Replacing the Amsler Grid

A New Method for Monitoring Patients with Age-related Macular Degeneration

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Purpose: To investigate a method that uses hyperacuity, the Macular Computerized Psychophysical Test (MCPT), to evaluate the central macular visual field in patients with age-related macular degeneration (AMD).

Design: Prospective case-control study of a diagnostic test.

Participants and Controls: One hundred eight eyes of 108 Patients with AMD and 51 eyes of 51 age-matched patients with no retinal disease. Patients with AMD included 32 (30%) patients with choroidal neovascularization (CNV), 23 (21%) with geographic atrophy (GA), 35 (32%) with AMD with high-risk characteristics (HRC), and 18 (17%) with early AMD with non-HRC.

Testing: Each subject underwent the MCPT, in which a virtual line composed of dots (white dots on a black background, maximal contrast) is flashed across different macular loci to a perifoveal radius of 7°. Patients' responses were recorded and automatically analyzed using a specific algorithm developed before the onset of the study. All patients also underwent a supervised Amsler grid examination on the encounter before or after the MCPT in random order.

Main Outcome Measures: Distortion, scotoma, or blurring perceived by the patient after a swift change of fixation was considered positive on the MCPT. Any perception of distortion, scotoma, or blurring was considered positive on the Amsler grid.

Results: Of the 32 patients with CNV, 30 (94%) were found positive on the MCPT and 11 (34%) were found positive on the Amsler grid. Of the 23 GA patients, 21 (91%) were found positive on the MCPT and 7 (30%) were found positive on the Amsler grid. Of the 35 HRC patients, 28 (80%) were found positive on the MCPT and 3 (9%) were found positive on the Amsler grid, and of the 18 early AMD with non-HRC patients, 8 (44%) were found positive on the MCPT and 3 (17%) were found positive on the Amsler grid. Of the 51 controls, 3 (6%) were positive on the MCPT and 1 (2%) was positive on the Amsler grid.

Conclusions: The MCPT was superior to the Amsler grid in detecting AMD-related lesions in this cohort. Studies are underway to determine whether the MCPT is feasible for home monitoring to provide early detection of progression to CNV. *Ophthalmology 2003;110:966–970 © 2003 by the American Academy of Ophthalmology.*

Age-related macular degeneration (AMD) is a major cause of severe vision loss and of legal blindness in people older than age 65 in the Western world.[1–3] It is estimated that 18% of patients with intermediate AMD in at least one eye, and 43% of patients with advanced AMD in one eye only develop choroidal neovascularization (CNV) within 5 years.[4] CNV often results in deterioration of vision, causing 90% of all cases of severe vision loss caused by AMD.[5]

Laser photocoagulation has been proven beneficial when a well-demarcated CNV lesion is juxtafoveal or extrafoveal. The likelihood of successful photocoagulation decreases with time of diagnosis, because lesions extend toward the geometric center of the foveal avascular zone. When the lesion is subfoveal, laser photocoagulation has been proven beneficial only if the lesion is relatively small.[6–8] Photodynamic therapy with verteporfin can safely reduce the risk of vision loss in some patients with subfoveal CNV.[9–12] A greater benefit occurs in patients with smaller lesions (≤ 4 Macular Photocoagulations Study (MPS) disc areas), especially for lesions composed of occult with no classic CNV and possibly minimally classic AMD lesions.[12]

Therefore, early detection of AMD-related lesions is

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Figure 1. Photograph of a patient performing the Macular Computerized Psychophysical Test.

crucial in the management of these patients.[13,14] For this reason, patients at risk are encouraged to perform self-monitoring, often using an Amsler grid or being alert to new symptoms of metamorphopsia, visual field scotoma, blurred vision, or micropsia. The Amsler grid has previously been shown to be an unreliable tool for diagnosing central visual field defects in patients with AMD.[15–18] Although the threshold Amsler grid has been reported to show a better performance, 50% of all scotomas in the macular region still remain undetected by either one. Moreover, when scotomas of 6° or less were evaluated, the detection rate was even lower.[19] The reasons for poor performance of the Amsler grid might include the following:

