Age-related Macular Degeneration—Disease, Risk Factors, and Treatments

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Abstract

Age-related macular degeneration (AMD) is a progressive disease of the posterior segment of the eye. It has been diagnosed worldwide and primarily affects individuals over 50 years of age. The incidence of the disease increases with age and with the presence of certain genetic factors, which may indicate a disposition for disease progression. In addition to genetic factors and age, other factors may be involved in developing AMD. These include obesity and smoking, which are also linked to various cardiovascular conditions. There are two forms of AMD: wet and dry. Both forms may involve the build-up of drusen deposits in the posterior segment of the eye, but the wet form tends to be more severe due to the proliferation of blood vessels into the macula and retinal areas of the back of the eye, thus causing an individual's vision to become 'blocked' or 'shaded' usually beginning at the center of the visual field. There are a variety of treatment options for AMD including surgery in the form of laser or photo therapy. The most current treatment options involve the injection of a biologic into the posterior segment of the eye. There are some severe adverse events with this approach but they tend to be rare.

Keywords

Drusen, VEGF, macula, posterior segment

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Age-related macular degeneration (AMD) is a progressive, noncurable disease primarily affecting the elderly. In addition to age the most important single contributing factor to the condition is an individual's genetic makeup. As with many diseases, genetic predisposition greatly increases the likelihood of developing the syndrome. This disease may manifest itself in families, not unlike cancer or cardiovascular disease. The development of AMD is also strongly linked to obesity and smoking. Gender has also been implicated, but the data supporting this specific factor is more tenuous. Most of the current treatments involve the injection of a biologic into the posterior segment. Supplements have been recommended and have shown promise in delaying disease onset in some individuals.

Age-related Macular Degeneration The Disease

There are two types of AMD and they are referred to as wet or dry. Wet AMD occurs when blood vessels will appear growing from the choroid located from approximately behind the retina in the posterior section of the eye. The development of these blood vessels is triggered by vascular endothelial growth factor (VEGF). The intrusion of these blood vessels may cause retinal detachment or at the very least interference with the retinal segment. They may grow through Bruch's membrane leading to fluid leakage near or around the macula. Part of this fluid contains protein and with this leakage comes vision loss and photoreceptor damage. About 10 % of the total number of AMD cases are this more extreme (wet)

form of the disease.¹ Dry AMD, which is considered less severe, occurs when cellular debris known as drusen accumulates between the retina and choroid. The retinal pigment layer of the epithelium degrades and atrophies over time. The loss of the associated rods and cones in the eye causes vision degradation. It should be noted that drusen does build up naturally with increasing age, and its appearance does not always lead to AMD.² The disease progresses slowly in older individuals with drusen being visualized as white or yellow–white areas under the retinal pigment epithelium. The pigments may remain small and not affect vision to a great extent. Other signs may include pigmentary alterations and loss of lines of vision. The affected individual may experience vision loss from the 'center, outward.' As such there is blurred or distorted vision. There may be a loss of contrast sensitivity, especially in terms of color. The macula comprises only about 2 % of the retina, but about 50 % of the visual cortex processes information from the macula. So when the macula is compromised in any way, severe quality of life concerns may result. These may vary between individuals.

Who is Affected?

By far the biggest risk factor for developing AMD is age.³ It is estimated that around eight million Americans age 54 and older will develop AMD and of those one million will develop advanced AMD. In the UK, 75 % of the individuals who go blind will do so because of the development of AMD. Thirty per cent of individuals who are affected occur in the 75–85 age range.⁴ This percentage may increase if family history is factored in. A more

recent observation has been the correlation with of AMD development with cardiovascular risk factors.⁵ This observation is somewhat tenuous with the exception of the link to smoking, which has been shown to be a positive risk factor in both diseases. According to recent research, white females are a stronger at risk group for development of the disease, but this is not supported by overall trends.^{1,6}

There have been links to chronic obesity, especially in men, and smoking as a contributing factor for the development of AMD. Combinations of these factors including age increase the risk for disease development even more.

Other implied risk factors include hypertension, increased cholesterol levels, and elevated high-density lipoprotein (HDL) cholesterol. However, the scientific literature are not conclusive on these factors. As mentioned, an individual's genetic makeup has also been linked to development of AMD. The genes for factors H, B, and 3 have been linked to the disease. These genes are part of the controlling mechanism of the complement activation system, and thus inflammation, which is a key sign of AMD.

Treatment Options

Laser Surgery

Treatment with laser surgery can be successful in a limited number of cases provided certain conditions are met. Laser treatment may delay the development of choroid neovascularization by a few months in patients with unilateral advanced AMD.⁷ But the symptomology will return in time.

