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RETINAL DISORDERS

Quantitative analysis of central visual field defects in macular edema using three-dimensional computer-automated threshold Amsler grid testing

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Abstract
Purpose To evaluate the central visual field (CVF) with specialized Amsler grid testing methods that include contrast sensitivity evaluation, in an attempt to detect abnormalities not identified with standard methods and to define new patterns of CVF deficits in two different diseases.
Methods 3D computer-automated threshold Amsler grid testing (3D-CTAG) was performed at five levels of contrast in one eye of 37 patients with diabetic macular edema (DME, $n=16$) and exudative age-related macular degeneration (AMD, $n=21$).
Results 3D-CTAG abnormalities were detected in six patients (16%) who had no abnormalities with conventional Amsler grid testing. DME patients had more foci of CVF deficits (3.56±2.92 defects/eye), than AMD patients (1.24±0.89 defects/eye; $P<0.0002$). The shape of the 3D-CTAG abnormality in DME was an inverted cone, while the deficits in AMD were always cylindrical. All eyes showed significant increases in CVF deficit surface area at minimum contrast levels when compared to maximum contrast (295% greater with DME, $P<0.02$ and 150% greater with AMD, $P<0.03$).
Conclusion 3D-CTAG detected CVF abnormalities not identified with conventional Amsler grid testing in 16% of subjects. Low-contrast conditions elicited a larger defect in both DME (3-fold) and AMD (1.5-fold). DME and AMD have unique 3D-CTAG profiles, enabling diagnostic discrimination. Measuring CVF defects with 3D-CTAG can quantitatively index disease severity and may be useful in longitudinal studies of the natural history of disease, as well as providing a quantitative outcome measure of the response to therapy.

Keywords Age-related macular degeneration · Amsler grid · Contrast sensitivity · Diabetic macular edema · Macular edema · Scotomas

The results of this study have been presented in part at the Western Retina Study Club meeting in Pasadena, CA, USA, March 2007 and at the Association for Research in Vision and Ophthalmology (ARVO) meeting in Fort Lauderdale, FL, USA, May 2007.

The principal investigator, JS, had full access to all the data in the study, and takes responsibility for the integrity of the data and accuracy of the data analysis. All authors agree to allow Graefe's Archive for Clinical and Experimental Ophthalmology to review their data if requested.

All human studies have been reviewed by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

Competing interests: Authors AAS and WF may have proprietary interest in the 3D computer-automated threshold Amsler grid test described in the study as patents on the technology are issued.

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Introduction

Amsler grid testing was first introduced in the 1940s to qualitatively detect metamorphopsia in the central 10° of the visual field [1]. It is presently used in clinical practice to

screen for central visual field abnormalities, but there is potential for this test to provide more than just screening. To do so, however, requires an improvement in the discriminating power of the test.

Recent modifications of Amsler grid testing were introduced to enhance the detection of central visual field abnormalities by testing changes in color and threshold through cross-polarizing lenses [2]. The most recent such modification, known as 3-dimensional computer-automated threshold Amsler grid (3D-CTAG), decreases the luminance of a white Amsler grid on a black background at several predetermined levels [3, 4]. Plotting the 3D-CTAG results for five different tested contrast levels along the *z*-axis (with the *x*-*y* plane being the tested central visual field) introduces a third dimension to the Amsler grid plot, that being contrast sensitivity [2–4]. Pilot studies have been performed on patients with diabetic retinopathy, age-related macular degeneration, glaucoma, ocular hypertension, and optic neuritis [3–8].

This study was designed to evaluate a larger number of cases, with the aim of determining whether lowering contrast can detect Amsler grid abnormalities not detected with conventional Amsler grid testing, and to qualitatively and quantitatively compare diabetic macular edema with exudative age-related macular degeneration. We hypothesize that varying contrast in Amsler grid testing will provide a superior mechanism for detecting central visual field abnormalities, and that the results will show both qualitative and quantitative differences that are characteristic for these two different diseases.

Materials and methods

Subjects

Thirty-seven patients were evaluated at the VMR Institute in Huntington Beach, CA. All subjects provided written informed consent, and the study was approved by the University of Southern California Institutional Review Board. Only one eye with a visual acuity of 20/80 or better was used from each subject. There were 16 eyes with diabetic macular edema (DME) and 21 eyes with exudative age-related macular degeneration (AMD). Tables 1 and 2 outline patient-specific clinical data at the time of examination. Subjects wore corrective lenses as needed to achieve optimal visual acuity during testing. A previous history of therapeutic modalities, such as panretinal photocoagulation, focal or grid laser treatments, photodynamic therapy or intra-vitreal injections, was not an exclusion criterion.

