

Age-related macular degeneration (AMD) is a disease associated with aging that gradually destroys sharp, central vision. Central vision is needed for seeing objects clearly and for common daily tasks such as reading and driving.

AMD affects the macula, the part of the eye that allows you to see fine detail. AMD causes no pain. In some cases, AMD advances so slowly that people notice little change in their vision. In others, the disease progresses faster and may lead to a loss of vision in both eyes. AMD is a leading cause of vision loss in Americans 60 years of age and older. It has two forms: wet and dry. — Macular Degeneration Foundation (www.eyesight.org)

Geographic Atrophy: The Advanced Form of Dry AMD

What is geographic atrophy? What treatments are coming?

By Elaine A. Richman, Ph.D.*

First, let's clear up some confusion about the difference between **dry age-related macular degeneration**, **geographic atrophy**, and **wet age-related macular degeneration**. If you are especially unsure about what distinguishes geographic atrophy (GA) from dry age-related macular degeneration (dry AMD), you are far from alone. Even clinicians and scientists tend to lump the two together. We decided to go to a leader in the field—known for her succinct explanations—to find the best and most understandable definitions possible.

The expert is Janet Sunness, M.D. Dr Sunness is head of Hoover Low Vision Services at the Greater Baltimore Medical Center. In the second week of June, she held a three-hour webinar, for physicians and researchers, to set participants straight about the characteristics, similarities, and difference among the three disorders, all of which affect the macula of the retina and can have a profoundly negative impact on vision. She also described studies that explain the “natural history” of geographic atrophy (GA) and experimental treatments for slowing the disorder.

- The **macula** is the part of the retina where our vision is normally the sharpest.
- **Atrophy** generally refers to the degeneration of cells in a portion of the body.

So, from this authoritative source, features that help define dry AMD, geographic atrophy, and wet AMD are as follows:

- **dry age-related macular degeneration**

One of the most common early signs of dry AMD is drusen under the retina. Drusen are tiny whitish-yellow blobs composed mainly of fat and protein. In the earliest stage, when the drusen are small and few, vision is not affected. As drusen enlarge, most people report that their central vision

is less sharp and that they need more light to perform normal everyday tasks.

About 85% of patients with AMD have the dry form. In some people, because of genetics, environmental exposure, or other risk factors, the disease progresses to the more severe geographic atrophy or wet AMD. The reason for developing one or the other is uncertain.

Dry AMD usually affects both eyes.

- **geographic atrophy**

Geographic atrophy is the advanced (late) form of dry AMD. Here, atrophy refers to the degeneration of the deepest cells of the retina. These are cells of the retinal pigment epithelium (**RPE**). This RPE normally helps maintain the health of the next deepest layer, the photoreceptor cells known as **rods** and **cones**. These photoreceptor cells are triggered by light to set off a series of electrical and chemical reactions that result in the brain interpreting what is in the visual field.

Degeneration of RPE cells leads to the death of rods and cones. What an eye doctor sees in a dilated eye exam in a

patient with GA is what Dr. Sunness describes as a “continent” of atrophy surrounded by a “sea” of retina (Figure 1). The continent appears different from the surrounding retina because of the loss of the pigmented RPE cells. Areas of GA look whiter than the surrounding retina.

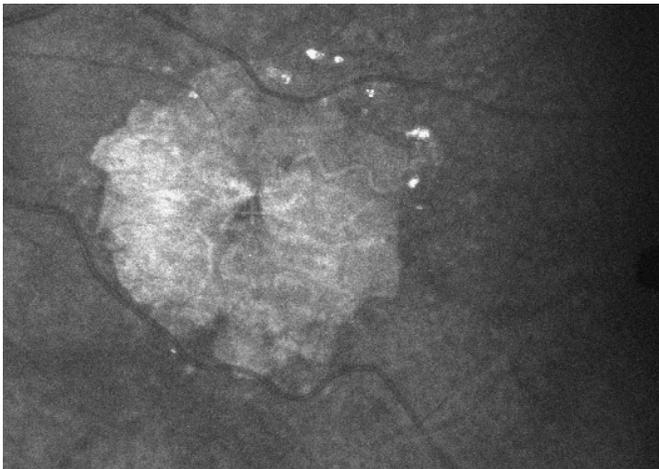


Figure 1. This is an autofluorescence image of a portion of a retina with geographic atrophy, as an eye doctor would see it in a dilated eye exam. The lighter "continent" of GA is surrounded by a sea of healthier looking retina.

