UNIVERSITY OF CALGARY
FACULTY OF MEDICINE

Saving Sight

Stopping the progression of macular degeneration

By John T. Huang, MD, FRCSC, DABOph; Farrah Rhemtulla BSc; and Peter T. Huang, MD, FRCSC, DABOph

In this article:

Age-related macular degeneration (AMD) specifically affects the outer aspects of the retina and portions of the choroid. The areas involved include the photoreceptors, the retinal pigment epithelium (RPE), Bruch's membrane, and the choroidal circulation. Bruch's membrane is the collagenous layer that separates the choroidal vasculature from the RPE and the photoreceptors.

How does macular degeneration progress?

The specific causes of AMD are unclear. However, the steps in the pathophysiology of AMD are well documented. AMD involves progressive damage to the RPE. The RPE separates the choroidal layer from the photoreceptors.

In later stages of AMD, choroidal neovascularization or localised atrophy damages the RPE and the photoreceptors.

In early AMD, drusen appear. Drusen are caused by the accumulation of membranous and lipophilic debris forming between the RPE and the choroid. There is also a thickening of the Bruch's membrane (Figure 1).

What is drusen?

The incidence of drusen increases with age. More than 50% of people over the age 70 will have it.[1]

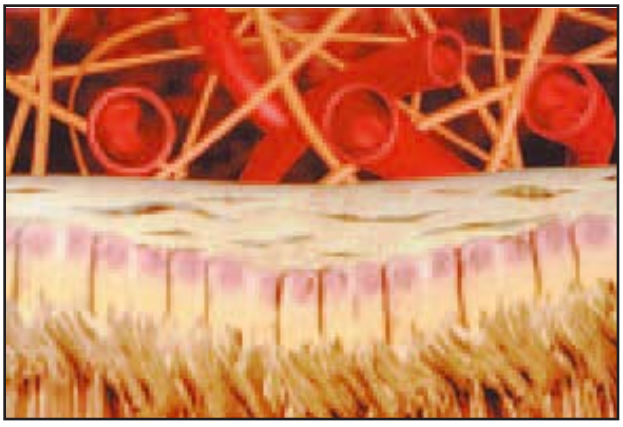

Figure 1. Drusen accumulation between RPE and choroid.

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The term AMD is used when the drusen affect vision and/or are documented to be increasing in size. The prevalence of AMD increases as patients get older. Four times as many patients over 75 have AMD versus those between the ages of 55 and 64. In non-neovascular AMD (dry AMD), localised areas of atrophy in the RPE may develop, which can result in the progressive loss of photoreceptors and a steady failure of central vision where there is involvement of the macula and fovea. About 10% of patients over the age of 60 have the non-neovascular form of AMD and about 2% of patients over 60 are legally blind in at least one eye due to dry AMD.[1]

Drusen can be categorised as small (< 64 microns wide), intermediate (64 to 125 microns wide) and large (> 125 microns wide). It is thought that intermediate and large drusen may be more prone to developing atrophy or neovascularization.

The boundaries of drusen can be described as either hard with discrete, well demarcated lines, soft with poorly demarcated lines, or confluent with contiguous boundaries between drusen (Figure 2). Soft or confluent drusen may be more likely to progress to atrophy or neovascularization.

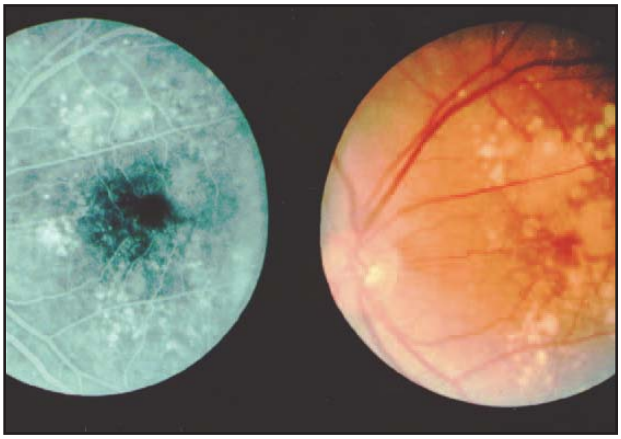

Figure 2. Fundus photograph (left) showing discrete AMD (1) with confluent drusen; (2). Fluorescein angiogram (right) showing drusen as they appear in dry AMD.

