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Quantification of dark adaptation dynamics in retinitis pigmentosa using non-linear regression analysis

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Purpose: Non-linear regression analysis was used to determine dark adaptation indices in people with retinitis pigmentosa and in control subjects.
Methods: Dark adaptation data were collected for 13 people with retinitis pigmentosa and 21 controls using the Goldmann-Weekers Dark Adaptometer. Data were analysed using an exponential non-linear regression model and dark adaptation indices derived. The results were compared to age-related values.
Results: The mean cone threshold of the group with RP (4.73 ± 0.19 log units) was significantly greater than that found in the control group (3.69 ± 0.12 log units). The rate of cone dark adaptation in the RP group was not significantly different from that of the control group. The α break in the RP group (6.46 ± 0.70 minutes) was delayed when compared to the control group (4.29 ± 0.21 minutes) and the rate of rod dark adaptation in the RP group was slower (10 ± 2 per cent per minute) than that of the control group (15 ± 1 per cent per minute).
Conclusions: This study has shown that a relatively simple data analysis can provide a more quantitative and intuitive description of dark adaptation rates in people with retinal disease. This technique will enable more effective use of dark adaptometry as a supplement to objective electrophysiology, when monitoring people with retinitis pigmentosa.

Key words: dark adaptation, retinitis pigmentosa

Dark adaptation describes the recovery of visual sensitivity in darkness following retinal bleaching by a strong adapting light. It is well known that the dark adaptation function is biphasic and non-linear, with cone vision recovering more rapidly and stabilising at a higher threshold value than rod vision. When measured under clinical conditions, the transition between the faster cone and slower rod functions occurs about five minutes into dark adaptation and is termed the α break. For a more complete discussion of dark adaptation, the reader is referred to standard texts such as Pitts[1] or Walraven and colleagues.[2] Abnormal dark adaptation is associated with a number of retinal diseases and with retinitis pigmentosa (RP) in particular. Previous studies of dark adaptation in RP have demonstrated an elevation of both cone and rod thresholds,[3] a delay in reaching the asymptotic rod threshold[4] or total elimination of the rod function.[5]

Most studies describe dark adaptation by reporting the α break and the final rod or cone thresholds by direct reading from the data plots.[6] Given wide fluctuations in clinical data it is considered difficult for the practitioner to determine precisely the α break, the absolute thresholds or rates of dark adaptation. Improved data analysis methods have been suggested. Dark adaptation data could be plotted on log time versus log threshold axes to emphasise sensitivity changes earlier in dark adaptation, as well as providing a simpler method to determine the α break.[7,8] While offering some advantages, this method has not been widely adopted. The recent availability of inexpensive computers and powerful statistical software has made modelling of non-linear systems more common.[9] Non-linear regression analysis has been applied previously to age-related dark adaptation data.[10] The current study uses non-linear regression analyses to compare dark adaptation dynamics in control and RP clinical groups. It is the aim of this study to demonstrate a simple computer driven data analysis method that may be used to interpret clinical dark adaptation data quickly and accurately.

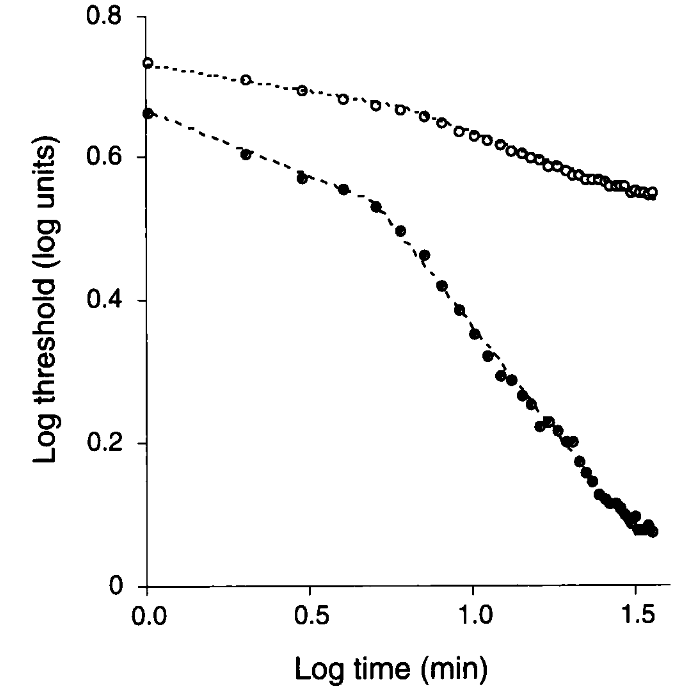

Figure 1. Decrease in threshold with time for control and RP subjects. The lower plot gives the mean data for 21 control subjects. The upper plot gives the mean data for 13 RP subjects. Note that the vertical axis is a double log axis (log of the log threshold).

