Dissociation of Visual Deficits in Ocular Hypertension

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Both acquired color vision deficiencies and abnormal pattern electroretinograms (PERGs) are observed in patients with ocular hypertension (OHT) as well as in patients with glaucoma. In the present study we determined the prevalence of both of these functional deficits in a large group of OHT patients (N = 130). Color vision was tested with the desaturated D-15 and a color confusion score was used to quantitatively assess the magnitude of the color vision deficiency. Steady-state PERGs were evoked with rapidly alternating high contrast checkerboard patterns. Color vision deficits were detected in 23% of OHTs while 11.5% of the patients exhibited significant PERG amplitude reductions. Only 2.3% exhibited both abnormalities. The results suggest that although color vision deficiencies and PERG abnormalities are both evident in OHT, they are often dissociated findings.


There have been significant improvements in the medical and surgical treatment of glaucoma during the last decade but there has been less progress in developing techniques for the early detection of the disease.1-4 Currently, patients usually are treated once there is evidence of nerve fiber loss (eg, a characteristic visual field defect or progressive cupping of the optic disc). In this regard patients with elevated intraocular pressure, a condition which often precedes glaucoma, present a particular challenge since accurate prediction of the patients with ocular hypertension (OHT) who will develop the disease might permit treatment prior to irreversible glaucomatous nerve fiber damage. At present, however, routine prescription of medical treatment for all ocular hypertensives is inappropriate because a relatively small percentage of these patients eventually develop glaucoma.5 As a consequence, better methods for detecting subtle changes in visual function that presage the clinical manifestations of glaucoma are being actively sought.

Many visual abnormalities are more prevalent in patients with either glaucoma or ocular hypertension than in age-matched, visually normal individuals.6-13 However, it is unclear whether the OHT patients who exhibit these functional deficits are prone to develop glaucoma. Only color vision deficits have been demonstrated to precede visual field loss in prospective studies of patients developing glaucoma,10 but many primary open-angle glaucoma (POAG) patients do not exhibit abnormal color vision while the percentage of OHT patients with color vision deficits exceeds the proportion expected to develop POAG.10-13

Because the pattern electroretinogram (PERG) is a retinal biopotential which is thought to reflect the physiological integrity of the retinal ganglion cells,14-15 this technique also has been proposed as a means for monitoring early glaucomatous optic nerve damage.16 Our previous studies,17-18 along with the results of others,19-21 have shown that a significant reduction in the amplitude of the pattern ERG is observed in glaucoma patients. We have also shown18,22 that pattern ERG amplitude is reduced in some OHT patients, but it has not been established that these patients will develop glaucoma. The aim of this investigation was to determine whether individual OHT patients exhibit both color vision and PERG deficits, and, if so, whether these functional disturbances are associated pathophysiologically.

Materials and Methods

One hundred and thirty patients with ocular hypertension were studied. Each patient underwent a complete ophthalmic examination that included visual acuity and refraction, applanation tonometry (Goldmann, Haag-Streit, Bern, Switzerland), gonioscopy, automated perimetry (Humphrey Instruments, San Leandro, CA; 30-2 with Statpac), funduscopy, automated perimetry (Humphrey Instruments, San Leandro, CA; 30-2 with Statpac), funduscopic examination and optic disc photography (X2). The patients were recruited for the study if they met the following inclusion criteria: (1) a history of elevated IOP (the average IOP on three consecutive visits ex-
ceed 21 mm Hg), in the presence of an anatomically open angle; (2) a normal visual field; (3) a visual acuity of 20/30 or better; and (4) an ophthalmic examination that was otherwise normal.

The visual fields were evaluated by a committee of glaucoma specialists who had no knowledge of the PERG and color vision results. The committee evaluated the visual fields taking into account the gray scale, as well as the Humphrey Statpac total deviation and pattern deviation values. Visual fields were considered abnormal if there were either: (1) one or more points with a $P$-value $< 0.005$; or (2) two or more points with a $P$-value $< 0.01$; or (3) four or more points with a $P$-value $< 0.02$. In instances where no points fell below the $P < 0.05$ cutoff, the visual fields were considered normal. Visual fields which failed to meet any of the above criteria were considered indeterminate and submitted to the committee for final arbitration. Optic disc excavation was determined from an examination of the color-stereo photos by members of the same committee and mean vertical cup-disc ratio (by color) was used to quantify cupping. The OHT group ranged between 42 and 75 years of age (mean 58.7 ± 8.4).

Sixty-eight individuals who volunteered for the study served as controls; 54 underwent color vision testing, PERGs were recorded on 47 and 33 received both tests. Each of the control subjects also received a complete ophthalmic examination to rule out ocular disease and only the data from eyes with 20/30 or better visual acuity were included in the analysis. The control subjects ranged from 37 to 77 years of age (mean 58.9 ± 9.6 years). All participants in this study were volunteers who gave their informed consent prior to testing.

