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GUEST EDITORIAL

Age-Related Macular Degeneration: What's New and on the Horizon

Age-related macular degeneration (AMD) is a condition that touches us all, being a leading cause of vision loss affecting almost 13% of people older than 80 years.[1] Aside from the development of anti–vascular endothelial growth factor (VEGF) agents that can arrest and even restore vision to some extent, in those with late-stage, neovascular AMD, there has been considerable effort made over the past decade to understand the genetic and environmental factors that lead to the development of advanced disease.[1] In addition, our knowledge of the pathogenesis of the disease has expanded considerably, especially with the advent of animal models of disease and new ocular imaging modalities. This information has provided a foundation for developing novel testing paradigms that are specifically aimed at detecting those patients most at risk of progressing to late-stage disease. This special issue of *Optometry and Vision Science (OVS)* includes a range of articles that outline recent knowledge in the pathogenesis and management of AMD.

It is well accepted that the early stages of typical AMD include the presence of drusen of varying size with or without accompanying pigmentary changes.[1,2] Using recently available imaging techniques, it is now possible to follow changes at the cellular level. Indeed, Nivison-Smith et al.,[3] in this issue, link histopathology with imaging from optical coherence tomography to describe the cellular changes that occur during different stages of AMD. In addition, Hogg[4] highlights an unusual form of retinal deposit called reticular pseudodrusen that, unlike conventional drusen, appear to be located at a subretinal level and that may also be a risk factor for progression to late-stage disease. Presentation of AMD in different racial groups is an important consideration for clinicians.[5] Sasaki et al.[6] note that about 50% of Japanese people will develop polypoidal vasculopathy (PCV), rather than typical AMD. They show that the presence of large drusen is a key early feature leading to typical late-stage AMD, as previously reported,[2] whereas pigmentary changes in the absence of drusen are associated with the development of PCV. These studies highlight the variation in disease presentation and progression. The challenge remains, however, with regard to how to predict those who will develop more advanced forms of AMD.

EARLY AMD: EFFECTS ON RETINAL PIGMENT EPITHELIAL CELLS AND PHOTORECEPTORS

Retinal pigment epithelial (RPE) cell dysfunction plays a central role in the development of subsequent photoreceptor deficits and is an important feature of the development of geographic atrophy (dry AMD[1]). Using fundus autofluorescence, RPE dysfunction or loss can be detected. This new imaging technique highlights localized regions where lipofuscin has accumulated within the RPE or other areas where RPE cells are lost. Batioglu et al.[7] examined the spectrum of fundus autofluorescence patterns that develop in patients with AMD and described whether specific patterns are more likely to be associated with development of choroidal neovascularization.

Given the importance of RPE cell dysfunction in AMD, novel approaches to studying RPE cells are being established. Davidson et al.[8] provide an overview of how fibroblasts isolated from skin biopsy samples from patients can be used to grow RPE cells (from induced pluripotent stem cells) and thereby model the disease in a Petri dish. This technology has the potential to greatly enhance our knowledge of how the inheritance of specific genetic risk factors influences RPE cell function. Davidson et al. also describe the use of stem cells for restoring areas of RPE cell loss, thus providing a possible treatment for those with vision-threatening geographic atrophy.

A range of photoreceptor effects are likely to occur early in AMD because of reduced nutrient or retinoid flow across a thickened Bruch membrane to photoreceptors. As outlined by Land et al.,[9] imaging of the retina using scanning laser ophthalmoscopy combined with adaptive optics enhances resolution and allows visualization of cone photoreceptors. Thus, a direct means of assessing the effects of disease, and the influence of genetic risk factors, on cone integrity is now possible.

Psychophysical methods offer sensitive markers of early visual dysfunction. Liu et al.,[10] review a number of methods for detecting subtle changes in vision during the course of AMD. Jackson et al.[11] highlight that dark adaptation is progressively affected in those with AMD over a 12-month period. Downie et al.[12] show that cone contrast thresholds are also affected for all cone types in intermediate AMD. Feigl and Zele[13] provide a compelling review highlighting that recently identified pupil pathways originating from intrinsically photosensitive ganglion cells within the retina are affected early in AMD. Sabeti et al.[14] describe a novel device that allows the sensitive measurement of pupil change in response to a multifocal stimulation. Finally, McKeague et al.[15] provide important background information for conducting color assessment testing and novel flicker tests. Overall, these functional and imaging methods are aimed at detecting AMD patients who are at the greatest risk of progressing to late-stage disease.

