Further studies supporting the identity of congenital tritanopia and hereditary dominant optic atrophy

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Dominant inherited optic atrophy is usually a stationary disorder with typical findings of temporal optic nerve pallor, abnormal distance acuity, minimal visual-field defects, and characteristic color confusions in the blue-green region of the spectrum. Variability in the severity of these abnormalities is common, even within the same family. In patients with minimal disease, distance acuity may be close to normal and optic pallor may be so subtle that a definitive diagnosis cannot be made unless other obviously affected members of a family are seen. Our studies indicate that patients with dominantly inherited optic atrophy have similar color vision to that previously reported for subjects with congenital tritan defects. In fact, the almost identical color-vision profiles and pattern of inheritance of the two conditions lead us to question the existence of congenital tritan defect as an independent entity. Criteria are suggested for distinguishing the two conditions. It is emphasized that the utmost care should be taken to rule out dominant optic atrophy in future subjects in whom congenital tritanopia is suspected, both because of the strikingly similar characteristics of the two conditions, if these are indeed separate entities, and because the diagnosis of hereditary dominant atrophy may be easily missed.

Key words: hereditary dominant optic atrophy, congenital tritanopia, visual-field defects, color confusion, visual defects, optic nerve pallor.

We have been puzzled for several years by our failure to find a single case of congenital tritanopia. Many other workers with a major interest in color blindness have also never seen a patient with congenital tritanopia. Included in this group are Alpern, Linksz, François, Blackwell, and Rubin, who have all written on the subject of color blindness. Neither Tredelenburg, who described methods for discovering and testing tritanopes, nor Pitt, who discussed the properties of tritanopia, could find a single typical case.

This is indeed surprising if the incidence of congenital tritanopia is really somewhere between 1/10,000 and 1/65,000 as Wright, Kalmus, and Schmidt claim. Furthermore, Wright claims that tritanopes know they are color defective. Of 16 tritanopes that
were diagnosed on the colorimeter, all were aware of their blue and green confusions, and seven were, in addition, aware of pink, orange, and brown confusions. It would therefore be anticipated that at least some of the workers cited above would have seen a tritanope since they have screened populations for color blindness and some have even searched for color defectives by advertising.

A possible explanation is that there is a subtle retinal or optic-nerve disease with the color-vision defect described for congenital tritanopia, which may have been called congenital tritanopia by some workers. We initially explored this possibility several years ago and concluded that hereditary dominant optic atrophy (HDOA) has all the characteristics described for congenital tritanopia.8

HDOA is obvious in some families but in others it may be missed. Fourteen patients from three such families were studied in great detail and their data, described in a previous report,8 illustrate several features of HDOA which demonstrate how this condition may be confused with, or may even be what other workers are calling congenital tritanopia.

First of all, patients with HDOA are often unaware that they have a visual problem.9-14 Visual acuity, both for distance and near, may be close to normal. Near vision is usually not notably impaired until distance vision is worse than 20/60. Visual fields may be normal or only mildly impaired and night vision is normal. A patient may even be unaware of a moderately severe visual acuity defect since the disease usually begins early in life possibly even at birth, and is usually stationary. Therefore, the patient accepts whatever his vision is in early life as “normal vision,” particularly if it does not interfere with his daily activities. Progression, when it occurs, is mild and very slow and certainly can go unnoticed.

Of our 14 patients studied in detail,8 six were unaware of a visual problem until this was detected at our Eye Clinic. Five of these six patients were beyond the age of 30 and would therefore be similar to the age range of many of the tritanopes previously reported. It has been only in the last five to ten years that routine visual screening has become a practice in many school systems and five of our younger patients with HDOA were discovered to have a visual defect in this manner.

Altogether, then, only three of the 14 patients previously reported8 were aware of a visual defect since birth, or early childhood. However, most of our patients, similar to Wright's tritanopes,4 were aware of abnormal color vision. None of the three patients from one family that we have followed for close to 12 years has shown any evidence of progression during this time.

