FUNCTIONAL AND MORPHOLOGIC BENEFITS IN EARLY DETECTION OF NEOVASCULAR AGE-RELATED MACULAR DEGENERATION USING THE PREFERENTIAL HYPERACUITY PERIMETER

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Purpose: To estimate the usefulness of preferential hyperacuity perimetry (PHP) in detecting conversion of early to late age-related macular degeneration in the Carotenoids and co-antioxidants in patients with Age-Related Maculopathy, a multicenter randomized controlled clinical trial.

Methods: This was a nested case control study within the Carotenoids and co-antioxidants in patients with Age-Related Maculopathy (CARMA) clinical trial and included all participants enrolled in a single center (n = 200). Data are from participants who progressed to neovascular age-related macular degeneration (nvAMD) during time on study, Group 1 (n = 10) before the use of PHP and Group 2 (n = 10) during use of PHP. We also randomly selected 21 other participants (Group 3) who did not progress to nvAMD during time on study as a control group. Change in best-corrected visual acuity and contrast sensitivity and size of neovascular lesion at detection of conversion to nvAMD in Groups 1 and 2.

Results: At detection of nvAMD, mean best-corrected visual acuity in Group 1 was 57.5 letters versus 67.4 in Group 2. In Group 1, the change in best-corrected visual acuity from baseline to detection of nvAMD was twice that of Group 2 (21.6 ± 9.0 versus 11.9 ± 10.7) with a mean difference of 9.7 letters (95% confidence interval, 0.41 to 19.0, P = 0.04, independent-samples t-test). The size of the neovascular lesion at detection was 3.06 mm² in Group 1 versus 0.89 mm² in Group 2 (P = 0.02). Two thirds of the participants in Group 2 were asymptomatic at detection of nvAMD compared with one fifth in Group 1. Preferential hyperacuity perimeter distortion maps were abnormal in 9 of 10 eyes in Group 2, which were confirmed by optical coherence tomography. Of the 21 eyes in Group 3, PHP maps were normal in 18 and abnormal in 3.

Conclusion: Preferential hyperacuity perimetry detected abnormalities in central visual function with high reliability. Eyes with nvAMD lesions detected by PHP had smaller lesions and better function when compared with the group before the introduction of PHP. The false-negative rate was <10% on PHP. The PHP distortion map was helpful in alerting clinicians to the presence of subclinical nvAMD.

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The development of neovascularization when not involving the foveal center can go unrecognized by patients particularly when the fellow eye remains unaffected by late age-related macular degeneration (AMD). Intuition and clinical experience suggest that treatment when provided early particularly if the neovascular AMD (nvAMD) lesions are small and appear before the onset of fibrosis will yield the best functional outcomes. In the present era, new therapies have emerged that preserve and improve visual function by reapposition of the tissue layers separated by exudative pathology. As this occurs through
restoration of competence to previously leaking blood vessels, the early detection of the neovascular lesion is even more important as once disorganization of the retinal cellular and photoreceptor mosaic has occurred, lost visual function cannot be restored. It has been noted that even when patients are aware of subtle abnormalities of central vision, few seek specialist advice immediately after onset of their symptoms. Thus, there is a need for both patient education and for a specific and sensitive monitoring test that can be applied in the home setting that can indicate the onset of nvAMD.

The preferential hyperacuity perimeter (PHP) is one such device. It has been shown to detect choroidal neovascularization with a sensitivity twice as high as the Amsler grid a chart-based visual screening system. The PHP exploits the ability of the human visual system to perceive even minute differences in the relative localization of two objects in space, a phenomenon termed hyperacuity. When there is separation of the retinal layers through breakdown of the blood retinal or blood retinal pigment epithelial barriers, distorted vision is the consequence. Through presentation of lines with artificial distortions (ADs) of different intensities on the PHP, the presence of a real distortion in the patient’s central visual field can be detected as the brain ignores the smaller deviation when a larger one is introduced. While the PHP has been used to confirm its value in known cases of nvAMD, to date there have been no studies that have tested its ability to detect the earliest lesions on conversion from early to late AMD.