GA tends to progress slowly. Progression is currently studied using a technique called autofluorescence (**AF**) imaging to define the areas of GA. A newer technique called high density optical coherence tomography (**OCT**) allows the doctor to visualize the different layers of the retina, and to determine when cells are becoming thinned or destroyed. Doctors use the term “scotoma” to refer to the blind spot in a person’s vision caused by the absence of cells in the part of the macula that has degenerated. By measuring enlargement of the area of atrophy, a doctor can estimate

the loss in visual function. (Low vision specialists train patients to use healthy portions of the retina to view the otherwise missing visual field.)

Dr. Sunness estimates that 3.5% of the U.S. population age 75 and older has GA. In people older than 90, the percentage is 22%.

GA is explained in more detail below. This includes details about how GA progresses (its “natural history”) and about clinical trials that test ciliary neurotrophic factor (CNTF) and the drug fenretinide for slowing GA progression. Fenretinide received fast-track designation from the FDA in April 2009, which means that the FDA believes that more rapid approval of the drug might be possible based on strong results from early studies.

- **wet age-related macular degeneration**

Wet AMD occurs when small blood vessels beneath the macula send off tiny blood vessels that leak fluid. You may have heard the term choroidal neovascularization (CNV) to describe the phenomenon.

The fluid displaces the macula from its normal flat position, which causes vision to become distorted. This can cause

serious and permanent vision loss especially of central vision. Two new drugs for treating wet AMD, named Avastin and Lucentis, are having a remarkable effect on wet AMD. Both work by blocking the formation of the abnormal blood vessels. The drugs are administered by injection into the eyeball. Vision loss for most of the patients treated with these drugs has been stabilized; some patients have even experienced improvement in their vision.

No such drug treatment currently exists for dry AMD or geographic atrophy.

More general facts about AMD

Age-related macular degeneration receives a lot of attention from physicians, scientists, pharmaceutical companies, biotech start-ups, policymakers, consumer action groups, and, of course, patients and their families. What makes it so important?

- AMD has a major influence on quality of life.
- Its economic impact is profound.
- As the population ages, more and more people will be affected.

In countries of the Western world, age-related macular degeneration is the leading cause of vision loss in people over age 50. It affects about 25-30 million people. In the U.S., according to a 2007 report from Prevent Blindness America, the direct medical cost (mainly outpatient services) of AMD is approximately \$80,000,000 per year—not including the cost of lost productivity, the cost of unpaid care from friends and family, nursing home care when required, or the cost of government programs like the Department of Education’s Independent Living Services for Older Individuals Who are Blind, or the American Printing House for the Blind, or the Library of Congress’ National Library for the Blind and Physically Handicapped.

A priority for the **Macular Degeneration Foundation** (MDF) is improving quality of life for people with macular disease by helping them with the challenges of macular disease. Contact Foundation President Liz Trauernicht (liz@eyesight.org) for information, news, hope, and encouragement. MDF also support researchers who are investigating treatments.

GA risk factors, incidence, and natural history

Geographic atrophy is more common in whites, in people with a light colored iris, in cigarette smokers, in older age, and in people with a greater retinal area containing drusen. GA also appears to have a genetic component.