Not only may affected individuals with HDOA believe that their eyes are normal, but an examiner may miss the diagnosis, particularly in mild cases, which are frequent. This is more likely to occur if the examiner relies on the history of the patient and tests only near vision. Distance acuity may be as good as 20/30 or better and, therefore, not considered to be abnormal. In a few patients, distance acuity may even be normal.9-10 Five of our 14 patients had distance vision of 20/30 or better and all nine subjects with distance vision of 20/60 or better had near vision sufficient to read fine print (J-2 or better) without bringing the subject material closer than the test distance customarily used for a normal individual.

Visual fields, tested in the usual clinical manner, frequently show only mild abnormalities, or at times, appear normal. In several of our patients visual field defects were not detected on the Goldmann perimeter unless a blue-colored test object was used.

Even the optic nerve may show only questionable pallor or appear normal in some individuals. Usually, though, some affected members of a family will show obvious optic pallor and, therefore, it is of vital importance to examine the optic discs of more than one member of an affected
family (even those who claim to be normal). Temporal pallor, the most frequent optic-nerve change, was definitely borderline in some of our patients. In fact, two patients were originally referred to us because the ophthalmologist was uncertain of the cause of abnormal distance acuity. In both cases other members of the family who exhibited obvious optic atrophy had not been examined. Kjer, in his very extensive study of this disease, cites four patients for whom the original examining ophthalmologist had not considered the disc pallor to be pathological. It may be that the basic defect is retinal in this condition, explaining the occasional absence of optic pallor and the minimal visual field defect in many cases.

Obviously, then, the diagnosis of HDOA may be often missed. However, it is the striking similarities between HDOA and congenital tritanopia that have particularly led us to the belief that these two conditions may be the same. The inheritance of both conditions is autosomal dominant with frequent intrafamilial as well as interfamilial variation in manifestation. No other optic-nerve abnormality and only a few retinal abnormalities have dominant inheritance. Those retinal diseases with this type of inheritance, such as vitelliruptive macular degeneration, or some cases of retinitis pigmentosa, almost always have obvious visual complaints, if they have a significant color defect, and show obvious progression with time. It is of interest that the incidence of HDOA is close to 1/50,000, which is in the range reported for congenital tritanopia.

Most important, though, are the identical color vision abnormalities of the two conditions. In both conditions a tritan axis is noted on the Farnsworth-Munsell 100 hue test, whereas the Rayleigh match on the anomaloscope is normal or only mildly abnormal. This combination of findings is not seen in any other acquired retinal or optic nerve disease, except possibly in early glaucoma. A tritan axis on the 100 hue test is typical of most macular diseases; however, these patients almost always show a red shift of the Rayleigh equation and, in addition, frequently a wider than normal equation. In addition, we have found that patients with minimal or early macular disease frequently show only anomaloscopic abnormalities without changes in the 100 hue test. In other types of acquired optic-nerve disease, a deutan axis on the 100 hue test and a green shift of the Rayleigh match on the anomaloscope are usually found. Only in glaucoma is a tritan axis on the 100 hue test characteristic. Here, though, a concomitant disturbance on the anomaloscope, similar to that described for most macular diseases, is also usually found. An abnormal performance on the 100 hue test with a normal performance on the anomaloscope may be found in some patients with relatively early disease, but there is no other reason why glaucoma should be confused with HDOA or congenital tritanopia. Therefore, in general, the color vision of patients with HDOA is distinctly different from that of patients with other acquired retinal or optic nerve diseases.

We have also studied neutral points and color confusions in our patients with HDOA. The neutral points of these patients varied from 579 to 585 nm. when matched to a 2,500 K. light, and were in the range reported for tritanopes by others. Also, the color confusions of our subjects with HDOA corresponded to those reported for tritanopes. For example, Wright most commonly found that tritanopes confused 530 and 420 nm. Our optic atrophy subjects matched 410 with 520 nm., 510 with 420 nm., and other similar combinations. When the neutral points and color matches of our subjects were plotted on the chromaticity diagram, convergence to the blue end of the spectrum in the area of the tritanopic-convergence locus was found.