The Carotenoids and co-antioxidants in patients with Age-Related Maculopathy study participants at every study visit had both these tests undertaken at every visit on study eyes.

**Materials and Methods**

**Patient Demographics and Study Procedures**

In the Belfast site, 200 patients with late AMD in 1 eye only or intermediate AMD in both eyes were enrolled between June 2004 and March 2007. Participants were randomly assigned to receive an oral preparation of either antioxidants or placebo. The eligibility criteria and the Carotenoids and co-antioxidants in patients with Age-Related Maculopathy clinical trial protocol has been published. A portfolio of tests of functional and morphologic outcomes including best-corrected visual acuity (BCVA), contrast sensitivity (CS), photopic interferometric acuity, shape discrimination testing, Raman spectroscopy, and stereoscopic fundus photography were performed at every study visit.

Color fundus images captured on a Topcon TRC EX Fundus camera (Topcon, Newbury, UK) from all Carotenoids and co-antioxidants in patients with Age-Related Maculopathy study participants at every study visit were systematically graded to detect features of early and/or late AMD based on the Wisconsin age-related maculopathy grading system. Grading was performed on anonymized digital images, which were displayed on screen using a specially designed grading platform (EyeQPro; Digital Healthcare Ltd, Cambridge, United Kingdom). If subretinal fluid, visible choroidal neovascularization, pigment epithelial detachment, hemorrhage, and/or exudate were detected, a diagnosis of nvAMD was made and an estimate of lesion size was obtained by outlining the lesion components of visible
choroidal neovascularization, pigment epithelial detachment, and contiguous hemorrhage.

**Preferential Hyperacuity Perimetry**

Preferential hyperacuity perimetry was included in the portfolio of tests between October 2006 and April 2008. When PHP data were missing, this was either because of inability of the participant to undertake the test or because the participant did not wish to take the test owing to constraints on their time. The PHP test is based on the principle that visual attention is attracted to the most prominent stimulus as the brain ignores other stimuli if these are substantially smaller.\(^2\)\(^3\)\(^4\) It is used to identify and quantify the size of a pathologic distortion (PD), resulting from macular pathology. Depending on the magnitude of the AD, the patient may perceive only the AD (if there is no PD or if the PD is small), only the PD (if the AD is small), both the AD and the PD (if the two are equivalent in size), or neither (if the AD falls on a region of scotoma). Preferential hyperacuity perimetry was performed on the commercially available equipment (ForeseePHP 2.05; provided courtesy of Notal Vision Ltd, Tel Aviv, Israel). The instrument has a chin rest at a fixed distance from a touch-sensitive screen. The rest is adjusted so that the eyes are perpendicular to the center of the screen. Trial frames are used to provide the appropriate refractive correction for a distance of 50 cm and to occlude the fellow eye. Lines with AD are projected onto the touch-sensitive screen.

A stimulus–response cycle starts with the display of a central dot on the screen, which is the point for gaze fixation. The stimulus, comprising a horizontal (or vertical) series of dots where some of the dots are misaligned to create an AD, is then flashed for a short duration on the display. The examinee responds by marking the location where the distortion was perceived on the screen. If the eye being tested has a macular lesion, the patient’s own PD acts as a competitive stimulus to the AD. If the signal stimulus coincides with the projected retinal lesion, the examinee may perceive distortion, scotoma, and/or blurring of part of the signal stimulus instead of (or in addition to) the AD. The standardized protocol for PHP testing includes an explanatory tutorial followed by a trial run. When the examiner is satisfied that the examinee has understood the procedure, the test starts. The entire process including the tutorial takes around 20 minutes.

The test progresses with a succession of stimuli with different AD sizes, presented to cover the central 14° of the visual field, at a spatial resolution of 0.75°. By altering the magnitude of the AD, the system calculates the relative magnitude of the perceived pathology. A cluster of abnormal responses indicates the existence of a functional abnormality and at the end of the test, the collection of responses is automatically compiled to produce a 2-dimensional map of the visual field (Figure 1).