Color vision was evaluated with the desaturated D-15 test.23 Color vision data were obtained from both eyes of each participant but only the results from a single eye (chosen randomly unless only one eye met the inclusion criteria) were included in the analysis. A MacBeth (Kroll-Morgan Co., Newburgh, NY) easel lamp (standard illuminant C) was used in all cases and no time limit was imposed. A color confusion score (CCS) was used to quantify the D-15 results. The desaturated D-15 was scored by calculating the cumulative distance (in uniform color space) between contiguous caps. From this the CCS was generated by determining the ratio of the actual cumulative distance for any subject to the minimum possible distance (ie, a perfect score) and expressing this value as a percentage.23 Using this metric, the greater the deviation from a perfect score the higher the CCS.

PERGs were recorded using the DTL microfiber electrode24 inserted in the lower fornix and running from the medial to the lateral canthus. A Ag-AgCl EEG electrode, placed adjacent to the lateral canthus served as reference. A similar electrode attached to the forehead provided the ground. The PERGs were differentially amplified (80k), bandpass filtered (1.0–30.0 Hz), recorded over 150 msec epochs and signal averaged (250 repetitions) using a Nicolet MED-80 computer (Nicolet Instrument Co., Madison, WI). A high contrast (76%) black-white checkerboard pattern with a photopic space-averaged luminance (40 cd/m$^2$) was generated on a television monitor. The entire checkerboard array subtended 10° by 12° at the 1 m viewing distance. Four different check sizes (0.25°, 0.5°, 1.00° and 2.00°), each counterphasing at the same temporal frequency (16.0 rps), were used to evoke steady-state PERGs. Each stimulus condition was repeated twice in every testing session, using a randomized block design. The resulting PERG waveforms were averaged off-line. During testing patients wore their habitual distance correction fit with a plus 1 diopter spherical correction to compensate for the test distance.

Results

The color confusion score (CCS) was used to quantify the D-15 results for both the control group and the OHT patients (Fig. 1). There was a large overlap in the distribution of the CCSs for the two groups, but the distributions were significantly different (Mann-Whitney, $U = 2614$, df = 184, $P < 0.01$). Mean CCS for the OHT patients was 44.17, mean CCS for the control group was 25.97 and a large proportion of the OHT patients (23%) deviated from the control group mean by 2.0 standard deviations or more. This group was defined, therefore, as having
abnormal color vision. There was no significant difference in either age, IOP or C/D ratio between the patients with normal and abnormal color vision.

Steady-state PERGs were obtained for each of the four check sizes and the N1-P1 amplitude was determined for each response (Fig. 2). In the control group mean PERG amplitude was maximum for the 0.5° checks and decreased for both larger and smaller checks (Fig. 3). A similar trend was apparent for the OHT patients, although PERG amplitude was lower for all four check sizes (Fig. 3). Furthermore, low amplitude responses (at least 2.0 standard deviations below the control group mean) were evident for many of the OHT patients (11.5%). The significance of this between-group difference was confirmed with an analysis of variance (F = 4.13, df = 1/175, \( P < 0.05 \)). Post-hoc analysis (Table 1) revealed that the significant ANOVA was primarily due to a between-group difference for the 1.0° checks (Fig. 4). No significant difference in either age, IOP or C/D ratio was evident between the OHT patients with normal and abnormal PERGs.

To evaluate the association between the color vision and PERG results in patients with OHT, we first examined the correlation between CCS and PERG amplitude (Fig. 5) using the 1.0° checks since they provided optimal discrimination between the OHT patients and the controls. No significant correlation was found (Spearman, \( R = -0.167, df = 130, P > 0.05 \)). This analysis also revealed that none of the patients with abnormal color vision exhibited significant PERG amplitude reductions (more than 2.0 standard deviations below the control group mean) for this check size. Further analysis of the data for all check sizes revealed no significant difference in PERG amplitude between the two subgroups (ANOVA, \( F = 1.47, df = 1/128, P > 0.05 \)), while the percentage of PERG abnormalities was essentially identical for the patients with normal (11%) and with abnormal color vision (13%). It is also noteworthy that 23% of the OHT patients had an acquired dyschromatopsia, 11.5% had reduced PERG ampli-
tudes, but only 2.3% of the patients exhibited both abnormalities.

Discussion

Color vision, contrast sensitivity, temporal resolution and visual evoked potential abnormalities are often observed in both glaucoma patients and ocular hypertensives, but the prevalence of these deficits in OHT patients typically exceeds the predicted frequency of conversion to POAG. These findings clearly indicate that there are many subtle changes in visual functioning associated with OHT, but they also demonstrate that the presence of these functional deficits is, at best, equivocal evidence that the patient is at an increased risk of developing POAG.

