorted vision, relative scotoma, and micropsia, and manifest a small hyperopic shift. Younger patients usually present with unilateral involvement, while older patients are more likely to show bilateral disease.

The most common type is acute CSC, mainly seen in younger patients. Typical manifestations include solitary and localized neurosensory retinal detachment and serous PEDs. FA demonstrates one or multiple focal leaks at the level of the RPE in “ink-blot” or “smoke-stack” patterns. ICGA shows multifocal areas of choroidal hyperpermeability as hyperfluorescent patches in the mid phase study [28, 30, 35]. Other ICGA findings of CSC include areas of delayed choroidal filling and prominent venous dilation. Most acute cases of CSC resolve withing 4–6 months. When serous retinal detachment persists over several months, small yellowish dots appear beneath the detachment. These dots probably represent shed outer segments of photoreceptor, with some phagocytized by macrophages [36]. These dots appear hyperautofluorescent with fundus autofluorescence (FAF) [36]. In chronic CSC, which may be defined by duration >6 months, or more importantly by presence of RPE damage, more diffuse RPE abnormalities with flat and broad areas of serous retinal detachment are commonly observed. These findings often extend inferiorly, in the form of a descending tract, most readily visualized with FAF as granular and sometimes confluent hypoautofluorescence with a hyperautofluorescent margin. FA shows multiple indistinct leaks inside granular window defect. Multifocal areas of choroidal hyperpermeability are seen on ICGA, which may become widespread. A rare variant of chronic CSC is bullous retinal detachment.

OCT is an essential tool to evaluate the areas of SRF and PEDs in both acute and chronic CSC. In acute CSC, well-defined serous retinal detachment with or without serous PEDs is typically confined to the macula; however, when SRF persists, elongated photoreceptor outer segments are often observed together with subretinal fibrin, intraretinal lipid deposition, and subretinal yellowish dots [36]. In chronic CSC, the retinal detachment are usually shallow and broad, with attenuation of outer retinal layers related to chronic serous detachment. Intraretinal fluid, sometimes referred to as “cystoid macular degeneration”, may develop in some cases when there are defects in the external limiting membrane allowing fluid to enter the retina [37]. Recent research using EDI-OCT and SS-OCT has revolutionized

Table 1 Clinical and multi-modal imaging features of pachychoroid spectrum of disorders

	Pachychoroid spectrum					
	Central serous chorioretinopathy (CSC)	Pachychoroid pigment epitheliopathy (PPE)	Pachychoroid neovasculopathy (PVN)	Polypoidal choroidal vasculopathy/ aneurysmal type 1 neovascularization (PCV/ AT1)	Focal choroidal excavation (FCE)	Peripapillary pachychoroid syndrome (PPS)
	Common choroidal features					
Fundus	Reduced fundus tessellation in areas of increased choroidal thickness					
EDI-OCT or SS-OCT	1 Focal or diffuse choroidal thickening a. Subfoveal choroid may be normal but extrafoveal area of increase thickness (>50 μm more than subfoveal measurement) may be detected 2 Dilated choroidal vessels (pachyvessels) a. Increased diameter of choroidal vessel lumen on cross-sectional OCT b. Large caliber vessels in Haller's layer on en face OCT, but inward displacement of pachyvessels often leads to their visualization in a more superficial en face plane 3 Thinning/absence of choriocapillaris and Sattler's layer overlying pachyvessels. Pachyvessels may occupy the full extent of the choroidal thickness If luminal volume increase in pachyvessels is offset by reduction in inner choroidal volume resulting from inner choroid atrophy, it is possible for an eye to display pachychoroid phenotype without increased choroidal thickness					
ICGA	• Dilated choroidal vessels • Choroidal filling defects, delayed arterial filling in early phase, focal or punctate hyperfluorescence areas suggestive of possible choroidal ischemia • Choroidal vascular hyperpermeability, best observed in mid to late phase. CVH may also be observed in contralateral eye without active disease, and/or persist after resolution of active disease CVH is usually correlated with increased choroidal thickness. However, eyes with increased choroidal thickness may not display CVH					
	Retinal features specific to individual condition Note: These changes are observed to correlate spatially with choroidal changes described above					
OCT	• Well-defined serous retinal detachment in acute CSC • PED • Shallow, broad retinal detachment in chronic CSC • Elongated photoreceptor outer segments • Outer retinal atrophy (disruption to EZ, thinning of ONL) • Cystoid macular degeneration in chronic CSC	• Focal RPE abnormalities overlying pachychoroid disease changes • Absent SRF	• Type 1 NV overlying pachychoroid disease changes appearing as shallow irregular RPE detachment (double-layer sign)	• Type 1 NV with aneurysmal lesions are located between RPE and the inner collagenous layer of BM • Exudative changes tend to originate from aneurysms	• Abrupt changes of choroidal thickness beneath the FCE lesion • Increased choroidal thinning with highly reflective choroidal tissue and poorly defined CSI beneath area of FCE • Normal, smooth inner scleral surface suggesting absence of scleral excavation or ectasia • Conforming no separation between photoreceptor tips and RPE • Non-conforming photoreceptor tips appear detached from underlying RPE, with a hyporeflective intervening space	• Maximal choroidal thickness occurs close to the optic nerve rather than subfoveally • Nasal macular intraretinal and/or subretinal fluid
FAF	• May show signs as seen in PPE • Vertical, gravitational tracts of RPE hypopigmentation	• Granular hypo-AF • Mixed stippled hyper-AF and hypo-AF		• Granular hypo-AF • Ring-shaped abnormalities with hypo-AF center and hyper-AF surrounding may be seen	• Hyper-AF or hypo-AF appearances	• Mottled hypoautofluorescence in peripapillary area • Gravitational tracks may be seen

Table 1 (continued)

	Pachychoroid spectrum					
	Central serous chorioretinopathy (CSC)	Pachychoroid pigment epitheliopathy (PPE)	Pachychoroid neovasculopathy (PVN)	Polypoidal choroidal vasculopathy/ aneurysmal type 1 neovascularization (PCV/ AT1)	Focal choroidal excavation (FCE)	Peripapillary pachychoroid syndrome (PPS)
	• Geographic areas of speckled hyper-AF					
OCTA	No evidence of choroidal neovascularization	No evidence of choroidal neovascularization	• "Tangled network" of flow signal corresponding to type 1 neovascularization	• Flow signal representing type 1 neovascularization is usually well visualized • Variable flow signal within aneurysms has been described	NA	NA
FA	• Leaks at the level of RPE • Ink-blot or smoke-stack leakage pattern common in acute CSC • Multiple indistinct leaks inside granular window defect in chronic CSC			• Exudation from aneurysms/ BVN typically leads to occult pattern of leakage and staining • Occasionally classic pattern of leakage may be seen in the presence of significant RPE erosion from underlying aneurysms or secondary type 2 neovascularization	• Hyperfluorescence corresponding to transmission defects associated with RPE attenuation in mid or late phase FA • Absence of leakage unless complicated by CNV or CSC • Hypofluorescence related to RPE alterations	• Speckled hyperfluorescent window defects and staining typically in area between optic disc and fovea • May be associated with disc leakage
ICGA	• Choroidal hyperpermeability • Choroidal venous dilation and vascular congestion • Choroidal filling delay	• Choroidal hyperpermeability	• Choroidal hyperpermeability	• Choroidal hyperpermeability • Branching vascular network with terminal aneurysmal dilatations	• Early hypofluorescence suggesting filling detects • Late phase: punctate, patchy, or diffuse hyperfluorescence around FCE	• Large choroidal vessels are more prominent nasal than temporal to the fovea • May show peripapillary choroidal hyperpermeability
Other features	• Bullous variant may be seen	• RPE mottling on funduscopic examination, frequently extrafoveal in location and may be confused with pigmentary AMD or pattern dystrophy • Drusenoid RPE lesions (pachydrusen) • Reduced fundus tessellation • Patients are relatively younger than those with AMD	• Lack of other identifiable risk factors for CNV such as soft drusen, myopic degeneration, inflammation, or angioid streaks	• Chronic multiple recurrent exudative changes • Hemorrhage from aneurysms may occur • Lack of soft drusen, reticular pseudodrusen, intraretinal RPE migration, geographic atrophy	• Fundus may appear normal or show non-specific pigmentary changes or indistinct yellow-whitish spot(s) • May be associated with moderate myopic refractive error	• May be associated with choroidal folds • Usually associated with crowded disc • Hyperopic refractive error is common

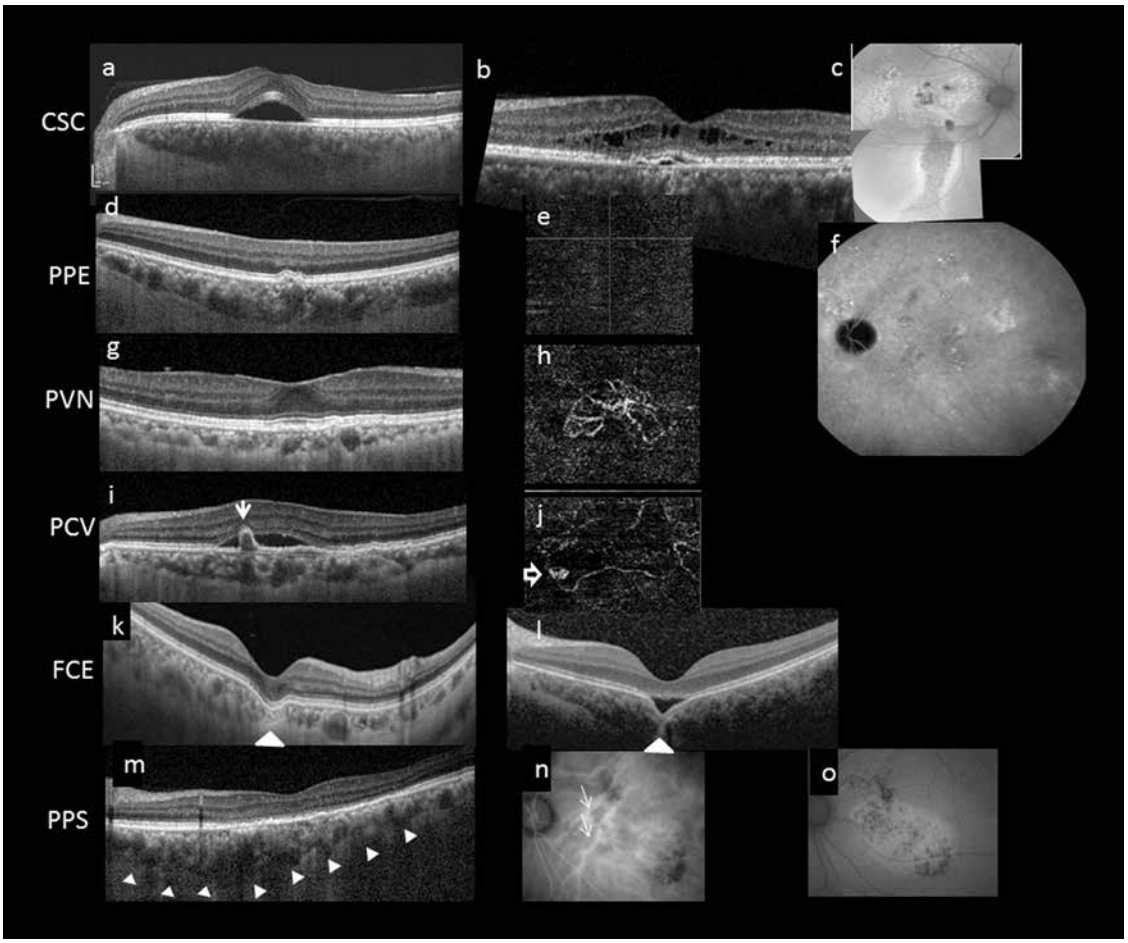

Fig. 2 Multimodal imaging features of pachychoroid disease. Several clinical manifestations have been described to reside within the pachychoroid disease spectrum, including central serous chorioretinopathy (CSC) (**a**–**c**), pachychoroid pigment epitheliopathy (PPE) (**d**–**f**), pachychoroid neovasculopathy (PVN) (**g**, **h**), polypoidal choroidal vasculopathy (PCV)/aneurysmal type 1 neovascularization (AT1) (**i**, **j**), focal choroidal excavation (FCE) (**k**, **l**), and peripapillary pachchoroid syndrome (PPS) (**m**–**o**). Note that the choroidal features described in Fig. 1 can be seen in all cases in Fig. 2. In acute CSC (**a**), a solitary neurosensory detachment is commonly seen. In contrast, in chronic CSC (**b**), the neurosensory detachment tends to be shallower and broader. A shallow pigment epithelial detachment (PED), shallow subretinal fluid (SRF), and cystic intraretinal fluid can also be seen in this case. The RPE changes are best evaluated using fundus autofluorescence (FAF). In chronic CSC (**c**), multiple areas showing mixed hyperautofluorescence and hypoautofluorescence can be seen in the posterior pole. A downward gravitational tract of hypoautofluorescent can be seen. PPE is thought to be a forme fruste of CSC. On irregular RPE elevation overlying pachychoroid disease features without subretinal fluid can be seen in **d**. OCTA confirmed absence of neovascularization (**e**) and FAF showed milder granular autofluorescence disturbance than in **c**, without a gravitational tract. Cross-sectional OCT findings in PCN may be similar to those in chronic CSC and PPE, characterized by irregular RPE elevation with or without SRF. OCTA can readily detect the presence of neovascularization (**h**). Features of PCV/AT1 overlap significantly with PCN, with the additional feature of aneurysms. Although indocyanine green angiography (ICGA) is considered the gold standard for diagnosing PCV/AT1, common features on OCT include irregular RPE elevation overlying pachychoroid disease changes and narrow-peaked PEDs (arrow). In the corresponding OCTA (**j**), an aneurysm (hollow arrow) can be seen to arise from a branching vascular network. FCE is characterized by a localized area of choroidal excavation on OCT. In the conforming type (**k**), the photoreceptor tips are not separated from the underlying RPE, whereas in the non-conforming type (**l**) a hyporeflective space can be observed between the photoreceptor tips and RPE. Unusual hyperreflective choroidal tissue (arrowhead) can be seen to bridge the space between the bottom of the excavation and the outer choroidal boundary. Dilated choroidal vessel and thickened choroid can be seen on either side of the excavation. In PPS, the choroid is thicker on the nasal side to the fovea compared to the temporal side in the cross-sectional OCT (**m**). More dilated choroidal vessels (white arrows) are seen on the nasal side compared to the temporal side of the fovea on ICGA (**n**). Fundus autofluorescence illustrates mottled autofluorescence temporal to the disc and extending downwards (**o**)

our understanding of CSC. Many reports have demonstrated a pathologically thickened choroid in CSC eyes [14, 38]. In addition, the mean subfoveal choroidal thickness in symptomatic eyes is usually greater than that in asymptomatic fellow eyes [39]. Yang and associates [22] demonstrated that CSC eyes had significantly larger hyporeflective vascular lumen than that seen in the choroid of normal control eyes. The dilation of choroidal vessels in the Haller layer

appears to account for thickened choroid seen in CSC [40]. Using binarization method to determine the sizes of the hyporeflective lumen and hyperreflective stroma, larger hyperreflective stroma in the inner choroid has been found and is thought to be related to the inflammation and edema occurring during the acute stage of CSC, in addition to dilation in the larger vessels in the outer choroid [41]. The application of OCT angiography (OCTA) is very helpful for detecting choroidal neovascularization (CNV) secondary to chronic CSC (see section "Pachychoroid neovasculopathy") [42]. However, for CSC itself the clinical utility of OCTA is still being explored.

Pachychoroid pigment epitheliopathy

The term PPE was first introduced by Warrow and colleagues to refer to a condition characterized by RPE changes which occurred in the posterior pole over regions of choroidal thickening [6]. While these changes had been observed in uninvolved fellow eyes of patients with unilateral CSC, the authors noted that a significant number of patients who lacked a history neurosensory detachment presented with a similar pigment epitheliopathy in one or both eyes. These patients were often misdiagnosed with pigmentary age-related macular degeneration (AMD), and sometimes with pattern dystrophy or "retinal pigment epitheliitis" [7]. However, PPE is usually asymptomatic. The clinical appearance of the pigment epitheliopathy included mottling of the RPE, irregular areas of RPE elevation termed "drusenoid RPE lesions", and an absence of soft drusen seen in eyes with AMD. FAF showed similarly mottled hypoautofluorescence but also revealed hyperautofluorescent features which correlated with foci of apparent RPE thickening or hyperplasia seen on cross-sectional OCT [4]. The choroids of patients with these findings exhibited hyperpermeability with ICGA in the distribution of the pigment epitheliopathy, as well as pathologically dilated vessels in Haller's layer [4]. Reduced fundus tessellation was also noted and, together with the frequently extrafoveal location of the pigment epitheliopathy and the relatively young age of the patients, helped to distinguish this condition from non-neovascular AMD.

Since none of the eyes had manifested neurosensory detachment, PPE was considered a forme fruste of CSC. Moreover, it was subsequently observed that patients with PPE could go on to develop type 1 neovascularization, with or without aneurysmal (polypoidal) lesions, without necessarily developing CSC [4, 43, 44].

Pachychoroid neovasculopathy

Although development of secondary CNV has been described in CSC [33, 45], the incidence has not been well established. Differentiating chronic CSC from AMD can be challenging as the two conditions may have very similar features on FA and ICGA, characterized by RPE atrophy and diffuse leakage. With advances in choroidal imaging, differences in choroidal features have been noted among patients presenting with type 1 neovascularization. Fung described a subgroup of patients presenting with type 1 neovascularization with clinical and imaging findings more consistent with long-standing CSC than with AMD [12]. Increased choroidal thickness, absent or minimal soft drusen, and younger age were among the key features which differentiated this group of patients from neovascular AMD. Some of these eyes also had aneurysmal (polypoidal) structures within their type 1 neovascular network. Importantly, Fung's study established a clear temporal sequence of CSC which predated the development of type 1 neovascularization (mean interval of 139 months), and thus support a pathogenic sequence. The authors also emphasized that this type of neovascularization should be differentiated from that occurring in typical neovascular AMD [12].

Subsequently, the occurrence of type 1 neovascularization was described in eyes with other pachychoroid disease entities. Pang and Freund described development of type 1 neovascularization in three eyes over background changes consistent with PPE, and introduced the term "PNV" to describe this condition [7]. The authors proposed that PNV resides within the pachychoroid disease spectrum and occurs due to a pachychoroid-driven process involving choroidal congestion and hyperpermeability. Characteristic features of PNV include presence of type 1 neovascularization which appears on OCT as a shallow irregular separation of the RPE from Bruch's membrane which appears as "double layer sign" overlying pachyvessels [46]. The presence of heterogeneously hyperreflective material in the sub-RPE space further suggests the presence of sub-RPE neovascularization. Small peaked PEDs may develop the margin of these lesions within which aneurysmal (polypoidal) lesions may be identified with ICGA or OCTA. Eyes with PNV display background features common to the pachychoroid disease spectrum, including an absence of soft drusen and reduced fundus tessellation indicative of a thickened choroid in the area of the type 1 neovascular lesion. Characteristic choroidal findings of the pachychoroid phenotype described in section "Choroidal features common to pachychoroid disease entities" can be seen on OCT. Importantly the areas of type 1 neovascularization are correlated spatially to areas displaying pachychoroid features [4]. RPE changes overlying areas of pachyvessels can be seen as abnormal FAF. Presence of neovascularization can be confirmed by detection of leakage on FA, typically in the form of late leakage with undetermined origin, and a corresponding late staining "plaque"

on ICGA. Although similar angiographic signs may be seen in chronic CSC as a result of diffuse RPE disturbance and choroidal hyperpermeability, eyes with PNV do not exhibit the classic serous macular detachment or the characteristic changes on FAF such as descending tracts seen in CSC [43]. These differences might be helpful to determine whether SRF in an eye is the consequence of PNV or CSC.

With the advent of OCTA, the diagnosis and confirmation of neovascularization has become easier in cases of suspected PCN. Neovascularization can be identified non-invasively as a tangled network of flow signal between the RPE and Bruch's membrane corresponding to the flat-irregular PED identified on structural OCT (Fig. 3) [42, 44, 47]. In a series of 88 patients with chronic CSC, neovascularization was detected in 35.6% of eyes with shallow irregular PEDs using OCTA [47]. Eyes with pachychoroid features and a shallow irregular PED on SD-OCT should therefore be evaluated in more detail with OCTA, as these eyes frequently harbor neovascular tissue.

Polypoidal choroidal vasculopathy/aneurysmal type 1 neovascularization (AT1)

Idiopathic PCV was first described by Yannuzzi et al. [48] in 1990 as a novel clinical entity in which hemorrhagic and exudative neurosensory detachments occurred in the peripapillary region and macula of a predominantly black cohort of middle aged women. In 1995, Spaide and colleagues described the characteristic ICGA findings of this disorder which included a branching vascular network (BVN) with terminal aneurysmal (polypoidal) dilatations [49]. Lacking the benefit of depth-resolved structural OCT, these authors localized these structures to the inner choroid. A recent editorial highlighted the results from newer multimodal imaging demonstrating that PCV is in fact a variant of type 1 (sub-RPE) neovascularization, as both the vascular dilations and their feeding vascular network are consistently found in a potential space bounded anteriorly by the RPE and its basal lamina and posteriorly by the inner collagenous layer of Bruch's membrane [50]. These authors reasoned that there was ample evidence from imaging to support that the "polypoidal" lesions are in fact vascular structures with the potential to rupture and bleed, as opposed to fleshy masses of tissue arising from epithelial surfaces, as the term "polypoidal" suggests. They noted that following its original description, the term "PCV" had been used in reports spanning a wide range of different clinical presentations, thus creating confusion as to whether PCV was a distinct disease or a neovascular growth pattern occurring in multiple different pathologic settings leading to sub-RPE angiogenesis. The authorship, which included Lawrence Yannuzzi, who coined the term "PCV",

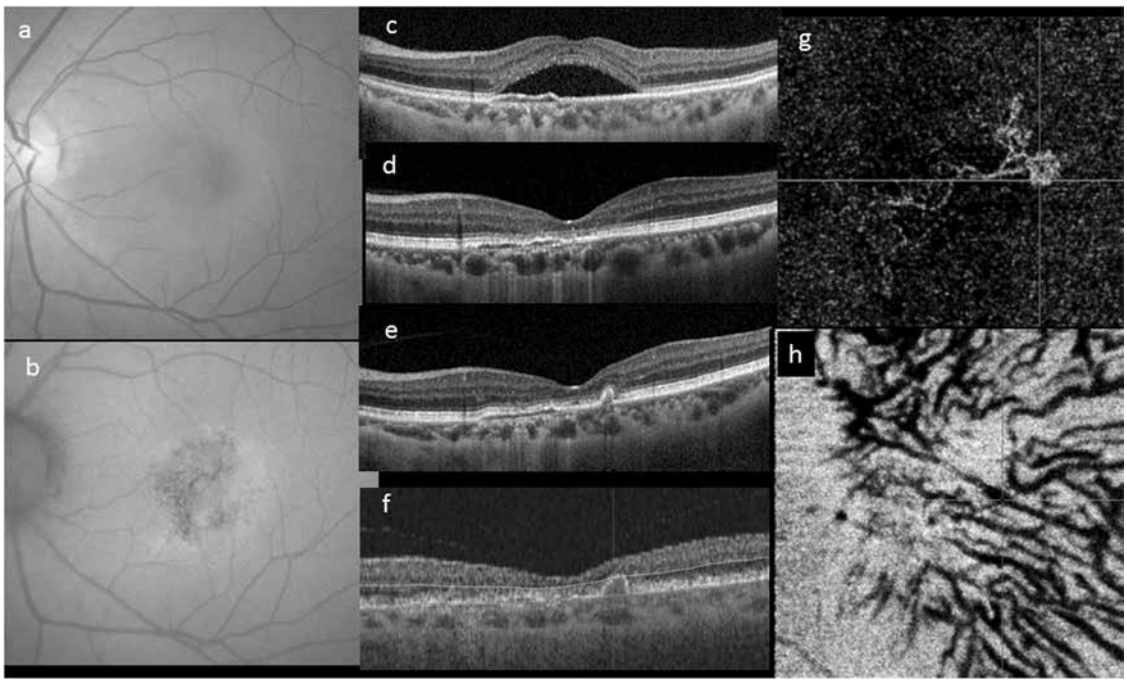

Fig. 3 Evolution of a case over 4 years. A 46-year-old woman first presented with a solitary neurosensory detachment and mottled fundus autofluorescence (**a**–**c**). A shallow elevation of the RPE was noted. The SRF resolved spontaneously within 3 months and the eye remained unchanged for the following 4 years (**d**). During routine follow-up, development of a narrow-peaked PED without SRF was noted on OCT (**e**). OCTA showed a localized area of abnormal flow signal within the narrow-peaked PED (**f**). En face OCTA showed a neovascular network with aneurysms its temporal margin (**g**). The outline of pachyvessels can be seen as dark silhouettes in the OCTA segmented through Haller's layer (**h**)

suggested renaming this form of sub-RPE vascular proliferation "AT1" in an effort to clarifying its true nature. In the rest of this review, we shall refer to this entity as PCV/AT1.

PCV/AT1 is a common occurrence in Asian patients with neovascular AMD, in whom it primarily originates within the macula rather than in the peripapillary region [51]. While sharing many of the same systemic and genetic risk factors with white AMD patients, Asian AMD patients with PCV/AT1 are less likely to manifest certain non-neovascular AMD features such as soft drusen, cuticular drusen, reticular pseudodrusen (subretinal drusenoid deposits), and geographic atrophy. The reported prevalence of PCV/AT1 among Asian neovascular AMD patients ranges from 20 to 60% [51]. This wide range of reported prevalence may arise from inconsistent criteria used for identifying the aneurysms occurring in these patients [52]. The prevalence of PCV/AT1 in white patients with neovascular AMD has been reported to be much lower at 4–12%, but this may be an underestimation as ICGA is not routinely performed by most ophthalmologists in the United States [51]. The propensity to form aneurysms suggests there may be specific pathophysiologic mechanisms driving the formation of aneurysms in PCV/AT1 eyes including atherosclerosis and other vascular wall alterations, and changes in intravascular flow dynamics. These mechanisms are supported by several clinicopathologic studies, demonstrating hyalinization within vessel walls from tissue obtained from eyes of Asian AMD patients with PCV/AT1 [53].

The advent of SD-OCT, EDI OCT, and SS-OCT has provided valuable information on the pathophysiology of PCV/AT1. As mentioned above, both the BVN and the aneurysms occurring in PCV/AT1 are consistently identified below RPE and its basal lamina and anterior to the inner collagenous layer of Bruch's membrane, confirming an origin as type 1 (sub-RPE) neovascularization [46].

In PCV/AT1 patients with visual symptoms of recent onset, the exudative changes typically originate from the aneurysms, not from the neovascular complex (BVN) feeding these lesions. This observation suggests that in many cases, PCV/AT1 may originate from non-exudative type 1 lesion in eyes with long-standing pachychoroid neovascularization. Once exudation begins, it can sometimes resolve spontaneously, presumably due to thrombosis of leaking aneurysm. However, the remaining type 1 lesion forming the BVN will usually show continued growth, forming new aneurysms over time which typically occur at the margins of the neovascular lesion. Growth of the BVN may continue for years, or even decades, with a remitting-relapsing course that is clinically associated with chronic, multiple, recurrent exudative changes. During this process, the aneurysms may hemorrhage and the associated type 1 lesion (BVN) may evolve into a more active form of neovascular proliferation producing additional exudation [54]. It is generally accepted that PCV/AT1 has a better visual prognosis than typical neovascular AMD, as progression is slow and subretinal fibrous proliferation is unusual in the absence of large subretinal hemorrhage. However, the visual prognosis is variable over its natural course and with long-term follow-up, many patients eventually lose central vision [54, 55].

Recent studies using EDI-OCT and SS-OCT have demonstrated that patients with PCV/AT1 frequently have thick choroids in contrast to choroidal thinning that is often observed in eyes with typical neovascular AMD [16]. The presence of choroidal thickening and choroidal hyperpermeability in patients with PCV/AT1 suggests a link between this entity and the pachychoroid disease spectrum, in particular PNV. A number of studies have reported the occurrence of aneurysms originating from type 1 lesions in eyes with PVN and other pachychoroid disease entities [11, 12]. Although the mean choroidal thickness is greater in PCV/AT1 eyes than in eyes with typical neovascular AMD, there is a pronounced inter-individual variability with values distributed over a wide range. In one study including over 300 eyes, the mean subfoveal choroidal thickness was ~270 µm, with a wide range (40–650 µm) [10]. The subfoveal choroidal thickness exhibited a bimodal distribution, with peaks at 170 and 390 µm, suggesting that PCV/AT1 cohorts may in fact contain two overlapping phenotypes of which only one exhibits markedly increased subfoveal choroidal thickness. In that cohort, subfoveal choroidal thickness was >200 µm in 61%, and <200 µm in 39% (Fig. 4). However, in over 90% of both groups, pachyvessels were observed below the presumed origin of the BVN feeding the aneurysms, these pachyvessels occupied nearly the full thickness of the choroid and demonstrated overlying attenuation of the inner choroidal layers. The area of maximal choroidal thickness correlated spatially with the distribution of pachyvessels and with the disease focus, even in eyes in which the absolute choroidal thickness was not particularly high [10]. Quantitative values of total choroidal thickness at the disease focus were significantly greater than those measured at the fovea and these disease sites had significantly lower inner choroidal (choriocapillaris/Sattler layer) to total choroidal thickness ratios compared with the fovea. In eyes with peripapillary PCV/AT1, in which the disease focus is located around optic nerve, away from the fovea, similar morphologic changes within the choroid have been observed. The normal choroidal thickness profile is U-shaped with the thickest area located beneath the fovea, correlating with the need for a robust choroidal circulation in the macula due to a high metabolic demand and need for heat dispersion. In contrast, in eyes with peripapillary PCV/AT1, the thickest point in

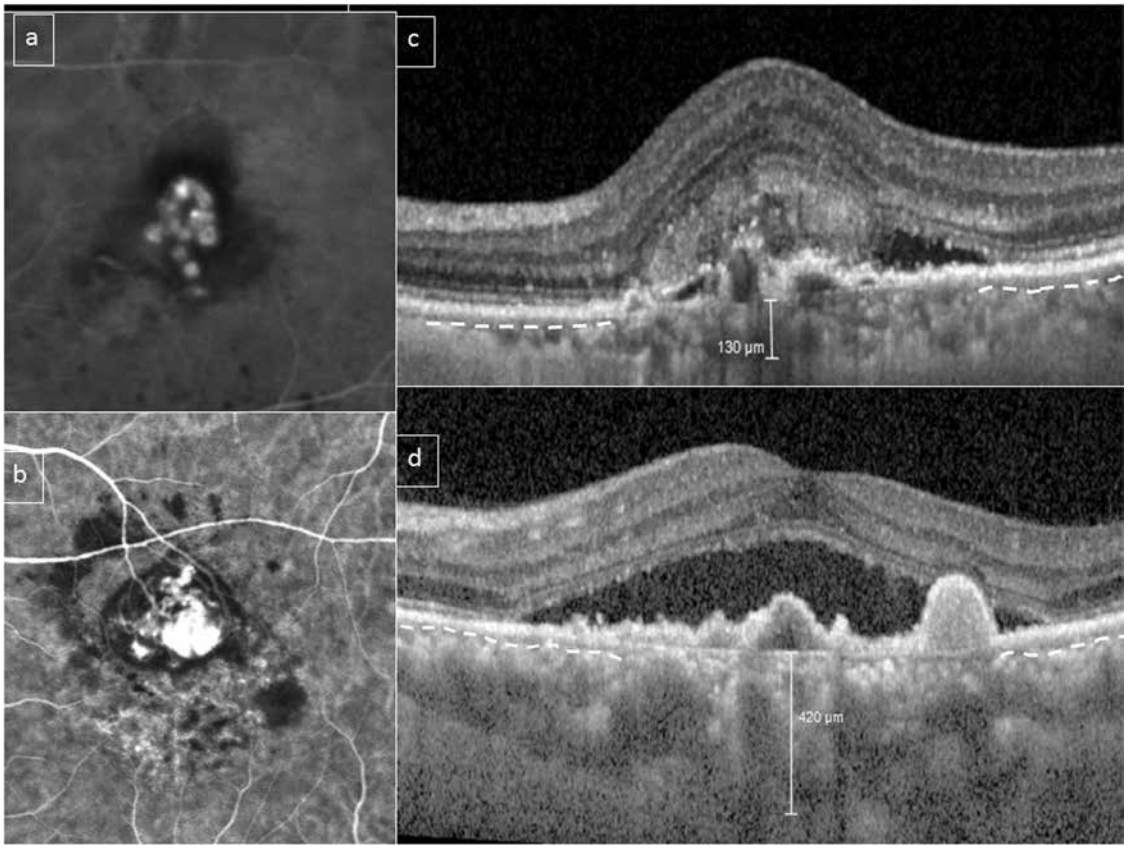

Fig. 4 Choroidal features in polypoidal choroidal vasculopathy (PCV)/aneurysmal type 1 neovascularization (AT1). A bimodal distribution of choroidal thickness has been described in PCV/AT1. This figure shows two eyes with PCV/AT1 confirmed with indocyanine green angiography (ICGA) (**a**, **b**). Subfoveal choroidal thickness was 130 and 420 µm, respectively (**c**, **d**). However, in both cases, choriocapillaris/inner choroid (outline by dashed white line in preserved areas) appears to be compressed and attenuated by underlying outer choroidal vessels in the subfoveal area (**c**, **d**)

the choroidal U-shape curvature is shifted nasally. In these eyes, the choroid is thicker on the nasal side of the fovea than on its temporal side [10, 56].

Focal choroidal excavation

FCE is characterized by localized area(s) of choroidal excavation without evidence of posterior staphyloma or scleral ectasia in patients who typically lack a history of disease known to result in choroidal thinning [8, 57]. Most patients with FCE have been diagnosed in their fourth to fifth decade, but no gender predilection has been found. Most cases described have moderate myopia. Patients tend to be asymptomatic or report mild blurring of vision or metamorphopsia. Fundus examination may appear normal or show non-specific pigmentary changes or indistinct yellow-whitish spots in an area of reduced fundus tessellation. OCT is the preferred diagnostic imaging modality. Two patterns of excavation have been described. In conforming FCE, the photoreceptor tips are in direct contact with the RPE, whereas in non-conforming FCE the photoreceptor tips appeared to be detached from the underlying RPE, and a hyporeflective cleft, presumably representing SRF, can be observed in the intervening space [8, 58]. Unusual hyperreflective choroidal tissue is observed to bridge between the bottom of the exaction and the outer choroidal boundary in some eyes [59, 60]. A smooth CSI is observed [59, 60]. Findings on FA include atrophic RPE window defect leading to varying degrees of hyperfluorescence and hypofluorescence. Hypofluorescence on ICGA and abnormal staining in the late phase suggest choriocapillaris loss [61]. Pachychoroid features have been described in eyes with FCE, including increased subfoveal choroidal thickness and choroidal vascular hyperpermeability in ICGA [59, 61]. FCEs were located within or adjacent to areas of fluorescein leakage and choroidal hyperpermeability, supporting the pachychoroid features likely have etiologic significance [59].

Following initial reports of sporadic cases describing association of FCE with CSC and PCV, the association of FCE with other conditions within the pachychoroid disease spectrum was described by several investigators [59, 62–64]. Lim et al. reported the prevalence of FCE in the presenting and contralateral eyes of patients with CSC, CNV,

or PCV. FCE was found in 18 (2.3%) of 598 eyes evaluated. FCE was detected in 6.0% of eyes presenting with PCV and 1.0% of eyes presenting with CNV. In addition, FCE was detected in 2.9% of contralateral eyes of patients presenting in PCV and in 1.2% of patients with CSC [62]. Ellabban et al. reported prevalence of FCE in 7.8% of eyes with CSC [59]. CNV associated with FCE may be type 1 or type 2 [63]. Luk et al. also reported that FCE was found in 7 (6.0%) of 116 patients with CSC and 4 patients had bilateral FCE [65]. These patients tend to be much younger than those presenting with neovascular AMD. The CNV lesions in these cases tends to be located within the boundary of the FCE, suggesting that the CNV growth pattern and extent may be determined by the degree of damage to the RPE/BM complex resulting from the FCE, as well as age [63, 64].

There are limited reports regarding the long-term course of eyes with FCE, but most studies to-date have reported relatively stationary lesions [57, 59, 60, 62].

Peripapillary pachychoroid syndrome

Peripapillary pachychoroid syndrome was recently described by Phasukkijwatana and colleagues as distinct variant of the pachychoroid disease spectrum in which maximal choroidal thickness occurs close to the optic nerve rather than subfovealy [23]. These patients typically present with nasal macular intraretinal and/or SRF and occasional optic nerve edema. Other sequelae of the pachychoroid disease phenotype are often present, including pigment epitheliopathy, serous PEDs, and gravitating autofluorescence tracks can occur and tend to be localized to the peripapillary region. In their initial series, Phasukkijwatana et al. reported that of 31 study eyes of 16 patients, 77% had choroidal folds, 39% had axial lengths <23 mm, and 80% had hyperopic refractive errors. None of the subjects had inflammatory eye disease, and the range of findings was felt to be distinct from the uveal effusion syndrome.

Current understanding of pathogenesis

The apparent complexity of the pathogenesis of the pachychoroid disease spectrum testifies to our incomplete understanding of the subject. This is due in part to the relatively recent introduction of pachychoroid terminology and the evolving nature of its definition. Nevertheless, there are chains of thought, which have been articulated consistently through much of the literature on CSC and which continue to inform our efforts in delineating pachychoroid disease and its boundaries.

CSC is recognized primarily by the development of neurosensory detachments at the posterior pole, but the manifestations occurring at the level of the RPE and outer retina appear to be secondary not merely to chronic SRF but to a disease which is primarily choroidal [66]. Just as a phenotypic spectrum is unraveled by extending the catalog of features backwards and forwards in time, so too might pathogenesis be elucidated.

Time-resolved multimodal imaging supports this approach in pachychoroid disorders as well, showing, in the earliest stages of disease, that choroidal hyperpermeability to ICG dye precedes clinically detectable features [35]. The earliest clinical features are those of PPE, in which RPE disease occurs at locations coinciding with regional choroidal hyperpermeability and focal choroidal thickening. Similarly, in both CSC and PNV, the defining clinical features of each occur in association with regional hyperpermeability and focal choroidal thickening. These observations raise the question as to how choroidal changes, manifesting as hyperpermeability in the first instance, might lead to RPE sequelae.

It is well documented in the ICGA literature that choroidal hyperpermeability is a function of the choriocapillaris. Indeed, scrutiny of ICGA images from eyes with pachychoroid disease shows that while hyperpermeability is seen regionally, it is absent at foci within those regions where the choriocapillaris is atrophic [4]. Moreover, the clinical complications of PPE, chronic CSC, and PNV at the tissue level occur at locations where the choriocapillaris appears structurally attenuated on OCT. This observation has been explored by Lee's group in two recent studies of PCV/AT1, the first of which explored the validity of the ratio of choriocapillaris thickness to total choroidal thickness, as a quantitative representation for choriocapillaris attenuation and as a possible outcome measure for defining the pachychoroid disease phenotype [10]. The authors found choroidal thickness to be distributed bimodally in a cohort of patients with macular PCV/AT1. They also demonstrated a reduced ratio of choriocapillaris to total choroidal thickness, even among the eyes with thinner choroids. The second study included eyes with peripapillary PCV/AT1 and found that maximal choroidal thickness occurred at the site of peripapillary disease, and not at the fovea [56]. Maximal choroidal thickness was attributable to dilated Haller's layer vessels with a reduced ratio of choriocapillaris to total choroidal thickness.

Taken together, these findings suggest a sequence wherein choriocapillaris hyperpermeability (choroidal dysfunction) is followed by structural choriocapillaris attenuation, RPE complications, and neovascularization with or without the occurrence of aneurysms. The emphasis in defining pachychoroid disease has therefore shifted away from absolute choroidal thickness thresholds toward a morphological definition which forms a better foundation for formulating mechanistic hypotheses. For example, it has been suggested that choriocapillaris attenuation produces an

ischemic mileu which promotes VEGF expression supporting neovascularization [43, 44, 50].

The notion that choriocapillaris dysfunction and structural attenuation should lead to RPE dysfunction is acceptable intuitively, but the relative specificity of certain patterns of retinal pigment epitheliopathy for pachychoroid disease is more difficult to explain. For example, patients with PPE or chronic CSC often exhibit reticular or stellate pigment epithelial figures, which may be scattered in the posterior pole but may also be seen in the nasal retina. Unlike the reticular pigmentary changes seen in AMD, those of pachychoroid disease often feature hyperautofluorescent foci at which the RPE appears thickened or hyperplastic on OCT. The basis for these differences remains unresolved but clues may lie in a deeper understanding of apolipoprotein E and lipofuscin metabolism to explain differences in pigment epitheliopathy between pachychoroid and AMD. A lesion resembling drusen seen in AMD can occur in some eyes with pachychoroid disease. These "drusenoid RPE lesions" described by Warrow et al. [6] were later renamed "pachydrusen" by Spaide, who described a morphology, distribution, and grouping pattern which differed from the soft drusen occurring in typical AMD [67]. Spaide proposed that choroidal characteristics may act as a modulator that alters the manifestation of AMD, whether in the phenotype of drusen or neovascular subtype. Eyes with thick choroids have a propensity to have pachydrusen and type 1 neovascularization with or without aneurysms [67, 68].

The pathogenesis of pachychoroid disease itself remains unknown. There is a volume of evidence that points to aberrant steroid metabolism as an upstream factor, which in the older literature, helped to distinguish CSC from inflammatory disorders that are associated with serous or exudative retinal detachment. This altered response to steroids is thought to explain why patients with CSC often report having experienced a period of psychological stress or sleep deprivation at the time of peak symptoms, even when they have not been exposed to exogenous steroids. It has been shown recently that mineralocorticoid receptors are expressed in the choroid [69]. Stimulation of these receptors increases choroidal thickness and congestion and the effect is reversed by mineralocorticoid receptor antagonists [70]. The effects of spironolactone and eplerenone have been studied in humans but with limited or unpredictable benefit which might be due to variations in oral bioavailability [71]. In addition to environmental factors, there is also evidence that suggests choroidal thickness may be heritable [72]. The observation of significant variation of choroidal thickness among different ethnicities further supports this hypothesis [73].

The mechanisms that underlie the formation of serous PEDs and serofibrinous retinal detachments also remain elusive. It has been suggested that choroidal thickening might be associated with increased hydrostatic pressure which challenges the Bruch's membrane–RPE complex and eventually overcomes the tight junctions between RPE cells resulting in focal and diffuse leakage and occasionally an RPE "blowout" phenomena.

Neovascularization in PNV may have a different etiology compared to typical neovascular AMD, which may have important implications in management. Some authors speculate that the neovascular process may be triggered by focal RPE disturbances and inner choroid attenuation overlying pachyvessels in CSC and PPE [45]. Others have proposed that chronic inflammation involving the choriocapillaris may also play a role in angiogenesis [29]. A study evaluating the frequencies of 12 known AMD risk alleles reported nearly identical genetic profiles in patients developing neovascularization in the context of either typical AMD or pachychoroid disease phenotypes [74]. However, the frequencies of these risk allelles were low and not significantly different between non-neovascular pachychoroid disease patients and normal subjects, suggesting that these AMD risk alleles influence neovascularization but do not determine the pachychoroid disease phenotype itself [74]. In a study evaluating Japanese patients, an association was found between PNV and *ARMS2* rs10490924 and *CFH*, but with a smaller effect size compared to typical neovascular AMD [75].

Given the currently available data, pachyvessels and attenuation of inner choroid seem to be key features of pachychoroid changes in eyes with PCV. Loss of the choriocapillaris may produce a relatively ischemic environment, leading to overexpression of angiogenic factors. Changes of overlying RPE/Bruch complex, such as irregularities, thinning, convex elevation, and disruption are frequently seen on OCT. Expansion of Haller vessel volume within a limited space and the absence of a buffer choriocapillaris might induce damage to focal areas of overlying tissues mechanically, inducing atrophic changes of RPE and a focal break in Bruch's membrane. Whether the occurrence of dilated Haller vessels (pachyvessels) is a primary event or secondary to the inner choroidal attenuation is still under investigation. It is possible that ischemic, inflammatory, or involutional insults to the inner choroidal circulation result in loss of inner choroid, inducing arteriovenous shunting with resultant venous dilation.

The etiology of FCE is also unclear. Some investigators proposed that FCE may be a congenital malformation [8]. The observation of abnormal choroidal tissue beneath the excavation suggests that FCE may have formed from RPE retraction caused by focal scarring of choroidal connective tissue from previous inflammatory processes [59]. FCE has been likened to an inverse PED, which may compress choriocapillaris and further exacerbate choroidal ischemia

already present as a result of pachyvessels, and lead to further local damage of the RPE/Bruch membrane complex and predispose to the development of NV or CSC [57, 58].

A putative hypothesis linking the spectrum of pachychoroid disease proposed that the pachychoroid disease phenotype may be an inherited trait. If the RPE is able to overcome the chronic fluid overload, patients will continue to manifest the uncomplicated pachychoroid phenotype. However, in some eyes, features of PPE may develop along with progressive dysfunction of RPE. With further RPE damage, increasing breakdown of the RPE barrier and concomitant choriocapillaris loss may lead to the development of CSC. Neovascularization (PPN) may ensue with further damage to Bruch's membrane and outer retinal ischemia. Recent OCTA studies have detected non-exudative type 1 neovascularization in the contralateral eyes of patients with CNV or PCV/AT1 [76, 77]. The presence of PPE has been found to be a significant risk factor for such "silent" lesions [77]. With longitudinal follow-up, the risk of developing exudation was significantly higher in eyes harboring these lesions [76, 77].

Finally, aneurysms may develop in some long-standing neovascularization, particularly in lesions with high blood pressure and/or neovascular flow [78].

Management considerations of pachychoroid disorders

In general, most pachychoroid disease in asymptomatic patients can be observed and monitored without treatment. Observed cases might include eyes with PPE, FCE, eyes with CSC and extrafoveal SRF and/or PED, and PCV/AT1 with inactive non-leaking aneurysms. However, in patients experiencing vision loss due to pachychoroid disease, treatment should be considered to improve or stabilize visual function. These cases might include CSC eyes with persistent central SRF and/or large PEDs, PCN associated with macular exudation, and PCV/AT1 macular exudation originating from either the aneurysm or the associated BVN.

Treatment of symptomatic CSC

In view of the strong association between exogenous steroids and CSC, a careful history should be carried out in patients with CSC to inquire about the use of all forms of exogenous steroids. In CSC patients who are taking corticosteroid, cessation or tapering of steroid therapy should be the first-line of management of CSC if the underlying medical condition allows. In an observational case series, it was reported that 88% of eyes with severe CSC had resolution of SRF and reattachment of neurosensory retina after discontinuation of corticosteroids [79]. Non-prescription items such as traditional herbal medicine like ginseng and cordyceps may also act on steroid receptors and might also need to be stopped.

