Impairment of colour contrast sensitivity and neuroretinal dysfunction in patients with symptomatic HIV infection or AIDS

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Abstract

Ophthalmic and neurological complications are frequent findings in patients with AIDS. Little is known about neuroretinal dysfunction in patients with HIV infection. The purpose of this study was to measure and evaluate colour vision in patients with HIV infection or AIDS. Colour contrast sensitivity tests were performed on 75 patients (150 eyes) in different stages of HIV infection. A highly sensitive computer graphics system was used to measure tritan, deutan, and protan colour contrast thresholds. Patients were classified into three clinical groups: (a) asymptomatic HIV infection, (b) lymphadenopathy syndrome or AIDS-related complex, and (c) AIDS. Overall, tritan ($p<0.0001$), deutan ($p=0.003$), and protan ($p=0.009$) colour contrast sensitivities were significantly impaired in patients with HIV infection compared with normal controls. Colour thresholds in patients with asymptomatic HIV infection (mean tritan threshold: 4·33; deutan: 4·41; protan: 3·97) were not impaired compared with normal controls. Colour vision was slightly impaired in patients with lymphadenopathy syndrome or AIDS-related complex (tritan: 6·25 ($p<0.0001$); deutan: 4·99 ($p=0.02$); protan: 4·45 ($p=0.05$)). In patients with AIDS the impairment was even more marked (tritan: 7·66 ($p<0.0001$); deutan: 5·15 ($p<0.0009$); protan: 4·63 ($p=0.004$)). Analysis of covariance controlling for age demonstrated a close association between impairment of tritan colour contrast sensitivity and progression of HIV disease ($p<0.0001$). Following Köllner's rule, our study suggests that neuroretinal dysfunction occurs in patients with symptomatic HIV infection or AIDS. This is emphasised by the finding that the relative impairment in tritan vision compared with deutan/protan vision might reflect the difference in the number of cones or receptive fields. Measurement of tritan colour contrast sensitivity appears to be an appropriate and easily applicable method to detect early neuroretinal dysfunction in patients with HIV disease.

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A new method for testing colour vision was recently described by Arden *et al*[1] when stimuli of varying colour contrast sensitivities are generated on a television monitor using a computer system. It has been shown that this system is able to detect and quantify changes in colour contrast sensitivity below the threshold of other commonly used colour test systems.[2,3] This computer graphics system was used to measure colour contrast sensitivity in patients infected with HIV-I in the different stages of the disease.

Neurophysiological, neurological, and neuro-ophthalmic deficits have been reported in patients with AIDS.[4–7] Recently, Quiceno *et al*[8] reported deficits in colour vision in patients with AIDS, but no specific colour axis of error was identified. There is a report suggesting that neurophysiological abnormalities occur in patients with asymptomatic HIV infection, but visual evoked potentials with pattern stimuli are noted to be normal in those patients.[9] The purpose of this study was to measure the colour contrast sensitivity in all patients with HIV infection and normal controls. In addition, the results from patients with asymptomatic HIV infection, patients with symptomatic HIV infection (without AIDS), and patients with AIDS were compared.

Patients, material, and methods

SUBJECTS

The study group consisted of 75 outpatients (150 eyes) with HIV infection seeking consultation at the department of ophthalmology of the University of Munich. Those patients with visual acuity below 0·8 with best correction, hereditary deut-/prot-/tritanomalia, hereditary deut-/prot-/tritanopia, diabetes mellitus, history or use of dideoxyinosine or dideoxycytidine, AIDS dementia, or opportunistic infections of the eye or the brain at the time of the study were excluded. Visual acuity was determined, and patients were refracted on an autorefractor if visual acuity was <1·0. Informed consent was obtained from all patients. All 75 patients were male, 68 reported homo-/bisexual orientation, and seven patients heterosexual orientation. No patient reported the use of illegal drugs. The mean age was 40·3 years with an SD of 9·6 (age range from 24 to 62 years).