METHODS

Subjects

Thirteen subjects with RP (10 female, three male) were recruited from the Retinitis Pigmentosa Society of NSW, the National Foundation of Blind Citizens in New South Wales and the Low Vision Clinic of the School of Optometry University of NSW. The mean age of the RP subjects was 42 ± 13 (SD) years with a range of 19 to 62 years. The visual acuity for the better eye ranged between 6/5 and 6/30. The mean duration from initial diagnosis of RP was 20 ± 12 years with a range of two to 41 years. To be included in the RP group the subjects needed to be diagnosed with RP by an ophthalmologist, be aged between 18 and 65 years, have a central visual acuity of better than 6/36, no clinically significant media changes and no physical disability or hearing impairment. Twenty-one people (nine male, 12 female) aged 22 to 52 years were recruited as the control group. The mean age was 33 ± 6 years with a range of 22 to 52 years. All the control subjects were free from ocular pathology. The visual acuity of members of this group was 6/6 or better. The research followed the tenets of the Declaration of Helsinki, informed consent was obtained from the subjects after explanation of the nature and possible consequences of the study and the research was approved by the University of New South Wales Human Subjects Ethics Committee.

Dark adaptation

Dark adaptation was measured using a Goldmann-Weekers Adaptometer (Haag-Streit, Switzerland). The luminance level of the test light with the filter wedge set at its lowest transmission value was 1.01 cd/m^2. The test field was the 5.5 degree opal glass. The dazzling lights were two 15-watt bulbs giving a bowl luminance of 226 cd/m^2 (about half of that recommended by the manufacturer). The reduced luminance was used to minimise any risk of retinal light damage.[11] The pupil of the preferred eye was dilated with one drop of 0.5 per cent tropicamide and dark adaptation performed when a dilatation of six millimetres was noted. The pupil dilation was constant during the period of the study. Subjects pre-adapted to the dazzling lights for five minutes and visual thresholds were recorded using the recommended method at one-minute intervals for 35 minutes.

Data analysis

The chart from the adaptometer was removed and the horizontal and vertical positions of each datum point measured. The measurements were converted to the appropriate time and log threshold values. The derived data were analysed using a previously described non-linear regression technique.[10] Briefly, the dark adaptation function was modelled as two intersecting rod and cone exponential functions with the intersection being the α break. Reiterative non-linear regression analyses were performed until a set of predetermined convergence criteria were met and a series of exponential constants for both rod and cone portions of the dark adaptation function were calculated. These constants included the cone asymptotic threshold, the α break time and the exponential constant (E) of both the rod and cone portions of the dark adaptation function. The calculated constants were used to derive a

Parameters		RP	Control	Statistical significance	Haag-Streit data	Haag-Streit data
Age (years)		42 ± 13	33 ± 6		20 to 40	60 to 80
Cone	log threshold	4.73 ± 0.19	3.69 ± 0.12	$p < 0.001$	4.17	4.15
	exponential constant	1.26 ± 0.17	1.56 ± 0.14	$p = 0.08$		
	% change/min	67 ± 5	76 ± 3	$p = 0.10$	74	54
Rod	exponential constant	0.11 ± 0.02	0.17 ± 0.01	$p = 0.04$		
	% change/min	10 ± 2	15 ± 1	$p = 0.03$	13	13
α break (min)		6.46 ± 0.70	4.29 ± 0.21	$p = 0.01$	4.66	5.79

Table 1. Calculated dark adaptation indices. The columns give the data from control and RP groups. Data supplied with the Goldmann-Weekers Adaptometer are analysed and given for comparison in the last two columns of the table (see Herse[10] for more information). Estimates of error are standard error of the mean. Statistical differences between the control and RP group means are given.

descriptor for the rates of change in visual threshold, the percentage threshold change per minute (per cent/minute), which is defined as 100 (1-exp^{-E}). The SAS NLIN program[10] was used to perform this analysis. Statistical significance between group means was determined using Student t tests with the α level set at 0.05.

RESULTS

The data are shown in Table 1 and Figure 1. The mean cone threshold in the RP group was 1.04 log units greater than that found in the control group. This result supports similar findings reported in other studies.[3,10,12] The mean cone exponential constant and the calculated rate of change of the cone threshold (percentage change per minute) in the RP group was not significantly different from that found in the control group.