In most cases of acute CSC, SRF spontaneously resolves. Therefore, treatment for acute CSC may be deferred for up to 4–6 months depending on the degree of symptoms and amount of subfoveal fluid [80]. Early treatment may be considered in patient highly symptomatic patients, those demanding rapid recovery of vision, or patients with poor vision in the fellow eye. However, up to 50% of cases experience recurrences after complete resolution of SRF [81]. For acute CSC, conventional thermal laser photocoagulation to extrafoveal leaking points identified on FA has been used as a treatment option since the 1980s, and has been shown to reduce the duration of CSC by 2 months [82]. The mechanism of action is thought to be restoration of RPE barrier function by sealing the RPE defect and preventing further accumulation of SRF. However, a long-term follow-up study of CSC patients treated with focal thermal laser photocoagulation showed little improvement in visual acuity after treatment [83]. In addition, focal thermal laser photocoagulation can be associated with a risk of iatrogenic CNV especially when a laser spot size of <100 μm is used. Therefore, many clinicians have shifter to newer treatment modalities for CSC associated with persistent macular fluid.

Recently, subthreshold micropulse laser photocoagulation producing less thermal injury to the RPE and the neurosensory retina has been used to treat CSC with persistent fluid. Like thermal laser, subthreshold micropulse laser appears to be most effective in eyes with focal leaks detected with FA. However, since subthreshold micropulse laser does not produce a visible laser burn during treatment, it has been used to treat RPE leaks closer to the fovea than those felt amenable to convention thermal laser. A randomized controlled trial compared the use of subthreshold micropulse laser or half-dose verteporfin photodynamic therapy (vPDT) to untreated control eyes and showed a significant improvement in visual acuity and central macular thickness following either subthreshold micropulse laser or vPDT treatment compared to controls [84]. Subthreshold micropulse using a yellow wavelength (577 nm) has been used to treat CSC and a short-term study showed a significantly higher proportion of eyes with resolution of SRF 6 weeks after treatment compared to eyes receiving half-dose vPDT [85]. However, subthreshold micropulse laser appears less effective in CSC eyes with diffuse RPE leakage and rescue vPDT is often needed in these cases [86]. One reason for the limited efficacy laser photocoagulation in CSC eyes with diffuse RPE leakage may be its limited effect on reducing choroidal thickness. One study showed that laser photocoagulation resulted in no

significant change in choroidal thickness up to 4 weeks after treatment despite resolution of SRF [38].

Verteporfin PDT is generally recommended for chronic CSC. The rationale for using vPDT to treat CSC is to target the primary pathology in CSC by reducing choroidal hyperperfusion and hyperpermeability. In the past, vPDT using the standard drug dosage and laser fluence was used in the treatment of CSC and treatment resulted in a high proportion of patients with complete resolution of SRF and reduction in the dilated choroidal vasculature [87]. However, potential adverse events with conventional full-dose PDT have been reported including transient visual loss, transient reduction in multifocal electroretinography response amplitude, RPE atrophy, secondary CNV formation, and even more serious complications such as choroidal ischemia and infarction. As CSC eyes usually have better visual acuity than eyes with other macular diseases considered for treatment with vPDT, a high safety margin is required when treating these cases. Therefore, half-fluence as well as half-dose verteporfin PDT has been performed in patients with CSC to enhance the safety of the treatment [80, 88]. The main therapeutic effects of vPDT in CSC are its impact on the choroidal circulation as vPDT has been shown to reduce the choroidal thickness in eyes with CSC [38]. In a study evaluating changes in choroidal structures after half-dose vPDT for CSC, vPDT not only decreased the choroidal thickness but also altered the intrachoroidal structures [89]. More specifically, the thickness of Haller layer significantly decreased after vPDT, while the thickness of choriocapillaris/Sattler layer remained unchanged. The hyporeflective lumen was also decreased, while the hyperreflective stroma did not change. Accordingly, vPDT may produce a treatment effect on the dilated choroidal vessels in Haller layer to return to a more "normal" choroidal structure.

A large number of studies have demonstrated good safety and efficacy in the use of half-dose vPDT in treating CSC patients [90, 91]. A randomized, double-blinded, placebo-controlled trial on the use of half-dose vPDT for acute CSC has demonstrated that patients treated with half-dose vPDT had significantly better visual acuity at 3, 6, 9, and 12 months compared with placebo [92]. Half-dose vPDT-treated group also had significantly lower OCT central foveal thickness at 1, 3, 6, 9, and 12 months [92]. In a long-term study, 75 eyes treated with half-dose vPDT were compared with 117 untreated control eyes with a minimum follow-up of 3 years [93]. Eyes treated with half-dose vPDT showed significantly better visual acuity at the last visit compared with untreated control. A survival analysis demonstrated that eyes treated with half-dose vPDT were significantly less likely to develop recurrent fluid compared to untreated controls. One study exploring the lowest effective verteporfin dose that can be used to treat acute CSC concluded that this was 30% of the standard full dose [94].

A number of systemic agents have been suggested to be useful in the treatment of symptomatic CSC. These include finasteride (an inhibitor of dihydrotestosterone synthesis) [95], mifepristone (a glucocorticoid receptor antagonist) [96], and mineralocorticoid antagonist such as spironolactone and eplerenone [97, 98]. A randomized, double-blinded, placebo-controlled cross-over study of 16 eyes of 16 patients with CSC showed significant reduction in SRF and subfoveal choroidal thickness in eyes of spironolactone-treated patients compared to those receiving placebo but no significant change in BCVA [97]. Another retrospective observational case series used spironolactone, eplerenone, or both consecutively over 12 months in 23 eyes of 14 CSC patients. These investigators found improvement in vision in all eyes but no significant reduction in choroidal or macular thickness [98]. However, a recent prospective, double-blind, randomized placebo-controlled study showed no benefits for the use of eplerenone for chronic CSC compared with placebo after 3 months of treatment [99]. Since many studies exploring the use of systemic agents to treat CSC with persistent fluid do not include a control group, it is often difficult to conclude whether anatomic and/or visual improvements observed in these reports are the result of the treatment or due to the natural history of a disease known to be associated with a highly variable course.

It has been postulated that CSC may be caused by choroidal lobular ischemia with an associated increase in local VEGF production. Therefore, reducing VEGF with the use of intravitreal anti-VEGF therapy might be a potential treatment for CSC. Although several studies have shown some positive effects from using intravitreal anti-VEGF therapy for CSC, a meta-analysis failed to demonstrate a true beneficial effect for the use of intravitreal bevacizumab in CSC [100]. No significant reduction in subfoveal choroidal thickness was observed in bevacizumab-treated eyes despite resolution of SRF. In the PROMETHEUS trial, patients with macular edema due to uncommon causes (i.e., causes other than diabetic retinopathy, neovascular AMD, or retinal vein occlusion) were randomized to receive intravitreal ranibizumab or sham. In this study, no significant visual benefit was observed in eyes with macular edema secondary to CSC [101]. Therefore, based on existing studies, there does not appear to be sufficient evidence to support intravitreal anti-VEGF therapy for treating persistent fluid in CSC eyes lacking evidence of macular neovascularization.

Treatment of neovascularization secondary to CSC and PNV

Although anti-VEGF therapy does not appear useful for treating CSC patients, these agents appear to have an

important role in the treatment of pachychoroid disease associated with CNV such as CSC with secondary CNV, FCE with secondary CNV, PCN, and PCV/AT1. A retrospective study of 46 eyes with CNV associated with CSC treated with intravitreal anti-VEGF therapy demonstrated a 1.16 line improvement in visual acuity after a mean follow-up of 38.3 months [102]. In the MINERVA study, eyes with CNV due to uncommon causes were randomized to receive intravitreal ranibizumab vs. sham injections [103]. Twenty-three eyes with CNV due to CSC treated with ranibizumab experienced a +6.6 letter gain in visual acuity at the primary endpoint of 2 months, compared to a +1.6 letter gain in the sham group. In cases with recurrent or persistent fluid, the addition of vPDT has been reported to result in variable levels of control [43].

Some investigators have observed that certain eyes with PNV respond favorably to intravitreal anti-VEGF therapy with a significantly longer retreatment-free interval than those seen in more typical neovascular AMD following an initial loading series injection [75]. The apparent lower dependence on repeated injections in these cases may relate to lower intraocular VEGF concentrations in PNV eyes compared to eyes with more typical neovascular AMD [104]. However, some eyes with PCN appear refractory to intravitreal anti-VEGF monotherapy. Anti-VEGF therapy in combination with vPDT appears useful in these cases, with some eyes achieving complete fluid absorption and visual improvement following combined therapy [105].

Intravitreal anti-VEGF therapy has been used to treat CNV associated with FCE. In a case report of extrafoveal CNV with hemorrhage occurring in an eye with pachychoroid disease and FCE, the patient experienced subjective improvement in vision following two monthly injections of intravitreal Aflibercept. EDI-OCT and OCT-A demonstrated resolution of macular exudation and near-complete regression of a CNV lesion which originated from within the FCE.

Treatment of symptomatic PCV/AT1

vPDT monotherapy is the treatment modality most commonly used for PCV/AT1 associated with pachychoroid disease, with most studies reporting favorable 1 year visual outcomes and regression of aneurysms [106, 107]. However, long-term recurrences following vPDT monotherapy for PCV/AT1 is common with up to 50–60% of eyes developing recurrent exudation after the first year post-vPDT [108]. It has been suggested that lesions in which the aneurysms appear to form grape-like clusters often evolve into more typical CNV lesions associated with persistent or recurrent exudation despite disappearance of the visible aneurysms following treatment [109]. Therefore, following treatment, PCV/AT1 patients should continue to be monitored indefinitely.

Intravitreal anti-VEGF therapy with or without adjunctive vPDT is now commonly used as the standard treatment of symptomatic macular PCV/AT1 related to pachychoroid diseases [110, 111]. The use of anti-VEGF agents for this purpose is supported by findings of elevated intraocular levels of VEGF in eyes with PCV/AT1 [110]. Recently, two large randomized controlled trials, EVEREST II and PLANET, provided level 1 evidence for the use of intravitreal anti-VEGF therapy with or without vPDT for the treatment of PCV/AT1 [112, 113]. In the EVEREST II study, 322 patients were randomized to combination therapy with ranibizumab and vPDT vs. ranibizumab monotherapy [112]. Results showed that at month 12, the mean visual acuity gain of 8.3 letters in combined therapy group was significantly higher than the mean gain of 5.1 letters seen in the ranibizumab monotherapy group. The proportion of eyes with complete polyp regression at 12 months was also significantly higher in eyes treated with combination therapy compared with ranibizumab monotherapy (69.3 vs. 34.7%). Combination therapy was also able to reduce the number of ranibizumab treatments over 12 months, with a median of 4.0 injections in the combination group and a median of 7.0 injections in the monotherapy group. Change in central choroidal thickness was evaluated as one of the secondary outcomes in the EVEREST II study. The combination therapy cohort had a higher reduction (55.2 μm) in central choroidal thickness compared with the ranibizumab monotherapy cohort (30 μm) [114].

In the PLANET study, eyes with PCV/AT1 received three initial loading doses of aflibercept at 4 weekly intervals followed by regular fixed dosing of aflibercept with or without subsequent rescue vPDT [113]. The mean visual acuity improvements at 52 weeks were similar between eyes with or without rescue vPDT, with 10.9 letters and 10.7 letters, respectively. The rate of polyp closure was also similar between aflibercept-treated eyes with or without rescue vPDT, with rates of 44.8 and 38.9%, respectively. The changes in choroidal thickness for eyes in the PLANET study have not been reported. In another study evaluating the use of combined therapy with either ranibizumab or aflibercept followed by vPDT, choroidal thickness appeared to be an important factor with respect to visual outcomes [115]. At 12 months, better visual acuity and better visual acuity improvement were significantly associated with a greater subfoveal choroidal thickness at baseline in eyes treated with photodynamic therapy combined with intravitreal ranibizumab or Aflibercept. Other studies suggest that eyes with thicker and/or hyperpermeable choroids are more likely to respond poorly to intravitreal anti-VEGF monotherapy [2, 18].

Future research directions

Significant advances have occurred in our understanding of the pachychoroid disease spectrum. However, further research is needed to clarify several areas of uncertainty. For instance, it remains unclear why some eyes with thick choroids with large vessels show no evidence of RPE alterations or SRF (uncomplicated pachychoroid). Similarly, elucidating the pathophysiology leading to a "switch" from the non-neovascular pachychoroid disease entities PPE, CSC, FCE, and PPS to the neovascular variants (PCN and PCV/AT1) will be important in developing future therapies. The mechanisms which lead to the characteristic choroidal changes in the pachychoroid disease phenotype, as well as genetic and/or environmental factors remain to be clarified. To evaluate whether venous congestion may indeed be responsible for the dilated choroidal vessels, future imaging studies which enable in vivo determination of flow direction and velocity will need to be developed. Similarly, improved resolution of various imaging techniques will be necessary to allow more accurate quantification of choriocapillaris thickness and blood flow. If these questions can be answered, therapies aimed at modulating the pathologic changes within the choroid may be developed as a common therapeutic platform for all the conditions within the pachychoroid disease spectrum.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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REVIEW ARTICLE

从基础研究的角度关注亚洲发生的年龄相关性黄斑变性

摘要

息肉状脉络膜血管病变（PCV）是新生血管性年龄相关性黄斑变性（AMD）的一种特殊表型，好发于亚洲人群，较高加索人更为常见。近年来研究集中关注于PCV与典型AMD的不同之处。尽管典型AMD和PCV在视网膜脉络膜交界面异常血管生成的过程中具有多种相似的发病机制，但PCV具有不同的临床特征，如脉络膜新生血管末端瘤样扩张，由脉络膜肥厚引起的内层脉络膜变性，较少见玻璃膜疣等。最新研究提出，炎症、血管生成因子和脂类代谢均在新生血管性AMD的发生中起到重要作用。此外，虽然研究较少关注脉络膜在AMD中的作用，但是大量证据表明脉络膜毛细血管和脉络膜在典型AMD和PCV玻璃膜疣发生中起到关键作用。本综述讨论了AMD的基本发病机制，探讨了典型AMD和PCV之间的差异。

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REVIEW ARTICLE

Asian age-related macular degeneration: from basic science research perspective

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Abstract

In Asian populations, polypoidal choroidal vasculopathy (PCV), a distinct phenotype of neovascular age-related macular degeneration (AMD), is more prevalent than Caucasians. Recently, there has been significant focus on how PCV differs from typical AMD. Although typical AMD and PCV share a variety of mechanisms by which abnormal angiogenic process occurs at the retinochoroidal interface, PCV has different clinical characteristics such as aneurysm-like dilation at the terminal of choroidal neovascular membranes, less frequent drusen and inner choroidal degeneration due to the thickened choroid. Recent studies support an important role for inflammation, angiogenesis molecules and lipid metabolism in the pathogenesis of neovascular AMD. Furthermore, although less attention has been paid to the role of the choroid in AMD, accumulating evidence suggests that the choriocapillaris and choroid also play a pivotal role in drusenogenesis, typical AMD and PCV. This review discusses the basic pathogenic mechanisms of AMD and explores the difference between typical AMD and PCV.

Introduction

Age-related macular degeneration (AMD) is a chronic, progressive disease with two end stages, exudative AMD and geographic atrophy (GA). Exudative AMD is characterized by choroidal neovascularization (CNV), which leads to leakage of fluid, lipids, and blood in the retina. Exudative AMD is more common than GA and an important cause of irreversible vision loss in Asian countries [1]. With an aging population, the size of the affected patient population will inexorably continue to increase. It is estimated that 288 million people will be affected by AMD by 2040, with 113 million people in Asia [1]. The patient's quality of life (QOL) is diminished by visual impairment due to AMD to the same extent as that of serious systemic diseases, and although current treatments offer a good cost–benefit balance in terms of medical economics, significant improvements in QOL remain a distant prospect. The presence of drusen and retinal pigment epithelial (RPE) abnormalities which are clinical signs of early and intermediate AMD respectively, are associated with an increased risk of progression to advanced AMD.

Importantly, exudative AMD in Asian countries is now categorized into typical AMD and polypoidal choroidal vasculopathy (PCV). When the frequency of exudative AMD classified as typical AMD and PCV was investigated, 35–61% and 33–55% patients diagnosed with AMD were reported to be suffering from typical AMD and PCV respectively [2, 3]. PCV accounts for a much larger proportion of cases in Asia compared to that in Europe and North America, and in recent years, the pathology of PCV has been widely studied in Asian countries using a variety of approaches.

Basic definitions of PCV

PCV meets the late AMD criteria in the International ARM epidemiological study group and is categorized as a form of neovascular AMD [4]. However it has distinct clinical characteristics from typical AMD (Fig. 1). The definitive diagnosis of PCV is made by indocyanine green (ICG) angiography which reveals a branching vascular network

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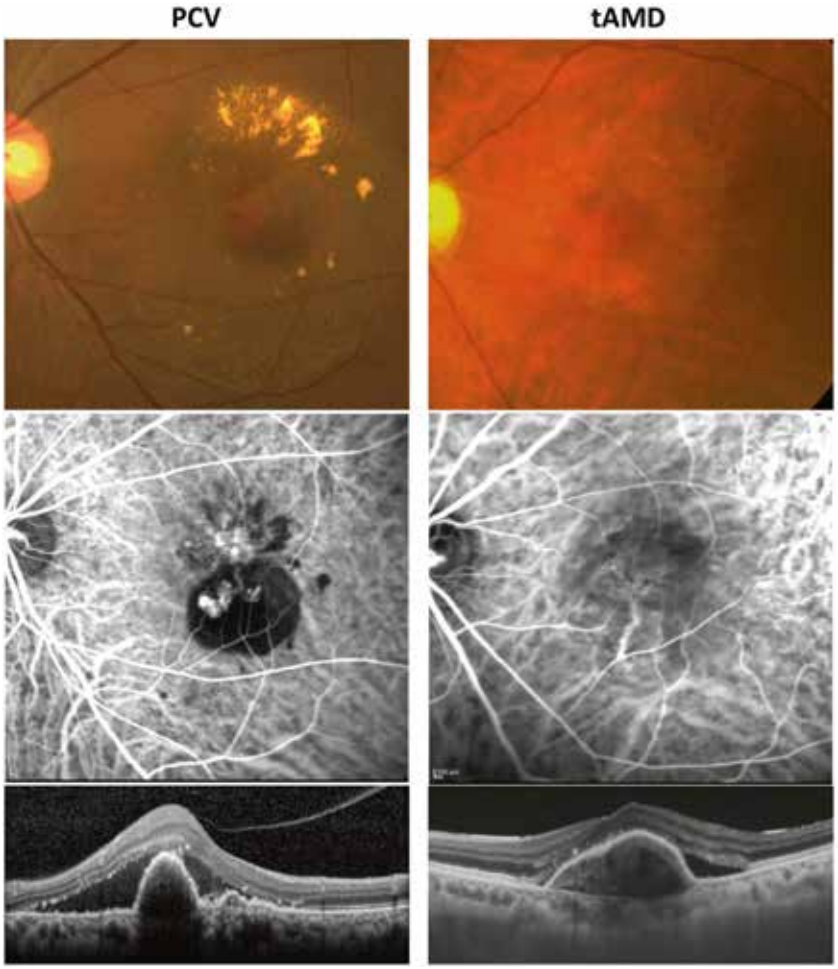

Fig. 1 Multimodal imaging of typical AMD and PCV

(BVN) with adjoining polypoidal lesion(s) [5]. It is generally agreed that BVNs are the growth of abnormal blood vessels from the choroid and located in Bruch's membrane, a similar location to the occult CNV observed in typical AMD. Polypoidal lesions show either coil-like or aneurysmal configuration on ICG angiography. Histologically, neovascularization in PCV is characterized by pronounced degenerative processes in choroidal vessels, such as loss of vascular endothelial cells and α-smooth muscle actin positive smooth muscle cell loss [6, 7]. (Fig. 2) Such degenerative changes in the choroid are possibly responsible for the aneurysm-like dilation of the neovascular membrane and common bleeding events observed in PCV patients. Other distinct features include relatively younger age, male predominance, and unilateral presentation.

To begin with, the pathogenic mechanisms and processes of typical AMD and PCV are complex and multi-layered, which brings about many key areas of potential research and therapeutics.

Pachychoroid and PCV

It is widely accepted that a substantial proportion of PCV occurs in eyes with a "pachychoroid" configuration and that the choroid is a key contributor to the development of PCV. (Fig. 3) "Pachychoroid" is defined as characteristic anatomical and functional alterations of the choroid including increased choroidal thickness, which may be diffuse or focal, and/or choroidal hyperpermeability on ICG angiography. The most salient feature of the pachychoroid is "pachyvessels" or dilated choroidal veins at the level of Haller's layer with thinning of the overlying Sattler's layer and choriocapillaris. Based on multimodal imaging studies, pachychoroid has been postulated to be associated with increased hydrostatic pressure in the choroid causing disruption of Bruch's membrane, RPE dysfunction, and inner choroidal ischemia [8], and has been considered an underlying cause of a disease spectrum that includes pachychoroid pigment epitheliopathy, central serous chorioretinopathy, and pachychoroid neovasculopathy (type

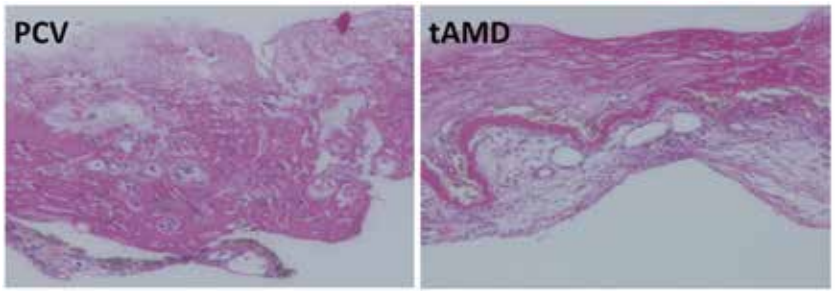

Fig. 2 H&E staining of surgically excised tissue removed from PCV and typical AMD. PCV (left panel): H&E staining shows dilated vessels, with thickened and hyalinised vessel walls. There is also obstruction of hyalinised vessels. Typical AMD (right panel): H&E staining shows fibrovascular tissues with fibrosis, fibroblast-like cells and small vascular channels. Original magnification: x50

1 neovascularization associated with shallow irregular RPE detachment with or without polyps). It is likely that pachychoroid is also associated with focal choroidal excavation [9], geographic atrophy (pachychoroid geographic atrophy [10]), peripapillary exudative changes (peripapillary retinoschisis [11] and peripapillary pachychoroid syndrome [12]) and drusen with a peculiar shape (pachydrusen [13]), although there is some debate as to whether pachychoroid is a primary cause of these conditions.

The recent expansion of our understanding of pachychoroid has raised fundamental questions as to whether PCV differs from typical AMD. Indeed, pachychoroid neovasculopathy includes not only PCV, but also type 1 CNV in typical AMD. Now that PCV and type 1 CNV associated with pachychoroid are understood as pachychoroid-driven disorder, some researchers assume that these 2 conditions are not distinct diseases but simply represent different stages of the same spectrum disorder. However, despite a growing body of literature, it is difficult to diagnose pachychoroid unambiguously due to a lack of expert consensus on the definition. Further studies are needed to reconstruct the classification of neovascular AMD.

Basic mechanisms of typical AMD and PCV

PCV is a multifactorial disease with both genetic and environmental factors contributing to its pathogenesis. Both typical AMD and PCV arise from abnormal blood vessels, resulting in fluid accumulation, recurrent exudative, and hemorrhagic pigment epithelial detachments with associated serous macular detachment.

Genetic factors in typical AMD and PCV

Susceptibility genes associated with PCV are similar to those associated with typical AMD. Fan et al. demonstrated that 34 known AMD loci accounted for up to 36.8% of phenotypic variations for PCV and that there is a high genetic correlation between typical AMD and PCV [14]. Gene loci associated with PCV susceptibility are implicated in complement and immune response, angiogenesis signaling pathways, lipid transport, oxidative stress pathways, and extracellular matrix (ECM), and they are involved in a variety of mechanisms by which abnormal angiogenic processes occur at the retinochoroidal interface.

There is some evidence to suggest there are different genetic factors between typical AMD and PCV. For example, *FGD6* is significantly associated with PCV but not with typical AMD [15]. In addition, there are differences in the effect of rare coding variants on AMD susceptibility between European and Asian population. Of note, *CETP* (*D442G*) is an East Asian-specific but otherwise uncommon mutation strongly associated with neovascular AMD with an odds ratio of 1.70 [16]. The study also reported three other novel loci (*C6orf223 A231A*, *SLC44A4 D47V*, and *FGD6 Q257R*) associated with neovascular AMD susceptibility in East Asian. Target sequencing of AMD susceptibility in Japanese patients also identified enrichment of low-frequency variants in *CETP*, *C2*, and *CFB* [17], whereas in European populations, there was no significant enrichment of rare variants in these genes. Such differences may represent genuine differences in genetic architecture in AMD between Asians and Europeans.

However, it is widely accepted that there is an overall similarity in the background genetic factors of typical AMD and PCV. Emerging clinical evidence [18, 19] suggest that some of the earliest events in typical AMD start with alterations in the RPE/Bruch's membrane and the choriocapillaris complex [20, 21]. Subsequent pathways of the pathogenesis of typical AMD and PCV differ, especially with regards to the extent of the involvement of the RPE/Bruch's membrane and the choriocapillaris.

Age-related changes of RPE in AMD

The RPE plays important roles in retinal homeostasis as follows; (1) provision of nutrients needed for photoreceptor cells; (2) transportation of ions, water, metabolic end

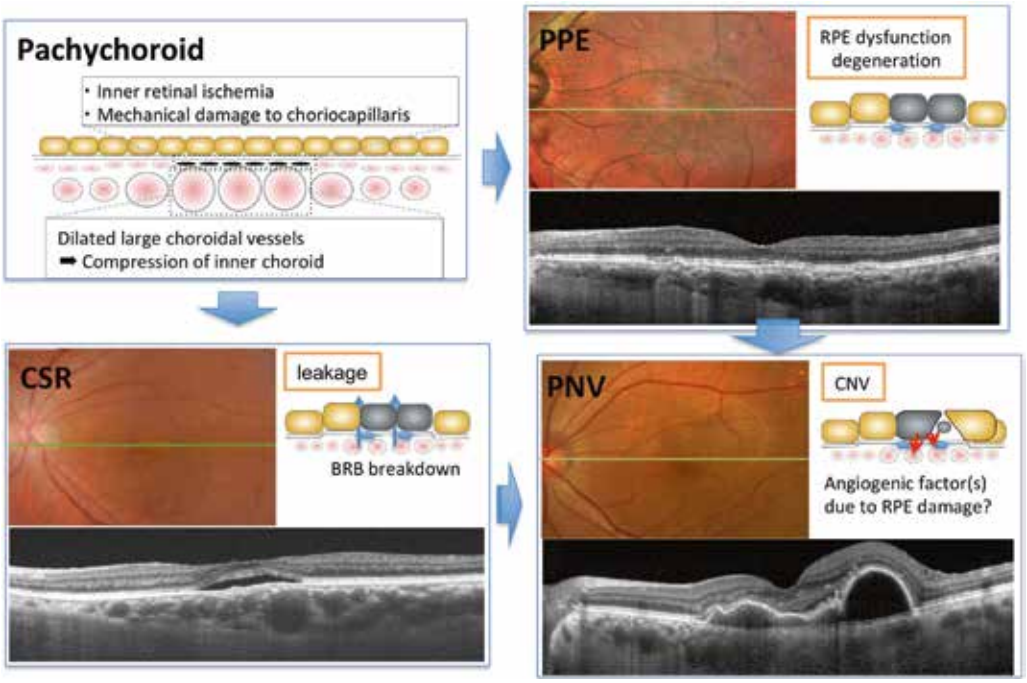

Fig. 3 Pachychoroid spectrum diseases. "Pachychoroid" is defined as characteristic anatomical and functional alterations of the choroid, including increased choroidal thickness and/or increased choroidal hyperpermeability on ICG angiography. Pachychoroid is considered responsible for pachychoroid spectrum diseases including pachychoroid pigment epitheliopathy, central serous chorioretinopathy and pachychoroid neovasculopathy. *CSR* central serous chorioretinopathy, *PPE* pachychoroid pigment epitheliopathy, *PNV* pachychoroid neovasculopathy

products from the subretinal space to the choroid; (3) formation of the blood retinal barrier; (4) phagocytosis of the shed photoreceptor outer segments, and (5) secretion of growth factors. Bruch's membrane is lamellar extracellular material (ECM) composed of five layers, i.e., inner basal lamina of RPE, outer collagenous zone, elastic zone, inner collagenous zone, and outer basal lamina of choriocapillaris. Bruch's membrane inner border is well demarcated, whereas the outer limit is ill-defined with expansions of Bruch's membrane in the choroid forming intercapillary pillars [22]. Progressive age-related changes that characterize early AMD includes thickening of Bruch's membrane, accumulation of extracellular deposits such as basal laminar deposit and membranous debris. There is an age-related reduction in hyaluronic acid [23] as well as accumulation of proteoglycans [24], collagen [25], elastin [23], lipids [26], and advanced glycation end products [27]. These pathological changes at the level of Bruch's membrane have been considered to play important roles in AMD. Mechanistically, a vast amount of literature shows that age-related thickening of Bruch's membrane results in impaired diffusion of oxygen, nutrients, ion, water, and metabolic end products from the RPE and thereby causing RPE dysfunction. Drusen are membranous debris located between the RPE basement membrane and the inner collagenous layer [28] and are considered to be incompletely digested material from RPE [20]. Soft drusen are a clinical hallmark of early AMD and are considered as independent risk factors for late AMD. These drusen are composed of proteins such as complement and β-amyloid, and lipids including unesterified cholesterol and cholesteryl-esters. Importantly, soft drusen are less frequently observed in eyes with PCV compared to those with typical AMD [29, 30] and its role in PCV pathogenesis is less clear.

Age-related changes of the choriocapillaris in AMD

The choroid is a vascularized tissue with poor autoregulatory mechanisms and consists of four layers; (1) outermost suprachoroid lamina, (2) Haller's layer (large choroidal veins), (3) Sattler's layer (medium-sized choroidal arterioles and venules), and (4) choriocapillaris (inner sinusoidal capillary network). Choroidal stroma is composed of pigmented cells, fibroblasts, melanocytes, and ECM such as collagen and elastin. The choroid also has multiple functions such as (1) nutrient transport, (2) waste removal, and (3) immune cell tracking [31]. Transport between the choroid and the RPE occurs at the level of choriocapillaris, a thin sheet (7–10 μm) of fenestrated capillaries. There is a close association between the degeneration of the RPE and choriocapillaris. Although less attention has been paid to the role of the choroid in AMD,

accumulating evidence suggests that the choriocapillaris and choroid also play a pivotal role in drusenogenesis, typical AMD and PCV [32]. First, there is an age-related thinning of the choriocapillaris and capillary lumen diameters [33]. Although the precise etiology and biochemical pathway is unknown, such changes of the choriocapillaris are considered as a process of normal aging and are present before the onset of clinical manifestation. Histological studies appear to support a role for widened intercapillary stroma, but not sclerotic changes of the choriocapillaries, for these changes [33]. Concomitantly, there is ghost vessels formation due to loss of functional endothelium. Such changes with normal aging are also of clinical significance. In early AMD, drusen are closely related to the choriocapillaries associated with the collecting venules of the choroid [34]. It is postulated that decreased choriocapillary vessel density results in drusen formation due to insufficient clearance of RPE-derived debris. In neovascular AMD, histological studies have demonstrated that there was loss of choriocapillaris adjacent to CNV and large areas that lacked choriocapillaries were reportedly completely covered by RPE [21]. Interestingly, areas with active CNV always had reduced choricapillaries with intact RPE. This contrasts to geographic atrophy, where there are some areas of normal choriocapillaris with atrophied RPE [21]. Furthermore, in typical AMD, CNV is frequently localized to watershed zone as demonstrated by ICG angiography [35]. The watershed zone is considered to be most vulnerable to ischemia in the event of a fall in the perfusion pressure in the vascular bed, and is therefore susceptible to CNV development. The finding that choroidal blood flow is decreased in eyes with an increased risk of CNV in AMD [36] and in eyes with RPE hypertrophy [37] supports this hypothesis. Therefore, the loss of choriocapillaris and reduced choroidal flow are also important factors contributing to exudative AMD [21], although there has been a debate as to whether the choriocapillaris degeneration is a cause or consequences of the inflammatory response that causes the pathogenic changes in the choroidal/RPE ECM.

Contrary to the prevailing view that the ischemia is associated with CNV in typical AMD, abnormal vessels in PCV frequently co-localize with dilated choroidal vessels [38]. Additionally, choroidal vascular hyperpermeability and choroidal thickening are more frequently reported in PCV compared to typical AMD [39]. The most likely mechanism is thickening and increased rigidity of the sclera, probably due to a change in the structural composition of the sclera in the eyes with PCV similar to those with uveal effusion syndrome; that is, dilation of the choroidal vessels could be related to an increased resistance of choroidal venous flow due to impeded venous drainage via vortex veins. Genetic factors are likely to play a role, although the detailed mechanisms are still unknown. Recent investigators postulated that the dilated outer choroidal vessels would mechanically compress the inner choroid and choriocapillaris and might induce ischemic changes [40].

Thus, pathologic changes occurring at RPE/choroidal interface and choriocapillaris play a critical role in the pathogenesis of typical AMD and PCV. However, differing histological and clinical manifestations of PCV from those of typical AMD suggests that there are factors that contribute to the different physical characteristics of the angiogenic process. As discussed in the next chapter, several hypotheses have been postulated; however the main differences in abnormal angiogenic process between typical AMD and PCV are still unknown.

Mechanistic insights into the pathogenesis of typical AMD and PCV

Inflammation - complement and immune response

Complement activation in drusen

It is widely accepted that cellular damage induced by inflammation as part of the complement activation pathway of our immune system contributes to the pathogenesis of typical AMD and PCV. The complement system is a part of the innate immune system, which helps to protect host cells from pathogens, removes debris and modulates immune reactions. There are three major pathways of complement activation, i.e., classical pathway, lectin pathway and alternative pathway. Activation of C3 by a C3 convertase, regardless of how it is activated, results in the generation of anaphylatoxins C3a and C5a, opsonins C3b, iC3b, and C3d, and membrane attack complex (MAC) C5b-9 (Fig. 4) [41]. MAC formation is the final event occurring downstream of complement cascade which induces dysfunction of the target cells by forming membrane-spanning pores [42]. It has been also demonstrated the formation of anaphylatoxins C3a and C5a, resulting from dysregulation of complement pathways, can elicit aberrant activation of macrophages further aggravating the inflammation. Based on histological findings, complement activation in the drusen has been considered to play an important pathogenic role in AMD [20, 41, 43]. A polymorphism in the complement factor H (*CFH*) gene, a negative regulator of the complement pathway, increases the risk of AMD and PCV by 1.75 and 1.85 fold respectively [14]. Other gene loci in the complement pathways (*C2-CFB-SKIV2I*, *C3*, *C9*, and *CFI*) have consistently been shown to be associated with AMD risk. In this regard, it is of note that the complement component C3 and other complement pathway proteins are detected in the drusen. Our groups and others found there is an age-related increase in the complement pathway protein C3 [44].

Drusen also trigger further inflammation and C-reactive protein, a CFH-binding protein [45], is also implicated in this process. Drusen accumulation is also enhanced by local inflammation resulting from RPE disorders [20].

Complement activation in the choriocapillaris

While many studies have focused on the impact of complement activation on RPE cells, several studies indicate complement activation first occurs in the choriocapillaris. First, although RPE is exposed to MAC in advanced AMD, activation of MAC first occurs at the level of choriocapillaris in early AMD as demonstrated by a histological study [42]. In addition, the eyes harboring the risk allele of *CFH* (*Y402H*) shows increased C-reactive protein in the choroid [46], probably reflecting chronic local inflammation and cellular injury. Moreover, in neovascular AMD, persistent labeling of MAC at the level of the choriocapillaris is reported even after the degeneration of the endothelium was complete. These lines of evidence suggest complement activation occurs in the choriocapillaris at initial stage of AMD. Interestingly, complement activation also triggers innate inflammatory responses in choroidal endothelial cells. Choriocapillaris is the only capillary system in which the endothelial cells express intercellular adhesion molecule-1 (ICAM-1), an important molecule that mediates the infiltration of leukocytes [47]. In vitro, C5a increases the expression of ICAM-1 [48], suggesting complement activation contributes to the recruitment of leukocytes. Further evidence to support the role of complement pathway molecule on the choroid comes from animal experiments. In aged mice, there was deposition of amyloid beta and tau proteins in the choroidal arteries, and both amyloid β and phosphorylated tau were expressed at significantly high levels in CFH knockout mice [49]. Amyloid β and phosphorylated Tau in association with brain blood vessels are known to disrupt endothelial cell function; therefore, it is plausible that the accumulation of these proteins results in the disruption of choroidal vessels, potentially thinning the choriocapillaris and thus disrupts outer retinal perfusion.

Role of immune cells

Among infiltrating leukocytes, the role of macrophages has been most intensively studied. Macrophages accumulate around drusen and remove debris and cholesterol from the Bruch's membrane in the young choroid. In contrast, macrophages also have opposite destructive effects and are involved in the pathogenesis of CNV [50]. (Fig. 5) We and other groups have demonstrated that macrophages recruited to CNV lesion express vascular endothelial growth factor (VEGF) -A and depletion of monocytes and macrophages results in a reduced CNV size in a laser-induced mouse model [51]. Such diverse effects of macrophages may be carried out by distinct macrophage subpopulations. We speculate that macrophages' polarization from protective to destructive phenotypes is due to continuous stimulation by molecular "garbage" such as oxidized lipid products whose generation-disposal balance becomes impaired with aging. In contrast to the roles of macrophages, roles of lymphocytes and granulocytes in CNV are less clear [52]. Of note a recent study identified mast cell degranulation in the choroid of all stages of AMD [53]. Mast cells were distributed in the choroidal stroma at the level of Sattler's and Haller's layer but were not present at the level of choriocapillaris except for the eyes with geographic atrophy where mast cells were also found at the level of choriocapillaris in regions with complete RPE atrophy. Although further studies are needed, it is interesting to postulate that mast cells would release diverse factors that mediate pro- or anti-inflammatory functions which lead to thinning of the choroid, degradation of vascular membranes and Bruch's membrane, resulting in RPE degeneration and thinning of the choriocapillaris which contribute to the pathogenesis of CNV.

The innate immune response occurring in the choroid is likely to be associated with the pathogenesis of PCV. As mentioned previously, while the concept that drusen-triggered activation of immune system contributes to typical AMD is widely accepted, there remain several controversies with regards to the role of drusen in PCV. Unfortunately, there are no histological studies investigating the choroid of eyes with PCV; however, immunohistological studies using surgically excised PCV specimen showed CD68-positive macrophages around the hyalinised vessels [7], supporting the role of macrophages in the pathogenesis of PCV. Recent evidence suggests that functional skewing of immune cells towards pro-angiogenic and pro-inflammatory phenotype is a key event happening in exudative AMD. The immune cells are shown to be plastic, and polarized cells have the capacity to redifferente and reprogrammed upon various stimuli. Therefore, future studies on the immune cells, especially focusing on their polarization and signaling pathways would pave a way to a new treatment.

The inflammasome has also emerged as another immune component related to AMD [54]. Previous studies reported that the inflammasome, which is typically synthesized by immune cells could be activated in the RPE and could mediate both protective and destructive signals in AMD [55, 56]. This was followed by numerous studies that linked inflammasome activation in RPE and AMD [57]. However, a recent study pointed out the problems related to the use of non-specific and unreliable commercially available

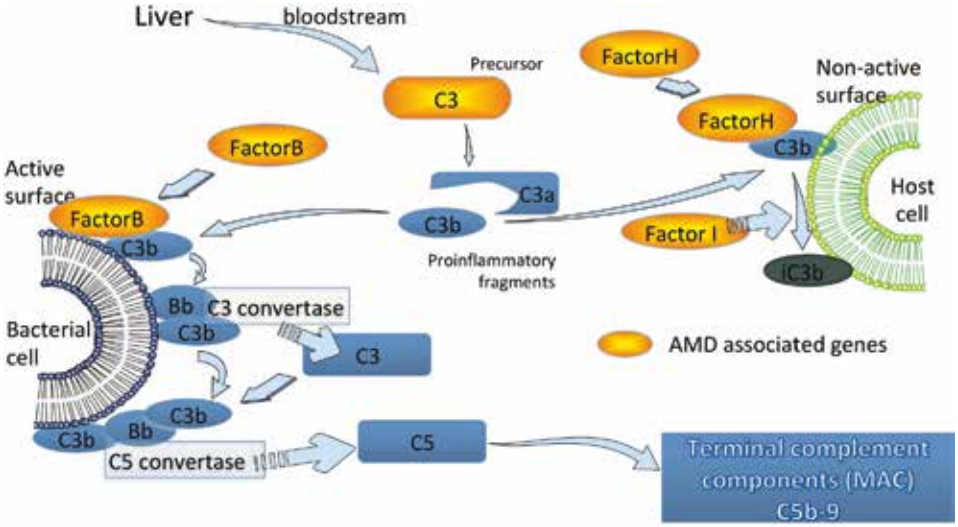

Fig. 4 Complement pathway. C3 convertase generated either by the classical, lectin, or alternative pathway, cleaves C3 into C3a and C3b, and results in C3b amplification loop. Cascade then proceeds to the activation of a C5 convertase of the classical (C4b2aC3b) or alternative (C3bBbC3b) pathway. Further, C5 convertase initiates the activation of late components of the complement system to form membrane attack complex (MAC). MAC formation is the final event occurring downstream of complement cascade inducing dysfunction of the target cells by forming membrane-spanning pores. Both complement factor H (CFH) and factor I (CFI) promote the cleavage of C3b to its inactive form and act as negative regulators. Genetic studies have identified associations of multiple SNPs associated complement genes including *CFH*, *CFI*, *CFB*, *C2*, *C3*, and *C9*, and AMD susceptibility

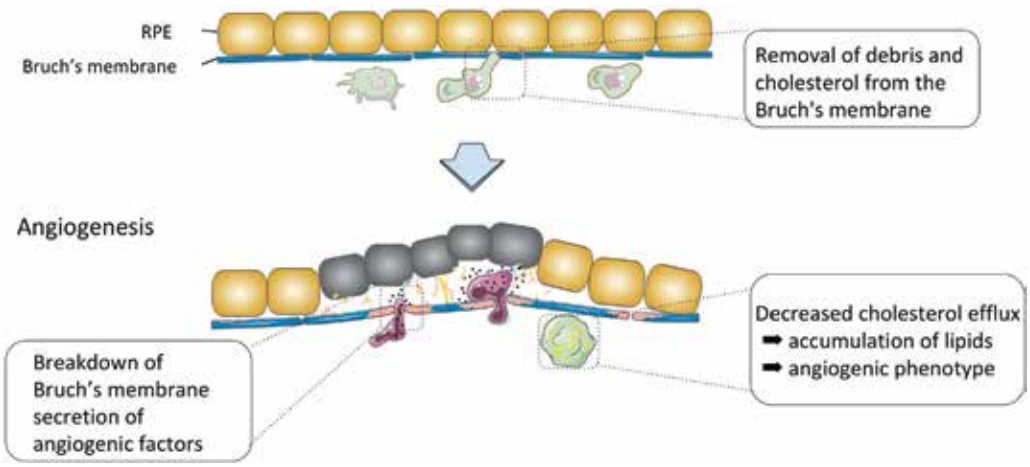

Fig. 5 Diagram showing roles of myeloid cells in AMD. Macrophages accumulate around drusen and remove debris and cholesterol from the Bruch's membrane in the young choroid. In contrast, macrophages have opposite destructive effects and are involved in the neovascular process. Recruited macrophages replace choroidal capillaries, erode Bruch's membrane including intercapillary pillars and facilitate CNV growth. Macrophages also produce diverse proangiogenic factors such as vascular endothelial growth factor (VEGF) and inducible nitric oxide synthase (iNOS), further promoting angiogenesis

antibodies in these experiments and clearly demonstrated no significant NLRP3 (a pivotal cytosolic innate immune sensor and regulator of inflammasome) expression in RPE cells [58]. Their results suggest that RPE cells do not contain significant amounts of NLRP3 that contribute to AMD pathogenesis and call into question the notion that inflammasome activation is involved in the pathogenesis of AMD. Further molecular analysis and independent verification are still awaited to confirm/refute previous studies regarding the roles of inflammasome activation in AMD.

Angiogenesis and signaling pathways

CNV is stimulated by angiogenic factors, which is triggered by ischemia, hypoxia and inflammation. Reduction in anti-angiogenic factors in the RPE may also contribute to the

formation of CNV [21]. Bruch's membrane represents a physical barrier to the inward growth of choroidal vessels. In PCV, it is generally agreed that BVN is localized above the Bruch's membrane, although some of them can be below the Bruch's membrane (in the choriocapillaris and the large choroidal vascular layer) [38, 59]. Therefore, CNV in AMD and abnormal blood vessels in PCV require matrix metalloproteases or serine proteases to digest ECM or basement membrane of the choroid, to penetrate into the Bruch's membrane. Interestingly, although most of the risk variants for geographic atrophy and neovascular AMD are shared, a variant upstream of *MMP9* was found to be exclusively associated with neovascular AMD, but not with GA [60], supporting the idea MMP9 is involved in the angiogenic process in neovascular AMD. The digestion of ECM is also mediated by macrophages at least in part. At the initiation stage of CNV, macrophages are shown to accumulate in areas where Bruch's membrane is thin. There are three possible roles of choroidal/Bruch's membrane macrophages in the pathogenesis of CNV, i.e., replacement of choroidal capillaries, erosion of Bruch's membrane including intercapillary pillars and facilitation of CNV [50]. It has been hypothesized that macrophages infiltrate into the compromised areas of Bruch's membrane and are responsible for digesting collagen. Recruited macrophages also produce diverse proangiogenic factors such as vascular endothelial growth factor (VEGF) and inducible nitric oxide synthase (iNOS) [61], further promoting angiogenesis.

Recent whole-genome exome sequencing identified a significant association between a rare variant in the *FGD6* gene (*FGD6 K329R*) and PCV, but not typical AMD [15]. The authors hypothesized *FGD6* would regulate proangiogenic activity in PCV. An abnormal vascular structure that resembles polyps was observed in six out of the 10 retinas receiving the *FGD6 R329* virus injection, but only one out of ten in the retinas receiving viruses expressing *FGD6 K329* and none in the GFP controls, suggesting that retinas expressing *FGD6 R329* have higher probability to cause distorted blood vessels. Their finding suggests that *FGD6 R329* can induce the development of an abnormal vascular network in vivo and that this protein might contribute to the unique abnormal vascular network of PCV. Future research in terms of targeting the gene products of *FGD6 R329* could be a potential area to explore for neovascular AMD.

Lipid transport

Genome wide association studies have demonstrated an association between Asian exudative AMD and *cholesterol ester transfer protein* (*CETP*) [16, 17]. Interestingly Asian specific *CETP D442G* mutation is known to impair *CETP* function and increase serum high-density lipoprotein (HDL) cholesterol levels. In Asian population, higher HDL was an independent risk factor for neovascular AMD including typical AMD and PCV [62]. Similarly, genome-wide association studies conducted in Western countries have shown an association between AMD and *hepatic lipase* (*LIPC*), which also affects serum HDL cholesterol levels. Additionally, there is an association between *apolipoprotein E* (*ApoE*) and *ATP-binding cassette transporter A1* (*ABCA1*) gene and AMD susceptibility, further supporting a link between lipoprotein and AMD. To date, however, the association between serum lipid and AMD has been inconsistent. In contrast to *CETP* gene, the HDL-raising allele of the *LIPC* gene was associated with a reduced risk of AMD [63]. Higher total cholesterol and low-density lipoprotein (LDL) levels were associated with an increased risk of AMD, whereas higher HDL levels reduced the risk of advanced AMD. A recent study using Mendelian randomization supports that HDL cholesterol is a causal risk factor for AMD. Unexpectedly, the study found no causal effect of LDL-cholesterol or triglycerides. They also found variants in the CETP gene locus associated with increased HDL is associated with increased AMD risk although variants in LIPC gene locus that increases HDL associated with the opposite effect [64]. Perhaps the racial differences in the effects of the CETP and LIPC gene loci on HDL levels and subsequently AMD risks could be explored in larger studies.