BLOOD TESTS AND CLASSIFICATION OF HIV INFECTION

The sera from all patients were positive for HIV-I or HIV-II antibodies as determined by a licensed enzyme linked immunosorbent assay (Boehringer, Ingelheim). Western blot immunoelectrophoresis showed HIV-I infection in all patients. Staging was done according to the

Walter Reed and the Centers for Disease Control (CDC) classifications.[10 11] Patients in Walter Reed 1 were reclassified as patients with asymptomatic HIV infection (CDC classification II). Patients in Walter Reed 2 to Walter Reed 5 were reclassified as lymphadenopathy syndrome/AIDS-related complex (CDC classification III, IVA, or IVB). Patients in Walter Reed 6 or Walter Reed 2/K to Walter Reed 6/K or Walter Reed 2/N to Walter Reed 6/N were reclassified as AIDS (CDC classification IVC or IVD). The control group consisted of 70 male visitors or patients (140 eyes) who were HIV antibody negative with no known disease or abnormality of the anterior or posterior segment of the eye. The mean age of the control group was 39·6 years (SD 11·9; age range 14 to 71 years).

COLOUR CONTRAST SENSITIVITY

The computer graphics system originally described by Arden *et al* in 1988[1] was used with the modifications described by Arden *et al* in 1991.[3] In short, a monitor with a 90 Hz refresh rate, and dot pitch of 0·31 mm with a 980*760 pixel resolution (non-interlaced) was used to display the colours. A 100 MHz card, based on Hitachi ACRTC chip set with single pixel scrolling, pan and zoom facilities, and foreground/background display with alternate screens was used with a Brooktree '24-bit' palette. A personal computer (Compac Inc) with an 80286 CPU and an 80287 mathematical co-processor was used with software programs written in 'C'.

The stimuli composed of letters were displayed for 200 ms/s in the centre of a large uniform field. The letters were 8·1 cm high and traced from a standard optotype. The relative luminance of the blue:green and red:green guns was measured firstly by heterochromatic flicker photometry. Then, colour contrast thresholds were determined along protan/deutan and tritan colour confusion axes, which were orthogonal to each other in 'Commission Internationale d'Eclairage' colour space. The colour contrast thresholds were measured by a modified binary search scheme starting with a stimulus slightly above the mean threshold for most people (in this study the value=12). The subject then indicated whether detection had occurred. When the colour stimulus was detected, the signal presented became the new upper bound and half the contrast became the lower bound (value=6). When the stimulus value 12 was not detected, value 12 became the lower bound and value 24 the upper bound. Thresholds were measured to within 0·3 (which is the limit for the precision of the analogue to digital converter system).[1] The stage of the disease was not known to the investigators.

Table 1 Colour contrast sensitivity thresholds (mean (SD)) in patients with HIV infection. z Values are reported for the three overall comparisons. Results of the analysis of covariance are reported after grouping the patients into those with asymptomatic HIV infection, lymphadenopathy syndrome or AIDS related complex, and AIDS

	Number of cases	*Tritan threshold*	*Deutan threshold*	*Protan threshold*
Overall comparisons				
HIV infection	150	6·65 (2·52)	4·99 (1·26)	4·49 (1·21)
Normal controls	140	5·09 (1·21)	4·58 (1·28)	4·14 (1·24)
z Values (95% confidence interval)		1·29 (1·09 to 1·49)	0·32 (0·11 to 0·53)	0·28 (0·08 to 0·49)
p Value*		p<0·0001	p=0·003	p=0·009
Comparisons between groups of HIV infected patients				
Asymptomatic	20	4·33 (1·02)‡	4·41 (1·18)‡	3·97 (1·32)‡
LAS/ARC	60	6·25 (1·82)§	4·99 (1·23)¶	4·45 (1·18)¶
AIDS	70	7·66 (2·93)§	5·15 (1·29)‖	4·63 (1·33)**
Correlation with age		0·36 (p<0·001)	0·23 (p=0·006)	0·20 (p=0·01)
p Value†		p<0·0001	p=0·007	p=0·01

*Critical p value=0·0167.
†Analysis of covariance with age as covariate.
§p<0·0001, ‖p<0·001, **p<0·005, ¶p<0·05, ‡not significant: nominal p values for impairment compared with the normal controls.
LAS=lymphadenopathy syndrome; ARC=AIDS related complex.

