

Original Article

Localized scotomata detected with temporal modulation perimetry in central serous chorioretinopathy

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ABSTRACT

Aim: Flicker deficits have been reported in various maculopathies, including age-related macular degeneration. We test whether flicker losses exist in patients with central serous chorioretinopathy (CSC) and whether the size and flicker frequency of the target is important in detecting such losses.

Methods: We examined four CSC patients with temporal modulation (flicker perception) perimetry using the Medmont auto-flicker module (Medmont Pty Ltd, Melbourne, Vic. Australia), as well as static perimetry and colour vision. One case was examined using sophisticated laboratory equipment to precisely measure their temporal contrast sensitivity function (temporal CSF or de Lange curve) using larger targets to consider the effect of target frequency and size. Two patients were followed longitudinally and tested after resolution of the maculopathy. We compared our patients with an age-matched control group of 11 people.

Results: Temporal modulation perimetry detected larger and more localized defects in all cases of active CSC compared with static perimetry. There appeared to be size and frequency tuning to the deficit, with greatest loss being found at 16 Hz with small (0.5°) targets. The losses resolved in one case where the retina recovered in 4 weeks, but remained to a lesser degree in another case who suffered a 2 year long fluctuating course before the CSC subsided.

Conclusions: Temporal modulation perimetry detects a loss of flicker sensitivity in patients with CSC. Deeper and more

clearly defined scotomata are found with a flickering stimulus compared with a steady state one. The greatest losses of flicker sensitivity are found with 16 Hz modulation and with small targets located directly over the lesion. The duration of the disease may be important for recovery of flicker sensitivity. Temporal modulation perimetry appears to be a valuable tool for the confirmation of functional loss due to CSC.

Key words: central serous chorioretinopathy, flicker perimetry, maculopathy, temporal modulation perimetry.

INTRODUCTION

Losses of flicker sensitivity have been reported in eye diseases that affect both the optic nerve^{1–7} or retina.^{8–12} In many cases, flicker has been considered as a sensitive testing medium because it can precede visual losses measured using temporally static targets by several years.⁶

The way that flicker thresholds have been measured has varied between studies and deserves some scrutiny in order to understand the mechanisms involved. One method for determining flicker sensitivity establishes the critical fusion frequency (CFF; highest flicker frequency to produce a flickering percept) for a fixed level of target contrast. This method is similar to measuring visual acuity in the spatial domain and is likewise unrepresentative of sensitivity across a range of frequencies and contrasts. It has been used extensively by many investigators and, most recently, by Lachenmayr *et al.*,² where CFF has been found to be abnormal in glaucomatous eyes. Another interesting clinical application of flicker sensitivity is the brightness matching method developed by Aulhorn.³ This method uses the

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Brüke–Bartley luminance enhancement effect found between 8 and 12 Hz and has been shown to be abnormal in patients with optic neuritis.³ Finally, flicker sensitivity can be measured by establishing the temporal modulation threshold. With this technique, the temporal frequency is fixed and target contrast at flicker threshold is determined. When applied across the visual field, this procedure has been called temporal modulation perimetry (TMP) or flicker perimetry.⁶ It is this last method of testing (TMP) that is used in the present study.

One of the interesting observations made with TMP is that flicker threshold losses precede and exceed those found with conventional static perimetry in cases of glaucoma.⁶ Similarly, flicker losses exceed those found with static perimetry in optic nerve hypoplasia.⁷ This may be explained if the temporal deficit reflects loss or under-development of some of the nerve fibres involved in signalling the test frequencies. However, flicker losses can also be found in outer retinal disease.

Eisner reports profound (> 10 SD) reductions in flicker sensitivity (which he called PRFS) in patients who are otherwise normal but have systemic hypertension.⁵ Likewise, Mayer^{11,13} reports abnormal temporal modulation thresholds in some patients with age-related macular degeneration (ARMD). Temporal modulation thresholds from 2.5 to 14 Hz were found to have better sensitivity for predicting subretinal neovascular membrane (SRNVM) formation than fundus grading or fluorescein angiography.^{11,13} We have previously shown that TMP can detect pigment epithelial detachment (PED) caused by occult SRNVM.¹² In that case, we found gross TMP deficits in the presence of normal static thresholds.¹²