The mean CCS is greater for the OHT patients than for the age-matched controls, indicating that color vision is poorer among OHT patients. Using a non-parametric analysis of the CCS distribution we observed a statistically significant difference between the OHT patients and the age-matched normals with 23% of the patients in our sample exhibiting significant deficits. Adams and coworkers tested glaucoma patients, glaucoma suspects and age-matched normals with the desaturated D-15 and observed a 78% sensitivity and an 89% specificity for this test while noting that 58% of the glaucoma suspects exhibited abnormalities. The difference between our results with OHT patients and the data obtained by Adams and coworkers for glaucoma suspects may stem from the fact that we adopted a more stringent pass-fail criterion and tested a larger number of individuals.

Studies of glaucoma patients as well as animal models of glaucoma and optic nerve damage have revealed that patients with POAG exhibit significant PERG abnormalities. In addition, our earlier results indicated that the magnitude of the PERG amplitude reductions associated with POAG is greater for higher temporal frequency stimuli (ie, steady-state PERGs) than for lower temporal frequencies (ie, transient PERGs). This led us to suggest that the high temporal frequency attenuation of the PERG reflects a selective loss of the larger retinal ganglion cells (ie, y-cells). Histologic evidence appears to support this conclusion. Therefore, we have explored the use of steady-state PERGs for monitoring retinal integrity in OHT patients. In a previous study we noted a 95% sensitivity and an 86% specificity for the steady-state PERG. In both this and previous studies, we found that some OHT patients exhibit significant reductions in the amplitude of the steady-state PERG. However, in the current study the prevalence of significant PERG abnormalities (11.5%) was less than when we examined OHT patients who were at high risk of losing visual field.

In our OHT sample color vision defects occurred more frequently than PERG abnormalities, suggesting that the desaturated D-15 is more sensitive than the PERG in detecting subtle visual deficits in OHT patients. In this regard it should be noted that while this study did not compare the sensitivity of these two tests in glaucoma patients, Drance has recently reported that the steady-state PERG has greater sensitivity in these individuals than the FM 100-hue test.

Although many studies have used psychophysical and electrophysiological methods to discriminate glaucoma patients from age-matched controls, relatively few studies have attempted to differentiate from among OHT patients those who will later develop glaucomatous visual field loss. Epidemiologic evidence suggests that 0.5–2.0% of patients with mildly to moderately elevated IOP (ie, 21–35 mm Hg) will develop visual field loss each year. Long-term studies (15–20 year follow-up) suggest similar values. The prevalence of significant PERG abnormalities in our sample (11.5%) approaches the percentage of OHT patients expected to develop glaucoma within 5 years. This figure increases when patients who are at high risk of developing POAG are studied. Taken together, this evidence might indicate that the steady-state PERG is a more specific indicator of the patients at risk of developing glaucomatous visual field loss than the desaturated D-15. However, longitudinal data will be necessary to establish the exact sensitivity and specificity of either test for differentiating among OHT patients. With this in mind, a prospective study of this issue is currently underway.
While the presence of a variety of visual defects in OHT patients is well documented, the prevalence of OHT patients exhibiting multiple deficits has not been determined. Even though there was some evidence of visual dysfunction in 32.2% of our OHT sample, no significant correlation between the results of the two tests was observed. In fact, only 2.3% of the patients who were sampled exhibited both deficits. These findings indicate that results on the two tests are largely dissociated and demonstrate that neither deficit is a necessary precursor of the other. Our findings also indicate that while the results on both tests may be influenced by elevated IOP, the deficits do not seem to be related pathophysiologically. This may appear surprising since both tests monitor central visual function, but differences in the nature of the two tests could account for the dissociation. The desaturated D-15 involved a static measure of color vision within the central 1°-2° of the visual field, while the PERG stimulus was a rapidly oscillating, achromatic checkerboard pattern subtending more than 10°. Therefore, the observed color vision defects might reflect visual deficits mediated by the subpopulation of retinal ganglion cells which are both color sensitive and prominent in the macula (ie, the x-cells). Conversely, the observed PERG abnormalities could reflect visual deficits mediated by another class of retinal ganglion cells (y-cells) which are more sensitive to dynamic, achromatic stimuli and increase in prevalence as a function of retinal eccentricity.

In spite of the fact that an understanding of visual functioning in OHT patients is necessary to fully elucidate the pathogenesis of glaucomatous visual loss, few studies have examined visual functioning in a large group of OHT patients. This study of 130 OHT patients confirmed the presence of both color vision deficiencies and PERG abnormalities in these patients. The study clearly illustrates a dissociation between these deficits in individual OHT patients which may be attributed to a differential sensitivity of subpopulations of retinal ganglion cells. Investigations of the progression of these deficits could clarify further the pathophysiological processes underlying ganglion cell loss in glaucoma.

Key words: glaucoma, ocular hypertension, color vision, D-15, PERG, electrophysiology, psychophysics

Acknowledgments

The authors wish to thank Dr. B. Becker, Dr. M. Kass and Dr. W. M. Hart, Jr. for their participation as members of the committee that evaluated all visual fields and disk photographs included in the study. The authors also wish to thank Dr. M. O. Gordon for her assistance with the study design and statistical analysis.

References