Evaluation of Acquired Color Vision Deficiency in Glaucoma Using the Rabin Cone Contrast Test

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Purpose. To evaluate acquired color vision deficiency in glaucoma by using the Rabin cone contrast test (RCCT).

Methods. Twenty-seven eyes of 27 patients with glaucoma (glaucoma group) and 27 eyes of 27 normal subjects (control group) were included in this study. Long (L), medium (M), and short (S) CCT scores (L CCTs, M CCTs, and S CCTs, respectively) were measured using the RCCT in both groups. Visual field examinations were performed with Humphrey automated perimetry using the Swedish interactive thresholding algorithm 30-2, and the mean deviation (MD) was evaluated. The macular ganglion cell/inner plexiform layer (GCIPL) thickness was measured using high-definition optical coherence tomography in the glaucoma group.

Results. The mean M CCTs and S CCTs in the glaucoma group were significantly lower ($P < 0.05$ for both comparisons) than in the control group (M CCTs, 80.7 ± 16.8 vs. 91.9 ± 8.22; S CCTs, 83.9 ± 19.5 vs. 97.4 ± 3.77, respectively); the L CCTs did not differ significantly ($P = 0.065$) from those of the controls (91.8 ± 12.8 vs. 97.4 ± 3.50, respectively). The M CCTs and S CCTs were correlated significantly with those of MD (M CCTs, $r = 0.47$; S CCTs, $r = 0.44$; $P < 0.05$ for both comparisons) and GCIPL thickness (M CCTs, $r = 0.70$; $P < 0.0001$; S CCTs, $r = 0.57$; $P < 0.01$).

Conclusions. The chromatic discrimination thresholds measured by RCCT in the glaucoma group were significantly different from those measured in the control group and were correlated with the MD and GCIPL thickness. The RCCT may be useful for evaluating acquired color vision deficiency in glaucoma and may help advance current understanding of the pathophysiology of glaucomatous damage.

Keywords: color vision, cone sensitivity, glaucoma

Color vision deficiency in glaucoma was first described in 1883.[1] Blue-yellow deficiencies generally are associated with early glaucoma, and red-green deficiencies generally are associated with advanced glaucoma.[2–6] However, it is difficult to measure or quantify acquired color vision deficiency, and color tests performed with standardized color test charts such as the pseudoisochromatic plates or panel D-15 frequently characterize it as combined or nonspecific color vision deficiency.[7]

Recent investigations of chromatic discrimination using computer-generated color tests have shown that color contrast thresholds are elevated in patients with glaucoma.[8–10] In these tests, the subject is asked to report the presence of a color target such as a spot, bar, or grating on a background of a different color. Regan et al.[11] designed a sophisticated computerized color vision test known as the Cambridge Colour Test. The stimulus arrays resemble the plates of a traditional pseudoisochromatic test, such as those of the Ishihara test. The target is C shaped, differing in chromaticity from the background. This test has been used to evaluate acquired color vision deficiency.[12–15] Another current computerized test is the Color Assessment Test developed by Birch et al.,[16] which is being used in occupational environments. This test is based on a spatiotemporal luminance masking technique devised by Birch et al.[16] In this technique, part of a uniform background is formed by spatially discrete elements that are equal in time-averaged luminance with respect to the background. During the stimulus presentation, each element scintillates while its luminance varies. These two tests are capable of quantifying the degree of color vision loss by use of color thresholds.

Rabin et al.[17] developed a new computer-based, cone-specific (L, M, S) contrast sensitivity test. The Rabin cone contrast test (RCCT) uses a randomized series of red, green, and blue letters visible to a single cone type (long [L], medium [M], short [S]) in decreasing steps of contrast to measure the threshold for letter recognition. The RCCT, which provides numeric scores of color vision and identifies the type and severity of color vision deficiency, can be completed in only 6 minutes. The RCCT offers an intuitive, robust index of color vision that accurately detects the type of color vision deficiency. The rapid, threshold letter recognition task is well suited for clinical application. The authors reported that it has sensitivity and specificity comparable to those of anomaloscope test results for hereditary color vision deficiency detection and categorization. We hypothesized that the RCCT may also be useful to evaluate acquired color vision deficiency in glaucoma, and we used the test to evaluate color vision deficiencies in patients with glaucoma.

