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Age-Related Macular Degeneration: A Leading Cause of Blindness among Older Adults

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Age-related macular degeneration (AMD) is the leading cause of blindness among older adults in North America. This article reviews the clinical spectrum, risk factors, pathophysiology, and potential therapeutic options for this disease. Despite significant advances in the treatment of certain forms of AMD, there is currently no cure for this degenerative condition. The substantial personal, social, and economic burden of AMD requires that those who provide care to older adults have a general understanding of this cause of blindness. It is important for the ophthalmologist and primary care physician to address modifiable risk factors for the progression of AMD such as poor cardiovascular status and smoking, which may worsen visual loss. In addition, educating patients and their families regarding risk factors and potential treatment options may greatly benefit those affected by AMD.

Key words: *blindness, geriatric, age-related macular degeneration, choroidal neovascularization, ranibizumab, bevacizumab*

Introduction

Age-related macular degeneration (AMD) is a significant cause of blindness among older adults. The functional centre of the retina, known as the macula, is affected in this condition. Macular vision is important for both reading and facial recognition. While diagnosed and treated primarily by ophthalmologists, AMD can have a profound personal, social, and economic impact. Therefore, it is important that the geriatrician or general practitioner have an understanding of this disease and its implications for older adults. This article reviews not only the epidemiology, genetics, pathophysiology, ophthalmic manifestations, natural history, and treatment considerations for AMD, but the personal, social and economic impact of this disease as well.

Epidemiology

Age-related macular degeneration has traditionally been classified into two categories: atrophic (or dry, geographic, nonexudative) AMD and exudative (or wet, neovascular) AMD. The more common form is atrophic AMD, which comprises approximately 90% of individuals affected with AMD.[1] Symptoms of atrophic AMD may range from no symptoms to a reduction in contrast sensitivity to gradually reduced central visual acuity, which may in some cases be severe. Exudative AMD often causes a sudden decrease in central vision ranging from new distortion to profound loss of central vision. The prevalence of visually significant AMD increases with age and is present in approximately 9% of adults aged 52–85 years.[2] This makes AMD the most common cause of blindness in the developed world among older adults. Both genders and various ethnic groups are affected by AMD with relatively similar frequencies.

Genetics

A hereditary component to AMD has long been suspected due to the common occurrence of AMD in families. Progress in genetic studies of AMD, such as family based linkage analyses and case-control association studies, have brought

increasing awareness to the hereditary nature of AMD.[3] For example, variants in the complement factor H gene and LOC387715 have consistently been shown to be major risk factors for AMD. The practice of genetic testing for AMD is still in its infancy and generally controversial because of the wide overall prevalence of these genes in the general population.

Pathogenesis

The initiating cause of AMD remains unknown. However, the final common pathway involves damage to the retinal pigment epithelial cells and underlying connective tissues beneath the neurosensory retina. The accumulation of metabolic byproducts of aging cells[4] and chronic microvascular ischemic insults[5] have been hypothesized as the fundamental abnormalities in AMD. While recently published research has implicated chronic inflammation in the pathogenesis of AMD, other mechanisms such as light toxicity have not been convincingly linked to the disease.[6]

One of the major factors associated with the pathogenesis of the exudative variety of AMD is vascular endothelial growth factor (VEGF). This potent angiogenic molecule causes new vessel growth and vascular leakage, and has been the target of recent advances in therapy for exudative AMD.[7]

Ophthalmic Manifestations

Both atrophic and exudative AMD are characterized by drusen (accumulations of extracellular material) in the macula. These focal, yellow-white, discrete and/or soft or fluffy appearing lesions are comprised of eosinophilic material located beneath the retinal pigment epithelium. Soft drusen have been associated with a higher risk of progression to exudative AMD.[8]

Visual loss may be significant in atrophic AMD and is typically related to areas of atrophy of the retinal pigment epithelium, and not to drusen alone. The term *geographic atrophy* is used to describe the observation of large areas of hypopigmentation caused by severe attenuation of retinal pigment epithelial cells that normally support photoreceptor function of the neurosensory retina (Figure 1a). Hyperpigmented clumps of retinal pigment epithelial cells may also be present and are part of the spectrum of atrophic AMD.