The PHP output report provides the following information:

- An overall reliability score and predetermined acceptability threshold.
- A hyperacuity deviation map displaying a spatial representation of metamorphopsia visual field defects.

Patients were supervised during administration, and the test was repeated if the reliability statistic was below the acceptable threshold.

**Optical Coherence Tomography**

Tomographic testing was undertaken on the Stratus OCT 3 (Carl Zeiss Meditic, Inc, Dublin, CA). All participants were imaged using a 6-mm linear cross-hair pattern centered on the fovea and a fast macular thickness map consisting of 6 linear B scans, in an asterisk pattern spaced 30° apart, each B scan consisting of 512 A scans, 6 mm in length. The captured OCT scans were scrutinized for the presence of pigment epithelial detachments, subretinal or intraretinal fluid, and/or thickening of the outer high-reflectivity band indicating the presence of neovascular tissue.

**Data Management**

Best-corrected visual acuity (BCVA), CS, and AMD severity grading were available for study visits (planned or unscheduled). Data are from three separate groups of patients: Group 1 (n = 10) developed neovascular AMD between June 2004 and October 2006 before PHP testing was introduced. Group 2 (n = 10) developed neovascular AMD after October 2006 but before April 2008. New-onset neovascular AMD was defined as the presence of blood, subretinal fluid, exudate, neovascular membrane, and/or pigment epithelial detachment in the macular retina in an eye previously free of neovascularization. Preferential hyperacuity perimetry and OCT outputs at a visit before conversion and at conversion were available for all but one participant in this group. Group 3 (n = 21) randomly selected participants who were classified by the photographic reading center as showing no progression to neovascular AMD during time on study. Preferential hyperacuity perimetry and OCT outputs were available at the exit visit for all the participants in this group.
Statistical Analysis

No sample size calculations were performed as this was an opportunistic study superimposed onto an existing controlled clinical trial. Data pertaining to BCVA, CS, and lesion area sizes that were collected at every study visit were analyzed using the Statistical Packages for Social Sciences (SPSS Version 15; SPSS, Business Analytics, IBM UK, Middlesex, United Kingdom). Changes in BCVA and CS from baseline to the point in time when detection of nvAMD occurred were analyzed by the independent-samples t-test. The difference in nvAMD lesion area between Groups 1 and 2 was analyzed using nonparametric tests (Mann–Whitney U test).

Results

Functional Outcomes

Table 1 shows the average BCVA and CS in study eyes for all 3 groups at baseline and also when conversion to nvAMD was detected in Groups 1 and 2 and those recorded at the final visit in Group 3.

Baseline average BCVA and CS were identical between study eyes in the 3 groups (Table 1). When conversion to nvAMD was detected, study eyes in Group 1 had worse BCVA (57.5 ± 10.6 letters) compared with those in Group 2 (67.4 ± 12.9 letters), a difference of approximately 10 which is the equivalent of 2 Early Treatment Diabetic Retinopathy Study lines.

The mean change in BCVA from baseline to the point in time when detection of nvAMD was documented was larger in Group 1 (21.6 ± 9.0) when compared with that of Group 2 (11.9 ± 10.7) with a mean difference of 9.7 letters (95% confidence interval, 0.41 to 19.0, \(P = 0.04\), independent-samples t-test).

Mean CS at nvAMD detection was also worse in Group 1 (22.7 ± 9.0) compared with Group 2 (29.1 ± 3.3). The mean fall in CS letters from baseline to nvAMD detection was 9.9 in Group 1 versus 2.7 in Group 2, representing a mean difference of 7.2 letters between groups (\(P = 0.15\), 95% confidence interval, 1.6 to 12.8).

In Group 3 participants who did not convert to nvAMD during time on study, there was no change in mean visual acuity or CS between baseline and the final visit.

