Dark adaptation testing in heterozygotes of Usher's syndrome

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SUMMARY Fourteen heterozygous carriers of Usher's syndrome were evaluated by ophthalmoscopy and dark adaptation testing. The normal findings in our study are discussed and compared with those of previous reports, which suggested that abnormal dark adaptation thresholds and fundus abnormalities may be seen in heterozygotes.

Usher's syndrome is an autosomal recessively inherited trait that is characterised by a congenital neurosensory hearing defect of varying severity associated with retinitis pigmentosa. The syndrome has been estimated to account for 3% to 6% of congenital deafness and 50% of deaf-blindness (Vernon, 1969). The incidence of the disease is approximately 3 per 100 000 people, and the incidence of carriers is approximately 1 in 100 of the general population (Vernon, 1969).

Previous reports from the ophthalmic literature have noted that heterozygous carriers of Usher's syndrome may show raised dark adaptation final thresholds (De Haas *et al.*, 1970). In some carriers the increase is associated with fundus changes characteristic of gyrate atrophy of the choroid and retina (Holland *et al.*, 1972). Because of the importance of identifying heterozygotes, we examined 14 Usher's syndrome carriers to confirm the presence of either dark adaptation abnormalities or fundus abnormalities, particularly those suggestive of gyrate atrophy of the choroid and retina.

Subjects and methods

All subjects were the natural parents of at least 1 child with a congenital neurosensory hearing defect and retinitis pigmentosa. Affected offspring showed characteristic fundus abnormalities including bone spicule pigmentation, waxy disc atrophy, and attenuated retinal vessels. Additionally, all affected offspring complained of night blindness and showed constricted peripheral fields.

Each heterozygote was questioned about ocular, auditory, and neurological as well as general medical complaints. All had a complete ophthalmological assessment that included the determination of best corrected visual acuity; slit-lamp examination of the anterior segment, lens, and vitreous; and dilated fundus examination by both direct and indirect ophthalmoscopy.

After maximal pupillary dilatation the heterozygous parents had monocular dark adaptation testing by a Goldmann-Weekers dark adaptometer. All were similarly tested by a protocol that began with an initial 5 minutes of adaptation to a white light of 1600 lux. After bleaching, dark adaptation thresholds were measured during a 30-minute period for 2 separate circular 2° test targets obtained by an orange, short-wavelength, cut-off filter (Corning 3482) having 90% transmission at 590 nm and 50% transmission at 555 nm and a blue band-pass filter (Corning 4305) having a transmission peak at approximately 460 nm and 50% transmission at 360 and 540 nm. Each of the chromatic stimuli was presented alternately in an on-off fashion at the rate of 1 second on and 1 second off. The measurements were recorded on a standard log luminance versus time graph. Fixation was maintained with a movable, dimly lit, red fixation light while measurements were made at a retinal locus 15° above the fovea. At each test time 2 on (or ascending) and 2 off (or descending) thresholds were determined. An ascending threshold was the intensity at which the subject first saw the test light as its luminance was increased. The descending threshold was the intensity at which the subject ceased to see the test light as its luminance was lowered. The approximate true absolute threshold was calculated as the average of the 2 ascending

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Fig. 1 Dark adaptation curve from normal subject with blue and orange filters

and descending thresholds obtained during a test time. Reliability was ascertained by noting the consistency of threshold responses for each subject within each test period. At the 15° locus both cone and rod thresholds and cone-rod break times were obtained. After 30 minutes of testing in the dark, rod thresholds were also measured at 30° and 45° superior and 15°, 30°, and 45° inferior to the fovea by setting the calibrated red fixation target to the appropriate retinal locus.

A technique using alternate orange and blue filter test targets, similar to those described by Zeavin and Wald (1956), provides a way for distinguishing cone and rod thresholds and for measuring cone-rod break times on dark adaptation testing. During initial stages of dark adaptation, when cone receptors determine visual thresholds, the orange threshold lies about 0.15 log units below the blue; whereas later, when rod receptors determine thresholds, the blue threshold lies about 0.95 log units below the orange. Cone-rod break times are determined from the point at which the curves for the orange and blue filters cross (Fig. 1).

