Risk factors for age-related macular degeneration

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Introduction

Age-related macular degeneration (ARMD) leads to the loss of central vision, due to degenerative defects in the macula lutea.[1] The degeneration is associated with death of the rods and cones in the retinal pigment epithelium with (exudative) or without (nonexudative) the complications of vascular invasion and choroidal neovascularization. Age-related macular degeneration is the major cause of blindness and the leading cause of severe visual loss among the elderly in the West.[2] The prevalence of advanced ARMD is estimated to be 1.5%.[3] For people 43 to 54 years of age, the prevalence of all ARMD has been estimated to be 8.5%, whereas in the population aged 75 years and over, the prevalence increases to 37%.[4,5] Occurrence of ARMD is pan-ethnic. Among 3,351 Chinese , the overall incidence of ARMD has been reported to be about 6%, while the incidence for people aged over 65 years has been reported to be about 17%.[6] A pilot study in Hong Kong involving 355 Chinese randomly recruited from the general population and aged over 40 years showed a prevalence of 19%.[7]

To date, there is no known cure for the disease. Treatment options are limited and ineffective.[8] Laser photocoagulation is suitable for treating only a highly selected group of patients with new blood vessel growth in and around the fovea. Furthermore, laser photocoagulation merely delays but does not prevent subsequent visual loss, especially in ARMD with neovascularization or geographic atrophy.[9] Effective treatment modalities should be facilitated by understanding the etiology of the disease, which is clearly multifactorial. While age is the undisputed and the most important risk factor, cigarette smoking, sunlight, diet and hypercholesterolemia have been incriminated to be associated with the development of ARMD. There is also a strong genetic susceptibility to the development of ARMD, as evidenced by familial and molecular genetic studies.

Smoking

Cigarette smoking may contribute directly or indirectly to the development of ARMD through various mechanisms.[10] Firstly, the prolonged hypoxic effects of smoking, including elevated carboxyhemoglobin levels and depletion of oxygen, may lead to the formation of a tubular capillary network from choriocapillaries.[11,12] Choroidal neovascularization is invasive to the retinal pigment epithelium and causes disciform macular degeneration.[13,14] Secondly, smoking decreases plasma levels of HDL cholesterol but increases total cholesterol, LDL cholesterol, platelet adhesiveness and fibrinogen. These atherosclerotic factors promote ischemia and microinfarction in the macula.[15-17] Thirdly, oxidants present in cigarette smoke or generated through the activation of phagocytic cells stimulate lipid peroxidation of polyunsaturated fatty acids in photoreceptor outer segments and lead to development of ARMD.[18,19] Fourthly, smoking reduces the concentration of antioxidants, such as ascorbic acid and carotene, in blood and consequently in the retina.[20-22] The retina is thus more prone to damage by oxidative stress and free-radical reactions.

After adjustment for other established or putative risk factors, including age, plasma levels of carotenoid and cholesterol,

alcohol consumption, vitamin intake, diabetes and hypertension, prolonged cigarette smoking has been shown to increase the risk of ARMD in males and females.[21,23,24] There is also a dose-dependent effect.[25] The risk of ARMD among former smokers remains elevated several years after cessation of smoking.[26] For nonexudative ARMD, there are conflicting conclusions from different studies. However, large-scale and prospective studies involving thousands of study subjects mostly show statistically significant correlation, including dose-response effects.[25,26] Negative associations are always reported in retrospective cross-sectional studies with small sample sizes, such as fewer than a few hundred study subjects.[27-29] Smoking is therefore an independent risk factor for ARMD, especially the exudative form.

Sunlight exposure

Animal studies and human case reports have suggested that exposure to intense bright light or UV radiation may cause structural and functional changes in the retinal pigment epithelium, as seen in ARMD.[30,31] Light from indirect ophthalmoscopy induces morphological changes in the retinal pigment epithelium and causes the formation of subretinal pigment epithelial plaque.[32] Light exposure may cause photic injury to the retina by enhancing the production of superoxide radicals, which stimulate lipid peroxidation.[33,34] The outer segment membranes of the retina, which is rich in polyunsaturated fatty acids, are particularly vulnerable. Antioxidants, such as ascorbic acid, which suppress lipid peroxidation, play a protective role in the retina against oxidative injury.[35,36]