Morphologic Outcomes

In Group 1, the reading center recorded the presence of a visible nvAMD lesion in fundus images of 9 of the
10 eyes with 7 graded as having subfoveal involvement. In Group 2, a visible nvAMD lesion was reported by the reading center in 7 of the 10 eyes of which only 4 were classified as having a subfoveal lesion.

The mean area of the visible neovascular lesion was statistically significantly larger at 3.06 ± 0.89 mm² in Group 1 compared with 0.89 ± 1.14 mm² in Group 2 ($Z = -2.269, P = 0.023$).

**Preferential Hyperacuity Perimetry and OCT outcomes and comparisons**

Group 1 participants had never been monitored with the PHP. Preferential hyperacuity perimetry was available on 9 of 10 participants in Group 2 and an abnormal profile consistent with metamorphopsia was detected in all these. Symptoms of distortion and central blurring had been reported by 5 of the participants in Group 2. In the remaining 5, the study team had been alerted to the conversion to nvAMD by the abnormal PHP. Tomographic features of nvAMD were found in 6 participants in Group 2. In the remaining 3 participants, OCT scans were normal at the time when distortion was first demonstrated on the PHP. Repeat OCT testing carried out at a subsequent visit scheduled within 6 weeks of detection of the metamorphopsia on PHP revealed the presence of fluid in the macular tissue compartments in all 3 of these cases. Figures 1 and 2 demonstrate fundus findings, OCT morphology, and PHP in a representative case from Group 2.

Of the 21 eyes randomly selected from Group 3, 18 had normal PHP outputs. Three showed minor

<table>
<thead>
<tr>
<th>Group 1 (n = 10) (usual care)</th>
<th>Baseline Letters Read</th>
<th>Letters Read at Conversion or at Final Visit</th>
<th>Change in BCVA</th>
<th>CS at Baseline</th>
<th>CS at Conversion</th>
<th>Change in CS</th>
<th>Lesion Area (Disk Areas)</th>
</tr>
</thead>
<tbody>
<tr>
<td>79.1 ± 3.99</td>
<td>57.5 ± 10.6</td>
<td>-21.6 ± 9.01</td>
<td>32.9 ± 3.1</td>
<td>22.6 ± 9.01</td>
<td>-9.89 ± 7.87</td>
<td>3.06 ± 3.2</td>
<td></td>
</tr>
<tr>
<td>Group 2 (n = 10) (PHP monitored)</td>
<td>79.3 ± 5.46</td>
<td>67.4 ± 12.9</td>
<td>-11.9 ± 10.7</td>
<td>31.8 ± 2.78</td>
<td>29.1 ± 3.35</td>
<td>-2.70 ± 2.9</td>
<td>0.89 ± 1.1</td>
</tr>
<tr>
<td>Group 3 (n = 21) (control)</td>
<td>82.7 ± 9.06</td>
<td>81.8 ± 9.6</td>
<td>-0.95 ± 3.0</td>
<td>32.0 ± 3.79</td>
<td>33.9 ± 3.99</td>
<td>-1.91 ± 3.92</td>
<td>NA</td>
</tr>
</tbody>
</table>

NA, not applicable.
Changes suggestive of metamorphopsia, but these had been considered by the clinical team to be insignificant. In all these 3 cases, repeat OCT testing and fundus imaging confirmed absence of nvAMD and the presence of drusen corresponding to the PHP distortion map.

Discussion

The present study found that Group 2 participants who were monitored with the PHP had conversion to nvAMD detected at a much earlier stage than Group 1 participants. At detection, BCVA in Group 2 was statistically significantly better than that in Group 1. Furthermore, the fall in BCVA from baseline was 4 lines in Group 1 compared with 2 lines in Group 2. Also, better mean CS at detection and smaller falls in this parameter were observed in eyes in Group 2 when compared with eyes in Group 1. However, these differences did not reach statistical significance owing to the small sample size and the wide confidence limits for this parameter. In terms of nvAMD lesion detection, it was notable that the independent reading center estimations of the size of the neovascular lesion also confirmed that lesions were smaller in Group 2 compared with Group 1 and that involvement of the fovea was also less likely in the former compared with the latter. All these findings support the view that distortion was unmasked by the PHP, allowing earlier detection of conversion to nvAMD.