1. Awareness of visual field defects is limited, with the patient frequently not being cognizant of any defect until the scotoma is considerably large and already includes central vision because of foveal involvement of the lesion. This can be partly explained by cortical completion (the "filling-in phenomenon").[16] The correlation between scotoma size and detection rate has been demonstrated by Schuchard.[19] In addition, experimental studies performed on cats and monkeys have demonstrated a direct correlation between retinal lesion size and the ability of the brain to perform completion.[20]
2. The inability to properly maintain fixation while testing the peripheral visual field.
3. The crowding effect caused by the multiple lines that are peripherally presented in the Amsler grid, causing low sensitivity of the test and adding to its poor performance.[21]
4. The noninteractive nature of the Amsler grid, rendering it unsuitable for monitoring patients, because factors such as quality of examination performance and reliability measures cannot be assessed.
5. Low compliance to perform the Amsler grid at home.

To try and address some of these shortcomings a new method using the hyperacuity function, the Macular Computerized Psychophysical Test (MCPT) was developed to evaluate the central macular visual field and potentially

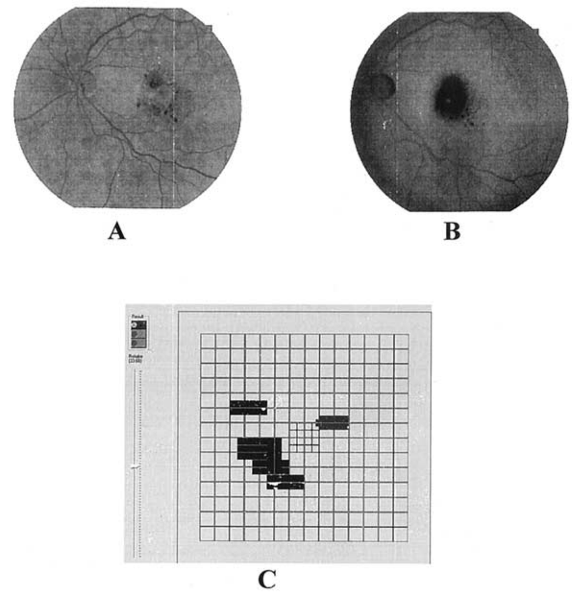

Figure 2. Demonstrates test results of a 75-year-old woman with a visual acuity of 20/80 in her left eye. Fundus examination revealed a subfoveal area of retinal pigment epithelium (RPE) elevation, more pronounced superonasal to the fovea. **A,** Early phase frame of fluorescein angiogram shows subfoveal mottled area of hyperfluoresence, more intense superonasally, with increasing hyperfluorescence in the late phase frames, **B,** compatible with the diagnosis of subfoveal choroidal neovascularization. The MCPT, **C,** demonstrates a visual field defect at a lower temporal area (corresponding to the superonasal area of intense hyperfluorescence).

provide early detection of neovascular AMD. Hyperacuity (also termed "Vernier acuity") is defined as the ability to perceive a difference in the relative spatial localization of two or more visual stimuli.[22,23] Hyperacuity threshold may be as low as 3 to 6 seconds of arc,[22,23] and the hyperacuity stimuli are highly resistant to retinal image degradation and thus suitable for assessing retinal function in patients with opaque media as well.[24,25] No systematic variation of hyperacuity threshold had been found with increasing age in a study group of patients whose age ranged from 20 to 85 years.[26] Retinal pigment epithelium (RPE) elevation, such as that which occurs in AMD, causes a shift in the regular position of photoreceptors. Hypothetically, such a shift would cause an object to be perceived at a different location from its true location in space. This perceived shift in object location recorded by the MCPT takes advantage of the human phenomenon of hyperacuity and may be, in fact, the anatomic explanation for metamorphopsia. The aim of this study was to evaluate the MCPT in patients with AMD.

Methods

The study was approved by the institutional review board, and all prospective patients signed a written informed consent to participate.