In contrast to the mild to moderate vision loss associated with atrophic AMD, the loss of sight due to exudative AMD may be severe. The hallmark of this variant of macular degeneration is choroidal neovascularization (CNV). New vessels extend from the vascular tissues of the outer eye known as the choroid through spaces in connective tissue to form neovascular membranes deep to the retina.[9] This results in hemorrhage, edema, and fibrosis in the macula related to the leaking vascular membranes, which may profoundly affect central vision (Figure 1b).

Patients affected with visually significant AMD report central blurred vision or visual distortion. Decreased reading or driving ability, particularly under dim conditions, are common complaints. The onset of vision loss is usually gradual in atrophic AMD but may be relatively acute in exudative disease.

Natural History and Prognosis

Among individuals with atrophic AMD visual acuity may remain stable and even asymptomatic for years. Factors such as soft confluent drusen and geographic atrophy outside the visual centre have been linked to visual deterioration.[10] In contrast, the natural history of exudative AMD is characterized by steady and often profound vision loss in the involved eye over the course of several months. Also, the presence of CNV in one eye is associated with an increased risk of the development of CNV in the fellow eye.[11] The end stage of exudative AMD is a subretinal disciform scar caused by the involution of the CNV that leaves the patient with a dense central visual blind spot, or scotoma. Loss of peripheral vision is rare in AMD; however, breakthrough bleeding of an extensive CNV membrane may result in vitreous hemorrhage.

Treatment for Atrophic AMD

The management of atrophic AMD consists of patient education, visual monitoring, and nutritional supplementation. Individuals with AMD are instructed to monitor their vision using an Amsler grid (Figure 2). The appearance of new wavy lines or missing areas of the grid may be a sign of new or worsening exudative AMD. Smoking cessation and the improvement of cardiovascular risk factors have known important benefits on the development and progression of AMD. Therefore, it is important that patients with all types of AMD receive appropriate counselling from their ophthalmologist and primary care physician.[12]

The Age-Related Eye Disease Study (AREDS) demonstrated that oral intake of high-dose antioxidant vitamins and minerals modestly decreased the risk of developing severe visual loss in patients with certain patterns of atrophic AMD.[13] However, the benefit of these nutritional supplements was only observed in those having moderate to severe atrophic AMD with progressive clinical changes. The precise combination of supplements is referred to as the "AREDS Formula," shown in Table 1. Since beta carotene has been linked with lung cancer in smokers and asbestos workers, this supplement should be avoided in current or ex-smokers

Table 1: The Age-Related Eye Disease Study's (AREDS) Guidelines for Nutritional Supplementation for the Prevention of Exudative Age-related Macular Degeneration

Recommended intake:
Vitamin C: 500 mg/day
Vitamin E: 400 IU/day
Beta carotene: 15 mg/day
Zinc oxide: 80 mg/day
Cupric oxide: 2 mg/day

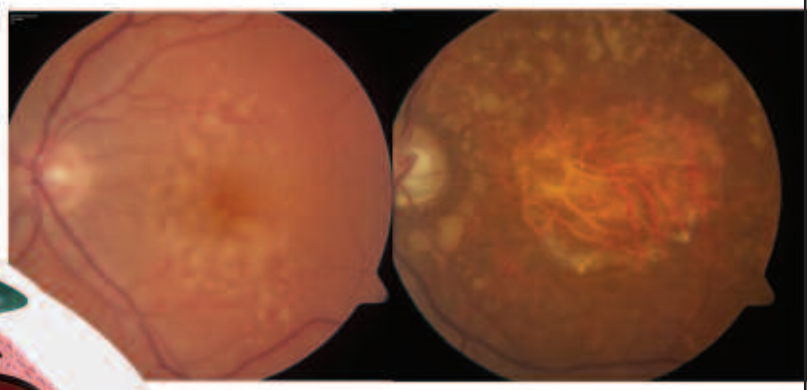
Source: Age-Related Eye Disease Study Research Group, 2001.[13]

