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Major review

Association of age-related macular degeneration and reticular macular disease with cardiovascular disease

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ABSTRACT

Age-related macular degeneration is the leading cause of adult blindness in the developed world. Thus, major endeavors to understand the risk factors and pathogenesis of this disease have been undertaken. Reticular macular disease is a proposed subtype of age-related macular degeneration correlating histologically with subretinal drusenoid deposits located between the retinal pigment epithelium and the inner segment ellipsoid zone. Reticular lesions are more prevalent in females and in older age groups and are associated with a higher mortality rate. Risk factors for developing age-related macular degeneration include hypertension, smoking, and angina. Several genes related to increased risk for age-related macular degeneration and reticular macular disease are also associated with cardiovascular disease. Better understanding of the clinical and genetic risk factors for age-related macular degeneration and reticular macular disease has led to the hypothesis that these eye diseases are systemic. A systemic origin may help to explain why reticular disease is diagnosed more frequently in females as males suffer cardiovascular mortality at an earlier age, before the age of diagnosis of reticular macular disease and age-related macular degeneration.

1. Introduction

In 1888, Haab first described age-related macular degeneration (AMD),[43] although Verhoeff and Grossman indicated in 1937 that clinical and histologic features of AMD may have been observed as early as 1875.[100] In the United States advanced AMD is the leading cause of blindness in older adults, affecting over 2 million people.[A] The 2 forms of advanced AMD consist of "wet" AMD, otherwise known as choroidal neovascularization (CNV) or more generally as exudative AMD, and "dry" AMD, also known as geographic atrophy (GA).[34] Most patients in the first stages of AMD have lipid-rich deposits under the retinal pigment epithelium (RPE) known as soft drusen.

Drusen were first identified in 1854 by Donders.[26] They are now understood to be extracellular deposits of material lying between the RPE and the inner collagenous zone of Bruch membrane.[1] Disagreement remains regarding the cause of

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drusen, but 3 main theories have been proposed. In 1854, Donders suggested that drusen are the product of a direct conversion of the RPE. This became known as the "transformation theory."[1,26] In 1856, Muller proposed that drusen are the product of deposition by an otherwise normal RPE.[1,69] In the 1960s, Friedman hypothesized that drusen arise from blood constituents, noting a close association between drusen and the collecting choroidal venules.[1,32] Although the presence of drusen is required for a diagnosis of AMD, researchers have yet to determine whether drusen cause advanced AMD or whether they are a marker of a process that results in advanced AMD. It is also now recognized that small, hard drusen less than 65 μm in size are not associated with AMD; hence, only intermediate drusen (between 65–125 μm) and large drusen (greater than 125 μm) qualify for a diagnosis of early AMD.[23] Drusen have a high content of esterified cholesterol, and the source of these lipids is still under intense investigation.[25,75]

Mimoun and colleagues, in 1990, noted a special type of drusen in the macula of patients with AMD that they described as "les pseudo-drusen visibles en lumière bleue," which translates to "pseudodrusen visible in blue light," for their visibility in blue light fundus photography.[66] One year later, Klein and colleagues, in the Wisconsin Age-Related Maculopathy Grading System, classified "pseudodrusen" as a type of soft drusen.[51] Arnold and colleagues reported the presence of yellow interlacing networks 125–250 μm in width that they called "reticular pseudodrusen" (RPD).[7] They used histologic findings of 1 eye without the neural retina to suggest that these lesions indicate poor choroidal perfusion in addition to choroidal fibrosis and found that RPD increase the risk for the CNV form of late AMD.[7] With the use of scanning laser ophthalmoscopy to further investigate similar lesions, Smith and colleagues proposed the term *reticular macular disease* (RMD) for the disease process itself within the classification of AMD, with RPD referring to the representative phenotypic En face imaging features of RMD.[92]

The relationship between AMD and RMD has been a topic of interest since the discovery of RPD and the proposal that the lesions are indicative of choroidal fibrosis and poor choroidal perfusion by Arnold and colleagues in 1995.[7] Associations between RMD and CNV were recognized since about 2006.[19,90] There is also evidence that subretinal drusenoid deposits (SDD) may be more generally associated with other retinal degenerations. Hyper-reflective deposits in the subretinal space have been identified on spectral domain optical coherence tomography (SD-OCT) in retinal degenerations distinct from AMD, including pseudoxanthoma elasticum with angioid streaks, fundus albipunctatus, and vitamin A deficiency retinopathy.[4,38,111] None of these other disorders, however, have associated choroidal thinning, which leaves open the possibility that the dual pathology of RMD, SDD, and choroidal thinning is indeed specific to AMD and is consistent with a hypothesis that RMD may be systemic in nature. In addition, SDD, but not soft drusen, are associated with decreased longevity through an undetermined causality.[54] Systemic disorders such as pre-eclampsia may be associated with SDD.[84] There is a preponderance of females among patients with both AMD and RMD. In addition, patients with AMD or RMD tend to be older than those with AMD alone. Because hypertension, smoking, and angina all increase the risk for AMD, and AMD has been associated with many cardiovascular genes, efforts to explain the increased proportion of females with RMD or AMD and the other associations alluded to previously have led to the hypothesis that RMD may actually be a manifestation of systemic disease, especially cardiovascular disease (CVD), which typically results in a shorter life span in men than in women. This hypothesis would suggest that those women with CVD live long enough to develop AMD or RMD more frequently, which is exactly what is observed.[34,54]

We will discuss the relationship between AMD and RMD and explore how these diseases may be linked to CVD through a discussion of AMD and RMD epidemiology and genetics.

2. The pathogenesis of AMD and its relationship with CVD

Although the pathogenesis of AMD is not completely understood, several hypotheses have been proposed to attempt to explain the disease process. Friedman, after noting that the degenerative changes in elastin and collagen of atheromatous plaques were similar to those seen in the aging Bruch membrane affected by AMD, proposed that AMD is a vascular disorder.[33,35] Combining the findings of others with his own work, Friedman described a pathogenesis similar to atherosclerosis, with accumulation of lipids in the sclera and in Bruch membrane increasing the postcapillary resistance of the choroidal vasculature and thereby decreasing choroidal blood flow, as well as elevating hydrostatic pressure. He noted that this elevation of hydrostatic pressure, in turn, leads to a leakage of proteins and lipids that form basal deposits within Bruch membrane and drusen between Bruch membrane and the RPE.[13,24,33,35,36,73] In addition, Beatty and colleagues,[10] and Bok,[12] suggested that inflammation and oxidative stress may play a role in both CVD and AMD, thus linking them further together. Several other studies have reported degenerative changes in the choriocapillaris and decreased choroidal circulation in histopathologic and blood flow studies of patients with AMD.[15,42,65,85] Metelitsina and colleagues found the decreased choroidal blood flow in patients with AMD further compounded by coexisting hypertension,[65] a systemic connection.

Given the hypothesis of Friedman and other studies that have shown a relationship between CVD and AMD, several investigators have recently looked at patient cohorts with CVD to determine if these groups of patients are in fact at increased risk for developing AMD. In the Blue Mountains Eye Study, Tan and colleagues examined the relationship between cardiovascular risk factors and the long-term incidence of AMD in a prospective cohort and found significant associations. In particular, they found that high-density lipoprotein (HDL) cholesterol levels were inversely related to the incidence of late AMD, elevated total cholesterol or HDL cholesterol ratios predicted CNV and GA, and diabetes predicted incidence of GA, but not CNV. In addition, a history of any CVD (including stroke, myocardial infarction, or angina) predicted incident early AMD and incident soft or reticular drusen. They found no association between any