Screening for CMV retinitis using chromatic discrimination thresholds and achromatic contrast sensitivity

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Abstract

Background—Many patients with cytomegalovirus retinitis (CMVR) are unaware of visual disturbance so screening is advocated for patients with HIV and low CD4 counts. Many tests of retinal function have been recommended but few are effective at detecting CMVR. We assess the potential of chromatic discrimination thresholds and achromatic contrast sensitivity as screening tests for patients with CMVR.

Method—11 HIV+ patients with CMVR, 16 age matched HIV+ patients, and 29 age matched controls were recruited. Visual acuity, chromatic discrimination thresholds, and achromatic contrast sensitivity were measured. Fundal examination was performed by slit lamp biomicroscopy for HIV+ patients. Those with CMVR were photographed and the CMVR graded from the photographs.

Results—Loss of chromatic discrimination was found in patients with CMVR (tritan p<0.0005, red/green p<0.05). The same group had deterioration in achromatic contrast sensitivity at 2.2, 3.4, and 10 cpd (p<0.05). There was correlation between the zone of CMVR with chromatic gratings (tritan r=0.83, p<0.0005). No statistically significant difference was found between the HIV+ patients and the controls for all tests (p>0.1).

Conclusions—HIV+ patients with CMVR have a loss of chromatic discrimination and achromatic contrast sensitivity and this may be used to screen HIV+ patients for CMVR.

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Cytomegalovirus retinitis (CMVR) is the leading cause of visual loss in patients with HIV infection. Most patients with early CMVR are unaware of any visual disturbance and so screening for CMVR has been advocated for patients with CD4+ counts of <75 × 10⁹/L.3 Several screening methods have been tried, including detection of CMV virus in the plasma and urine. Shinkai et al found a 2.3-fold increase in CMVR in patients with CMVuria; others showed a relative risk for CMVR development of 23 using CMV DNA polymerase chain reaction, using it to determine pre-emptive therapy. However, these methods have limitations in the diagnosis of ocular disease.

Visual field analysis has been used to detect scotomata in patients with CMVR and other investigators have used entoptic visual fields to detect disturbances in continuous random particle motion. Teich et al developed a self screening chart for CMVR which assesses the inner 40 degrees of field. Their results showed 63% of patients with CMVR noted a scotoma. The electroretinogram (ERG), pattern ERG, and visual evoked cortical responses (VECR) may also be affected, particularly in those with CMV retinitis. There are also reports of reduced chromatic discrimination sensitivity in patients with HIV retinopathy.14

In this study we looked at achromatic contrast sensitivity and chromatic discrimination sensitivity in patients with CMVR, comparing them with HIV+ patients and healthy controls; assessing chromatic discrimination sensitivity and achromatic contrast sensitivity as potential screening techniques for patients with CMVR.

Methods and subjects

Subjects were recruited from a CMVR clinic (Sussex Eye Hospital), the Department of HIV Medicine (Royal Sussex County Hospital), and healthy volunteers. We examined 11 patients with CMVR. They were age matched with 16 HIV+ patients and 29 controls taken from our laboratory’s standard control data. Exclusion criteria for all groups included congenital colour deficit, evidence of other ocular pathology, a history of systemic disease known to affect the eye (for example, diabetes), and any medication (for example, digoxin) that could affect colour vision. Ethical approval was given by the East Sussex ethics committee and informed consent was obtained from all patients.

Chromatic discrimination sensitivity and achromatic contrast sensitivity were measured using the Sussex grating machine (SGM). The SGM was used to measure chromatic discrimination along the red-green (constant S-cone) and tritan (constant L/M-cone) confusion axes.

Chromatic stimuli were presented in the form of a static, sinusoidal, low spatial frequency (0.66 cpd) grating on a high resolution cathode ray tube (CRT) (luminance 20 cd/m²). Test subjects were positioned 2 metres from the CRT so that the stimuli subtended a central visual angle of 4°. Following a warning tone the subjects were forced to choose between indicating whether stripes were seen
or not. To confirm the subject understood the procedure, a short practice routine was performed binocularly. The test was then performed monocularly on each eye.

Chromaticity of the gratings was modulated about the white point (Comité International de l’Eclairage (CIE) 1976 u’ v’ coordinates: 0.21, 0.47) along either the red-green or tritan axis. The chromatic amplitudes at which the subject could just distinguish gratings was determined using a double staircase reversal algorithm as described by Cornsweet.29 Two spectrally randomised, interleaved staircases were used for each chromatic axis tested, the chromatic amplitude of the stimulus increased or decreased until the subjects changed their response. When this occurred, the chromatic amplitude was recorded and the direction of the stimulus sequence was reversed from ascending to descending, or vice versa. This procedure continued until five reversal points had been achieved and the mean of these points was taken as the chromatic discrimination threshold. All procedures were carried out under automated software control. A complete test session, involving giving instructions to the subject, a practice routine, and measurement of red-green and tritan discrimination of both eyes, took 15 minutes.