Methods

The 3D-CTAG evaluation was performed in a dimly lit examination room using an IBM-compatible Pentium II PC running Windows 98 with a 17-inch touch-sensitive computer monitor. The monitor was not recalibrated between tests, but the settings were maintained at the same contrast and brightness throughout the study. Each patient was seated at a fixed distance of 30 cm from the central fixation marker at a height adjusted to match his or her eye level (0° horizontally and 0° vertically from central fixation). The

Table 1 DME patients' clinical data

Patient, eye	Age	Sex	VA	Prior laser treatments	Foveal thickness
BR, OS	60	F	20/30−2	3 MLP	0.482 mm
JB, OS	72	F	20/200	0	0.588 mm
AJ, OD	60	M	20/20	0	0.346 mm
JK, OS	54	F	20/60	2 PRP	n/a
AP, OD	52	M	20/40	10 MLP	n/a
RB, OS	76	M	20/26	3 MLP	0.272 mm
MB, OS	42	M	20/20−1	3 MLP	0.250 mm
JF, OD	78	F	20/80+2	6 MLP	0.465 mm
TW, OD	38	M	20/50	1 MLP	0.259 mm
ET, OS	45	F	20/26−1	0	n/a
ME, OD	67	F	20/25−1	2 MLP	0.325 mm
CA, OS	61	F	20/70	0	n/a
WC, OD	69	M	20/20	1 MLP	0.215 mm
ML, OD	50	M	20/30	3 PRP, 1 MLP	n/a
JB, OS	54	F	20/50	not available	0.579 mm
AJ, OS	60	M	20/50	1 MLP	0.338 mm

F = female, M = male; MLP = macular laser photocoagulation, PRP= panretinal photocoagulation

Table 2 AMD patients' clinical data

Patient, eye	Age	Sex	VA	Prior treatments	Foveal thickness
JM, OS	84	F	20/25−2	6 injections	0.263 mm
RG, OS	83	M	20/20−3	0	n/a
CN, OS	85	F	20/60−2	0	0.382 mm
ID, OS	89	F	20/20+2	8 injections	0.263 mm
MB, OD	82	F	20/20−2	0	0.184 mm
JW, OS	74	M	20/25	0	0.316 mm
DB, OD	81	F	20/20	3 injections	0.246 mm
DD, OS	66	F	20/40	5 injections	0.338 mm
MF, OS	82	F	20/50−1	0	0.342 mm
NW, OS	73	F	20/40−1	1 injection	0.421 mm
JR, OS	86	M	20/25−3	0	0.228 mm
AA, OS	75	M	20/40+3	6 injections	0.171 mm
JW, OS	102	F	20/50+1	9 injections	0.298 mm
SK, OS	61	M	20/30	1 injection	0.421 mm
KH, OS	63	F	20/40	1 laser	n/a
PP, OD	67	F	20/100	1 laser	0.368 mm
LH, OS	90	F	20/400	3 injections	0.171 mm
RW, OD	68	M	20/30	2 injections	0.368 mm
KH, OD	83	M	20/50	1 injection	0.360 mm
EK, OD	63	F	20/400	0	0.285 mm
MM, OD	76	F	20/26−3	not known	0.254 mm

eye not being tested was covered using an eye cover. A series of five Amsler grids at pre-selected gray scales (i.e., contrast levels) was displayed by the computerized test program. The grid line spacing was consistently set to 1° to mimic the standard Amsler grid and to normalize the angular resolution among patients.

Patients were asked to focus on a central, shape-changing marker to help maintain fixation. Patients with central scotomas who had difficulty using the central fixation point were instructed to use the four edges of the computer screen as a reference frame for fixation. At each pre-selected grayscale level (i.e., 5%, 10%, 20%, 40% and 100% contrast) patients were asked to trace directly onto the computer screen the areas of the grid that were distorted. The lowest contrast level (the darkest grid) represented a measurement of 100% contrast sensitivity at which the grid was barely discernable by the patient. Any signs of distortion, blurred lines or absence of gridlines were considered an indication to record the deficiency by tracing the region with a finger on the touch screen. The fifth and final grid displayed represented white gridlines on a black background, which simulated a standard Amsler grid at absolute contrast. Following the computerized exam in both eyes, patients were tested using the conventional Amsler grid at the same distance of 30 cm from the grid. The total time required to test an eye was typically 5–6 minutes. Each tested grid demonstrated "horizontal cuts" in the hill of vision at predetermined "heights" along the *z*-axis, which, taken together, were immediately mapped as a 3-dimensional graphical representation of the hill of vision [3–5].