The reporting of flicker losses with various retinopathies warrants further consideration, as the studies where this was found used different test methods and perhaps their findings are not comparable. The flickering stimulus used by Mayer was a 2.8° red target presented on a time-averaged white background of 120 cd/m². This relatively large stimulus will isolate an L-cone flicker channel, but its size will limit its capacity to detect localized or small lesions.¹⁴ Moreover, it is not clear whether the red target is an important factor in their results. Eisner and Samples investigated different colour stimuli and showed that intermediate wavelengths (530–560 nm) give the greatest losses in glaucoma.⁵ They suggest that such losses may involve abnormal lateral interactions in spectrally opponent cells. In that experiment, Eisner and Sample produced a luminance step in association with the flickering spot (equivalent to light chopping). The processes mediating detection could involve the luminous increment or the flickering component or some interaction of both. However, Eisner claims that flicker thresholds can be isolated adequately with such stimuli provided that the subject is required to respond to the percept of flicker.¹⁵

Although Eisner makes this claim, subject reliability or compliance were never established.

Vingrys adopted a similar strategy to Eisner but used a modified commercial perimeter for the testing of flicker thresholds.⁷ This perimeter presents a 0.5° flickering luminous stimulus (565 nm) on a 3 cd/m² background. We support Eisner's suggestion, by showing that this multi-dimensional spot configuration can isolate flicker thresholds when the subject is asked to respond to the percept of flicker. We also suggest that a temporally unmodulated false-positive monitor needs to be incorporated into the test in order to ensure compliance with the desired sensorial response.

Although these studies differed in their test methods, they have an important commonality and conclusion: that flickering targets can detect areas of retinal ischaemia,¹³ serous elevation¹² or compromised blood flow.⁵

In the present study, we have used a series of cases to test the hypotheses that: (i) TMP is more sensitive to early retinal compromise than is static perimetry in cases of central serous chorioretinopathy (CSC); and (ii) small targets have advantages for detecting this dysfunction. For this purpose, we chose to investigate the serous elevation of the sensory retina as found with CSC because, in most cases, it imparts a temporary deficit in retinal function and, more importantly, is a condition that affects young and otherwise healthy individuals who may be expected to be free of systemic hypertension or ischaemia.¹⁶ We support both hypotheses by finding that flicker is more sensitive to the early losses of visual function produced by CSC and that localized stimuli do have significant advantages in detecting these losses.

METHODS

The study was approved by The University of Melbourne ethics committee and all subjects provided informed consent prior to participation. All subjects undertook a routine eye examination, colour vision testing, static perimetry and TMP using a Medmont automated perimeter (Medmont Pty Ltd, Melbourne, Vic. Australia). One subject with CSC had their temporal contrast sensitivity function (temporal CSF or de Lange curve) precisely measured using sophisticated laboratory equipment and larger targets to consider the effect of target frequency and size. All subjects with CSC were independently diagnosed by an ophthalmologist and all had fluorescein angiograms taken, as needed, to either confirm the diagnosis or monitor progression.

Equipment

The Medmont M600 perimeter was used to perform the visual field evaluation. A detailed description of an early model of this perimeter is given elsewhere.¹⁷ In brief, this is

a light-emitting diode (LED; $\lambda_{\max} = 565$ nm) bowl perimeter with a 3.2 (cd/m^2) background that eliminates the black hole effect with a translucent covering. The LED subtend 0.5° in diameter and have a maximum spot brightness of 320 cd/m^2 . The spots are arranged concentrically at various eccentricities, ranging from 1° to 50° ; however, for these cases, the macula pattern was used (1 – 10°). The macula pattern presents 48 spots at 1° , 3° , 6° and 10° rings as well as a blind-spot monitor. The macula pattern has been shown to have a high sensitivity and specificity for the detection of foveal compromise when compared with the Humphrey 10–2 program.¹⁸ Thresholding is achieved by a 6/3 dB staircase with two crossings used to confirm threshold. Target duration for static presentation was 200 ms and 800 ms for the flickering spot.