GENETIC AND ENVIRONMENTAL RISK FACTORS FOR DISEASE

Age-related macular degeneration is a multifactorial disease that is influenced by a range of genetic and environmental factors.[1]

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The role of the immune system is now well accepted. Identification of the role of complement factor H, an important regulator of the innate immune system, in the development of AMD arose from genetic studies on patients with a rare kidney disease, type 2 membranoproliferative glomerulonephritis, because these patients develop hallmark signs of AMD, including drusen and choroidal neovascularization.[16] Complement factor H is known to be associated with this kidney disease; however, it should be noted that patients with chronic kidney disease are no more at risk of developing AMD than the general population.[17] The results of the first Genome Wide Association Studies reported in 2005 indicated that inheritance of a single nucleotide polymorphism in the gene encoding complement factor H, CFHY402H, was strongly associated with developing AMD, increasing the odds of late-stage disease by between 3.45 and 7.4 times.[18,19] Since that time, the number of genetic variants known to be associated with late-stage AMD has increased dramatically, providing a rationale for personalized medical care of those with AMD.[20]

Screening for genetic risk factors aids in identifying those most at risk of developing late-stage disease. In addition, a person's genetic makeup may influence the response a person has to anti-VEGF treatment.[21] A better understanding of the how genetics influences the development or progression of disease may shed light on the etiology of the disease. The influence of specific genes on the development of a disease has often been validated using animal models, especially mice, with important information gained regarding the genetic mutation and its influence on cell signaling and integrity. However, in the case of AMD, some caution needs to be taken as outlined by Fletcher et al.[22] in their overview of animal models of AMD.

LIFESTYLE AND DIET: CAN THIS INFLUENCE DISEASE PROGRESSION?

With advances in genetic and functional testing of patients with AMD, it is now possible to intervene at an early stage of disease to slow progression. There continues to be significant interest in the potential role that diet and nutrition, in particular antioxidants, may have in preventing and/or attenuating the progression of AMD. Two large, multi-center, randomized controlled clinical trials, Age-Related Eye Disease Study (AREDS)[23] and AREDS2,[24] now provide high-level evidence in relation to the potential role for different forms of nutritional supplementation to impart protective effects in AMD. The study designs and reports of these studies are inherently complex and have received criticism for some acknowledged limitations. Nonetheless, a pertinent question is what do their findings mean for clinical practice, particularly in the context of recent questioning of the safety and efficacy of vitamins in general?[25] In this edition of *OVS*, Downie and Keller[26] critically evaluate the currently available evidence relating to nutrition and AMD, with particular reference to the key findings of AREDS and AREDS2.

An important modifiable risk factor for the late-stage advanced disease is smoking, reported to increase the risk of advanced AMD by up to 2.75 times in those smoking more than 40 pack years.[4] However, as noted by Swanson,[27] smoking is often underreported. By using a biochemical measure of nicotine levels, they show that about 5.4% of patients in their study failed to report smoking, implying that advice and counseling about the risks of smoking may need to be broadened beyond those patients who self-report smoking.

CLINICAL MANAGEMENT OF LATE-STAGE AMD

Clinicians will be well aware of the exciting advances in treatment of neovascular AMD over the last decade from the initial results of the ANCHOR and MARINA trials.[28,29] The dawn of anti-VEGF agents has meant that it is now possible to prevent sudden vision loss from choroidal neovascularization in a majority of patients. Indeed, Ng et al.[30] show that there has been a substantial increase in the usage of anti-VEGF agents for both typical AMD and PCV in one center. However, the treatment regimen for neovascular AMD can have a profound effect on a person's quality of life, as described by McCloud et al.[31] Loss of central vision can affect mutual gaze. That is the perception that someone is looking at them, which is an important nonverbal social cue. Sheldon et al.[32] investigated this issue in patients with central vision loss and demonstrate that those with central vision loss have remarkably intact mutual gaze.

Clinical trials evaluating anti-VEGF agents show that a small percentage of patients do not respond to anti-VEGF therapy and lose central vision.[28,29] As documented by Dilks et al.,[33] regions of the visual cortex normally reserved for the processing of foveal vision were recruited in a patient with no central vision to process information originating from the peripheral retina; this finding implies that significant neural reorganization occurs after loss of central vision. Clinical management of those who have lost central vision can be challenging. This special issue includes a range of papers relating to the management of low vision in patients with AMD. Alexander et al.[34,35] consider how lighting affects a person's ability to walk with precision and also negotiate a curb. Loss of central vision can also affect a person's ability to process a visual scene, an issue that has been investigated and described by Tran et al.[36]

In summary, over recent years, there have been significant advances in our understanding of AMD. The articles contained in this special issue highlight the exponential growth in knowledge on all facets of AMD care. The management of those with AMD is no longer just a futile exercise in monitoring a person's loss of vision but rather offers the potential for slowing vision loss. The future for even better treatment and visual outcomes is bright.

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