REVIEW ARTICLE

Age-related macular degeneration and polypoidal choroidal vasculopathy in Asia

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Abstract

Age-related macular degeneration is the leading cause of irreversible blindness in patients aged 55 years or more in developed countries. In recent years, various epidemiological, genetic and clinical studies from Asian populations have demonstrated that age-related macular degeneration in Asians has its unique perspectives in terms of epidemiology, genetic factors, phenotypic presentations, clinical subtypes and management approach. In particular, polypoidal choroidal vasculopathy is prevalent in Asian populations compared with Caucasians. This review highlights and contrasts the clinical features and management of age-related macular degeneration and polypoidal choroidal vasculopathy in Asians.

Key words: Aged; Asian Continental Ancestry Group; Macular degeneration; Visually impaired persons

Introduction

Age-related macular degeneration (AMD) is a major cause of blindness in the elderly in Asian countries, and the number of sufferers is expected to grow significantly.[1] These projected demographic shifts may be due to the urbanization of Asians, westernization of lifestyles, increasing population longevity, as well as the public's ever-increasing disease awareness and diagnostic attentiveness. Most of our past understanding on AMD comes from studies in white and black populations. In recent years, with the increase in publications especially of epidemiological studies from Asia, we now know that Asian AMD has its own unique features in terms of epidemiology, genetics, phenotypic presentations, clinical subtypes and responses to treatment.

Epidemiology of age-related macular degeneration in Asia

Asia has mixed populations of different races and ethnicities. Not surprisingly, studies on the prevalence of AMD in Asia show wide variations. Based on increasing evidence from recent population studies, the perception that AMD is much less common in Asians than in white Caucasians is no longer tenable. The Hisayama Study in Japan[2] reported that in a Japanese population aged 50 years or older, the prevalence of early AMD was 12.7% and late AMD was 0.87%; the frequency of neovascular AMD being significantly higher in men. The Singapore Malay Eye Study demonstrated the prevalence of early and late AMD in Singapore Malays aged 40 to 80 years to be 3.5% and 0.34%, respectively.[3] The Shihpai Eye Study in Taiwan described an elderly Chinese population of 65 years or above with a prevalence of early AMD was 9.2% and of late AMD was 1.9%.[4] In the Beijing Eye Study in China, the prevalence of early and late AMD in Chinese aged 40 years or older was reported to be low, being 1.4 % and 0.2%, respectively.[5] The overall impression was that the prevalence of AMD in Asians does not differ greatly from that in white Caucasians (**Table 1**[2-6]).

Other than race and ethnicity, there are other factors that might account for inconsistencies and disparities in prevalence between different Asian populations.[6] These include: different systems for classifying AMD, the proportion of patients with dense cataracts making fundus pictures unreadable, as well as different dietary intakes,

Table 1. Prevalence of age-related macular degeneration (AMD) in Asian populations.[2-6]

Population	Study (region)	Early AMD (%)	Late AMD (%)
Japanese	The Hisayama Study (Japan)[2]	12.7	0.87
Chinese	The Beijing Eye Study (China)[5]	1.4	0.2
Chinese	The Shihpai Eye Study (Taiwan)[4]	9.2	1.9
Malay	The Singapore Malay Eye Study (Singapore)[3]	3.50	0.34
Indian	Andhra Pradesh Eye Study (India)[6]	-	1.90

Table 2. Associations, genotype frequencies and odds ratios of susceptibility genes and single nucleotide polymorphisms (SNPs) in age-related macular degeneration (AMD) of different populations.[7-10,12-15]

Gene	SNPs	Chinese[8,9,12,15]	Japanese[10,14]	Caucasian[7, 13]
Complement factor H (*CFH*) on chromosome 1q31	Try402His polymorphism rs1061170:T>C	**No association** C allele: 5.8% in cases vs 2.9% in controls (Hong Kong); 10.3% in cases vs 8.0% in controls (Beijing Chinese)	**No association** C allele: 4% in cases vs 4% in controls	**Strong association with odds ratio of 6.32 for CC genotype** C allele: 34.9% in cases vs 58.9% in controls
Promoter of high-temperature requirement A-1 (*HTRA1*) genes on chromosome 10q26	rs11200638:G>A	**Very strong association with odds ratio of 10.00 for the AA genotype** (Hong Kong Chinese) 67.8% in cases vs 42.4% in controls; odds ratio was 7.90 for the AA genotype (Beijing Chinese)	**Very strong association with odds ratio of 10.02 for the AA genotype** 69% in cases vs 32% in controls	**Strong association with odds ratio of 6.56 for AA genotype** A allele: 40.3% in cases vs 25.2% in control
Hypothetical LOC387715 in the chromosome 10q26 region (upstream of *HTRA1*)	rs10490924:G>T	**Very strong association with odds ratio of 11.14 for the TT genotype** (Hong Kong Chinese) T allele: 64.9% in cases vs 43.2% in controls; odds ratio was 5.45 for the TT genotype (Beijing Chinese)	**Strong association with odds ratio of 6.20 for the TT genotype** T allele: 68% in cases vs 33% in controls	**Strong association with odds ratio of 6.09 for TT genotype** T allele: 39.7% in cases vs 24.7% in control