Results

The visual acuity and ophthalmological examination findings for all 14 heterozygous carriers of Usher's syndrome were normal. None was observed to have gyrate atrophy of the choroid and retina, and there were no complaints of nyctalopia. On dark adaptation testing, cone and rod thresholds were within the normal range at all retinal loci tested. Tables 1 and 2 compare results at 15° superior to the fovea for normal and heterozygous carriers. Final rod thresholds at 30° and 45° superior to the fovea and at 15°, 30°, and 45° inferior to the fovea were within ± 0.5 log units of the values obtained at 15° superior to the fovea for normal controls and

Table 1 Dark adaptation recordings for 13 normal eyes

Age (yr)	Sex	Cone threshold (log units)	Rod threshold (log units)	Cone-rod break time (min)
27	F	2×10^4	2×10^2	12.0
54	M	2×10^4	4×10^2	12.5
56	F	6×10^4	3×10^2	10.0
67	M	3×10^4	4×10^2	10.0
25	M	6×10^4	1×10^2	9.0
55	F	1×10^5	2×10^2	8.5
40	F	1×10^5	2×10^2	10.0
38	F	4×10^4	2×10^2	10.0
25	M	4×10^4	1×10^2	8.0
24	F	3×10^4	6×10^2	10.0
32	M	3×10^4	2×10^2	9.0
45	M	3×10^4	3×10^2	9.0
56	F	4×10^4	2×10^2	12.5

Table 2 Dark adaptation recordings for 14 heterozygotes results were obtained on one eye

Age (yr)	Sex	Cone threshold (log units)	Rod threshold (log units)	Cone-rod break time (min)
35	F	6×10^4	2×10^2	8.0
52	F	1×10^5	3×10^2	8.5
54	M	1×10^5	3×10^2	9.0
51	F	2×10^4	1×10^2	9.0
49	F	4×10^4	2×10^2	9.0
50	M	4×10^4	2×10^2	9.0
45	F	2×10^4	5×10^2	10.5
38	M	6×10^4	6×10^2	12.0
54	M	1×10^5	3×10^2	9.0
67	M	6×10^4	3×10^2	13.5
68	F	3×10^4	4×10^2	11.5
52	F	2×10^4	3×10^2	13.0
47	F	6×10^4	2×10^2	11.5
67	M	4×10^4	4×10^2	13.0

heterozygotes. All 14 heterozygotes showed a normal cone-rod break time measured 15° superior to the fovea.

Discussion

In patients with Usher's syndrome elevated rod thresholds on dark adaptation testing are found even in initial stages of the disease. Eventually cone thresholds are also elevated. In our study of 14 subjects heterozygous for Usher's syndrome no abnormalities were seen on careful ophthalmological examination. Final cone and rod thresholds on dark adaptation examination were found to be within a normal range at 6 loci on the retina by separate 2° orange and blue targets.

Our data do not support previous findings of raised rod dark adaptation thresholds ranging from 1 to 2 log units above normal in 5 of 13 heterozygous carriers of Usher's syndrome (De Haas *et al.*, 1970). Even 'minor degrees of impairment' in 3 additional carriers noted by the same authors were not seen in the present study. In addition, fundus changes showing phenotypic similarities to those noted in gyrate atrophy of the choroid and retina, as reported by Holland *et al.* (1972) in 2 definite and 1 possible heterozygous carriers, were not seen in our 14 subjects.

The 13 heterozygotes reported by De Haas and co-workers were from 3 separate families. The two heterozygotes from family A, aged 61 (VI-2) and 14 years (VIII-1), were the mother and daughter of a patient with congenital deafness and retinitis pigmentosa. They were found to have elevated rod final thresholds of 0.5 and 1.5 log units, respectively. Both complained of nyctalopia and showed abnormal electro-oculogram light/peak to dark/trough ratios. The 61-year-old subject showed fundus changes of choroidal atrophy and a few 'spidery pigment spots'. The fundus of the 14-year-old subject was normal.

Seven of 8 other siblings of the affected patient also had a pigmentary retinopathy. Their disease was characterised by a paucity of bone corpuscular pigmentation, slight pallor of the optic disc, and narrowing of retinal arteries. Further, 4 of the affected members in their fourth decade showed normal central acuity. While all affected patients showed raised rod final thresholds on dark-adaptation testing, in 1 instance the rod final threshold was only slightly raised, while other patients showed final thresholds ranging from 1 to 2.5 log units above normal. The preservation of normal central acuity in at least some affected members, in addition to the less extensive ophthalmoscopically apparent fundus findings and milder degrees of elevated rod

final thresholds on dark adaptation, are more consistent with a dominantly inherited form of pigmentary dystrophy than with an autosomal recessively inherited form of dystrophy, as seen in Usher's syndrome. Moreover, if variable expressivity is presumed, dominant inheritance is further suggested by the possibility of 3 generation transmission. A marked variability in expressivity is consistent with a Mendelian dominant form of inheritance. Although speculative, in our judgment family A could be affected by 2 separate and distinctly different genetic diseases, one being an autosomal recessive form of congenital deafness and the other an autosomal dominant form of pigmentary dystrophy.

