Distinguishing wet from dry age-related macular degeneration using three-dimensional computer-automated threshold Amsler grid testing

Craig D Robison, Renu V Jivrajka, Simon R Bababeygy, Wolfgang Fink, Alfredo A Sadun, J Sebag

ABSTRACT

Background/aims With the increased efficacy of current therapy for wet age-related macular degeneration (AMD), better ways to detect wet AMD are needed. This study was designed to test the ability of three-dimensional contrast threshold Amsler grid (3D-CTAG) testing to distinguish wet AMD from dry AMD.

Methods Conventional paper Amsler grid and 3D-CTAG tests were performed in 90 eyes: 63 with AMD (34 dry, 29 wet) and 27 controls. Qualitative comparisons were based upon the three-dimensional shapes of central visual field (VF) defects. Quantitative analyses considered the number and volume of the three-dimensional defects.

Results 25/34 (74%) dry AMD and 6/29 (21%) wet AMD eyes had no distortions on paper Amsler grid. Of these, 5/25 (20%) dry and 6/6 (100%) wet (p=0.03) AMD eyes exhibited central VF defects with 3D-CTAG. Wet AMD displayed stepped defects in 16/28 (57%) eyes, compared with only 2/34 (6%) of dry AMD eyes (p=0.002). All three volumetric indices of VF defects were two- to four-fold greater in wet than dry AMD (p<0.006). 3D-CTAG had 83.9% positive and 90.6% negative predictive values for wet AMD.

Conclusions 3D-CTAG has a higher likelihood of detecting central VF defects than conventional Amsler grid, especially in wet AMD. Wet AMD can be distinguished from dry AMD by qualitative and quantitative 3D-CTAG criteria. Thus, 3D-CTAG may be useful in screening for wet AMD, quantitating disease severity, and providing a quantitative outcome measure of therapy.

INTRODUCTION

Throughout the western world, age-related macular degeneration (AMD) is the leading cause of blindness in persons older than 65 years of age. An estimated 1.75 million Americans and 3.55 million Europeans have AMD, with a prevalence of exudative AMD approaching 8.29/100 in Caucasian persons older than 80 years. By 2020, this number is expected to grow by more than 50%. AMD currently accounts for 54.4% of blindness and 22.9% of low vision among white persons, 14.3% of blindness and 14.1% of low vision among Hispanic persons, and 4.4% of blindness and 3.2% of low vision among black persons.

Traditional screening for AMD has included the paper Amsler grid, despite low sensitivity and high false-negative readings, especially concerning scotomas of 6° or less. With the advent of anti-vascular endothelial growth factor (VEGF) therapy and the prospect of other more potent treatments, there is an increased need for earlier detection of treatable disease and a way to quantitatively monitor its response to therapy.

Three-dimensional computer-automated threshold Amsler grid (3D-CTAG) testing improves upon the traditional paper Amsler grid by assessing central visual fields (VF) at several contrast sensitivity levels, not just one. Clinical studies have found non-invasive 3D-CTAG testing to be fast (<5 min per eye), easy (intuitive use of finger), accurate (<1°) and comprehensive. Conditions such as glaucoma, ocular hypertension, macular oedema and ethambutol-induced optic neuropathy have successfully been quantitatively characterised with this approach. These previous studies demonstrated a high reproducibility (90%) of 3D-CTAG detection of central VF defects in repeat testing.

Previous studies in AMD have shown that the central VF defects detected with 3D-CTAG testing correspond to anatomical defects seen on fluorescein angiography. To date, however, 3D-CTAG has only qualitatively (not quantitatively) characterised non-exudative (dry) and exudative (wet) AMD. What has been lacking is a quantitative index of central VF defects in AMD. 3D-CTAG testing and analysis may provide a rapid, reproducible and non-invasive test useful for screening as well as monitoring patients with AMD.