Subjects

The five study groups consisted of patients who had non-neovascular AMD without high-risk characteristics (HRC, defined as the

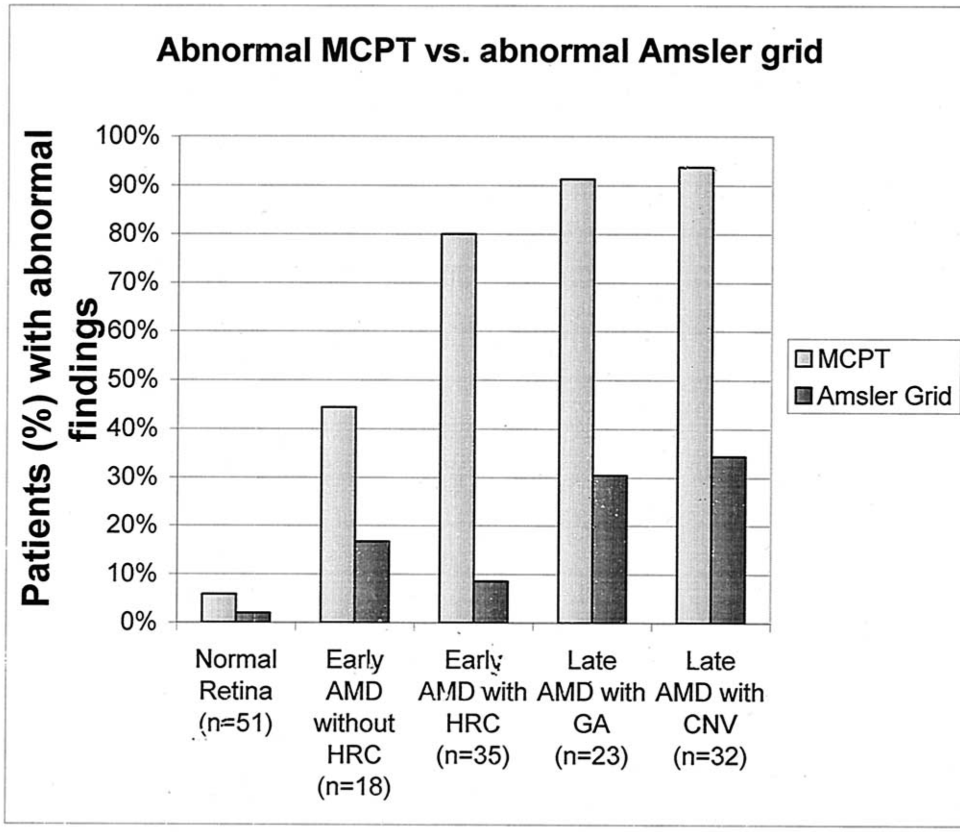

Figure 3. Comparison between detection rate of the Macular Computerized Psychophysical Test (MCPT) and Amsler grid. AMD = age-related macular degeneration; CNV = choroidal neovascularization; GA = geographic atrophy; HRC = high-risk characteristics.

presence of six or more large drusen), non-neovascular AMD with HRC, non-neovascular AMD with geographic atrophy (GA, defined as a well-demarcated area of atrophy of the RPE in which larger choroidal vessels could be seen), or neovascular AMD (defined on fluorescein angiography), all within 3000 μm from the foveal geometric center, as well as a group of patients who attended the same outpatient clinic but had no macular findings. They were all 50 years of age or older. The patients with corrected visual acuity less than 20/200, with retinal disease other then AMD or optic nerve disease, or any significant media opacity precluding a clear view of the macular area on biomicroscopy or fundus photography were excluded from the study.

Classification Protocol

The group of patients with no retinal disease were diagnosed and classified solely according to the clinical examination of a retina specialist, and some of the patients with non-neovascular AMD were diagnosed and classified solely according to the clinical examination of a retina specialist. All neovascular AMD patients were classified after confirmation of the diagnosis by fluorescein angiography that had been performed as part of standard care, not specifically for the purpose of this study. In these cases, the fluorescein angiograms were performed after the completion of study procedures.