The calculated mean α break in the RP group was delayed by 2.16 minutes, when compared to the control group. This finding is consistent with previous studies.[3,13] The mean α break for the control group was similar to reported normal values.[1,10]

By observation, the rod threshold for the RP group was raised by about 2.3 log units, when compared to the control group. This is consistent with the reported increase of 1.6 to 3.5 log units in RP rod threshold.[3,14] The rod threshold observed for the control group was similar to other reported normal values.[8,10] The mean rod exponential constant in the RP group was 0.06 log units less than that found in the control group. The calculated rate of rod threshold change per minute in the RP group was almost 35 per cent slower than that of the control group.

DISCUSSION

Non-linear regression analysis was used successfully with data obtained from both control and RP subjects. The time taken to perform each analysis depended on the computer but was usually less than 15 seconds. The success of this clinical trial demonstrates the robustness of the analysis method.

Previous studies of dark adaptation in RP have not measured or considered the rate of change in threshold as an important index of visual function. This is unfortunate as it undervalues a chief complaint of most people with RP: an inability to see in environments with changing light levels. The clinical photostress test, in which the photopigments are bleached with an ophthalmoscope and the time taken to recover to one line above the initial visual acuity is measured, provides some indication of dynamic adaptation rates. This gross clinical test is predominantly foveal in nature and uncalibrated, and gives little information about rod mediated vision. Only a moderate correlation has been reported between clinical photostress data and cone photopigment levels in people with RP.[15] These results suggest that the clinical photostress test provides little useful information concerning dark adaptation dynamics in people with RP. In comparison, the non-linear regression procedure used in this study allows individual dark adaptation data to be relatively rapidly analysed and both component dark adaptation indices determined. These indices may be useful in monitoring visual performance in people with progressive retinal dysfunction.

It must be noted that the data of this study offer only a preliminary indication of the values that might be needed for clinical comparisons. Larger population studies are indicated. Age-related norms are necessary to enable comparison with adaptation rates in cases of disease. The values of age-related norms used in this study have been determined using data provided by Haag-Streit with the dark adaptometer and are shown in Table 1.[10] The cone dark adaptation rate in people aged 10 to 20 years was considerably faster than that in people aged 60 to 80 years (Table 1). Linear regression analysis of the dark adaptometer data suggests that the cone dark adaptation rate decreases at about 0.5 per cent/minute/year. The cone dark adaptation rate of people aged 20 to 40 years (74 per cent/minute) was consistent with the cone dark adaptation rate found in the control group of this study (76 per cent/minute). Conversely, rod dark adaptation rates calculated from the dark adaptometer data appear to remain constant with age (Table 1). The rod dark adaptation rate found in the control group of this study was similar to that found using the Haag-Streit data.

It is interesting to see where the data from the RP subjects fit into the age-related values for dark adaptation dynamics. The mean age of the RP subject group was 42 years. The mean cone dark adaptation rate for the RP subjects (67 per cent/minute) was intermediate between the cone values for controls aged 20 to 40 years (74 per cent/minute) and 40- to 60-year-olds (57 per cent/minute). This suggests minimal cone dysfunction in most of this group and correlates with the good central visual acuity of the subjects with RP. The mean rod dark adaptation rate in RP group (10 per cent/minute) was noticeably slower than the rod values of the 60- to 80-year-old group (13 per cent/minute).

Dark adaptation testing is seldom performed due to long test time, its subjective nature and data variability due to learning and fatigue effects. The electroretinogram (ERG) and electrooculogram (EOG) are more commonly used to assess retinal function in people with RP.[16] The time efficiency of ERG testing cannot be denied but the time-dependent aspects of photoreceptor function should be investigated. A recent report has shown that rod dark adaptation curves can be derived from a-wave recovery in a rod specific ERG,[17] however, the ERG cannot, by definition, assess non-retinal aspects of visual function. It is possible that psychophysical aspects of the dark adaptation function offer some information that is not obtained from electrophysiology. Current technology including light emitting diodes, automated perimeters and laptop computers have been employed to modernise and accelerate the process of data collection in dark adaptometry.[6,18-20] This study has shown that a relatively simple data analysis can provide a more quantitative description of dark adaptation rates in patients with retinal disease. This technique will enable more effective use of dark adaptometry as a supplement to the objective electrophysiology when monitoring people with retinitis pigmentosa.

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