However, there are discrepancies in the evidence for a causal relationship between sunlight and ARMD. In a case-control study, no association between recreational or occupational exposure to sunlight and ARMD was found.[28] The Maryland Watermen study, which involved 838 watermen aged 30 and over, showed no association between ARMD and cumulative exposure to either UV-A or UV-B within age groups or after age adjustment.[37] A similar conclusion was also reached in a cross-sectional population-based study on about 5000 subjects aged between 43 and 84 years.[38] However, in the same study, uses of hats and sunglasses were inversely associated with soft indistinct drusen (odds ratio (OR) 0.61, 95% confidence interval (CI) 0.28-0.98). The amount of summer outdoor time was associated with exudative macular degeneration (OR 2.26, 95% CI 1.06-4.81) and late maculopathy (OR 2.19, 95% CI 1.12-4.25). Furthermore, cumulative ocular exposure to blue light in the 20 years before examination was associated with an increased prevalence of severe macular degeneration (OR 1.35, 95% CI 1.00-1.81).[39] In a retrospective investigation in Australia, ocular sun exposure had been significantly greater in 409 ARMD patients than 286 control subjects.[40] The patients were more sensitive to glare and less capable of developing a skin tan.

While most evidence supports an association between ocular exposure to sunlight and ARMD, large-scale and longitudinal studies involving documentation of individual sunlight sensitivity and the amount of exposure are required to assess the relationship further.

Diet

Saturated fat and cholesterol

A high intake of dietary saturated fat increases blood cholesterol concentrations and increases the risk of atherosclerosis.[41] Elevated lipid levels in the blood circulation may promote degenerative changes in the macula. An association between serum cholesterol concentration and neovascular exudative macular degeneration has been reported.[42] People with an intake of saturated fat and cholesterol in the highest quintile had significantly higher odds of 80% and 60% higher, respectively, for early ARMD than those in the lowest quintile, after adjustment of confounding factors, including intake of carotenoids and vitamin C and E, gender, smoking habit, body mass index, sunlight exposure, diabetes, hypertension and cardiovascular disease.[43] The odds ratio for late ARMD among those with a high intake of both saturated fat and cholesterol compared with those with a low intake was similar to that for early ARMD (OR 1.5, 95% CI 0.5-4.5), but it was not statistically significant.

ARMD could be viewed as an aging process of the sclera that is initiated by lipoidal infiltration, which resembles arteriosclerosis.[44] Saturated fat and cholesterol are risk factors for atherosclerosis and arteriosclerosis. They may cause lipoidal infiltration in the sclera, decrease compliance of the sclera and choroidal vessels, increase resistance of choroidal vessels and decrease choroidal perfusion. This would finally lead to impaired transport across the retinal pigment epithelium and hence the formation of drusen, retinal pigment epithelium atrophy and lipoidal infiltration of Bruch's membrane. High lipid levels in the blood circulation may also encourage direct deposition of fat in Bruch's membrane, which may then interfere with the flow of metabolites in and out of the retinal pigment epithelium. Such changes can also lead to detachment of the retinal pigment epithelium and hence detachment of the choroidal neovascular membrane.[45]

Antioxidants

Antioxidants in the diet may prevent or impede the progression of ARMD. In a rat model, supplements of carotenoids, vitamin C and vitamin E help to protect the retina from oxidative damage initiated by absorption of light.[46] Vitamins C and E probably act as antioxidants against free-radical reactions of superoxide radicals formed by light-induced oxidation of nucleotide molecules in the retina. These vitamins thus exert a protective effect against photic injury to the retina. A higher dietary intake of carotenoids is associated with a lower risk of ARMD.[47] In particular, those in the highest quintile of carotenoid intake have a 43% significantly lower risk when compared with those in the lowest quintile, after adjustment for other dietary and demographic confounding factors. Primates accumulate two variants of carotenoids, lutein and zeaxanthin, in the retina as the macular pigment. The pigmentation is most dense at the center of the fovea and declines rapidly in more peripheral

regions. Intake of lutein and zeaxanthin is strongly associated with a reduced risk of maculopathy.[47] Retinal degeneration is also more common in monkeys with vitamin E or vitamin A deficiency.[48] The presence of carotenoids and antioxidant vitamins may therefore delay some of the destructive process in the retina and the retinal pigment epithelium caused by oxidative stress and lipid peroxidation.