Methods

The current study included 27 patients with glaucoma (glaucoma group) and 27 normal volunteers with healthy eyes (control group) who were evaluated in the Department of

Ophthalmology, Shiga University Medical Science Hospital. Examinations with Ishihara pseudoisochromatic plates (Kanehara-Shuppan Co. Ltd., Tokyo, Japan) and standard pseudoisochromatic plates part 1 (Igaku-Shoin, Tokyo, Japan) were performed to exclude patients with congenital color vision deficiency.

The patients with glaucoma underwent a comprehensive ophthalmic examination that included a medical history review, measurement of the best-corrected visual acuity (BCVA) determined with Landolt C charts, measurement of intraocular pressure (IOP), slit-lamp examination, gonioscopy, and fundus examination. Visual field examinations were performed with Humphrey automated perimetry (Humphrey field analyzer using a 30-2 grid and the Swedish interactive threshold algorithm [Carl Zeiss Meditec, Dublin, CA, USA]). The inclusion criteria for patients with glaucoma were a BCVA of 20/20 or better, a refractive error of −10.00 diopters or less, an open angle on gonioscopic examination, characteristic glaucomatous structural changes, and glaucomatous visual field defects with or without an elevated IOP. The criteria for the glaucomatous visual field defects included glaucoma hemifield test results outside the normal limits, pattern standard deviation with a P value of <5% or a cluster of fewer than three points in the pattern deviation plot in one hemifield (superior or inferior) with a $P < 5\%$, one of which must have a $P < 1\%$.[18] If both eyes of a patient had glaucoma, the eye with the better visual field was included in this study. If a patient had one glaucomatous eye, the glaucomatous eye was included in this study. Macular scanning was obtained using high-definition optical coherence tomography (OCT; Cirrus; Carl Zeiss Meditec). The ganglion cell analysis algorithm was used to detect the macular ganglion cell-inner plexiform layer (GCIPL) and measure the average thickness of the overall GCIPL.

The eyes of the volunteers were categorized as normal if they had a BCVA of 20/20 or better, a refractive error of −10.00 diopters or less, an IOP of 21 mm Hg or less, and an optic disc head that appeared normal. Only one eye of each patient was randomly selected. Subjects with normal eyes did not undergo visual field examinations and OCT examinations.

The exclusion criteria for both groups were congenital color vision deficiency, cataract with nuclear sclerosis exceeding 2+ (according to the Emery-Little system[19]), evidence of vitreoretinal disease, history of any ophthalmic surgery, systemic disease that might affect visual function (e.g., diabetes, hypertension, anemia, cerebrovascular disease, or renal disease), or a history of dementia.

Rabin Cone Contrast Test

The L, M, and S cone contrast test scores (L CCTs, M CCTs, and S CCTs, respectively) were measured using the commercially available Rabin Cone Contrast Test (Provideo CCT Plus system; Innova Systems, Burr Ridge, IL, USA) in both study groups. The RCCT measures the contrast threshold levels of red, green, and blue cones. The RCCT presents a randomized series of red, green, and blue letters visible to a single cone type (L, M, or S). A letter of one color (D, E, F, H, N, P, R, U, V, Z in Arial bold font; L and M cones, 20/300; S cone, 20/400) is presented in the center of the display (Inspiron One 2330 computer; Dell, Round Rock, TX, USA). The letter and background have the same luminance and differ only in chromaticity. Due to overlapping cone functions, it is impossible to limit stimulation to a single cone type, but by maintaining equal stimulation in the letter and background (undetectable) for two cone types while systematically stimulating the third, the letter is detectable only by a single class of cones. The subject identifies the letters aloud. The letters decrease from a clearly visible cone contrast to a threshold level (L and M cone, 27.5%–1%; S cone, 173%–7%). The RCCT is conducted monocularly in a dark room at 36 inches; distance correction (+0.75 diopter) is worn if improved visibility of the letters is reported. The cone contrast sensitivity scores are normalized to a 100-point scale (passing scores are 75 points or more).