This study therefore aimed to further characterise dry and wet AMD using 3D-CTAG using both qualitative as well as quantitative assessments of central VF defects. The objective was to determine the potential utility of 3D-CTAG to screen for wet AMD as well as provide insight as to whether this test might be used to quantitatively monitor the response to therapy. It was hypothesised that 3D-CTAG would increase the sensitivity for detection of wet AMD and provide quantitative indices that would distinguish wet from dry AMD.

MATERIALS AND METHODS

Subjects

This cross-sectional study included 63 eyes of 43 patients with AMD. Eyes from age-matched controls without maculopathy (n=27) were also tested, bringing the total study population to 90 eyes in 70 subjects. Of the 63 eyes with AMD, there were 19 men (44%) and 24 women (56%), with a mean age of 77.4±10 years (values are mean±SD). Of these, 34 were diagnosed with dry AMD (mean age 75.9±9.5 years) and 29 eyes were diagnosed with wet AMD (mean age 77.7±9.9 years) (p=0.49).
Mean visual acuity (VA) in dry AMD eyes was logarithm of the minimum angle of resolution (logMAR) 0.20 (range 0.00–0.85) (Snellen 20/52), while VA in wet AMD eyes was logMAR 0.42 (range 0.00–1.60) (Snellen 20/55) (p=0.009). There were 27 control eyes without maculopathy (mean age 68.0±10.9 years) who had a mean VA of logMAR 0.12 (range 0.00–0.40) (Snellen 20/28).

All subjects were evaluated by a single Vitreo-Retinal Surgeon (JS) using physical examination and diagnostic testing (fluorescein angiography and combined optical coherence tomography (OCT)/scanning laser ophthalmoscopy (SLO)) in each case. The clinical diagnosis for study entry was clear-cut evidence of exudative disease. No questionable cases were included.

Fundus photography and fluorescein angiography were performed (Topcon Imagenet 2000; Topcon, Tokyo, Japan) to diagnose and classify each eye as dry (drusen, chorio-retinal atrophy and pigment clumping) or wet (choroidal neovascularisation with clinically significant leakage in each case) or clear-cut absence of any evidence of exudative disease. No questionable cases were included.

RESULTS

Sensitivity of 3D-CTAG

Paper Amsler grid testing revealed VF defects in 23/29 (79%) wet AMD eyes and 9/34 (26%) dry AMD eyes. Among the eyes that did not demonstrate visual defects on the traditional paper Amsler grid, 6/6 (100%) of the wet AMD eyes (p=0.03, signed rank sum test) and 5/25 (20%) dry AMD eyes (p=0.06, signed rank sum test) exhibited defects with 3D-CTAG. Tables 1 and 2 display the sensitivities for detection of dry and wet AMD using the traditional paper Amsler grid and the 3D-CTAG, respectively. Figure 1 compares the traditional paper Amsler grid and the 3D-CTAG with respect to test results in dry and wet AMD, revealing a greater detection rate of abnormal findings in wet AMD (29/29 eyes; 100%) and dry AMD (14/34 eyes; 41%) using 3D-CTAG compared with paper Amsler grid testing. Control eyes without maculopathy (n=27) did not have central VF defects on 3D-CTAG testing.

Qualitative analysis of 3D-CTAG in dry versus wet AMD

Dry AMD (figure 2) exhibited uniform (steep-walled; ie, same area of VF defect observed at all five contrast levels), cylindrical, three-dimensional defects in 12/14 (86%) eyes. Partial defects (abnormalities detected at low contrast levels that are absent at higher contrast levels) were evident in the remaining 2/14 (14%) dry AMD eyes.

