VISUAL FUNCTION
BIOMARKERS NEEDED FOR DRY AMD

Early detection may allow treatment, and possibly reversal. Part 2 of a two-part series.

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In the previous installment of Innovations (found online at bit.ly/shapiro916), we reviewed color discrimination tests, shape discrimination tests, and low-luminance visual acuity, all of which can be used to measure disease progression in dry age-related macular degeneration (AMD). In this installment of Innovations, we review perimetry-based tests and dynamic tests, two types of tests poised to provide information that will guide physicians’ treatment patterns for patients experiencing disease progression but no vision loss.

PERIMETRY-BASED TESTS

Perimetry is the systematic measurement of visual field function. Standard automated or white-on-white perimetry involves the projection of a white stimulus on a white background to determine threshold values to enable a systematic assessment of the visual field. The intensity of the dimmest stimulus that can be detected 50% of the time at each testing location is recorded. Maps of visual sensitivity are thus generated. The test is sensitive and allows rapid turnaround of reproducible, quantitative information.

Flicker perimetry evaluates the test-taker’s ability to detect an alternating light/dark (flickering) stimulus at various locations in the field of view. Three types of flicker perimetry tests have been employed. Contrast modulation flicker uses a stimulus of the same luminosity as the background, and the amplitude of flicker required for detection by the patient is determined for different rates of flicker. Critical flicker fusion uses a stimulus that has maximum contrast with the background, and the maximum rate or frequency of flicker that can be differentiated from a steady background is assessed. Luminance pedestal flicker uses a flickering stimulus superimposed on a pedestal of steady light, and the amount of flicker required for a subject to identify when the stimulus is flickering is evaluated.

For flicker perimetry testing in patients with early AMD, the flickering stimulus is presented as a single foveated Gaussian blob. The size used is a standard Goldman size 3 at 4 Hz and 14 Hz frequencies. This test has good diagnostic capability, has been shown to provide reliable outcomes, and is sensitive to disease severity.

Research is under way at Ora to develop improved flicker fusion tests targeting different parts of the visual system, studying luminosity, scotopic flicker fusion (measuring rod function), mesopic flicker fusion (measuring rod and cone function), and variable contrast flicker fusion, tailored to a specific group of patients (eg, patients with early AMD). This area, which has been largely unexplored, may enable early diagnosis.

Microperimetry enables correlation of function with structural changes in a localized area of the retina. In microperimetry testing, the patient is asked to fixate on a target and is presented with lights of varying intensity. The stimulus moves with the eye to concentrate on one region of the retina. The individual responds by pressing a button each time the stimulus is detected. A computer-generated map of the retina provides information on the patient’s visual function in the areas tested. This test can be used to monitor visual function of a particular area of the retina relative to structural changes over time.

DYNAMIC TESTS

Dynamic tests evaluate photopigment regeneration, providing valuable information on the integrity of the retinal pigment epithelium–photoreceptor complex.

In the photostress test, Snellen visual acuity is assessed in one eye, after which the eye is exposed to bright light from an ophthalmoscope for 10 seconds to allow bleaching of more than 95% of the eye’s photopigment. The patient is then asked to read the line of letters immediately above his or her best line of acuity while the recovery time is tracked. The procedure is then repeated for the other eye. This test enables discrimination between retinal and postretinal (optic nerve) disease. Patients with macular defects typically take 1.5 to 3 minutes longer than normal individuals for photorecovery to occur after bleaching. Unlike in patients
with AMD, in patients with optic nerve disease, bleaching of the retina has no effect on the recovery time. AMD patients displaying soft or reticular drusen, with or without pigmentary changes (no late AMD), were found to have significantly longer recovery periods than healthy individuals.2,6

In a study assessing macular recovery time by measuring recovery of L-cone sensitivity after photostress, eight patients with early to intermediate dry AMD and four controls were tested three times within 2 weeks at baseline, and again after 1 year. After assessing baseline cone threshold, photostress was applied with a diffused fluorescent light source of approximately 40,000 cd/m², viewed for 90 seconds from a distance of 12 inches. This exposure was safe and sufficient to bleach 90% to 95% of the cone photopigment. The Roland Consult dark adaptometer was used to assess cone sensitivity at baseline and after photostress. The stimulus used was a red light at 625 nm wavelength that stimulated the L-cones on the fovea. It produced a stimulus spot 2° in size, located at 5°, 10°, 20°, 30°, 40°, or 50° position. The test subjects were asked to press a button to indicate stimulus detection, and the results were graphed on a computer. The test showed significant differences between patients with AMD and control individuals and has potential as a quantitative measure of macular function in AMD.7,8

In dark adaptation testing, the eye is subjected to a bright light to bleach most of the rods and cones, after which the eye is stimulated with a bright light of about 420 nm wavelength against a pitch-black background. Adaptation thus measured provides functional information about the rods and cones. Thereafter, the adapting light is extinguished, and the test subject is asked to decrease the intensity of the test light until it is almost undetectable. This determines the detection threshold.9

Dark adaptation is abnormal in patients with AMD, but the lengthy test procedure makes its use inconvenient in the clinic. Cathode ray tube (CRT) monitors can help track dark adaptation over a short time with useful clinical outcomes.4 In order to investigate the relationship between clinical macular changes and retinal function in AMD, investigators measured rod dark adaptation recovery rate after bleaching 30% of the photopigment in individuals with normal fundi and with AMD.10 A CRT was used to generate a 2° stimulus at 3.5° inferior retina along the vertical meridian. The 3.5° eccentric location is an area at which the rods are most vulnerable early in AMD. The study authors found that this measurement showed concordance across the spectrum of early AMD changes.10

AdaptDx (MacuLogix) is an FDA-approved automated instrument for the measurement of dark adaptation function. The measurement is conducted in a darkened room, takes 5 minutes, and requires no previous adaptation. The device measures rod-mediated sensitivity recovery (the rod intercept) after the stress of mild 20% to 95% photobleaching at a wavelength of 505 nm.11 The patient indicates detection of the spot of light by clicking a handheld button. The stimulus is 2° in size and is located at 5°, 8.5°, and 12° at eight azimuthal locations.12 If an abnormal result is found in the 5-minute screening, a more detailed examination can be conducted on the machine, taking 20 minutes more.13

CONCLUSION

Vavvas et al recently reported the regression of drusen deposits, with associated improvements in visual acuity, in a high-risk subgroup of AMD patients after the administration of a high dose of atorvastatin. Their finding suggested that early AMD may be a reversible condition.14 However, in order to cure dry AMD, better ways of diagnosing visual function changes in the early stages of the disease are needed. There is a need for improved biomarkers that facilitate accurate assessments of early AMD changes and prediction of the risk of progression. Advancing the development of these visual function biomarkers may hold the key to developing future treatments for the most common cause of vision loss in people older than 55 years. 

References

4. Tran BK, Herbert Jr CP. Discrepancy between visual acuity and microperimetry in AMD patients: visual acuity appears as an inadequate parameter to test macular function. Xin Mei / Augenheilkd. 2015;21(4):529-532.