Molecular genetics

The familial trait of macular dystrophy has been observed for more than three decades.[49] One study showed that 20% of individuals with macular detachment and degeneration had a family history of central vision defects.[50] There was concordant occurrence of drusen in the eyes in sibling pairs but not in spouses.[51] In a case-control study, 20 of 81 ARMD siblings were affected, while only one of 78 normal control siblings had ARMD.[52] This represented a relative risk to a sibling of an affected patient to be 19.3 times higher than that of a control sibling. In a retrospective study of 177 first-degree relatives of 119 ARMD patients and 146 relatives of 72 normal controls, a significantly higher proportion (23.7%) of ARMD was present in the relatives of the former than of the latter (11.6%).[53] The age- and sex-adjusted odds ratio was 3.1 (P=0.03). There is strong genetic predisposition for ARMD.

Stargardt disease, also known as fundus flavimaculatus, is the most common hereditary form of macular degeneration, with an incidence of approximately 1 in 10,000 in Caucasians. It is an autosomal recessive disorder of the retina and is usually associated with early- or juvenile-onset macular degeneration. Linkage analysis and detailed chromosomal studies on expressed sequence tags and yeast artificial chromosomes obtained from human retina cDNA have led to the identification of the retina-specific ATP-binding transporter gene (*ABCR*) as the causative gene of Stargardt disease.[54] *ABCR* is located on chromosome 1p13-21, spanning a 7.1 kb sequence with a known open reading frame of 6705 bp in 51 exons encoding for 2235 amino acids.[55] *In situ* hybridization has shown that *ABCR* is expressed exclusively in the rod inner segments of photoreceptor cells in the retina. It is completely absent in cone photoreceptors, although cone dysfunction is a common feature of Stargardt's disease. There may be two explanations. Cone dysfunction is caused by defects in the retinal pigment epithelium due to primary lesions in the photoreceptor rod. It is also possible that a different gene is involved in cones. Whether *ABCR* defects occur in forms of retinopathy other than ARMD remains to be investigated.

A total of 23 identified *ABCR* mutations have so far been reported.[56,57] They are single point substitutions or small insertions or deletions scattered throughout the coding sequence. *ABCR* sequence analysis may allow establishment of an unequivocal genetic test for early or presymptomatic diagnosis of ARMD, although ethnic-specific or common mutations in different populations are still to be found by large-scale studies. Meanwhile, understanding of the functions of the ABC transporter protein will provide information for the design of specific therapeutic agents for treatment of ARMD.

The apolipoprotein E (*APOE*) gene has been shown to be a susceptibility gene for ARMD. *APOE* is a protein component of most major plasma lipoproteins and plays an important role in cholesterol transport and lipid metabolism. It is a ligand for lipoprotein receptor binding and a transporter for lipids.[58] The *APOE* gene is located on chromosome 19q2 and contains a 5' regulatory sequence of about 1.4 kb and 4 exons spanning 3.6 kb. *APOE* is highly polymorphic, with 3 major isoforms: apo E2, E3 and E4 encoded by alleles ε2, ε3 and ε4 respectively.[59] The *APOE* genotype is strongly associated with a wide spectrum of familial and sporadic forms of disorders: dyslipidemia, cardiovascular diseases and Alzheimer's disease.[60] While the ε4 allele poses increased risk of developing Alzheimer's disease, ε4 allelic frequency has been found to be lower (P<0.0009) in patients with exudative ARMD than in control subjects.[61] In 88 ARMD patients aged 55 and over, ε4 was associated with a lower risk (OR 0.43), while ε2 was associated with higher risk (OR 1.5), when these patients were compared with 901 control subjects.[62] A protective role of the ε4 allele against ARMD is apparent.

The polygenic nature of ARMD is exemplified by the mapping of another locus on chromosome 1q25-q31, designated as the *ARMD1* gene.[63] So far this gene has been linked to ARMD in only one family, and more about its features, functions and association with ARMD are still to be investigated.

Conclusion

Although there are still a lot of unknowns about ARMD, it is for sure that ARMD is a multifactorial disease and both nature and nurture are playing their roles.[64] Acquired risk factors include smoking, sunlight and saturated fat and cholesterol. There are at least three putative mechanisms of ARMD: 1. direct stimulation of subretinal vessels; 2. increase in atherosclerotic and hypoxic damage to the choroidal vasculature; 3. increase in oxidative damage to the outer retinal cells. Smoking seems to affect the macula by all three mechanisms, while saturated fat and cholesterol mainly involve the second mechanism. Sunlight can induce formation of superoxide radicals, which in turn cause oxidative damage of the outer retinal cells. On the other hand, antioxidants like carotene and vitamins seem to have a protective role in reducing oxidative stress by acting as scavengers for free radicals. Antioxidants may also maintain the normal function of blood vessels that supply the macular region.[47] On the nature side, recent studies indicate that susceptible patients could be genetically primed for the disease.

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