The same system was used to produce achromatic gratings of various spatial frequencies (0.33, 0.66, 2.2, 3.3, 10, and 17 cpd) to measure contrast sensitivity. These were presented to the patient in a random order. The SGM had a built-in calibration facility based on a radiometric photodiode. Regular checks were made to guard against variations of the CRT electron guns and other sources of error. A standardised equiluminant grating was used as had been assessed in previous studies with the SGM.17–19

Visual acuity was measured with a standard illuminated Bailey-Lovie logMAR acuity chart. The tests were performed with emmetropic correction. The pupils were dilated and ophthalmic examination was performed. Retinal examination was performed with a Volk superfield lens by one of two ophthalmologists (RSB or TLJ) followed by retinal photography if CMVR was detected. Photographs were taken graded using the Studies of the Ocular Complications of AIDS (SOCA) grading system.1 The disease was described according to location within the retina—zone 1, within 3000 μm of the centre of the fovea or 1500 μm from the disc; zone 2, from zone 1 to the ampulla of the vortex veins (equator of the globe); zone 3, from zone 2 to the ora serrata.

STATISTICAL METHODS

One eye from each subject was randomly selected and age matched for patients in the CMVR group, HIV+ group, and the control groups. If a patient had unilateral CMVR, then only the affected eye was included in the analysis. Student-Newman-Keuls tests were carried out to determine differences of age, visual acuity, chromatic discrimination, and contrast sensitivity between the groups. For chromatic discrimination sensitivity, the sign of the data was reversed from plus to minus as the threshold measuring system is opposite to that used for achromatic contrast sensitivity. The CD4 counts of the CMVR groups and the HIV+ groups were compared with the Mann-Whitney U test. Patients with CMVR were further divided into those with zone 1 disease, those with zone 2 disease, and those with zone 3 disease and the results analysed using Spearman rank correlation. All data are presented as the mean (SD) and p values <0.05 were considered significant.

Results

Eleven patients with CMVR were recruited (age 42.6 (5.5) years), and age matched with 16 HIV+ patients (age 41.1 (4.5) years) and 29 healthy controls (42.9 (8.3) years). There was no difference in age for all study groups (Student-Newman-Keuls: p>0.05). The CMVR group had an HIV viral load of 2.3 × 10^6 (2.8 × 10^6) and a CD4 count of 75.7 (51.7) ×10^6/l, the HIV+ group having a significantly higher CD4 count at 429.8 (172.6) ×10^6/l (Mann-Whitney U test: p<0.001). Five patients with CMVR had zone 1 disease, four zone 2 disease, and two zone 3 disease. The CMV was controlled with either cidofovir (10 patients) or intravitreal ganciclovir (one patient). None of the HIV+ patients had HIV related retinopathy. Results of age, visual acuity, chromatic discrimination, and contrast sensitivity thresholds are summarised in Table 1.

There was no difference in logMAR visual acuity among the CMVR group (0.09 (0.22); Snellen equivalent: 6/7.5), HIV+ group (0.01 (0.07); Snellen equivalent: 6/6), and control group (−0.02 (0.10); Snellen equivalent: 6/6) (Student-Newman-Keuls test: p>0.1). Similar analysis showed that the CMVR patients had significant loss of chromatic discrimination sensitivity (Fig 1), especially along the tritan confusion axis, when compared with those of the normal control group (TDT: p<0.0005; RGDT: p<0.05) and those with HIV+ (TDT: p<0.0001; RGDT: p<0.05). However, no statistically significant difference was observed between HIV+ patients and controls (p>0.2).

Student-Newman-Keuls analysis also showed that TDT could discriminate CMVR...
Chromatic discrimination thresholds of CMVR patients were significantly worse. Figure 1 shows the mean achromatic contrast sensitivity for CMVR, HIV+, and control patients. Contrast sensitivity was particularly a factor in patients with CMVR losing contrast sensitivity. Discussion

Visual dysfunction in HIV+ patients has been widely reported, but there is little information on the additional effect of CMV infection on retinal function. In this study CMVR was associated with significant reduction in chromatic discrimination sensitivity, particularly along the tritan confusion axis. There was no chromatic or achromatic loss in our HIV+ (no retinopathy) group. These results are consistent with Quiceno et al who found no loss of colour vision in HIV+ patients without AIDS. This group did however find that colour vision and contrast sensitivity were reduced in patients with AIDS. Contrast sensitivity was particularly affected at 3–10 cpd; this was mirrored in this study with patients with CMVR losing contrast sensitivity between 2.2 and 10 cpd.

Some have suggested that optic nerve dysfunction may reduce contrast sensitivity in these patients, as there is little loss at lower frequencies. However, in this trial the tritan chromatic threshold was particularly affected indicating damage to the inner nuclear layer. Geier et al tested patients with HIV related ocular microangiopathic syndrome for protan, deutan, and tritan contrast sensitivity. The tritan sensitivity was the most affected by the disease. The most significant predictor for chromatic discrimination sensitivity loss was the number of cotton wool spots. Tritan loss probably indicates damage to the neuroretina as S-cones are involved in 25% of receptor fields.

