COLOR PLATES TO HELP IDENTIFY PATIENTS WITH BLUE CONE MONOCHROMATISM

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A new color vision test distinguishes patients with X-chromosome-linked blue cone monochromatism from those with autosomal recessive rod monochromatism. The test consists of two instructional and four test plates. Each test plate has three identical blue-green arrows and one purple-blue arrow; test plates differ from one another only with respect to the chroma of the purple-blue arrow. All five patients with blue cone monochromatism, aged 5 to 31 years, easily distinguished the purple-blue arrow on all four test plates, whereas none of the seven patients with rod monochromatism, aged 6 to 60 years, could distinguish the purple-blue arrow on all four plates. If a boy has a reduced visual acuity, normal rod electroretinograms, and 30-Hz cone electroretinograms reduced more than 97% below normal, this test can be used to determine whether his condition is an X-chromosome-linked one or an autosomal recessive one.

A young male patient may have photophobia, color blindness, a visual acuity of about 20/200, nystagmus, and a normal or nearly normal fundus appearance on ophthalmoscopic examination. If full-field rod electroretinograms are normal and full-field cone electroretinograms to 30-Hz white flicker are more than 97% below normal, the findings are compatible with the diagnosis of X-chromosome-linked blue cone monochromatism or autosomal recessive rod monochromatism. Separation of blue cone monochromatism from rod monochromatism can be achieved with spectral sensitivity measurements under light-adapted conditions. Under light-adapted conditions, patients with blue cone monochromatism, who have blue (that is, shortwave-sensitive) cone function as well as rod function, show a peak sensitivity near 440 nm, whereas patients with rod monochromatism, who have only rod function, show a peak sensitivity near 504 nm. However, reliable psychophysical spectral sensitivity functions under light-adapted conditions are virtually impossible to obtain in children less than 8 years
old. Separation of the blue cone electroretinogram, which is maximally only a few microvolts in amplitude in the presence of a bright adapting field, has also been difficult to achieve in young patients with photophobia and nystagmus. This clinical problem prompted us to develop a color vision test that could be taken in an outpatient setting by young boys and aid in separating those with blue cone monochromatism from those with rod monochromatism.

We compared the performances of patients with blue cone monochromatism and those with rod monochromatism on this color vision test. We also compared their test results with those of other patients with hereditary cone malfunctions, including a patient with dominantly inherited congenital tritanopia, one with X-chromosome-linked deuteranopia, one with X-chromosome-linked protanopia, and two patients with dominantly inherited cone degeneration.

**Subjects and Methods**

The color vision test consists of two instructional and four test plates, each 10.5 × 10.5 cm.

The Figure reproduces instructional plates 1 and 2 (A and B) and test plates 1 and 4 (C and D). We selected instructional plate hues so that three of the four arrows on each plate were blue-green as on the test plates and so that the odd arrows could be identified easily by patients with rod monochromatism and blue cone monochromatism. We selected test plate hues with dominant wavelengths of 468 nm (purple-blue) and 491 nm (blue-green) to be on the shortwave side of the rod absorption spectrum and the longwave side of the blue cone absorption spectrum and with respective reflectances such that they would be matched in brightness for the rods but mismatched in brightness for blue cones.

The pilot studies tested two patients with rod monochromatism who matched in brightness a series of purple-blue arrows varying only in chroma (that is, saturation) with our reference blue-green arrow. We observed differences in their selection of which purple-blue arrow matched our reference blue-green arrow; this may have been the result of variations in photoreceptor absorption of light because of differences in the color of their crystalline lenses or the densities of their macular yellow pigment. Therefore, we varied slightly the chroma of the purple-blue arrow across four test plates to be certain that the three blue-green arrows and the one purple-blue arrow appeared to be the same for patients with rod monochromatism on at least one test plate.

Specifications for the colors of the arrows were as follows. Instructional plates 1 and 2 each had three blue-green arrows identified as 5.0 EG (blue-green)4/8 glossy by the Munsell Color System. The odd arrow (light gray) on plate 1 was identified as N (neutral) 7/glossy, and the odd arrow (light green) on plate 2 was identified as 5.0 BG 6/8 glossy. Test plates 1 to 4 also had three identical blue-green arrows (5.0 BG 4/8 glossy). The odd purple-blue arrows on test plates 1 to 4 were, respectively, 7.5 PB (purple-blue) 4/9 glossy, 7.5 PB 4/10 glossy, 7.5 PB 4/11 glossy, and 7.5 PB 4/12 glossy.