Researchers believe that a gene called toll-like receptor 3 (TLR3) is likely involved in GA. When they compared the gene in people with GA, wet AMD, dry AMD, and no AMD, they found a significant association between *low* activity of the TLR3 gene and *protection* against geographic atrophy. When the gene becomes activated, maybe related to a viral infection, it appears to play a role in GA. Other genes have also been implicated in GA including ones with names like CFH, ARMS2, and C3. People with certain variations of the normal CFH, ARMS2, and C3 genes may be at higher risk for GA. These are exciting findings. They suggest that inflammation may play a role in the development of advanced AMD and that treatments affecting the inflammatory response may help to delay the development of vision loss. Identifying these genes is just a beginning. Now scientists need to figure out how the genes cause the atrophy and death of RPE cells and photoreceptors.

Dr. Sunness says that more than half of patients with GA in one eye develop GA in the other eye. The size and shape of

the continent representing cell loss tends to be similar between eyes although the ability to see as measured by visual acuity tests in both eyes can differ because of the exact location of the cell loss. A study called the Framingham Eye Study found that as much as 20% of legal blindness in the U.S. is tied to GA. Dr. Sunness feels that this underrepresents the real vision problems associated with GA. Legal blindness is defined as vision that is 20/200 or worse in both eyes. (20/200 means that a person sees at 20 feet what someone with normal vision sees at 200 feet.) It does not address GA-related difficulties with dim lighting or blind spots caused by atrophy in portions of the retina that are not measured by common visual acuity tests.

The natural history of geographic atrophy

Many of Dr. Sunness' patients want to know how quickly their vision loss will progress. She tells them that, in general, enlargement of the atrophied area of the retina advances between 1.5 and 2.5 mm² per year (the latter being about the size of the letter O in ONE CENT on the back of a U.S. penny). The best predictor of enlargement rate is a person's past history, meaning how quickly or slowly the GA advanced previously.

In a person with GA in both eyes, the rate of enlargement of the atrophic area tends to be similar and progress in tandem. Researchers sometimes use bilateral GA to test a treatment in one eye (treatment eye) while leaving the other eye untreated (control eye) for comparison. Dr. Sunness has done a careful statistical analysis showing that testing a treatment in just one eye in patients with bilateral GA and using the other eye for comparison would require only 38 patients to detect a treatment-related 25% lower rate of GA progression in the treated eye. This is in contrast to needing 158 patients in a treatment group and 158 patients in a control group when both eyes are treated with a drug that is administered systemically.

People with macular degeneration often complain that their reading speed is not what it used to be. A drop in the speed at which a person with GA reads can indicate an increase in the size of the geographic atrophy. In other words, reading rate declines as the area of GA grows. This fact is sometimes used by researchers for assessing the impact of AMD on quality of life (QOL). The Food and Drug Administration is talking with researchers who want QOL to be considered in the approval process for new drugs and devices for treating AMD, rather than or in addition to improvement on the traditional eye chart. The researchers argue that increased

speed of reading is a measurable outcome and an indication of treatment success.

Another event in GA is something called low luminance deficit (**LLD**) (difficulty reading in dim light). “This is one of my patients’ greatest complaints,” says Dr. Sunness. “They complain, for example, of not being able to read menus in dimly lit restaurants.” She and her colleagues have discovered a relationship between LLD and worsening performance over time in reading an eye chart.

“Forty percent of people with GA require print to be twice as large after two years of worsening,” says Dr. Sunness. She adds, “Educating patients with GA about obtaining their best possible vision is extremely helpful for them and rewarding for me. There are three basic lessons for them to learn. One, they need things bigger, which magnification provides. Two, they need things bolder, meaning contrast and lighting have to be good. Three, they need to learn to look around the boulder that is their scotoma. Helping people with scotoma awareness helps them function better.” Hoover Low Vision Services and other low vision centers teach about applying this information.