Lipid and drusen

The presence of cholesterol and apoproteins (Apo B, E, A–I, C–I, and C–III) in drusen and basal linear deposits links AMD with lipoproteins involved in the pathogenesis of atherosclerosis, which also features extracellular lipoprotein deposition and end-stage changes including calcification and neovascularization [65, 66]. The retina requires cholesterol to achieve normal structure and function. Local biosynthesis is not the only source of cholesterol for the retina as cholesterol from the systemic circulation can cross the RPE. RPE controls both cholesterol input and output by means of both passive and active mechanisms. RPE uptakes HDL and LDL via scavenger receptor and LDL receptors from the blood circulation and secrete excess fatty acids and cholesterol, ApoB, E. Cholesterol in Bruch's membrane lipoproteins is likely to be derived from endogenous synthesis, taken-up plasma lipoproteins and phagocytosed photoreceptor outer segment [66]. However, dysregulation of cholesterol uptake and/or removal, together with age-related change in the elastic layer of Bruch's membrane lead to the accumulation of lipoproteins in the inner collagenous layer with aging. Lipoproteins subsequently form lesions to trigger inflammation, complement activation and cytotoxicity. Due to decreased permeability of Bruch's membrane,

ApoB, E containing lipoproteins secreted by RPE builds up, and individual lipoproteins fuse over time to produce drusen that are largely composed of lipids including unesterified cholesterol and cholesteryl-esters.

Accumulation of lipids is partly due to retention of lipoproteins as a result of impaired reverse cholesterol transport which leads to drusen formation. The importance of HDL and apo-AI for cholesterol efflux has been demonstrated in many studies in non-ocular tissues such as macrophages. In non-ocular tissues, nascent (pre-β-1) HDL particles bind to *ABCA1* and promote lipid efflux from the tissue. Moreover, incubation with apoA-I, the major apolipoprotein component of HDL, increases efflux. In this process, *ABCA1* transporter on the surface of macrophages transfers free cholesterol from the cells to ApoA-I, which forms pre-β-1 HDL particles. Thereafter, free cholesterol is esterified by lecithin: cholesterol acetyltransferase, and transported to the liver for excretion into bile acid. The ATP-binding cassette G1 transporter (ABCG1) and scavenger receptor class B type I (SR-BI) also contribute to the efflux of cholesterol from peripheral tissues through large and less dense HDL particles. However, the mechanism by which lipids efflux from the RPE into the choroidal circulation is poorly understood. Similar to macrophages, RPE cells express components of reverse cholesterol transport molecules such as apo E, SR-BI, and ABCA1/G1 and lipids are reportedly transported through RPE for efflux from the cells. HDL is shown to bind to the effluxed lipids from the RPE [67]. Interestingly, the RPE cells efflux cholesterol towards both the subretinal and choroidal compartments using ABCA1/G1 [68]. Regarding oxysterols, RPE cells also likely participate in the clearance of dietary oxidized LDL through CD36 scavenger receptor [69]. There are other mediators of cholesterol efflux such as albumin, plasminogen and exosomes in serum. It is also possible that there is monocyte clearance system in which circulating monocytes invade the Bruch's membrane and accumulate lipid. It is unknown, however, how the recruited monocytes migrate back into the circulation and how much macrophages contribute to the clearance of subretinal lipid. Importantly, several studies demonstrated that increasing cholesterol efflux capacity by means of pharmacological interventions (e.g., statins [70] and ApoA-I mimetic peptides [71]) may reduce drusen burden. However, recent studies suggest that increasing HDL or ApoA-I concentrations do not necessarily improve cholesterol efflux capacity and that HDL functionality is more important [72]. It is also important to note that different statins may differently impact cholesterol efflux capacity, and some types of statins are known to decrease cholesterol efflux [72]. Further studies are warranted to address whether lipid efflux capacity is associated with AMD risk, and if so, which groups of AMD patients would benefit most from such therapy.

Lipids as signaling molecules and fuel substrate

Most of the recent studies on lipids are directed towards understanding the mechanism underlying lipid accumulation in RPE/Bruch's membrane. However, lipids may affect AMD not only by modulating cellular debris, but also by modulating phenotypic changes of macrophages. In this regard, it is of note that cholesterol metabolism is one of the most important factors that modulate macrophage polarization. Excess cholesterol accumulated in macrophages is removed through ABC cassette transporter, *ABCA1/G1*, and a recent study demonstrated that down-regulation of ABCA1 in macrophages results in an accumulation of free cholesterol within senescent macrophages [73]. Subsequently, elevated lipid polarizes macrophages to an alternatively activated phenotype that promotes angiogenesis and accelerates neovascular AMD.

It is also important to note lipids are used as fuel substrate. Traditionally, the retina has been assumed to rely exclusively on glucose for energy, and less characterized are the functions of lipid metabolism in the retina as a pathway to generate ATP. However, a recent study clarified that retina uses fatty acid β-oxidation for energy [74]. VLDL receptors (VLDLR) bind triglyceride-rich chylomicrons and VLDLs, allowing lipoprotein lipase to release long-chain fatty acids. Lipid β-oxidation commonly occurs in the heart and skeletal muscle, where abundant amounts of VLDLR facilitate fatty acid uptake. Genetic ablation of *Vldlr* in mice makes these animals susceptible to neovascularization. In *Vldlr* knockout mice, the researchers found retinal lipid uptake and lipid β-oxidation were curtailed. Increased level of circulating fatty acids in *Vldlr* knockout mice could activate a lipid sensor, free fatty acid receptor 1 (Ffar1). This in turn suppresses the expression of the glucose transporter Glut1, thereby impairing glucose entry into photoreceptors. In consequence, fuel shortage and a reduction in the levels of Krebs cycle intermediate α-xketoglutarate promote neovascularization by stabilizing hypoxia inducible factor-1 and VEGF. This mechanism, although needs to be more characterized, may explain neovascular drive due to the reduced availability of lipids that is independent of drusen and inflammation. If proven, therapy against chylomicrons and VLDLs, on top of essential dietary control of lipid intake, could be investigated as a potential preventive therapy for AMD.

Animal models of AMD

Animal models of early AMD

Currently, animal models that accurately mimic the disease pathologies and progression of typical AMD or PCV

are still lacking. Several mouse models for AMD were developed based on genetic risk factors. These genetically modified genes in mouse models include complement related genes such as *CFH* (CFH knock-out mice [75] and knock-in mice expressing human Y402H variant of *CFH* [76]), cholesterol-related genes such as *ApoE* (ApoE-null mice [77], ApoE-Leiden mice, and transgenic mice expressing the human ApoE2, ApoE3, or ApoE4 alleles [78]) and oxidative-stress related genes such as SOD1 and 2 (SOD1/2 knockout mice [79, 80]). Although these mouse models replicate some hallmarks of AMD, such as Bruch's membrane thickening and drusen-like deposits, CNV is rarely present in these models. There had been no studies that demonstrated the thinning of choroicapillaris in animal models. For example, both *ApoE* knockout mice and transgenice mice, only when fed with high-fat diet, show Bruch's membrane thickening [77, 78]. *CFH* knockout mice show minor changes such as a loss of retinal function and increased C3 deposition that occurs at 2 years of age [75], whereas mice expressing either Y402 or H402 variant of human *CFH* develop C3b deposits and subretinal macrophage infiltration at 12 to 14 months of age [76]. Some animal models exhibit drusen-like deposits; however, these are located in the subretinal space, but not in the sub-RPE space, and differ from human drusen with regards to the composition. Of note, drusen-like deposits can be related with a mutation in CRB1 gene, which is present in several laboratory mouse strains [81], and may have no relevance with the AMD gene mutations these mice carry. Furthermore, *CETP*, a crucial cholesterol-related gene in Asian AMD, is absent in mice, highlighting the difficulty in replicating the human cholesterol-metabolism abnormality occurring in human AMD in mice. In summary, these mouse models could be useful to investigate the early events occurring in AMD. More studies however will be required to understand how the findings in mice translate to humans to ultimately understand biological and physiological mechanisms in human AMD.

Animal models of late AMD

Developing a mouse model exhibiting cardinal features of typical AMD or PCV has been challenging, and many studies have employed laser-induced CNV model that partially mimic the pathogenic mechanisms of CNV. There is, however, some experimental support for the role of high temperature requirement factor A1 (HtrA1), one of four known proteases belonging to the broadly conserved family of HtrA proteins, in PCV. *HtrA1* is linked to typical AMD/PCV and regulates the transforming growth factor β and matrix metalloproteinases in chronic inflammation. Although there is some debate, AMD/PCV-associated single nucleotide polymorphisms in the promoter of *HtrA1* has been shown to be associated with an increased expression level of HtrA1 [82–84]. *HtrA1* risk allele is associated with increased HtrA1 expression. Recently, *HtrA1* transgenic mouse strains have been developed by three independent research groups and are reported to show a large number of phenotypes that resemble the human PCV [85–87], i.e., (1) capillary structural abnormalities in the choroid; (2) without any other signs of AMD; and (3) the degradation of choroid vessel walls.

Jones et al. generated a mouse line overexpressing human *HtrA1* in mouse RPE [86]. The mice expressed human HtrA1 in the RPE and secreted HtrA1 was also detected in the basal side of RPE, i.e., Bruch's membrane and in the choroid. On ICG angiography, the investigators detected cardinal features of PCV, namely, numerous hyperfluorescent dots, large polypoidal lesions, and branching vascular network in 59% of the mice they examined. Histologically, the PCV-like lesions in the *HtrA1* transgenic mice contained abnormally dilated, thin-walled vessels beneath the RPE. Severe degeneration of the elastic lamina or tunica media of choroidal vessels, as well as fragmentation of the elastic layer in Bruch's membrane, were observed in the same model. These studies demonstrated that transgenic mice overexpressing human *HtrA1* show PCV-like abnormal capillary structures in the choroid. In these mice, the tunica adventitia, which contains a large amount of collagen fibers and the tunica media, which is composed predominantly of smooth muscle, were severely degenerated in choroid arteries. Histological analysis showed that the integrity of the elastic lamina of the Bruch's membrane was also severely compromised; however, the choroidal vessels were reportedly more severely damaged than that of the Bruch's membrane.

Vierkotten et al. generated transgenic mice overexpressing mouse *HtrA1* in the RPE [87]. The investigators found ultrastructural changes in the elastic layer of Bruch's membrane of the *HtrA1* transgenic mice up to one year. Expression of major components of the ECM as well as ECM proteins involved in elastogenesis were changed; there was a degradation of fibronectin with the generation of fibronectin fragments, together with a reduction of fibulin 5 and tropoelastin.

Nakayama et al. also generated mice ubiquitously overexpressing mouse *HtrA1* [85]. Importantly, fluorescein angiography demonstrated leakage in the late phase suggestive of CNV in these mice. Histological study demonstrated subretinal CNV formation originating from the choroid as well as ruptures in the Bruch's membrane. These various mouse models are useful in conducting future research trials for AMD.

Functional biology of HtrA1

HtrA1 is involved in divergent biological pathways and has also been implicated in several pathologies including cancer, Alzheimer's disease, arthritis and familial ischemic cerebral small-vessel disease. For example, HtrA1 is downregulated in cancer of diverse origins, and functions to regress solid tumors. Diseases such as the cerebral arteriopathy, autosomal recessive with subcortical infarcts, and leukoencephalopathy (CARASIL) syndrome and the cerebral small vessels disease (CSVD) are caused by mutations or deletions that impair HtrA1 function. In Alzheimer's disease, HtrA1 is involved in the degradation of tau protein [88] and Apo-E protein [89]. HtrA1 is also upregulated in inflammatory diseases such as osteoarthritis and rheumatoid arthritis.

HtrA1 belongs to the serine peptidase family and is composed of 4 distinct protein domains: an Insulin-like growth factor binding domain (IGF-BD), a Kazal-type motif (KM), a trypsin-like peptidase (proteolytic) domain, and a PDZ domain. Majority of HtrA1 is found in extracellular space, and signal peptide in the N-terminus of the protein is essential for both the expression and the secretion of the HtrA1 protein. Secreted HtrA1 is involved in the homeostasis of the ECM. The remaining fraction localizes to the cytoplasm, microtubules and nucleus.

Degradation of divergent ECM proteins

HtrA1 has been shown to promote degradation of a substantial number of ECM components, such as fibronectin, type III collagen, decorin, aggrecan. ECM proteins. HtrA1 is able to proteolytically degrade apoE4. Protein fragments or aggregates that are produced or degraded by HtrA1 either cause disease or modulate disease. It may also be possible that proteolytic cleaved fragments of extracellular proteins may possess biological activities and HtrA1 is involved in this process [90]. Interestingly, a recent study demonstrated thrombospondin-1 is a substrate for HtrA1, and proteolytically released fragment of thrombospondin-1 promotes tube formation by endothelial cells [91]. Moreover, independent of catalytic activity, secreted HtrA1 inhibits transforming growth factor (TGF)-β/BMP signaling pathways by interacting with their receptors and inhibit Wnt pathway by interacting with β-catenin [92].

Degradation of growth factors

HtrA1 also degrades growth factors such as insulin-like growth factor-binding protein 5 (IGF-BP-5), fibroblast growth factor-8 (FGF8) and TGF-β, [93] thereby functioning as an antagonist. Conversely, macrophage inhibitory factor was also shown to interact with HtrA1 and inhibit the proteolytic activity of HtrA1 [94].

Intracellular HtrA1 and tubulins

Intracellular HtrA1 is localized to microtubules in a PDZ domain-dependent, nocodazole-sensitive manner and promotes polymerization of microtubules. Downregulation of HtrA1 attenuates cell migration [95]. The microtubule-associated protein tau aggregates into intracellular neurofibrillary tangles. HtrA1 has recently been reported to have a non-proteolytic activity that enables it to disentangle Tau neurofibrillary tangles, suggesting that it can regulate the levels and aggregation of Tau. In the RPE, intracellular HtrA1 regulates degradation of tubulin [96]. Using RPE monolayer culture, the investigators also found degradation of tubulin results in impairment of phagocytotic activity of RPE cells [96].

Functions of HtrA1 in the context of CNV

Despite a number of in vitro studies, the functions of HtrA1 in vivo remain largely unknown. A recent study has demonstrated there is a prominent immune complex deposition, complement activation, and infiltration of inflammatory cells in mice showing severe PCV phenotype [97]. A HtrA1 inhibitor was ineffective in treating existing lesions, but anti-inflammatory glucocorticoid was effective in preventing PCV progression. We conclude that PCV initiation is caused by ECM protein-mediated proteolytic degradation due to increased HtrA1 activity while progression is driven by chronic inflammation. It is unclear whether HtrA1 upregulates VEGF expression, with studies showing upregulation in *HtrA1* transgenic mice [86] and decreased expression in *HtrA1* knockout mice [98] whereas other studies showing no change using *HtrA1* transgenic mice [87], suggesting upregulation of VEGF, if any, is not direct consequence of overexpressed HtrA1, but is probably due to secondary events after progression of the disease. A recent study using human induced pluripotent stem cells (iPSCs)-derived RPE cells from patients diagnosed with AMD showed that iPSC-derived RPE cells expressed AMD-related proteins and those from the AMD donors had significantly increased complement and inflammatory factors, which are most exaggerated in HtrA1 lines [99], supporting the hypothesis that HtrA1 is associated with chronic inflammation. Mechanistically, the degradation of the elastic layer is likely caused by elastase activity of HtrA1; [86] however, another study failed to detect any elastase activity of HtrA1 [87]. It is also possible that increased fibronectin fragments, that are degraded by HtrA1, stimulate the release of cytokines and matrix metalloproteases from the RPE [87]. With conflicting evidence of the effects of

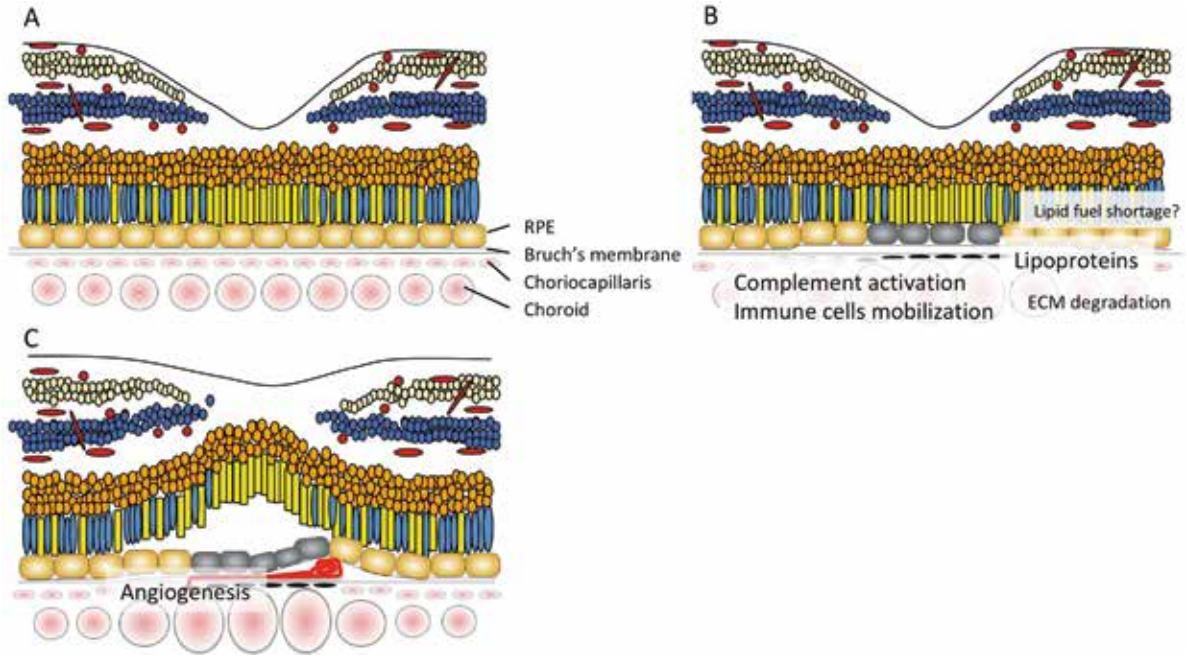

Fig. 6 Pathology of PCV. **a** Normal retina. **b** Lipoproteins accumulate in Bruch's membrane, however, soft drusen are less frequently observed in eyes with PCV compared to those with typical AMD. Although complement pathway molecules are found in drusen in the context of typical AMD, its activation typically takes place in the choriocapillaris when drusen are absent. Activation of complement pathway molecules, and matrix metalloproteases and serine proteases, HtrA1 degrade ECM. Subsequent macrophage mobilization exacerbates inflammation. **c** Breakdown of Bruch's membrane takes place before inward progression of abnormal blood vessels occurs. Angiogenesis is driven by macrophage and RPE derived VEGF, iNOS, FDG6, and other cytokines

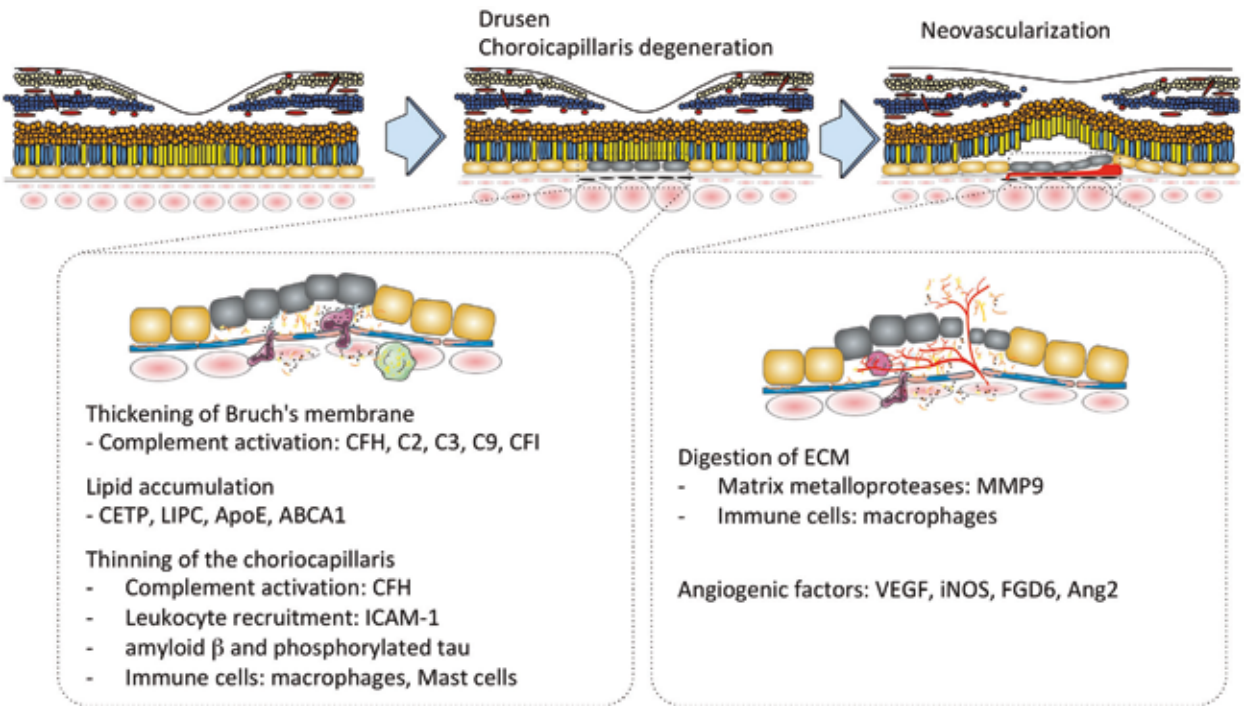

Fig. 7 A proposed pathogenic model of PCV is represented here. Degradation of the choriocapillaris and Bruch's membrane, which can be initiated by complement activation, leukocyte recruitment and inflammatory mediator lead to thinning of the choriocapillaris and dilated choroidal vessels may be one of the underlying mechanisms responsible for PCV

HtrA1 on VEGF levels and other inflammatory mediators on AMD, it remains to be confirmed by future studies in the pathogenesis of AMD.

Future directions

A pathogenic model of PCV described in this review is summarized in Figs. 6 and 7. Degradation of the choriocapillaris and Bruch's membrane, which can be initiated by matrix metalloproteases and serine proteases, HtrA1, that leads to thinning of the choriocapillaris and dilated choroidal vessels may be one of the underlying mechanisms responsible for PCV. Further studies are necessary to understand how and why typical AMD and PCV are different. We also need to understand how immune systems in the choroid change with aging and disease. Specific areas that need to be developed to understand the molecular basis of PCV include a comprehensive understanding of the functions of genes associated with PCV risk focusing more on the choroid. Continued work using animal models would provide a more accurate and detailed picture of how inflammation, angiogenic factors and lipid metabolism contribute to PCV pathogenesis. Although *HtrA1* transgenic mice do not fully replicate all of the robust phenotypes seen in humans, the *HtrA1* transgenic mouse model provides the best opportunity to investigate the pathogenesis of PCV and may have advantages over human samples in terms of genetic simplicity and limited influence of environmental factors.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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REVIEW ARTICLE

传染性葡萄膜炎：亚洲视角

摘要

眼内感染的临床表现多种多样，是目前诊断和治疗的主要挑战。结核病，登革热和基孔肯雅热感染仍是亚太地区与葡萄膜炎相关的主要地方性疾病。这些感染临床需要高度重视和实验室检查，包括眼部液体和或组织检查以确诊。由结核病，登革热和基孔肯雅病引起的传染性葡萄膜炎可能具有一些特征性的临床表现和特殊的影像学表现，这些都可为早期诊断提供线索。现代成像技术的应用，包括光学相干断层扫描增强深度成像模式、光学相干断层扫描血管造影和超广角眼底成像，极大地提高了诊断和评估传染性葡萄膜炎准确性。在这篇综述中，我们讨论了由结核病，登革热和基孔肯雅热引起的葡萄膜炎的流行病学，临床表型，影像学特征以及诊断和治疗。

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The ROYAL COLLEGE of OPHTHALMOLOGISTS

REVIEW ARTICLE

Infectious uveitis: an Asian perspective

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Abstract

Several intraocular infections can present with protean manifestations posing major diagnostic and management challenges. Infections such as tuberculosis, dengue and chikungunya fever have continued to remain major endemic diseases that are associated with uveitis in the Asia Pacific region. These entities often require a high index of clinical suspicion and laboratory analysis including assays of ocular fluids and/or tissues for confirmation of the diagnosis. Infectious uveitis caused by tuberculosis, dengue and chikungunya can present with characteristic clinical features and imaging findings on ancillary investigations; that may provide clue to the early diagnosis. Use of modern imaging modalities such as enhanced-depth imaging optical coherence tomography, optical coherence tomography angiography and ultra-wide field fundus photography greatly aid in the evaluation of these conditions. In the current review, we have discussed the epidemiology, clinical phenotypes, imaging characteristics, diagnosis and management of uveitis caused by tuberculosis, dengue and chikungunya.

Introduction

A number of infectious agents, including a host of bacteria, viruses, fungi, and parasites lead to ocular inflammation with development of various chorioretinal manifestations. These infections are especially common in Asia Pacific countries and other developing countries of the world, unlike western countries where autoimmune uveitis is the most common form [1–3]. An early diagnosis is imperative for the initiation of specific therapy that would help in preventing the severe visual loss.

Since several decades, tuberculosis (TB) has remained endemic in Asian countries with India, with a large population size, accounting for nearly 20% of the global tuberculosis burden. TB is also common in other countries of the Pacific region (Singapore, Malaysia, Bangladesh, and Nepal, among others), and Island countries such as Fiji [4–7]. Currently, the diagnosis of TB uveitis is a conundrum because the only way to determine tubercular etiology is using a conglomerate of clinical signs, radiologic findings, and immunologic tests.

Certain viral infections such as dengue and chikungunya are highly endemic in the Asia Pacific countries. This may be attributed to the conducive weather and abundance of the arthropod vectors in this part of the world [8–11]. Due to various contributory factors such as overcrowding, lack of hygiene, excessive rainfall, and poor outreach measures, frequent outbreaks of dengue and chikungunya fevers are common especially in the monsoons. The most common clinical presentation of these viral illnesses is development of high-grade fevers, rash, arthralgia, low platelets, and muscle/bone pain. However, both dengue and chikungunya may result in severe sight-threatening ocular inflammation that may lead to permanent visual disability.

In this index review, infectious uveitis (namely TB, dengue, and chikungunya) that continue to plague Asian countries have been described. A brief update on the epidemiological patterns of these conditions, along with their clinical features, imaging characteristics, and management has been provided. Illustrative case examples have been provided to give the reader insights into the challenges encountered while managing these patients.

Intraocular tuberculosis

TB is a leading infectious cause of morbidity and mortality and Asian countries such as India and China contribute significantly toward the global disease burden. TB has been

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declared as a global emergency by the World Health Organization (WHO). Nearly one-third of the world's population is infected by *Mycobacterium tuberculosis* [5–7]. Intraocular TB (IOTB) represents an extrapulmonary form of the disease. Therefore, though rare, IOTB is an important cause of uveitis in both developed and developing countries.

An update on epidemiology of tuberculosis in Asia

TB is highly prevalent in Asian countries. Estimates by the WHO suggest that 4.9 million prevalent cases (one-third of the world's burden of TB) are found in the South-East Asia Region. High number of cases, including extensively drug-resistant TB have been reported from Bangladesh, India, Indonesia, Myanmar, and Thailand [12]. The WHO statistics for India for 2016 give an estimated incidence of 2.79 million cases of TB. India also has more than a million "missing" cases every year that are not notified and most remain either undiagnosed or unaccountably and inadequately diagnosed and treated in the private sector [13].

Based on the diagnostic criteria used, the incidence of IOTB in India has varied from 0.6% of all uveitis patients in South India (1995) [14] to 10.1% in North India (2004) [15]. In 2017, a report from a major tertiary care center in North India reported that 23% cases of infectious uveitis were attributed to TB [16]. This finding was supported by a study from South India in the same year [17]. Similarly, in Sri Lanka, IOTB was responsible for significant number of patients with posterior uveitis (11%), intermediate uveitis (8%), and panuveitis (11%) [18]. In Philippines (2017), IOTB accounts for more than 25% cases of infectious uveitis, more common than toxoplasmosis. Taiwan reported TB as the most common cause of infectious uveitis (9%) [19]. A study from Singapore also reported that TB was the most common cause of panuveitis, especially among Malays and Indians [20].

TB also forms an important cause of infectious uveitis in children. In a study on pediatric uveitis from North India, TB was identified in 15% cases of infectious uveitis [21]. Out of 20 children diagnosed with intermediate uveitis from South India, 9 were diagnosed with TB in 2017 [22].

Clinical presentation of intraocular tuberculosis

The choroid is the most commonly affected structure in IOTB. Posterior uveitis is the most common form of involvement in IOTB [4, 23, 24]. It is well known that IOTB can have protean clinical manifestations leading to a diagnostic challenge. It can have varied presentations such as granulomatous uveitis and may mimic several inflammatory and non-inflammatory conditions such as tumors, macular degeneration, as well as non-infectious autoimmune uveitic entities [13]. Moderate to severe visual impairment can occur in 42% patients with IOTB, especially in cases of posterior and panuveitis. Therefore, it is relevant to understand the common clinical presentations of the disease.

Selected observations from the COTS-1: The Collaborative Ocular Tuberculosis Study-1 (COTS-1) is a recently completed multicenter retrospective collaborative study between 30 uveitis centers across the world with participation of more than 40 uveitis experts around the world. COTS-1 was a big data analysis that studied the current practice of IOTB worldwide. The study consisted of 962 patients most of whom were of Asian ethnicity (74.4%) [11]. The broad aims of the study were as follows: to determine the global epidemiological profile of IOTB; how do experts diagnose and manage IOTB; what are the treatment outcomes of IOTB.

A total of 945 patients (1485 eyes) diagnosed with IOTB from 2004 to 2014 were included in this study. The COTS-1 showed that individuals with Asian ethnicity (both native and immigrants) are at a high risk of developing features of IOTB. Based on the anatomical location of uveitis, COTS-1 report showed that TB serpiginous-like choroiditis (which represents one of the most characteristic manifestation of the disease) was the most prevalent phenotype in the Asia Pacific region, whereas it was much less prevalent in the West [25]. The common phenotypic variants reported with IOTB included SLC (46.1%), choroidal tuberculomas (13.5%), and multifocal choroiditis (9.4%) [25]. Presumed TB retinal vasculitis was seen in 251 out of 945 patients, most commonly Asians (71%) [26].

The following section summarizes the various forms of IOTB and highlights their clinical and imaging features.

Choroidal tubercles

Choroidal tubercles are the most common clinical manifestations among patients with systemic TB [23, 27]. Choroidal tubercles form as a result of hematogenous dissemination of the bacilli from pulmonary and other extrapulmonary sites. These tubercles may be unilateral or bilateral, solitary, or multiple (but usually ≤5 in number), discreet grayish-white to yellowish subretinal lesions with indistinct borders. Choroidal tubercles are usually located in the posterior pole or mid-periphery [27].

On fluorescein angiography (FA), choroidal tubercles are hypofluorescent in the dye transit and become hyperfluorescent in the late frames. Optical coherence tomography (OCT) is useful in confirming the presence of a choroidal tubercle.

Choroidal granulomas/subretinal abscess

Solitary large choroidal granuloma may present as an elevated yellowish subretinal mass lesion with exudative

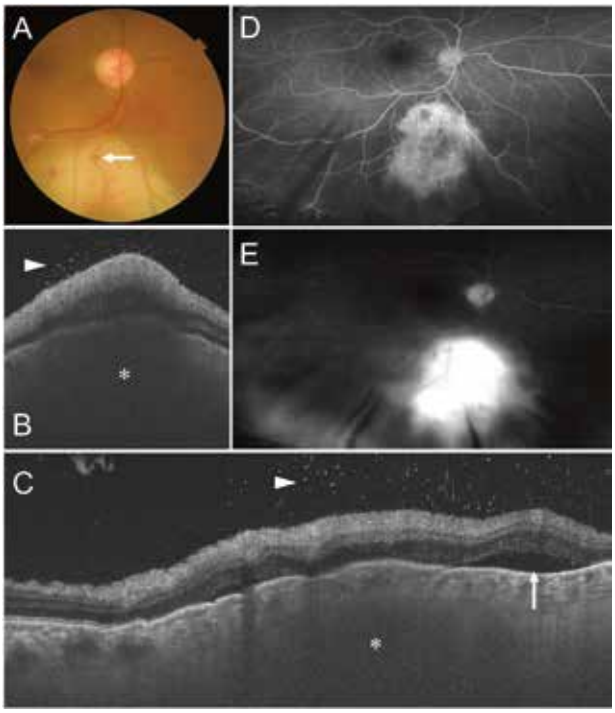

Fig. 1 Figure shows multimodal imaging of a 55-year-old female who presented with diminuition of vision in the left eye. There was presence of a large subretinal lesion with overlying hemorrhages (white arrows) and exudative fluid (**a**). Swept-source optical coherence tomography (SS-OCT) (**b**) B-scan passing through the lesion showed a large choroidal granuloma (asterisk), retinal edema, as well as vitritis (arrowhead). Another OCT B-scan shows presence of retinal pigment epithelial elevation due to choroidal granuloma (asterisk), vitreous cells (arrowhead), and subretinal fluid (white arrow) (**c**). Fluorescein angiography (FA) in the early phase showed early hyperfluorescence with areas of blocked fluorescence due to overlying hemorrhages (**d**). In the late phase, FA showed intense hyperfluorescence with peripheral leakage suggestive of an inflammatory choroidal lesion (**e**). The patient was diagnosed with tubercular choroidal granuloma due to positive laboratory tests

retinal detachment and fluid (Fig. 1). A choroidal granuloma may clinically resemble non-inflammatory conditions such as central serous chorioretinopathy, choroidal metastases, melanoma of the choroid, and other non-uveitic entities such as age-related macular degeneration [4, 23, 27, 28]. The subretinal abscesses are more yellowish in color than a small choroidal granuloma and may have overlying retinal hemorrhages [29].

On FA, the lesions show early hypofluorescence and late hyperfluorescence. There may be blocked fluorescence due to the overlying hemorrhages. On ICGA, subretinal abscesses appear hypofluorescent throughout the early as well as late phase [30–32]. OCT is useful in detecting exudative retinal detachment associated with choroidal granulomas [28, 33]. Enhanced-depth imaging OCT (EDI-OCT) shows choroidal changes that correlate well with the findings on indocyanine green angiography (ICGA). A recent study showed that all choroidal granuloma lesions generated an increased transmission of the OCT signal towards the sclera [34]. Compared with small lesions, large granulomas were more likely to be full-thickness, round-shaped, with defined margins, lower reflective than the surrounding structures, and with a homogenous internal pattern. Granulomas in patients affected by TB-related uveitis were more likely to have a lobulated shape and non-homogeneous internal pattern [34, 35].

Serpiginous-like choroiditis

Tubercular serpiginous-like choroiditis (TB SLC) is a characteristic entity which is very common among young to middle-aged adults from TB-endemic areas in the Asia Pacific region [23, 36, 37]. TB SLC was first described by Gupta et al. in 2003 in 11 eyes of 7 patients. All the patients in the series had strongly positive tuberculin skin test and lesions on chest radiography. For the first time, the authors concluded that these lesions showed a good response to anti-tubercular therapy [38]. Following this report, there were several reports from different parts of the world that associated SLC with TB [39–41]. In a recently published report, *Mycobacterium tuberculosis* DNA was isolated in an Asian Indian male with SLC lesions on vitreous biopsy. Chorioretinal biopsy sample showed granulomatous inflammation with central choroidal necrosis and disruption of the outer retina/retinal pigment epithelium [42].

TB SLC can be distinguished from autoimmune garden variety of choroiditis by its subtle differences. Unlike autoimmune serpiginous choroiditis, TB SLC occurs at a younger age, can be associated with mild vitritis and is commonly bilateral. It may have different morphological patterns:

1. *Multifocal pattern*: This pattern is characterized by the presence of multifocal discreet lesions that are yellowish-white in color, measuring a maximum of one disc diameter in size with well-defined margins and slightly raised edges [36]. These progress over a few weeks and gradually become confluent (Figs. 2 and 3) [36, 43].
2. *Placoid pattern*: The diffuse placoid pattern of TB SLC presents with a large plaque-like lesion and an active serpentine edge [44]. The edges are yellowish and elevated whereas the center of the lesion is less elevated with pigmentary changes. This pattern suggests healing process in the center of the lesion with activity in the periphery of the lesion. Choriocapillaris atrophy is commonly seen in the center of the lesion with visible underlying choroidal vessels [36, 43].

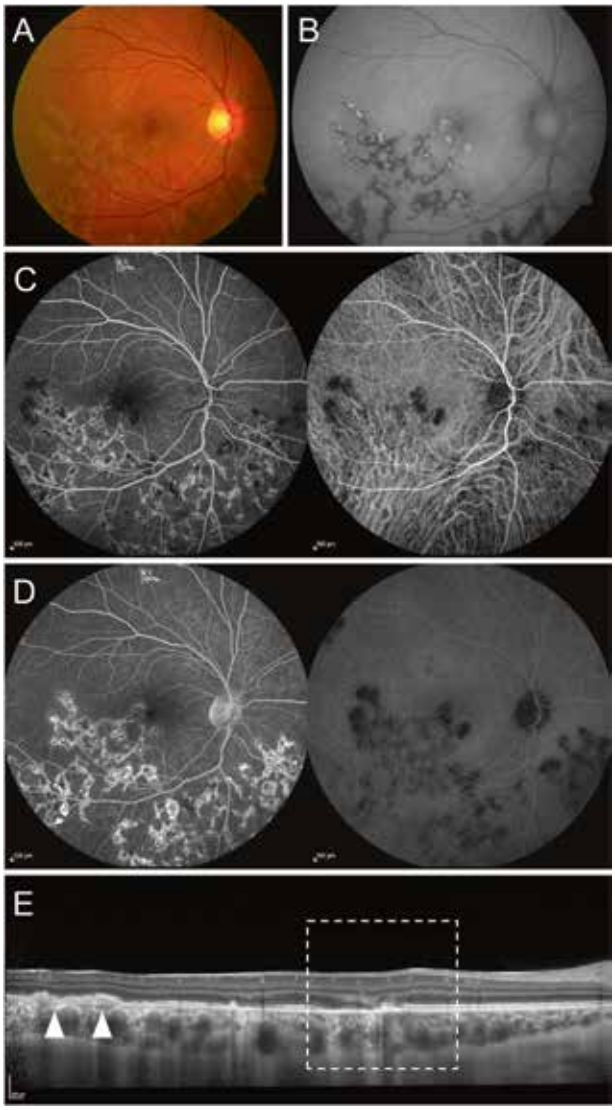

Fig. 2 Fundus photograph of a patient with tubercular serpiginous-like choroiditis (TB SLC) shows presence of yellowish serpentine choroiditis lesions in the posterior pole with fuzzy edges and ill-defined margins (**a**). The autofluorescence imaging shows mixed hyper-autofluorescent (within the lesion) and hypo-autofluorescence of the lesions suggestive of activity (**b**). Early phase of the combined fluorescein angiography (FA) and indocyanine green angiography (ICGA) shows hypofluorescence of the active lesions (**c**), and in the late phase (**d**), the lesions are hyperfluorescent on FA and continue to remain hypofluorescent in the ICGA. The optical coherence tomography (dense scan) passing through the choroiditis lesions show outer retinal disruption (white arrowheads), choriocapillaris ischemia, and disruption of the photoreceptor layer (white dashed square) (**e**)

3. *Mixed pattern*: This pattern of TB SLC presents with overlapping features in opposite eyes.

Imaging features of TB SLC

Fluorescein angiography and indocyanine green angiography: There is a uniform agreement in the literature on the appearance of active and inactive lesions of TB SLC on FA and ICGA. Multifocal TB SLC lesions are hypofluorescent in the early phase with late hyperfluorescence on FA. The advancing edge of the lesions may show early hypofluorescence with late hyperfluorescence. On the other hand, in placoid TB SLC lesions, the center of the lesion shows mixed hyperfluorescence while the advancing edge shows early hypofluorescence with late hyperfluorescence on FA. On ICGA, both the lesions remain hypofluorescence from early to late phase during the active stage [36, 43, 45, 46].

Fundus autofluorescence (FAF) features of TB SLC: FAF features of TB SLC are relevant in the understanding of the healing patterns of the disease. Based on the FAF appearance of the lesions, our group has shown that in the early active disease, the lesions appear predominantly hyper-autofluorescent on FAF (stage 1). With progressive healing, FAF shows a combination of hypo- and hyper-autofluorescence signals, where the distinct hypo-autofluorescent (inactive) rim surrounds the hyper-autofluorescent (active) center (stage 2). As the healing process continues, there is a progressive increase in the hypo-autofluorescence of the lesion with an intermixed hyper-autofluorescent stippled pattern (stage 3). A resolved fully resolved/healed lesion shows uniform hypo-autofluorescence (stage 4) [45, 47, 48].

A case report by Gupta and Biswas in 2014 [49] defined a sequential pattern of FAF during the entire course of TB SLC, i.e., evolution, progression, and healing. In the evolution phase, they showed that the lesions were hyper-autofluorescent. They also noticed faint hyperautofluorescence extending over a large area that was predictive of future extent of the lesion. The authors defined progression when the advancing edge showed more hyper-autofluorescence. During healing, there was sharpening of hyper-autofluorescent borders, and few specks of hyper-autofluorescence were seen within the hypo-autofluorescent lesion [49]. Piccolino et al. also described similar FAF features; however, they suggested that even early active lesions of TB SLC may have hypo-autofluorescence within the lesion [50]. Carreno et al. have described a similar pattern of FAF findings in TB SLC: active inflammation, transitional, and inactive inflammation characterized by increasing hypo-autofluorescence as the lesions begin to heal [51].

In a study by Khanamiri and Rao, during the active stage, the authors have stated that there may be no FAF abnormalities in the first 1–2 days after clinical presentation. Subsequently, acute lesions show hyper- and hypoautofluorescence patches with sharp margins. After 2 weeks, the lesions show granular/speckled pattern of autofluorescence. Healed lesions appear uniform hypo-autofluorescent [46].

Ultra-wide field imaging of TB SLC: The relatively new ultra-wide field (UWF) imaging technique allows 200

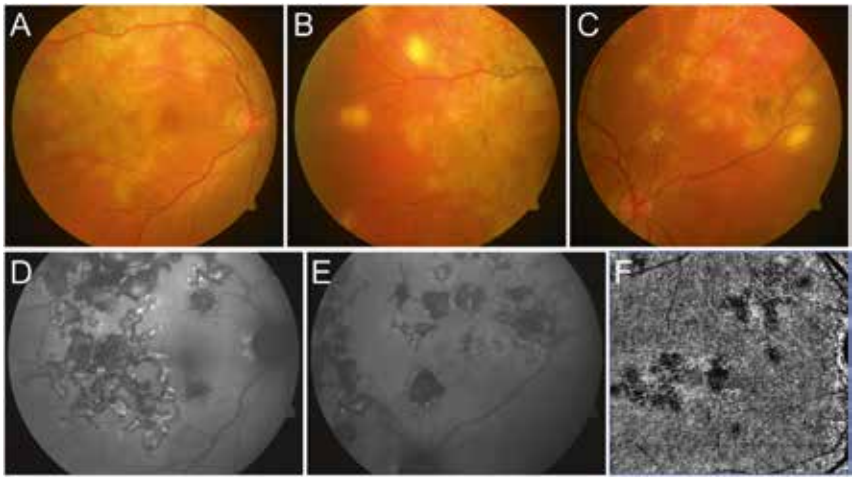

Fig. 3 Figure shows fundus imaging of a 35-year-old Asian Indian male who presented with characteristic choroidal lesions in the right eye. Fundus photographs (**a**–**c**) shows presence of multiple yellowish-white multifocal choroiditis lesions with fuzzy appearance, ill-defined margins and early pigmentary changes suggestive of active serpiginous-like choroiditis. The patient had a necrotic tuberculin skin test and few subcentimetric lymph nodes in his chest. Fundus autofluorescence imaging (**d**, **e**) shows hyper-autofluorescence within the lesions along with hypo-autofluorescence of the superior lesions. Optical coherence tomography angiography en face scan passing through the choriocapillaris slab (**f**) shows presence of dark flow deficit areas suggestive of choriocapillaris hypoperfusion, which is seen in active tubercular choroiditis

degrees of the retina to be captured in a single image thereby allowing simultaneous capture of all retinal lesions in a single frame. As shown by Aggarwal et al., UWF imaging is a very useful tool in the management of IOTB as it helps to capture peripheral areas of retinal non-perfusion, active retinal vasculitis, neovascularization, and choroiditis lesions which would otherwise be missed on conventional fundus imaging [52–54]. UWF imaging revealed additional TB SLC lesions in 39 out of 44 eyes (88.6%) compared to conventional imaging. It has been shown to provide additional information in 90.9% of the eyes with TB posterior uveitis and affected management decisions in over 45% of the eyes [52].

OCT features of TB SLC: Various studies have shown the role of OCT in detecting retinochoroidal changes in TB SLC. In the active stage of the disease, OCT B-scans passing the active edge of TB SLC lesion show a localized, fuzzy area of hyperreflectivity in the outer retinal layers involving the RPE, ellipsoid and myoid zone, external limiting membrane (ELM), and the outer nuclear layer (ONL) with no increased backscattering from the inner choroid. As the lesions heal, there is disappearance of the hyperreflective fuzzy areas which are replaced by irregular, hyperreflective knobbly elevations of the outer retinal layers. The RPE, ellipsoid and myoid zones, and the ELM cannot be distinguished at this stage [24, 43, 45, 55].

Rifkin et al. have shown that EDI-OCT is very useful in detecting active choroidal infiltration with RPE elevation in patients with TB SLC. The authors proposed that this finding may be useful in distinguishing TB SLC from the autoimmune garden variety of serpiginous choroiditis [56].

OCT angiography in TB choroiditis: The novel technique of OCT angiography has recently shown novel findings that greatly aid in understanding the pathology and sequelae of chorioretinal changes in TB SLC. OCT angiography provides high-resolution imaging of the choriocapillaris in different stages of this disease. In the acute stage, Mandadi et al. have shown alterations in choriocapillaris flow (flow deficit) that may progress to atrophy during the inactive stage (Fig. 3). Morphologic information obtained from OCT angiography images correlates well with and supplements other imaging techniques such as ICGA and EDI-OCT [57].

Recently, OCT angiography has also been shown to be useful in detecting novel type 1 choroidal neovascular (CNV) lesions among patients with TB SLC. Aggarwal et al. demonstrate that type 1 CNV can lead to significant visual loss even in the healed stages of the disease. OCT angiography is useful even in cases where conventional multimodal imaging, including FA and OCT, fail to make a definitive diagnosis [58].

Presumed tubercular retinal vasculitis

Presumed TB retinal vasculitis is characterized by peripheral occlusive retinal periphlebitis with inflamed retinal vessels and features of distal retinal ischemia such as cotton-wool spots or lack of blood flow on fundus imaging. TB vasculitis can present with sequelae such as peripheral retinal neovascularisation and recurrent vitreous hemorrhage leading to tractional retinal detachment and/or macular scarring. This condition may mimic other causes of retinal vasculitis such as other infective causes

(toxoplasmosis, viral retinitis, syphilis, toxocariasis, among others) and non-infective causes such as birdshot chorioretinopathy, systemic vasculitides, among others [26, 59, 60].