Ninety-seven per cent (28/29) of wet AMD eyes displayed abnormalities at all five contrast levels. Of the 28 wet AMD eyes that had visual defects at all contrast levels, 16/28 (57%) had larger visual defects at low levels of contrast with smaller cylindrical defects at higher levels of contrast. As shown in

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Sensitivity for detection of age-related macular degeneration (AMD) with traditional paper Amsler grid testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paper Amsler grid</td>
<td>Wet AMD</td>
</tr>
<tr>
<td>Visual defects</td>
<td>23</td>
</tr>
<tr>
<td>No visual defect</td>
<td>6</td>
</tr>
<tr>
<td>Total</td>
<td>29</td>
</tr>
<tr>
<td>Sensitivity (%)</td>
<td>79</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Sensitivity for detection of age-related macular degeneration (AMD) with three-dimensional contrast threshold Amsler grid (3D-CTAG) testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>3D-CTAG</td>
<td>Wet AMD</td>
</tr>
<tr>
<td>Visual defect</td>
<td>29</td>
</tr>
<tr>
<td>No visual defect</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>29</td>
</tr>
<tr>
<td>Sensitivity (%)</td>
<td>100</td>
</tr>
</tbody>
</table>
Figure 3, these eyes had large central VF disturbances at low contrast levels (high contrast sensitivity) with a step-down progression to smaller cylindrical defects at increasing contrast levels (small central absolute scotoma with surrounding relative scotoma, or non-uniform cylindrical central VF abnormalities). VF defects in the remaining 12/28 (43%) wet AMD eyes remained cylindrical at all five tested levels (16/28 vs 12/28 p=0.45, $\chi^2$ test for equal proportions) meaning there was no increase in the area of central VF abnormalities at lower contrast levels.

Quantitative analysis of 3D-CTAG in dry versus wet AMD

One-hundred per cent of wet AMD eyes had at least one central VF defect and 14% had more than one defect. In contrast, only 41% of dry AMD eyes had a single defect, and only 5% had more than one defect. The mean number of defects observed with 3D-CTAG was 0.44±0.56 (s.d. for the upper end) and 0.44–0.44 (s.d. for the lower end) versus 1.24±0.79 for wet AMD (p<0.001, GEE).

The mean LAG, which characterises the area of the three-dimensional defect with respect to the lowest and highest contrast sensitivity levels, was 29.5 ±41.7% (s.d. for the upper end) and 29.5–41.7% (s.d. for the lower end) for dry AMD and 66.7±30.9% for wet AMD (p<0.001, GEE). The mean PAG, which characterises the area of the preserved VF with respect to the highest and lowest contrast sensitivity levels, was 36.2±47.5% (s.d. for the upper end) and 36.2–47.5% (s.d. for the lower end) for dry AMD versus 89.5±21.1% for wet AMD (p<0.001, GEE). The mean DAG, which expresses the symmetry between PAG and LAG, was 6.7±15.2% (s.d. for upper end) and 15.2–15.2% (s.d. for lower end) for dry AMD versus 22.6±26.4% (s.d. for upper end) and 22.6–26.4% (s.d. for lower end) for wet AMD (p=0.006, GEE).

Distinguishing dry AMD from wet AMD with 3D-CTAG

Univariate stepwise logistic regression analyses were performed to distinguish wet AMD from dry AMD. The results of multiple logistic regression analysis using stepwise selection are shown in table 3. There was a high specificity for the presence of a ‘step’ in wet AMD, defined as a cylindrical defect at low contrast sensitivity levels with a larger cylindrical defect at higher contrast sensitivity levels (94.1%), and the presence of more than one 3D-CTAG defect (97.1%). These findings each had a low sensitivity resulting in low predictive values. When stepwise selection was employed for wet AMD, the presence of more than one defect, the presence of a ‘step’, and a ‘hill-of-vision’ volume loss of less than 2% resulted in a high sensitivity (89.7%), specificity (85.5%), positive predictive value (83.9%) and negative predictive value (90.6%).

DISCUSSION

When compared with traditional paper Amsler grid testing, 3D-CTAG had a higher likelihood of detecting central VF abnormalities in AMD. In dry AMD the sensitivity increased from 26% to 41%, while in wet AMD it increased from 79% to 100%. This study therefore suggests that similar to the findings in glaucoma, 13 3D-CTAG increases the ability to detect VF abnormalities in AMD compared with the traditional paper Amsler grid.