Figure 1:

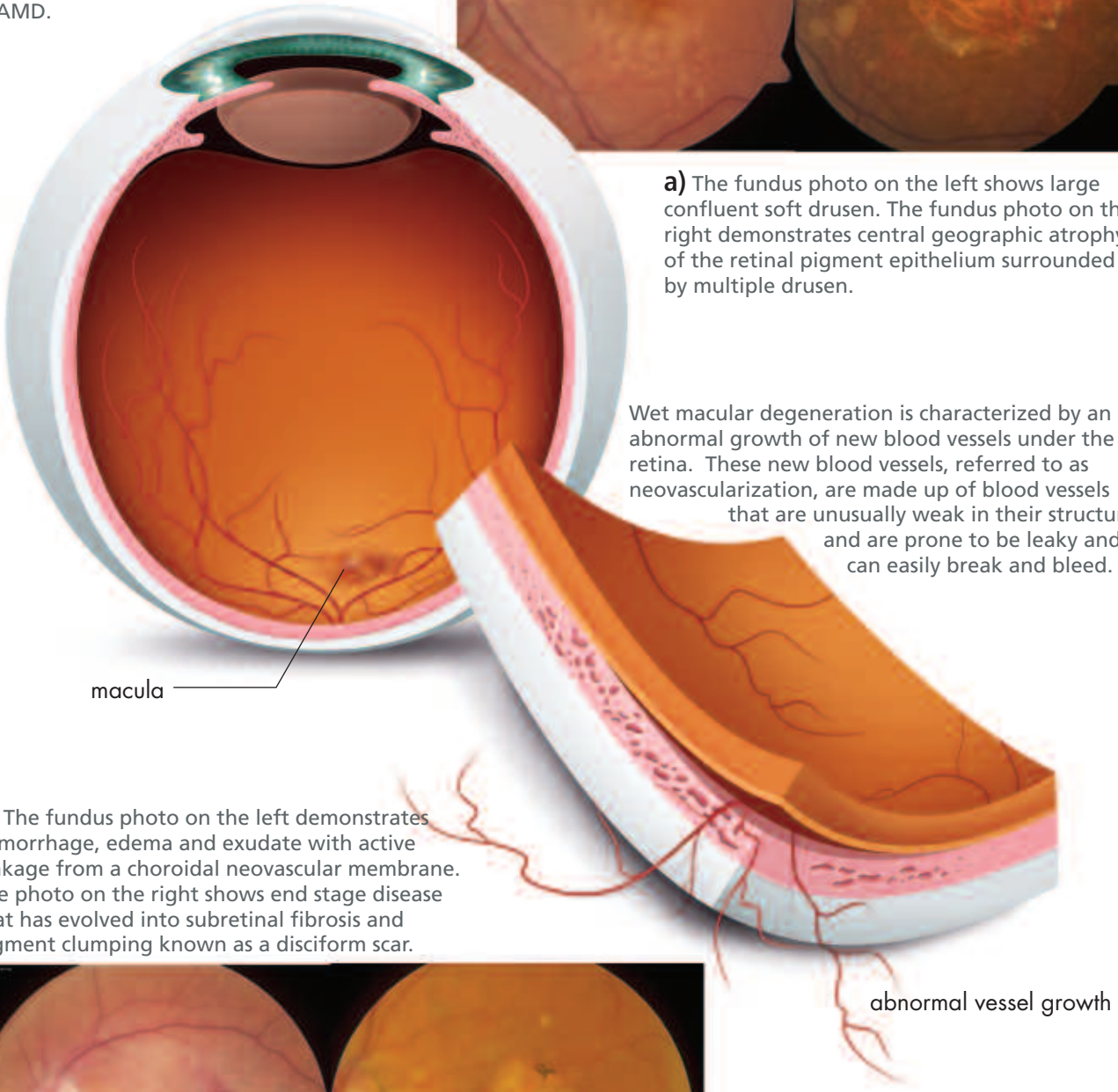
Age-related Macular Degeneration

Epidemiology

Age-related macular degeneration has been classified into two categories: atrophic (dry) AMD and exudative (wet) AMD. The more common form is atrophic AMD, which comprises approximately 90% of individuals affected with AMD.