Temporal modulation perimetry testing was conducted using the automatic flicker thresholding module. In this module, flicker frequency is varied as a function of eccentricity, being fixed at 16 Hz at 1° , 16 Hz at 3° , 12 Hz at 6° and 9 Hz at 10° . Subjects are requested to respond to the percept of 'flicker', 'shimmer' or 'twinkle'. They were told to expect non-flickering spots and not to respond to the mere presence of a light. Static near-threshold spots are presented as part of the false-positive monitor in order to ensure that subjects comply with the request to respond to flicker. These are shown very frequently early in the test to assist in the learning process. Prior to each test, each subject was given a 2 min supervised practice session with feedback to ensure compliance with the required sensorial attribute. All subjects performed static perimetry followed by the flickering test. This choice of test order was deliberate to ensure that any learning effects would not bias the results in favour of greater losses with flicker testing. If the tests were conducted with flicker first and static second, then greater losses with flicker could be attributed to learning effects rather than to stimulus features. With static testing first and flicker second, any learning effect would lead to an underestimation of a greater loss with flicker. Most testing was completed within 5–6 min. Therefore, fatigue should not be a factor in our outcomes.

One subject had their de Lange function (temporal CSF) measured during the acute phase of the disease using laboratory based equipment. The de Lange curve was determined at 1, 2, 4, 8, 16 and 32 Hz on a calibrated and gamma-corrected TV monitor with a frame rate of 90 Hz driven by a VSG2/1 video board (Cambridge Research Systems, Cambridge, UK). The average background luminance of the screen was 30 cd/m^2 . The test stimulus had the same luminance as the background. The stimulus was a 3° spot shown in a 1 s raised-cosine temporal envelope (Hann window) and was presented using a two interval–forced-choice paradigm. Each interval was preceded by an auditory

signal. Testing was conducted with a 3/1 dB, two up/one down staircase with the average of the last eight reversals taken as threshold. Stimuli were located either foveally or centred over the region of the defect (4° inferior on the 300° meridian).

Colour vision testing was achieved using the D15 panel. Scoring considered the nature of transpositional errors with two or more minor transpositions being judged as failure.

Subjects

A total of 15 subjects were tested. Four were patients with CSC (aged 24–44 years; mean 33.7 ± 8.3 years) and 11 were age-matched controls (aged 22–44 years; mean 29.6 ± 7.5 years). All had normal systemic and ocular health (other than the CSC) and none had systemic hypertension or was being treated with any medication. For the controls, one eye was randomly assigned to be tested and all control eyes had visual acuities of 6/6 or better. Table 1 gives a summary of the CSC patient details. Two of our patient group (cases 2 and 3) were followed longitudinally until resolution of the chorioretinopathy.

Data analysis

Visual field data were compared by considering the summary indices (mean and pattern defect) for both the flicker and static conditions. These were analysed with a one-way ANOVA and Student–Newman–Keul's post hoc comparisons with an alpha of 0.01 for all testing.

RESULTS

Most CSC patients had abnormal colour vision and reduced visual acuity ($< 6/6$) in the affected eye (Table 1), whereas these results were normal in their fellow eyes and returned to normal in affected eyes for those two patients who were followed longitudinally. No control had abnormal colour vision or visual acuity.

No normal observer had any difficulty performing the perimetric tasks. All controls gave normal fields to static and

Table 1. Visual acuity and colour vision outcomes for our patient group

	Visual acuity	Colour vision
Case 1	6/12	BY
Case 2	6/7.5 (6/4.8)	P (P)
Case 3	6/7.5 (6/4.8)	BY (P)
Case 4	6/7.5	P

The panel D15 result is shown as BY when prominent blue–yellow errors were made or P for passing performance. Values in parentheses show outcomes after resolution of the serous elevation.

flickering targets (data not shown). False-positive (FP) rates for controls show that they complied with the perceptual requirement of responding to flicker with a mean FP rate of 3.5% (range 0–25%) for the flicker test. The CSC group also had reliable FP rates (all 0%) and, thus, complied with the instruction to respond to the percept of flicker. The static FP rates were identical for both groups and can be considered normal.¹⁹

Figure 1 is a frequency histogram of the perimetric summary indices for both static and flicker outcomes. The mean defect for the CSC group is normal, in most cases overlapping that of the control group except for one observer with flicker testing. In contrast, the pattern defect shows abnormally high values for the flicker test for all CSC subjects. These normalized with time for one individual who recovered, but remained abnormal for the other.