We have had the opportunity to do further color vision testing in three of the 14 patients described in our previous report. These tests have included a detailed assessment of wavelength discrimination,
saturation discrimination, color matching, and an assessment of the luminosity function. The results of these tests will be described in this report and a comparison will be made of similar data obtained from tritanopes.

Subjects
Detailed clinical data from these three patients studied are given in our other report. Patient 1 (Family 2, Ib*), age 45, had 20/30 vision in each eye. Patient 2 (Family 3, Iib*), age 39, had 20-30 vision in the right and 20/25 vision in the left eye. Patient 3, the 13-year-old daughter of Patient 2 (Family 3, IIb*), had 20/60 vision in each eye. Neutral points in the tritanopic range were obtained in Patients 1 and 3 and, therefore, they were considered to have similar color vision to tritanopes. Patient 2, with no tritanopia, was considered to have similar color vision to tritanomals or incomplete tritanopes. Reliable luminosity and hue discrimination data were obtained from all three subjects, dichromatic coefficient data from Patients 1 and 3, and saturation discrimination data from Patient 1.

Method
Apparatus. The apparatus used for wavelength discrimination has been described previously. The observer views a three-degree bipartite field presented in Maxwellian view. The split field is illuminated by the outputs of two Bausch and Lomb grating monochromators supplied by a tungsten ribbon lamp oriented at 45 degrees to either of the monochromators. For color matching and saturation discrimination a four-channel colorimeter was used (Fig. 1). The source, S, is a miniature tungsten halogen lamp operated at a color temperature of 3,000 K. This lamp is mounted in a housing which allows us to sample output in three directions: (1) The monochromator channel, MC: A lens, L1, matching the f number of a crossed Czerny-Turner monochromator focuses an image of the bulb filament on the entrance slit of the monochromator. At the exit slit, the beam is focused on an aluminum-coated, variable beam splitting wedge oriented at 45 degrees, W1, and is then focused onto the rear projection screen, RPS1. Behind the rear projection screen is a field lens, FL, which places the image of the rear projection screen in the plane of the observer's pupil. Light from RPS1 passing by the edge of the mirror, M1, forms the left half of the bipartite field. (2) Channels A and B: For channel A, the light from source S is collimated, passes through the beam splitter, BS, and is then reflected and refocused on wedge 1, where it combines with the output of the monochromator channel. Channel B is formed by the portion of the collimated beam of channel A, which is reflected by the beam splitter, BS. This beam is then refocused on the aluminum-coated variable beam splitting wedge, W2, and then collimated onto the rear projection screen, RPS2. A mirror, M2, reflects light from RPS2 to the eye, providing the right half of the bipartite field. One vertical edge of the mirror serves as a border between the two halves of a bipartite viewing field. (3) Channel C: The light from S is collimated and then refocused onto wedge 2, where it combines with the output of channel B.

The observer, looking through the artificial pupil, AP, sees a one-degree bipartite circular
In heterochromatic flicker photometry a standard field (inset on Fig. 1); one half represents the luminance from the standard, there is a pronounced appearance of flicker which is minimal when channel C. An achromatizing lens, \( AL \), is placed in the plane of the artificial pupil to compensate for the chromatic aberration of the eye.

Two interference filters, 650 and 480 nm., were chosen as primaries for the color matching. The 650 nm. filter was set in the common path of channels A and B and the 480 nm. filter was set in channel C. The 650 nm. primary could thus be a positive primary when channel A was blocked and a negative primary when channel B was blocked. For saturation discrimination the interference filters were replaced by neutral density and Corning color correction filters to yield an apparent color temperature at the source of 6,000 K.