Equipment and Methodology

The MCPT was operated on a standard PC with an ordinary mouse and keyboard. The patient or examiner generated the stimuli by bringing a cursor to a point on the screen. This task initiated a stimulus and simultaneously forced fixation (specifically, task-oriented fixation). A virtual line composed of dots (white dots on a black background, maximal contrast) appeared at random order across different macular loci to a perifoveal radius of 7°. If the virtual line is projected to a retinal lesion, the subsequent swift change of fixation by the patient enables any existing distortion, scotoma, and/or blurring to be perceived by the patient.

Any existing visual field defect was recorded immediately if the virtual line was perceived as being partly misaligned, blurry, or missing. The patient's responses were recorded and automatically analyzed by a specially developed algorithm. Flash duration alters the sensitivity of the test. For flash durations of $\geq$180 ms (the average duration for the initiation of a saccade), the dots located on a retinal lesion theoretically should be perceived as being either misaligned or missing for a short duration until the fovea refixates on the virtual line. This shift in fixation theoretically should cause the apparent movement of these dots from a misaligned position to an aligned one, thus giving the patient the perception of movement (unpublished data). For flash durations $\leq$ 180 ms, such apparent movement could be extinguished and the sensitivity of the test reduced as the flash duration is decreased.

Figure 1 shows an example of a patient performing the MCPT. Using a PC mouse, patients were instructed to click on a central dot, after which a virtual line was seen on the screen. Task-oriented fixation was incorporated to try to eliminate the tiresome need for continuous fixation. When misaligned/missing dots were perceived, the patient marked them on the screen by using the keyboard or the mouse. The algorithm developed was used to

Table 1. Macular Computerized Psychophysical Test and Amsler Grid Test Results Stratified by Groups

	Macular Computerized Psychophysical Test	Amsler	No. of Patients	*P* value*
Controls	P	P	0	
	N	N	47	
	P	N	3	
	N	P	1	
			51	0.32
Early AMD, no HRC	P	P	3	
	N	N	10	
	P	N	5	
	N	P	0	
			18	0.02
Early AMD with HRC	P	P	3	
	N	N	7	
	P	N	25	
	N	P	0	
			35	<0.0001
GA	P	P	7	
	N	N	2	
	P	N	14	
	N	P	0	
			23	<0.0001
CNV	P	P	11	
	N	N	2	
	P	N	19	
	N	P	0	
			32	<0.0001

*McNemar's test.
AMD = age-related macular degeneration; HRC = high-risk characteristics; N= negative; N N = No. of patients with negative findings in both tests; N P = No. of patients with negative findings in the MCPT and positive findings in the Amsler grid; P = positive; P N = No. of patients with positive findings in the MCPT and negative findings in the Amsler grid; P P = No. of patients with positive findings in both tests; .

Table 2. Sensitivity, Specificity, Positive Predictive Value, and Negative Predictive Value Calculated for Each of the Age-Related Macular Degeneration Groups for both the Amsler and Macular Computerized Psychophysical Test

	Macular Computerized Psychophysical Test			Amsler Grid	
Early AMD, no HRC	D+	D−		D+	D−
T+	8	3	T+	3	1
T−	10	48	T−	15	50
Sensitivity	44.44%			16.67%	
Specificity	94.12%			98.04%	
PPV	72.73%			75.00%	
NPV	82.76%			76.92%	
Early AMD with HRC	D+	D−		D+	D−
T+	28	3	T+	3	1
T−	7	48	T−	32	50
Sensitivity	80.00%			8.57%	
Specificity	94.12%			98.04%	
PPV	90.32%			75.00%	
NPV	87.27%			60.98%	
GA	D+	D−		D+	D−
T+	21	3	T+	7	1
T−	2	48	T−	16	50
Sensitivity	91.30%			30.43%	
Specificity	94.12%			98.04%	
PPV	87.50%			87.50%	
NPV	96.00%			75.76%	
CNV	D+	D−		D+	D−
T+	30	3	T+	11	1
T−	2	48	T−	21	50
Sensitivity	93.75%			34.38%	
Specificity	94.12%			98.04%	
PPV	90.91%			91.67%	
NPV	96.00%			70.42%	

AMD = age-related macular degeneration; CNV = choroidal neovascularization; D+ = with AMD; D− = without AMD;
GA = geographic atrophy; HRC = high-risk characteristics; T+ = the test result was positive; T− = the test result was negative. PPV = Positive Predictive Value; NPV = Negative Predictive Value.

automatically analyze patient's responses, perform verification of indistinct areas, and delineate the disease stage.