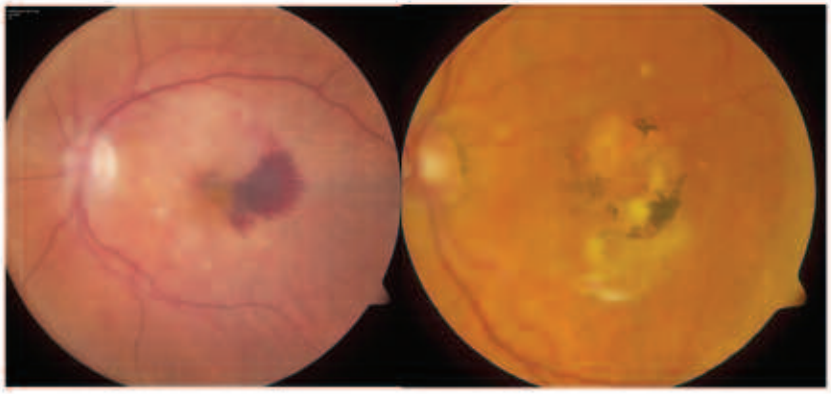


a) The fundus photo on the left shows large confluent soft drusen. The fundus photo on the right demonstrates central geographic atrophy of the retinal pigment epithelium surrounded by multiple drusen.



Wet macular degeneration is characterized by an abnormal growth of new blood vessels under the retina. These new blood vessels, referred to as neovascularization, are made up of blood vessels that are unusually weak in their structure and are prone to be leaky and can easily break and bleed.

b) The fundus photo on the left demonstrates hemorrhage, edema and exudate with active leakage from a choroidal neovascular membrane. The photo on the right shows end stage disease that has evolved into subretinal fibrosis and pigment clumping known as a disciform scar.



and others with occupational risk factors.[14] The AREDS-2 and other clinical trials are actively investigating the role of other nutritional supplements such as lutein and zeaxanthin as well as omega-3 fatty acids in the prevention of exudative AMD. Although prescribing high-dose antioxidant AREDS Formula vitamins may be minimally helpful in selective patients, its widespread use for all patients with AMD is controversial and likely not warranted. Furthermore, there is no evidence that taking these supplements has any beneficial effect on other retinal conditions nor in those individuals with a healthy ocular status.

Treatment for Exudative AMD

The management of CNV and exudative AMD has changed dramatically over the past several years and continues to evolve rapidly with many new therapies and combinations of existing therapies in clinical trials. It has never been possible to consider reversing visual loss in the history of AMD until recently.

Historically, one of the first treatments developed for exudative AMD was thermal laser photocoagulation of the CNV. The disadvantage of this modality was that while treating the neovascular growth, the laser destroyed the overlying retina. Since most CNV lesions involve the central area of the macula, thermal laser would only be considered for a small proportion of patients with exudative AMD. Furthermore, recurrence rates of the CNV following thermal laser treatment were high. Due to the availability of newer treatments, thermal laser treatments of macular CNV are rarely performed today.

The next revolution in the treatment of exudative AMD was the development of photodynamic therapy (PDT) with verteporfin for ocular use. This currently remains a treatment option for exudative AMD. This treatment involves the use of a lower intensity energy laser (sometimes called a cold laser) that is targeted at the CNV, which has been primed to the laser's effects by the systemic infusion of the light-sensitive dye, verteporfin. In this manner, exudative AMD lesions under the centre of the macula may be treated with less damage to the overlying tissues.[15] Most individuals who undergo PDT require treatments every few months in order to keep the CNV lesion quiescent.