Eales' disease is a condition characterized by occlusive vasculitis and development of retinal neovascularization. Biswas et al. have been instrumental in providing an update on the current understanding and etiopathogenesis of this condition [61, 62]. Eales' disease is presently thought to be due to hypersensitivity reaction to tubercular proteins. In a study, significant number of patients operated for epiretinal membrane were positive for Mycobacteria when tested by polymerase chain reaction (PCR) [63]. Verma et al. have shown presence of *Mycobacterium tuberculosis* DNA in an enucleated eyeball using nested PCR technique [64]. More recently, our group has shown that *Mycobacterium tuberculosis* genome was present in more than 50% vitreous fluid samples of patients with Eales' disease with a significant bacillary load [65]. Therefore, there is increasing evidence that Eales' disease could indeed represent TB vasculitis especially in endemic Asian countries, and these patients must be thoroughly investigated for evidence of TB infection in the body [61].

There is no definitive method of establishing TB as the etiology of retinal vasculitis. Therefore, these cases are considered to be *presumed* tubercular in nature. Usually, the diagnosis of TB retinal vasculitis is suspected by the treating uveitis experts by considering various clinical, immunological, and radiological criteria, and excluding other infectious and non-infectious known etiologies [26, 66, 67]. Among individuals with Asian ethnicity, majority of the patients with TB retinal vasculitis will present with an occlusive disease. It is pertinent to note that most Caucasian patients may not have an occlusive disease [26]. Such differences may be related to the genetic differences (e.g., HLA) between these ethnicities of patients.

While there is a lack of consensus on the diagnostic criteria and management of TB retinal vasculitis, this condition has shown good anatomic and visual response with prompt ATT and/or steroid therapy in smaller studies [59, 68].

Unusual clinical phenotypes

Rarely, in endemic countries, IOTB may present with uncommon phenotypes such as panophthalmitis and endophthalmitis, which may mimic as ocular tumors [69, 70]. Tuberculous optic neuropathy is also uncommon, and may manifest as papillitis, neuroretinitis, and optic nerve tubercle [71–73]. Optic nerve head tubercle may present as an elevation at the optic nerve head with surrounding exudation and fluid. Choroidal involvement in IOTB may also have rare phenotypic presentations. In the COTS-1, IOTB was diagnosed in patients with ampiginous choroiditis, acute posterior multifocal placoid pigment epitheliopathy (APMPPE), and other types of choroiditis that did not fit into any of the classical descriptions [25]. Such forms of choroidal involvement in IOTB has not been previously reported.

TB panuveitis may be confused with other forms of granulomatous panuveitis. Many patients may require extensive clinical, laboratory, and imaging workup, including invasive microbiological and histopathological evidence in order to establish a diagnosis. In a case report published by our group in 2016, we describe a monocular Asian Indian female who presented with significant panuveitis which was misdiagnosed as sympathetic ophthalmia. The correct diagnosis could be established only when the non-seeing phthisical fellow eye was enucleated and careful histopathological examination revealed presence of acid-fast bacilli (AFB) on Ziehl–Neelsen staining, tubercular granulomas, and the sample tested positive for TB on PCR [74].

It must be kept in mind that in rare phenotypic presentations, the diagnosis of TB may be presumptive, based on a constellation of clinical, radiological, and laboratory findings. It must be emphasized that in a lot of patients, unequivocal evidence of the infection is often unavailable.

Diagnosis of intraocular tuberculosis

The diagnosis of IOTB is indeed challenging. Till date, there are no randomized controlled trials that have defined the diagnosis of IOTB. Furthermore, there are no consensus guidelines amongst the uveitis experts world over regarding the diagnosis of IOTB. The criteria that have been applied for diagnosing IOTB by various studies include [4, 23, 45, 75]:

1. Clinical signs suggestive of IOTB including:
    a. *Anterior uveitis*: Granulomatous or non-granulomatous, iris nodules, ciliary body granuloma.
    b. *Intermediate uveitis*: Granulomatous or non-granulomatous with exudates in the pars plana or peripheral uvea, with/without snow balls.
    c. *Posterior and Panuveitis*: choroidal tubercle, choroidal granuloma, subretinal abscess, serpiginous-like choroiditis.
    d. Other features such as retinal vasculitis, neuroretinitis, optic neuritis, endophthalmitis, panophthalmitis, scleritis.
2. Exclusion of other uveitic entities based on clinical manifestations of disease and regional epidemiology.

3. Investigations documenting the mycobacteria or its genome:

    a. Demonstration of AFB by microscopy or culture of *Mycobacterium tuberculosis* from ocular fluid
    b. Positive polymerase chain reaction from ocular fluid for IS 6110 or other conserved sequences in mycobacterial genome
    c. Evidence of confirmed active extra-pulmonary TB (by microscopic examination or culture of a tissue sample from the affected tissue)

4. Corroborative investigations such as:

    a. Positive Mantoux test
    b. Interferon Gamma Release Assay (IGRA) such as QuantiFERON TB Gold
    c. Evidence of healed or active TB on chest radiography

There is no single gold standard test available for diagnosing IOTB. Tests such as Mantoux test and interferon gamma release assays may be highly positive in some centers (especially in Asian countries) due to endemicity of TB in the region. Therefore, it is necessary to develop a prospectively derived clinical risk score that will help to improve the diagnosis and management of IOTB.

Therapies for intraocular tuberculosis

Standard therapy for intraocular tuberculosis

Anti-tubercular therapy (ATT) consists of a combination of four drugs namely isoniazid, rifampin, ethambutol, and pyrazinamide. These four agents constitute the first-line agents and are started empirically in patients with systemic TB. The four agents are given in the following doses: isoniazid (5 mg/kg/day), rifampicin (10 mg/kg/day), ethambutol (15 mg/kg/day), and pyrazinamide (20–25 mg/kg/day) along with pyridoxine (vitamin B6) (10 mg/day).

In 2008, Bansal et al. reviewed the role of ATT in the treatment of active TB uveitis in a large retrospective interventional series ($n = 360$). In this study, the authors observed that among the 216 patients who received ATT, the recurrences of uveitis substantially decreased compared to 144 patients who did not receive ATT (15.74% versus 46.53%; $p < 0.001$). Therefore, the authors speculated that since the disease occurs due to a hypersensitivity reaction, ATT may have an important role in treating latent TB infection in the body, eliminating future recurrences of IOTB [76]. While the study by Bansal et al. was performed in a highly endemic region of world for TB, i.e. India, Agrawal et al. published a retrospective study highlighting the role of ATT in a low endemic country (UK) in 2015. In this study, patients who received long-term treatment with ATT showed reduced recurrence of the disease [77].

In 2016, a major review and systematic analysis of 28 studies (a total of 1917 patients) published by Kee et al. reviewed the role of ATT for IOTB. The study results showed that among patients who received ATT, the non-recurrence of inflammation was observed in pooled estimate of 84%. While the study results showed benefit of ATT in reducing recurrences, there were limitations due to lack of a control group and non-standard recruitment and treatment criteria [78].

The standard therapy for IOTB as per the recommended guidelines consists of four drug regimen mentioned above. Ethambutol and pyrazinamide are stopped after a period of 2 months. There is regular monitoring of liver function tests when a patient is started on ATT.

Thus far, there is no definite guideline on the duration of ATT in patients with IOTB. Agrawal et al. have shown beneficial results in patients who receive ATT for ≥9 months [77]. In a study from Singapore by Ang et al., 186 patients with IOTB were included, of whom 46 received more than 6 months of ATT. The authors showed that patients who completed >9 months ATT were less likely to develop recurrences compared with those not treated with ATT ($p = 0.027$) [79]. Till date, however, there is no common consensus among uveitis experts regarding the regimen and duration of ATT, as shown in the COTS-1 study [25].

Managing inflammation in intraocular tuberculosis—oral corticosteroids

There is no uniform recommendation regarding the use of concomitant corticosteroids along with ATT in IOTB. Corticosteroids are employed to reduce the intraocular inflammation since IOTB is hypothesized to occur due to type IV hypersensitivity reaction to tubercular proteins. Oral corticosteroids may also play a role in reducing inflammatory macular edema [80]. However, unlike in the case of meningeal and pericardial TB where there are clear guidelines supporting the use of systemic corticosteroids, their use in IOTB is considered to be controversial by certain authors [81].

Various series have reported the use of oral corticosteroids along with ATT as a combination (oral prednisolone 1 mg/kg/day) for IOTB with favorable control of inflammation [23, 36, 37, 68, 76, 77, 82]. Corticosteroids can be tapered over the next 6–12 weeks depending upon the severity of inflammation and occurrence of paradoxical worsening of the disease [83]. Certain authors favor the use of corticosteroids only when the lesions are involving or threatening the macula in order to decrease macular scarring [84].

Paradoxical worsening

One of the most clinically intriguing features of TB SLC is the paradoxical worsening of the disease after initiation of anti-tubercular therapy (ATT). The worsening of these lesions occurs due to a combination of factors including enhanced delayed hypersensitivity of the host, decreased suppressor mechanisms, and increased exposure to the mycobacterial antigens or a response to mycobacterial antigens such as tubercular proteins [37, 85, 86]. Cheung and Chee have described a case of a 77-year-old woman with biopsy-proven TB cervical lymphadenitis who developed choroiditis in one eye after initiation of ATT. The authors identified mycobacterial DNA from the vitreous tap using polymerase chain reaction, and a diagnosis of paradoxical worsening following ATT was made [87]. In a case series by Basu et al., 4 patients with IOTB (including 1 patient with intermediate uveitis; 1 patient with TB granuloma, and 2 patients with TB SLC) who were started on ATT developed paradoxical worsening (appearance of new lesions or worsening of existing lesions). Therefore, paradoxical worsening is a major challenge in the management of IOTB [82].

With the recent introduction of ultra-wide field (UWF) retinal imaging, the detection rates of paradoxical worsening have significantly increased. Using conventional imaging, paradoxical worsening was reported in 14% patients after 2 to 6 weeks of initiation of ATT [37]. With UWF imaging, paradoxical worsening may be observed in over 36% patients after initiation of ATT [52, 88, 89]. In a series by Agarwal et al., OCT angiography was shown to be very useful in the detection of choriocapillaris alterations in patients of TB SLC developing paradoxical worsening [88]. Patients who develop paradoxical worsening may require increase in the dosage of corticosteroids, or addition of intravenous methylprednisolone pulses. Topical steroids may be employed in cases with anterior segment inflammation. Systemic immunosuppressants and steroid sparing agents such as azathioprine may be added as and when required depending on the discretion of the treating uveitis specialist.

Novel local and systemic therapies

In order to improve the outcomes of IOTB by reducing the systemic corticosteroid-related adverse effects in severe or long-standing inflammation, and address various challenges such as paradoxical worsening of the disease, a number of alternative therapeutic strategies have been tried. Intravitreal injection of depot steroid (dexamethasone implant, Ozurdex ®) has been employed in the management of TB multifocal serpiginoid choroiditis [90, 91]. In a case report by Fonollosa et al., Ozurdex implant was shown to be useful in continuous progression of the lesions despite ATT and oral corticosteroids [90]. Similarly, Jain et al. showed that Ozurdex implant is useful in cases where the disease continues to progress, or there is intolerance to oral corticosteroids [91]. In a larger series by Agarwal et al., 19 eyes of 17 patients with IOTB (including intermediate uveitis, retinal vasculitis, and TB SLC) received Ozurdex implant with favorable resolution of inflammation, and improvement in visual acuity [92].

Intravitreal methotrexate has also been employed in the management of IOTB. In a series by Julian et al., 3 eyes of 2 patients with active presumed TB choroiditis received intravitreal methotrexate due to progressive macular threatening disease. In all 3 eyes, healing of choroidal lesions without any adverse event occurred within 1 month of the injections [93]. Sahin et al. published a similar favorable experience with intravitreal methotrexate in 2 cases of IOTB [94].

Interferons (IFN) are a group of low molecular weight polypeptides secreted by activated immune cells and possess high activity and various functions. IFNs alpha/beta signaling by the retinal pigment epithelium has been linked to high *Mycobacterium tuberculosis* disease activity in patients with active disease, leading to inhibition of the outgrowth of intracellular mycobacteria [95]. In a series of 12 eyes (6 patients) by Invernizzi et al., IFN-alpha 2a was employed in the management of presumed chronic TB uveitis patients in whom the uveitis was recurrent upon tapering of corticosteroids below 7.5 mg/day. The use of subcutaneous IFN-alpha 2a showed good results in all the eyes with resolution of inflammatory signs (vitritis and vasculitis), decrease in retinal thickening, and improvement in visual acuity without any major complications [96]. IFN-alpha 2a has also been used by Oray et al. in 5 patients with presumed IOTB for recurrent cystoid macular edema after completion of ATT. IFN-alpha 2a were shown to be safe and effective in managing macular edema in this series [97].

The challenge in the management of intraocular tuberculosis

Till date, there are no uniform guidelines in the management of IOTB. There are several regional variations in treatment practices for IOTB including the regime, duration of ATT, concomitant use of corticosteroids and immunosuppressive agents (both systemic and local). The treatment in a majority of IOTB cases is directed in consultation with the attending pulmonologist/internist based on guidelines that vary depending on the region of their practice. In the COTS-1 [25], analyses revealed variation in outcomes between different ethnic groups and geographical regions. For instance, the proportion of patients that received treatment with both ATT and corticosteroids was highly variable

between Asia (80.4%), Australia (60.0%), and the West (62.9%). Thus, Asian patients are most likely to receive a combination of ATT and steroids compared to the Western countries. In addition, treatment outcomes on survival analysis were superior in patients of Asian ethnicity.

Dengue fever-associated uveitis

Dengue fever is a mosquito-borne viral illness caused by a flavivirus which has four serotypes. The most common arthropod vector for this condition is *Aedes aegypti*, which is common in tropical and subtropical regions. The mortality and morbidity due to dengue fever has tremendously increased in the tropical and sub-tropical zones of the world. Dengue fever can present with various vitreoretinal manifestations, where inflammation and ischemia are the hallmark features of the disease.

Epidemiology of dengue fever and recent outbreaks in Asia

Dengue is endemic world over in areas such as United States, Southeast Asia, and the Western Pacific. This arthropod borne disease is endemic in more than 100 countries, and is regarded as the most common mosquito-borne disease in humans [98–100]. The first case of dengue fever-related posterior uveitis was in 1979 amongst tourists who returned from dengue-endemic countries. More than 50 million dengue infections are estimated to occur annually throughout the world. Since the beginning of the 21st century, most cases have been reported from the South East Asian countries. There are four serotypes of the dengue virus. In countries such as Singapore, the number of cases have been steadily rising over the last few years [101]. Dengue and related uveitis have been reported from Singapore, Sri Lanka, Thailand, Taiwan, India, Mexico, and Brazil [102–107]. In Malaysia, a total of 101,357 dengue cases and 237 deaths were reported in 2016 [108]. Frequent outbreaks are also reported from Taiwan. From 2007 to 2011, a total of 3,322 confirmed dengue cases were noted in Taiwan, particularly from Kaohsiung city [109]. In 2017, the data from the National Vector Borne Disease Control Program (NVBDCP), India showed the highest number of cases and deaths due to dengue fever [110].

Chorioretinal manifestations of dengue fever

Ocular involvement in dengue may be unilateral or bilateral. Anterior segment features of dengue infection include subconjunctival hemorrhage, keratitis, anterior uveitis, and angle closure glaucoma. Most common posterior segment manifestations of dengue fever include macular edema, hemorrhages, foveolitis, cotton wool spots, and microaneurysms [111–113].

1. *Dengue maculopathy*: Dengue maculopathy is a common posterior segment condition and its incidence may correlate with the severity of systemic disease. Patients with dengue maculopathy may complain of visual symptoms such as blurring or scotomas due to outer retinal involvement [114, 115]. Fundus examination of this condition reveals arteriolar sheathing, cotton-wool spots, microaneurysms, intraretinal cystoid spaces, and macular edema (Fig. 4), perifoveal telangiectasia and intraretinal hemorrhages. There may be presence of well-defined yellowish subretinal lesions in the macular along with retinal striae radiating around the fovea (*foveolitis)*. These lesions may represent disruption of photoreceptors (Fig. 5) [116–120].

Acute macular neuroretinopathy: It is notable that acute macular neuroretinopathy (AMN) has been recently reported to be an unusual manifestation of dengue maculopathy [121, 122]. AMN presents with hyper-reflectivity of the outer retina (outer plexiform layer and outer nuclear layer), and disruption of ellipsoid zone, external limiting membrane (ELM) and inter-digitation zone.

2. *Dengue vasculopathy*: Dengue-related uveitis has been reported to present with retinal vasculitis. Vasculitis may be associated with retinal ischemia, intraretinal hemorrhages, and other manifestations such as branch retinal arteriolar occlusion. Capillary endothelial dysfunction or occlusion of precapillary arterioles due to immune complex deposition may be the likely underlying mechanism of retinal vasculitis in dengue fever [112, 113, 120].

3. *Dengue chorioretinitis*: One of the possible manifestations of dengue posterior uveitis includes chorioretinal involvement presenting with severe vitreous inflammation and exudative retinal detachment. Chorioretinitis may present with single or multiple multifocal lesions involving the macula along with retinal pigment epithelium disturbances. Chorioretinitis may evolve into atrophic perifoveal pigmentary scars (nummular scars). There may be associated

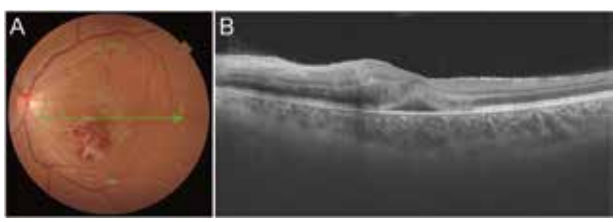

Fig. 4 Fundus photograph of a 23-year-old male who presented with low vision in the left eye 15 days after a severe febrile illness is shown (**a**). The patient was diagnosed with dengue fever based on NS1 antigen test positivity. The platelet nadir was 20,000/mm^3. There was an altered foveal reflex with whitish retinal opacification along with retinal edema and hemorrhages. Optical coherence tomography B-scan shows presence of serous subretinal fluid, retinal thickening, and intraretinal cystoid spaces suggestive of dengue maculopathy (**b**)

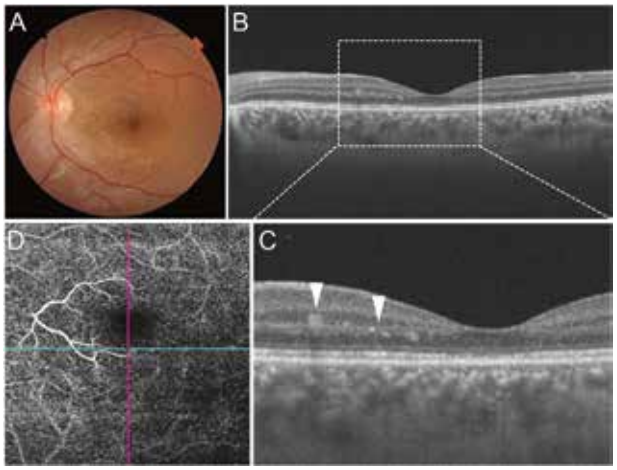

Fig. 5 Multimodal imaging of a patient (32-year-old female) with dengue maculopathy is shown here. The patient complained of scotoma in front of both her eyes 2 weeks after subsidence of dengue fever (tested positive for NS1 antigen). Fundus photograph revealed mild optic nerve hyperemia, and an altered red foveal reflex with yellow spots in the nasal macula (**a**). Optical coherence tomography B-scan (**b**) shows no evidence of retinal thickening; however, careful examination (**c**) revealed hyper-reflective spots in the outer nuclear layer (arrowheads). The deep retinal capillary plexus on optical coherence tomography angiography (**d**) showed evidence of capillary flow deficit suggestive of retinal vascular micro-occlusion

choroidal thickening and evidence of neuroretinitis or papillitis [118, 119].

Imaging features of dengue-related uveitis: FA is a useful imaging modality to determine the extent and severity of retinal manifestations such as maculopathy and retinal vasculitis. Foveolitis appears as retinal pigment epithelial hyperfluorescence that appears in the early phase and persists till the late phase. There may be presence of macular periphlebitis and occlusion. Common findings include arteriolar leakage, macular edema, and disc leakage. ICGA may show presence of hypofluorescent spots suggestive of involvement of choriocapillaris and the retinal pigment epithelium [122–124].

OCT imaging is useful to diagnose presence of macular edema as well as other changes such as foveolitis. The OCT classification consisting of three patterns of dengue maculopathy as proposed by Teoh et al. [125] is as follows:

Type 1: diffuse retinal thickening: Type 1 maculopathy included patients with diffuse retinal edema with an increase in central and paracentral retinal thickness and loss of the normal foveal dimple. Patients with type 1 maculopathy were described to carry the best visual prognosis.

Type 2: cystoid macular edema: Type 2 maculopathy was characterized by large intraretinal cystoid spaces extending through the level of photoreceptors with reflective septae separating the cystoid cavities.

Type 3: foveolitis: Type 3 maculopathy was characterized by an area of thickening and high reflectivity in the outer retina at the foveal region. There may or may not be associated retinal edema.

The most common feature of OCT in dengue maculopathy is diffuse retinal thickening. Disruption of external limiting membrane, ellipsoid zone, and inter-digitation zone may also be noted in these patients [120, 125–127].

Dengue-induced inflammatory, ischemic foveolitis and outer maculopathy (DIII-FOM): In a recent outbreak of dengue virus fever in North India (2017), a number of patients presented with a unique set of posterior segment features such as mild posterior vitritis, disruption of outer retinal layers, conical retinal elevations, and retinal capillary flow deficits on OCT angiography. In these patients, both ischemia and inflammation appear to be the central mechanisms of visual loss due to dengue fever. Therefore, based on their clinical phenotype and fundus imaging characteristics, we have coined a new term for this entity, DIII-FOM (Fig. 6).

Management of dengue-associated uveitis

There are no available guidelines regarding management of dengue-related maculopathy. Dengue maculopathy may be self-limiting in nature. In the presence of significant inflammation, topical, periocular, and systemic steroids may be used. Patients with AMN associated with dengue fever may also benefit from initiation of corticosteroids. However, there are no prospective trials assessing the efficacy of therapy till date. Thus, there is no clear evidence supporting the role of either steroids or intravenous immunoglobulin for the treatment of dengue retinochoroiditis or vasculitis [116, 120].

Chikungunya-associated uveitis

Chikungunya fever is a common arthropod-borne viral illness that commonly affects Asian countries and Pacific islands. Epidemics of chikungunya have been reported from several Asian countries such as India in the recent past. Chikungunya is caused by an *Alphavirus* which belongs to the family *Togaviridae*, a single-stranded RNA virus. The arthropod vector for chikungunya is the *Aedes aegypti* mosquito.

Epidemiology of chikungunya

Chikungunya fever can affect all ages and both sexes equally. This condition is endemic in Asia and Africa. The chikungunya virus was first isolated in Tanzania in 1953. More than 266,000 people were infected during the 2007 outbreak in Réunion and 1,400,000 cases were reported in India in 2006 [128]. Several outbreaks of chikungunya have

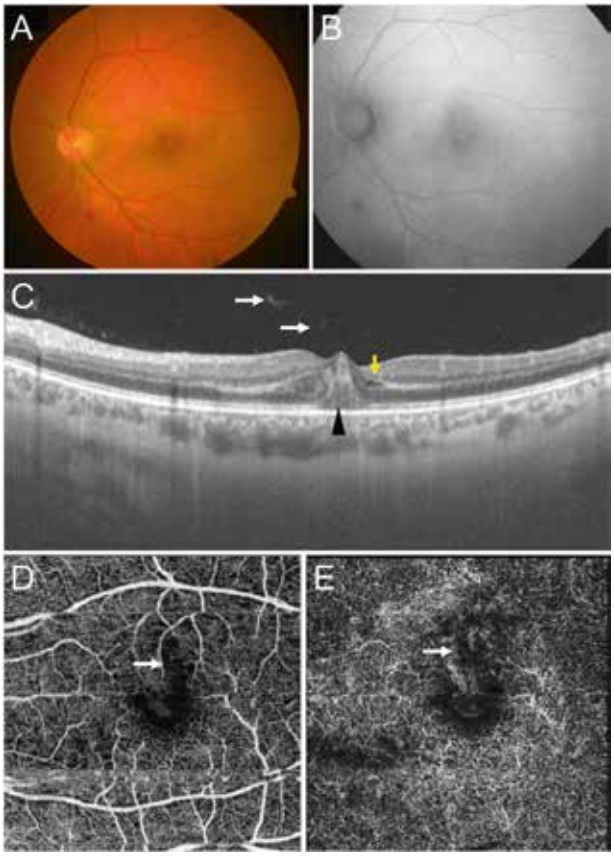

Fig. 6 A patient with dengue-induced ischemic inflammatory foveolitis and outer maculopathy (DIII-FOM) shows retinal hemorrhages in the macula with greyish white parafoveal lesions (**a**). Autofluorescence imaging shows hypo-autofluorescence in the macular region (**b**). The optical coherence tomography (OCT) scan shows vitreous cells (white arrows), hyper-reflectivity of the outer plexiform (OPL) and outer nuclear layers, and hyper-reflective "conical foveal elevation" involving all retinal layers (black arrowhead) (**c**). There are cystoid spaces in the left eye (yellow arrow). OCT angiography shows an area of flow deficit (white arrow) in the perifoveal region in the superficial (**d**) and deep plexus (**e**)

been reported between 1957 and 1974. The disease is also endemic in Seychelles, Madagascar, Comoro Islands, Mauritius, and Mayotte. Other countries that are affected include Sri Lanka, Maldives, Malaysia and Indonesia [129–132]. Viral mutations may lead to newer genotypes of the Chikungunya virus (such as A226V) which have increased virulence and infectivity. Due to the lack of herd immunity and increased travel/globalization, even visitors who hail from Europe, Canada, United States, and Australia are susceptible to chikungunya fever [129, 133].

Chikungunya virus-associated uveitis

Chikungunya fever may have ocular manifestations which may be unilateral or bilateral. Ocular inflammation associated with chikungunya may present with symptoms such as redness, pain, diplopia, and retro-orbital heaviness. Anterior uveitis is the most common feature of this condition. There may be concomitant corneal involvement with dendritic pattern of keratic precipitates. Other features include raised intraocular pressure, episcleritis, and lagophthalmos [111, 134, 135].

Posterior segment manifestations of chikungunya infection include choroiditis, retinitis, optic neuritis, neuroretinitis, and panuveitis. The most common posterior segment features are retinitis with surrounding retinal edema and opacification. Retinal lesions may be associated with mild vitritis and disc edema. Severe inflammation may result in exudative retinal detachment, retinal vasculitis, and intraretinal hemorrhages. Published reports suggest that long-term implications of chikungunya-related posterior segment manifestations are poorly understood [117, 136–139].

Imaging features of chikungunya-related uveitis: Imaging tools such as FA and OCT are very useful in the evaluation and management of patients with chikungunya uveitis. FA reveals presence of early hypofluorescence followed by late hyperfluorescence corresponding to the area of retinitis. Similar to choroiditis associated with other etiologies, Chikungunya choroiditis shows early hypofluorescence followed by late leakage of dye on FA. On OCT, macular edema and retinal thickening may be observed (Fig. 7). OCT may also reveal presence of AMN in patients with chikungunya [135–138]. Features of AMN include hyper-reflectivity of the outer plexiform layer, outer nuclear layer, and disruption of ellipsoid zone, ELM and inter-digitation zone [140].

Management of chikungunya-related uveitis

There is no specific anti-viral therapy against Chikungunya virus. Therefore, the treatment of chikungunya is largely symptomatic including management of fever, intravenous fluid therapy, and symptomatic pain relief. Ocular inflammation can be treated with topical steroids and cycloplegic agents. Majority of patients with chikungunya posterior uveitis recover well with good visual outcome. In the presence of significant inflammation, including manifestations such as vision-threatening retinitis and AMN, systemic corticosteroids can be initiated to control the tissue damage [135, 136, 140].

Summary and conclusions

In the Asia Pacific region, TB, dengue and Chikungunya remain the major infections that continue to remain endemic and affect a large number of individuals. All the three entities are associated with potentially severe vision

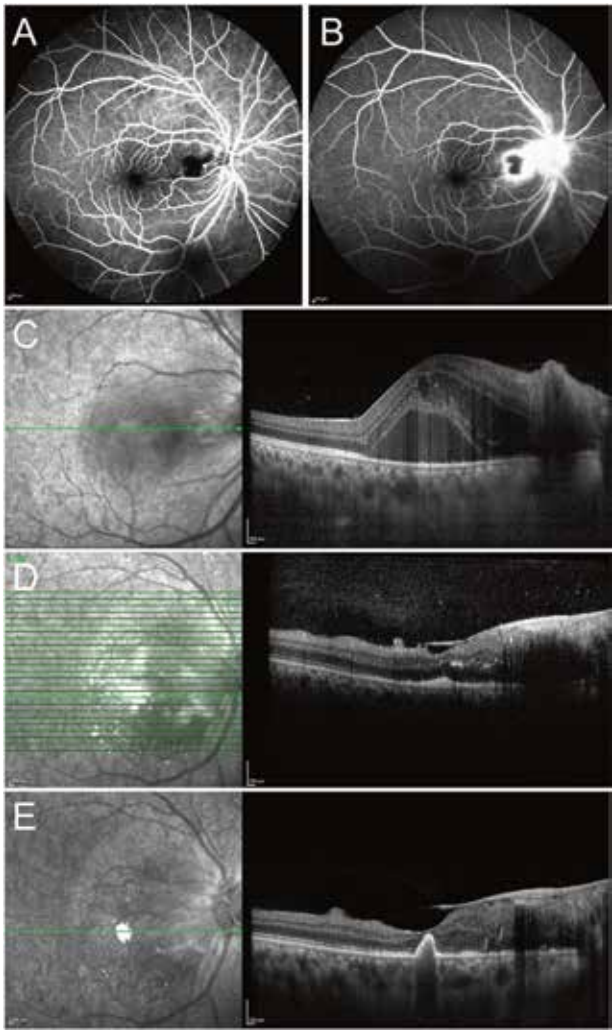

Fig. 7 Fluorescein angiography (FA) and optical coherence tomography (OCT) of a 34-year-old male with retinitis. The patient tested IgM positive for chikungunya virus infection. FA imaging in the early phase shows hypofluorescence (**a**) followed by intense leakage in the late phase (**b**) suggestive of retinitis. OCT scan at presentation (**c**) shows retinal edema, intraretinal fluid, serous retinal detachment, and disruption of retinal layers. The patient was treated with oral corticosteroids and he also received an injection of posterior subtenon triamcinolone acetonide. At 3 months, there was significant resolution of retinal edema and serous retinal detachment (**d**). At 7-month follow-up, retinal thickening and retinitis lesions have resolved, and a thick epiretinal membrane is seen on OCT (**e**). (Image courtesy: Dr. Ankush Kawali, MS, Consultant, Uveitis Department, Narayana Nethralaya, Bangalore, India)

threatening uveitis. Entities such as TB may have protean clinical manifestations and may present with diagnostic challenges, especially because they can cause myriad conditions, including choroiditis, vasculitis, panuveitis, optic neuritis, endophthalmitis, and scleritis, among others. For establishing a proper diagnosis of IOTB, it is necessary to consider various factors such as endemicity, geographical location, ethnicity, and immigration status, as well as clinical and imaging features. Similarly, dengue and Chikungunya present with retinitis and/or vasculitis of varying severity. While there is no definitive therapy for these viral entities, supportive therapy corticosteroids may help to reduce the inflammatory damage. In summary, with the recent increase in the outbreaks and epidemics of dengue and Chikungunya fever, it is important to recognize the potentially vision-threatening posterior segment manifestations of these conditions.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest

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REVIEW ARTICLE

亚太地区非传染性葡萄膜炎

摘要：

葡萄膜炎是一种影响视力的疾病。高达35%的患者可能有视力障碍。葡萄膜炎有60多种病因。过去的报告显示20%–40%的葡萄膜炎是非传染性的。其中一部分可能与系统性风湿病和自身免疫病有关，但一部分只影响眼部。因为受到遗传、种族、环境和社会经济因素的影响，一些葡萄膜炎的流行病学和临床发病情况在世界各地不同。

亚太地区有30多个国家。该地区葡萄膜炎的流行病学和类型差异很大。然而，一部分葡萄膜炎，如贝塞氏病、结节病和小柳原田病，在该地区更为常见。许多作者对该病的流行病学、危险因素和免疫发病机制进行了大量研究。本文综述了非传染性葡萄膜炎的流行病学和亚太地区这三种葡萄膜炎的发病特点。

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The ROYAL COLLEGE of OPHTHALMOLOGISTS

REVIEW ARTICLE

Noninfectious uveitis in the Asia–Pacific region

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Abstract

Uveitis is a sight-threatening disease. Up to 35% of patients may have impaired vision. Inflammation of the uvea tissue has more than 60 etiologies. Previous reports have shown that 20–40% of uveitis cases were noninfectious. Some of them may be associated with systemic rheumatological and autoimmune diseases but some may affect the eyes only. The epidemiology and clinical situations of some specific uveitis entities vary worldwide because they are influenced by genetic, ethnic, environmental, and socioeconomic factors. The Asia–Pacific region comprises more than 30 countries. Epidemiology and patterns of uveitis vary greatly in this region. However, some uveitis entities, such as Behcet's disease, sarcoidosis, and Vogt–Koyanagi–Harada disease, are more common in this region. Many studies on the epidemiology, risk factors, and immune pathogenesis of this disease have been conducted. In this article, we review the epidemiology of noninfectious uveitis and special situations of these three uveitis entities in the Asia–Pacific region.

Introduction

Uveitis is a group of disease entities with more than 60 etiologies. These sight-threatening diseases are defined as intraocular inflammation involving the iris, ciliary body, and choroid, and represent one of the leading causes of visual impairment among the working-age population, contributing to 5–20% of legal blindness in developed countries. Previous reports have shown that up to 35% of patients with uveitis experience transient or permanent visual impairment in one or both eyes [1]. These visual disturbances are followed by mainly direct ischemic and inflammatory damage of ocular tissue or serious ocular complications.

Etiologies of uveitis can be classified into four categories. Studies have revealed that 30–60% of uveitis cases are idiopathic. Localized or systemic infections of virus, bacteria, parasite, or tuberculosis may lead to uveitis. Noninfectious uveitis can be related to systemic rheumatological and autoimmune diseases—such as ankylosing spondylitis, Behcet's disease, sarcoidosis, Vogt–Koyanagi–Harada (VKH) disease, juvenile rheumatoid arthritis, and multiple sclerosis—or can be ocular only

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Table 1 Estimated incidence and prevalence of uveitis in Asia–Pacific countries

Country	Year	Sample size	Age group	Incidence (1/10,000)	Prevalence (1/10,000)	Sex Male: Female	Methodology
Australia [13]	2012	1881	≥20 years	N/A	80.0 &	N/A*	Multi-clinic based
China [10]	2002	10,500	All age	N/A	15.2	1.19: 1	Community-based
India [12]	2011	5150	≥40 years	N/A	31.7	2.76: 1	Community-based
India [11]	2000	10,000	≥30 years	N/A	73.0	1.04: 1	Community-based
Japan [9]	1996	1,800,000	All age	N/A	4.0	N/A	Questionnaires
South Korea [15]	2018	1,000,000	All age	10.6	17.3	1.18: 1	Registry database
Taiwan [14]	2012	1,000,000	All age	11.1	19.4	1.23: 1	Registry database

&: Prevalence of previous anterior uveitis was 0.21%, and the prevalence of previous posterior uveitis was 0.59%

*: N/A: Data not available

—with etiologies such as multifocal choroiditis, multiple evanescent white dot syndrome, birdshot retinochoroidopathy, serpiginous choroiditis, or Fuchs heterochromic iridocyclitis.

The medications and treatment strategies for uveitis for cases with noninfectious etiologies or from infectious pathogens differ. Therapy for noninfectious uveitis should focus on reducing the severity of inflammation, decreasing the frequency of recurrence, and preventing ocular or systemic side effects. Currently, oral corticosteroids and conventional synthetic immunomodulatory therapy agents, including cyclosporine, tacrolimus, methotrexate, azathioprine, mycophenolate, leflunomide, chlorambucil, and cyclophosphamide, are the mainstays of treatment. Anti–tumor necrosis factor alpha (anti-TNF-α), interferon, anti-interleukin-6, and other biologic agents have also demonstrated their efficacy in controlling noninfectious uveitis [2]. Recently, an anti-TNF-α antibody, adalimumab, was approved for treating noninfectious nonanterior uveitis in many countries [3, 4].

Generally, infectious uveitis is more common in developing countries, and noninfectious uveitis is more common in developed countries. However, genetic and cultural factors are also associated with some specific uveitis entities. For example, toxoplasmosis infection–induced uveitis represents 10% of uveitis cases in the United States but constitutes less than 0.1% of uveitis cases in China [5]. Nevertheless, the incidence of Behcet's disease and VKH disease are much higher in Asian populations than those in Western countries [6–8]. Although countries in the Asia–Pacific region vary greatly in economic status, they share similarities in culture, race, and environments. In this article, we review the epidemiology and recent studies of specific uveitis entities in this region.

Epidemiology and distribution of etiologies

Incidence and prevalence of uveitis in the Asia–Pacific region have seldom been reported (Table 1). Nakao and Ohba sent questionnaires to all ophthalmic clinics in Kagoshima prefecture of Japan and estimated that the prevalence of endogenous uveitis in 1996 was 4/10,000 [9]. In 2002, Hu et al. conduced a house-to-house survey in a town in southern China and estimated that the prevalence of uveitis was 15.2/10,000 [10]. Two community-based surveys, the Andhra Pradesh eye disease study and the Aravind comprehensive eye survey, estimated the prevalence of uveitis in southern India as 73/10,000 in urban Hyderabad city and 31/10,000 in rural Tamil Nadu [11, 12]. The central Australian ocular health study estimated that the prevalence of anterior uveitis presenting in remote clinics of central Australia was 21/10,000, and the prevalence of posterior uveitis was 59/10,000 [13]. Hwang and Rim used nationwide health insurance databases to estimate the epidemiology of uveitis in Taiwan and South Korea. Their results indicated that the incidence of uveitis was 11.1/10,000 person-years and 10.6/10,000 person-years, and the prevalence was 19.4/10,000 and 17.3/10,000 in Taiwan and South Korea, respectively [14, 15]. Most results have shown that the prevalence of uveitis was higher in males than in females in these countries.

Causes of uveitis were usually categorized into three groups in the literature. In previous series, "noninfectious uveitis" referred to those uveitis with specific systemic or intraocular rheumatological diagnoses, "infectious uveitis" referred to those uveitis of which the pathogens have been identified. Uveitis of those the exact etiology or diagnosis could not be made were usually categorized as "idiopathic uveitis" or "uveitis with unidentified etiology". Generally, uveitis with idiopathic etiology was more common to be noninfectious. The distribution of uveitis etiologies varies in the Asia–Pacific region (Table 2). Uveitis is most commonly caused by noninfectious etiologies, except in Myanmar and Nepal, where noninfectious uveitis respectively represents 11 and 19% of cases; idiopathic uveitis represented 35 and 56%, respectively [16, 17]. Idiopathic uveitis represents the majority of uveitis cases in Bangladesh (47%), South Korea (58%), and Sri Lanka (65%) [18–20]. In Australia, 42–45%

Table 2 Distribution of etiology and disease entities of uveitis in Asia–Pacific countries

Country	Period	Cases	Etiology		Specific disease entity (%)			
			Non-inf.	Idio.	Beh.	VKH	Sarc.	AS or B27
Australia [21]	1980–1985	245	41.5%	45.7%	4.2	0.0	2.4	20.8
Australia [22]	2009–2015	1165	45.2%	33.4%	2.1	1.8	6.7	22.7
Bangladesh [18]	2009–2015	652	N/A	46.6%	0.7	8.4	7.3	10.1
China [5]	1996–2003	1752	52.1%	44.8%	16.5	15.9	0.2	3.3
China [40]	2008–2011	199	41.2%	50.8%	10.1	9.5	0.0	2.0
China [6]	2014–2015	606	54.8%	38.9%	15.3	20.6	0.8	5.1
India [33]	1992	465	29.2%	58.7%	0.2	3.9	2.2	0.0
India [34]	1996–2001	1233	34.3%	51.2%	1.9	3.6	0.2	6.5
India [35]	1996–2001	8759	24.9%	44.6%	0.6	1.4	4.0	4.1
India [36]	2012	343	44.6%	26.2%	0.0	2.9	9.3	16.9
India [37]	2011–2014	1912	27.1%	39.4%	1.1	3.0	2.2	9.
India [38]	2013	352	33.5%	33.0%	0.3	6.0	6.8	10.8
India [39]	2014	1123	25.7%	38.6%	0.4	4.9	4.6	4.5
Japan [7]	1981–1994	551	63.1%	30.7%	27.9	10.3	18.1	2.6
Japan [32]	1994–2003	1240	41.9%	49.8%	6.7	9.7	14.9	4.0
Japan [27]	1999–2001	189	41.3%	42.3%	5.8	10.1	9.5	N/A
Japan [28]	2003–2008	735	N/A	N/A	7.6	7.9	9.8	4.5
Japan [29]	2009–2010	2556	N/A	49.8%	3.9	7.0	10.6	N/A
Japan [31]	2010–2012	695	43.9%	38.0%	4.6	4.0	8.1	0.1
Japan [30]	2011–2015	502	34.9%	47.8%	4.2	7.0	9.4	1.2
Myanmar [16]	2013–2014	139	10.8%	34.5%	0.0	1.4	0.0	3.6
Nepal [17]	2014	1113	19.4%	56.4%	0.4	1.8	1.7	6.6
New Zealand [23]	2008–2014	1148	74.1%*	N/A	1.6	1.0	5.0	28.7
Philippines [24]	2010–2015	595	74.5%*	N/A	1.3	9.2	0.0	0.0
Singapore [26]	1997–2010	1249	42.6%	24.9%	1.8	8.7	1.4	18.7
Singapore [26]	2014	148	33.1%	30.4%	1.4	5.4	4.7	13.5
South Korea [19]	2013	602	24.8%	58.1%	7.1	2.3	2.7	8.8
Sri Lanka [20]	2010–2014	750	18.7%	64.7%	1.2	1.3	6.0	3.3
Taiwan [44]	1984–1986	240	83.3%	10.0%	17.9	9.2	0.4	45.8
Taiwan [45]	1991–2000	160	46.9%	38.1%	8.8	16.3	2.5	16.3
Taiwan [46]	2001–2014	450	57.3%	26.4%	3.8	10.4	2.7	24.9
Taiwan[&] [98]	2009–2014	832	N/A	N/A	2.8	N/A	1.4	5.9
Thailand [41]	2005–2006	200	40.5%	13.0%	4.0	11.0	0.0	6.0
Thailand [8]	2007–2012	446	38.3%	48.4%	6.7	22.4	0.0	2.0
Thailand [42]	2010–2011	254	43.7%	29.1%	7.1	11.0	0.8	10.6
Thailand [43]	2014–2015	758	41.0%	16.5%	5.7	13.5	1.2	12.4
Vietnam [25]	2011–2015	212	36.3%	36.3%	6.6	14.2	3.3	1.9

Non-Inf.: noninfectious; Idio.: idiopathic; Beh.: Behcet's disease; VKH: Vogt–Koyanagi–Harada disease; Sarc.: sarcoidosis; AS: ankylosing spondylitis; B27: human leukocyte antigen-B27; N/A: data not available; *: including idiopathic etiology; [&]: only calculated when systemic involvement presented

of uveitis cases were noninfectious, and 33–46% were idiopathic [21, 22]. Studies in New Zealand and the Philippines have shown that infectious uveitis only represents a quarter of all cases [23, 24]. A report from Vietnam revealed similar proportions of idiopathic, infectious, and noninfectious uveitis [25].

Varying uveitis patterns have been found in many countries. For example, compared with patients before 2010, recent patients in Singapore showed a higher percentage of infectious uveitis [26]. Studies in Japan have revealed that 35–63% of uveitis cases were noninfectious, and 31–50% were idiopathic [7, 27–32]. These studies

have also demonstrated that the patterns and specific entities of uveitis, including endophthalmitis, sarcoidosis, Bechet's disease, VKH disease, and anterior uveitis, have changed with time. Changing of the uveitis pattern has also been observed in India [33–39]. Studies have revealed a decrease in idiopathic uveitis and an increase in viral retinitis and tuberculosis-induced uveitis. Studies in China, Taiwan, and Thailand have revealed relatively consistent patterns of uveitis. Noninfectious uveitis represents 41–55% of cases in China and 38–44% in Thailand [5, 6, 8, 40–43]. It also represents the majority of uveitis cases in Taiwan, accounting for 47–83% of etiologies [44–46].

Generally, ankylosing spondylitis and human leukocyte antigen (HLA)-B27 are the most common etiologies of anterior uveitis in countries other than Japan. Study has reported that the prevalence of HLA-B27 positive population in Japan was as low as 0.4%. On the other hand, VKH disease, Behcet's disease, and sarcoidosis are three major etiologies of intermediate, posterior, and panuveitis in Asia–Pacific countries.

Table 3 Uveitis among patients with Behcet's disease in Asia–Pacific countries

Country	Year	Cases number	Uveitis
Australia [47]	2004	31	66.0%
China [48]	2006	1996	34.8%
China [49]	2012	334	26.4%
Hong Kong [47]	2004	37	35.0%
India [50]	1995	58	43.0%
Japan [51]	2011	412	65.0%
Japan [52]	2017	7950	37.3%
Japan [53]	2018	3213	27.7%
South Korea [54]	1997	1155	28.5%
South Korea [55]	2001	1527	50.9%
South Korea [56]	2014	3674	36.0%
Russia [57]	2012	250	54.0%
Singapore [47]	2004	37	41.0%
Taiwan [58]	2018	236	18.2%
Thailand [59]	2006	23	52.2%

Behcet's disease

Behcet's disease is a systemic inflammatory disorder in which oral ulcers, genital ulcers, and uveitis are the three main clinical features. The exact pathogenic mechanism of this disease remains unclear; however, genetic, infectious, and immunologic factors have been found to be strongly associated with it. The disease usually affects individuals aged between 20 and 40 years. Studies in Asia–Pacific countries have reported that 18–66% of patients have uveitis (Table 3) [47–59]. Interestingly, a decreasing trend in the prevalence of uveitis in Behcet's disease has been noticed in China, Japan, and Korea.

Ocular features of Behcet's disease in the acute stage include nongranulomatous anterior uveitis, vitreous haze, retinal hemorrhage or exudates, macular edema, and chorioretinitis (Fig. 1). The disease can be highly threatening to vision because final visual acuity can be worse than 20/200 in 19–28% of patients [60, 61]. The main causes of visual impairment in these patients were macular scar, optic nerve atrophy, and phthisis bulbi after multiple recurrences.

Epidemiology of Behcet's disease in the Asia–Pacific region

Although it could be found worldwide, the highest prevalence of Behcet's disease was found in the ancient silk road area that bridges Asia, the Middle East, and the Mediterranean. The incidence of Behcet's disease was reported as 0.4 cases per 10,000 person-years in South Korea and 0.2 cases per 10,000 person-years in Taiwan [58, 62]. The highest prevalence in the Asia–Pacific region has been reported in China at 14.0–110.0 out of 10,000, followed by Japan at 11.9–22.0, and South Korea at 3.3–3.6 [63–65]. However, Behcet's disease has seldom been diagnosed in Bangladesh, India, Myanmar, Nepal, New Zealand, the Philippines, Singapore, and Sri Lanka [16–18, 20, 23, 24, 26, 33–39]. Most reports have shown the disease to predominantly affect males, although in some countries female patients were more common [58].