How does atrophy affect vision?

When there is a contiguous area of attenuation or atrophy of the RPE cells, it is referred to as geographic atrophy (Figure 3). The underlying choroidal vessels are more readily visible and the overlying outer retina may appear thin. Often the choriocapillaris is attenuated or atrophied as well. In this case, vision loss is often severe.

Dr. J.T. Huang is clinical associate professor, and director of undergraduate medical education, division of ophthalmology, University of Calgary, Calgary, Alberta.

Ms. Rhemtulla is an ophthalmic assistant. She has completed her BSc in biological sciences and a BSc in psychology, University of Calgary, Calgary, Alberta.

Dr. P.T. Huang is clinical associate professor and head of division, division of ophthalmology, University of Calgary, Calgary, Alberta.

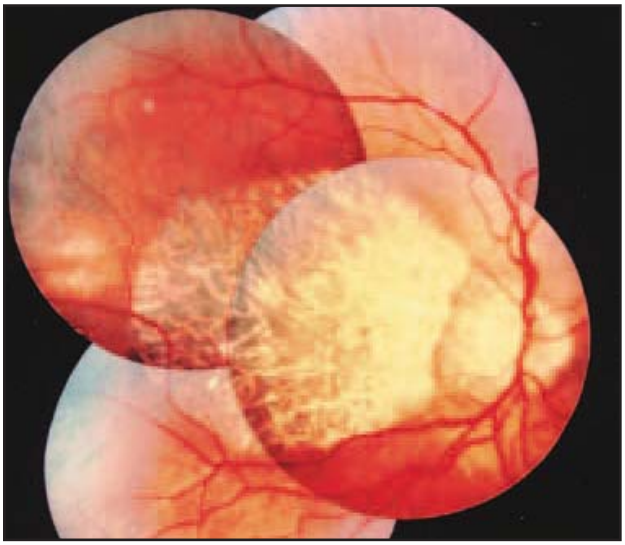

Figure 3. Geographic atrophy in dry AMD.

If the atrophy does not cover a contiguous area, then it may appear as a mottled area of depigmentation called non-geographic atrophy or RPE degeneration. The photoreceptors, although not visible, will usually be attenuated or absent over areas overlying atrophied RPE. RPE atrophy in AMD is associated with visual loss, the extent of which is dependent on the severity of atrophy and its location relative to the foveal centre.

As atrophy progresses, calcific drusen may be seen alongside dystrophic calcification occurring within the drusen material. At times, pigment laden cells, either RPE cells or macrophages that have ingested pigment, may migrate to the photoreceptor level, resulting in focal clumps or reticulated patterns of hyperpigmentation.

What are the signs?

Patients with drusen or abnormalities of the RPE should be taught how to recognise symptoms of AMD, including testing each eye individually for any new metamorphopsia, scotoma or other significant changes in vision. An amsler grid mounted to a refrigerator door can facilitate daily testing for patients. New symptoms as described should result in the patient contacting their family physician and/or ophthalmologist.

What are some preventive measures?

For patients with drusen and AMD, several epidemiologic studies have demonstrated positive associations between certain micronutrients, such as antioxidant vitamins, and decreased risk of AMD and its progression. The Age-Related Eye Disease Study Research Group released a final report in October 2001 demonstrating the benefits of the combined use of antioxidants (vitamin C, 500 mg; vitamin E, 400 IU; and beta carotene, 15 mg) and zinc, 80 mg, as zinc oxide.[2] The most conclusive benefits were experienced by patients with extensive intermediate size drusen; at least one large druse; non-central geographic atrophy in one or both eyes; or advanced AMD or vision loss due to AMD in one eye. The benefits are most conclusive with non-smoking patients. The demonstrated benefits of the usage of these supplements will likely increase the popularity of products, such as Icaps®, Ocuvite®, and Vitalux®.

The conclusion of this six-year, 11-centre study involving 3,640 patients, was that patients with documented drusen or those over the age of 55 should have regular dilated eye exams to determine their risk of developing advanced AMD.

It should be also noted that though there are no studies demonstrating a direct relationship between AMD and ultraviolet light, the usage of sunglasses or hats outdoors is not discouraged.