To insure that the arrows were identical in size and shape on all six plates, we initially constructed an arrow pattern by placing four white press-on arrows at angles of 90 degrees to one another on black cardboard. We took a 35-mm slide with high contrast black and white (Kodak Ortho) film; the arrows then appeared to be transparent and the remainder of the slide was black. The pattern was enlarged so that the spacing and size of the arrows conformed to the dimensions derived from the calibration in the lower right corner of the Figure. A 10.5
Figure (Berson and associates). Reproductions of color plates that help distinguish patients with blue cone monochromatism from those with rod monochromatism. A and B are the two instructional plates and C and D are two of the four test plates. These reproductions should not be used to test patients because the printed colors may not be the same as those of our original plates. The plates should be constructed according to the Munsell Color System and to scale (bar gauge at lower right designates 10 mm) and should be viewed under a Macbeth lamp.

× 10.5-cm square was cut from the film with the pattern centered within it. We then placed this black film with four transparent arrows over the appropriate colored Munsell sheets* and fixed it to a white cardboard square of equal dimension to the film. We encased each plate in clear plastic to avoid smudging of the arrows by the examiner or the patient during the test procedure. We elected to place our plates on cardboard pages by slipping two diagonal corners of the plates through slits in the page so that each plate could be easily removed from a loose-leaf notebook and rotated; the plates should not have any holes or clipmarks that might give clues to a patient about their orientation.

*Available from Munsell Color, 2441 N. Calvert St., Baltimore, MD 21218.
We use the following procedure for administering the test. The patient is seated and views the plates on a desk at a distance of about 40 cm. The patient wears any prescription lens (untinted) that is normally worn; one eye is patched. The room is darkened and the plates are then illuminated with a Macbeth lamp; the lamp provides a spectrum equivalent to standard illuminant C. The examiner says, "I am going to show you a series of pictures with arrows pointing in different directions. I will ask you to point to the arrow that looks different. Here is an example." The examiner then shows instructional plate 1 and points to the odd gray arrow. The examiner then removes this plate from the patient's view, randomly rotates it, and again places it in front of the patient, stating, "Let's see if you can pick out the arrow that is different." The patient can also be asked to point in the same direction as that of the odd arrow to confirm that he can see the arrows. This procedure is repeated several times until the examiner is certain that the patient can identify the odd arrow. The examiner then repeats this procedure with instructional plate 2, making six consecutive presentations of this plate, each preceded by random rotation of the plate out of the patient's view. If the patient can correctly identify the odd arrow on all six presentations, then it is clear (P<.001) that the patient is not selecting the odd arrow at random and therefore understands the test. If the patient cannot identify the arrow on plate 2, than he is re-instructed on plate 1 and then shown plate 2 again. Only if the patient can perform plate 2 can the subsequent testing be considered valid.

Once the patient passes plate 2, the examiner states, "Now you know how to do the test. On the following plates, point to the arrow that is different. If you cannot see a difference, you can guess." The examiner then presents test plates 1 to 4, respectively, six consecutive times; before each presentation the examiner randomly rotates the plate out of the patient's view. The patient is given about 30 seconds to make each choice. After testing of the first eye is complete, the same sequence (including presentation of the instructional plates) is repeated on the second eye with the first eye patched.

To pass the test with each eye, the patient must correctly identify the odd (purple-blue) arrow on at least three of six presentations on each of the four test plates to ensure the P<.001 level of confidence that he is not selecting the odd arrow by chance. We adopted this criterion for passing this test because if one assumes that the patient with rod monochromatism is selecting arrows at random, the probability (from the binomial distribution) that this individual will identify the correct arrow by chance on three out of six presentations of a given plate is 0.169. The probability of this occurring by chance on each of four plates is 0.0008 (that is, 0.169^4). Therefore, we chose the criterion of at least three correct selections out of six presentations on each of four test plates because this was the least stringent criterion with a probability of less than .001.

Patients selected for this study included six females (aged 6 to 60 years) and one male (aged 29 years) with rod monochromatism (Patients 6 to 12). All but Patients 6 and 10 were from families in which at least one affected member had been tested and found to have a spectral sensitivity with a peak near 504 nm in both the dark-adapted and light-adapted states. All seven had corrected visual acuities between 20/200 and 20/600. Their results were compared with those of five males, aged 5 to 31 years with blue cone monochromatism (Patients 1 to 5), identified by spectral sensitivity measurements of some affected males who showed a peak sensitivity near 440 nm meters in the
light-adapted state and near 504 nm in the dark-adapted state. All had corrected Snellen visual acuities between 20/100 and 20/800 in each eye. After 45 minutes of dark adaptation, all patients with rod monochromatism or blue cone monochromatism had normal rod-isolated electroretinographic responses to full-field blue-light stimuli ≥ 100 µV and full-field cone responses to white 30-Hz flicker less than 1.5 µV in amplitude or more than 97% reduced below our lowest normal value of 50 µV. \(^\text{14}\)

