AMERICAN ACADEMY™
OF OPHTHALMOLOGY

Decreased Visual Function Scores on a Low Luminance Questionnaire Is Associated with Impaired Dark Adaptation

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Purpose: We investigate whether responses on a Low Luminance Questionnaire (LLQ) in patients with a range of age-related macular degeneration (AMD) severity are associated with their performance on focal dark adaptation (DA) testing and with choroidal thickness.

Design: Cross-sectional, single-center, observational study.

Participants: A total of 113 participants older than 50 years of age with a range of AMD severity.

Methods: Participants answered the LLQ on the same day they underwent DA testing using a focal dark adaptometer measuring rod intercept time (RIT). We performed univariable and multivariable analyses of the LLQ scores and age, RIT, AMD severity, subfoveal choroidal thickness [SFCT], phakic status, and best-corrected visual acuity.

Main Outcome Measures: The primary outcome of this study was the score on the 32-question LLQ. Each item in the LLQ is designated to 1 of 6 subscales describing functional problems in low luminance: driving, emotional distress, mobility, extreme lighting, peripheral vision, and general dim lighting. Scores were computed for each subscale, in addition to a weighted total mean score.

Results: Responses from 113 participants (mean age, 76.2±9.3 years; 58.4% were female) and 113 study eyes were analyzed. Univariable analysis demonstrated that lower scores on all LLQ subscales were correlated with prolonged DA testing (longer RIT) and decreased choroidal thickness. All associations were statistically significant except for the association of choroidal thickness and "peripheral vision." The strongest association was the LLQ subscale of driving with RIT ($r = -0.97$, $P < 0.001$). Multivariable analysis for each of the LLQ subscale outcomes, adjusted for age, included RIT, with total LLQ score, "driving," "extreme lighting," and "mobility" also including choroidal thickness. In all multivariable analyses, RIT had a stronger association than choroidal thickness.

Conclusions: This cross-sectional analysis demonstrates associations of patient-reported functional deficits, as assessed on the LLQ, with both reduced DA and reduced choroidal thickness, in a population of older adults with varying degrees of AMD severity and good visual acuity in at least 1 eye. These analyses suggest that local functional measurements of DA testing (RIT) and choroidal thickness are associated with patient-reported functional deficits. *Ophthalmology 2017;■:1–8 Published by Elsevier on behalf of the American Academy of Ophthalmology*

Age-related macular degeneration (AMD) has been the leading cause of central vision loss in people aged 65 years or older in developed countries.[1,2] Decreases in central vision from late AMD are well established, and even intermediate AMD can display small but statistically significant reductions in central acuity compared with those without AMD.[3–5] Visual function questionnaires document the impact of poor acuity on a person's daily living and have become a useful patient-reported outcome measure.[6–8] With the exception of trials involving geographic atrophy,[6] clinical trials in AMD have focused on central acuity as the primary outcome measure.[9–17]

However, earlier cell changes accompanying AMD have direct links to additional measures of retinal function. Histopathologic examination of eyes of patients with AMD has demonstrated preferential loss of rods in the photoreceptor layer of the retina with cones persisting as the last surviving photoreceptors.[18–20] Studies using multiple approaches to measure rod and cone function have documented preferential reduced rod function in eyes with AMD.[21–26] A focal dark adaptometer able to focus on areas 0.5 to 3 mm from the fovea, areas thought to have earliest rod loss, has demonstrated impairments in eyes with nonadvanced AMD compared with older eyes without AMD even when visual acuity varied little between severity groups.[23] Increasing AMD severity was associated with increased RIT, an outcome of dark adaptation (DA), with eyes having reticular pseudodrusen (RPD) demonstrating the most significant delays.[23] As efforts are under way to identify functional outcomes that would be meaningful in

http://dx.doi.org/10.1016/j.ophtha.2017.05.005
ISSN 0161-6420/17

early disease, measures of DA have the potential to be an informative measure. To demonstrate the relevance of this outcome measure in clinical trials, patient-centered validation of DA is needed.

Recent questionnaires developed for assessing functioning in low luminance or "night vision" have shown differences in patients with AMD.[27–31] The Low Luminance Questionnaire (LLQ) was designed specifically for the purpose of assessing difficulties at night and in low luminance.[32] Other visual function questionnaires, such as the National Eye Institute Visual Function Questionnaire,[33] Visual Function Index,[34] Activities of Daily Vision Scale,[35] and others,[36–38] are focused primarily on assessing visual difficulty in photopic or mesopic conditions, and have few questions related to performance on low-luminance tasks. In the development of the LLQ questionnaire, all subscales were significantly associated with impairments in DA parameters that rely on rod-mediated function but not with cone-mediated parameters.[32] While the development of the LLQ and other questionnaires are aimed at assessing function in low luminance,[29,39] few have been able to relate the questionnaire to direct functional testing of DA in patients.