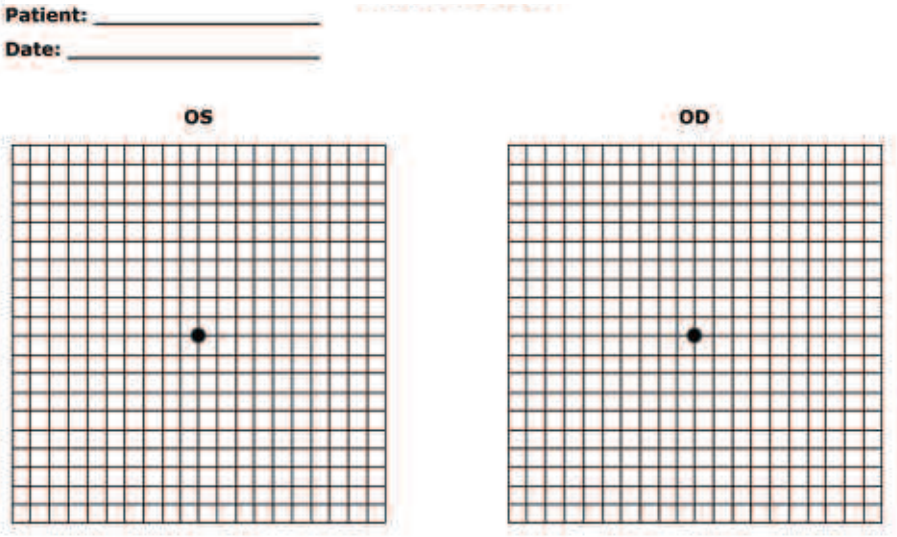
Currently, the most widely used method for treating exudative AMD is the intraocular use of drugs that block the action of vascular endothelial growth factor (VEGF). These drugs are derived from monoclonal antibodies and are designed to bind intraocular VEGF molecules, thus reducing the stimulus for CNV formation. Anti-VEGF agents must be injected into the eye in order to perform their therapeutic duties. Clinical trials that have led to the approval of these agents have employed dosing schedules of one injection every 4–6 weeks, due to the limited half-life of the drug.

The first of these drugs to be approved for treating all types of exudative AMD was pegaptanib sodium (Macugen®, Eyetech-OSI). This drug blocks only the VEGF-165 isoform, which is thought to be the most pathogenic isoform of VEGF. Clinical trials demonstrated that patients who were treated with pegaptanib sodium lost fewer letters of visual acuity than control subjects.[16] However, patients treated with pegaptanib still lost vision over the course of the study.

The next injectable anti-VEGF medicine to be approved for exudative AMD was ranibizumab (Lucentis®, Genentech). This drug differs from pegaptanib in that it blocks all isoforms of the VEGF molecule. Clinical trials demonstrated that a monthly injection schedule of ranibizumab was superior to both placebo and PDT treatment in preserving vision.[17] Interestingly, injection of ranibizumab was shown to improve visual acuity and visual function in treated eyes.

Another anti-VEGF drug often used in the growing armamentarium of intraocular treatments for exudative AMD is bevacizumab (Avastin®, Genentech). This drug has been approved as an intravenous chemotherapy for metastatic colon cancer. However, it has been used extensively in an off-label capacity as an intraocular treatment for exudative AMD. Uncontrolled case series have shown this therapy to have a safety and efficacy profile similar to that of ranibizumab.[18] In addition, experimental studies have revealed no ocular toxicity from the injection of bevacizumab.[19] A prospective randomized controlled trial comparing the effects of ranibizumab versus bevacizumab is currently being undertaken with support from the

Figure 2: Amsler Grid



Patient is instructed to stare at the central dot with one eye at a time. Wavy or incomplete lines may be indicative of exudative age-related macular degeneration.

Source: Courtesy Jules Stein Eye Institute.

Key Points

Age-related macular degeneration (AMD) has traditionally been classified into two categories: the more common atrophic (or dry, geographic, nonexudative) AMD and less common exudative (or wet, neovascular) AMD.

The management of atrophic AMD consists of patient education, visual monitoring, and nutritional supplementation; smoking cessation and the improvement of cardiovascular risk factors have known important benefits on AMD.