Procedure. Wavelength discrimination thresholds were obtained by an ascending method of limits. The experimenter set the wavelength and luminance of the standard field and the wavelength of the variable field. The luminance of the variable field was manipulated by the experimenter. All luminance corrections were determined in advance of the session using heterochromatic flicker photometry with normal observers. The luminance level was 16 td. for the spectral region 440 to 700 nm. and 8, 3, and 0.8 td. for 430, 420, and 410 nm., respectively. Initially the two fields were set at equal wavelengths and the experimenter manipulated the variable field luminance until the observer reported that the fields were the same brightness and hue. The experimenter then changed the wavelength of the variable field in 1 nm. steps until the observer reported that the fields no longer matched in hue when the luminances were equated. The variable wavelength was then noted and a new standard wavelength was chosen. A number of wavelengths were sampled in ascending order between 410 and 650 nm.

For determination of the color mixture functions, we used equal luminance primaries and an equal luminance spectrum. The luminance level was 9 td. as determined by measurement of the light reflected off the flicker disc using a calibrated Ilford SEI exposure photometer. When all three channels plus the monochromator are set at the same luminance, then rotation of the wedges changes only the color balance.

The initial step in the procedure was to obtain an equal luminance spectrum for the monochromator using heterochromatic flicker photometry. In heterochromatic flicker photometry a standard white light is alternated with a variable radiances at a rate of 8 to 12 cps. When the monochromatic light is of a different luminance from the standard, there is a pronounced appearance of flicker which is minimal or absent when the luminances are equal. The observer’s task is therefore to adjust the radiance of the monochromic beam until the sensation of flicker is absent or minimal. This procedure was performed at 10 nm. intervals on normal observers and checked at six wavelengths for the optic atrophy patients. Equal luminance primaries were established by direct brightness matching to the monochromator channel at matched wavelengths. A wavelength was set on the monochromator and the primaries were set in appropriate channels. The MC wedge was set to give maximum output of the MC channel relative to channel A. For wavelengths excluding 450 to 470 nm., channel A was then occluded. The observer was given control of wedge 2 and instructed to set wedge 2 to give a color match. For wavelengths 450 to 470 requiring desaturation of channel A, wedge 2 was set at maximum and the observer manipulated \( W \) to give a color match. The data were then converted into the system used by Wright in which the spectral coefficients, \( B\lambda \) and \( R\lambda \), are set equal at 582.5 nm.

For determination of saturation discrimination, the color-correcting filters were inserted in channels A and C, and channel B was omitted by removing the beam splitter. With the monochromator occluded, the luminance of channel A was set at 9 td. by heterochromatic flicker photometry and then channels A and C were matched in brightness directly. Normal observers were used for this procedure. When the monochromator was occluded the two halves of the field matched in brightness and color. Wedge 1 was set to give maximum output of channel A, and then by rotating wedge 1 the proportion of light from the monochromator was increased until the observer reported a color difference between the fields. Since the fields were equal in brightness, the purity threshold is the negative logarithm of the percent of monochromatic light in the mixture.

Wavelengths were scanned in random order at 10 nm. intervals between 420 and 700 nm.

Results

Wavelength discrimination. The data from the three subjects and for normal observers are shown in Fig. 2. In all three subjects, discrimination is abnormal in the blue and blue-green regions of the spectrum with worse performance between 440 and 450 nm. Patients 1 and 3, with color vision similar to a tritanope, had a discontinuity with virtually no discrimination between 430 and 450 nm. Discrimination was markedly improved for both patients for shorter wavelengths in the far violet. Patient 2, with color vision similar to a tritanope.
Fig. 2. Average wavelength discrimination data from four trained normal subjects and from three patients with dominant optic atrophy. In all three subjects discrimination is abnormal in the blue-green region of the spectrum. Patients 1 and 3 had a discontinuity with virtually no discrimination between 430 and 450 nm. Discrimination was markedly improved for both patients for lower wavelengths in the far violet.