Macular thickness was determined using combined Optical Coherence Tomography - Scanning Laser Ophthalmoscopy (OPKO Inc., Miami, FL, USA).

Statistical methods

The results were plotted in three dimensions, with the visual field abnormalities expressed as a function of the *x*- and *y*-coordinates of the Amsler grid at various contrast sensitivities, which are represented on the *z*-axis (Figs. 1 and 2). These images were then modified using MATLAB

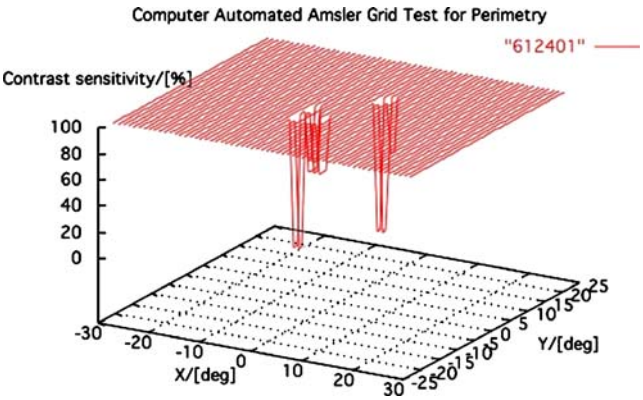

Fig. 1 3D-CTAG plot shows multi-focal deficits shaped as inverted cones in a subject with diabetic macular edema

(by MathWorks) graphics technology to develop topographical figures of the 3D graphs (Figs. 3 and 4). The findings were analyzed according to previous studies [5, 9] in terms of visual field abnormality in the *x*-*y* plane at minimum contrast compared to the area at maximum contrast and the volume of abnormality at all five contrast levels analyzed together. The Student's unpaired *t*-test was used when comparing the absolute number of defects and surface areas at maximum and minimum contrast between the DME and AMD patients. A chi-squared test was used to test statistical significance in the differences in surface area deficit between the DME and AMD groups.

Results

Of the 37 eyes studied, six (16%) had no defects using the standard Amsler grid but were found to have central visual field abnormalities on 3D-CTAG testing. AMD was present in 5/6 (84%) of these cases. No subjects had abnormal findings on the conventional grid and normal 3D-CTAG testing.

Patients with DME (n=16) displayed inverted cones (sloping borders) in all cases (Figs. 1 and 3), while the wet AMD patients (n=21) presented cylinder-shaped (vertical borders) profiles with a step-off of larger diameter defects at low contrast levels (Figs. 2 and 4). In four eyes with wet AMD, there were both absolute and relative scotomas, as illustrated by the step-off of a larger cylindrical diameter at lower contrast levels in Fig. 2.

In DME, 15/16 (94%) subjects had multiple 3D-CTAG abnormalities. In AMD patients, multiple defects were detected in only 1/21 (4.8%). The average number of deficits in DME (3.56±2.96 defects/eye) was significantly greater than those in AMD (1.24±0.89 defects/eye; P< 0.0002, Student's unpaired *t*-test).

In DME patients, the average surface area at minimum contrast was 204.88±209.88 deg^2, while at maximum contrast the area of abnormality was 69.5±75.5 deg^2. This 295% increase in surface area abnormality at low contrast levels was statistically significant (P<0.02, Student's *t*-test). The AMD population also had a larger central visual field abnormality at minimum contrast (surface area=114.52± 116.28 deg^2), which was 150% greater than the central visual field abnormality at maximum contrast (surface area= 75.95±59.83 deg^2; P<0.03). Furthermore, the difference in