levels of industrialization, and lifestyle factors (smoking, environmental factors such as sunlight exposure).

Two diseases that are commonly found in Asians can also affect the accuracy of an AMD diagnosis. One is central serous chorioretinopathy, which presents with pigmentary changes at the posterior pole with or without associated scattered drusen, which may masquerade as dry or early AMD.[7] Another is polypoidal choroidal vasculopathy (PCV), which can manifest like exudative or late AMD.[8] Future research in Asia will emphasize the incidence and risk factors of AMD and its subtypes. The target will be towards prevention of blindness with specific treatment directed to specific disease entities.

Genetics of age-related macular degeneration in Asia

Several research initiatives demonstrate the important role of genetics in the development of AMD. Genetic loci are strongly associated with AMD and population studies have revealed genetic heterogeneity. There are also differences in the occurrence of disease-susceptible genes and single nucleotide polymorphisms (SNPs) between white Caucasians and Asians.

The complement factor H (*CFH*) gene is involved in chronic inflammatory responses and drusen formation. This gene encodes a protein that regulates the complement, inflammation system, which is important for clearing out pathogens and cellular debris. SNP is a site in the genome, where a single base in the DNA often differs from person to person. A variation in SNP (rs1061147) of the *CFH* gene may result in a *CFH* protein with reduced ability to bind to C-reactive protein (CRP). Excessive levels of CRP might lead to overactivity of the complement system and chronic inflammation at the macula, resulting in cellular damage and drusen deposits. In 2005, *CFH* was the first strong genetic factor identified for exudative AMD. The Y402H is present in 34.9% of Caucasian populations, and is estimated to have a role in almost 60% of AMD cases at the population level.[9] Its frequency, however, is low in the Chinese[10,11] and Japanese[12] populations, and no obvious associations with wet AMD has been noted in either of these populations (**Table 2**[7-10,12-15]). In contrast, *CFH* polymorphism Tyr402His appears strongly linked to the pathogenesis of AMD in Indians.[13]

In 2006, two other genetic factors, *HTRA1*, a serine protease gene (SNP rs11200638) and hypothetical LOC387715 (SNP rs10490924), were found in Hong Kong Chinese[14] and white Caucasians[16] with wet AMD, and they showed