Behcet's disease is a major cause of noninfectious uveitis in many Asia–Pacific countries. It represents 4% of all uveitis cases in Australia, 10–17% in China, 4–28% in Japan, 7% in South Korea, 4–18% in Taiwan, 4–7% in Thailand, and 7% in Vietnam [5–8, 19, 21, 25, 27–31, 40–46]. Several studies have revealed that the incidence and severity of Behcet's disease–related uveitis have decreased with time [66, 67]. The reason for this is unclear; changes in unknown environmental factors may be a possible explanation.

Special circumstances in the Asia–Pacific region

Despite that the prevalence and incidence was not the highest, Japan has been the focus of most studies of Behcet's disease. Many genetic factors and infectious and immunologic issues have been explored and discussed. Clinicians in countries other than Japan usually diagnose Behcet's disease based on the international study group criteria for Behcet's disease, whereas ophthalmologists in

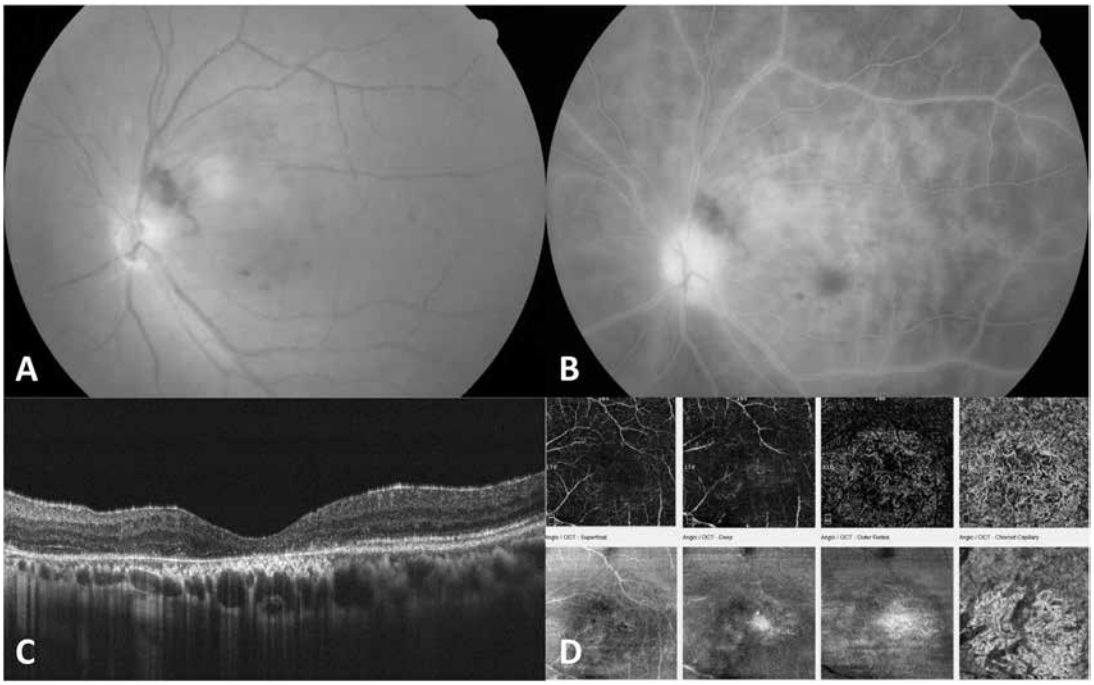

Fig. 1 A 46-year-old male had an acute attack of uveitis and was diagnosed with Behcet's disease. **a** Fundus photography showed retinal hemorrhage and choroiretinitis lesion near the macula in his left eye. **b** Fluorescein angiography revealed diffuse dye leakage from the retinal capillary and optic nerve in a "fern-like pattern". Macular edema was also observed. **c** Eight years after the initial attack, optical coherence tomography showed a macular scar with disruption of the ellipsoid zone. **d** Optical coherence tomographic angiogram eventually disclosed ischemic change and enlargement of the foveal avascular zone

Japan usually diagnose based on the criteria proposed by the Japanese Research committee [68] (Table 4). An ocular attack score specific to Behcet's disease was also developed for monitoring severity and predicting the outcome of patients with uveitis [69].

The treatment strategy for Behcet's disease in Japan also differs from the recommendation made by the European League against Rheumatism, which suggests that systemic corticosteroids be used in combination with other immunomodulatory agents. Systemic corticosteroids are not suggested for Behcet's patients in Japan since studies have found that long-term steroid therapy may result in poor visual outcome and uveitis may frequently recur during tapering [70]. Systemic infusion of infliximab is usually prescribed if the inflammation cannot be controlled by colchicine or cyclosporine. Japan is one of the first countries where biologic immunomodulatory agents were approved and funded for treating uveitis. Many Japanese studies have proven its effectiveness in decreasing inflammation for cases of Behcet's uveitis [70]. Using infliximab may not only reduce the frequency of uveitis flare-ups but also alleviate the signs of vasculitis and dye leakage in fluorescence angiography. Alternatively, adalimumab has been approved for treating noninfectious uveitis, including Behcet's disease–associated uveitis, in many countries including South Korea and Taiwan.

Sarcoidosis

Epidemiology and clinical manifestations

Sarcoidosis is a systemic granulomatous disease that affects various organs. The exact immunopathogenesis remains elusive. Genetic factors and pathogenic participation may both play roles. Overall, 30–70% of patients with systemic sarcoidosis may be affected by uveitis during the clinical course [71, 72]. Western literature generally shows that 3–10% of uveitis cases are associated with sarcoidosis. In the Asia–Pacific region, sarcoidosis accounts for 1.5–14.9% of all uveitis cases (Table 5). In general, sarcoidosis-associated uveitis is characterized by bilateral anterior or posterior granulomatous inflammation in a relapsing or recurring pattern. In the anterior segment, anterior uveitis with iris nodules or mutton-fat keratic precipitates is commonly seen. In the vitreous cavity, vitritis and haze with snowballs are classical presentations (Fig. 2a). Posterior findings typically include active and atrophic peripheral chorioretinal granulomas and periphlebitis (Fig. 2b, c).

The prevalence of sarcoidosis is influenced by multiple factors. For example, studies have indicated that Japanese populations are more susceptible to ocular involvement (50–93.5%) compared with populations from other countries (23–60%) [71, 73–75]. This can be attributed to

Table 4 Comparison of three major diagnostic criteria for Behcet's disease used in the Asia-Pacific countries

Proposed committee	Major criteria/symptom/sign	Minor criteria/symptom/sign	Definition of diagnosis
The international study group for Behcet's disease[a]	Recurrent oral ulceration	Recurrent genital ulceration Eye lesions Skin lesions Positive pathergy test	Major criteria plus any two of the minor criteria
The Behcet's disease research committee in Japan[b]	Recurrent aphthous ulcers on oral mucosa Skin lesions Ocular lesions Genital ulcers	Arthritis without deformity or sclerosis Epididymitis Intestinal lesions Vascular lesions Central nervous system findings	Complete: All 4 major findings Incomplete: 3 major findings, 2 major findings plus 2 minor findings, Characteristic ocular disease, plus 1 other major finding or 2 minor findings
The international criteria for Behcet's disease[c]	Ocular lesions Genital aphthosis Oral aphthosis	Skin lesions Neurological manifestations Vascular manifestations Positive Pathergy test*	Presentation of any major sign/symptom is count as 2 points, presentation of any minor sign/symptom is count as 1 point. *Pathergy test is optional. Diagnosis could be made if the scoring ≥ 4 points

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b. Behcet's disease research committee of Japan. Behcet's disease guide to diagnosis of Behcet's disease (1972). Jpn J Ophthalmol 1974; 18: 291–294

c. International team for the revision of the international criteria for Behcet's disease. The international criteria for Behcet's disease (ICBD): a collaborative study of 27 countries on the sensitivity and specificity of the new criteria. J Eur Acad Dermatol Venereol 2014; 28(3): 338–347

Table 5 Percentage of sarcoidosis among all patients with uveitis

Country/region	Percentage (N)	Author, year
Literature from Asia-pacific region		
Hokkaido, Japan	14.9% (1240)	Kitamei et al, 2009 [32]
Japan (nationwide)	10.6% (3830)	Ohguro et al, 2012 [29]
Tokyo, Japan	8.1% (695)	Nakahara et al, 2017 [31]
Singapore	1.4% (1249)	Siak et al, 2016 [26]
Taiwan	2.7% (450)	Chen et al, 2016 [46]
New Zealand	5% (1148)	Wong et al, 2016 [23]
Sri Lanka	6% (750)	Siak et al, 2017 [20]
Australia	6.7% (1165)	Zagora et al, 2017 [22]
Korea	2.7% (602)	Lee et al, 2017 [19]
Literature outside Asia-pacific region		
United States	2.2% (853)	Oruc et al, 2003 [99]
United Kingdom	9.7% (3000)	Jones et al, 2015 [100]

ethnicity, environmental factors, and possibly the availability of surveillance tools. Physicians in Japan are highly aware of this disease, because sarcoidosis is the most common entity in uveitis [29]. Ancillary tests for angiotensin-converting enzyme or serum-soluble interleukin 2 receptor (sIL-2R) are readily available in Japan. These factors may all contribute to the final diagnosis.

Diagnostic criteria for ocular sarcoidosis

No single clinical or laboratory diagnostic biomarker for sarcoidosis exists. Therefore, a collaboration of uveitis specialists from four continents (Asia, Africa, Europe, and North America) created the international workshop on ocular sarcoidosis diagnostic criteria for sarcoidosis [76]. Takase et al. performed a case–control study recruiting 50 biopsy-proven sarcoidosis cases and 320 control patients with other uveitis etiologies in Japan, and the sensitivity, specificity, positive predictive value, and negative predictive value of the criteria were 1.00, 0.96, 0.78, and 1.00, respectively [77]. Acharya et al. studied an international cohort with 884 cases from 12 countries. Of the 264 cases suspected to have ocular sarcoidosis, 97 (37%) did not meet the criteria. These results suggested that the sensitivity of this proposed criteria is more applicable to Asia–Pacific region, especially the Japanese population, because its criteria were based on the clinical data of many Japanese patients [78].

Studies regarding the immunopathogenesis of sarcoidosis

Studies increasingly suggest that the immunopathogenesis of sarcoidosis is highly associated with environmental and

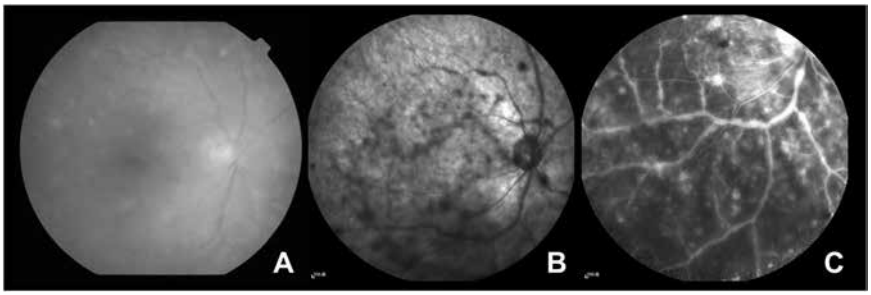

Fig. 2 A 67-year-old female with sarcoid uveitis presented with bilateral panuveitis, mutton-fat keratic precipitates, iris nodules, and vitreous snowballs. Elevation of serum angiotensin-converting-enzyme level and bilateral hilar lymphadenopathy were noted. **a** Fundus photography revealed vitreous haze with multiple yellowish deep chorioretinal nodular lesions. **b** Vitreous opacity was clearly shown on infrared imaging. **c** Segmental phlebitis with leakage and multiple choroidal hyperfluorescent spots were revealed on fluorescein angiogram

infectious factors. *Propionibacterium* species and *Mycobacterium tuberculosis* have long been suspected to be the initial trigger of the disease. Abe et al. identified *Propionibacterium acnes* in 77.5% of sarcoid lymph nodes, compared with 21.1% found in nonsarcoid tissues [79]. Yamada et al. revealed that the mean signal counts of *P. acnes* DNA were significantly higher in granulomatous areas than that in nongranulomatous areas in sarcoid lymph nodes [80]. Other studies have confirmed this finding[81],.

Because hilar or mediastinal lymphadenopathy is one of the hallmarks of sarcoidosis, it is reasonable to suppose that the triggering microorganism enters the human body through the respiratory tract. Research on animals revealed that inadequate response of toll-like receptor 2 to the pathogen (such as deficient myeloid differentiation primary response protein 88 (MyD88) activity) might result in impaired bacterial clearance [82]. In this case, subsequent systemic spread of the pathogen via the bloodstream results in the involvement of multiple organs. Intracellular proliferation of *P. acnes* in macrophages triggers T-helper cell hypersensitivity and granuloma formation. Aberrant aggregation of serum amyloid A within granulomas and cascades of cytokines (e.g., interferon-γ, interleukin-2, and TNF-α) promotes chronic granulomatous inflammation such as sarcoidosis [83].

Treatment

In general, the treatment of sarcoid uveitis follows the general stepladder approach in noninfectious uveitis. As the disease responds favorably to steroid treatment, in isolated iridocyclitis with minimal intermediate or posterior segment involvement, topical steroid could suffice to control the disease. In cases of panuveitis, however, systemic therapy should be administered, with a starting dose of 0.5 ~ 1 mg/kg per day and gradual tapering. In cases of asymmetric presentation, or with systemic comorbidities, local steroid injection can be considered, including subtenon/orbital floor injection of triamcinolone, or intravitreal injection of dexamethasone implant. In cases with refractory or persistent relapsing-remitting courses, traditional immunosuppressive agents should be applied. Antimetabolites (methotrexate, azathioprine, or mycophenolate) or calcineurin inhibitors (cyclosporine or tacrolimus) can be administered as a single agent or as combined usage [2].

If the traditional treatment failed to achieve favorable clinical response, further escalated management with biologics should be considered. Anti-TNF-α agent is the first choice of biologics for ocular sarcoidosis. Two recent pivotal multinational phase 3 trials established the effectiveness of adalimumab (a fully humanized monoclonal antibody) in treating noninfectious uveitis. In VISUAL 1 study, 18 subjects with active sarcoid uveitis responded to adalimumab, with a 50% reduction in experiencing treatment failure than the placebo group [3, 84]. In VISUAL 2 trial, 229 inactive uveitis cases (including 32 cases with sarcoidosis) were investigated. Adalimumab administration also showed a significant prolonged time to treatment failure [4].

VKH disease

Introduction and clinical features

VKH disease is a multisystemic disorder characterized by bilateral granulomatous panuveitis with exudative retinal detachments from inflammation of the choroid (Fig. 3). VKH disease occurs more commonly in patients with a genetic predisposition to the disease, including those from Asian, Middle Eastern, Hispanic, and Native American populations, but not blacks of sub-Saharan African descent. This suggests that risk factors of VKH disease do not depend on skin pigmentation alone. T-cell-mediated

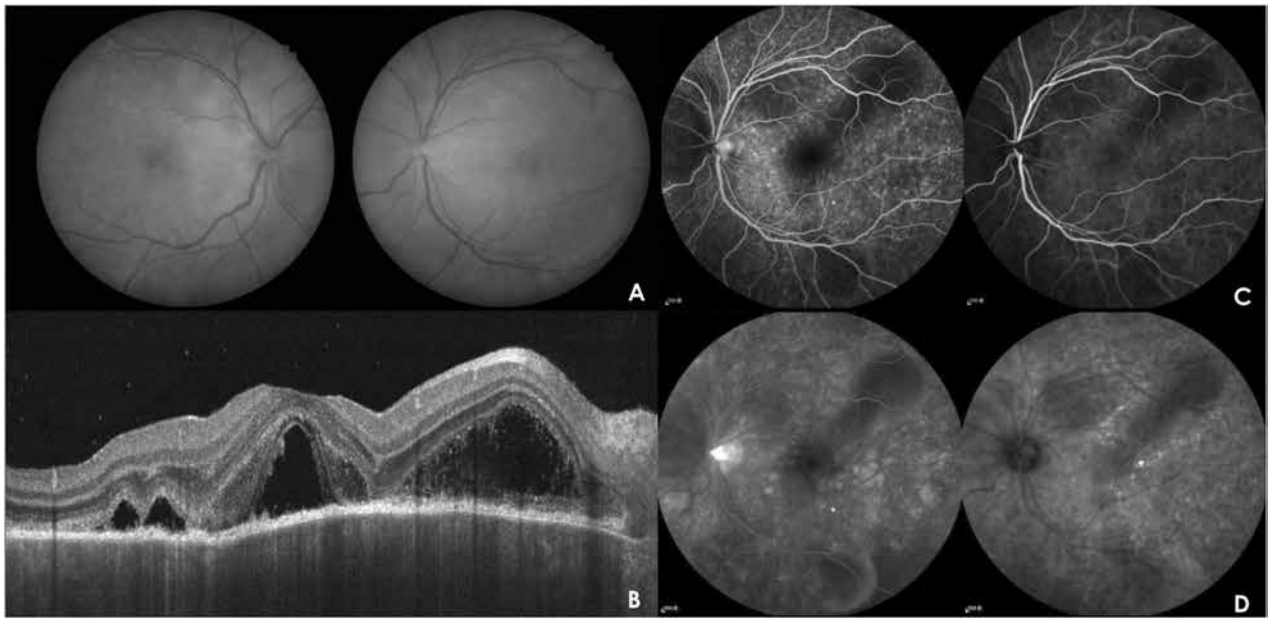

Fig. 3 A 23-year-old male patient with Vogt–Koyanagi–Harada disease. **a** Color fundus photographs revealed bilateral multifocal exudative retinal detachment with disc hyperemia. **b** Optical coherence tomography showed subretinal fluid divided into multiple compartments by septa formed by inflammation. **c** Mid-phase fluorescein angiography (FA) demonstrated multifocal pinpoint leakage with classic "starry sky" appearance. Indocyanine green angiography (ICGA) showed hypofluorescent dark spots as well as choroidal vessel leakage. **d** Late-phase FA and ICGA revealed pooling of dye with large placoid areas of hyperfluorescence

autoimmune responses against antigenic components of melanocytes and melanocyte-associated antigens are thought to be the main driving forces of the disease.

Systemic symptoms of VKH disease include headache, orbital pain, fever, nausea, meningism, vertigo, and tinnitus. These symptoms usually precede the onset of ocular disease by a few days and are followed by an acute uveitic phase that may last for weeks. The hallmark ocular presentation in the acute phase is bilateral exudative retinal detachment. The convalescent stage follows several months after the first episode of ocular inflammation, with developing signs of depigmentation of the eye and skin. Sunset-glow fundus changes representing choroidal depigmentation exhibiting bright orange-red reflex are more common in Asians. Perilimbal depigmentation can be observed in up to 85% of Japanese patients, whereas Caucasians and other non-Japanese patients with VKH disease, such as Singaporean [85] and Chinese patients [86], rarely develop the sign. The diagnostic criteria for VKH disease are based on clinical findings of ocular and extraocular manifestations. However, cerebrospinal fluid analysis is more commonly performed to confirm the diagnosis in Japan than in other countries.

Epidemiology

VKH disease has worldwide distribution but a predilection for darkly pigmented peoples, particularly those with Asian, Middle Eastern, Hispanic, and Native American ancestry.

Table 6 Percentage of Vogt-Koyanahi-Harada disease among all uveitis

Country/region	Percentage (N)	Author, year
China	15.9% (1752)	Yang et al, 2005 [5]
Southern Vietnam	14% (212)	Nguyen et al, 2017 [25]
Thailand	13.5% (758)	Sukavatcharin et al, 2017 [43]
Taiwan	10.4% (450)	Chen et al, 2016 [46]
Hokkaido, Japan	9.7% (1240)	Kitamei et al, 2009 [32]
Philippines	9.2% (595)	Abano et al, 2017 [24]
Singapore	8.7% (1249)	Siak et al, 2016 [26]
Japan (nationwide)	7.0% (3830)	Ohguro et al, 2012 [29]
South India	4.3% (1123)	Sabhapandit et al, 2017 [39]
Tokyo, Japan	4.0% (695)	Nakahara et al, 2017 [31]
North India	3.0% (1912)	Dogra et al, 2017 [37]
South Korea	2.3% (602)	Lee et al, 2017 [19]
Australia	1.8% (1165)	Zagora et al, 2017 [22]
Sri Lanka	1.3% (750)	Siak et al, 2017 [20]
New Zealand	1% (1148)	Wong et al, 2016 [23]

VKH disease is less common in countries where Caucasian populations are predominant (Table 6). In a retrospective chart review conducted in a tertiary hospital in China, VKH disease was the second most common identifiable cause of uveitis (15.9%), with the first being Behcet's disease [5]. Southern Vietnam also has a preponderant population of patients with VKH disease (14%), and VKH disease was

the most frequently identified cause of noninfectious uveitis in that region [25]. A review of the literature on the epidemiology of uveitis in the Asia–Pacific region indicates that China has the highest frequency of VKH disease among countries in the region. This is followed by Vietnam, Taiwan, Hokkaido (Japan), the Philippines, Singapore, and New Zealand, where VKH disease only contributes to 1% of uveitis cases (Table 1). The frequency of VKH disease as diagnosed uveitis in tertiary centers may be changing. A study from Tokyo University Hospital indicated a decrease in patients with VKH disease from 6.3% in 2004–2006 to 4% in 2010–2012. The authors attributed this finding to the increase in optical coherence tomography in community-based clinics, making diagnosis easier and allowing more patients to be treated rather than referred to university hospital-based clinics [31].

Gender predilection of VKH disease seems to vary globally. Studies from the Philippines and India have suggested that women are affected more frequently than men, whereas men and women are equally represented in other studies from the Asia–Pacific region [24, 25, 43, 85].

VKH disease research in the Asia–Pacific region

Because VKH disease is an inflammatory disease affecting mainly the choroid, extensive research has focused on the evaluation of choroidal ultrastructural changes before, during, and after treatment of the disease. The advent of multimodal imaging and especially enhanced depth imaging optical coherence tomography (OCT) has improved the understanding of this challenging illness. Fong et al. first used OCT in 2011 to evaluate the structural changes of the choroid in patients with VKH disease and found loss of inner choroidal focal hyperreflectivity [87]. Nakayama et al. used OCT to reveal decreasing choroidal thickness with high-dose corticosteroid treatment and suggested that choroidal thickness as measured by OCT may serve as a marker for the degree of choroidal inflammation in acute VKH disease [88]. OCT can also be a useful tool for detecting latent choroidal inflammation in VKH disease in eyes with remission subfoveal choroidal thickness greater than 240 microns. Tagawa et al. noted the choroid in eyes of patients with VKH disease thickened significantly prior to anterior segment recurrence [89].

Novel parameters derived from OCT may provide further insights. The luminal/stromal ratio as measured by binarization of OCT images was found to be a predictive factor for the progression of peripapillary atrophy, subsequent chronic recurrences, and total dose of corticosteroid, thus serving as a marker for the degree of choroidal inflammation in VKH disease [90]. Moreover, pathological changes of VKH disease can be evaluated through polarization-sensitive OCT to document in vivo the choroidal melanin loss in chronic VKH disease [91]. The definitive pathophysiology of VKH disease remains elusive, and further research is warranted to understand the immunogenetic and infectious basis of the disease.

Therapy

Early treatment with systemic high dose corticosteroid remains essential to the treatment of acute VKH disease. Systemic corticosteroid treatment should be tapered off slowly and the duration of the treatment should be greater than 6 months for the treatment of acute VKH in order to decrease the risk of recurrence manifested as exudative retinal detachment, and to improve final visual acuity [92, 93].

Park et al. investigated whether route of corticosteroid administration during the acute stage of VKH disease affects depigmentary change as determined by Sunset-glow fundus scores and subfoveal choroidal thickness (SCT) during the convalescent stage [94]. Compared to oral administration of prednisolone with the initial dosage of 0.8– 1.0 mg/kg/day for at least 2 weeks, intravenous infusion of methylprednisolone 1 g/day for 3 days initially resulted in less depigmentary changes and greater SCT during the convalescent stage. In addition to corticosteroids, immunosuppressive agents such as cyclosporine A, methotrexate, azathioprine, mycophenolate mofetil, and alkylating agents have been used successfully to treat VKH. The international uveitis study group and the American uveitis society have recommended treatment of VKH with immunosuppressive agents necessary in order to decrease recurrences [95].

In challenging cases with poor treatment response to corticosteroids and immunosuppressive agents, biologic agents such as adalimumab, rituximab, and infliximab have been shown to be effective in these cases [96, 97]. These biologic agents provide a quick and effective way to suppress the intraocular inflammation and increase the possibility of tapering systemic corticosteroid. Nevertheless, reactivation of tuberculosis is a possible side effect when the patients were treated with Anti-TNF-α agents. Screening of systemic tuberculosis should always be performed prior to these anti-TNF therapy.

Summary

Noninfectious uveitis represents a large proportion of all uveitis in Asia–Pacific countries. The distribution of patterns and entities of uveitis vary with genetic, ethnic, environmental, and cultural factors. This review finds that the variation exists not only between countries but also times and locations within countries. Nevertheless, Behcet's

disease, sarcoidosis, and VKH disease remain the three of the most common causes of noninfectious uveitis in Asia–Pacific countries. Many studies of these diseases have been conducted in this region. Although the understanding of these diseases has improved recently, the exact mechanism and immune pathogenesis of these diseases remain unclear. A collaborative study exploring genetic and environmental factors, pathogenesis, and treatments of specific disease entities might improve knowledge and patient outcomes in the future.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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The ROYAL COLLEGE of OPHTHALMOLOGISTS

REVIEW ARTICLE

美瞳隐形眼镜引起的（眼部）感染的文献综述

摘要：

本文对现有的关于美瞳隐形眼镜引起的（眼部）感染的文献进行了全面综述。本文就感染的危险因素，如晶状体相关因素、配药相关因素及患者相关因素进行了详细讨论。

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The ROYAL COLLEGE of OPHTHALMOLOGISTS

REVIEW ARTICLE

A review of cosmetic contact lens infections

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Abstract
This paper provides a comprehensive review of the existing literature surrounding cosmetic contact lens infections. In this paper, lens-related, dispensing-related and patient-related factors are examined in detail.

Introduction

Cosmetic contact lenses, although originally developed for patients with disfiguring abnormalities of the iris and cornea (Fig. 1), are also used by healthy individuals for cosmetic enhancement (Fig. 2) [1, 2]. These lenses can either modify or augment the appearance of an individual's eye and are commonly referred to as circle, decorative or "big-eye" lenses [3, 4]. Novelty lenses are also available and frequently used by patients for fancy dress events [5].

Cosmetic contact lens wearers make up a significant and growing proportion of the contact lens wearing population in Asian countries, such as Taiwan, Korea, Singapore, Malaysia, Thailand, Hong Kong and China, ranging from 24% in Taiwan to 39% in Singapore of contact lens wearers surveyed [6, 7]. The increased use of cosmetic lenses has been reported particularly, in young emmetropic individuals [8, 9]. These lenses are often used by females, with industry-led surveys reporting up to 88 percent of women surveyed expressing an interest in changing the appearance of their eyes with coloured contact lenses [10].

Complications associated with the use of cosmetic contact lenses are similar to those associated with conventional contact lens use [11]. Of these, contact lens-related microbial keratitis represents the most feared complication. Microbial keratitis can be a visually devastating disease and is associated with significant personal and societal costs [12, 13]. The incidence of disease has yet to be reported due to difficulties in estimating penetrance of wear within the community. However, a case control study has established that cosmetic contact lens wearers are at a 16.5 fold increased risk of infection compared with wearers of lenses used for refractive correction [14]. Cosmetic contact lens wearers made up 12.5% of corneal infections presenting to 12 university hospitals in France while also appearing to be overrepresented in a South Korean study, comprising 42.1% of cases presenting to 22 institutions and clinics [8].

This review aims to explore the lens, patient and dispensing-related factors that may contribute to the risk of microbial keratitis in cosmetic contact lens wearers (Table 1). We will also examine the microbiological characteristics of microbial keratitis associated with cosmetic contact lens wear.

Lens-related Factors

The production of cosmetic contact lenses involves a range of methods used to achieve realistic colouring effects [15]. These methods include dye dispersion tinting, vat-dye tinting, dye printing and chemical bond tinting techniques for translucent tints, while opaque tints may be achieved with dot-matrix printing, laminate, or opaque backing techniques (Fig. 3) [15]. These characteristics have been associated with visual disturbances, which may include visual field limitations, blurring of peripheral vision and increased higher-order aberrations resulting in a reduction in contrast sensitivity [16–20].

Exposed pigments on the surface of cosmetic contact lenses can predispose wearers to a host of complications

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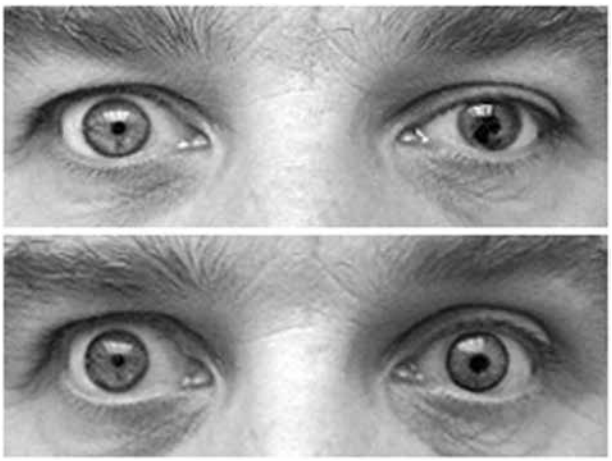

Fig. 1 Use of a prosthetic contact lens in a patient with an iris coloboma to achieve a more natural appearance. Images courtesy of Orion Vision Group

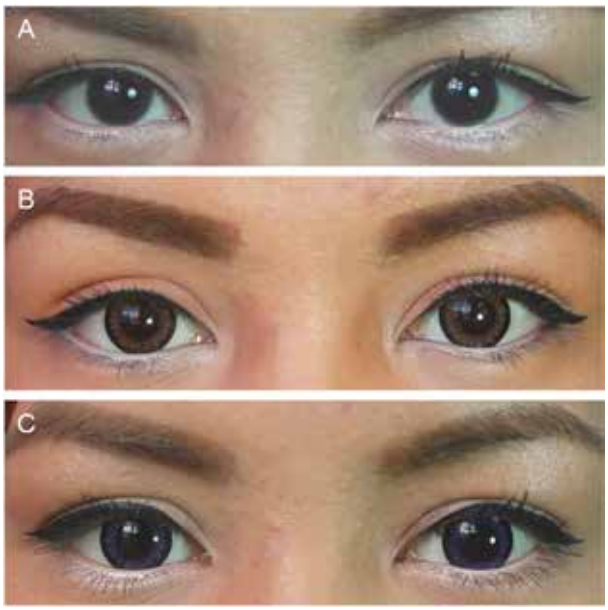

Fig. 2 Use of brown (**b**) and blue (**c**) cosmetic contact lenses to achieve a varied cosmetic effect in an individual. Panel (**a**) demonstrates the appearance prior to lens wear

[21–23]. Although specifics surrounding materials used to achieve these coloured effects are limited, chlorine, titanium and iron elements have been retrieved [22]. Dye pigments used in the manufacturing process may induce toxic reactions, with resultant corneal epithelial trauma and possible long-term implications on systemic health [22]. Systemic iron absorption for instance, may result in secondary hemochromatosis and immune mediated organ dysfunction secondary to cellular iron toxicity [24, 25]. The use of cosmetic contact lenses during procedures, such as intense pulsed-light therapy, may also result in corneal deposition of pigments [21]. Laminate technologies have been developed as a more stable and safe method to generate coloured patterns. This method permits encapsulation of dyes and tints within layers of the lens polymer, thus limiting exposure of the ocular surface to these substances [15]. In a study performed by Chan et al., moistened cotton buds were used to apply a gentle rubbing force to the surface of cosmetic contact lenses [26]. Following which, the tip of this cotton bud was inspected for the presence of any pigments. Only 2 out of 15 brands of commercially available cosmetic contact lenses tested demonstrated permanency of pigments with a gentle rubbing force applied to the surface of lenses using moistened cotton buds [26]. Pigments were retrieved in 6 out of 8 of the included lenses where manufacturers had reported embedded or sandwich designs for their lenses. Lenses which failed this test further demonstrated higher levels of bacterial adherence [26]. A separate study performed on tinted contact lenses using a variety of imaging techniques including light microscopy, atom force microscopy, focused ion beam milling, scanning electron microscopy, and anterior segment fourier-domain optical coherence tomography did not identify disparities between reported manufacturing techniques and imaging findings [27]. These findings taken together would suggest there is considerable variability in manufacturing quality even within laminate designs.

In addition, increased surface roughness of cosmetic contact lenses compared to conventional contact lenses has also been demonstrated [27, 28]. The extent of this characteristic has been described to be dependent on the manufacturing technique applied, with no differences identified by Jung et al. in contact lenses where colourants were buried in contact lenses [27]. However, in contact lenses with surface pigment, a considerable difference was noted between the roughness of front and back surfaces [27]. The undulating lens surface and uneven application of pigments may not only be associated with discomfort, but can also result in mechanical trauma to the palpebral conjunctiva or corneal surface [26, 29, 30]. This has been suggested as a possible mechanism underlying bilateral diffuse lamellar keratitis following cosmetic contact lens wear in a post-laser-assisted in-situ keratomileusis patient [31]. Surface roughness may further decrease lens wettability and facilitate adherence and proliferation of microorganisms and protein deposits [26, 32, 33]. These factors may be relevant in the development of microbial keratitis.

Given the popularity of these lenses, counterfeit and unapproved cosmetic contact lenses (Fig. 4) have made their way into various supply routes worldwide [34, 35]. This is of concern, as the quality and safety of these products are not established. A significant proportion of unused counterfeit and unapproved decorative, non-corrective contact lenses tested by the United States Food and Drug Administration demonstrated microbial contamination with

Table 1 Comparison of various factors between cosmetic and conventional contact lenses

Factors	Cosmetic contact lenses	Conventional contact lenses
Dispensing factors		
Unlicensed vendors	Plano cosmetic contact lenses may still be perceived as cosmetic devices in certain countries and can be sold through unlicensed vendors [43, 44, 59–61]. Patients may neither be provided with adequate assessments or appropriate counselling [26, 46–50].	Only licensed eye care professionals can prescribe conventional contact lenses for refractive purposes in many countries. They are able to instruct and counsel lens wearers regarding appropriate lens wear habits.
Counterfeit lenses	Counterfeit cosmetic contact lenses have found their way into conventional supply routes. These lenses possess different lens properties [34]. Microbial contamination of unused lenses and lens solution within the original packaging has also been described [35, 36].	
Lens factors		
Lens tinting	Tinting applied to lenses through various techniques may result in visual disturbances [16–20].	Light handling tints are often incorporated into lenses to provide increased user visibility. Handling tints have not been shown to affect vision or colour perception.
Exposed pigments and surface roughness	Exposed pigments may induce toxic reactions, result in systemic absorption of chemicals and greater bacterial adherence [22, 24, 25]. Increased surface roughness, particularly in contact lenses with surface pigment may result in discomfort and mechanical trauma, decrease lens wettability, and facilitate adherence and proliferation of microorganisms and protein deposits [27–33].	
Patient-related factors		
Demographics	Users are more likely to be younger, female and emmetropic [3, 8, 9, 32, 62].	
Lens wear experience	Cosmetic contact lens wearers are likely to be contact lens naïve and may incorrectly assume that cosmetic lenses are accessories that do not require proper lens evaluation, fitting and care [2]	Contact lens users using lenses for refractive purposes are more likely to have undergone assessment by licensed eye care professionals.
Cosmetic agents	Similar findings would be expected.	Cosmetic agents used may adhere to the lens surface and alter lens properties despite cleaning. This may contribute to bacterial adherence and proliferation [63, 64].
Non-compliance with recommended lens wear habits	Patients are less likely to adhere to recommended safe lens wear practices and scheduled follow-up consultations [3, 44, 62, 65].	
Wear frequency	Infrequent disinfection and replacement of contact lens solutions and lenses due to less frequent lens wear [2].	

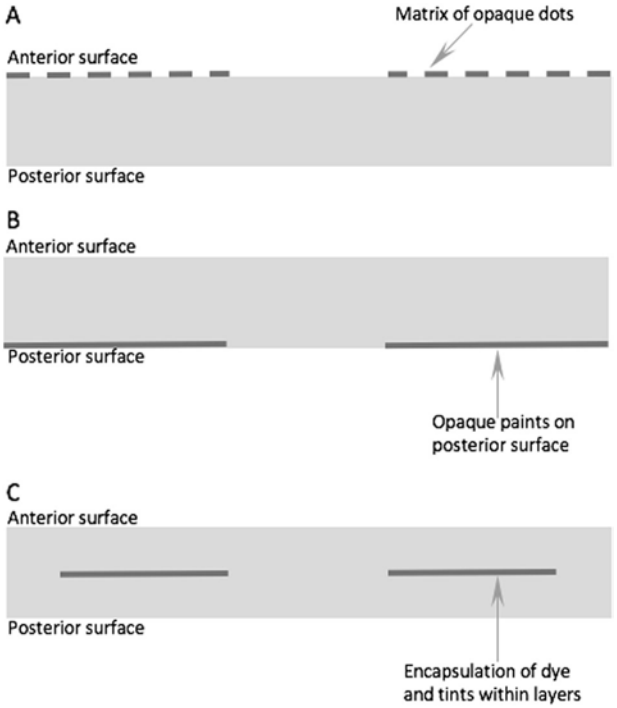

Fig. 3 An illustration of dot-matrix (**a**), opaque backing (**b**) or laminate construction (**c**) techniques to apply opaque tints to cosmetic contact lenses

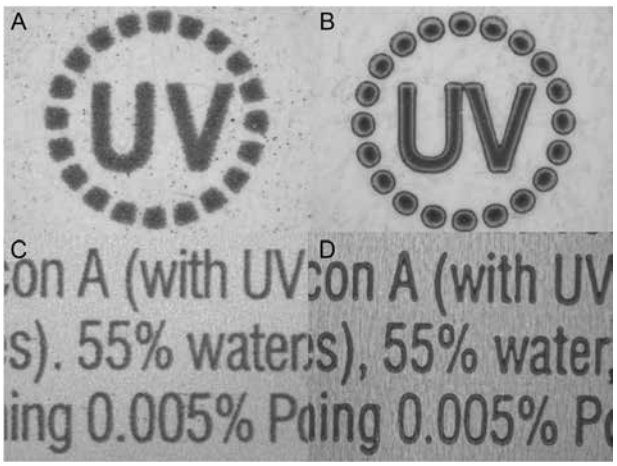

Fig. 4 Comparison in packaging between counterfeit (**a**, **c**) and authentic (**b**, **d**) and coloured contact lenses. Images courtesy of Health Sciences Authority Singapore

pathogenic organisms isolated from both the lenses and lens solution within the packaging [35, 36]. These lenses have also been demonstrated to possess altered lens properties; including lower water content and increased lens thickness compared to the original products [36]. These findings increase the risks of developing complications such as hypoxic related complications, and contact lens-related discomfort and dryness.

Cosmetic contact lenses are also more likely to be worn occasionally compared to conventional lenses used for refractive correction [2]. These lenses may be stored in contact lens solutions for prolonged periods [2]. The lack of frequent disinfection and replacement of contact lens solutions decreases the antimicrobial efficacy of the solutions and may encourage microorganism adhesion, proliferation and possible formation of biofilms on both contact lenses and contact lens cases [37, 38]. The development of biofilms not only provides potential areas of attachments for microorganisms, but also protects bacteria from disinfectants [39–41]. These factors may contribute to a higher bacterial load inoculated on the ocular surface and increase retention time, which in-turn increases the risks of developing microbial keratitis [42].

Dispensing-related Factors

Challenges exist in the regulation of cosmetic contact lenses [2]. Regulation of the supply and distribution of medical devices is important in ensuring their quality and safety [35]. Plano cosmetic contact lenses were, until recent times, perceived as novelty items or cosmetic devices [43]. Their sale through unlicensed vendors such as flea markets and street-side stalls, video stores, hair salons and gas stations, in addition to internet retailers has been documented [44]. These lenses are often sold in colourful, eye-catching packaging to appeal to a younger audience [3]. However, increased exposure to these products may result in an increased number of infections [32].

The internet offers an attractive method of retailing products, as transactions are completed virtually without a need for consumers to be physically present. This also obviates the need for a physical store, hence reduces overheads, which increases profit margins and reduces costs passed on to consumers. However, internet purchase of contact lenses is an independent risk factor in the development of microbial keratitis [45].

Wearers purchasing contact lenses from these supply routes are often not adequately assessed, counselled or instructed on safe contact lens wear practices or potential complications [26, 46–50].. These users are also less likely to be compliant with safe lens wear practices [51]. A survey of medical students who were contact lens wearers demonstrated that only 2% of respondents were adequately counselled about complications associated with contact lens wear [52].

In response to increasing reports of complications, cosmetic contact lenses were reclassified as medical

devices by the Food and Drug Administration in the United States [53]. A warning was issued against the use of such lenses without proper fitting and counselling in 2006 [53]. Unlicensed imports were also seized, whilst warnings were issued regarding improper marketing and distribution of such lenses by distributors. While many non-licensed distributors voluntarily withdrew products, contact lens manufacturers have also been actively assisting the regulation of this industry. For instance, CIBA Vision sent cease-and-desist letters to multiple vendors in the United States distributing cosmetic lenses illegally, and proceeded with legal action against recalcitrant companies [54].

Cosmetic contact lenses have since been gradually classified as medical devices in countries such as Malaysia, China and Korea [26, 55–57]. Supply of contact lenses to wearers has also been restricted to licensed eye care professionals in countries such as Singapore [58]. While efforts have been made by various authorities to educate and prosecute offenders, regulation of this industry remains tenuous and unlicensed vendors are often able to circumvent existing regulations to reach out to potential customers without provision of prerequisite professional advice or supervision through internet and makeshift stalls [59–61]. Counterfeit cosmetic contact lenses are also sold through conventional supply routes such as optical shops, with licensed merchants purchasing these lenses through third parties at reduced cost [34].

Patient-related factors

These problems are further exacerbated by the demographics of the population likely to utilise cosmetic contact lenses. Cosmetic contact lens wearers are more likely to be young, female, emmetropic and contact lens naïve [3, 8, 9, 32, 62].

Up to 6% of contact lens wearers surveyed in Hong Kong were emmetropes, who were likely to be cosmetic contact lens wearers, while 15% of asymptomatic cosmetic contact lens wearers surveyed in Thailand were emmetropes [3, 9]. Emmetropic cosmetic contact lens wearers may perceive lenses as cosmetic accessories and incorrectly assume that proper lens evaluation, fitting and care is not required [2]. Cosmetic and novelty lenses may be more commonly used in conjunction with cosmetics for attendance at events. It has been demonstrated that cosmetic agents such as hand creams, make-up removers and mascara may adhere to the lens surface and alter lens properties despite subsequent cleaning [63, 64]. This may further contribute to bacterial adherence and proliferation. In a Korean survey of contact lens-related complications, 62.2% of patients who presented with cosmetic contact lens complications were emmetropic individuals [8].

Steinmann et al. have reported that up to 50% of all decorative lens wearers are first-time contact lens wearers, while Abbouda et al. who examined the attitude and practice of teenage contact lens wearers have suggested that younger contact lens wearers do not adequately comply with contact lens care practices and are less likely to be involved in their own care [44, 65]. For instance, in a study by Mahittiokorn et al., 42% of cosmetic contact lens wearers reported considering using lenses that had fallen on the floor without prior cleaning or rinsing [3]. Patients presenting with cosmetic contact lenses related microbial keratitis are typically younger and less experienced contact lens wearers [32]. This group of patients who presented to healthcare institutions with cosmetic contact lens-related complications were also less likely to adhere to scheduled follow-up consultations compared to counterparts wearing conventional contact lenses [62]. The findings by Abbouda et al, mirror findings of the Contact Lens Assessment in Youth (CLAY) study, which has demonstrated the greatest risk of developing corneal infiltrates in patients was between the age of 15–25 [65, 66]. It was further found that patients younger than 15 years of age were more compliant with recommended lens wear habits [66].

Multiple studies have demonstrated high rates of non-compliance amongst conventional contact lens wearers [8, 67–70]. Even when lenses are dispensed by eye care professionals, large proportions of patients are non-compliant with safe lens wear practices [8, 67, 69, 70]. A study surveying 500 healthcare workers in Pakistan further corroborated these results [68]. This is likely to be worse in the cosmetic contact lens population. Cosmetic contact lens wearers have been reported to delay presenting to an eye care specialist compared to conventional contact lens wearers, which has been identified as a risk factor for poorer visual outcomes [13, 32, 46, 71]. As a greater proportion of cosmetic contact lens wearers purchase lenses from non-conventional and unregulated routes, these individuals are less likely to have received adequate contact lens safety advice and may not be connected to eye care providers, which can contribute to their delayed presentation for treatment [46, 71]. A study by Singh et al. found that all 13 patients in their case series who developed microbial keratitis from cosmetic contact lens wear, were from lower socioeconomic classes [2]. While this has not been confirmed in an epidemiological study, conceivably this factor may act as a barrier to accessing healthcare and contribute to delayed presentations with resultant increased disease severity.

Causative organisms

A range of pathogens have been implicated in the development of contact lens-related microbial keratitis. Bacterial keratitis typically predominates in temperate climates, while rates of fungal keratitis make up a larger proportion of microorganisms in tropical regions [72, 73]. It has been suggested that severe contact lens-related microbial keratitis is more likely to occur in warmer, humid weather compared to cooler conditions [74–76]. Commonly implicated bacteria include *Pseudomonas, Staphylococcus and Streptococcus* spp [2, 44, 70, 77–82]. *Pseudomonas aeruginosa* is the most common species, accounting for up to 60% of culture proven infections in contact lens wearers. *Pseudomonas* spp. was the most commonly isolated organism in a series of cosmetic contact lens wearers with microbial keratitis reported in India, Malaysia, Hong Kong, Australia and New Zealand [2, 79, 80, 83].

Microorganisms use a variety of techniques to increase their adherence and virulence [38, 84]. Bacteria have been shown to possess varied ability to adhere to various contact lens materials and grow on tear film components adsorbed on the surface of worn lenses [39] Other mechanisms include formation of biofilms on either contact lenses or lenses by microorganisms such as *Pseudomonas aeruginosa, Staphylococcus aureus, and Elizabethkingia* species [29, 39, 42, 84].

In patients with contact lens-related fungal keratitis, *Fusarium*, Aspergillus and less frequently *Candida spp*. have been reported [80]. These organisms are of greater significance in subtropical and tropical climate, such as in the south-eastern Asian region.