Patients also ask Dr. Sunness about how cataract surgery might affect their GA. She tells them that a recent study with her collaborators at Johns Hopkins and University of Bonn found that cataract surgery does not affect disease progression. When they ask about wet AMD developing in an eye with GA, she tells them that the risk exists but it is small. About using the anti-oxidant vitamin formula based on the AREDS study—the Age-Related Eye Disease Study of the National Institutes of Health—she says there is no evidence that the vitamin retards the development of GA or its progression, but it is still useful for reducing the risk of developing wet AMD.

There is much more to learn about GA. New studies are revealing more and more about how it progresses. One such study is the Germany-based FAM Study (shorthand for the “Prospective Natural History Study of Fundus Autofluorescence Imaging in Age-Related Macular Degeneration (FAM-Study) Using Confocal Scanning Laser Ophthalmoscopy”). It uses a new technology that allows researchers to track the advancing edge of GA in the retina more closely than ever.

As researchers parse out the details of GA, including natural history and biological and environmental factors, they are

very likely to find information that will help them assign patients with GA to the most appropriate clinical trials and, ultimately, to treatments that address each unique patient.

Clinical trials for geographic atrophy

Because GA is slowly progressive, there is a large window of time to treat it and retain good vision. Clinical trials of experimental compounds are planned or ongoing. One type involves a growth factor (naturally-occurring proteins that affect cell health) and another involves the drug fenretinide.

- The company Neurotech announced in March 2009 that high doses of the protein ciliary neurotrophic factor (CNTF) delivered via a unique encapsulated cell technology (ECT) slowed vision loss in a clinical trial of patients with geographic atrophy. Ninety-six percent of study participants had their vision stabilized compared to 75% of GA patients in an untreated group. CNTF is secreted by cells placed within a capsule that is implanted inside the eye.

Not only was vision stabilized. The researchers also saw an increase in the thickness of the retina, which could signal the rescue of photoreceptor cells. Cells that are

undergoing atrophy can recover if they are not too far gone.

Neurotech is continuing its work with NT-501 in late-stage clinical trials. The study is ongoing but not recruiting new patients.

- Fenretinide is under development by Sirion Therapeutics. The company announced in April 2009 the results of its clinical trials showing slower growth of GA, especially in study subjects receiving the higher of two doses being studied (100 mg and 300 mg). At 300 mg daily, the effect occurred no matter the size of the GA; at 100 mg daily doses, the impact was limited to smaller-sized lesions. The effect of fenretinide began to appear as early as 6 months after treatment began. At 18 months, researchers saw a median growth rate of GA of 23% in a treatment group compared to 42% in a placebo group. Sirion is planning additional clinical trials. With the fast track designation they received from the FDA based on these results, they are optimistic about bringing this product to market for patients with geographic atrophy.

Closing remarks

Geographic atrophy is an advanced form of dry age-related macular degeneration. It occurs as cells of layers of the retina in the region of the macula—the portion of the eye needed for sharp, central vision—degenerate and die away. It is slowly progressive and, as of now, there is no cure or solid explanation of its cause. Age, cigarette smoking, and genetics appear to play a role. GA is different from wet AMD although both begin as dry AMD. We do not know why some people advance to one form of AMD or the other.

Expert Janet Sunness, M.D., is studying how GA progresses, which is critically important for recognizing the impact of treatments being developed to slow its progress. Dr. Sunness, who is also a low vision specialist, teaches her patients how to maximize the vision they have. She stresses better light and contrast, magnification, and strategies for peering around the blind spots in the visual field that represent the degenerated retinal cells.

Clinical trials of two types of treatment for GA recently showed promising results. One involves implanting cells in the eye that then secrete a growth factor for sustaining the health of RPE and photoreceptor cells. Another is a drug that is taken by mouth and appears to work by preventing the build up of potentially harmful byproducts of metabolism.

These are experimental treatments and, if they continue to show good results, could possibly be commercially available in about 5 years.

The **Macular Degeneration Foundation** is pleased to provide this update on geographic atrophy. As always, we invite your emails on this topic and others involving health and disease of the macula. Email: liz@eyesight.org or Website: www.eyesight.org

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