Table 1. Demographics of the Study Groups

Characteristic	Glaucoma Group	Control Group
Men/women	17/10	17/10
Mean age ± SD, y	63.7 ± 9.5	59.3 ± 11.0
Mean BCVA ± SD, logMar	−0.13 ± 0.06	−0.10 ± 0.06
Mean IOP ± SD, mm Hg	14.3 ± 3.6	13.7 ± 2.9
Mean refractive error ± SD	−2.84 ± 3.16	−2.63 ± 3.01

BCVA, best corrected visual acuity; logMar, logarithm of the minimum angle of resolution; IOP, intraocular pressure; SD, standard deviation.

Statistical Analysis

All statistical analyses were performed using Prism 6 software (GraphPad, Inc., La Jolla, CA, USA). The Mann-Whitney U test was used to compare the baseline characteristics between the 2 groups and the RCCT scores between the 2 groups. The Fisher exact test was used to compare the number of eyes with failing scores (<75) between the two groups. The Spearman rank correlation test was used to analyze the correlation between the RCCT scores and mean deviation (MD) or GCIPL thickness in the glaucoma group. A P value of <0.05 was considered significant.

The institutional review board of Shiga University of Medical Science approved the review of patient data for this study. All participants provided written informed consent and the study adhered to the tenets of the Declaration of Helsinki.

Results

No patient failed color vision testing with the Ishihara pseudoisochromatic plates and standard pseudoisochromatic plates part 1 in the both glaucoma and control groups. The mean ± SD patient age was 63.7 ± 9.5 years in the glaucoma group and 59.3 ± 11.0 years in the control group. Table 1 shows the patient demographics in the two groups. There were no significant differences between the two groups in terms of age, sex, BCVA, IOP, or refractive error. The numbers of eyes with failing scores (<75) are shown in Table 2. Four eyes (15%) in the glaucoma group and no eyes in the control group had reduced L CCTs, a between-group difference that did not reach significance ($P = 0.11$). However, 11 eyes (41%) in the glaucoma group and 1 eye (4%) in the control group had reduced M CCTs, and 9 eyes (33%) in the glaucoma group and 1 eye (4%) in the control group had reduced S CCTs. Both between-group differences were significant ($P < 0.005$).

The mean L CCTs tended to be lower in the glaucoma group than in the control group (L CCTs, 91.8 ± 12.8 vs. 97.4 ± 3.50, respectively), but the differences did not reach significance ($P = 0.065$). The mean M and S CCTs were significantly lower (M CCTs, 80.7 ± 16.8 vs. 91.9 ± 8.22, respectively, $P < 0.05$;

Table 2. Number of Eyes With a Failing Score (<75)

Group	L CCT	M CCT	S CCT
Glaucoma/total	4/27	11/27	9/27
Control/total	0/27	1/27	1/27

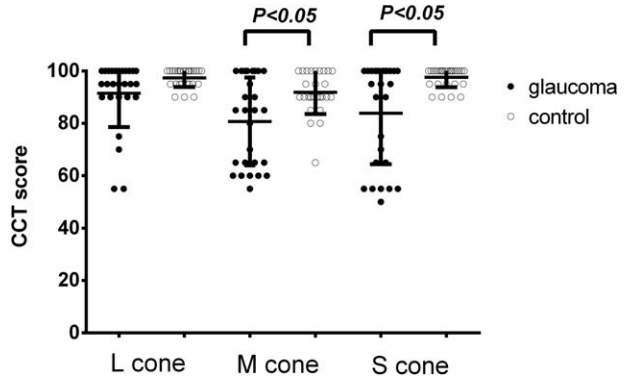

FIGURE 1. RCCT results for each cone are compared between those of the glaucoma group (•) and the control group (○). The mean M and S CCTs in the glaucoma group are significantly lower ($P < 0.05$ for both comparisons) than those in the control group (M CCTs = 80.7 ± 16.8, vs. 91.9 ± 8.22, respectively; S CCTs = 83.9 ± 19.5 vs. 97.4 ± 3.77, respectively).