STATISTICAL ANALYSIS

The primary issue of the study was to detect an impairment in at least one of the three colour axes of colour contrast sensitivity between patients with HIV infection and normal controls. A multiple significance level of $\alpha=0{\cdot}05$ was accepted. The Bonferroni adjustment was used to determine the critical p value for a single one sided Student's t test: $p_{crit}=0{\cdot}05/3=0{\cdot}0167$.[12 13] Another issue addressed in this study was to establish an association between the severity of the HIV infection and impairment of colour contrast sensitivity. The severity of the disease was staged according to the three categories mentioned above. A correlation of colour contrast sensitivity with age has been reported.[3] Therefore, analysis of covariance with age as a covariate was performed.[14] Numerical one sided p values are reported for those calculations and the results were interpreted with the intention of looking for 'near regular patterns'.[15] Correlations were calculated using the Pearson correlation coefficient method. Statistical analysis was carried out on an IBM/PS2 using the SPSS/PC+ V2.0 Program (SPSS Inc: SPSS-PC+ V2.0 Base Manual. SPSS Incorporation, Chicago, 1988).

Results

Overall comparisons revealed elevated thresholds of colour contrast sensitivity in all three colour axes (Table 1). The mean value for the tritan threshold was 6·65 (SD 2·52) in patients with HIV infection. The difference from the normal controls was highly significant (mean z value: 1·29; p<0·0001). The 95% confidence interval for the difference from the normal controls after z transformation was 1·09 to 1·49. The mean thresholds for deutan and protan were 4·99 (1·26) and 4·49 (1·21). The difference from normal controls was significant for the deutan (mean z value: 0·32; p=0·003) and the protan axes (mean z value: 0·28; p=0·009). The 95% confidence intervals for the difference after z transformation were 0·11 to 0·53 and 0·08 to 0·49, respectively. Thirty five per cent of patients with HIV infection presented with abnormal responses (outside 2 SD above the mean value; calculated for the normal controls) for tritan vision. Eleven per cent of patients with HIV infection presented with abnormal responses for protan vision, and 12% for deutan vision. The tritan threshold was four times higher than deutan (4·0:1) and protan (4·6:1) thresholds.

Comparisons between the three clinical groups of HIV infection suggest a close association between progression of the disease and

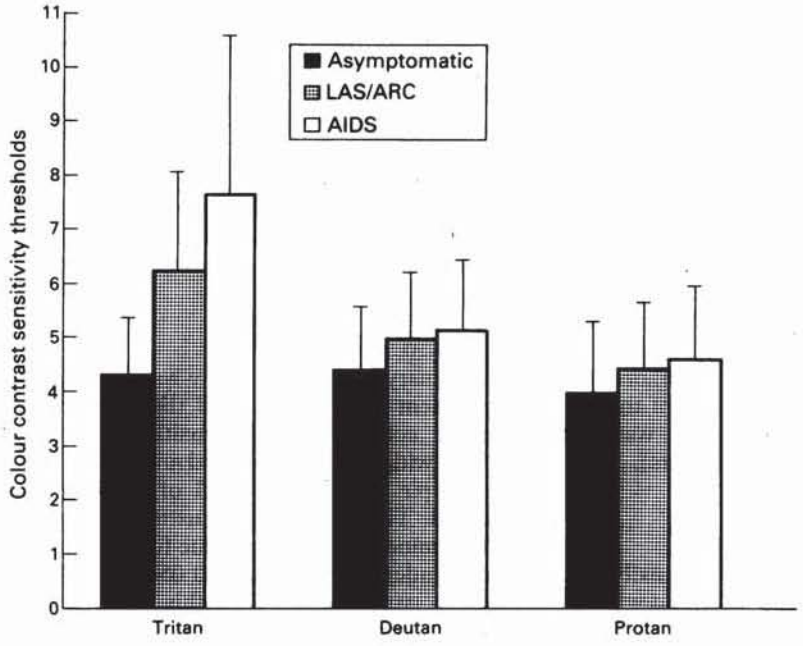

Figure 1 Tritan, deutan, and protan contrast sensitivity thresholds (mean value+SD) in patients at different stages of HIV disease: asymptomatic patients (eyes: n=20); patients with lymphadenopathy syndrome (LAS) or AIDS related complex (ARC) (n=60); and patients with AIDS (n=70).