3D-CTAG detected qualitative and quantitative differences in the central VF abnormalities of patients with dry AMD compared with wet AMD. In contrast to dry AMD, wet AMD displayed a larger abnormality at lower contrast levels than at higher contrast levels. Nazemi et al16 qualitatively described dry AMD central visual defects as having a steeper slope and wet AMD defects as having a shallower slope, which is consistent with our findings. However, those studies did not undertake an in-depth quantitative analysis of either dry or wet AMD. As
reported herein, the DAG (difference between the preserved area grade and the lost area grade) is a quantitative index of central VF defects that is useful in distinguishing wet AMD from dry AMD. As described, 3D-CTAG abnormalities in dry AMD characteristically presented as cylindrical defects, and thus had a DAG approaching zero. This was found in all dry AMD eyes tested. Wet AMD eyes demonstrated larger central VF defects at lower contrast levels, with a ‘step’ at intermediate and higher contrast levels. This resulted in DAG measurements in wet AMD eyes that were three-fold higher than in dry AMD eyes ($p < 0.01$).

Since this study found a positive predictive value of 83.9% and negative predictive value of 90.6%, combining the qualitative findings with quantitative indices of 3D-CTAG testing into a diagnostic algorithm for the detection of wet AMD has potential utility in screening for wet AMD in various healthcare settings. 3D-CTAG also has the benefit of ease of use with minimal technological requirements. The only task a patient is asked to perform is to trace the delineation of distortions on an Amsler grid with their index finger while maintaining fixation; a computer mouse is not involved. 3D-CTAG has the added advantage over standard-automated perimetry tests, such as the Humphrey VF analyser, of being able to utilise either central vision or peripheral vision for fixation. While it is true that AMD is likely to cause unstable fixation in standard automated perimetry devices with a central fixation marker in an otherwise isotropic hemisphere (cupola), the 3D-CTAG features the use of a rectangular screen with four distinct corners in addition to the central fixation marker. This allows the subject to maintain fixation with their peripheral, preserved vision.\(^{16}\)

In addition, 3D-CTAG is quick and non-invasive, thus mitigating a learning effect and fatigue inherent to all VF testing. This is particularly true in patients undergoing Humphrey VF testing on both eyes, with average time of testing of up to 8 min per eye.\(^ {20}\) Our average testing time per eye, including using the five contrast sensitive threshold values, was less than 5 min per eye.

A concern in VF testing for glaucoma is the masking of a defect secondary to the Troxler effect. However, in our previous study\(^{12}\) an enlarged blind spot was detected with 3D-CTAG, even though the physiological blind spot is not detected in this test. Hence, despite the usual problem with Troxler suppression of arcuate scotomas in glaucoma, we are able to

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**Table 3** Univariate logistic regression (adjusted for the correlation between eyes within patients) for wet age-related macular degeneration (AMD) using stepwise selection