S CCTs, 83.9 ± 19.5 vs. 97.4 ± 3.77, respectively, $P < 0.05$) in the glaucoma group than in the control group (Fig. 1). In the glaucoma group, the correlations were statistically significant between L CCTs and M CCTs ($r = 0.42$, $P < 0.05$) and M CCTs and between L CCTs and S CCTs ($r = 0.48$, $P < 0.05$) but not between L CCTs and S CCTs ($r = 0.216$, $P = 0.28$).

The mean MD in the glaucoma group was −5.7 ± 4.7 decibels (dB) (range, −0.48 to −13.77 dB). The M and S CCTs were correlated significantly with the MD (M CCTs, $r = 0.47$, $P < 0.05$; S CCTs, $r = 0.44$, $P < 0.05$). The mean GCIPL thickness in the glaucoma group (68.9 ± 8.31 μm [range, 56–83 μm]) was significantly correlated with the M and S CCTs (M CCTs, $r = 0.70$, $P < 0.0001$; S CCTs, $r = 0.57$, $P < 0.01$). However, the L CCTs were not correlated significantly with the MD or GCIPL (MD, $r = 0.037$, $P = 0.85$; GCIPL, $r = 0.27$, $P = 0.17$) (Figs. 2, 3).

DISCUSSION

In the current study, the mean M and S CCTs in the glaucoma group were significantly lower ($P < 0.05$ for both comparisons) than in the control group. The mean L CCTs in the glaucoma group tended to be lower than in the control group, although the differences did not reach significance ($P = 0.065$). Loss of blue-yellow sensitivity is the most common form of acquired color vision deficiency in patients with glaucoma.[2–6] A few previous studies have reported selective loss of red-green sensitivity. Greenstein et al.[20] studied foveal chromatic sensitivity in glaucoma by using flicker photometry and reported similar sensitivity losses for both the red-green and blue-yellow opponent systems. Alvarez et al.[21] reported selective loss of red-green chromatic sensitivity in glaucoma. Castelo-Branco[15] examined acquired color vision deficiency in glaucoma by using the Cambridge color test and reported the presence of macular function damage in the both blue-yellow and red-green opponent pathways. Rabin[22] used the RCCT to quantify the threshold of cone-specific contrast of acquired color vision deficiency under various ocular conditions and in various diseases and reported that M cone contrast sensitivity was more susceptible than L and S cone sensitivity. Our current results are consistent with results of these reports. Foveal chromatic sensitivity loss may not be restricted to the blue-yellow opponent pathway but may also include the red-green opponent pathway. In addition, the current study shows statistically significant correlations between L CCTs and M CCTs ($r = 0.42$, $P < 0.05$) and M CCTs and S CCTs ($r = 0.48$, $P < 0.05$) in eyes affected by glaucoma. Using the Color Assessment Test by Birch et al.,[16] Rauscher et al.[23] found that red-green loss is almost as common as blue-yellow loss in glaucoma patients. Our current results also imply a correlation between red-green and blue-yellow loss in glaucoma patients.

In the current study, 11 eyes (41%) and 9 eyes (33%) in the glaucoma group had failing M CCTs and S CCTs, respectively. The failing scores of our study were relatively small. Measuring foveal color contrast sensitivity, Falcao-Reis et al.[24] found color contrast sensitivity thresholds of more than 2 SD above the normal mean in 69% of glaucoma patients and 32% of ocular hypertensive patients. Color contrast thresholds overlapped among those of normal subjects, ocular hypertension patients, and glaucoma patients. An appropriate cutoff point to separate normal from glaucoma patients would therefore be difficult to find. In addition, our RCCT results reflect foveal performance, whereas early glaucomatous damage occurs in the peripheral part of the vision field.[25] Using a peripheral color contrast test of their own devising, Yu et al.[10] showed that all glaucoma patients had more than 2 SDs above the normal mean threshold. Thus, the peripheral loss of color vision in glaucoma may well be greater than the foveal loss.