The most widely used method for treating exudative AMD is the intraocular use of drugs that block the action of VEGF, which are derived from monoclonal antibodies and are designed to bind intraocular VEGF molecules, thus reducing the stimulus for CNV formation.

Preserving vision among individuals with AMD may decrease the risk of other severe events associated with poor visual function such as hip fractures and could ultimately lead to potential health care savings.

National Eye Institute of the National Institutes of Health.

Other Treatment Considerations in Exudative AMD

Clinicians and investigators have attempted to combine the various treatments discussed above in their search for optimal treatment results. The combination of PDT plus intraocular injection of triamcinolone acetate has been shown to have a synergistic effect in the treatment of exudative AMD.[20] Triamcinolone acetate, a steroid agent, is believed to be anti-angiogenic although the exact mechanism remains unknown. Various researchers have also combined PDT with ranibizumab or bevacizumab in order to decrease the need for monthly injections.[21]

While the incidence of significant eye complications such as bleeding, pain, or infection from an intraocular injection is low in published studies, the potential socioeconomic side-effects of monthly injections on patients and physicians has been recognized to be extremely high. The clinical trials that led to the approval of injectable anti-VEGF agents provided no guidelines on when it may be safe to stop performing monthly treatments. While recent studies have explored various dosing regimens, there remains little consensus as to the optimal frequency strategy for anti-VEGF injections.[22]

On-label systemic use of bevacizumab for metastatic colon cancer treatment has been associated with adverse events such as hypertension, transient ischemic attack, stroke, and death. However, the incidence of systemic complications from intraocular injections of ranibizumab or bevacizumab have been low in published studies.[23] The concern over an increased risk of stroke with the 0.5 mg dose of ranibizumab has led the pharmaceutical company that produces this drug to issue a letter of warning to retina specialists. However, the incidence of these vascular events is higher among older adults with AMD in general. Although there are no published guidelines, many retina specialists prefer to withhold injectable anti-VEGF agents in patients with a recent history of a significant cardiovascular event, such as stroke or myocardial infarction.

Personal, Social, and Economic Impact of AMD

As AMD has become increasingly common with the growth of the older adult population, the socioeconomic impact of AMD and its treatment has been recognized to be significant. Recently published data indicate that the costs of eye care related to AMD totaled hundreds of millions of United States dollars per year even before the availability of PDT and injectable anti-VEGF drugs.[24] Additionally, older adults often require that their children or friends take time off work in order to accompany them to the ophthalmologist for examinations and frequent injections. With the advent of these newer and increasingly costly therapies, coupled with the increasing numbers of older adults and the potential loss of productivity of caregivers, these costs will continue to escalate. However, preserving vision among individuals with AMD may decrease the risk of other severe events associated with poor visual function such as hip fractures and could ultimately lead to potential health care savings.

The personal toll taken on individuals with AMD may be high as well. Up to 60% of individuals with vision loss related to AMD report a significant decline in their ability to perform activities such as reading, driving, or watching television.[25] Indeed, the incidence of depression among persons with AMD-related vision loss is significant. It is important for all caregivers to recognize and consider depression when managing this population.[26]

Visual rehabilitation and mobility training are valuable treatment considerations for persons with visually significant AMD. With the aid of magnification devices and other tools, low-vision specialists are often able to dramatically increase the quality of life of individuals who may not benefit from the current therapies for AMD.[27] Even those with mild to moderate visual loss may benefit significantly from visual rehabilitation and mobility training.

Conclusion

Age-related macular degeneration is a common and debilitating disease of older adults. Although great progress has been made in the treatment of certain forms of this disease, a cure for AMD remains elusive. Because of the new vision-saving therapies available for those with exudative AMD, it is important for health care providers to better understand AMD and its potential treatment options, in order to provide the best visual potential for their older patients. The social and economic impacts of AMD will be felt even more strongly in the coming years. Health care providers who treat older

adults must have a basic understanding of AMD in order to provide the best care for their patients.

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