Ultimately, if the central vision in both eyes is significantly affected by AMD, the patient's functional abilities may be improved through low-vision rehabilitation and the use of optical and non-optical devices.

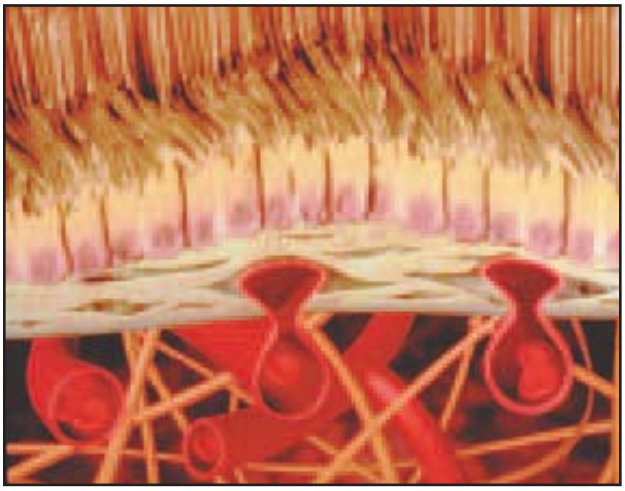

Figure 4. Neovascular vessels grow from choroid.

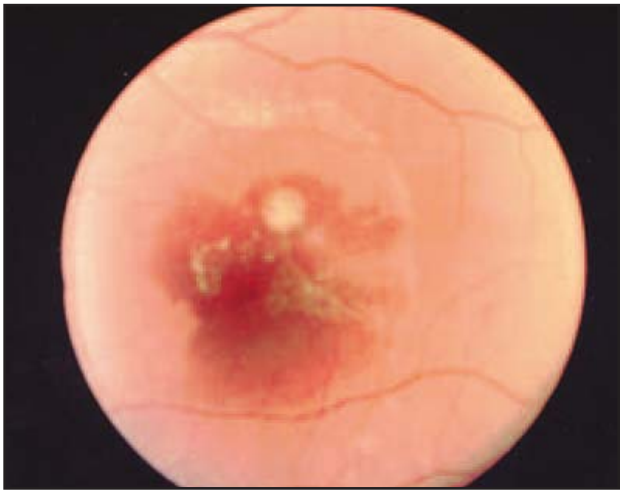

Figure 5. Central macular hemorrhage with surrounding edema.

What are the effects of wet AMD?

In neovascular AMD (wet AMD), the loss of vision is more severe and rapid. Wet AMD accounts for only about 10% of AMD patients, but the impact on vision can be severe. Though wet AMD is less prevalent, it causes 80% to 90% of all severe visual loss from AMD, making vision 20/200 or worse.[1] The key change that causes the impact is the growth of new blood vessels from the choroidal layer towards the RPE and sensory retina. This is called choroidal neovascularization (CNV) (Figure 4).

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CNV is accompanied by breaks in Bruch's membrane and fibrous tissue buildup. CNV also causes serous and hemorrhagic detachments of the retina and RPE that result in central vision loss (Figure 5).

There are two basic patterns of CNV—classic and occult. Classic CNV appears as a well-demarcated area of uniform hyperfluorescence in the early phase of angiograms. Occult CNV involves a fibrovascular retinal pigment epithelial detachment seen later in the angiogram or there is a RPE fluid leakage that is not discrete and appears in late phases of angiography. Most CNV have a combination of classic and occult components.

How to treat CNV?

When untreated, disciform scars form where there is CNV. As noted, hemorrhage and fluid leakage into and beneath the sensory retina can also occur.

Neovascular AMD can be treated with thermal lasers in 10% to 20% of patients. Those with extrafoveal, juxtafoveal or very small, well-demarcated subfoveal lesions can be well treated. Half of treated patients will have recurrent CNV within three years of their initial treatment.

Extrafoveal is where the lesion is > 200 microns from the foveal centre. Juxtafoveal is where the lesion is within 200 microns of the foveal centre, but not under the foveal avascular zone.

Fluorescein angiography and Indocyanine Green angiography are used to specifically delineate the area of CNV involvement.

The majority of patients with neovascular AMD have CNV under the foveal centre. These subfoveal lesions are associated with a poor visual prognosis and are often not treatable with thermal lasers. Treatment may be ineffective and can result in immediate visual loss.