The current study shows a significant decrement in M and S but not L CCTs in the glaucoma group. The healthy human crystalline lens gradually becomes yellow as part of the normal aging process. This yellowing may preferentially affect the blue-yellow losses. However, there were no significant differences in age between the two groups in this study. Moreover, patients with severe cataract (nuclear sclerosis exceeding 2+, BCVA <20/20) were excluded from this study. The current results show that pre-receptor spectral filters are unlikely to have a significant effect. Another possible explanation may be related to cone numbers. Listed in order of abundance from most to least, these are L, M, and S cones (7%). If we posit that inputs from cones are balanced by gain mechanisms,[26] damage to the

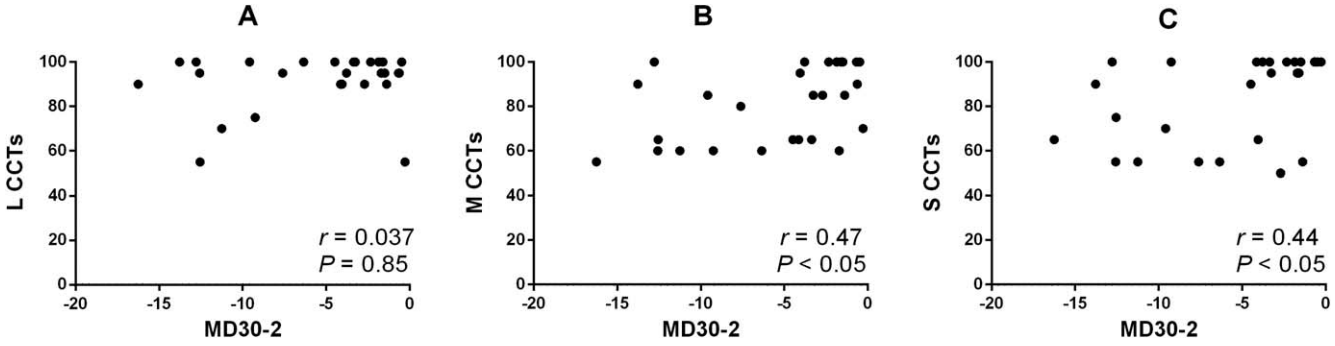

FIGURE 2. Correlation between CCT scores and MD in the glaucoma group is shown. (**A**) Correlation between L CCTs and MD. (**B**) Correlation between M CCTs and MD. (**C**) Correlation between S CCTs and MD. Correlations were determined by the Spearman rank correlation test.

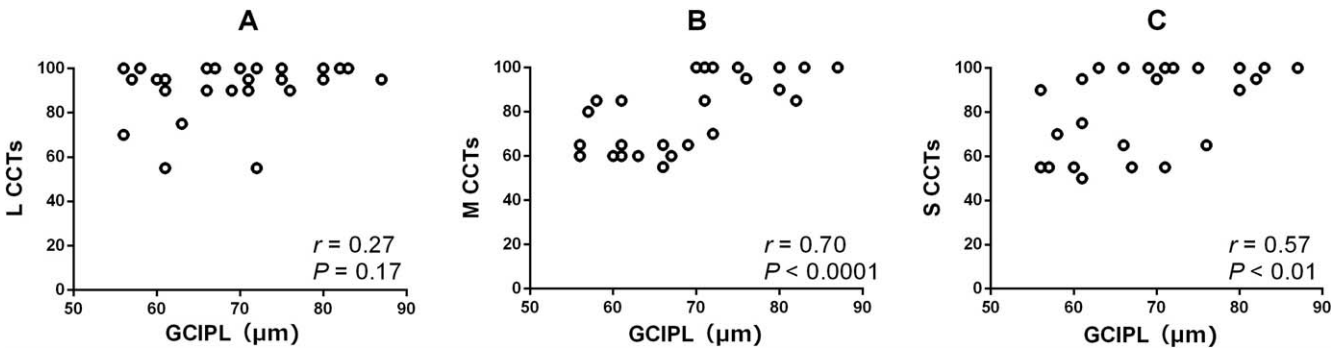

FIGURE 3. Correlation between the CCT scores and GCIPL thickness in the glaucoma group. (**A**) Correlation between L CCTs and GCIPL. (**B**) Correlation between M CCTs and GCIPL. (**C**) Correlation between S CCTs and GCIPL. Correlations were determined by the Spearman rank correlation test.

gain mechanisms may affect the pathways in a manner inversely proportional to the size of the cone population. Fewer cones may increase vulnerability to pathology.