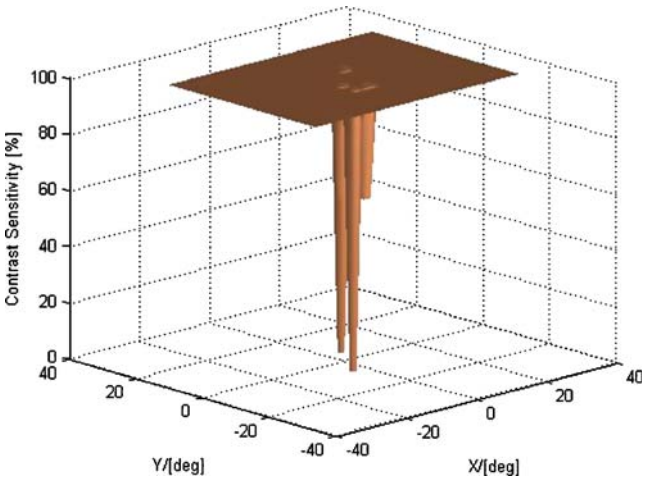

Fig. 3 Topographical fully shaded depiction, equivalent to the grid-like display of the 3D-CTAG test result in Fig. 1 in a person with diabetic macular edema recorded by the 3D computer-automated threshold Amsler grid [3–5]

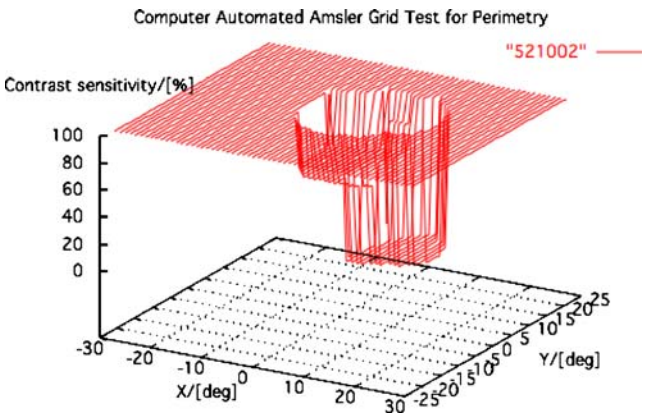

Fig. 2 3D-CTAG test result in a subject with age-related macular degeneration shows a uni-focal, cylinder-shaped abnormality (absolute central scotoma) at all contrast levels, with a step-like pattern at lower contrast, representing the surrounding area of relative scotoma

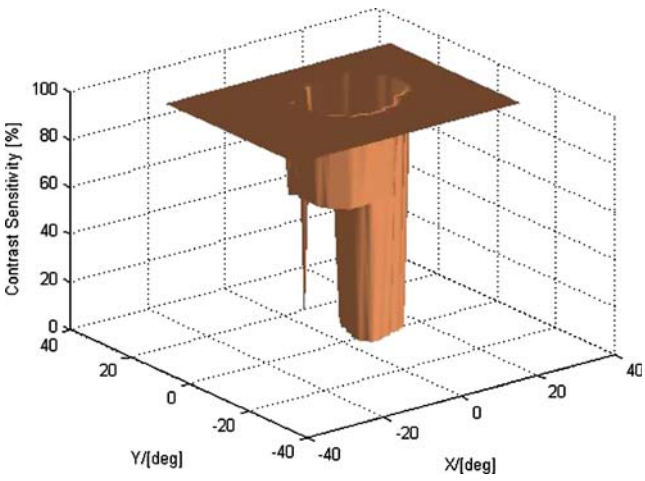

Fig. 4 Topographical fully shaded depiction, equivalent to the grid-like display of the 3D-CTAG test result in Fig. 2 in a person with age-related macular degeneration recorded by the 3D computer-automated threshold Amsler grid [3–5]

abnormal surface area in DME was significantly larger than the differences in AMD patients ($P<0.004$, chi-squared test). This explains why DME induces conical defects, because at maximum contrast the deficits are much smaller than at low contrast. In AMD, there was less of a difference between minimum and maximum contrast, resulting in a cylindrical central visual field defect. Overall, when comparing the ratios of surface area deficit at minimum contrast versus maximum contrast, there were statistically significant differences between the DME and AMD groups ($P<0.04$, Student's unpaired *t*-test).

Despite the striking differences between the two diseases in the number of defects and the differences in the surface area abnormalities from low to high contrast, there was no significant difference in the total volume of the three dimensional visual field affected by the disease between DME (3.51%±2.99) and AMD (3.01%±2.75; $P<0.597$). Within the entire study group, the average volume of loss was 3.27%±0.03 (range=0.26% to 10.7%), suggesting that the volumetric assessment of central visual field deficits due to DME and AMD provides less information than the other indices. Additionally, there was no correlation between 3D-CTAG indices and OCT measurements as the latter is a measure of foveal function, which has a minimal impact on 3D-CTAG testing.