Thus, the purpose of this study is to investigate whether patient-perceived difficulty in low luminance, as assessed by patients' responses on the LLQ, correlates with their performance on DA testing in patients with a spectrum of AMD disease severity who maintain good visual acuity. Such validation would further support RIT as a clinical measure that reflects patient-relevant visual difficulties in low luminance not captured by conventional photopic high-contrast visual acuity.

Methods

Study Population

Participants included adults older than 50 years of age both with and without AMD who were recruited from the eye clinic at the National Eye Institute, National Institutes of Health, Bethesda, Maryland, between May 2011 and January 2014. Patients were excluded for (1) advanced AMD in both eyes at baseline visit; (2) any other active ocular or macular disease (i.e., glaucoma, diabetic retinopathy, Stargardt disease); (3) a condition preventing compliance with the study assessment; (4) cataract surgery within 3 months before enrollment; (5) history of vitamin A deficiency; (6) high oral intake of vitamin A palmitate supplement ($\geq$10 000 international units per day); and (7) active liver disease or history of liver disease. Study eyes were required to have a best-corrected visual acuity (BCVA) of 20/100 or better.

After examination, eligible participants were separated into groups according to their fundus features. The grading criteria for AMD groups have been described by Flamendorf et al,[23] but are described briefly as follows. Eligible eyes were screened for the presence of RPD, and these eyes were placed into a separate group (RPD group). The remaining eyes were grouped according to increasing order of AMD severity on the basis of the presence of large drusen ($\geq$125 mm), advanced AMD, or both. The control group, group 0, consisted of participants without any large drusen or advanced AMD (choroidal neovascularization [CNV] or central geographic atrophy [CGA]) in either eye. Group 1 consisted of participants with large drusen in 1 eye only and no late AMD in either eye. Group 2 included participants with large drusen in both eyes without any late AMD. Group 3 included participants with large drusen in 1 eye and late AMD in the other eye (CGA or CNV). Each participant had only 1 study eye assigned to undergo the DA testing. In participants without any large drusen, either eye could be designated the study eye. In participants with large drusen in 1 eye only, the eye with large drusen was the study eye. In participants with large drusen bilaterally, either eye could be the study eye. In participants with advanced AMD in 1 eye, the nonadvanced eye was the study eye to avoid influences of noncentral fixation and to exclude testing that might reflect poor DA due to the presence of fluid or blood in the retina rather than the psychophysical measurement of retina function. The study was approved by the Institutional Review Board of the National Institutes of Health, and the tenets of the Declaration of Helsinki were followed. Although not a clinical trial, the study is registered on clinicaltrials.gov (identifier NCT01352975). All participants provided written informed consent after the nature and possible consequences of the study were explained. The analysis included 113 participants who had LLQ results, DA testing results, and subfoveal choroidal thickness (SFCT).

Examination and Imaging

All participants underwent a complete ophthalmic examination, including measurement of BCVA with the Early Treatment Diabetic Retinopathy Study logarithm of the minimum angle of resolution (logMAR) visual acuity chart, measurement of intraocular pressure, slit-lamp examination, and dilated fundus examination. Contrast sensitivity was determined for each eye using standard administration of the Pelli-Robson contrast sensitivity chart.[40] Presence of AMD features (drusen, pigmentary change, pigment epithelial detachment, CNV, CGA) and other ocular findings (e.g., phakic status) were documented. Color fundus photographs and fundus autofluorescence images were acquired with the TRC-50DX retinal camera (Topcon Medical Systems, Tokyo, Japan). Infrared reflectance and fundus autofluorescence images and spectral-domain optical coherence tomography (OCT) scans were acquired with the Heidelberg Spectralis (Heidelberg Engineering). Each set of spectral-domain OCT scans consisted of 37 B-scans, each of which comprised 24 averaged scans, obtained within a 30°$\times$15° rectangle centered on the fovea. In addition, enhanced depth imaging OCT scans were acquired for improved visualization of the choroid in a single horizontal scan centered at the fovea obtained over a distance of 30° consisting of 100 averaged scans.

Low Luminance Questionnaire

The LLQ is a 32-item questionnaire designed to assess the degree of difficulty experienced by participants at night and in other low light environments.[32] Each item is scored on a scale of 0 to 100, with 0 representing the greatest difficulty and 100 representing the least. Items are assigned to 1 of 6 subscales: dim lighting, driving, emotional distress, extreme lighting, mobility, and peripheral vision. Item scores are averaged to give 1 score per subscale. Each subscale is then weighted by number of items and averaged to yield a total mean LLQ score.[16] The questionnaire was administered before DA testing by a staff member masked to participants' DA testing performance.

Dark Adaptation Testing

Dark adaptation was measured using a prototype of the AdaptDx dark adaptometer (MacuLogix, Hummelstown, PA). Details about the testing procedure have been documented.[41] In brief, the