To determine whether the ability to perform this color vision test was specific for blue cone monochromatism in patients with different types of hereditary cone malfunction, this test was also given to a man, previously described, \(^\text{15}\) with dominantly inherited congenital tritanopia (Patient 13), a boy with X-chromosome-linked deuteranopia (Patient 14), and a boy with X-chromosome-linked protanopia (Patient 15). These patients had normal visual acuities and normal full-field electroretinograms. A father and son, previously described, \(^\text{16}\) with dominantly inherited cone degeneration, were also tested (Patients 16 and 17). The father had a visual acuity of 20/200, absent color vision on the Farnsworth D-15 panel, a normal rod electroretinographic response to blue light, and a full-field cone electroretinographic response to 30-Hz white flicker of 1.4 µV; his son had a visual acuity of 20/30, a protan axis of confusion on the Farnsworth D-15 panel, a normal rod electroretinographic response, and a full-field cone electroretinographic response of 3.3 µV.

**RESULTS**

All patients were able to distinguish the odd arrow on each instructional plate. The Table shows the results for the test plates. All five males with blue cone monochromatism identified the purple-blue arrow without any errors on all four

<table>
<thead>
<tr>
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<td>Performance on Test Plates</td>
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<table>
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<tr>
<th>Patient</th>
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<tr>
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*Plus indicates passed; that is correctly identified the purple-blue arrow at least three of six times on a given plate. Minus indicates failed, that is could not identify the purple-blue arrow at least three of six times on a given plate.
test plates with each eye. In contrast, none of the patients with rod monochromatism were able to distinguish the purple-blue arrow at least 50% of the time on all four test plates. The patients with blue cone monochromatism identified all the arrows easily, whereas those with rod monochromatism had great difficulty even with the occasional test plates that they could perform.

The patients with congenital tritanopia, deuteranopia, and protanopia easily identified the purple-blue arrow on all four test plates without any errors. The patient with advanced dominantly inherited cone degeneration failed three of the four test plates, whereas his son, whose condition was less advanced, passed all four test plates.

**DISCUSSION**

This color vision test, which can be used even by young children in a clinical setting, can help determine whether a male patient has X-chromosome-linked blue cone monochromatism or autosomal recessive rod monochromatism. Patients with blue cone monochromatism easily identified the purple-blue arrow on all test plates, whereas the patients with rod monochromatism were unable to distinguish the purple-blue arrow on all four test plates. If a boy is found to have blue cone monochromatism, his parents can be advised that each male child has a 50% chance of being affected and that each female child has a 50% chance of being a carrier. If a boy is found to have rod monochromatism, his parents can be advised that each child has a 25% chance of being affected.

Boys with blue cone monochromatism or rod monochromatism are often identified when they are 5 or 6 years of age when they are discovered to have abnormal visual acuities. Our color vision test was designed so that young boys could understand and perform it. Patients with blue cone monochromatism and rod monochromatism also perform differently on the Sloan achromatopsia test, but 5- to 7-year-old children have difficulty understanding this test. Patients with blue cone monochromatism, in contrast to those with rod monochromatism, usually show a deutan-like axis of confusion on the Farnsworth D-15 panel, but young children have difficulty performing this test in a reproducible manner. Smith and Pokorny reported that patients with blue cone monochromatism fail the red-green screening plates and pass the blue-yellow plates on the AOH-R-R test, but this test is not now commercially available. Both patients with rod monochromatism and those with blue cone monochromatism fail most Ishihara plates and therefore this test does not have value in this differential diagnosis. Testing with the Nagel anomaloscope with red and green primaries also does not aid in this differential diagnosis.

As a group, the seven patients with rod monochromatism (Table) passed our test criteria on an individual test plate five of 28 times (0.179). This finding is consistent with the idea that these patients were selecting arrows by chance with a predicted probability from the binomial distribution of 0.169. Alternatively, patients with rod monochromatism may differ slightly from one another with respect to prephotoreceptor absorption of light, thereby resulting in their ability to perform accurately one or two of our four test plates. Because of the latter possibility, we continue to use all four test plates rather than rely on fewer test plates.

Accurate performance of our color vision test by a color-deficient male by itself does not establish the diagnosis of X-chromosome-linked blue cone monochromatism. For example, male patients with X-chromosome-linked protanopia or
deuteranopia or dominantly inherited tritanopia could easily perform this test. A man with advanced dominantly inherited cone degeneration failed our test whereas his son whose condition was less advanced passed it. Therefore, we reserve our color vision test for males whose parents have no obvious signs or symptoms of advanced cone degeneration, who have normal rod electroretinographic responses, and who have 30-Hz cone electroretinographic responses more than 97% below normal (that is, less than 1.5 μV in our test system). We are interested in learning how two other groups of patients—those with incomplete achromatopsia who have slightly different color vision and X-chromosome-linked disease and those with achromatopsia and color vision similar to that of patients with blue cone monochromatism but who have autosomal recessive disease—will perform on these plates.

REFERENCES