In family B, reported by the same authors, 2 of 3 heterozygotes tested were found to have elevated rod final thresholds of 1 and 2 log units. Although the technique of testing in the subjects was not cited, in most instances an elevated rod final threshold of 2 log units would be associated with a subjective complaint of nyctalopia. Neither of these two subjects, IX-1 or IX-2, complained of night blindness. Further, the absence of subjective complaints and the normal electroretinogram findings in the presence of the apparent elevation in rod final thresholds suggest that the young ages of these patients, 10 years and 7 years, may have contributed to the abnormal findings on dark adaptation, since accurate performance on dark adaptometric testing necessitates an attentive, co-operative subject.

In family C, described by De Haas and co-workers, 2 subjects, III-1 (age 71 years) and III-2 (70 years), were found to have elevated rod final thresholds of 1 and 1.5 log units, respectively. Only subject III-2 complained of nyctalopia. Subject III-1 was cited as having nuclear cataracts. Two additional family members, V-7 and V-8, showed only minimal (0.5 log units) elevation of rod final thresholds.

Since age is a factor in determining the significance of rod final thresholds, important variables such as pupillary diameter and degree of lens opacities must be considered in the interpretation of rod final threshold values. The authors did not state how these important variables were considered in their 2 heterozygous subjects who were in their eighth decade of life. Since they did not indicate either the specific manner in which thresholds were measured on the other 2 subjects with minimal degrees of elevation (for example, size of the test target, locus of the retina being tested) or their range of normal values, it was difficult to interpret the significance of a 0.5 log unit elevation.

Holland *et al.* (1972) reported gyrate-atrophy-like changes in 2 sisters (ages 80 and 75 years), one of whom was a definite heterozygote for Usher's

syndrome while the other had a 50% probability of carrying the gene for this disease. Both sisters were aphakic and highly myopic. Only 1 complained of night blindness and showed an elevated rod final threshold on dark adaptation testing. The abnormal fundi and abnormal electroretinogram amplitudes noted in these 2 subjects are typical of those seen in high myopia unassociated with the autosomal recessively inherited genetic disease gyrate atrophy of the choroid and retina. The late onset (age 50) of nyctalopia in one of these 2 sisters and the absence of this symptom in the other are highly inconsistent with gyrate atrophy of the choroid and retina. The onset of nyctalopia is apparent in the majority, if not in all, gyrate atrophy cases by the second and third decade of life.

A third case cited by the same authors was that of a 16-year-old male heterozygote who was also myopic and showed a minimal (0.2 log unit) elevation of rod final threshold on dark adaptation testing. This patient showed two 1.5 disc diameter circular areas of peripheral choroidal atrophy in his right eye, which suggested to Holland and co-workers phenotypic similarities to early changes of gyrate atrophy. The patient, however, did not complain of nyctalopia. The fundus changes and minimal degree of dark adaptation elevation are consistent with the patient's 5 to 6 dioptres of myopia, and particularly in the absence of night blindness, most likely do not indicate early changes of gyrate atrophy of the choroid and retina.

Our ophthalmological findings are not consistent with those of Kloepper *et al.* (1966), who found signs of retinitis pigmentosa and cataract in 13%

of 31 known carriers of Usher's syndrome. It is noteworthy that with only a few exceptions a 'slight' hearing impairment measured audiometrically was found by these authors in known heterozygous carriers. In a previous publication Hallgren (1959) could not detect an increased prevalence of eye disease in heterozygotes. Data regarding the prevalence of hearing impairment in carriers were cited as being inconclusive.

From our study of 14 patients heterozygous for Usher's syndrome and a review of the pertinent literature we conclude that neither ophthalmoscopically apparent abnormalities nor raised dark adaptation cone or rod thresholds will be of value in identifying carriers of this disease.

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