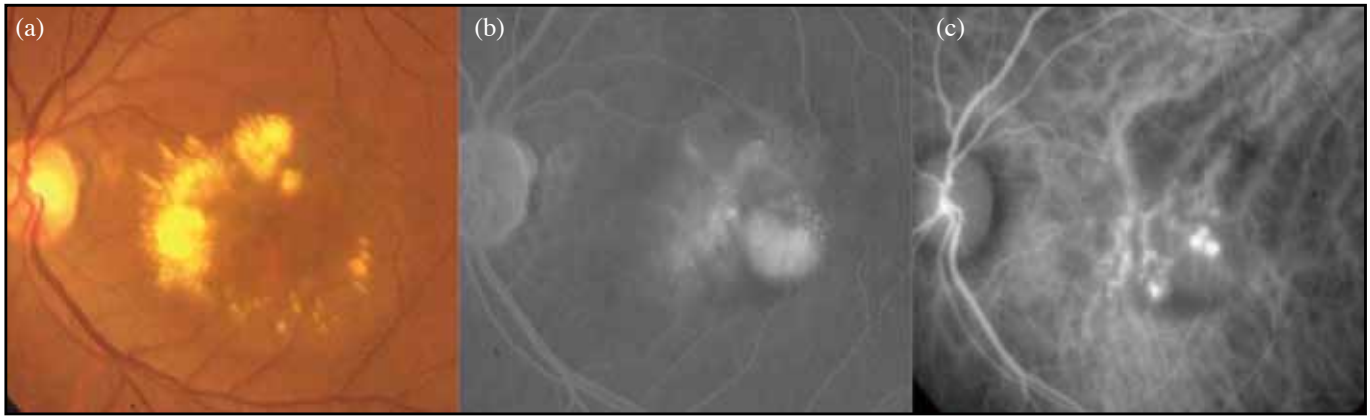

Figure 1. (a) Fundus photograph of a 65-year-old Chinese man presenting with progressive metamorphopsia in his left eye for 3 months. The best-corrected visual acuity was 20/70. This photograph shows extensive hard exudates in the subretinal level together with clear subretinal fluid at the macula. (b) Mid-phase fluorescein angiography demonstrates pigment epithelial detachment with uniformed hyperfluorescence and generalized fluorescence pooling at the macula on a background of retinal pigment epithelium transmission defect in the mid-phase. (c) Early-phase indocyanine green angiography shows multiple polypoidal vascular lesions and interconnecting vessels arising from the dilated anterior choroidal vessels.

Table 3. Differences between typical age-related macular degeneration (AMD) and polypoidal choroidal vasculopathy (PCV).

Typical AMD	PCV
Manifestations and phenotypic pattern	
Grayish membrane, tendency to grow through retinal pigment epithelium (RPE)	Reddish mass, nodular elevation at sub-RPE level
Solitary; tendency at central macula	Multiple centers; vascular lesion at paramacular region
Other features of AMD, such as drusen in involved and fellow eyes	Commonly no drusen in involved or fellow eyes
Age-group	
Old patients	Younger patients
Natural course	
More aggressive in growth; rapid drop in vision	Slow growing; waxes and wanes; can last for months to years
Vascular fragility causing massive bleeding is occasionally possible	Vascular fragility causing massive bleeding is very likely
End stage: fibrotic scarring or disciform scar is likely	End stage: atrophic maculopathy with minimal scar formation; massive scarring is unlikely (unless with secondary choroidal neovascularization)
Fluorescein angiography	
As classic or occult patterns	Most present as occult pattern
Indocyanine green angiography	
Smaller calibre vessels involvement as hot spot or plaque; diffuse late staining	Aneurysm-like dilation structure with or without interconnecting branching vascular network vessels
Optical coherence tomography	
Diffuse retinal edema and intraretinal cyst are most common; diffuse sub-RPE thickening	Nodular RPE detachment; subretinal fluid

a strong association with choroidal neovascularization (CNV) formation. Individuals with the risk allele of *HTRA1* gene increase the production of HTRA1 protein. The latter is a member of the heat shock serine proteases which is expressed in human retina and up-regulated by cellular stress. Patients with homozygote alleles are genetically predisposed to 10- and 6-fold increased risk of wet AMD in Chinese and Caucasian populations, respectively.

The 2 major genes implicated in the development of AMD—*CFH* and *HTRA1*—are believed to govern 2 different biological mechanisms. *CFH* affects drusen formation in dry AMD, while *HTRA1* influences the development of CNV (the hallmark of wet AMD). This may account the distinct AMD phenotypes in Asians and white Caucasian populations. Even more complex scenarios involve gene-gene and gene-environment interactions, which can affect overall disease susceptibility and non-responsiveness to treatment.[16-18]

Clinical subtype of age-related macular degeneration in Asian populations

Using fluorescein angiography, exudative AMD can be classified as classic or occult CNV. The spectrum of disease associated with AMD has expanded with advancements in diagnostic technologies. Indocyanine green angiography