Discussion

Three-dimensional computer-automated threshold Amsler grid testing (3D-CTAG) detected abnormalities in patients with DME and exudative AMD that were not detectable by conventional testing. Previous studies [3–8] have shown that incorporating varying contrast levels into visual field testing helps identify visual field defects arising from diverse etiologies [10]. Studies in optic neuropathies [2] found a six-fold increase in scotoma detection yield over standard Amsler grid testing, demonstrating the potential of 3D-CTAG to detect scotomas not seen with conventional Amsler grid testing methods. The study reported herein found that 16% of subjects had normal conventional Amsler grid test results but abnormalities on 3D-CTAG testing, confirming the findings of Wall and May [11, 12]. Thus, this approach appears to have greater sensitivity than conventional Amsler grid testing. The present study also found that mapping central visual field abnormalities in 3D with contrast defines signature patterns for different diseases, attesting to specificity in the 3D-CTAG testing paradigm. That the results of this study found no correlation with visual acuity and OCT-SLO measures of foveal thickness is not surprising, since these are indices of foveal integrity, and the fovea contributes very little to the visual function measured by 3D-CTAG.

The 3D-CTAG pattern for DME was multiple inverted cones. With focal macular edema, the leakage from isolated microaneurysms is responsible for focal dysfunction in specific locations of the retina [13]. That each diabetic patient in this study had multiple areas of abnormality, all shaped like inverted cones, suggests that this approach is sensitive enough to detect the multi-focal pattern of leakage typical for DME. Moreover, the subjects in this study had mild to moderate DME (see Table 1), suggesting that the 3D-CTAG approach is useful, even in early disease. In contrast, a study comparing Amsler grid testing with entopic perimetry testing in DME found entopic perimetry to be 100% more sensitive than the Amsler grid in detecting visual field defects [14, 15]. In that study, however, all subjects were pre-screened to select only those with significant functional maculopathy, as indicated by an abnormal Humphrey Visual Field. Thus, it would appear that 3D-CTAG testing was able to detect abnormalities in their early stages of disease, while entopic perimetry may be more useful in more advanced disease. Interestingly, Brown argued that using a threshold Amsler grid required specialized equipment [15]. Currently, the 3D-CTAG has been upgraded to a simple computer program that is quick and easy to operate.

AMD patients with varying histories of prior treatment (see Table 2) had uni-focal cylinders with a characteristic step-like pattern, where the central abnormality was present at all contrast levels (absolute scotoma), with a surrounding relative scotoma that was seen only at low contrast levels. It is likely that the absolute scotoma is due to the neovascular membrane, while the surrounding edema, arising from the subretinal neovascular membrane, induces the surrounding relative scotoma. 3D-CTAG was able to distinguish between these two aspects of maculopathy in AMD. A recent study by Nazemi et al. [5] looked closely at 3D-CTAG findings in AMD, and compared the results to fluorescein angiography. This study also found a characteristic combination of steep slopes interrupted by stepwise shallow slopes with scalloped shaped borders. The isolated steep slopes were indicative of non-exudative AMD in patients displaying absolute scotomas, while the shallow areas suggested sites of neovascularization confirmed by the fluorescein angiograms.

The potential utility of this test in the clinical setting is further enhanced by its convenience, as well as the practical implications for disease detection and monitoring. By modifying the well-established traditional Amsler grid to a computerized version, the 3D-CTAG adds objective quantization and a third dimension (contrast sensitivity) to measures of visual field. In comparison to standard forms of automated perimetry, test administration is accomplished with much greater speed, which makes its use in routine clinical care practical. Furthermore, charting and storage of

patients' test results can easily and economically be maintained electronically. While at present macular edema is diagnosed with fluorescein angiography and characterized with OCT (macular thickness measurements), neither of these modalities assesses the functional impact of macular edema. These patients may demonstrate anatomical changes in OCT evaluation of their macular edema; they may also display altered physiology on 3D-CTAG testing, thus enabling the clinician to monitor function in patients with macular edema. Computerized contrast Amsler grid testing offers such assessment with a higher sensitivity than conventional testing, enhances the characterization of any defect with a third dimension, and provides quantitative indices of disease, enabling more than just structural evaluations. Indeed, the quantitative nature of 3D-CTAG evaluations could enhance both clinical research and practice.

In summary, the qualitative nature of 3D-CTAG enables distinction between different disease states. The quantitative results of this test provide new indices of visual dysfunction that could enable the development of new staging systems of disease severity, useful for tracking disease progression. These 3D-CTAG numerical indices could also be used as quantitative outcome measures of therapeutic efficacy in both research and clinical care settings.

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