Of significance, *Acanthamoeba* keratitis is a challenging condition to treat and has been increasingly reported in recent years, with case reports from the United States, New Zealand and Korea identifying cases of *Acanthamoeba* keratitis related to the use of cosmetic contact lenses [46, 85–87]. It has been suggested in a multicentre survey in the United Kingdom that up to 93% of patients presenting with a diagnosis of *Acanthamoeba* keratitis are contact lens wearers [88]. A more recent survey demonstrated similar findings, with 93.5% of patients presenting with *Acanthamoeba* keratitis reporting contact lens wear [89]. In these individuals, domestic water sources and subsequent contamination of contact lenses and associated lens care products have been identified as possible sources of contamination [90]. Kilvington et al. using mtDNA testing confirmed identical isolates recovered from the cornea and bathroom tap water in six out of eight contact lens wearers with *Acanthamoeba* keratitis [90]. In Korea, 4.2% of contact lens storage cases and 7.7% of domestic tap water samples recovered *Acanthamoeba* [91, 92]. A study involving Scottish patients with *Acanthamoeba* keratitis demonstrated higher rates of recovery (54 vs. 31%) of *Acanthamoeba* in their home water supply compared to healthy contact lens wearing controls [93]. A larger proportion of cases were also identified to have used tap water in their contact lens care regime compared to controls, including the use of tap water for rinsing lens storage cases (79 vs 43%) or contact lenses (21 vs 13%) [93]. A study from Thailand by Mahittikorn et al. also demonstrated retrieval of *Acanthamoeba*-like trophozoites from 2% of cosmetic contact lenses obtained from healthy volunteers [3]. However, the contamination rates of domestic water sources reported in Asia are still comparatively lower compared to studies performed in other parts of the world.

Recommendations

This is a challenging situation requiring greater oversight of the licensing, manufacturing and distribution of cosmetic contact lenses. The main difficulty however is the unregistered manufacture, distribution and sale of these products. The discrepancies between manufacturing claims of laminated construction techniques and reported findings of pigments on lens surfaces are of concern [26]. Reporting channels for complications associated with cosmetic contact lenses to regulatory authorities should also be established and promoted amongst eye care and health professionals, while recognising that these practitioners are generally not part of the supply chain and may not see these wearers until they present with a problem. Other potential aspects include establishment of a regional registry to assist with information sharing and tracking of unlicensed vendors.

While a number of case reports have identified risks associated with these products, the size of the problem is still unknown. The magnitude of the population wearing these lenses in the community remains unclear due to the presence of non-traditional supply routes. Population based studies may allow estimates of incidence rates and potential risk factors [94]. This may in turn help to guide informed strategies to limit the risk associated with these products.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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The ROYAL COLLEGE of OPHTHALMOLOGISTS

REVIEW ARTICLE

亚洲的视网膜母细胞瘤

综述：

了解亚太地区的视网膜母细胞瘤发病特点非常重要，因为它在全球疾病总量中占有相当大比例。然而，这些国家大多缺乏理想的优质科学文献。该区域各国在技术和社会经济发展方面的巨大差异导致临床表现和生存数量的不同。了解该病的社会经济方面的特点有助于制定文化相关和经济可行的干预措施。

摘要：

亚太地区是全球主要的视网膜母细胞瘤（RB）患病地区，因此了解亚太地区RB的患病情况具有重要意义。根据2013年人口估计，全球患RB儿童中的43%(8099名儿童中的3452名)生活在亚太地区的6个国家：印度1486名儿童、中国1103名儿童、印度尼西亚277名儿童、巴基斯坦260名儿童、孟加拉国184名儿童、菲律宾142名儿童。各国在技术和社会经济方面存在着巨大差异，导致了临床表现和生存数量的不同。发展中国家面临的挑战不仅是技术方面的，还有社会方面的。学习理解该疾病的社会经济方面的特点以制定与文化相关和经济可行性的干预措施很重要。可能采取的措施包括疾病的教育咨询、普遍筛查、对社会经济地位低的人群给予高补贴/免费治疗、通过政府和非政府组织筹集资金、提高筛查及诊断和治疗方面的人才的认识和培训，以及发展具有远程眼科服务的新型专业中心。

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The ROYAL COLLEGE of OPHTHALMOLOGISTS

REVIEW ARTICLE

Retinoblastoma in Asia

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Abstract

Asia-Pacific region bears a significant global burden of retinoblastoma (RB), therefore understanding RB in Asia-Pacific region is important. Based on the year 2013 population estimates, 43% (3452 of 8099 children) of the global burden of RB lives in 6 countries of Asia-Pacific region: 1486 children in India, 1103 children in China, 277 children in Indonesia, 260 children in Pakistan, 184 children in Bangladesh, 142 children in Philippines. There exists a wide disparity, technological and socio-economical, within countries in this region resulting in a varied pattern of clinical presentation and survival varies. Challenges in developing nations are not just technological, but also social. Opportunities emerge for research to study and understand the socio-economical aspects of the disease to develop interventions that are relevant culturally and feasible economically. Possible steps include disease education and counselling, universal screening, highly subsidized/free of cost treatment for low socioeconomic strata, raising funds through the government and non-governmental organizations, sensitization and training of man-power in screening, diagnosis and treatment, and developing new specialized centers with tele-ophthalmology services.

Introduction

Retinoblastoma (RB) is the most common primary intra-ocular malignancy of childhood worldwide with a uniform incidence rate across population at 1 in 15000–20000 live birth corresponding to about 9000 new cases every year [1,2]. In the last 100 years significant progress has been made in the diagnosis and management of RB keeping the principles of Life, Globe & Vision salvage in order of priority [3, 4].

Prognosis and survival depends on early diagnosis and appropriate treatment [5]. With more than 90% of RB children living in under developed nations, it is troubling that these children die of a potentially curable tumor with high survival rates [6, 7]. In developed countries, the goal of treatment has shifted from globe salvage to vision preservation [8–10]. However, preventing death is a major challenge in under developed nations where most children have advanced disease at presentation [11–14].

Obvious drastically different outcomes between developed and under-developed nations are troubling [7, 15]. Various factors in combinations, both technological and social, are responsible for poor outcomes seen in less privileged nations (Table 1) [16].

Together, 43% (3452 of 8099 children) of the global burden of RB lives in these 6 countries: 1486 children in India, 1103 children in China, 277 children in Indonesia, 260 children in Pakistan, 184 children in Bangladesh, 142 children in Philippines [17]. Interestingly, owing to the explosive population growth in Asia-Pacific region, recently RB has outnumbered uveal melanoma to become the most common ocular malignancy globally [2]. With the current trend observed, the global burden is expected to increase by 100 cases a year.

Understanding RB in Asia-Pacific region is important [17]. However, scarce optimal quality scientific literature exists from most of these countries. Moreover, there exists a wide disparity, technological and socio-economical, within countries in this region resulting in a varied pattern of clinical presentation and survival varies. Opportunities

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Table 1 Various factors in combinations, both technological and social, are responsible for poor outcomes seen in less privileged nations

- Lack of awareness about RB in general population- delay in seeking medical attention
- Lack of National Screening Program
- Lack of training in screening, diagnosis and referral of RB: primary health care workers, pediatricians, gynecologist, primary physician, medical graduates
- Few treatment centers with trained personal specialized in treating RB
- Inadequate Infrastructures
- Accessibility
- Financial issues
- Socio-economic factors, extended family pressure, religious belief, gender bias
- Alternative indigenous system of treatment
- Poor compliance to treatment
- Lack of multi-disciplinary team in one roof
- Lack of proper counselling and support group
- Lack of prosthetic shell fitting clinic
- Lack of support from government and non-government NGO, telemedicine facility, National cancer registry.

emerge for research to study and understand the socio-economical aspects of the disease to develop interventions that are relevant culturally and feasible economically.

Retinoblastoma in India

India carries the biggest burden of Retinoblastoma, both in Asia-Pacific region and globally, with an estimated 1500 new cases detected every year. We conducted a systemic PubMed search of all articles, published between 2008 and 2018, reporting the presentation, treatment and survival of RB in Indian children. Data from 4 large series constituting a total of 2697 RB children were gathered and analyzed [18–21].

Table 2 shows the baseline characteristics of 2591 RB children at presentation. "Familiar" cases constituted approximately 4–6.3% of the total case [18–21]. Kaliki et al. reported that the mean age at presentation for "familiar" cases was 24 months vs. 29 months in the overall group [19].

Although no sex predisposition have been noted for RB worldwide, a male preponderance was noted in all studies constituting approximately 60% of all cases [18]. Singh et al. reported that among children with advanced disease at presentation 87.2 % were girls and 81.0% were boys

Table 2 Baseline characteristics of 2591 RB children at presentation in India

	Chawla et al. [18]	Singh et al. [20]*	Kaliki et al. [19]#
Time span of the study	2009–2013	1998–2014	2000–2015
Total eyes/ children	667 children	618/467	2074/1457
Familiar cases (%)	6.3	4	4
Male/Female (%)	61.2/38.8	61.7/38.3[a]	56/44
Rural/ Urban (%)		53.5/46.5[b]	
Unilateral / bilateral (%)	67.6/32.4	67.7/32.3	57/43
Leucocoria presenting symptom (%)	83	60.6	75
Children with proptosis at presentation (%)	17	4.4	6
Mean age at presentation - overall (months)	29	34.4 +/−24.6	29
• Unilateral/Bilateral	36/18	36/30	34/21
• Male/Female			29/28[c]
• Intra-ocular/Extra-ocular	24/37.5		27/44
• Familiar cases			24
Delay in seeking medical consultation (months)	3	8.3 +/−13.8	
Age > 5 years at presentation (%)	7.5	10.9	7
Intra-ocular/ Extra-ocular (Orbital) (%)	72.3/27.7	64.5/35.5	91/9[c]
Stage at presentation (%)			
• 0		64.5	45
• 1			45
• 2			2
• 3	23.3	33.8	6[c]
• 4	4.3	1.7	3
Group at presentation (%)			
• A		12.2	6
• B	15		15
• C			7
• D	14	77.8[d]	22[c]
• E	64		51

*Clinical features at presentation were based on individual eyes

#Grouping and staging at presentation was not based on worst eye

[a]A total of 87.2% of female had advanced disease at presentation as compared to 81.0% of male ($p = 0.052$)

[b]In all, 12.9% of the children were "below poverty line"

[c]The mean age of presentation for female children, occurrence of extra-ocular disease, ICIoR Group D and IRSS Stage 3 gradually decreased over the 15 years study period ($p < 0.05$)

[d]In all, 234 of 301 patients in the intra-ocular group presented with advanced disease

($p = 0.052$) [20]. Nearly 53.5% of the children were from rural areas and 13% children were from below poverty line (BPL) families in one series [20].

Leukocoria was the most common presenting symptom in approximately 61–83% of the cases [18–21]. Proptosis was seen in 2.8–17% of children at presentation [18–21].

The overall mean age of presentation was 29–34 months with 7–10.5% of children being older than 5 years at presentation [18–20]. Singh et al. and Chawla et al. reported a mean delay in presentation was 3 and 8.3 months, respectively [18–20]. One study found a statistically significant difference between intra-ocular and extra-ocular groups in the median lag period [18].

Children with unilateral RB constituted approximately 56–61.7% of the cases [18–21]. Children with unilateral RB presently late as compared to children with bilateral RB (34–36 vs. 18–30 months) [18–21]. Chawla et al., Singh et al. and Kaliki et al. reported 27.6% (23.3% Stage 3 & 4.35% Stage 4), 35.5% (33.8% Stage 3 & 1.7% Stage 4) and 9% (6% Stage 3 & 3% Stage 4) children had extra-ocular RB at presentation [18–20]. Proptosis was the most common presenting symptom, although few neglected case presented with a fungating orbital with metastasis [18–20].

Among those with intra-ocular RB, advanced disease (Group D/E) was present in 73–78% children [18–20].

Kaliki et al. performed a sub-group analysis found that the mean age of presentation for female child, occurrence of extra-ocular disease, ICIoR Group D and IRSS Stage 3 has gradually decrease over the 15-year study period ($p < 0.05$) [19].

Table 3 below shows the treatment, globe salvage and survival rates of 2697 RB children in India. 49.5 and 60.4% of children in Chawla et al. and Shah et al. series underwent primary enucleation [18–21]. Kalaki et al. observed that in eyes undergoing primary enucleation high-risk characteristic on histo-pathological examination (HPE) was noted in 35 and 23% eyes in India and United States, respectively ($p = 0.003$) [22].

Chawla et al. reported an overall 28.2% globe salvage rate in eyes with intra-ocular RB eyes (Group A: 100%; Group B: 94%; Group C: 83%; Group D: 54%; Group E: 0%) [18]. Singh et al.reported 100, 100, 94.7, 17.4 and 0% globe salvage rate in Group A, B, C, D and E, respectively [20]. Similarly, Shah et al. reported 100, 100, 100, 29.4 and 0% globe salvage rate in Group A, B, C, D and E, respectively [21].

Overall survival rates reported were 75.7–92% in the 4 studies with a mean/median follow-up of 21–44 months [18–21]. Chawla et al. reported the survival probability in the extraocular group was 60, 43 and 35%, respectively, at the end of 1 year, 2 years and 5 years, as compared with 93, 85 and 78% in the intraocular group ($p < 0.001$) [18]. Shah et al. reported 55.5% overall survival rate in children with Stage 3 and 4 disease at presentation [21]. Kaliki et al. analyzed 80 patients with stage 3 or stage 4 disease at presentation and found that the survival rate were 71 and 0% in stage 3 and 4, respectively [23].

Kaplan–Meier survival analysis showed 83–94%, 73–91% and 68–90% overall survival at 1, 3 and 5, respectively in large case series [18–21]. Chawla et al. reported that on multivariate analysis of various prognostic factors, stage of the disease at presentation had a significant association with survival outcomes (extraocular vs intraocular, HR: 5.04, $p < 0.001$) [18]. However, gender and laterality did not have any significant association with survival outcomes [18].

Singh et al. observed that 25.6% of all RB children seen in their center refused any form of treatment [20]. More importantly, of those undergoing treatment 43.5% (151 children) were defaulter of which 37.4% (130children)

Table 3 Treatment, global salvage and survival rates of 2697 RB children in India

	Chawla et al. [18]	Singh et al. [20]*	Kaliki et al. [19]#	Shah et al. [21]
Primary enucleation	49.4	—	—	60.4
HRC in specimens of primary enucleations	—	21[a]	—	14.1
Median follow-up (months)	21	28.5 +/−44.4	44	35.4
Globe salvage rate-overall for intra-ocular RB (%)	28.2	—	—	—
• A	100	100	—	100
• B + + +	94	100	—	100
• C	83	94.7	—	100
• D	54	17.1	—	29.4
• E	0	0	—	0
Survival rates-overall (%)	75.7[b]	96.2[c]	92	89.6
• Stage 3	—	—	71 [23]	55.5
• Stage 4	—	—	0 [23]	
Kaplan–Meier analysis				
• 1 years	83	—	94	93.1
• 3 years	73	—	91	90.2
• 5 years	68	—	90	89.2

*Clinical features at presentation were based on individual eyes

#Grouping and staging at presentation was not based on worst eye

[a]A total of 16 of 77 eyes undergoing primary enucleation with available histopathology reports had HRC

[b]Survival was 86.2 and 48.2% in the intra-ocular and extra-ocular group, respectively

[c]Of the 347 patients who underwent treatment, at the last follow-up 3.7% children expired, 6.3% children were alive with local recurrence and 2.3% children had metastasis

Table 4 Details of RB children who died during the course of treatment in India

Details of children who died	Chawla et al. [18]	Singh et al. [20]*	Kaliki et al. [19]#
• Age at presentation v/s overall	35/29		44/32.6
• Extra-ocular disease	58.8	92.3%	69
• Advanced intra-ocular disease (D/E)			100
• Lag period	12		
• H/o familiar RB	8.9		

*Clinical features at presentation were based on individual eyes

#Grouping and staging at presentation was not based on worst eye

were subsequently lost to follow-up [20]. Singh et al. reported an overall enucleation acceptation rate of 79.7% [20]. Chawla et al. reported that of 10% RB children that were lost to follow-up, all (100%) of them had advanced disease (Intra-ocular Group D/E & Extra-ocular RB) [18]. These figures are alarming.

Table 4 shows details of RB children who died during the course of treatment. Chawla et al. and Kaliki et al. observed that the mean age of these children at presentation was 35 and 44 months vs. 29 and 32.6 months of the overall group, respectively [18, 19]. Most of these patients had advanced disease at presentation: 58.8–92.3% children had extra-ocular disease [18–20]. More importantly, 8.9% these children had a family historyr RB [18].

Management of Orbital Retinoblastoma in India

Contrast Magnetic resonance imaging (MRI) is the imaging modality of choice for orbital retinoblastoma to access the optic nerve and orbital extension and detect pineal tumor (trilateral retinoblastoma). Systemic evaluation and metastatic work up, including a detailed physical examination, which includes orbital examination and regional lymph node examination, complete haemogram, chest X-ray, ultrasonography of the abdomen, bone marrow biopsy, and cerebrospinal fluid cytology, are necessary to stage the disease. Whole body bone scans using Technetium-99 and Flourine-18 flourodeoxyglucose positron emission tomography (PET CT) scans are also useful for early detection of subclinical systemic metastasis [24, 25]. If regional lymph nodes are enlarged, a fine needle aspiration biopsy should be done to look for malignant cells.

In the past, orbital exenteration was used to treat patients with overt orbital disease. There is now evidence to show that a multi-modal approach comprising of neo-adjuvant chemotherapy, enucleation surgery, EBRT, and adjuvant chemotherapy is effective in cases with orbital and optic nerve spread, thus obviating the need for exenteration and better survival [26–29]. This approach consists of 3–6 cycles of high-dose systemic chemotherapy that induces tumor regression and makes the eye amenable to enucleation. More effective tumor control and a better safety profile was observed with VEC protocol as compared a 5 drug protocol consisting of carboplatin and etoposide, alternating with cyclophosphamide, idarubicin and vincristine [30]. Enucleation surgery is then followed by external beam radiotherapy 40–50c Gy given in fractionated doses to the orbit. High dose chemotherapy is continued for 12 cycles under close follow-up with a view to eradicate microscopic residual disease and prevent distant metastasis. CNS relapse was the most common cause of death in both groups [30].

Chawla et al. in a sub-group analysis of children with orbital RB at presentation at their center found that at last follow-up 39.2, 9 and 51.8% children were alive with no recurrence/metastasis, alive with metastasis and expired, respectively [18]. Metastasis to the CNS was noted in 15.7% and carried a poor prognosis [18]. Second malignant neoplasms were another major concern for survival with osteosarcoma being the commonest secondary malignancy. None of the cases was treated with orbital exenteration in this study [18].

Retinoblastoma in Thailand

The current population of Thailand is ~69 million (United Nations estimates). According to the nation-wide multicenter population-base prospective study of the incidence and survival rate of childhood cancer from Thai Pediatric Oncology Group (ThaiPOG), retinoblastoma is the 7th most common childhood cancer with the incidence of 3.1 per million population with overall survival probability at 5 years of 73% [31].

There are seven centers that provide treatment for retinoblastoma in Thailand, 4 in Bangkok (capital city) and 3 in each part of Thailand, north, northeast, and south. The survival rate of retinoblastoma in Thailand varies among each center and region of the country. Previous report from 3 cancer centers in north, northeastern and south Thailand during 1990 and 2009, which included 75 retinoblastoma patients, showed the survival rate of 40, 50 and 75%, respectively [32]. The survival rate of retinoblastoma patients from a single institute in Bangkok, which included 90 retinoblastoma patients during 1997 to 2006, showed the survival rate of 85% [33]. The overall survival rate of retinoblastoma patient from recent study in our center during 2007 to 2017 was 93% (Rojanaporn, personal communication).

Retinoblastoma in our center

Ramathibodi Hospital is a university hospital of the Faculty of Medicine Ramathibodi Hospital, Mahidol University, located in Bangkok, the capital city of Thailand. Our center

is currently the only center in Thailand and South East Asia region that has all the treatment modalities for retinoblastoma including systemic chemotherapy, intra-arterial chemotherapy (IAC), subtenon chemotherapy, intravitreal chemotherapy, cryotherapy, transpupillary thermotherapy (TTT), external beam radiotherapy (EBRT), and plaque brachytherapy with Ruthenium-106 (Ru-106).

Treatment of retinoblastoma

Treatment strategies were selected based on the disease stage, laterality, tumor location, visual prognosis, and input from the patient's family. EUA was performed during the course of treatment to evaluate treatment response.

Primary enucleation was recommended in unilateral advanced ICRB group D, or ICRB group E. However, in Thailand, where samsara is a common Buddhist belief, enucleation is assumed to affect one's well-being in the next life, making the procedure highly stigmatized. In cases that the parents strongly denied enucleation, we had to offer IAC or CRD, knowing that the chance of globe salvage is very poor. In this group of patients, enucleation after the failure of previous treatment would be more acceptable to the parents.

Extraocular retinoblastoma

Patients with extraocular tumors were given 3–6 cycles of high-dose chemotherapy, followed by enucleation or exenteration, external beam radiation therapy (EBRT), and adjuvant chemotherapy for 12 cycles, as previously described [28, 29].

Our 10-year results

There were 92 eyes of 61 retinoblastoma patients who were treated in our center during 2007 to 2017. The median age at diagnosis was 8 months (range, 1–48 months). Twenty-nine patients (47.5%) were male. Thirty patients (49%) had unilateral retinoblastoma. Two patients had familial retinoblastoma (3.3%). The most common presenting symptoms were leukocoria (72%) and strabismus (12%). According to IRSS classification, 45 eyes (49%) were IRSS stage 0, 44 eyes (48%) were IRSS stage I, and 3 eyes (3%) were IRSS stage III. Most of our patients (76%) presented with advanced retinoblastoma. Of 92 eyes, 38 eyes (41%) had ICRB group E, 25 eyes had ICRB group D (27%), and 7 eyes (8%) had extraocular retinoblastoma at presentation. Of 85 eyes with intraocular tumors, 67 eyes (79%) received globe salvage therapy, including CRD alone in 36 eyes (42%), CRD combined with other treatment modalities (IAC, IVT, Ru-106, or EBRT) in 25 eyes (29%) and primary IAC in 6 eyes (7%). Secondary enucleation was performed in 22 eyes (26%) after demonstration of poor response to globe salvage therapy, while primary enucleation was performed in 18 eyes (21%), which were eyes with advanced ICRB group D or ICRB group E. High-risk pathological features were found in the enucleated eyes of 8 patients with unilateral tumor, which all received post-enucleation adjuvant chemotherapy.

At the median follow-up period of 26.8 months, the overall globe salvage rate of intraocular retinoblastoma was 53%, with a globe salvage rate of 100% in ICRB Group A, B and C, 60% in Group D, and 21% in Group E. The overall survival rate was 93%. Four patients passed away due to brain metastasis, febrile neutropenia, chemotherapy toxicity and secondary acute myeloid leukemia.

Genetic testing

Genetic testing was done in 52 patients (Rojanaporn, personal communication). We screened *RB1* mutations in our patients by using direct sequencing in combination with Multiplex Ligation-dependent Probe Amplification (MLPA). Of 52 patients, 27 patients (52%) had unilateral retinoblastoma, and 25 patients (48%) had bilateral retinoblastoma. Germline mutation was detected in 92% of bilateral retinoblastoma patients. Interestingly, we found high incidence of germline mutation in our unilateral retinoblastoma patients (33%).

Retinoblastoma in Singapore

Singapore has had a unique experience regarding the incidence and management of retinoblastoma. Singapore's population has grown from 3.25 million in 2002 to the current population of about 6 million. Consequently, the annual incidence has risen from 1–3 patients to 2–5 patients per year. There are 2 main centers that manage retinoblastoma in Singapore. We herewith share the 15-year experience of the Retinoblastoma service, Dept. of Ophthalmology, National University Hospital. This dedicated team is comprised of Ophthalmic oncologists (Oculoplastic surgeon, Vitreoretinal surgeon, Pediatric Ophthalmologist), Pediatric oncologist, neurointerventional radiologist, ophthalmic pathologist and the Ocularists. Given Singapore's geographical location within Southeast Asia, comprising 11 nations, it is one of the centers of referral for challenging medical conditions. Consequently, retinoblastoma patients at various stages and for varied indications are referred to the National University Hospital [34]. Most patients were referred from Indonesia, Vietnam, Myanmar, Malaysia & Brunei with occasional patient from Russia, Sri Lanka, India, Philippines and Papua New Guinea. Each of these nations has unique cultural, religious and economic background with highly variable basic medical and advanced

Table 5 Retinoblastoma presentation at National University Hospital, Singapore

Age at presentation	1–72 months (mean 16.4 months)[a]
Gender	Female 34 (56%); Male 27 (44%)
Laterality	Unilateral 36;Bilateral 25
Nationality (in descending order)	Indonesia 29.5%, Vietnam 21.3%, Singapore 20%, Brunei 9.8%, Malaysia 6.6%, Myanmar 4.9%, Others(India, Sri Lanka, Papua new Guinea, Timor Leste & Russia)
Grouping	Group A 1.16%, Group B 8.2%, Group C 26.3%, Group D 39.3%, Group E 24.7%
Staging	Stage 0 83.6%, Stage I 8.2%, Stage II 1.6%, Stage III 1.6%, Stage IV 4.92%
Interventions prior to referral	None 85%, Enucleation of 1 eye 11.5%, enucleation of both eyes 1.6%, Intravitreal anti-VEGF injection 1.6%.

[a]Excluding one 24 year old patient with advanced unilateral disease at presentation

surgical/interventional medical services. Since the development of a dedicated Retinoblastoma service, there had been significant changes in ophthalmologic and systemic assessment, and thus their staging and management with evolution from the historical Reese-Ellsworth classification to the currently practiced International (ICRB) Classification [35].

86 eyes of 61 patients were managed over a 15-year period. A summary of the retinoblastoma patients is shown in Table 5.

Following a complete evaluation with appropriate Grouping and Staging, one or more of various interventions were performed. The most common immediate intervention was primary ocular enucleations, in 15 of 86 eyes (17.4%). 3 of these 15 eyes (20%) had histopathologic high-risk characteristics, warranting adjuvant chemotherapy. Eighteen patients who had been referred primarily for ocular enucleation underwent neoadjuvant chemotherapy. Chemotherapeutic regimens included VETOPEC (Vincristine, Etoposide and escalating doses of Cyclophosphamide) in three patients (prior to 2004) and VEC (Vincristine, Etoposide and Carboplatin) in 15 patients since. Of the 15 patients who received VEC regimen, 13 had bilateral retinoblastoma and two had advanced unilateral retinoblastoma. While all Group E eyes were unsalvageable, requiring enucleation, all contralateral eyes were salvaged, most with functional vision to lead independent and subsequently disease free lives.

Intraarterial chemotherapy for retinoblastoma was introduced at the National University Hospital, Singapore in 2014 and to date remains the only centre to offer it. Eight patients underwent intraarterial chemotherapy with an age range of 8–34 months. Spectrum of indications included parental choice to avoid systemic chemotherapy and enucleation ($n = 4$), only remaining eye with advanced disease having failed systemic chemotherapy ($n = 2$) and parental choice despite advanced Group E disease ($n = 2$). Spectrum of chemotherapeutic agents administered intraarterially included Melphalan, Topotecan and Carboplatin ($n = 8$). The number of cycles administered ranged from 2–5 cycles. Four of eight eyes (50%) were salvaged with intraarterial chemotherapy and consolidation therapy. Tumor Groups of these four salvaged eyes included Group C ($n = 2$), Group D ($n = 1$) and Group E ($n = 1$). One child who had failed intraarterial catheterization at 12 months of age underwent bridging chemotherapy followed by subsequent successful IAC with globe salvage. Another child with bilateral advanced retinoblastoma, post-enucleation of one eye, underwent 5 cycles of IAC. While the posterior segment tumor completely resolved she developed anterior chamber seeds, was advised intracameral chemotherapy but defaulted follow-up. Except for two patients with failed cannulation there were no major complications encountered.

Consolidation treatments

With emerging trend of chemoreduction and increasing globe salvage, local consolidation treatment is being increasingly offered. These include transpupillary thermotherapy, transscleral cryotherapy and intravitreal chemotherapy. While exenterations, periocular chemotherapy and external beam radiotherapy are rarely performed these days, plaque brachytherapy, and intracameral chemotherapy are becoming more important with globe salvage treatment.

Outcomes

Principles of management of retinoblastoma include life salvage, followed by globe salvage and whenever possible vision salvage. When enucleation is performed, socket rehabilitation with a primary orbital implant and customized ocular prosthesis are just as important and becomes the 4th goal of ideal management.

Life: 57 of 61 patients were alive and disease free at last follow-up post treatment. Spectrum of the four patients who succumbed to the disease all of whom were referred from the region are shown in Table 6 below.

Table 6 Spectrum of presentation of 4 patient mortalities at National University Hospital, Singapore

Patient 1	3-yr old with recurrent orbital disease and intracranial extension, with history of enucleation without histopathology control
Patient 2	3-yr old post-enucleation of one eye without histopathology control, presenting with metastasis and undiagnosed Group C tumor in the contralateral eye.
Patient 3	6-yr old who had undergone enucleation followed by external beam radiotherapy, referred for management of advanced contralateral disease with vitreous seeding, with incidental finding of an undiagnosed pinealoblastoma.
Patient 4	5-yr old diagnosed as 'Coat's disease' who had undergone multiple intravitreal anti-VEGF injections presenting with Stage IV metastastic disease.

Globe & Vision salvage: All 13 patients (100%) with bilateral retinoblastoma who underwent systemic chemoreduction with VEC protocol, had at least one globe salvaged, with functional vision sufficient to lead independent lives with low vision management where indicated. Four of eight eyes (50%) who had undergone intraarterial chemotherapy had globe salvage, one of them with 20/40 vision.

Socket rehabilitation: All patients who underwent either a primary or a secondary ocular enucleation received primary orbital implantation with an alloplastic implant followed by customized ocular prosthesis [36]. Two of these eyes developed recurrent exposure of the orbital implant requiring secondary orbital implant exchange ($n = 1$) or dermis fat graft placement ($n = 2$) with satisfactory outcome. Five of six patients who had undergone ocular enucleation prior to referral with second eye disease underwent secondary orbital implantation and customized ocular prosthesis.

Discussion

RB has transformed the molecular understanding about cancer pathogenesis [37]. Over the last century, retinoblastoma management has evolved from >95% mortality to >95% survival in developed nations [4]. Although no validated geographic or population preponderance has been noted, Asia-Pacific and Africa has the greatest disease burden owing to the large population with high birth rates [1]. Studies from different parts of the world have shown a wide variation in the clinical presentation and survival outcomes of children affected by retinoblastoma [7]. Analyzing retinoblastoma outcome data Canturk et al. found that survival correlates with human development index: 40% (range 23–70) in lower-income countries (LICs), 77% (range 60–92%) in lower-middle income countries (MICs) and 79% (range 54–93%) in upper MICs [15]. In Great Britain for the study period of 1998–2002 the 5 year survival rates was 97% for unilateral Rb and 100% for bilateral Rb [8]. In US over the period of 30 years the 5 years reported actuarial survival rates increased from 92.3% (1975–1984), to 93.9% (1985–94) to 96.5% (1995–2004) [9]. Survival rates reported from India were 75.7 to 92% with a mean/median follow-up of 21–44 months [18–21]. Survival rates reported from less developed countries like Taiwan, Africa, Kenya, and Nepal are 64.41, 57.7 and 26.6%, 23.8%, respectively [11–14].

There is little awareness about retinoblastoma in developing countries, even when a history of familial RB exists. This is exemplified by the fact that children with familial RB do not present early (24 months in familiar group vs. 29 months in overall group) and have significant mortality (constitute 8.9% children of those who died) [18]. Some of the reasons being, lower literacy rate, inadequate health-care facilities at the primary and secondary levels of health care, delays in the referral system, lack of facilities for genetic counselling and testing in resource limited setting. Leander et al. showed that RB awareness program linked to the national vaccination campaign in Honduras resulted in early presentation of RB, the first inexpensive step towards improving survival [38].

Previous studies have found has no sex predilection in RB. In contrast, a male preponderance (nearly 60%) was noted in all studies from India [18–21]. This is attributed to lack of attention to the female child in resource-limited setting owing to socio-economic and cultural reasons [39].

Singh et al. found that nearly 53.5% of the children were from rural areas and 13% children were from below poverty line (BPL) families [20]. Children from rural background and economically backward classes constitute a risk group. Children with a lower socioeconomic status were less likely to receive the recommended therapy and experience less favourable outcomes as compared to those with a higher socioeconomic level [40]. Issues include poor awareness, lack of trained primary health care workers, belief in indigenous system of medicine, accessibility to specialized treatment centers located in first-tier cities and financial constraints [16]. Most children would have advanced disease at presentation requiring complex, multimodal long duration of treatment resulting in poor compliance to treatment and loss of follow-up. Co-morbidities like lack of immunization, respiratory and gastrointestinal infections and malnutrition are more prevalent which further increase the morbidity and mortality. Chawla et al. reported that 13 of 146 children had died of disease unrelated to RB [18].

Singh et al. and Chawla et al. reported a mean delay in presentation was 3 and 8.3 months, respectively [18, 20]. In

contrast, shorter median lag period was reported in developed countries: England 8 weeks, United States 1.5 months for unilateral RB [8, 9]. The difference in age of presentation among countries largely present the lag time to seek medical care, an indirect indicator of awareness about retinoblastoma and consequently advanced disease at presentation. Delay correlates with progression to advanced disease, which in turn is associated with higher mortality [5]. Chawla et al. reported that survival probability for children with lag period of less than 3 months was 89, 78 and 68%, respectively, at the end of 1 year, 2 years and 5 years, as compared with 76, 67 and 59% for those with a lag period of more than 6 months [18].

Incidence of orbital RB in developed countries is low. Ellsworth et al. reported the incidence rate of orbital RB was 8.2, 7.6 and 6.3% between the years 1925–1959, 1959–1974 and 1980–1986, respectively, further exemplifying the decreasing trend [41, 42]. In contrast, incidence rate as high as 36 and 40% have been reported from developing countries like Taiwan and Nepal, respectively [11, 43]. extra-ocular spread is associated with a 10–27 times higher risk of metastasis [44] and was predictive of low survival (hazard ratio 5.04, $P < 0.001$) [45]..

Chawla et al. reported that of the total 434 children with intra-ocular RB, 60 children died [18]. Various causes were responsible such as the presence of microscopic residual disease and non-compliance to treatment [18]. Factors contributing to mortality are advanced intra-ocular disease (73–78%) with high-risk HPE requiring complex multimodal treatment [22, 46]. Defining a standard of care that is valid in both developed and developing countries alike is difficult [4]. In ideal conditions, treatment of RB requires a multi-disciplinary team consisting of ophthalmologists, pediatricians, oncologist, anesthetist, geneticist, pathologists, trained nurses under one roof [47]. Although cure at any cost is the goal in all developed countries today, governments in less developed countries are plagued with multiple high priority diseases like malaria, pneumonia and diarrhea more than RB, a relatively rare disease. Compared to primary enucleation, globe salvage therapies require multiple cycles of chemotherapy with focal consolidations. Therefore, in terms of patient time, technological requirements cost and consequently poor compliance, enucleation may be preferred in less privileged countries.

Denial of treatment, poor compliance of treatment and low enucleation rates are issues unique to developing countries that needs to be addressed [16]. In a study by Chawla et al., lack of compliance towards treatment was noted in 25% cases that expired. Survival of patients whose families refused treatment even temporarily were significantly lower than those who did not refuse treatment [48]. Reasons for refusal included parental belief in alternative medicines, culture and social stigma. For example, fear of cosmetic disability hindering marital prospects post enucleation, especially of a female child, is common [16]. Moreover, refusal rate rises when health care specialists do not communicate effectively with the parents, meeting the psycho-social needs, explaining about retinoblastoma and its goals of treatment, management plan, excellent outcomes with good compliance and cosmetic rehabilitation post-enucleation [49]. Counselors, nurses, social workers, support groups may fill the void to gain the trust and overcome socio-cultural barrier in resource poor setting where health care system are over-burdened limiting the time a specialist can spend [49]. In developing nations care providers of traditional medicine are the first point of contact in most cases and preferred over the cosmetically disfiguring surgery of enucleation and monthly chemotherapy [16]. Because of the deep-rooted faith, appropriate and timely counselling by the care-providers of traditional medicine would be crucial in saving a life.

Concerted efforts towards overcoming socioeconomic and cultural factors will help in reducing the survival gap between the developed and developing countries. Possible steps include disease education and counselling, highly subsidized/free of cost treatment for low socioeconomic strata, raising funds through the government and non-governmental organizations. Sensitization and training of ophthalmologists and paediatricians for early detection of retinoblastoma through a nationwide awareness campaign is required. The use of telemedicine for continuing education and consultation, identification of an apex center that could mentor other centers using a twining model and imparting specific training to health care providers can help to reduce delays in referrals [50].

In conclusion, our challenges in developing nations are not just technological, but also social. The true advances will not be made until the survival advances are extended to all the children in less developed countries in a meaningful and effective way. Education and universal screening alone plays an important role in addressing this factor.

We would also like to emphasize that this article is a view point of the authors given the published data and may not represent entire Asia.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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The ROYAL COLLEGE of OPHTHALMOLOGISTS

REVIEW ARTICLE

基于深度学习算法的眼底彩照在糖尿病视网膜病变检测中的应用

摘要：

生物医学研究的显著进步已经进入大数据时代。利用人工智能使在更短时间内、人工干预更少的情况下从大量数据中提取有意义的信息成为可能。实际上，脑回神经网络(一种深入的学习方式)已经可以从图像中识别病理病变。糖尿病的发病率很高，成千上万的人需要进行糖尿病视网膜病变(DR)筛查。深层神经网络在视网膜图像筛查DR中呈现明显优势，提高了识别DR病灶及疾病危险因素的准确度和可靠性。本文旨在提供和比较目前各种深度学习模式用于糖尿病视网膜病变的诊断的证据。

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The ROYAL COLLEGE of OPHTHALMOLOGISTS

REVIEW ARTICLE

Fundus photograph-based deep learning algorithms in detecting diabetic retinopathy

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Abstract

Remarkable advances in biomedical research have led to the generation of large amounts of data. Using artificial intelligence, it has become possible to extract meaningful information from large volumes of data, in a shorter frame of time, with very less human interference. In effect, convolutional neural networks (a deep learning method) have been taught to recognize pathological lesions from images. Diabetes has high morbidity, with millions of people who need to be screened for diabetic retinopathy (DR). Deep neural networks offer a great advantage of screening for DR from retinal images, in improved identification of DR lesions and risk factors for diseases, with high accuracy and reliability. This review aims to compare the current evidences on various deep learning models for diagnosis of diabetic retinopathy (DR).

Introduction

Proliferative diabetic retinopathy and diabetic macular edema are the two retinal sight threatening complications of diabetes. Screening and timely treatment of these complications have been shown to reduce blindness [1] due to these complications in the countries where these services are well established such as the United Kingdom. In England and Wales, patients with diabetes diagnosed by their General Practitioners are registered in a diabetes register and diabetic retinopathy screening services invite each patient for annual screening of the retina under mydriasis using standard cameras [2]. The images are graded systematically by trained trainers and images may be arbitrated if required. The re-call and referral pathways are also well-defined with minimal standards set for each severity grade of diabetic retinopathy.

Attempts to replicate these systematic diabetic retinopathy screening programs in low and middle income countries have not been successful. There are several challenges faced by these countries. First and foremost, the absolute numbers of people with diabetes and undiagnosed diabetes are significantly higher than in the United Kingdom. As an example, only about 4 million people with diabetes need to be screened annually for sight threatening complications in the United Kingdom. In contrast, there are over 70 million people with diabetes in India alone and an equal numbers of pre-diabetic or undiagnosed diabetes [3]. The primary care infrastructures of most low and medium income countries are in their infancy. Standard retinal cameras are too costly, electronic patient records are non-existent to develop a diabetes register and most importantly, there is significant shortage of trained personnel to capture the retinal images and grade them and to treat them. From the Asia-Pacific perspective, it is currently neither practical nor economical to have trained health care providers screen all 231 million (153 million and 78 million from Western Pacific and Southeast Asia, respectively) [4].

Therefore, there is an unmet and urgent need to develop bespoke clinical and cost-effective screening and treatment pathways that can cover at least the majority of the population with diabetes.

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Deep learning (DL) is a new Artificial Intelligence (AI) machine learning technique, and its use in the medical field has generated much interest over the last few years. DL mimics an infant's brain, which is like a sponge and learns through training. This technique can also be potentially used to detect diseases, as it can identify and classify data, image or a sound [5]. AI-chatbots with speech recognition capability have been explored to identify patterns in patient symptoms to form a potential diagnosis [6]. Researchers are using DL to train algorithms to recognize cancerous tissue comparable to trained physicians [7]. Likewise, the images from a fundus camera, microscope or radiography are being classified by DL and compared with the trained physician. Recently, DL has also been used to identify risk factors associated with cardiovascular diseases (e.g., blood pressure, smoking and body mass index) from retinal photographs [8].

Over the past 2 years, there are many evidences on the use of DL algorithms to identify diabetic retinopathy (DR) either a binary model or multi-classifier models. This review aims to compare the current evidences on various DL models for diagnosis of DR.

Overview of deep learning methods

DL algorithm is considered as a fourth industrial revolution. It is based on learning features from the data. It processes large amount of data and extracts meaningful patterns from them [9]. In deep neuronal learning, the convolutional neural networks (CNNs) learn to perform their tasks through repetition and self-correction. A CNN algorithm teaches itself by analysing a labeled training set of expert-graded images and provides a diagnostic output [10]. If the network's diagnosis is wrong, the algorithm adjusts its parameters suitably to decrease the error. The network repeats the process for every image, until the system's output agrees with that of the human expert graders. Once the algorithm optimizes itself, it is ready to work on unknown images. Deep neural networks can detect subtle changes, patterns or abnormalities that may be possibly at times be overlooked by human experts [11].

The DL architecture found to be most suitable for imaging data is that of the CNNs [12]. Such networks contain special type of layers that apply a mathematical filtering operation known as convolution, making the individual neuron process data only for its receptive subfield. As the input image is processed with successive convolutional layers of the network, the filters in the process get stacked together creating progressively more descriptive feature detectors. During training, these individual detectors are then adjusted to detect those specific image features that are required to solve a particular image recognition task. Trained with large annotated datasets, these CNNs allowed computers to start recognizing visual patterns [13].

The entire approach in DL in DR does not involve judgment of individual retinal lesions and the feature extraction process is entirely automatic. The core analysis engine of most of the AI software used for retinopathy detection contains DR analysis algorithms—those for image enhancement, interest region identification, descriptor computation and screening classification in conjunction with an ensemble of deep neural networks for classification tasks such as image quality detection, diabetic retinopathy severity classification and detection of diabetic macular edema (DMO). Referable DR (RDR) is the main parameter identified by most AI algorithms and is defined as the presence of (i) moderate non-proliferative DR (NPDR) or higher and/or (ii) CSMO. Sight threatening DR (STDR) is defined by the presence of severe NPDR, proliferative DR (PDR) and/ or DMO [14].

Deep learning algorithms in DR: current evidences

Different statistical measures are available to quantify the performance of the model. The performance is measured by: sensitivity, which measures how many positive samples were correctly identified and, specificity, which measures the proportion of correctly identified negative samples. The graphical plot of a receiver operating characteristic (ROC) curve is used to find a trade-off between them. Receiver operating characteristic curves make use of the fact that many methods of labeling the image (grading) generate probabilities of assigning an input data sample to each possible output label. By changing the probability threshold for a decision, the proportion between the positive and negative label outputs change and, in this way, either the sensitivity or specificity of the model increases. In order to measure the overall performance of the algorithm, independent of a specific threshold and application, the area under the ROC curve (AUC) is used. The value of AUC lies between 0.5, which corresponds to a random guess, and 1.0, which shows 100% of specificity and sensitivity. All the current evidences in DL use these measures to evaluate the performance.

One of the earliest studies [15, 16] on automatic detection of DR from color fundus photographs was by Abramoff et al. in 2008 [17]. It was a retrospective analysis done with non-mydriatic images from EyeCheck DR screening project. They were able to detect RDR with 84% sensitivity and 64% specificity. In 2013, Abramoff et al. [18] published the results of sensitivity and specificity of the

Iowa Detection Program (IDP) to detect RDR and found a high sensitivity of 96.8% and specificity of 59.4%. The area under the AUC was 0.937.

In 2015, Solanki et al. [19] used their EyeArt AI software with Messidor2 dataset. EyeArt screening sensitivity for RDR was 93.8%, the specificity was 72.2% and the AUC was 0.94. In their next study, they evaluated an automated estimation of microaneurysm (MA) turnover, a potential biomarker for risk of progression of DR the tool identified new and disappeared microaneurysms with 100% sensitivity.

Since 2012, a large number of commercially available software were developed by many companies for the automated detection of DR, known as automated retinal image analysis systems (ARIAS). Tufail et al. [20] conducted a study in 2013 and published in 2017 to evaluate these systems. Retinal images analysed by three automated retinal image analysis systems namely iGradingM (UK), Retmarker (Portugal) and EyeArt (USA) were compared to standard manual grading of DR by human graders/ophthalmologists. EyeArt and Retmarker have higher sensitivity for RDR than human graders.

Abramoff et al. [21] in 2016 showed in their study that the integration of CNN to an existing DR detection algorithm resulted in improved detection of RDR by minimising the number of false positives. Using the Messidor-2 data set, a sensitivity of 96.8%, and a specificity of 87% for RDR was obtained in their study. The specificity improved from 59.4 to 87% when compared with their previous study in 2013. This hybrid screening algorithm, known as the IDx-DR became the first commercially available AI device to get US Food Drug Administration (FDA) approval for DR screening in April 2018. The IDx-DR is able to detect RDR (more than mild [mtm] DR) with a sensitivity of 87.4% and a specificity of 89.5%.

In 2016, Gulshan et al. [22] reported the results of the Google DL DR validation study. The algorithm was trained using 128,175 macula-centered retinal images obtained from EyePACS in the United States and retinal images from eye hospitals in India. In the break-through major validation study of Google algorithm for DRdetection, Gulshan et al. reported a high sensitivity and specificity for RDR (sensitivity of 97.5% and specificity of 93.4% in the EYEPACS-1 and 96.1% sensitivity and 93.9% specificity for Messidor-2 set).

A study by Gargeya et al. [23] with another DL algorithm to detect all stages of DR, showed a sensitivity of 94% and a specificity of 98% for RDR, with an AUC of 0.97 with EyePACS. External validation was done on the MESSIDOR-2 and E-Ophtha datasets in this study. Their study focused on identification of mild NPDR and not just RDR.

The most recent major study that reported on validation of DL was by Ting et al. [24] in Singapore. Their study included multiple retinal images taken with conventional fundus cameras from multiethnic cohorts of people with diabetes and their algorithm showed a high sensitivity and specificity for identifying DR and other eye diseases such as age-related macular degeneration and glaucoma. The sensitivity and specificity for RDR was 90.5% and 91.6%, respectively and for STDR, the sensitivity was 100% and the specificity was 91.1% in their study.

Another breakthrough was the study from India that used EyeArt™, the AI software on Remidio Fundus on Phone (FOP) mydriatic smartphone-based retinal images and showed 95.8% sensitivity and 80.2% specificity for detection of any DR, and 99.1% sensitivity and 80.4% specificity in detecting STDR [25]. The sensitivity and specificity for RDR was 99.3% and 68.8%, respectively.

There are many other algorithms like automated retinal image analysis systems which are suitable for automated detection support for both retinal photography and optical coherence tomography (OCT). Pegasus, a retinal AI platform developed by Visulytix (London, UK), supports comprehensive image analysis with both fundus imaging and OCT of the macula. It screens for glaucoma and age-related macular degeneration simultaneously while providing the severity of DR with a referral commendation. It identifies specific pathological retinal lesions and hence also allows the user to open the AI black box.

Assessing ground truth in studies

Within the last few years, there has been an exponential growth in the number of studies published on automated methods, especially DL for DR classification. It is also becoming clear that different studies have implemented substantially different approaches in determining the reference standard ("ground truth") that was used to measure and report the performance of their algorithms. The methodology and the quality of the reference standard can have a significant impact on the performance of the algorithms and this makes it challenging to compare different algorithms based on the performances published in these studies.