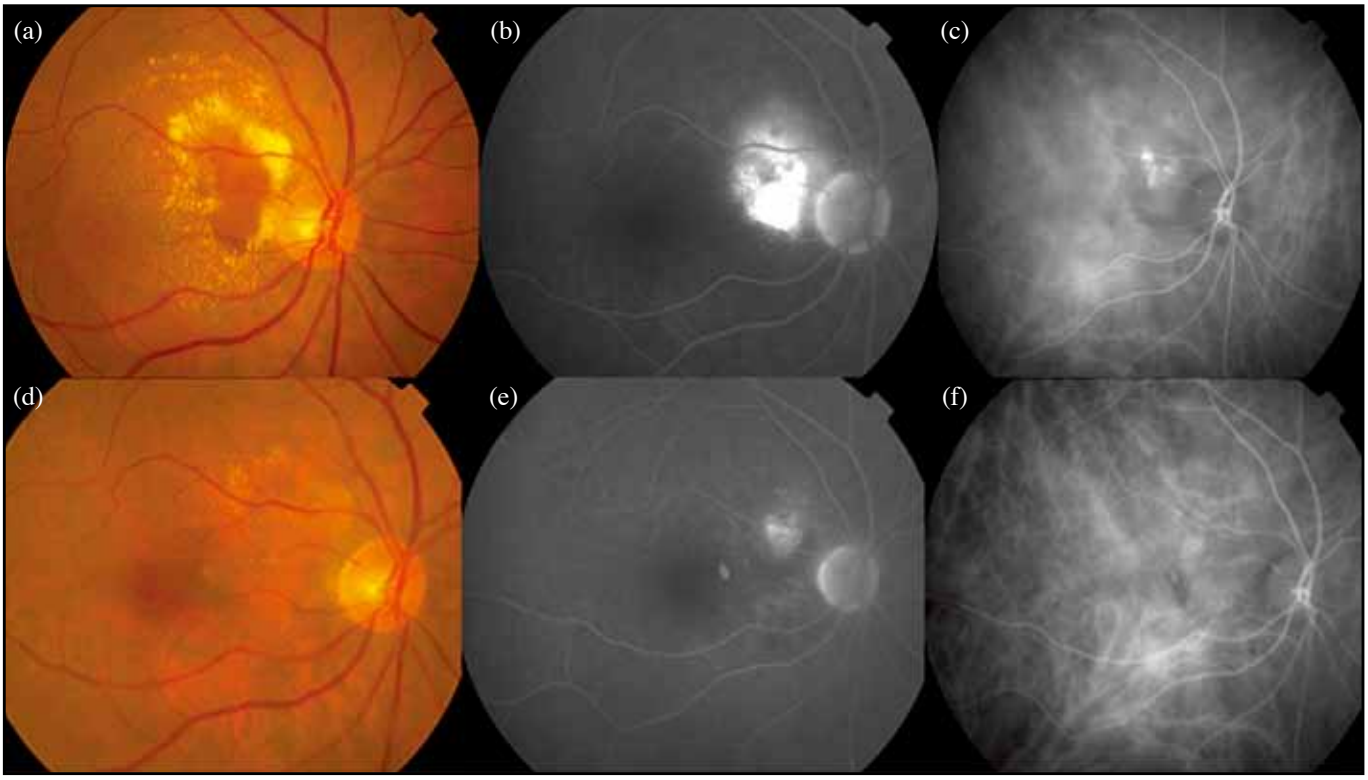

Figure 2. (a) Baseline fundus photograph, (b) fluorescein angiography, and (c) indocyanine green angiography of a 59-year-old woman presenting with serosanguinous maculopathy in the right eye secondary to an active polypoidal choroidal vasculopathy. The baseline best-corrected visual acuity (BCVA) was 20/200. Photodynamic therapy and intravitreal anti–vascular endothelial growth factor with bevacizumab were performed. At 1 year after treatment, the BCVA improved to 20/30. (d) Hard exudate and hemorrhage absorbed gradually and completely resolved by 12 months' post-treatment. (e) Fluorescence angiography showed resolution of leakage and hemorrhagic pigment epithelium detachment. (f) Indocyanine green angiography also demonstrated regression of the polyps and interconnecting vessels.

(ICGA) is able to delineate choroidal vascular abnormalities much more clearly, and new clinical entities such as PCV and retinal angiomatous proliferation (RAP) have emerged. It is well accepted that ICGA is the gold standard for the definitive diagnosis and characterization of PCV (**Figure 1**). Following treatment, each clinical entity is characterized by differences in clinical course, phenotypic presentation, pathogenesis and outcome (**Table 3**).

In a study of 155 Chinese patients with exudative AMD, 68% had CNV typical of AMD, 25% had PCV, 5% had RAP and 3% had mixed lesions.[19] In a similar retrospective study of 104 consecutive patients with ICGA from Hong Kong, PCV accounted for 19.2% of cases.[20] These are probably underestimations of the true prevalence, as in a study with 158 Japanese patients with exudative AMD, 55% were diagnosed to have PCV, 35% typical AMD, 5% as RAP and 5% had mixed lesions.[21]

Highly suspicious characteristic signs of PCV that should prompt ICGA include: massive subretinal hemorrhage, hemorrhagic pigment epithelial detachments, notched pigment epithelial detachments, absence of soft drusen in either eye with exudative maculopathy, clinically visible orange-red subretinal nodules, and presentation in late middle age (persons in their 50s or 60s).