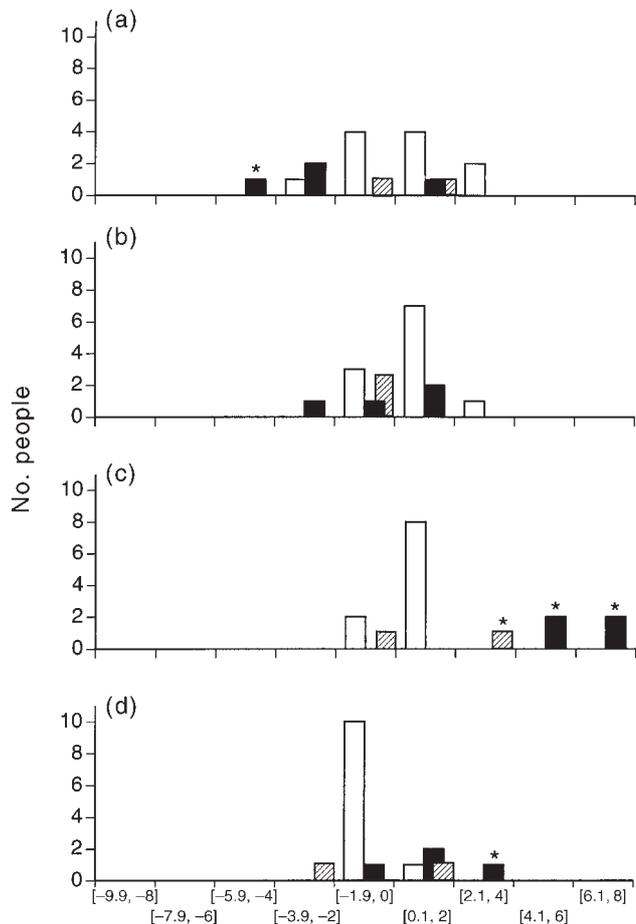


Figure 1. Cumulative frequency histograms for the mean (a,b) and pattern (c,d) defect indices returned by the perimeter for static (b,d) and flickering (a,c) targets. (□) age-matched controls; (■), four cases of central serous chorioretinopathy (CSC); (▨), two CSC cases after recovery. Asterisked values were identified by the perimeter as significantly abnormal ($P < 0.01$). The bin ranges have been indicated on the lowest graph.

The finding of abnormal pattern defects and normal mean defects with temporal modulation perimetry reflects a localized rather than a generalized loss in CSC. This is also demonstrated in Fig. 2 where flicker fields are shown overlying fluorescein angiograms for cases 1 and 2. Good localization occurs for both large lesions (case 1) and small lesions (case 2).

Case 3 also shows a deep, localized flicker defect with a minimal loss on static perimetry (Fig. 3). Here, the static field is suggestive of a minor reduction in sensitivity (5 dB loss) at two locations in the field, whereas the flicker result shows a deeper and larger scotoma (2–14 dB; up to 8 points). This case resolved ophthalmoscopically in

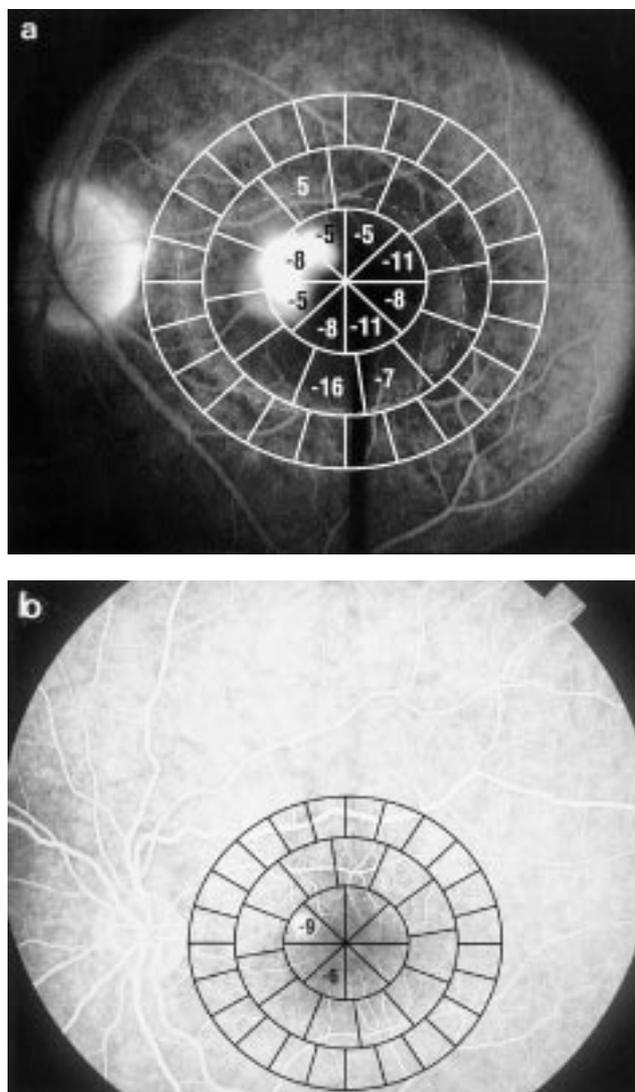


Figure 2. Flicker field results (difference from hill of vision, inverted to match retinal locus) overlying fluorescein angiograms to demonstrate localization of losses for both large (a) case 1 (the dashed line represents the boundary of serous elevation) and small (b) case 2 lesions.