The classification of an image between one of the five DR grades involves evaluation of subtle lesions on retinal images. Additionally, these retinal images may vary in quality resolution, color, among other characteristics based on the camera used to acquire and software used to visualize the image. This makes DR grading a challenging and subjective process resulting in significant intergrader variability, as has been demonstrated by several studies [26–29]. Studies generally have multiple graders that read the same

image and come up with a method to resolve the disagreement between the grades. One method includes assigning a senior grader as an arbitrator to resolve the disagreement among grades from other graders. A study [20] comparing different automated DR image assessment software, used a modified version of this technique to resolve any disagreement between human grades and automated software grades to come up with a reference standard. Another approach is to come up with a consensus grading outcome as the final reference standard grade. In this approach, the image is sequentially assigned to individual graders until a certain number (usually three) of consistent grading outcomes are achieved. A study [30] evaluating the feasibility of AI-based DR screening algorithm at endocrinology outpatient services used this approach. Another approach as employed by Gulshan et al. [22] is a simple majority decision where the reference standard grade is considered to be the one with which a plurality of graders agree from a group of 3 or more independent graders. Another method, usually known as "adjudication", is where a group of 3 or more graders first grade each image independently and then discuss all disagreements until they are resolved. Krause et al. [31] examined the variability in different methods of grading, definition of reference standards and their effects on building DL models for detection of diabetic eye disease. In their study, the adjudication process resulting in a consensus grade from multiple retina specialists provided a more rigorous and less noisy reference standard for DL algorithm development, which also led to superior algorithm performance. Their study shows an improvement in the algorithm AUC to 0.986 from 0.930 for predicting mild or worse DR when using adjudication as the reference standard compared to majority decision while increasing image resolution. The study also yielded other insights about the discussion precision above the level typically used in everyday clinical practice. Other reference standard definition methods such as arbitration, consensus and majority grade don't officially include a step where individual graders get to discuss the rationale for their initial grade. This may be an important step for graders to ensure there is a consistent understanding of the grading guidelines between them and can help resolve disagreement.

The study by Krause et al. [31] also recognized that, although precise, the adjudication process is time consuming, costly and may not be a very practical approach for grading thousands if not millions of images for training the DL algorithms. They demonstrated a more pragmatic approach of adjudicating a small subset (0.22% in their cases) of the image grades used for development to make a "tuning" set, which, combined with existing clinical grades for the training set, significantly improved model performance without the need for adjudicating the entire training set.

Development dataset size its implications

For DL algorithm development, the dataset is usually divided into a train set, a tune set and a validation (or test) set. The train set is used for training the model parameters and the tune is used for determining algorithm hyperparameters and other model optimization choices. Finally, the validation set is used for measuring the final model performance. A general and traditional rule of thumb that DL scientists have used for a dataset on the order of 10,000 images or less is to split up the dataset as 70/20/10 percent (train/tune/validation). With datasets sizes getting much bigger recently (millions of images in some cases), it might be an acceptable approach to have a much smaller split for the tune and validation set and assign the majority of the cohort to the train set. However, it is still critical to have reasonably sized tune and validation sets with appropriate representation of each of the output classes being considered since the performance of the algorithm will be measured against those sets. As discussed in the previous section, the quality and precision of reference standard for the tune and validation sets may be critical for achieving algorithm performance improvements.

The overall size of the dataset required for training DL algorithm is dependent on various factors, including but not limited to one's desired output, performance target, and variability of the input data and the labels. Starting with a general example, suppose the goal of the algorithm is to classify images into two categories: images with dogs and images with cats, then in such an example, the dataset required to achieve an acceptable performance might be much smaller than one needed to train an algorithm for a more difficult task, e.g., classifying images into different breeds of dogs. To extrapolate this to DR, an algorithm that only classifies images into RDR and non-referable for DR might require fewer training images than one classifying image into a five-point International Classification of Diabetic Retinopathy (ICDR) grades. In addition, if any of the desired output categories has a low prevalence in the development dataset, the algorithm might need more images for that category in order to perform well. For example, proliferative DR (PDR) has a low prevalence in the general diabetic population, and some of its manifestations could be very rare, so more PDR images might need to be supplied in the training dataset.

The desired performance for the algorithm also plays a critical role in determining the size of the dataset. It is important to set these performance targets based on how the

algorithm is expected to be used. For DR, this could be determined by the target user: eye care providers or primary care providers. It could also be influenced by where the algorithm is expected to be used (low resource settings or high resource settings), if it would be used for screening or diagnostics, and if the algorithm is expected to be used as a primary read device or an assistive tool.

Finally, the variability in development data could also lead to significant changes in the dataset size required for acceptable performance. In the case of fundus images, variability may be caused by usage of fundus cameras of different manufacturers, different models of the same manufacturer, and different image acquisition technique (field of view, field location, flash intensity, image resolution, camera operator etc.). Variability in the grades or labels for these images is also important to consider. If one is using existing clinical grades that come with the images, variability may come from the grading rubric that was used to grade those images. Even if different clinical sites grade use standard grading rubrics, there are often differences in how different they grade images because some may be grading for screening and others for diagnosis, treatment or management as their primary goal may be to have an effect on the overall DR grade. Having such insights about one's dataset helps in determining such variability. To compensate, dataset size may be increased, or potentially a smaller subset of images may be adjudicated for a high quality reference standard, which may help balance out some of the noise in the labels of the train set as discussed by Krause et al. [31].

Image quality and deep learning

For DR screening, a basic requirement is to be able to acquire an image of the patient's retina that shows the macula and optic disc with sufficient image resolution, contrast and fidelity. Retinal cameras have been used by ophthalmologists for decades to image, diagnose, and document retinal pathologies. The retinal camera technology has made several advancements over the last few decades with improvements including but not limited to better image resolution, non-mydriatic imaging, comfort usability for patient and operator, extent of the retina that can be visualized and reducing the cost of the device. There are even several smartphone camera attachments now available that demonstrate the feasibility of performing retinal imaging while compromising on field of view and image quality. Expansion of screening programs to remote and rural areas can benefit from such devices since they are usually inexpensive and portable. However, most of these devices require dilation to capture images of sufficient quality [32]. These devices are usually hand-held that can make patient alignment, fixation and focus more challenging compared with more traditional fundus cameras. The latter have internal and external fixation aids along with a chin rest and head rest to stabilize the patient for easier image acquisition. It is to be noted that some smartphone-based retinal cameras [25, 33] offer a much smaller field of view (~20°) compared to a 45° field offered by traditional desktop cameras. One of the smartphone based retinal camera devices has made an effort to overcome some of these limitations and has proposed a Fundus on Phone (FOP) device that fits right onto a slit lamp stand, providing the stability to the operator and patient. A study published comparing FOP to a traditional desktop based fundus camera showed that FOP had reasonable sensitivity and specificity in detecting DR of varying severity [34]. However, they also acknowledged in this single hospital study that the quality of the images of FOP system was not as good as that obtained from the conventional desktop camera. Several handheld non-mydriatic cameras (non-smartphone based) have also been available for retinal imaging. They also offer a relatively less expensive method of capturing fundus images compared to traditional non-mydriatic cameras and also offer similar field of view (40°–45°) without requiring dilation. These cameras do however still have the limitation of handheld operation resulting in instability for operator and patient, as mentioned earlier. A study [35] to validate one of these handheld cameras for DR concluded that such devices might be adequate for DR screening in primary care centers and mobile units; however, there is room for improvement in terms of image quality, ease of operation and patient comfort. Traditional desktop fundus cameras do address many of the limitations of the smartphone-based and handheld cameras, however they do have a larger footprint, making portability a challenge and can be cost prohibitive depending on where the care is being provided.

The Early Treatment Diabetic Retinopathy Study (ETDRS) group introduced stereoscopic color fundus photography in seven standard fields as the gold standard for the detection and classification of DR. It can be very time-consuming to capture a set of seven-field ETDRS images on traditional fundus cameras that require pupil dilation and a skilled operator. To address this, an ultrawide-field imaging device that can visualize the peripheral retina in a single capture without dilation, has been shown [36] to improve diagnosis and classification of DR.

For DL algorithms that can automatically classify fundus images for DR for screening purposes, the quality of images being input is key. Many of these DL algorithms are now trained on several thousands to even millions of images, and owing to a rich mix of images in this training data they are able to accept some noise, artefacts and misalignments. However, most algorithms also specify the minimum

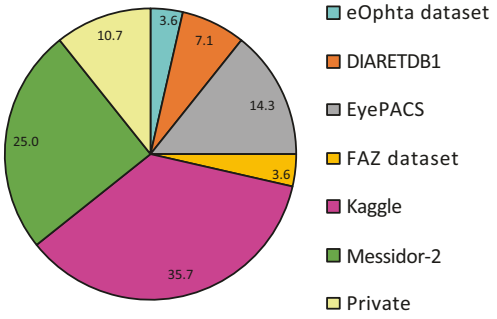

Fig. 1 Public datasets used % in the development and validation of deep learning algorithms ($n = 28$)

requirements in terms of image quality that will be acceptable for providing a diagnosis. One approach to convey image quality assessment is an image quality score (very commonly used in optical coherence tomography images, known as signal strength) and the second one may be to call an image of insufficient or sufficient quality for diagnosis by an algorithm similar to how it is done by IDx-DR [37]. It is important for groups that are setting up DR screening programs and plan to use automated DR classification methods to recognize that even though some cameras may offer inexpensive ways of capturing fundus images, if the rejection or ungradable rate for these images is too high, it could impact the success of the program. For all images that are deemed ungradable by the algorithm, it is prudent to recommend the patient to be seen by an eye-specialist since a referral/non-referral recommendation could not be made. If the rate of these ungradable images is high because of the quality of the retinal camera being used, the program may result in too many false positive referrals, leading to higher patient care costs, not to mention the frustration for the operator and patient if image retakes are needed.

Presence and absence of the disease and staging of the disease

The standardized diabetic retinopathy classification schemes enable a multidisciplinary approach where different medical specialists, including retina specialists, general ophthalmologists, optometrists, internists, endocrinologists, and family care physicians use the same language for giving an optimal care to the patient.

The AI systems have used binary information like presence or absence of DR [25, 38], and RDR or non-referable cases [17, 25] or multiple staging like the international clinical diabetic retinopathy disease severity scale for DR (ICDR) [14] and early treatment diabetic retinopathy study (ETDRS) [39] to classify the disease. For screening, both classifications have their own value. The five-point grading also provides information about urgency of referral rather than just RDR/no-referral. When the multiple staging is used, it is important to see that the sample size are calculated to power for individual stages, particularly the STDR.

Is there an effect of race/ethnicity or fundus pigmentation?

The density of the background pigmentation of the fundus oculi is different for different races. Some fundi are lightly pigmented often called “blonde” fundus and some are heavily pigmented called slate gray appearing fundus, both still within the range of normality. Although the lesions of DR are same across all races, the background color may make them simple or difficult to provide a confirmed diagnosis. Many of the AI algorithms have used Kaggle/Messidor/Eyepacs images for training them. Figure 1 shows public datasets used % in the development and validation of deep learning algorithms. These datasets are not representative of different races, thus the performance of the algorithm may differ across different races depending on pigmentation.

Ting et al. [24] reported the development and performance of their algorithm in multi-ethnic population and with different fundus camera. The DL system showed consistent results in darker fundus pigmentation in African American and Indian individuals to lighter fundus in white individuals.

Performances of deep learning algorithms for diabetic retinopathy

In DL, the performance of a model can be evaluated based on its prediction accuracy on separate test data samples which were not present in the training dataset. If the performance of a model is good on the training dataset but poor on the test dataset, the model has learned very specific patterns and is referred to as “overfitted” to the training data. A well-fitted model performs accurately on the training data and the test data. Table 1 compares various studies on DL for DR based on fundus photograph. Figure 2 shows the automated AI DR report of a normal retina (1 A) and for RDR/ STDR (IB)

The iDx-DR device combines an AI- and cloud-based algorithm with retinal fundus camera. Retinal images of sufficient quality are differentiated into negative (=non-referable = no or mild DR) or positive, indicative of a condition of more than mild DR resulting in the referral to an ophthalmologist (RDR) by the algorithm. The FDA approval was granted on the basis of a study of 900 patients with diabetes at ten primary care sites. The algorithm has correct identification of RDR in 87.4% of the individuals and a correct negative result in 89.5% [37]. However, the

Table 1 Comparison of performance of deep learning-based DR algorithms for retinal photographs

S. no.	Authors	Year	*N*	Public data base used	Reference standard	Grading method	Sensitivity	Specificity	AUC
1	Teng T et al. [52]	2002	NA	NS	NS	NS	NS	NS	NS
2	Arenas-Cavalli [53]	2015	450	NS	Ophthalmologist marked lesions/ features	NS	62.54%	91.89%	NS
3	Gupta S et al. [54]	2015	100	Messidor	Not specified	Not specified	87.00%	100%	NS
4	Bhaskaranand M et al. [55]	2016	40542	EyePACS	One Ophthalmologist	ICDR	90.00%	63.20%	0.879
5	Gulshan V et al. [22]	2016	139886	Messidor 2	Ophthalmologists majority consensus	ICDR	97.50%	93.40%	0.991
6	Pratt H et al. [56]	2016	80000	Kaggle	Kaggle grades	ICDR	30.00%- no DR vs any DR	95.00%- no DR vs any DR	NS
7	Pratumgul W et al. [57]	2016	600	NS	One Ophthalmologist	Normal, mild, moderate, severe	99.26%	97.77%	NS
8	Solanki K et al. [19]	2016	755	NS	NS	NS	90.50%	87.50%	0.965
9	Tufail A et al. [20]	2016	102856	NS	Manual Grade, Modified Arbitration	NHS DESP protocol	IGradingM-100%, Retmarker-85.00%, EyeNuk - 93.80%	iGradingM-0%, Retmarker-52.30%, EyeNuk-20.00%	NS
10	Walton B et al. [58]	2016	30030	PRIVATE	Optometrist or Ophthalmologist	ICDR	No DR x STDR: 66.40%	No DR x STDR: 72.80%	NS
11	Abbas Q et al. [59]	2017	750	DIARETDB1, FAZ, Messidor	NS	ICDR	92.18%	94.50%	0.924
12	Chandore V et al. [60]	2017	75000	Kaggle	Clinician rated	ICDR	88.88%	81.82%	NS
13	Dutta S et al. [61]	2017	1300	Kaggle	NS	NS	NS	NS	NS
14	Garcia G et al. [62]	2017	35126	EyePACS	EyePACS grades	ICDR	54.47%	93.65%	NS
15	Gargeya et al. [23]	2017	76885	EyePACS Messidor-2	Messidor-2 grades	NS	93.00%- No DR Vs Any DR	87.00%- No DR Vs Any DR	0.94
16	Lam C et al. [48]	2017	852	Kaggle,Tele Ophta	Two Ophthalmologists	Graded lesions	NS	NS	0.94: MA, 0.95: exudate
17	Lam C et al. [63]	2017	36555	Kaggle	NS	Normal, mild, moderate, severe	95.00%- Kaggle 90.00%-Messidor-2	96.00%- Kaggle 71.00%-Messidor	NS
18	Ling Dai et al. [64]	2017	646	DIARETDB1	Two Ophthalmologists	Graded MA	87.80%	96.10%	0.934
19	Raju M et al. [65]	2017	88252	Kaggle	Keggle	ICDR and laterality	80.28%	92.29%	NS
20	Rakhlin A et al. [66]	2017	NS	Kaggle and Messidor2	Messidor-2 and Kaggle grades	ICDR	99.00% -Messidor2 92.00% -Kaggle	71.00% -Messidor-2 72.00%-Kaggle	0.967-Messidor2 0.923-Kaggle
21	Takahashi H et al. [40]	2017	9939	NS	3 retinal specialists	Modified Davis grading		NS	NS

Table 1 (continued)

S. no.	Authors	Year	*N*	Public data base used	Reference standard	Grading method	Sensitivity	Specificity	AUC
22	Ting D et al. [24]	2017	297936	NS	2 senior nonmedical grades with extra 1 retina specialist for discordant cases	NS	Modified Davis grading-81% real prognosis- 96.00% rDR: 90.50% vtDR: 100%	rDR: 91.60% vtDR: 91.10%	rDR: 0.936 vtDR: 0.958
23	Torre J et al. [67]	2017	88650	EyePACS	NS	NS	NS	NS	NS
24	Xu X et al. [68]	2017	1000	Kaggle	One Ophthalmologist	HA, lesions; MA, blood vessels	NS	NS	NS
25	Bhattacharya S et al. [69]	2018	200	NS	NS	Normal X NPDR	89.09%	92.22%	NS
26	Desbiens J et al. [70]	2018	7000	Messidor-2	Ophthalmologist	ICDR	92.90%	98.90%	NS
27	Keel S et al. [30]	2018	58886	NS	Consensus grading	NHS DESP protocol	92.30%	93.70%	NS
28	Kermany D et al. [71]	2018	2000	NS	6 experts		96.80%	99.60%	NA
29	Krause J et al. [31]	2018	1605695	Messidor 2	Retina specialist face to face adjudication	ICDR/EyePACS	97.10%	92.30%	0.986
30	Kwasigroch A et al. [72]	2018	37000	NS	NS	ICDR	89.50%	50.50%	NS
31	Rajalakshmi R et al. [25]	2018	2048	NS	2 ophthalmologists with 3rd ophthalmologist as adjudicator	ICDR	No DR x DR: 95.80% No DR x STDR: 99.10%	No DR x DR:80.2% No DR x STDR: 80.4%	NS
32	Suriyal S et al. [73]	2018	16798	Kaggle	NS	DR and No DR	74.50%	63.00%	NS
33	Venugopal G et al. [74]	2018	NS	NS	NS	NS	86.30%	NS	NS
34	Voets M et al. [75]	2018	98679	Kaggle and Messidor2	One non-clinician	Moderate + NO DME	75.40%- Kaggle 57.60%-Messidor-2	55.40%-Kaggle 54.60%-Messidor-2	0.74-Kaggle 0.59-Messidor

NS not specified; *NHS DESP*, national health service diabetic eye screening program, *DR* diabetic retinopathy, *STDR* sight threatening diabetic retinopathy, *DIARETDB1* diabetic retinopathy database 1, *ICDR* international clinical diabetic retinopathy, *HA* Hemorrhages, *MA* microaneuryms, *DME* diabetic macular edema

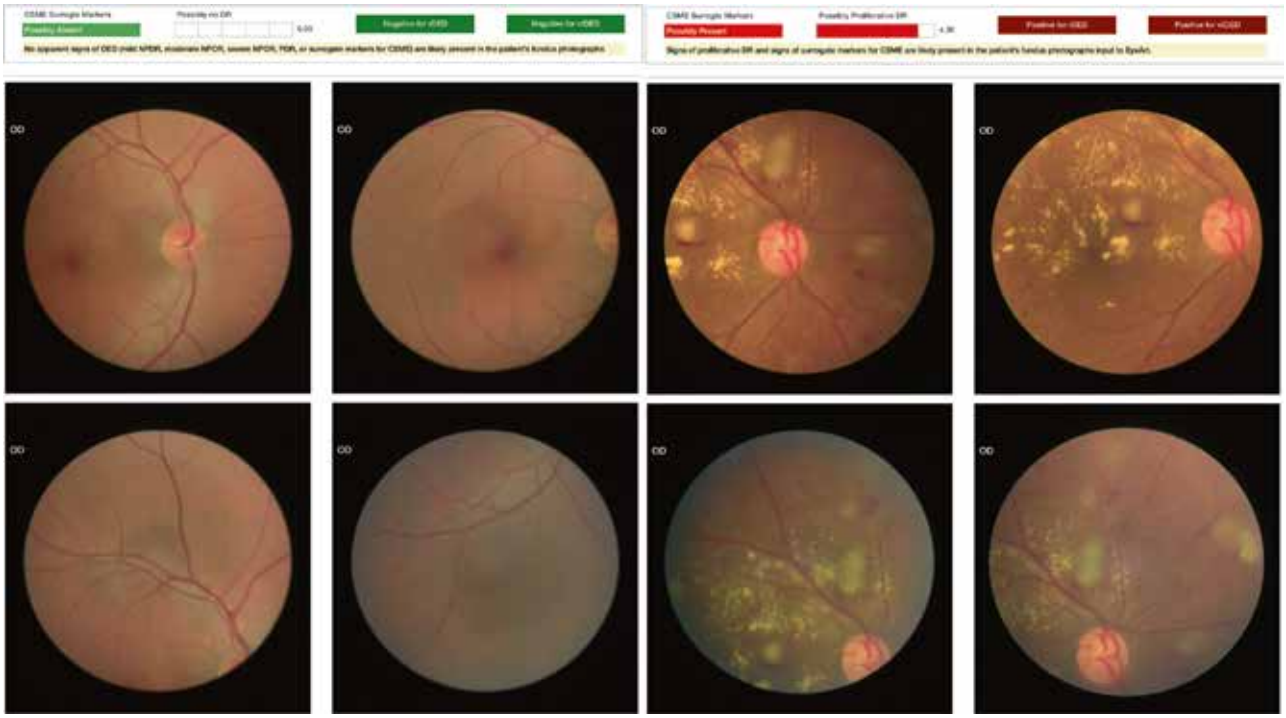

Fig. 2 Sample report of AI-based DR detection using EyeArt

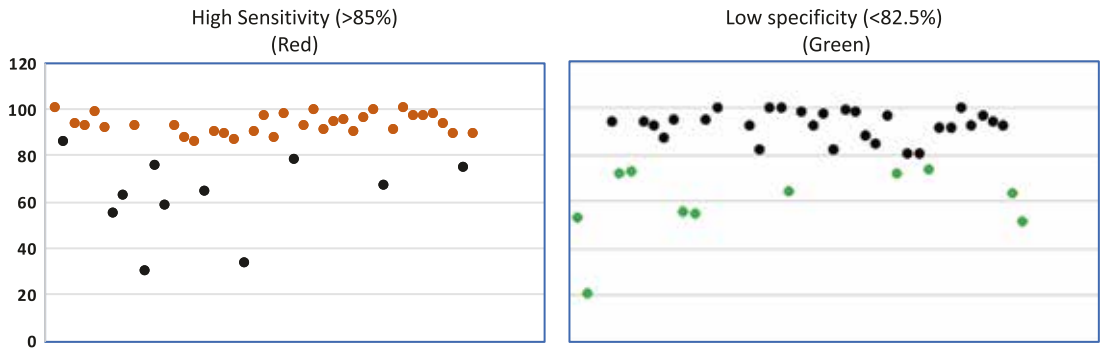

Fig. 3 Scatter plot showing sensitivity and specificity of various studies with cut-off point suggested for IDx algorithm

detection algorithm was trained on DR in untreated eye images, previous laser, pharmacological treatment or surgery were excluded. Moreover, those with manifest disease such as, severe NPDR or PDR were excluded. The FDA had set a mandatory level of accuracy as the primary endpoint for this trial with a sensitivity of more than 85% and a specificity of more than 82.5%. As it is intended to be a screening device, the FDA had chosen a higher sensitivity.

In other reported DR screening algorithms, the sensitivity varied from 87 to 97%, and the specificity from 59 to 98% (Table 1). So a majority of the available AI methods would be capable of being used for DR screening according to the requested FDA endpoints, and most of them seem to be performing better and faster than clinicians. Figure 3 shows the scatter-plot depicting the studies which meet the FDA cut-offs. However, a direct comparison of different algorithms is difficult because of significant differences in grading rubric, grader experience, image quality and most importantly reference standard.

Gulshan et al. [22] reported the diagnostic grading/staging on their two datasets (8788 images and 1745 images). For "moderate or worse DR only" the sensitivity was 90 and 87%, respectively, and the specificity was 98% in both datasets; for "severe or worse DR only" the sensitivity was 84 and 88% and specificity 99 and 98%; for "DMO only" the sensitivity was 91 and 90% and the specificity 98 and 99%, respectively. The performance was optimised by training on 60,000 images, and a further increase did not increase the performance of the algorithm. Thus with a large dataset, the algorithm could perform well on disease stages

as well. Likewise, Ting et al. [24] also confirmed using almost half a million images with a sensitivity and specificity for RDR versus sight-threatening diabetic only (excluding moderate DR) of 91%/92% versus 100%/91%.

Rather than taking clinical grades for DR, Takahashi et al. [40] focused on diagnostic grading/staging by using the ground truth of actual interventions (laser, injections, surgery, nothing) performed after an image was taken. They included 4709 images and categorical visual acuity changes (improved, stable, worsened) for training and tested the algorithm on 496 cases, reaching an accuracy of 96% in the prediction of interventions compared with three retina specialists who reached an accuracy of 92–93%. However, the false-negative rate – when the grade was "not requiring treatment" but treatment was actually needed – was 12%. The false positive rate – when the grade was "requiring treatment in the current visit" but treatment was actually not needed– was 65%. These high false positive rates can increase the patient load, thus limiting its utility.

Thus, AI-based DR screening algorithms have reached or may even outperform the level of accuracy of clinical experts.

Limitations and further advancements

Although the AI-based models have achieved high accuracy in diagnosis of DR, the current challenge is the clinical validation and real time deployment of these models in clinical practice. Most of the studies used training sets from homogenous population of a region or a publicly available dataset [21, 24, 41]. Diversifying the dataset, in terms of ethnicities, and camera to capture the images will address this challenge to some extents [42].

Data access and big data sharing are most important in DL as the neural networks are intrinsically "data hungry". The public availability of ImageNet in 2009 catalyzed AI and is still the base of retina-based image analyses [43]. Open access to scientific data including retinal images is an important area in the global research agenda. However, the medical data is fundamentally and legally different, thus posing a challenge for "open access".

Also, the questions on privacy protection are particularly sensitive in retinal imaging as anonymization is not completely achievable owing to the individual nature of the retinal vasculature which provides a fingerprint-like individual feature. Thus, it is not possible to completely anonymize any medical images (magnetic resonance imaging of the brain or ophthalmic images). Thus, it is now referred to "de-identification" or "de-personalization" of medical images

Also, the training and tuning datasets are often subjected to many variables such as field of view, magnification, image quality and artefacts. The most important aspect for accuracy and universality of an algorithm is the quality of ground truth. The more accurate and robust the ground truth is, better and more universal would be the algorithm. More evidence on methods of getting high quality ground-truth labels are required.

Almost all current systems of DL for DR are based on cross-sectional data. These algorithms cannot handle the time factor, such as the disease incidence and progression. Only few studies of AI for DR have demonstrated the power calculation, which is important for the independent dataset. Pre-determining the required operating threshold on training set should be calculated using the prevalence, type 1, type 2 errors, precision and confidence intervals at the least.

The other challenge, "elephant in the room" is the black-box phenomenon. In DL, it is challenging to understand how exactly a neural network reaches a particular decision, or to identify which exact features it utilizes. How can the results of AI-based algorithms be properly understood by clinicians and researchers? How can we ensure the reliability of algorithms, if we cannot understand how they operate? Potential solutions to this problem are multi-step algorithms that first detect certain clinically known features (using DL) and then predict or classify based on these features [44]. Researchers have been attempting to generate heat maps highlighting the regions of influence on the image which contributed to the algorithm conclusion [45, 46]. However, such maps are often challenging and difficult to interpret [47]. Sometimes, it may highlight an area, with no visible disease [35, 48]. A recent study [49] demonstrated how assistance (including heat maps) from a deep learning algorithm can improve accuracy of DR diagnosis and prevent underdiagnoses improving sensitivity with little to no loss of specificity.

The AI-DR screening systems have been developed and validated using 2-dimensional images and lack stereoscopic aspects, thus making identification of elevated lesion like retinal traction and vitreous traction challenging. Using the information from multimodal imaging in future AI-algorithms may potentially address this challenge. In addition, the medico-legal aspects and the regulatory approvals are different in various countries and settings, which also need to be addressed before its use in real clinical settings.

One of the most important challenges to the clinical adoption of AI-based technology is to understand how the patients perceive to entrust clinical care to machines. Keel et al. [30] studied the patient acceptability of AI based screening model in an endocrinology outpatient setting and reported that 96% of participants were satisfied or very satisfied with the automated screening model. If the AI systems gain widespread use, we will start identifying more people who need treatment. The health authorities have to plan for this anticipated increase in the volume of referrals in their health system. Finally, it is important to point out

that most AI-based applications in medicine are still in the translational stage and have not yet demonstrated their benefit in clinical trials.

Role of deep learning and DR screening and its future

Advances in mobile hardware for DL have enabled iPhone and Android smartphones to run AI diabetic retinopathy algorithm offline for medical imaging diagnostic support. Medios AI software for DR detection works offline on the iPhone and produces instant pdf reports highlighting the lesions (heatmaps). AI has been promising in classifying two-dimensional photographs of retinal diseases and relies on databases of annotated images. Recent novel DL architecture applied to three-dimensional optical coherence tomography (OCT) scans has shown makes excellent appropriate referral recommendation [50]. DL analysis of OCT scans for morphological variations in the scan, detection of intraretinal fluid or subretinal fluid, neovascularisation have started gaining great interest recently [51]. Research on AI assisted automated OCT analysis to assess OCT biomarkers to predict outcomes of treatment such as intravitreal injections for various retinal disorders is on-going.

The AI devices provides a screening decision without requiring an ophthalmologist to interpret the retinal images, hence can be used by physicians who may not normally be involved in eye care. The integration of AI into healthcare, would be expected to radically change clinical practice with more people getting screened for retinopathy. With the exponential increase in the prevalence of diabetes, AI can ease the pressure on the healthcare system, particularly in India and in other lower and middle income countries with large number of people with diabetes to be screened for retinopathy with limited resources. AI based software in ophthalmology provide an easier and more convenient option for the people to detect the disease at an early stage at the physician clinic and hence the patient satisfaction levels could be better. Automated DR screening methods can make the screening process more efficient, cost-effective, reproducible, and accessible. A multicentre study in India (SMART India) will evaluate the clinical and cost-effectiveness of automated DR screening in India. The study is funded by the Global Challenge Research Fund from the United Kingdom Research and Innovations (UKRI) with the aim of translating the results globally.

Conclusion

Automated analysis with integration of AI in DR detection can be safely implemented and appears to be a promising solution for screening large number of people with diabetes globally. DL has shown impressive results of high sensitivity and specificity in automated image analysis of fundus photographs. Artificial intelligence would act as an auxiliary part and a useful assistant in DR screening and provide diagnostic support and cannot replace the role of ophthalmologists in clinical diagnosis and management. Future development of AI technology will generate medical advances, and the physicians and ophthalmologists would need to learn how to utilize the technical advances with care. Robust diagnostic AI-based technology to automate DR screening would help increase referral of people with STDR and other retinal diseases to the ophthalmologist / retina specialist for further management and hence would aid in reducing visual impairment.

The ultimate approach and goal of the future to save healthcare resources and possibly be to incorporate AI into a retinal imaging device fundus cameras that can be used in various locations such as pharmacy, optical shop, etc to screen all people with diabetes.

Compliance with ethical standards

Conflict of interest Sunny Virmani is an employee of Verily Life Sciences LLC. The authors declare that they have no conflict of interest.

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REVIEW ARTICLE

急性闭角型青光眼—治疗策略，循证证据和经济方面的考虑

摘要：

原发性急性闭角型青光眼大发作时需要紧急处理，包括快速降眼压和解除相对瞳孔阻滞，相对瞳孔阻滞是闭角型青光眼大发作最常见的发病机制。降低眼压的紧急治疗策略包括药物治疗和氩激光周边虹膜成形术。在特殊情况下，可以考虑前房穿刺术和半导体激光经巩膜睫状光凝术。通过周边激光虹膜切除术和晶体摘除术可以减轻相对瞳孔阻塞；根据临床试验结果，晶体摘除术是更有效的治疗方法。然而，在急性情况下，晶体摘除在技术上要求很高。周边激光虹膜切除术具有减轻瞳孔阻滞作用，而且在大多数情况下也应当被考虑。晶体摘除术可以与手术相结合，如巩膜粘连松解、小梁切除术或内窥镜下睫状光凝术。在这此篇综述中，我们旨在讨论不同治疗方式的现有临床证据。我们进一步讨论了原发急性闭角型青光眼患者的经济因素，包括成本效益和预期寿命。

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The ROYAL COLLEGE of OPHTHALMOLOGISTS

REVIEW ARTICLE

Acute primary angle closure–treatment strategies, evidences and economical considerations

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Abstract

Acute primary angle closure requires emergency management that involves a rapid lowering of the intraocular pressure and resolution of relative pupil block – the most common mechanism of angle closure. Emergency strategies for lowering intraocular pressure include medical treatment and argon laser peripheral iridoplasty. Anterior chamber paracentesis and diode laser transcleral cyclophotocoagulation may be considered in special situations. Relative pupil block can be relieved by peripheral laser iridotomy and primary lens extraction; the latter is a more effective treatment according to the results of clinical trials. However, primary lens extraction can be technically demanding in the acute setting. Peripheral laser iridotomy has a role in relieving pupil block and should also be considered in most cases. Lens extraction may be combined with procedures such as goniosynechialysis, trabeculectomy or endoscopic cyclophotocoagulation. In this review, we aim to discuss the available evidence regarding the different treatment modalities. We also discuss the economic consideration, including cost-effectiveness and life expectancy, in the management of acute primary angle closure.

Introduction

Acute primary angle closure (APAC) is usually caused by an abrupt closure of the trabecular meshwork in the anterior chamber angle that leads to a sudden rise in intraocular pressure (IOP). It is understood that an exaggerated pupillary block disturbs the natural aqueous flow from the posterior to the anterior chamber, creating a pressure gradient and leads to a forward bowing of the peripheral iris. The iris apposes to the trabecular meshwork, and thus causes an acute angle closure. APAC is a subgroup of angle closure disease characterised by a sudden onset of headache, blurred vision, seeing halos around lights, corneal oedema, mid-dilated pupil, eye pain and redness. The treatment outcomes of APAC are quite different between Asian (more pigmented iris) and Caucasian eyes (usually less pigmented iris). Laser peripheral iridotomy (LPI) tend to be less effective in controlling the IOP in Asian eyes with APAC. Asian also has a much higher incident rate of APAC compare to the Caucasian population – with the crude incidence rate of 12.2 and 10.4 per 100,000 people per year in the above 30-year-old population of Singapore and Hong Kong, respectively [1, 2]. This is higher than the average incidence rate of 3.9–4.1 cases per 100,000 people per year in the European regions [3–5].

In APAC, both LPI and primary lens extraction by phacoemulsification and intraocular lens implant (phaco/IOL) were demonstrated to be effective to control IOP elevation. The latter has been shown to be the more effective treatment than LPI for IOP reduction at the early and mid-term IOP control. Together with the advancement of phaco/IOL technique, primary lens extraction is the more popular choice of treatment nowadays. However, operating on an eye with early aborted APAC is technically challenging and may increase the risk of complications because of the presence of corneal oedema, inflammation, shallow anterior chamber, floppy iris and unstable lens. Furthermore, "the best time window" for performing lens extraction after an APAC attack remains uncertain [6]. The long-term results (e.g. more than 5 years) of early lens extraction

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compared to the conventional LPI are also unknown. In this review, we summarise the approach of treating APAC at the initial acute stage and review the studies that consider IOP control in the mid and long term. We would also touch on the role of goniosynechialysis, trabeculectomy and endoscopic cyclophotocoagulation in treating APAC, as well as considering the economic aspect of treatment.

Treatment approach and considerations

The principle of treatment for APAC aims at (1) initial rapid reduction of IOP in order to limit optic nerve damage, followed by (2) elimination of pupil block, which reduces the risk of recurrent attack and the risk of progression to the chronic form of primary angle closure glaucoma (PACG).

(1) Initial rapid reduction of IOP

Rapid reduction of IOP is an important initial step of treating APAC because it prevents further glaucomatous optic nerve damaged. It also reduces pain and corneal oedema, which allows implementation of more definitive treatments; namely LPI and lens extraction. The use of topical and systemic IOP-lowering medication is usually sufficient to achieve the initial IOP control. Amongst the topical IOP-lowering medications, pilocarpine has a physiological advantage to counteract the angle closure mechanism by inducing miosis, pulling the peripheral iris away from the trabecular meshwork in order to break a mild acute attack. Notice that pilocarpine of high concentration (e.g. pilocarpine 4%) may also lead to increase vascular permeability, which could increase vascular congestion of the iris, pushes the lens-iris diaphragm more anteriorly and aggregates the pupillary block. APAC could also lead to pupillary sphincter ischaemia, rendering it irresponsive to the effect of pilocarpine. Multiple medications might be required to abort the APAC episode. However, a lot of these patients are elderly patients and some might have multiple medical conditions. They might not tolerate the potential side effects of these drugs, especially in the situation where systemic medications are required. Carbonic anhydrase inhibitor and hyperosmotic agents could lead to paraesthesia, drowsiness, confusion, loss of appetite, polydipsia and polyuria. For susceptible patients (e.g. patients with renal failure), it could lead to serious complications such as metabolic disturbance, respiratory failure, pulmonary oedema, congestive heart failure, acute renal failure and even intracranial haemorrhage. Rare but severe systemic complications include Stevens-Johnson syndrome, blood dyscrasias and anaphylactic reactions. A significant proportion of APAC patients do not respond to medical treatment alone adequately. In these cases, other interventions might be considered to achieve rapid IOP reduction.

Argon laser peripheral iridoplasty (ALPI) can mechanically open up the angle in APAC [7, 8]. A series of studies have proven its effectiveness and safety when applying to eye with APAC [9–12]. A randomised control trial (RCT) has also demonstrated that ALPI is significantly more effective in reducing IOP in APAC at 15 min, 30 min and 1 h after the start of treatment when compared to conventional systemic medication [13]. Although this difference in IOP became statistically insignificant from 2-h onwards, ALPI arguably has more advantages at the early stage treatment because of its superior efficacy in lowering IOP and more favourable side effect profile. However, the follow-up study of the same group of patients, that compared the clinical outcome of ALPI against systemic medication in the mid-term (mean follow-up duration of 15 months), suggested that there were no statistically significant differences in IOP control between the two groups [14]. Nonetheless, ALPI is an opinion to consider in the acute stage of the disease. In clinical practice, we should also be aware of the technique and potential complication of applying ALPI. The eye should be pre-treated with topical anaesthetic and pilocarpine. One should aim at producing a contraction burn at the most peripheral portion of the iris as possible with the setting of large spot size, long duration and low power Argon laser (e.g. 500 µm spot size, 0.5 s duration, start from a power of 240 mW) through an Abraham iridotomy contact lens. One of the potential complications of ALPI is corneal endothelial burn because of the proximity of peripheral iris and the cornea. The risk of complication is higher especially when APAC are usually handled by junior ophthalmologists as emergency cases, who might have limited experience in performing ALPI for eyes with shallow anterior chamber and corneal oedema. ALPI should be contraindicated in case of severe corneal oedema, flat anterior chamber and synechial angle closure.

Immediate anterior chamber paracentesis has also been proposed as an alternative procedure during the initial stage of APAC [15]. It can be a helpful procedure if maximally tolerated medication cannot adequately reduce IOP, and when ALPI or LPI is not possible (e.g. unavailability of laser, severe corneal oedema that blurred the anterior chamber view for laser application). It allows rapid reduction of IOP and corneal oedema, which makes early intervention by laser therapy possible. Anterior chamber paracentesis may pose many technical difficulties [16], mainly the concern of iris and lens damage from the paracentesis slit knife and potential further closure of the angle upon decompression. Another safe and easy alternative to perform anterior chamber paracentesis is the use of a half-inch 30-gauged needle [17]. During the

procedure, topical anaesthetic eye drops is applied and the conjunctival sac and lashes are prepared with povidone iodide solution. After rinsing out the povidone, the patient is positioned at the slit lamp and the lids are held open with a speculum. The 30-gauged needle hub, which had been bent into half an inch, is grasped between the thumb and forefinger and the back of the hand rested on the patient's cheek for stabilisation. The tip of the needle then enters the cornea inferotemporally, thought an adequately long intrastromal cornea track and enters into the anterior chamber. Notice that the needle is orientated such that it is parallel to the iris plane and directed away from the lens. This way it avoids accidental puncturing of the intraocular structures. The needle is withdrawn after 10 s of the anterior chamber entre. Throughout the procedure, the needle is used without a syringe. The pressure necessary to force fluid through a half-inch 30-gauged needle is about 12 mmHg so that the decompression stops automatically at that pressure and the anterior chamber would not flatten. The needle track is also self-sealed [17]. This technique could be considered if there is adequate space in the anterior chamber. It is important to note that anterior chamber paracentesis alone only temporarily reduce the IOP; the APAC episode may recur if the pupil block mechanism is not resolved promptly.

In cases were APAC could not be controlled by the methods mentioned above, alternative strategies could also be used. Diode laser transscleral cyclophotocoagulation (DLTSC) was reported to be a possible alternative in treating APAC [18, 19]. This allows more rapid lowering of IOP and reduces corneal oedema for further intervention. DLTSC achieves IOP-lowering effect by direct thermal destruction of the ciliary epithelial cells that produce aqueous. It may also induce localised inflammation that leads to a temporarily ciliary body shut down and/or increase uveoscleral outflow. However, it could lead to pain, inflammation and visual loss. Micropulse transscleral cyclophotocoagulation (Iris Medical Instruments, Mountain View, CA, USA) is also another alternative with potentially better safety profile [20, 21]. In the case of refractory APAC, especially for patients with multiple medical conditions that present with poor visual acuity, it is important to perform careful examination and investigation before further treatment. This includes fundi examination (if possible), B scan and ultrasound biomicroscopy. The aim is to look for secondary causes of acute angle closure such as lens subluxation [22] and haemorrhage of the posterior segment [23–27]. Massively detached choroid and retina due to haemorrhage could lead to forward displacement of the lens-iris diaphragm. In these situations, further invention (e.g. lens extraction) could lead to devastating complications, such as intraoperative suprachoroidal haemorrhage.

(2) Elimination of pupil block

Once the acute attack has been overcome, the aim of treatment is to prevent further acute and chronic angle closure by eliminating the pupil block mechanism. This can be achieved by primary lens extraction or creating a peripheral iridotomy(PI). Nevertheless, early phaco/IOL is generally demonstrated to be the more effective approach than LPI in terms of preventing progression to chronic PACG and reducing the use of medication [3, 32–36].

Primary lens extraction

Phaco/IOL deepens the anterior chamber and eliminates pupil block [28, 29]. Overall, patients with APAC had a 71% reduction from presenting IOP and rarely require long-term glaucoma medication when the surgery was performed soon after medical reduction of IOP [30]. Trabeculectomy after phaco/IOL was uncommon [30]. There are only several studies on this topic and that limits our assessment (Table 1). Jacobi et al. [29] provided some early evidence to justify early phaco/IOL. In this prospective, nonrandomised comparative trial, 43 German patients with APAC were treated by phaco/IOL and 32 patients were treated by conventional surgical peripheral iridectomy (SPI). The mean follow-up period was 10.2 months. APAC patients treated by primary phaco/IOL did significantly better in terms of IOP reduction and best-corrected visual acuity. They also required fewer anti-glaucoma medications and less additional surgical interventions compared to the patients who underwent SPI.

A prospective RCT by Lam et al. [31] supported this finding. It compared the effects of primary phaco/IOL versus LPI in the prevention of IOP rise in patients soon after APACs were aborted. The mean time between abortion of attack and phaco/IOL and LPI were 5.7 days and 4.3 days, respectively. 31 patients were recruited in each arm. One patient from each group passed away before the end of the study. At 18 month, the early phaco/IOL group demonstrated a significantly lower prevalence of IOP elevation, required less glaucoma medications to maintain IOP at <21 mmHg, larger degrees of open angle and less extensive peripheral anterior synechiae (PAS) on gonioscopy compared to the LPI group. However, there were no statistically significant differences in visual acuity, vertical cup to disc ratio (VCDR), median deviation (MD) and pattern standard deviation (PSD) on visual field (VF) between the two groups. None of these patients required further surgery to control IOP.

Later, Husain et al. [32] performed an RCT that compare the 2-year efficacy of primary phaco/IOL with LPI in the early management of APAC and coexisting cataract. Patients with APAC that had the IOP lowered to ≤30 mmHg

Table 1 Studies comparing the effects of early phacoemulsification and peripheral iridotomy in eyes with acute primary angle closure

Authors	Study design	Average follow-up (months)	No. of patients	Types of treatments	Age (range)	Preoperative IOP (mmHg)	Postoperative IOP (mmHg)	Postoperative medications per eye (%)	No. of additional surgery required (%)	Remarks (%)
Lam et al. [31]	RCT	18	31	Phaco/IOL	72.3 ± 7.3	59.7 ± 8.7I	12.6 ± 1.9	0.03 ± 0.18	0	↑IOP 1/30* (3.3)
			31	LPI	69.0 ± 7.8	57.9 ± 11.8	15.0 ± 3.4	0.90 ± 1.14	4 (12.9) repeated LPI	↑IOP 14/30* (46.7)
Husain et al. [32]	RCT	24	19	Phaco/IOL	65.9 (42–82)	57.4 ± 16.9	15.4 ± 7.7	NM 6 (32) patients	1 (5.3) TBx on day one	2 (10.5) treatment failure; 4 (21.1) control by medication
			18	LPI	66.1 (48–85)	55.8 ± 13.2	13.7 ± 6.1	NM 2 (11) patients	6 (33.3) phacoTBx, 1 (5.6) repeated LPI	7 (38.9) treatment failure; 2 (11.1) control by medication
Jacobi et al. [29]	Non-RCT	10.2 ± 3.4	43	Phaco/IOL	68.4 ± 7.2 (45–82)	40.5 ± 7.6	17.80 ± 3.40	0.18 ± 0.45	2 (4.6) filtration procedure, 3 (6.9) CPC	
			32	SPI	66.7 ± 8.8 (49–78)	39.7 ± 7.8	20.10 ± 4.20	0.45 ± 0.62	11(34.3) phaco/IOL, 5 (15.6) filtration procedure, 4 (12.5) CPC	
Imaizumi et al. [34]	NM	6	18	Phaco/IOL	73.1 ± 7.5 (66–90)	48.9 ± 13.9	13.0 ± 3.1	0	0	1 Phacodonesis
			8	LPI → Phaco/IOL	69.5 ± 4.6 (61–74)	17.0 ± 3.9	13.5 ± 1.1	0.25 ± 0.71	0	Significantly more posterior synechias
Moghimi et al. [35]	Prospective non-randomised	18.5 ± 5.2	20	LPI → phaco/IOL	61.1 ± 6.9	54.0 ± 9.4	13.90 ± 2.17	0.50 ± 2.20 1 (5) patients	0	
			15	LPI only	60.0 ± 8.9	57.1 ± 10.2	17.80 ± 4.16	0.80 ± 1.08 6 (40) patients	Prior to analysis, IOP of 5 patients could not be controlled with medication after LPI. They were excluded from the study (not included in the 15 patients). 3 underwent phaco/IOL and 2 underwent phacoTBx	

**One patient from each group deceased before the end of study.*

Abbreviations: IOP intraocular pressure, *Postop* post-operative, *RCT* randomised control trial, *phaco/IOL* phacoemulsification with intraocular lens insertion, *LPI* laser peripheral iridotomy, *NM* not mentioned, *phacoTBx* combined phacotrabeculectomy, *PI* peripheral iridotomy, *TBx* trabeculectomy, *SPI* surgical peripheral iridotomy, *CPC* cyclophotocoagulation, *LPI → phaco/IOL* laser peripheral iridotomy followed by phacoemulsification with intraocular lens insertion.

by medications within 24 h were treated either with LPI 72 h after the medical treatment or by phaco/IOL 5 to 7 days after the IOP was lowered. 18 patients and 19 patients were randomised to LPI and primary phaco/IOL group, respectively. Failure of IOP control was defined as IOP between 22 and 24 mmHg on 2 occasions (readings were taken within 1 month of each other) or IOP ≥ 25 mmHg on 1 occasion after week 2. Failure was also defined as loss of light perception attributable to glaucoma, the necessity for further operative intervention for glaucoma or recurrence of APAC. There was 1 patient who had IOP > 30 mmHg on day 1 after operation in the phaco/IOL group. Whereas for the LPI group, there was 1 transient haemorrahge, 1 corneal burn and 3 cases required repeated LPI because of closure of the initial LPI. At 2-year, there were significantly less treatment failure in the phaco/IOL group (2/19 [10.5%]) compared to the LPI group (7/18 [38.9%]; $P = 0.029$). Six patients in the phaco/IOL group required IOP-lowering medications, of which 2 were considered failures because of high IOP. Whereas 7 out of 18 patients were classified as failures in the LPI group – 6 underwent combined phacotrabeculectomy with Mitomycin C and 1 underwent repeated LPI because of APAC recurrence (the initial LPI was noted to have closed). Another 6 patients in the LPI group underwent cataract surgery because of decreased visual acuity and were not for IOP control – they were not classified as treatment failure. The study had very strict recruitment criteria and was targeting APAC with co-existing cataract; subjects would only be recruited if they have a best-corrected visual acuity of ≤ 6/15. That was one of the reasons why the authors were unable to recruit more patients then they initially intended to do. The authors concluded that phaco/IOL resulted in lower rate of IOP failure at 2 years compared with LPI if it is performed within the first week in patients with APAC and coexisting cataract.