It has been suggested that there are individual variations of spectral sensitivity of L and M cones in normal trichromacy. One source of variation is the Ser180Ala polymorphism in the L cone pigment gene.[27] Another source of variation is the existence of several types of L/M hybrid cone photopigments.[28,29] In addition, it is becoming increasingly appreciated that the ratio of L to M cones varies widely in the retina.[30,31] The variability of the photopigments with different spectral properties and the variability of L-to-M ratio in normal trichromacy may reflect the failure to isolate single cone responses. However, several studies have reported that individuals do not seem to have correspondingly different color vision.[32,33] Rabin et al.[17] (who developed the RCCT) reported that the RCCT has almost 100% specificity for confirming normal color vision and that the RCCT score was rarely outside normal limits, despite its relatively large variability in normal trichromacy. Our current results are consistent with those of that report. A plastic neural normalization mechanism may exist that allows the visual system to use information to compensate for individual differences in the cone ratio and make perception uniform.[26]

The M and S CCTs were correlated significantly with those of the MD ($P < 0.05$). Quantifying acquired color vision deficiencies using the Farnsworth-Munsell 100-hue test (100 hue FM), Flammer and Drance[6] and Papaconstantinou et al.[34] reported significant correlations between the total error score of the 100-hue FM and the indices of the visual field tests in eyes with glaucoma. However, 100-hue FM is not feasible for routine clinical use. The RCCT enables us to measure chromatic contrast threshold faster and more easily. The measurement of chromatic contrast threshold using the RCCT may be useful for monitoring glaucoma progression.

In the current study, the M and S CCTs were correlated significantly ($P < 0.01$) with the GCIPL thickness. Glaucoma is a disease caused by progressive retinal ganglion cell loss associated with characteristic structural changes. Recent advances in OCT techniques have allowed quantitative measurement of individual retinal layers and their changes. Several reports have found a qualitative correlation between local loss in visual sensitivity and local thickness of the GCIPL.[35–38] However, these reports failed to evaluate chromatic deficiency and used conventional white-on-white perimetry to detect loss of visual function. No relationship has been reported between structural changes detected by OCT and chromatic deficiency in glaucoma. Our results may suggest a correlation between anatomic abnormalities detected by OCT and chromatic discrimination thresholds measured by RCCT. However, we do not expect to find cone-specific sensitivity loss in glaucoma because this disease has its greatest effect on ganglion cells that transmit already-transformed color opponent signals; L and M cone isolating stimuli modulate not only red-green and but also blue-yellow color opponent pathways. In addition, L and M cone results reflect the relative inputs to this blue-yellow pathway. The reason that the M CCTs have the strongest correlation with the visual field indices and the thickness of GCIPL is not well understood. Our results confirm that color vision deficiency is acquired in glaucoma and may be useful to clarify the pathophysiology of glaucomatous damage.

The current study had some limitations. First, we screened for the presence of congenital color vision deficiency using pseudoisochromatic plates. However, the only way to ensure that color vision deficiency has a congenital cause is through analysis of molecular genetics.[39] Therefore, congenital color vision deficiency might not be excluded strictly in this study. Second, each step of the RCCT has been simplified to make the test easier to administer. Cone contrast thresholds for normal observers are usually at ceiling performance levels, making correlation with subtle deficiencies difficult. Third, this was a cross-sectional study, and we did not know whether low RCCT scores can predict glaucomatous progression. Confirmatory longitudinal studies are needed. Last, the number of current patients was small. A study with more patients is warranted to define more accurately the relationship between RCCT scores and conventional perimetric measures of glaucomatous damage.

In conclusion, the chromatic discrimination thresholds measured by RCCT in the glaucoma group were significantly different from that measured in the control group and were correlated with the MD and GCIPL thickness. The RCCT may be useful for evaluating acquired color vision deficiency in glaucoma and may help advance the current understanding of the pathophysiology of glaucomatous damage.

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