Treatment for exudative age-related macular degeneration in Asian populations

For typical neovascular AMD, if available, intravitreal anti–vascular endothelial growth factor (VEGF) monotherapy is still the preferred primary treatment. The current therapeutic standard is consecutive monthly injections of ranibizumab (Lucentis; Genentech, Inc, San Francisco, US) on a continuing, indefinite basis. This option, however, is not practical or achievable for various reasons, including treatment costs and burden. Bevacizumab (Avastin; Genentech, Inc, San Francisco, US), an anti-VEGF, is commonly used as an off-label alternative. In Asia, the choice between ranibizumab and bevacizumab depends mostly on accessibility of these treatments in the medical system, acceptance and affordability, and physician preference.[22,23]

The most favorable suggested strategy is to use 3-monthly intravitreal doses (loading phase) of either anti-VEGF agent administered to maximize the initial response. This is followed by an individualized maintenance phase, during which patients should receive treatment based on their respective response as judged by visual outcomes and optical coherence tomography (OCT) findings.

Anti-VEGF and photodynamic therapy (PDT) used as dual therapy or together with corticosteroids as triple therapy may address the different pathogenic pathways of wet AMD. Such strategies could be considered for patients with persistent disease despite anti-VEGF monotherapy, the intention being to reduce the number of retreatments and/or offer longer treatment-free periods.[24] Evidence suggested that any combination containing full fluence PDT results in functional visual acuity inferior to ranibizumab monotherapy. The negative effect is probably caused by the standard laser fluence (50 J/cm^2) of PDT on the choroidal blood supply. A successful combination therapy approach involves reduced fluence of PDT, whilst the optimal energy required further investigation.

For the clinical subtype with PCV, PDT has been well accepted as an effective treatment modality. PDT has shown good results for PCV, with stable or improved vision achieved in 81 to 100% of patients at the 1-year follow-up.[8,25] However, in some eyes with PCV, extensive subretinal hemorrhages are an unavoidable side-effect of PDT. Moreover, PDT appears to be less effective in PCV patients presenting late and in cases with secondary formation of fibrovascular tissue. Anti-VEGF monotherapy has been studied in PCV and demonstrated to improve visual acuity and outcomes measured by OCT, but results in only minimal or no regression of polyps as measured by ICGA.[26,27] In PCV with associated exudative changes, combining PDT's angiooocclusive effect on polyps with anti-VEGF's antipermeability effect may lead to better clinical outcomes (**Figure 2**). The recently completed EVEREST study, a multicenter randomized controlled trial, showed that a combination of PDT and ranibizumab therapy resulted in the highest proportion of patients with complete regression of polyps at 6 months (78% complete regression), compared to PDT monotherapy (71%) or ranibizumab monotherapy (29%).[28] Further studies are needed to determine the long-term role of combination therapy as primary therapy for treating PCV.

Several novel investigational agents are now being evaluated. VEGF Trap-Eye (Regeneron Inc., Tarrytown, US; Bayer HealthCare AG Inc., Leverkusen, Germany), a VEGF receptor fusion protein that binds all forms of VEGF with higher affinity than ranibizumab might have a future role in the treatment of PCV. Another potential therapeutic strategy involves blockade of VEGF effects by inhibiting the tyrosine kinase cascade downstream from the VEGF receptor. These may be the future directions in enhancing the treatment success in wet AMD in order to offer maximal possible gains for our patients.

Conclusions

AMD in Asian populations reveals many differences from the western populations, especially in phenotypic manifestations and prevalence of clinical subtypes. Diversity in genetic composition and environmental interactions are among the major reasons. Accurate diagnosis of AMD subtypes is important for appropriate patient management. In Asian populations, PCV constitutes a high percentage of patients with exudative AMD, and it is known that anti-VEGF therapy alone is inadequate in achieving optimal anatomic and angiographic results. Once the diagnosis of PCV is made by ICGA, by including PDT in the therapeutic protocol, modifications may be indicated in order to improve outcomes.

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