Fig. 3. Saturation discrimination of Patient 1. Discrimination was abnormal in the blue region of the spectrum between 400 and 450 nm. Saturation discrimination was unobtainable in the area of this patient's neutral point. Otherwise, saturation discrimination appeared to be normal.

anomal, showed no discontinuity, but poor discrimination at 460 nm, in the blue-green area and improved discrimination at the lower violet wavelengths. All three subjects had slightly elevated thresholds at the far red end of the spectrum, particularly at wavelengths longer than 630 nm., and for all discrimination was best in the yellow area of the spectrum.

Saturation discrimination. In the one subject studied (Patient 1) saturation discrimination was abnormal in the blue region of the spectrum from 400 to 460 nm. (Fig. 3). Saturation discrimination was unobtainable, of course, in the area of this patient's neutral point (572 to 575 nm.). Saturation discrimination was the same as normal elsewhere in the spectrum.

Color mixture data. Dichromatic coefficients. Dichromatic matches for Subject 2 were possible over only a small portion of the spectrum. These data are not plotted. On the other hand, Patients 1 and 3 were able to match all wavelengths in the spec-
Fig. 4. Dichromatic coefficients from Patients 1 and 3 are plotted along with average curves from seven tritanopes studied by Wright. These data show that Patients 1 and 3 were able to match all wavelengths in the spectrum with mixtures of only two spectral matching stimuli, namely wavelengths 480 and 650 nm., which were chosen for this purpose. Note how the curves from these two subjects fall along the average curves of Wright.

Discussion

Hue discrimination data from our patients with HDOA agree with data obtained by others from subjects with tritanopia. Two of our three subjects tested showed almost identical data to those obtained by Wright. As in Wright’s four tritanopes, best discrimination was obtained in the yellow region of the spectrum, discontinuity was noted in blue-green wavelengths where hue discrimination virtually disappeared, and good discrimination was again obtained in the far violet. Our third subject showed almost identical wavelength discrimination to that obtained by Fischer, Bouman, and ten Doesschate in one tritanope in whom the poorest discrimination was found in the region of 650 nm., with poor discrimination as well in the region of 450 to 480 nm.

Saturation discrimination has been previously studied only in two tritanopes and one incomplete tritanope. Their data were normal except in the region of a neutral point. We, however, found saturation discrimination abnormal at about 450 nm. and below. In the previous study no data were obtained at wavelengths lower than 450 and, therefore, our curves are quite similar to theirs when comparing spectral areas evaluated in both studies.

Color mixture data from two of our subjects agree almost precisely with those obtained by Wright from seven tritanopes, and Sperling from one tritanope. A normal luminosity curve in our three subjects with HDOA is similar to what has been reported for most tritanopes.

Our findings indicate then that color vision in HDOA and congenital tritanopia may be identical. Also, the hereditary pattern of the two conditions is the same. These findings certainly could be coincidental and it may be that both conditions are unique entities.

On the other hand, it is necessary to explain the failure of many experienced ob-
servers to find congenital tritanopia. Furthermore, it is puzzling why the genes for deutan and protan defects are located on the X-chromosome and that for tritan defects on an autosomal chromosome. It is also strange that there is a disease which serves as a model for congenital tritanopia, but none which bears more than superficial resemblance to the congenital deutan and protan defects.20

If congenital tritan defects exist, then certain criteria should be met before a case called congenital tritanopia or tritanomaly can be accepted as a unique entity, differing from dominant optic atrophy. First, it is necessary to show that both distance and near vision are normal. For example, it is not enough to say that visual acuity was sufficient to read small print,4 adequate to carry on a certain profession,22 or sufficient to permit reliable results to be obtained from color tests.28 Second, visual fields must be normal. Third, not only the affected individual, but other members of the family should have normal-appearing optic nerves as well as normal acuity. Further, the ophthalmoscopic examination should be done by someone who has evaluated many pathological optic nerves, because the changes can be quite subtle, as we have noted. Evaluation of previous reports of congenital tritanopes and tritanomals, particularly within the last 50 years, reveals that all these criteria have usually not been fulfilled. Even in the most recent report29 of congenital tritanomaly, it is difficult to accept the data as supporting this diagnosis.

REFERENCES

1. Personal communication.


