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Review

Genetic factors associated with the development of age-related macular degeneration

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ABSTRACT

Age-related macular degeneration (AMD) affects the macula and is the leading cause of significant and irreversible central visual loss. It is the most common cause of visual loss in people aged more than 60 years. This disease affects 2.5 million individuals in Europe. AMD is caused by both environmental and genetic factors. Numerous risk factors have been reported, but the pathogenesis of AMD is complex and fairly understood. Age, female gender, obesity, race, education status, family history, hyperopia, iris color, cigarette smoking, previous cataract surgery, history of cardiovascular and cerebrovascular disease, diabetes, sunlight exposure and many other factors have been shown to be associated with AMD development. Scientific evidence shows that genes may play a role in the development of nearly 3 out of 4 cases of this devastating eye disease. The genes that have been shown to be associated with AMD are genes encoding complement system components such as CFH, C2, C3, CFB, and other.

1. Introduction

Age-related macular degeneration (AMD) is referred to aging changes without any other obvious precipitating cause that occur in the central area of the retina (macula) in people aged 55 years and more [1]. Impairment of sight and blindness are debilitating and are among the three most feared medical conditions, after cancer and cardiovascular disease [2]. In developed countries, AMD is the most common cause of visual loss in persons aged more than 60 years [3]. More than 30% of adults >75 years-of-age have this disease; in ~6%–8% of these individuals, the disease progresses, causing the most severe degree of visual loss [4]. The prevalence of early AMD increased

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from 1.3% ± 0.3% per subject in the 30-year-old to 40-year-old group, to 3.6% ± 0.5% in the 41-year-old to 50-year-old group, to 7.9% ± 0.9% in the 51-year-old to 60-year-old group, to 10.0% ± 1.1% in the 61-year-old to 70-year-old group, to 8.3% ± 0.2% in the 71-year-old to 80-year-old group, and to 8.0% ± 5.5% in the ≥81-year-old group [5].

AMD is the third leading cause of blindness globally following cataract and glaucoma and it accounts for 8.7% of all blindness cases [6]. In Lithuania, AMD-related blindness accounted for 13.8% and took the second place in 2002 (Lithuanian Medical Social Expertise Commission). The number of AMD-affected people in the developed countries is increasing dramatically. In 2014, Wong et al. published a systematic literature review that aimed to estimate the number of people who will be affected by AMD in the future [7]. This study showed that the prevalence of any AMD was higher in Europeans than Asians and Africans (12.3% vs. 7.4% and 7.5%, respectively). Also, this study reported that the number of persons with AMD will globally increase to 196 million by 2020 and will reach 288 million by 2040 [7].

It is thought that AMD has a multifactorial etiology, the development of which may be caused by interrelation of environmental and body peculiarities; also genetic factors have an impact.

The aim of our article was to review literature, disclose the present view on the pathogenesis and classification of AMD, and reveal factors, especially genetic association, prognosis of the development of this disease.

2. Pathophysiology of age-related macular degeneration

Pathological changes in the macula, a special area of the retina, are associated with the development of AMD. The center of the macula is called the fovea and it contains a huge concentration of photoreceptors with cone cells, responsible for visual acuity and color perception, dominating (up to 200 000 cells/mm^2) [8,9]. The parafoveal area is a region, where rode cells dominate, surrounding the fovea and permitting night vision. In the early stages of AMD, photoreceptors are mostly damaged in the parafovea [10].

Macular degenerative changes occur due to modification of the retinal pigment epithelium and drusen formation in the Bruch membrane, which consists of the retinal pigment epithelium and the choroidal choriocapillary layer. Drusen are extracellular small nodule-shape deposits, made of phospholipids, collagen, and neutral lipids [11]. Also, drusen contain zinc, carbohydrates, and at least 129 different proteins, including apolipoproteins (e.g., apoE, apoB) and excluding structural extracellular matrix. Approximately 30% of the drusen, with a core diameter of 15 μm, consist of nonesterified cholesterol, nonfibrillar amyloid, and peanut agglutinin-binding carbohydrates [11]. These cores may represent nucleation sites for following deposition. Their accumulation alters the delivery of oxygen and nutrients, leading to lesions in the retinal pigment epithelium and a progressive degeneration of photoreceptors, while visual function impairment is associated with the amount of damaged photoreceptors [8].

Histologically drusen are divided into two types: soft and hard. Soft drusen are large, diffuse and composed of an amorphous, granular, and loose material with poorly defined borders [11]. Soft drusen, the main component of basal linear deposit is membranous debris, containing coiled membranes and vesicular outlines of putative retinal pigment epithelium origin. The deposit composition is solid neutral lipid-rich particles. These drusen can form exudative macular degeneration and later can induce the detachment of the neuroepithelium. If the process progresses, new vessel will grow, leading to exudative hemorrhage. Hard drusen are small, distinct, hemispherical, or round-shaped with well-defined borders. Druse composition is solid and hyalinized [11]. They have decreased RPE coverage, consistent with aberrant expression of amyloid A and vitronectin over small drusen. Usually, hard drusen consists of cholesterol, nonfibrillar amyloid, calcifications. Some of them may content nonesterified cholesterol-rich core, and some identified by more shells, which are rich in apoE, apoC-I, and esterified cholesterol [11]. Hard drusen can cause atrophy of the retinal pigment epithelium and the choriocapillary layer [8,9].

3. Classification of age-related macular degeneration

AMD is commonly categorized into early and late forms [8,11]:

- Early AMD is described by the presence of a large number of deposits known as drusen (≤10), which appear below the retinal pigment epithelium and causing more or less pigmentation areas called hyperpigmentation or hypopigmentation. The pigmentation regions are generally diffused [8,11].
- Late form of AMD is classified into dry (with geographic atrophy of the retinal pigment epithelium with the lack of neovascularization areas) and wet types (or exudative; with new blood vessel formations in choroid, called the choroidal neovascularization areas, further leading to the formation or the disciform scars) [8]. The wet type is the heavier form of the disease than the other types [11]. It causes severe damage to the retina and more frequently leads to devastating consequences such as vision loss [8].

4. Risk factors

Epidemiological studies have shown a complex interplay among genetic predisposition, systemic factors, lifestyle and environmental risk factors associated with the risk of AMD development. Age is one of the highest and invariable factors; persons aged between 60 and 80 years are at a 3-fold greater risk of developing advanced AMD compared with those younger than 60 years [12]. Smoking is another significant and modifiable factor. A lot of studies have shown the influence of smoking on AMD formation and have demonstrated that previous and current smokers are inclined to develop AMD at least 5–10 years earlier than nonsmokers [13]. Other factors implicated in the development of AMD are gender, family predisposition, color of the iris, ethnicity, sunlight exposure, body mass index, eating habits, oxidative stress, inflammation and increased levels of inflammatory marker in blood, low antioxidant levels in blood