Despite the demonstrated advantage of early phaco/IOL, lens extraction in eyes with APAC is known to be technically demanding. The patients are often anxious and the eyes are usually inflamed, with shallow anterior chamber depth, poor surgical view due to corneal oedema, high IOP, small pupils, floppy iris and sometime unstable lens. Under such condition, topical anaesthesia may not be sufficient for patients' comfort. This was reflected in Jacobi et al. [29] study, in which 5 out of 43 patients who underwent primary phaco/IOL had to undergo general anaesthesia because of anxiety. Intraoperative complication such as iris bleeding and corneal oedema could occur [31, 32]. The challenges of operating in this setting must be taken into account [33]. There is a higher risk of postoperative complication, such as cornea decompensating, wipe-out syndrome and posterior capsular rupture. The benefit of early lens extraction must be balanced with the risk of the operation.

Therefore, it is not an obligation to perform early primary phaco/IOL if the eye is not in good condition. LPI is still a very helpful technique to relief pupil block. A patent PI is effective in lowering IOP at the acute stage and preventing recurrence of APAC. It should be considered as the treatment of choice if primary lens extraction is difficult. A successful initial LPI probably would not jeopardise the effect of the subsequent lens extraction procedure. Imaizumi et al. [34] compared the results of phaco/IOL for 18 eyes that presented with APAC (i.e. no prior LPI) and 8 eyes that had been treated by LPI because of previous APAC (i.e. aborted APAC). At 6 month, there were no statistically significant differences in terms of IOP and medication use between the two groups (Table 1). This is similar to the result of a subgroup of patients in a nonrandomised comparative prospective study in Iran [35] (Table 1). In this study, 20 patients who had APAC and had been treated by LPI, underwent phaco/IOL due to the presence of significant cataract. After a mean follow-up period of 18.5 months, the mean postoperative IOP of the group was 13.9 mmHg and the mean number of medication use was 0.5 bottle. These study demonstrated that prior LPI probably would not jeopardise the result of the subsequent phaco/IOL. In Table 1, we have also listed other studies that involved early phaco/IOL for APAC. These studies have follow-up periods of up to 24 months. The effect of the two treatment modalities (LPI and phaco/IOL) beyond 2 years is unknown. The "best time window" for performing lens extraction after an APAC attack is also unknown [6]. With these uncertainties in mind, surgeons should weight-over the risk and benefit before deciding to treat newly aborted APAC by phaco/IOL or LPI.

Laser peripheral iridotomy

Both SPI and laser peripheral iridotomy (LPI) are effective means of lowering IOP at the initial stage of the acute attack. For Caucasian eyes with APAC, IOP could be sufficiently controlled with SPI or LPI in up to 65–76% of the time; with the additional use of medical therapy, this rate could be up to 84–99% [36–40]. LPI is now preferred because it is relatively non-invasive, easy to perform on outpatient bases, and has a lower risk of complications [41]. Neodymium-doped yttrium aluminium garnet (Nd:YAG) laser alone is sufficient to create LPI for Caucasian but not sufficient for Asian eyes that have more pigmented iris. It is important to note that sequential argon laser and Nd:YAG laser should be performed for the latter; this allows effective PI formation whilst minimising tissue damage to the heavily pigmented iris [42–44].

When sequential argon and Nd:YAG laser is applied to Asian eyes, LPI could also be an effective treatment modality of controlling IOP at the initial stage of the APAC.

This is demonstrated in a retrospective study done by Aung et al. (Table 2) [45]. In all, 111 eyes that presented with APAC and had undergone LPI were reviewed. Apart from 1 eye that required primary trabeculectomy because of non-patent LI, all the other eyes had IOP reduction to <21 mmHg without medication after the successful LPI. However, in the long-term, the results of LPI may not be as satisfactory. In the same study [45], which has a mean follow-up period of 50.3 months, only 46 out of the 110 eyes (41.8%) had no subsequent increase in IOP on follow-up. A total of 64 eyes (58.2% of 110) developed elevated IOP during the follow-up period – 49 eyes (44.5% of 110) developed increase IOP within 6 months, 5 eyes (4.5% of 110) in between 6 months to 1 year, and 10 eyes (9.2% of 110) after 1 year of APAC presentation. 26 eyes (23.6% of the 110) were controlled with topical medication, 36 eyes (32.4% of the 110) required trabeculectomy and the remaining two eyes had already lost light perception at presentation. The relatively poor outcome was echoed by a cross-sectional study of the same group [46] (Table 2). They demonstrated that 17.8% of the subjects were blind in the attacked eye and almost half had glaucomatous optic nerve damaged several years after APAC. The vision was also reduced in a large number of individuals, mainly because of coexisting cataract. Similarly, a prospective observational case series that aimed to evaluate the changes in the configuration of the drainage angle 1 year after APAC, showed that 19 out of 44 subjects (43%) developed IOP elevation during the follow-up period and required additional glaucoma medication [47]. Even in Caucasian patients, up to 56% of the patients who had APAC required further IOP-lowering medication or procedures after LPI [48].

However, the outcomes of LPI were more satisfactory in other studies. Tan et al. [49] reviewed 42 eyes with APAC. 41 eyes achieved persistently patent PI and one eye required phacoemulsification after two unsuccessful attempts of LPI. The mean follow-up period was 27.3 months. Nine eyes (21.4% of 42 eyes) developed an increase in IOP within a mean of 11.9 months after resolution of APAC. They were initially treated with topical medication with resultant IOP of <21 mmHg. Out of these 9 eyes, 7 eyes (16.7% of 42 eyes) underwent combined phaco/IOL and trabeculectomy with Mitomycin-C and one eye underwent combined phaco/IOL and glaucoma drainage device insertion. At the final follow-up, the mean IOP was 13.3 mmHg and none of the eyes (including those that underwent surgery) required additional topical medication. Similarly, in the Lai et al series [14] that included 79 APAC eyes (of 71 patients, they had either undergone ALPI or systemic medications prior to LPI), only 1 eye required cataract extraction within 6 months after the acute attack. This eye was operated because of chronic angle-closure glaucoma development. The mean follow-up duration was 15.7 months. There were no statistically significant differences in the mean IOPs and the requirements for glaucoma medication between the ALPI group and the medically treated group. The mean IOPs were 13.6 mmHg and 14.7 mmHg, respectively, whilst the mean number of medication were 0.3 and 0.5, respectively (Table 2).

The results of other studies mentioned in Table 1 also suggested that LPI could be an effective approach to control IOP in the mid-term. For instance, the patients who only underwent LPI in Lam et al. [31] and Moghimi S et al. [35] did not require additional surgery after a mean follow-up period of 18 months. In the Lam et al. series [31], the mean number of medications required to maintain IOP ≤21 mmHg was significantly higher in the LPI group (0.90) compared to the primary phaco/IOL group (0.03) at 18-month. In the 10-year follow-up, 2 patients from the LPI group had severe visual acuity loss (<0.1 Snellen visual acuity) in the LPI group and none in the phaco/IOL group. Overall, there was no significant difference in terms of the visual field results between the two groups at the 10-year follow-up (unpublished data).

Role of goniosynechialysis, trabeculectomy and endoscopic cyclophotocoagulation

It has been shown that the use of viscoelastic during phacoemulsification could lead to a certain extent of PAS breakdown and achieve an associated IOP reduction [50]. Goniosynechialysis was described as an effective intervention when performed in combination with phaco/IOL in the case of angle closure [51–53]. This can also be combined with laser iridoplasty to prevent PAS reattachment [54, 55]. However, the application of goniosynechialysis was not described specifically for APAC. It is also known that irreversible damage to the trabecular meshwork occurs especially in chronic synechial closure [56]. Therefore, we do not recommend aggressive goniosynechialysis for eyes with APAC because this could lead to surgical complications (e.g. hypaemia and fibrinoid anterior chamber reaction) without additional IOP reduction. Furthermore, eyes that had an acute on chronic type of presentation together with extensive glaucomatous optic neuropathy are probably more susceptible to damage. Aggressive goniosynechialysis could lead to IOP fluctuation during the procedure and thus lead to wipe-out syndrome.

Trabeculectomy alone may further shallow the anterior chamber and aggravate the angle closure. The success rate of trabeculectomy alone is as low as 56.2% percent in patients with medically unresponsive APAC [57]. Therefore, trabeculectomy alone is not recommended. After the acute phase of APAC, combined phacotrabeculectomy may

Table 2 Studies that examine the effects of laser peripheral iridotomy in patients with acute primary angle closure

Authors	Study design	Average follow-up (range) (months)	No. of eyes (patients)	Types of interventions	Age (range)	Preoperative IOP (range) (mmHg)	Postoperative IOP (range) (mmHg)	Postoperative medications per eye (%)	No. of additional surgery required (%)	Remarks (%)
Aung et al. [45]	Retrospective	50.3 (9–107)	110 (96)	LPI	63.7 (39–92)	52.8 (28–80)	NM	26 (23.6) [eyes required medication]	36 (32.7) TBx	↑ IOP 64/110 (58.1): 26/110 (23.6) controlled by medication, 36/110 (32.7) underwent TBx and 2/110 (1.8) NLP
		1 eye required primary TBx (not included in the analysis)								
Aung et al. [46]	Cross-sectional	75.6 ± 18.0 (49.2–121.2)	90 (90)	LPI	62.0 ± 9.0 (43–89)	NM	15.4	NM	34 (37.8) filtering surgery	16(17.8) attacked eyes blinded [5 (5.6) VA < 6/60; 6 (6.7) VF < 20°] 43 (47.8%) diagnosed glaucoma VF results: MD −11.0 ± 10.8 dB (−0.99 to −32.2); PSD 4.1 ± 2.9 dB (0.34−32.4)
		170 subjects with APAC were seen in the centre from 1990 to 1995. 32 (18.8%) deceased before the study, 22 (12.9%) lost contact, and 26 (15.3%) refused or were medically unwell for examination.								
Lim et al. [47]	Prospective observational case series	12	44 (44)	LPI	60.2 ± 10.7 (35–99)	53.3 ± 15.2 (26–78)	NM	NM	NM	↑ IOP 19/44 (41.3) required treatment Patients that required surgery during the period were excluded
Tan et al. [49]	Retrospective	27.3 ± 16.2	42 (41)	LPI	59.6 ± 11.3 (37–85)	55.0 ± 12	13.3 ± 2.92 (6–20)	0 (0.45 before the additional surgeries)	12 (28.6) phaco/IOL, 7 (16.7) phacoTBx, 1 (2.4) phacoGDD	-↑IOP 9/42 (21.4); 5 GON with compatible VF loss and 2 GON without compatible VF loss 1 phaco/IOL, 7 phacoTBx, 1 phacoGDD
Lai et al. [14]	RCT	16.4 ± 5.6 (7–29)	38 (32)	Medications →LPI	66.5 ± 8.5	57.1 ± 9.2 (40–74)	14.7 ± 4.6 (8–32)	0.5 ± 0.8	1 phaco/IOL	12 (31.6%) eyes required medication to control IOP; 1 eye need systemic medication
		15.0 ± 6.0 (6–36)	41 (39)	ALPI →LPI	70.0 ± 10.5	61.2 ± 10.6 (40–79)	13.6 ± 2.7 (9–21)	0.3 ± 0.7	1 phaco/IOL for CACG, 2 phaco/IOL for cataract	8 (19.5) eyes required medication to control IOP. 2 (4.9) eyes required systemic medication; 1 eye developed CACG with phaco/IOL done; 1 eye IOP controlled after LPI

Abbreviations: IOP, intraocular pressure; TBx, trabeculectomy; LPI, Laser peripheral iridotomy; ALPI, argon laser peripheral iridoplasty; NM, not mentioned; NLP, no light perception; VA, visual acuity; VF, visual field; MD, mean deviation; PSD, pattern standard deviation; GON, glaucomatous optic neuropathy; phaco/IOL, phacoemulsification with intraocular lens insertion; phacoTBx, combined phacotrabeculectomy; phacoGDD, combined aqueous shunt device and phacoemulsification; RCT, Randomised control trial; CACG, chronic angle closure glaucoma

be considered, especially if the IOP is poorly controlled by medication [58, 59].

Endoscopic cyclophotocoagulation (ECP) has been recently introduced as a treatment modality for glaucoma. It provides a more direct and targeted method of performing cyclophotocoagulation of the ciliary body. It achieves IOP lowering by reducing aqueous production. It should be performed in combination with phaco/IOL. A study also demonstrated that angle in areas treated with ECP were open with a corresponding flattened ciliary process, suggesting that it could cause anatomical changes on top of the reduction of aqueous production [60], which could be helpful if there is a component of plateau iris configuration in the APAC eye, although its effectiveness in this situation requires further study to verify.

Economical considerations in the management of APAC

Cost-effectiveness of treatment is less mentioned in APAC. One study reported the direct cost of treating APAC [61]. The study was performed in the era before the popularity of prostaglandin analogue and before the publications of the RCTs mentioned in Table 1 [31, 32]. It suggested that treating APAC produced a substantial financial burden on society and individuals. The results showed that, over a 5-year horizon, the total cost of patients who required trabeculectomy because of poorly controlled IOP was similar to patients who had adequate control with chronic use of medication. The authors also predicted that medical treatment would be a more expansive opinion than surgery. Recently, our cost-effectiveness analysis of phacoemulsification versus combined phacotrabeculectomy for treating primary angle closure glaucoma demonstrated that the cost-effectiveness was sensitive to the cost fluctuation of medication but was insensitive to the cost of surgery [62]. We suggested that, in the long-term, the cost of medication is probably the most important factor to determine the total cost of treatment [62]. Therefore, in terms of cost-effectiveness, early phaco/IOL (with or without initial LPI) that aims at medication reduction is probably preferable. Of course, the technical difficulties of the surgery should be taken into consideration and should be operated on by experienced surgeon. The potential benefit of uneventful phaco/IOL in terms of refractive error correction and reduction of topical medication side effects may also improve patients' quality of life [63].

It is also important to consider life expectancy and patients' health status when making the treatment decision. Many patients who have APAC are elderly subjects with an average age of above 60 (Tables 1 and 2). In the cross-sectional case series of Aung et al. [46], 32 patients (19% of 170) were deceased before the time of the examination (mean duration of evaluation from the time of APAC episode was 6.3 years) and numerous patients were medically unwell for examination. Life expectancy also influences the cost-effectiveness of a particular treatment [64–66]. Therefore, one should also take the overall health status of the patient into account when making the treatment decision.

Conclusion

Prompt reduction of IOP is important for APAC at presentation. This could mostly achieve by medical therapy. ALPI and anterior chamber paracentesis are also effective opinions. If the APAC is unresponsive to these treatments, careful evaluation is important and one should look for secondary causes of acute angle closure. Once the acute episode is aborted, primary phaco/IOL or LPI should be performed in order to eliminate pupil block. Overall, primary phaco/IOL is a more effective treatment modality in terms of long-term IOP control and reduction of medication use but it is technically more demanding. LPI is also an effective modality in the acute setting. However, the results might not be as satisfactory in the longer term. An initial LPI for eyes with APAC probably would not jeopardies the results of the subsequent phaco/IOL. The optimum timing for lens extraction remains unknown and further study is required.

Trabeculectomy alone is not a treatment opinion for APAC. Goniosynechialysis and ECP could be helpful in selective cases. These procedures should be combined with phaco/IOL. APAC produces a substantial financial burden. Reduction of cost of medication is a useful approach for reducing the total cost of treatment. Therefore, early phaco/IOL may be a cost-effective approach but this requires verification by future studies. Life expectancy and the patient's overall health status should also be taken into account when considering different treatment opinions.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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The ROYAL COLLEGE of OPHTHALMOLOGISTS

ARTICLE

亚洲印度地区的2009例眼球摘除术患者的病理组织学回顾分析

摘要：

目的：通过回顾亚洲印度地区的眼球摘除术适应症，研究眼球摘除术适应症未来22年的发展趋势。

方法：回顾性分析2009例行眼球摘除术的患者。

结果：眼球摘除术患者平均年龄155个月，病理组织学诊断包括良性肿瘤(n=22，1%)、恶性肿瘤(n=1472，73%)、急性创伤(n=93，5%)、视网膜血管疾病(n=50，3%)、炎症/感染病理(n=33，2%)或其他混杂/非特异性诊断(n=460，23%)。96%的患者临床诊断与病理组织学诊断有较好的相关性。年轻患者(≤20岁)最常见的眼球摘除术适应症是视网膜母细胞瘤(n=1257，82%;p<0.001)；中年人常见的眼球摘除术适应症是眼球萎缩或眼结核(n=163,39%;p<0.001)；老年人常见的眼球摘除术适应症是葡萄膜黑色素瘤(n=25,42%;p<0.001)。近年来，眼球萎缩/眼结核/疼痛性失明行眼球摘除术者(1996年-2000年 33%，2010年-2018年7%)和急性创伤行眼球摘除术者(1996年-2000年3%，2010年-2018年<1%；p<0.001)均呈现下降趋势。而眼内肿瘤行眼球摘除术者呈上升趋势，其包括视网膜母细胞瘤(1996年-2000年 56%，2010年-2018年 73%;p=0.01)和葡萄膜黑色素瘤(1996年-2000年3%，2010年-2018年11%;p < 0.006)。

结论:在亚洲印度地区人群中，恶性肿瘤仍然是青年和老年患者行眼球摘除术最常见的适应症，而对个性化眼球假体更好的晶状体形态的渴望是中老年人行眼球摘除术的主要指征。

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The ROYAL COLLEGE of OPHTHALMOLOGISTS

ARTICLE

Enucleation in Asian Indian patients: a histopathological review of 2009 cases

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Abstract

Objective To review the indications of enucleation in Asian Indian patients and study the trend over the 22-year period.

Methods Retrospective study of 2009 patients who underwent enucleation.

Results The mean age at presentation of patients who underwent enucleation was 155 months The histopathology diagnosis included a benign tumor ($n = 22$, 1%), malignant tumor ($n = 1472$, 73%), acute trauma ($n = 93$, 5%), retinal vascular disease ($n = 50$, 3%), inflammatory/infective pathology ($n = 33$, 2%), or other miscellaneous/non-specific diagnosis ($n = 460$, 23%). There was a good correlation between the clinical and histopathology diagnoses at 96%. The most common indication for enucleation in young patients (≤ 20 years) was retinoblastoma ($n = 1257$, 82%; $p < 0.001$), atrophic bulbi or phthisis bulbi ($n = 163$, 39%; $p < 0.001$) in middle-age adults, and uveal melanoma ($n = 25$, 42%; $p < 0.001$) in older adults. Over the years, there was a decreasing trend of enucleations for atrophic bulbi/phthisis bulbi/painful blind eye (33% from the years 1996 through 2000 to 7% from 2010 to 2018; $p < 0.001$) and acute trauma (3% from the years 1996 through 2000 to < 1% from 2010 to 2018; $p < 0.001$) and an increasing trend for intraocular tumors including retinoblastoma (56% from the years 1996 through 2000 to 73% from 2010 to 2018; $p = 0.01$) and uveal melanoma (3% from the years 1996 through 2000 to 11% from 2010 to 2018; $p < 0.006$).

Conclusion In Asian Indian population, malignant tumors remain the most common indication for enucleation in young and older patients, while desire for better cosmesis with customized ocular prosthesis is the main indication for enucleation in middle-age adults.

Introduction

Though there are various globe-salvaging medical and surgical treatment modalities, enucleation is still the treatment of choice for end-stage ocular disease. However, the indications and incidence of enucleation may vary in each country. Based on population-based surveys, the annual incidence of enucleation is gradually decreasing. In a study from United States of America (US), it was noted that the incidence of enucleation decreased from 6.82 per 100,000 population in 1956 through 1966, to 4.64 per 100,000 population in 1967 through 1977, to 2.80 per 100,000 population in 1978 through 1988 [1]. In studies from Iceland, it was noted that the incidence of enucleation in 1964 through 1992 was 2.66 per 100,000 which decreased to 1.48 per 100,000 during the years 1992 to 2004 [2, 3].

Over the years, there is a changing pattern of diseases leading to enucleation. A large study of 3264 globes over a six-decade period revealed that glaucoma was the most common cause of enucleation in 1950's and 1960's, acute trauma in 1970's and 1980's, and intraocular malignant tumors in 1990's and 2000's [4]. In this study, we evaluated the indications of enucleation and the changing pattern of diseases leading to enucleation in Asian Indian population over a 22-year period.

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Table 1 Enucleation in Asian Indian population: demographics

Feature	All cases $n = 2009$ n (%)	Young age (≤20 years) $n = 1531$ n (%)	Middle age (>20 to 60 years) $n = 418$ n (%)	Older age (>60 years) $n = 60$ n (%)	p-value
Age (months) Mean (median, range)	155 (48, 0.3–1020)	47 (36, 0.3–240)	452 (444, 241–720)	84 (840, 834–1020)	<0.001
Gender					
Male	1191 (59)	887 (58)	267 (64)	37 (62)	0.54
Female	818 (41)	644 (42)	151 (36)	23 (38)	0.34
Enucleation					
Primary	1536 (76)	1074 (70)	407 (97)	55 (92)	<0.001
Secondary	473 (24)	457 (30)	11 (3)	5 (8)	<0.001

Methods

Institutional review board approval was obtained for the study. Histopathological diagnoses of all cases performed in Ophthalmic Pathology Laboratory at LV Prasad Eye Institute, Hyderabad, India from January 1996 to March 2018 were reviewed. The patients who had undergone enucleation were included in this study. Those with inadequate data were excluded from the study.

The data extracted from the medical records included age at presentation, gender, and clinical diagnosis. Final histopathology diagnosis of each case was recorded from the histopathology records. The correlation between clinical and histopathology diagnoses was also reviewed.

The cases were classified and analyzed further based on age at presentation. Young age was defined as ≤ 20 years, middle age as > 20 to 60 years, older adults as age > 60 years. Primary enucleation was defined as enucleation done as a primary treatment for the ocular pathology and secondary enucleation, when enucleation was done when other conservative measures failed. The cases were further classified and analyzed further based on the decade at presentation.

The data were also analyzed based on the year of enucleation. The cases were divided into 5 groups, those in years 1996 to 2000, 2001 to 2005, 2006 to 2010, 2011 to 2015, and 2016 to 2018.

Statistical analysis

The statistical analysis was performed using the software STATA v11.0 (StataCorp, College Station, Texas, USA). The comparison of categorical data was performed using Chi-square test. The continuous data were compared using Kruskal–Wallis test. A p-value of < 0.05 was considered statistically significant. For post-hoc analysis, categorical and continuous data were compared using Chi-square and Mann–Whitney tests, respectively. Appropriate Bonferroni corrections were applied when performing pair-wise comparisons of three (age-wise) or five (year-wise) groups.

Results

Of > 20,000 cases reviewed in Ophthalmic Pathology Laboratory, 2009 (< 10%) enucleated cases were included in the study. Of these patients, 1531 (76%) were young, 436 (22%) were middle-age adults, and 60 (3%) were older adults. The mean age at enucleation was 155 months (median, 48 months; range, < 1 to 1020 months) (Table 1).

Overall, the most common indication for enucleation was retinoblastoma ($n = 1262$, 63%). There was a good correlation between the clinical and histopathology diagnoses at 96%. Primary enucleation (76%) was more common than secondary enucleation (24%). Primary enucleation was more common in middle-aged (97%) and older adults (92%) compared to young patients (70%) ($p < 0.001$). Secondary enucleation was more common in the young patients (30%) compared to middle-aged (3%) and older adults (8%) ($p < 0.001$). Retinal tumors were predominant in the young patients (86% in young, 2% in middle-age, and 0% in older adults; $p < 0.001$); uveal tumors in the middle-aged and older adults (< 1% in young, 38% in middle-age, and 55% in older adults; $p < 0.001$); and tumors arising from the conjunctiva or cornea were more frequent in the older adults (< 1% in young, 3% in middle-age, and 17% in older adults; $p < 0.001$). Based on etiology, malignant tumor (predominantly retinoblastoma; $p < 0.001$), and retinal vascular pathology (Coats disease; $p = 0.002$) were the common etiologies in the young patients; acute trauma ($p < 0.001$) and sequelae of prior trauma and infection ($p < 0.001$) were common in the middle-aged adults, and acute inflammation or infection (endophthalmitis and panophthalmitis; $p = 0.009$), benign tumors (choroidal hemangioma, $p = 0.009$; choroidal melanocytoma, $p < 0.001$; and choroidal osteoma, $p < 0.001$); and malignant tumors (choroidal metastasis, $p < 0.001$; ocular surface squamous neoplasia, $p < 0.001$; and uveal melanoma,

Table 2 Enucleation in Asian Indian population: diagnosis

Feature	All cases $n = 2009$ n (%)	Young age (≤20 years) $n = 1531$ n (%)	Middle age (>20 to 60 years) $n = 418$ n (%)	Older age (>60 years) $n = 60$ n (%)	p-value
Clinical diagnosis correlating with histopathology diagnosis					
Yes	1937 (96)	1479 (97)	403 (96)	55 (92)	0.96
No	72 (4)	52 (3)	15 (4)	5 (8)	0.16
Tissue of origin of the pathology					
Conjunctiva/cornea	26 (1)	3 (<1)	13 (3)	10 (17)	<0.001
Vitreous	2 (<1)	2 (<1)	0 (0)	0 (0)	0.73
Ciliary body/choroid	204 (10)	13 (<1)	158 (38)	33 (55)	<0.001
Retina	1316 (66)	1309 (86)	7 (2)	0 (0)	<0.001
Optic nerve	1 (<1)	0 (0)	1 (<1)	0 (0)	0.15
Non-specific	460 (23)	204 (13)	239 (57)	17 (28)	<0.001
Etiology					
Congenital anomalies	7 (<1)	7 (<1)	0 (0)	0 (0)	0.34
Retinal vascular pathology	50 (3)	49 (3)	1 (<1)	0 (0)	0.002
Acute Inflammation/infection	33 (2)	21 (1)	8 (2)	4 (7)	0.009
Acute trauma	93 (5)	24 (2)	68 (16)	1 (2)	<0.001
Sequelae of prior trauma or infection	332 (17)	157 (10)	163 (39)	12 (20)	<0.001
Benign tumor	22 (1)	7 (<1)	10 (2)	5 (8)	<0.001
Malignant tumor	1472 (73)	1266 (83)	168 (40)	38 (63)	<0.001
Histopathology diagnosis					
Congenital anomalies					
Clinical anophthalmos	1 (<1)	1 (<1)	0 (0)	0 (0)	0.86
Noorie's disease	1 (<1)	1 (<1)	0 (0)	0 (0)	0.86
Primary hyperplastic primary vitreous	2 (<1)	2 (<1)	0 (0)	0 (0)	0.73
Retinal dysplasia	3 (<1)	3 (<1)	0 (0)	0 (0)	0.63
Retinal vascular pathology					
Coats disease	50 (3)	49 (3)	1 (<1)	0 (0)	0.002
Acute Inflammation/infection					
Intraocular cysticercosis/ toxocariasis/parasitic granuloma	7 (<1)	7 (<1)	0 (0)	0 (0)	0.34
Endophthalmitis/ panophthalmitis	20 (<1)	9 (<1)	8 (2)	3 (5)	<0.001
Necrotizing granulomatous uveitis	6 (<1)	5 (<1)	0 (0)	1 (2)	0.08
Acute trauma	93 (5)	24 (2)	68 (16)	1 (2)	<0.001
Sequelae of prior trauma or infection					
Phthisis bulbi/atrophic bulbi/ Painful blind eye	325 (16)	150 (10)	163 (39)	12 (20)	<0.001
Benign tumor					
Ciliary body medulloepithelioma	5 (<1)	4 (<1)	0 (0)	1 (2)	0.06
Ciliary body leiomyoma	2 (<1)	0 (0)	2 (<1)	0 (0)	0.02
Ciliary body PECOma	1 (<1)	0 (0)	1 (<1)	0 (0)	0.15
Retinal pigment epithelial adenoma	1 (<1)	0 (0)	1 (<1)	0 (0)	0.15
Choroidal osteoma	1 (<1)	0 (0)	0 (0)	1 (2)	<0.001

Table 2 (continued)

Feature	All cases $n = 2009$ n (%)	Young age (≤20 years) $n = 1531$ n (%)	Middle age (>20 to 60 years) $n = 418$ n (%)	Older age (>60 years) $n = 60$ n (%)	p-value
Choroidal schwannoma	2 (<1)	0 (0)	2 (<1)	0 (0)	0.02
Choroidal melanocytoma	4 (<1)	2 (<1)	0 (0)	2 (3)	<0.001
Choroidal hemangioma	4 (<1)	1 (<1)	2 (<1)	1 (2)	0.009
Lymphoplasmacytic lesion of the uvea	1 (<1)	0 (0)	1 (<1)	0 (0)	0.15
Optic nerve sheath meningioma	1 (<1)	0 (0)	1 (<1)	0 (0)	0.15
Malignant tumor					
Ocular surface squamous neoplasia	25 (1)	3 (<1)	12 (3)	10 (17)	<0.001
Conjunctival sarcomatoid carcinoma	1 (<1)	0 (0)	1 (<1)	0 (0)	0.15
Retinoblastoma	1262 (63)	1257 (82)	5 (1)	0 (0)	<0.001
Uveal melanoma	172 (9)	6 (<1)	141 (34)	25 (42)	<0.001
Choroidal metastasis	12 (<1)	0 (0)	9 (2)	3 (5)	<0.001

PECO Perivascular epithelioid cell tumor

$p < 0.001$) were common in the older patients. Overall, based on age at enucleation, retinoblastoma ($n = 1257$, 82%; $p < 0.001$) was the most common indication of enucleation in young age, atrophic bulbi or phthisis bulbi ($n = 163$, 39%; $p < 0.001$) in middle-age adults, and uveal melanoma ($n = 25$, 42%; $p < 0.001$) in older adults (Table 2). The details of diagnosis based on the age at enucleation are listed in Table 3.

Of 2009 enucleations included in the study, 9% were performed from 1996 to 2000, 19% from 2001 to 2005, 32% from 2006 to 2010, 27% from 2011 to 2015, and 12% from 2016 to 2018. The mean age at enucleation gradually decreased over the years (150 months from the years 1996 through 2000, 157 months from 2001 to 2005, 182 months from 2006 to 2010, 132 months from 2011 to 2015, to 135 months from 2016 to 2018; $p < 0.001$). Over the years, there was a decreasing trend of enucleations for atrophic bulbi/phthisis bulbi/painful blind eye (33% from the years 1996 through 2000, 24% from 2001 to 2005, 19% from 2006 to 2010, 9% from 2011 to 2015, to 3% from 2016 to 2018; $p < 0.001$) and acute trauma (3% from the years 1996 through 2000, 7% from 2001 to 2005, 8% from 2006 to 2010, < 1% from 2011 to 2015, to < 1% from 2016 to 2018; $p < 0.001$) and an increasing trend for intraocular tumors including retinoblastoma (56% from the years 1996 through 2000, 58% from 2001 to 2005, 55% from 2006 to 2010, 71% from 2011 to 2015, to 76% from 2016 to 2018; $p = 0.01$) and uveal melanoma (3% from the years 1996 through 2000, 7% from 2001 to 2005, 8% from 2006 to 2010, 11% from 2011 to 2015, to 12% from 2016 to 2018; $p = 0.006$) Table 4.

Discussion

The indications for enucleation have varied over time depending on the time period and the geographic location. Studies from the US have revealed glaucoma (22%–35%), acute trauma (48%), intraocular tumors (21 to 48%) and painful blind eye (63%) [1, 4–8]. as the most common causes of enucleation. Studies from Europe have revealed blind painful eye (37% to 46%), tumors (26% to 34%), and trauma (39%) as the most common indications for enucleation [2, 3, 9, 10]. Studies from Iran and Arab Nations revealed trauma (33% to 50%) and malignant tumors (20%) as the most common indications for enucleation [11–15]. Studies from Nepal have revealed intraocular tumors (72%) as the most common indication for enucleation [16]. Studies from China have revealed trauma (63% to 66%) as the most common indications for enucleation/evisceration [17, 18]. There are limited studies from India. As per published literature, the most common indications for enucleation in Asian Indians are malignant tumors (49% to 61%) and inflammatory/infectious etiology (40%) [19–21]. In our study, the most common indication for enucleation was malignant tumors accounting for 73% of cases ($p < 0.001$), with higher proportion in young patients (83%) and older patients (63%). Acute trauma and sequelae of trauma were

Table 3 Enucleation in Asian Indian population: Diagnosis as per decade of life

	Age at presentation (years)								
	≤10 *n* = 1423 *n* (%)	>10 to 20 *n* = 108 *n* (%)	>20 to 30 *n* = 155 *n* (%)	>30 to 40 *n* = 86 *n* (%)	>40 to 50 *n* = 111 *n* (%)	>50 to 60 *n* = 66 *n* (%)	>60 to 70 *n* = 36 *n* (%)	>70 to 80 *n* = 17 *n* (%)	>80 to 90 *n* = 7 *n* (%)
Gender									
Male	830 (58)	57 (53)	106 (68)	55 (64)	67 (60)	39 (59)	25 (69)	10 (59)	2 (29)
Female	593 (42)	51 (47)	49 (32)	31 (36)	44 (40)	27 (41)	11 (31)	7 (41)	5 (71)
Enucleation									
Primary	972 (68)	102 (94)	153 (99)	84 (98)	108 (97)	62 (94)	34 (94)	15 (88)	6 (86)
Secondary	451 (32)	6 (6)	2 (1)	2 (2)	3 (3)	4 (6)	2 (6)	2 (2)	1 (14)
Clinical diagnosis correlating with histopathology diagnosis									
Yes	1376 (97)	103 (95)	150 (97)	83 (96)	107 (96)	63 (95)	33 (92)	17 (100)	5 (71)
No	47 (3)	5 (5)	5 (3)	3 (4)	4 (4)	3 (5)	3 (8)	0 (0)	2 (29)
Diagnosis									
Congenital anomalies									
Clinical anophthalmos	0 (0)	1 (< 1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Noorie's disease	1 (< 1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Primary hyperplastic primary vitreous	2 (< 1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Retinal dysplasia	3 (< 1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Retinal vascular pathology									
Coats disease	43 (3)	6 (5)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)
Acute Inflammation/infection									
Intraocular cysticercosis/ toxocariasis/parasitic granuloma	7 (< 1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Endophthalmitis/ panophthalmitis	9 (< 1)	0 (0)	0 (0)	4 (5)	2 (2)	2 (3)	0 (0)	2 (12)	1 (14)
Necrotizing granulomatous uveitis	4 (< 1)	1 (< 1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (3)	0 (0)	0 (0)
Acute trauma	13 (< 1)	11 (10)	32 (21)	17 (20)	13 (12)	6 (9)	1 (3)	0 (0)	0 (0)
Sequelae of prior trauma or infection									
Phthisis bulbi/atrophic bulbi/ Painful blind eye	83 (6)	74 (69)	84 (54)	26 (32)	35 (32)	18 (27)	7 (19)	3 (18)	2 (29)
Benign tumor									
Ciliary body medulloepithelioma	3 (< 1)	1 (< 1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (3)	0 (0)	0 (0)
Ciliary body leiomyoma	0 (0)	0 (0)	0 (0)	0 (0)	2 (2)	0 (0)	0 (0)	0 (0)	0 (0)
Ciliary body PECOma	0 (0)	0 (0)	1 (< 1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Retinal pigment epithelial adenoma	0 (0)	0 (0)	0 (0)	0 (0)	1 (< 1)	0 (0)	0 (0)	0 (0)	0 (0)
Choroidal osteoma	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (14)
Choroidal schwannoma	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)
Choroidal melanocytoma	1 (< 1)	1 (< 1)	0 (0)	0 (0)	0 (0)	0 (0)	2 (6)	0 (0)	0 (0)
Choroidal hemangioma	1 (< 1)	0 (0)	1 (< 1)	0 (0)	1 (< 1)	0 (0)	1 (3)	0 (0)	0 (0)
Lymphoplasmacytic lesion of the uvea	0 (0)	0 (0)	1 (< 1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Optic nerve sheath meningioma	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Table 3 (continued)

	Age at presentation (years)								
	≤10 $n=1423$ n (%)	>10 to 20 $n=108$ n (%)	>20 to 30 $n=155$ n (%)	>30 to 40 $n=86$ n (%)	>40 to 50 $n=111$ n (%)	>50 to 60 $n=66$ n (%)	>60 to 70 $n=36$ n (%)	>70 to 80 $n=17$ n (%)	>80 to 90 $n=7$ n (%)
Malignant tumor									
Ocular surface squamous neoplasia	0 (0)	3 (3)	5 (3)	2 (2)	3 (3)	2 (3)	4 (11)	5 (30)	1 (14)
Conjunctival sarcomatoid carcinoma	0 (0)	0 (0)	1 (< 1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Retinoblastoma	1252 (88)	5 (5)	3 (2)	0 (0)	1 (< 1)	1 (2)	0 (0)	0 (0)	0 (0)
Uveal melanoma	1 (< 1)	5 (5)	26 (17)	33 (38)	48 (43)	34 (52)	19 (53)	5 (30)	1 (14)
Choroidal metastasis	0 (0)	0 (0)	1 (< 1)	2 (2)	5 (5)	1 (2)	0 (0)	2 (12)	1 (14)

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more common in middle-aged adults (16%, $p<0.001$ and 39%, $p<0.001$, respectively) compared to younger patients (2% and 10%, respectively) or older adults (2% and 20%, respectively).

Amongst the malignant tumors, retinoblastoma (63%) was the most common cause for enucleation in our series. This corresponds to other studies from India, where retinoblastoma was the most common malignant tumor necessitating enucleation [19–21]. However, the rate of enucleations due to retinoblastoma was much higher in our study compared to other studies (37% to 49%), and this could be related to referral bias and the time period of the study [19–21]. The higher rate of enucleations for retinoblastoma in India could also be related to advanced disease at presentation compared to the West [22]. In the West, uveal melanoma is the most common malignant intraocular tumor necessitating enucleation [4, 5]. This difference could be related to the difference in the proportion of retinoblastoma versus uveal melanoma in the West and in India. While the estimated annual incidence of retinoblastoma is 258 in North America, it is over 1500 cases in India [23, 24]; and uveal melanoma is less common in Asia compared to light-eyed, fair-skinned Caucasians, with an estimated annual incidence of 857 cases in Asians versus 4351 in non-Hispanic Caucasians [23]. However, with improved treatment modalities in the West, there is a decreasing trend towards enucleation of the eye for uveal melanoma and retinoblastoma [4].

In our study, the indication for enucleation also varied based on the age group. Amongst the ocular malignant tumors, retinoblastoma (82%; $p<0.001$) was the most common indication for enucleation in younger patients, and uveal melanoma was the common indication in middle-aged (34%; $p<0.001$) and older adults (42%; $p<0.001$). Uveal melanoma is more common after the 6th decade in the West, but in India, it is more commonly seen in the 4th and 5th decade [25, 26]. Thus the common malignant intraocular tumor in middle-aged adults necessitating enucleation was uveal melanoma in our study. Enucleation for ocular surface squamous neoplasia and choroidal metastases was also more common in older patients compared to young patients and middle-aged adults, and this corresponds to the higher incidence of both these diseases in this age group.

In this study, the most common indication for enucleation in young patients was retinoblastoma (82%), atrophic bulbi or phthisis bulbi (39%) in middle-age adults, and uveal melanoma (42%) in older adults, suggesting ocular tumors in young and older age groups and desire for better cosmesis with a customized ocular prosthesis in middle-age patients. Similar to our study, in a study of 746 pediatric enucleations in the US, retinoblastoma ($n=330$, 45%) and trauma ($n=233$, 32%) were the most common diagnosis [6], though the enucleation rate was much higher at 82% for retinoblastoma and was much lower for trauma (acute trauma and sequelae of trauma) at 12% in our study. Over time, there was a steep decrease in pediatric non-retinoblastoma enucleations and an increase in retinoblastoma enucleations [6]. This is similar to our study where an overall decreasing trend was noted in number of enucleations for acute trauma (3% during 1996 to 2000 versus < 1% during 2016 to 2018; $p<0.001$) or sequelae of trauma (33% during 1996 to 2000 versus 3% during 2016 to 2018; $p<0.001$) and an increasing trend was noted in enucleations for retinoblastoma (56% during 1996 to 2000 versus 76% during 2016 to 2018; $p=0.01$). There was also an increased trend of enucleations for uveal melanoma over the years (3% during 1996 to 2000 versus 12% during 2016 to 2018; $p=0.006$). This is in contrast to studies from the West, where there was a decreasing trend of enucleations for uveal melanoma over the years [3–5]. The trend seen in our study corresponds to improved quality of care and

Table 4 Enucleation in Asian Indian population: trend over the years

Feature	Years 1996 to 2000 $n = 189$ (%)	Years 2001 to 2005 $n = 383$ (%)	Years 2006 to 2010 $n = 650$ (%)	Years 2011 to 2015 $n = 538$ (%)	Years 2016 to March 2018 $n = 249$ (%)	p-value
Mean age at presentation (months) (Median, range)	150 (48, 2 to 1020)	157 (48, 0.3 to 1008)	182 (48, 1 to 1020)	132 (36, 0.7 to 384)	135 (36, 1 to 984)	< 0.0001
Gender						
Male	116 (61)	249 (65)	380 (58)	300 (56)	146 (59)	0.71
Female	73 (39)	134 (35)	270 (42)	238 (44)	103 (41)	0.45
Diagnosis						
Congenital anomalies	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	N/A
Clinical anophthalmos	0 (0)	0 (0)	0 (0)	1 (< 1)	0 (0)	0.60
Noorie's disease	0 (0)	0 (0)	0 (0)	1 (< 1)	0 (0)	0.60
Primary hyperplastic primary vitreous	0 (0)	0 (0)	2 (< 1)	0 (0)	0 (0)	0.38
Retinal dysplasia	1 (< 1)	1 (< 1)	0 (0)	1 (< 1)	0 (0)	0.47
Retinal vascular pathology						
Coats disease	3 (2)	6 (2)	16 (2)	20 (4)	5 (2)	0.26
Acute Inflammation/infection						
Intraocular cysticercosis/ toxocariasis/parasitic granuloma	1 (< 1)	1 (< 1)	3 (< 1)	1 (< 1)	1 (< 1)	0.92
Endophthalmitis/panophthalmitis	0 (0)	4 (1)	13 (2)	3 (< 1)	0 (0)	0.02
Necrotizing granulomatous uveitis	1 (< 1)	0 (0)	3 (< 1)	2 (< 1)	0 (0)	0.58
Acute trauma	6 (3)	26 (7)	55 (8)	5 (< 1)	1 (< 1)	< 0.001
Sequelae of prior trauma or infection						
Phthisis bulbi/atrophic bulbi/ Painful blind eye	63 (33)	93 (24)	121 (19)	48 (9)	7 (3)	< 0.001
Benign tumor						
Ciliary body medulloepithelioma	0 (0)	2 (< 1)	2 (< 1)	0 (0)	1 (< 1)	0.51
Ciliary body leiomyoma	0 (0)	0 (0)	1 (< 1)	1 (< 1)	0 (0)	0.84
Ciliary body PECOma	0 (0)	0 (0)	1 (< 1)	0 (0)	0 (0)	0.72
Retinal pigment epithelial adenoma	0 (0)	0 (0)	1 (< 1)	0 (0)	0 (0)	0.72
Choroidal osteoma	0 (0)	0 (0)	1 (< 1)	0 (0)	0 (0)	0.72
Choroidal schwannoma	1 (< 1)	0 (0)	0 (0)	0 (0)	1 (< 1)	0.12
Choroidal melanocytoma	0 (0)	0 (0)	0 (0)	1 (< 1)	3 (1)	0.05
Choroidal hemangioma	0 (0)	0 (0)	1 (< 1)	1 (< 1)	2 (< 1)	0.22
Lymphoplasmacytic lesion of the uvea	1 (< 1)	0 (0)	0 (0)	0 (0)	0 (0)	0.05
Optic nerve sheath meningioma	0 (0)	0 (0)	0 (0)	1 (< 1)	0 (0)	0.60
Malignant tumor						
Ocular surface squamous neoplasia	0 (0)	2 (< 1)	12 (2)	6 (1)	5 (2)	0.14
Conjunctival sarcomatoid carcinoma	0 (0)	0 (0)	0 (0)	0 (0)	1 (< 1)	0.13
Retinoblastoma	105 (56)	223 (58)	360 (55)	384 (71)	190 (76)	0.01
Uveal melanoma	6 (3)	25 (7)	53 (8)	57 (11)	31 (12)	0.006
Choroidal metastasis	1 (< 1)	0 (0)	9 (1)	5 (< 1)	1 (< 1)	0.16

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preference for eviscerations for trauma and its sequelae and increased referral pattern to the institute for retinoblastoma and uveal melanoma over the years. Increasing evidence of low incidence of sympathetic ophthalmia in ocular trauma following eviscerations has also contributed towards the shift of trend towards eviscerations in these cases [27].

The drawbacks of the study include retrospective nature of the study and lack of data related to total number of patients with each disease pattern to exactly determine the proportion of patients undergoing enucleations for a particular ocular pathology, which is beyond the scope of this study. However, this large dataset of 2009 patients over a prolonged 22-year time period allows studying the trend of enucleations over the years in Asian Indians.

In summary, there are still a significant number of patients requiring enucleation for advanced intraocular tumors, especially retinoblastoma and uveal melanoma. Efforts towards early referral, early diagnosis, and appropriate treatment might reverse this trend of enucleation in the future. Acute trauma and sequelae of trauma are more common in middle-aged patients, indicating a need for better eye protection in this age group. Improved quality of care for non-tumor pathologies has decreased the morbidity related to enucleation.

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Summary

What was known before

- The traditional orbital wall reconstruction of blowout fracture is to visually inspect the fracture site and use eye measurements to cut a two-dimensional orbital implant that corresponds to the anatomical structure of the fracture site.
- The implants that do not fit the anatomical structure of a fracture site well can cause complications such as enophthalmos, diplopia and displacement of the implant.

What this study adds

- We introduced the surgical technique of orbital wall reconstruction using 3D-printed customized orbital implant templates with low cost and quantitatively demonstrated optimal reconstruction of anatomic contours.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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