Our population of patients with HIV had no recorded HIV retinopathy and no chromatic discrimination or achromatic contrast sensitivity loss. This is in contrast with other reports where reduced contrast sensitivity and colour perception were found in patients with HIV infection without retinopathy. In Muller’s study, HIV+ patients with normal retina had abnormal colour vision with a normal Halstead-Reiton test (for neuropsychological deficits) indicating that the colour loss was a retinal phenomenon and not a cortical process. Of note, however, was the presence of patients with previously documented, but quiescent, HIV retinopathy. This subgroup possibly affected the results. In our group there was no colour loss in the HIV+ patients without retinopathy. These patients had no microangiopathic damage and might have been at an earlier stage of HIV infection. In neither group was visual

Figure 1  Mean red-green and tritan discrimination thresholds for CMVR, HIV+, and controls. Chromatic discrimination thresholds of CMVR patients were significantly worse. (Tritan p<0.001; red-green p<0.05.) Error bars are standard errors.

Figure 2  Mean contrast sensitivity for CMVR, HIV+, and controls. Contrast sensitivity for CMVR patients was significantly reduced at 2.2, 10 (*p<0.05), 3.4 (**p<0.01). Error bars are standard errors.

Figure 3  Correlation of red-green and tritan discrimination thresholds (RGDT) with CMVR zones, r=0.76, p<0.005 for tritan discrimination threshold (TDT).

patients with zone 2 and zone 1 (p<0.05) disease from the control group but not those with zone 3 disease.

Figure 2 shows the mean achromatic contrast sensitivity of all spatial frequency gratings for the CMVR, HIV+, and control groups. A threshold deficit across all spatial frequencies for the CMVR group in comparison with the HIV+ and control groups was noted. Student-Newman-Keuls analyses showed that these deficits are significant for spatial gratings at 2.2, 10 cpd (p<0.05), and 3.4 cpd (p<0.005).

Spearman rank correlation analysis showed that chromatic and achromatic discrimination along with visual acuity yielded strong correlation with zone of CMVR. Tritan discrimination sensitivity, logMAR acuity, and achromatic sensitivity at 2.2 and 3.4 cpd showed a correlation with zone (TDT: r=0.83, p<0.005; logMAR: r=0.783, p<0.005; 2.2 cpd: r=0.765, p<0.01; 3.4 cpd: r=0.795, p<0.005; see Fig 3). However, there was no correlation for CD4 count or HIV viral load with visual acuity, achromatic contrast, and chromatic discrimination sensitivity.
dysfunction correlated to the severity of the HIV infection (defined by the CD4 count).

Other studies have shown widespread psychophysical changes in patients with localised CMVR (<10%) in the absence of HIV+ microangiopathy. HIV+ patients and patients with AIDS produced results that were consistent with mild uniform retinal damage. The group of patients with CMVR showed greater impairment than the HIV+ and AIDS group on all measures. Latkany et al argued that these results indicate a widespread occult microangiopathy in patients with CMVR. Alternatively in some patients there could be a direct effect of CMVR destroying retinal ganglion cells or creating a low grade chorioretinitis. This hypothesis may be supported by our findings of a clear correlation between tritan visual loss and the zone of CMVR (TDT: r=0.83, p<0.005). The more central the zone the more macular damage, and thus the more chromatic discrimination sensitivity was affected.

The analogy between HIV and diabetic microangiopathy has often been made. Chromatic discrimination sensitivity defects have been found in both conditions, particularly on the tritan axis. Testing patients with established AIDS and negligible viral load could provide evidence as to the origin of chromatic discrimination sensitivity loss. Most screening for CMVR has been focused at detecting the “at risk” individual. Cytomegalovirus (CMV) viraemia (detected by polymerase chain reaction) identifies 84% of patients at high risk of CMVR within 1 year, giving a clear indication of which patients should be screened ophthalmologically. It is, however, unable to determine whether patients have CMVR. Other methods have been used, including the Teich chart, which tests the central 45 degrees of vision. Using this technique the authors demonstrated a sensitivity of 63%, compared to a simple Amster chart at 37%. In this paper tritan CDT proved a reliable and easy to administer test for CMVR. Seventy per cent of patients with CMVR were detected. Those that were missed had small areas of zone 3 disease.

Others have used entoptic perimeter to locate peripheral scotomas found in patients with CMVR. This test gave a high sensitivity in the 11 patients screened. However, the area affected of retina by CMVR was not recorded, and so direct comparisons are not possible.

In the present study, a standard equiluminant grating was used for chromatic discrimination thresholding. A gold standard employed is heterochromic flicker photometry. However, patients with acquired colour vision loss lose other areas of visual function such as flicker detection and previous SGM studies have shown no difference between heterochromic flicker photometry and equiluminant grating. Many patients with acquired colour vision deficits are unable to perform the flicker photometry tests.

Early detection of new infection and reactivation of old CMVR lesions remains a clinical priority as early treatment reduces visual loss.

Chromatic discrimination sensitivity could provide a simple and cost effective method for CMVR screening.

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