elevation of tritan threshold ($p<0.0001$) (Table 1; Fig 1). Tritan contrast sensitivity in patients with asymptomatic HIV infection (mean threshold 4·33 (SD 1·02)) was not impaired compared with that in normal controls. However, the mean tritan threshold was significantly elevated in patients with lymphadenopathy syndrome or AIDS related complex (6·25 (1·82), $p<0.0001$); in patients with AIDS, this elevation was even more marked (7·66 (2·93), $p<0.0001$). No patient with asymptomatic HIV infection, 28% of patients with LAS or ARC, and 51% of patients with AIDS presented with abnormal responses for tritan vision. Deutan (4·41 (1·18)) and protan (3·97 (1·32)) thresholds in patients with asymptomatic HIV infection did not differ from those in normal controls, but there was a tendency towards a threshold elevation in patients with lymphadenopathy syndrome or AIDS related complex (deutan: 4·99 (1·23), $p=0.02$; protan: 4·45 (1·18), $p=0.05$). Both thresholds were similarly elevated in patients with AIDS (deutan: 5·15 (1·29), $p<0.001$; protan: 4·63 (1·33), $p<0.001$) when compared with the normal values. No patient with asymptomatic HIV infection, 3% of patients with LAS or ARC, and 20% of patients with AIDS presented with abnormal responses for protan vision. Similarly, no patient with asymptomatic HIV infection, 5% of patients with LAS or ARC, and 21% of patients with AIDS presented with abnormal responses for deutan vision.

The correlation coefficients of the colour contrast sensitivity with age were $r=0.36$ for tritan, $r=0.23$ for deutan, and $r=0.20$ for protan. The correlation coefficient between deutan and protan axis was $r=0.91$. The correlation coefficients of tritan axes with protan and deutan axes were $r=0.52$ and $r=0.61$, respectively.

Discussion

This study shows a decrease in colour contrast sensitivity in patients with symptomatic HIV infection and AIDS. However, colour vision was normal in patients with asymptomatic HIV infection. The decrease in colour vision was primarily evident for tritan colour contrast sensitivity, which was highly reduced in patients with symptomatic HIV infection and AIDS. The impairment of tritan vision increased as the disease progressed from symptomatic HIV infection to AIDS. The impairment in deutan and protan colour contrast sensitivity was less than that in tritan contrast sensitivity; but the deficits in deutan and protan vision were very evident among patients with AIDS. After transformation of the results in z values, tritan colour contrast sensitivity was impaired about four times more than the deutan and protan colour contrast sensitivity.

Köllner[16] demonstrated in 1912 that alterations of the optic nerve are accompanied by deficits in protan vision, whereas alterations of the neuroretina are accompanied by deficits in tritan vision. An impairment of tritan vision was the prominent finding in our study. Following Köllner's rule, we conclude that dysfunction of the neuroretina is seen in patients with lymphadenopathy syndrome, AIDS related complex, or AIDS.

Neurophysiological studies have shown that the total number of tritan photoreceptors is lower compared with deutan or protan photoreceptors, and that the relative frequency of the different cones is 1·0:2·5:4·1 (tritan:protan:deutan) in primates.[17,18] As tritan receptors are less numerous, damage to the neuroretina causes alterations of tritan vision first before alterations of deutan or protan vision occur.[16] One might speculate that the 4:1 ratio found for impairment of tritan and protan/deutan sensitivity might be related to the difference in the number of cones of blue-yellow and red-green receptive fields because, if damage occurs on retinal level, the relative impairment might be quantitatively related to a difference in the number of cones or receptive fields of the different colour systems. However, other explanations for the difference in the magnitude of impairment of tritan and protan/deutan sensitivity include a more limited response range and a higher fragility of the tritan colour vision system compared with the protan/deutan colour vision system.[19]

There was a high correlation between deutan and protan colour contrast sensitivity, which should be expected for physiological reasons.[20] Colour vision in humans is organised in two systems on the postreceptoral retinal level, the blue/yellow (S cone) and the red/green (L cone and M cone) systems, and both systems are organised in receptive fields. Therefore, the high correlation between protan and deutan thresholds can be interpreted as an indication of the reliability of our results.