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR (95% CI)</th>
<th>p Value</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Positive predictive value (%)</th>
<th>Negative predictive value (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of A/G defects</td>
<td>35.09 (2.18 to 565.1)</td>
<td>0.01</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hill-of-vision % volume lost</td>
<td>5.79 (0.003 to 9799)</td>
<td>0.64</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAG</td>
<td>1.03 (1.01 to 1.04)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAG ≥45.3</td>
<td>5.44 (1.95 to 15.18)</td>
<td>0.001</td>
<td>72.4</td>
<td>67.6</td>
<td>65.6</td>
<td>74.2</td>
</tr>
<tr>
<td>PAG</td>
<td>1.03 (1.02 to 1.04)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PAG ≥96.9*</td>
<td>3.99 (1.43 to 11.16)</td>
<td>0.008</td>
<td>69.0</td>
<td>64.7</td>
<td>62.5</td>
<td>71.0</td>
</tr>
<tr>
<td>DAG</td>
<td>1.06 (1.01 to 1.12)</td>
<td>0.03</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DAG &gt;0*</td>
<td>4.16 (1.41 to 12.27)</td>
<td>0.01</td>
<td>62.1</td>
<td>70.6</td>
<td>64.3</td>
<td>68.6</td>
</tr>
<tr>
<td>Total slope</td>
<td>1.03 (1.02 to 1.04)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LogMAR</td>
<td>14.20 (1.79 to 112.9)</td>
<td>0.01</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scotoma shape=Step</td>
<td>21.00 (2.99 to 147.6)</td>
<td>0.002</td>
<td>55.2</td>
<td>94.1</td>
<td>88.9</td>
<td>71.1</td>
</tr>
<tr>
<td>Number of defects &gt; 1</td>
<td>5.12 (0.43 to 61.69)</td>
<td>0.20</td>
<td>13.8</td>
<td>97.1</td>
<td>80.0</td>
<td>56.9</td>
</tr>
<tr>
<td>Step and &gt; 1 defect</td>
<td>20.33 (4.76 to 86.73)</td>
<td>&lt;0.001</td>
<td>66.5</td>
<td>91.2</td>
<td>86.4</td>
<td>75.6</td>
</tr>
<tr>
<td>Hill-of-vision % volume lost &gt; 0 and &lt; 2</td>
<td>9.60 (2.14 to 43.09)</td>
<td>0.003</td>
<td>51.7</td>
<td>88.2</td>
<td>78.9</td>
<td>68.2</td>
</tr>
<tr>
<td>Step and &gt; 1 defect and hill-of-vision % volume lost &gt; 0 and &lt; 2</td>
<td>51.12 (10.42 to 250.7)</td>
<td>&lt;0.001</td>
<td>89.7</td>
<td>85.3</td>
<td>83.9</td>
<td>90.6</td>
</tr>
</tbody>
</table>

*Step* indicates a cylindrical defect at high contrast levels with a larger cylindrical defect at lower contrast levels.

A/G, Amsler grid defect using 3D-CTAG; DAG, difference area grade; LAG, lost area grade; LogMAR, logarithm of the minimum angle of resolution; PAG, preserved area grade.

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\(\text{Figure 3}\) Three-dimensional contrast threshold Amsler grid (3D-CTAG) plot of central visual field abnormality in wet age-related macular degeneration (AMD). There is a non-uniform cylindrical abnormality; that is large area of abnormality at high contrast sensitivity levels with a distinct ‘step’ at lower contrast sensitivity level. This ‘step’ abnormality was found in 16/28 (51%) of eyes with wet AMD.

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\(\text{Table 3}\) Univariate logistic regression (adjusted for the correlation between eyes within patients) for wet age-related macular degeneration (AMD) using stepwise selection

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consistently find and characterise these VF defects. It appears, therefore, that all scotomas in VF areas that are represented in the visual cortex can be detected by 3D-CTAG.

Thus, future studies should be undertaken to evaluate 3D-CTAG testing in a prospective health screening setting. Future studies could also address a potential weakness of the present study, including subjects who were either normal (n=27) or had one of two diseases, that is dry (n=34) or wet (n=29) AMD, as well as not including fellow eyes from patients with bilateral pathology. A control group with similar VA but no macular disease should also be examined. Future studies might also include other maculopathies in the AMD study group. If these studies confirm the use of 3D-CTAG testing in AMD, subsequent studies could use 3D-CTAG to assess the efficacy of therapy for wet AMD. Studies might also be undertaken to compare 3D-CTAG with microperimetry, which evaluates set points in the central VF, polarisation-sensitive OCT, which has shown promise in identifying retinal pigment epithelium (RPE) disease, and preferential hyperacuity perimeter, which has similarly been shown to be superior to traditional paper Amsler grid testing.21–24

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Competing interests WF and AAS have proprietary interests in the three-dimensional computer-automated threshold Amsler grid test described in the study as patents on the technology have been issued. All remaining authors (CDR, SRB, RVJ and JS) have no proprietary or financial interest in the manuscript.

Patient consent Obtained.

Ethics approval This study was conducted with the approval of the University of Southern California Institutional Review Board, Los Angeles, California, USA.

Contributors All authors listed have been involved in the conception and design, acquisition of data or analysis and interpretation of data, drafting the article or revising it critically for important intellectual content, and final approval of the version published.

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