However, the present study has many limitations. The Amsler grid, the currently accepted screening tool for monitoring conversion to nvAMD, was not used as a comparator in the present study. The testing of the PHP device was added to the study protocol approximately 1 year after the study had begun. The number of participants who converted to nvAMD during time on study was small and grading of lesion size was performed on color images and not fluorescein angiograms. Nonetheless, the strengths of the present study include its longitudinal design and the documentation of both functional and morphologic beneficial effects at the point of detection of nvAMD through the use of a potential screening tool.

The PHP is a device that has been developed and used to unmask distortion associated with neovascular diseases affecting the macula of the eye. The PHP research group has already shown that the device is capable of detecting nvAMD with a sensitivity of 82% and that it differentiated eyes with nvAMD from those with intermediate AMD (high-risk drusen) with a specificity of 88%. In a further study of 179 participants who were assigned to 5 groups based on ocular characteristics (healthy macula [Group 1], small drusen [Group 2], large drusen [Group 3], geographic atrophy [Group 4], and nvAMD [Group 5]), it was shown that 100% of Group 5 had an abnormal distortion map on the PHP while only 53% of the same group had a positive result on Amsler testing. While a series of small studies from a variety of investigators support the findings of superior sensitivity of the PHP in the detection of nvAMD and other conditions with exudative manifestations when compared with the Amsler, most have not found improved specificity for the former when compared with the latter.

It is worth noting that all the studies undertaken to date including those by the PHP users group have used a cross-sectional design to determine whether the distortion maps reflect the severity and type of macular disease. On the contrary, the present study was linked to an ongoing clinical trial where patients were being monitored for progression to late AMD. Thus, we exploited the longitudinal follow-up design in an opportunistic manner to determine whether PHP could unmask functional deficits before the onset of symptoms. Our findings of better distance acuity and CS at the point of detection of nvAMD in the PHP-monitored group suggest that the distortion maps reflected subtle and subclinical visual deficits before the onset of overt sight loss. It is noteworthy that mean BCVA at detection of nvAMD in Group 1 was 57 letters (approximately 20/80 Snellen), which is consistent with the baseline visual acuity reported in many clinical trials and studies that have enrolled patients with nvAMD. By contrast, the mean BCVA in Group 2 was 10 letters better equivalent to 2 extra lines of acuity.

Functional vision is clearly dependent on retinal morphologic integrity. Therefore, it is intuitive that restoration of retinal morphology by treating the exudative manifestations of nvAMD before the onset of permanent structural damage will yield best functional results. The need for early detection is even greater now given the unequivocal demonstration of the efficacy of treatments using antibody inhibitors of vascular endothelial growth factor. It is recognized that at initial presentation there is a wide range of functional and morphologic severity of macular disease in patients with nvAMD. In the Choroidal Neovascularization Prevention Trial (CNVPT) study consisting of persons with intermediate AMD who were monitored longitudinally with regular assessments, two thirds of eyes had a presenting visual acuity worse than 20/40 at the time of detection of neovascularization. Furthermore, in one-half of those who developed nvAMD, the lesion was ≥2 disk areas. Thus, despite awareness of the risk of nvAMD in the CNVPT study, the majority of patients presented at a point in the natural history where, even if...
the patient does experience an improvement of some 15 letters following optimal treatment, the risk of residual vision loss remains high. By contrast, in the present study, the use of the PHP allowed us to detect the onset of neovascularization at a point in time when acuity was Snellen 20/40 or better and with nvAMD lesions <1 disk area on average. We therefore contend that the PHP is a promising device and merits further testing within a randomized controlled clinical trial comparing it with usual care.

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**References**