Phototherapy

This is an option that has been used to treat wet AMD. The drug verteporfin is administered by intravenous injection followed by light treatment.⁸ The combination of drug in the correct location in the eye causes destruction of the blood vessels and thus disease treatment. This method may correct acute problems, but will not affect the underlying disease issue. As with laser surgery, the disease progression may return in the form of blood vessel encroachment in the posterior segment.

Drug Therapy

The first approved AMD drug treatment was Macugen (pegaptanib). Macugen is composed of messenger mRNA (mRNA), and has shown some benefit in patients.⁹ It is administered by injection into the posterior segment of the eye. Other injectable approved therapy involves the use of biological products such as Avastin (bevacizumab) or Lucentis (ranibizumab) again delivered by syringe to the posterior segment of the eye. Published studies vary as to the effectiveness, but 30–40 % of individuals who receive either drug get positive results in terms of restoration of measureable lines of vision. Bevacizumab is approved as a cancer treatment and is a monoclonal antibody.¹⁰ In addition, ranibizumab is an antibody fragment comprising only the fraction antigen binding (FAB) region of the bevacizumab molecule. The fraction crystallized (FC) region of the antibody is not present. Thus, the molecule has a different molecular weight and stereochemistry. All these injectable products suffer from the same negative side effects in that they are uncomfortable or even sight threatening to inject. Cost has also been as factor, but this has lessened somewhat with the advent of generic compounds. Aflibercept formulated as Eylea is a more recent therapy for wet AMD. It is a recombinant fusion protein that comprises VEGF-binding proteins thus preventing VEGF from stimulating blood vessel growth.

Since all these drugs are injectable, they are administered in small amounts by a syringe to the posterior segment of the eye into the vitreous humor. At this point the drug is free to interact with VEGF-receptor sites on cells. The effect is to retard the growth of blood vessels into the retinal and macula space, thus preventing disease onset. All the drugs listed above are prescribed for monthly or twice a month use under a physician's care. In addition to retinal detachment, other dangers of this treatment are inflammation or infection. The risk is due to the actual administration of the drug.

Supplements

Supplements may also be used as treatment options. Lutein and zeaxanthin have been used to increase eye health specifically in the area of AMD.¹¹ The compounds may be taken as dietary supplements or from eating green vegetables. They are thought to affect the modulating processes for oxidant and light exposure. These compounds tend to reduce inner eye exposure to short wavelengths of light, thus preventing damage to cellular materials such as lipids, proteins, and nucleic acid, by oxidant damage. This breakdown of subcellular material(s) may lead to optic nerve damage, via either inflammation or development of neovascularization, in the retinal segment of the eye. These two supplements (along with neo-) are currently being marketed by Bausch & Lomb as Ocuvite. Other manufacturers supply them as well. They are usually administered as once-a-day oral capsule or tablets. They are recommended for individuals in the 'at risk' age group. The Age-Related Eye Disease Study (AREDS) (sponsored by the National Institutes of Health [NIH]) was designed to evaluate various supplements such as vitamins C and E and beta-carotene on the progression of AMD and cataract.¹² The overall conclusions from the study were that while the supplements had no effect on cataract they were effective at preventing vision loss due to AMD. In a subsequent study Age-Related Eye Disease Study 2 (AREDS 2), lutein and zeaxanthin were evaluated for their ability to prevent AMD progression.¹³ These supplements taken together were found to be an effective substitute for beta-carotene in modulating AMD disease progression.

Anti-AMD drugs delivered in drop form topically onto the surface of the cornea have not been shown to be effective at treating AMD. However, a recent study in animals have shown that Lucentis delivered via a hydrogel contact lens may be able to reach the retinal space of the eye.¹⁴ Other experiments with steroids have likewise shown measurable levels delivered to the retinal space. In the latter case results indicate that inflammation was modulated as a result of the presence of the steroid.¹⁴

Conclusion

AMD is a progressive disease with no overt signs or symptoms until actual visual loss. It affects millions of people worldwide, but there are specific risk factors such as age, smoking, obesity, and, importantly, genetic factors that lead to development of the disease.¹⁵ Combinations of the risk factors almost certainly affect an individual's risk compared with those that have only a single risk factor, but the data are not clear on this. It seems that the group that may be most at risk are overweight chronic smokers. Genetics also seem to be the strongest link for disease development. There is no cure but the treatment options that are available are effective in modulating the process of the disease in at least some people. If visual decay, which can be measured by loss of lines of vision, can be halted or reversed to at least some level then the quality of life of an affected individual must improve. This is what the newer therapies are

designed to do. The sometimes extreme side effects of the treatments, such as retinal detachment, are rare. Inflammation is more of a problem in terms of numbers of individuals affected, but a less serious complication. Increased public awareness coupled with better diagnostic techniques

and improved treatment methods are the best techniques available at this time to prolong an individual's quality of life through the course of the disease. As product costs decline these current therapies should be more readily available for use.¹⁶ ■

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