Several aspects of the results of our study should be discussed. Firstly, the pattern of association of colour vision impairment with progression of the disease was similar for the three colour axes, even if impairment of deutan and protan colour vision was not as prominent as that of tritan colour vision. Secondly, possible changes due to drug misuse were circumvented by our exclusion criteria. Thirdly, it is unlikely that an undetected opportunistic infection of the

eye was present, since no patient developed retinal or systemic cytomegalovirus infection or other opportunistic ocular infections within 2 months after testing for colour contrast sensitivity. Fourthly, the association between impairment of colour contrast sensitivity and progression of the disease was not related to age. The correlations between colour contrast sensitivity and age in our study were similar to the findings by Arden *et al.*[3] Analysis of covariance with age as covariate demonstrated that the impairment of colour contrast sensitivity was most closely related to the severity of the disease. This is corroborated by the finding of a faster progression of the disease in older patients, and a tendency towards a more severe disease in older patients due to the longer asymptomatic period of HIV infection.[21,22] Lastly, the impairment of colour vision is not related to the homosexual orientation of most of our patients, since in the asymptomatic patients no decrease of colour contrast sensitivity was shown.

It should be mentioned that the degree of the underlying colour vision impairment in patients with lymphadenopathy syndrome, AIDS related complex, and AIDS is very low. Therefore, the impairment of colour vision in patients with lymphadenopathy syndrome, AIDS related complex, or AIDS has no implications for daily life – for example, car driving.

Our findings are in accordance with several electrophysiological studies done on the eye.[6,9,23] No ocular electrophysiological changes were found in patients with asymptomatic HIV infection.[9] Reduction of the amplitudes in the pattern electroretinogram combined with P50 latency suggests an alteration of the neuroretina in patients with AIDS.[23] The results of the present study are also in accordance with papers reporting on clinical neurological complications in about 35% of patients with AIDS,[23] and on neuropathological changes seen in up to 88% of autopsy brains.[24–26] The data of the present study are not totally in accordance with a recent study reporting that neuro-ophthalmic abnormalities are present in only a minority (8%) of patients with AIDS.[27] Recently, Quiceno *et al*[8] were able to show a decrease in colour discrimination in patients with AIDS, but no significant decrease was found for patients with AIDS related complex, and no particular axis of error was identified applying the Farnsworth-Munsell 100-hue test.

Several mechanisms of damage to the neuroretina might be responsible for the dysfunction of the colour contrast sensitivity in patients with HIV infection. In patients with diabetic retinopathy an alteration of colour vision was reported by different authors, and tritan vision seems to be more impaired when compared with protan and deutan vision in patients with diabetic retinal microvasculopathy.[28–32] Therefore, microvascular changes known in patients with HIV disease should be considered. HIV-related retinal microvasculopathy is the most common ocular finding in severe HIV infection (with a frequency of 50% to 80% in patients with AIDS). The former causes retinal damage presenting as cotton wool spots or haemorrhages upon ophthalmoscopic examination.[33–35] According to retinal fluorescein angiography and pathological studies there is evidence that cotton wool spots in patients with AIDS might be caused by microvascular abnormalities,[34,36,37] and retinal microvascular alterations were observed in patients with AIDS or symptomatic HIV disease by fluorescein angiography.[36,38] Recently, we were able to demonstrate a close association between the occurrence of cotton wool spots and cerebral hypoperfusion, as well as between cotton wool spots and cognitive deficits.[39,40] We favour the hypothesis that the deficits in colour contrast sensitivity are primarily related to HIV related retinal microvasculopathy. Other pathogenetic factors also need to be discussed. HIV has been detected in the retina, in endothelial cells, in microglial cells, and in multinucleated giant cells.[41–45] Moreover, metabolic alterations may also be important in patients with symptomatic HIV infection.[46–48] It is possible that the neuroretinal dysfunction in patients with symptomatic HIV infection is caused by a combination of these factors.

Our results suggest that neuroretinal damage occurs in patients with symptomatic HIV infection or AIDS. Measurement of tritan colour contrast sensitivity might be an appropriate and easily applicable method for the measurement of early neuroretinal dysfunction in patients with HIV infection. The underlying pathogenic mechanisms need to be elucidated.

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