Can photodynamic therapy help?

Recently, photodynamic therapy (PDT), combining verteporfin injections and non-thermal lasers, has offered new hope to this category of patient. Photodynamic therapy in wet AMD is most effective where the CNV is 50% or more in the classic pattern and where the vision is initially 20/200 or better. Vision improves in 13% of treated patients and 60% of treated patients retain their vision. Patients treated with verteporphin are about 32% more likely to retain vision during the study period than those who are not treated. Additionally, there is slower lesion growth and reduced leakage from the component of the lesion that is classic CNV.

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These data are from a three year study completed in mid-2001 entitled the TAP (Treatment of AMD with PDT) study.[3] It should be noted that classic CNV is associated with an aggressive disease course and severe visual loss and the TAP results appear encouraging.

Data from the TAP extension study showed that 80% of patients at month 33 and month 36 did not require further retreatments.[4] From months 24 to 36, the retreatment rate fell from 44% to 20%. Year four of the study is expected to show further reductions. There is also no evidence of harm to vision by applying longer and repeated treatments. The incidence of severe vision decrease in the treatment group is still < 1%.

It should also be noted that a second study called the verteporfin in photodynamic therapy (VIP) trial has completed its second year.[5,6] This study has focused on patients who have occult CNV without classic subfoveal CNV. There appears to be a benefit of treatment here as well. So far, there has been 18% fewer vision loss of > 30 letters from baseline, and 22% less classic CNV development. There has been, however, a 4% rate of severe decrease after the first course of treatment.

It is thought that in this category of occult CNV, verteporfin treatment safely reduces risk of moderate and severe visual acuity loss. The best candidates appear to be relatively small lesions regardless of visual acuity or lower levels of visual acuity regardless of lesion size (>/= 20/100).[6]

Also, another trial is being conducted to determine the safety and efficacy of verteporfin treatment to reduce the risk of moderate and severe vision loss in eyes with subfoveal CNV due to pathologic myopia. The 24-month results appear to support this impression.

What is verteporfin?

Currently PDT is carried out using verteporfin. Verteporfin is a liposomal preparation that readily associates with low density lipoproteins (LDL) in blood plasma and is absorbed via LDL receptors in neovascular tissue.

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Three treatments can be carried out over 12 months, and this may be repeated in the second year as well as in the third year.

Verteporfin acts a photosensitizer that is activated by a non-thermal red light laser set at a frequency of 689 nm. The photoactivated verteporfin transfers chemical energy to molecular oxygen, generating a reactive form of oxygen (singlet oxygen) that in turn produces free radical reactivity. The oxygen derived free radicals react vigorously with the surrounding molecules to stimulate endothelial damage and platelet aggregation. The selective vascular thrombosis and occlusion of the CNV vessels occurs without the thermal damage seen with standard laser photocoagulation.

Adverse effects include transient vision blurring in up to 5% of patients.

Verteporfin is excreted via biliary excretion in the liver and is completely eliminated within 24 hours. The infusion of verteporfin is over 10 minutes and the non-thermal laser is applied within 15 minutes of the start of the infusion.

Adverse effects include transient vision blurring in up to 5% of patients. Less than 1% of patients have severe vision decrease or retinal vascular non-perfusion.[3] There can also be injection site edema, extravasation of the compound, fibrosis, hemorrhage, hypersensitivity, inflammation, and pain. The injection site problems are mostly minor and transient and occur in 0.5% of cases. Mild self-resolving photosensitivity occur in about 0.1% of patients and treated patients are to wear sunglasses when outside for at least two days.

Other side effects include back pain (0.1%), allergic reactions, and 0.1% GI cancers. The data on adverse effects is from the large scale verteporfin in AMD study (VAM Study).

Sunburn is a risk until the verteporfin is excreted and sunblock does not help. Operating lights may cause tissue necrosis and light filters must be used if emergency surgery is to be done, especially in abdominal surgery. All elective surgery must be rescheduled if verteporfin is to be used within two days of the scheduled surgery.

The laser used is a red non-thermal diode laser that does not burn the retina. The maximum lesion treatment size is 5,400 microns and the duration of treatment is 83 seconds. Currently, verteporfin therapy is covered by some provincial health-care plans and costs about $2,000 per treatment. CME

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Suggested Readings

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