Although RPE elevation could be both part of non-neovascular AMD (caused by drusen) or neovascular AMD (caused by fibrovascular elevation of the RPE), the elevation usually should be different in magnitude. Therefore, different threshold sensitivities should be used to differentiate among different disease stages.

Technicians conducted most of the test sessions. In addition, to study the patient's own performance, a subset of 36 (33%) randomly chosen AMD patients conducted the test independently after undergoing brief training in its use. The test was performed on a standard PC screen, 1024 horizontal, 768 vertical with the patient's own near correction, and at a distance of 0.5 m. Each subject also underwent a supervised Amsler grid examination in which the perception of distortion, scotoma, or blurring was considered positive. One hundred fifty-nine eyes of 159 consecutive patients were examined at the Tel-Aviv Medical Center and Maccabi Eye Institute, Tel-Aviv, Israel.

Statistics

The statistical analysis was performed using the JMP (SAS) program. McNemar's test was used to examine statistically significant association.

Results

In this pilot study, 108 eyes of 108 AMD patients and 51 eyes of 51 control patients with no retinal disease were examined. Ninty-four (60%) were women. Average age was 74 years, (median, 75; range, 52–101). Of the four groups of AMD patients, 32 (30%) had CNV (see example in Figure 2), 23 (21%) had GA, 35 (32%) had early AMD with HRC, and 18 (17%) had early AMD without HRC. The average visual acuity was 20/50 (median, 20/50; range, 20/20–20/120) in the CNV group, 20/40 (median, 20/40; range, 20/25– 20/200) in the GA group, 20/40 (median, 20/50; range, 20/20–20/120) in the early AMD with HRC group, 20/40 (median, 20/40; range, 20/20–20/75) in the early AMD without HRC group, and 20/40 (median, 20/40; range, 20/20–20/120) in the control group.

The comparison between the detection rate of AMD-related lesions using the MCPT and the Amsler grid is shown in Figure 3. The MCPT was positive in 30 patients (94%) with CNV, 21 (91%) with GA, 28 (80%) with HRC, and 8 (44%) with early non-HRC AMD. The Amsler grid was positive in 11 patients (34%) with CNV, 7 (30%) with GA, 3 (9%) with HRC, and 3 (17%) with early non-HRC AMD. Differences in detecting AMD-related lesions ranged from 0.32 in normal patients to <0.001 in early AMD with

HRC, CNV, and GA (Table 1). Of the 51 control eyes, 3 (6%) were positive on the MCPT and 1 (2%) was positive on the Amsler grid. The time to complete the MCPT was approximately 4 minutes when conducted by a technician and about 3 minutes when carried out by patients. Table 2 outlines the sensitivity, specificity, positive predictive value, and negative predictive value for each of the AMD subgroups, for both the MCPT and the Amsler grid.

Discussion

In this study, the MCPT had a greater positive predictive value and sensitivity compared with the Amsler grid in detecting AMD-related lesions. The algorithm produced an online automatic analysis and provided a real-time objective result according to the patient's responses. Moreover, the results confirmed the observations of others regarding the poor validity of the Amsler grid in detecting the neovascular form of AMD.[14,15]

The study has few limitations: the technician was aware of the diagnosis of the tested eye, the method of diagnosis was not consistent (it consisted of color photos performed only in some of the patients with non-neovascular AMD and of fluororescein angiography only in cases of neovascular AMD), and visual acuity examinations were not standardized. A multicenter study is underway to address these limitations. The false-positive rate in the two methods is relatively low and similar. The somewhat higher false-positive rate found in the MCPT might have been due to the suprathreshold sensitivity in which the MCPT was performed.

This study did not differentiate MCPT results between the examined test groups. Although the results indicate differences among the tested groups, validation of the ability of the MCPT to differentiate between groups awaits further studies, which are currently in progress.

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