4 weeks, at which time no flicker defect was evident with TMP (Fig. 3d). Case 2 is the other case with post-recovery data. This patient suffered a remitting and exacerbating

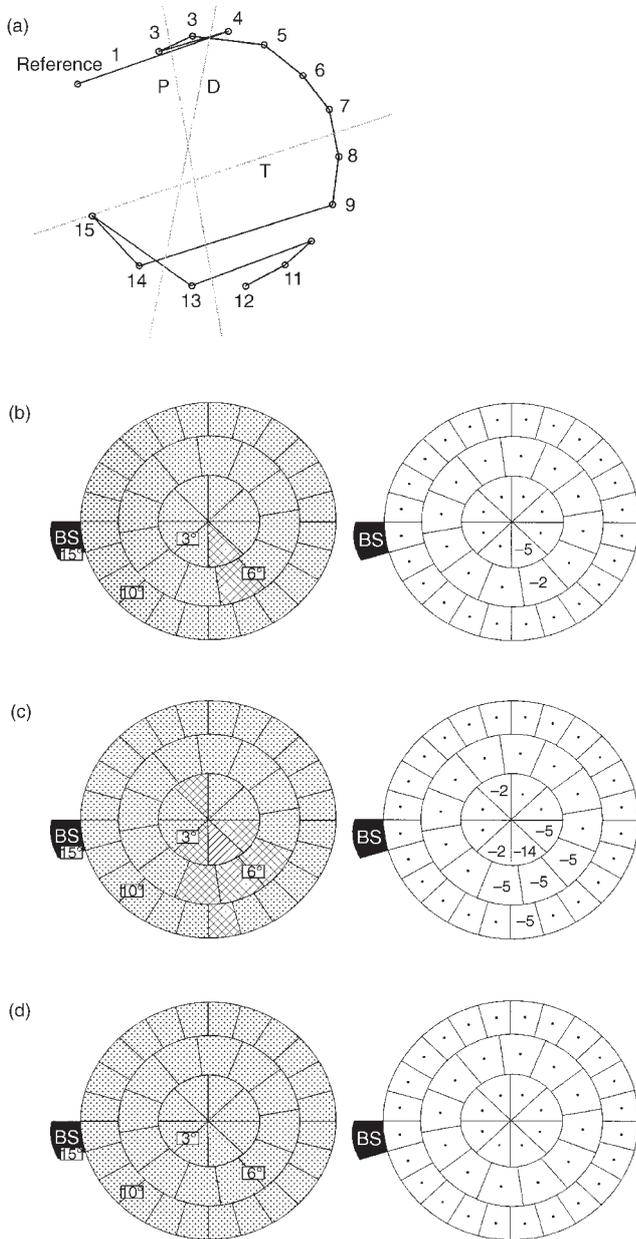


Figure 3. Clinical results for case 3 typical of the central serous chorioretinopathy (CSC) findings. (a) Panel D15 result showing the naval Protan (P), Deutan (D) and Triton (T) axes. (b) Steady state perimetry result with only two points outside the normal range for age. The age-matched normal comparison is on the left (shading corresponds to dB removed from age normal: ▨, +6 to -6 dB; ▩, -6 to -12 dB; ▧, -12 to -18 dB) and hill of vision result on the right (numeric value is dB removed from patient based expectation after allowing for mean sensitivity). (c) Temporal modulation perimetry result with a scotoma in the inferior macular field corresponding in size and location to the retinal lesion. (d) Post-recovery flicker result showing complete resolution of the scotoma seen in (3c). The static result was also normal (not shown).

course over 2 years before resolution and re-examination. In this case, a permanent loss of flicker sensitivity remains despite ophthalmoscopic resolution.

Another way of considering the field data is by plotting a linear histogram of the ordered data (Bébie curve) for both the static and flicker outcomes. These are shown in Fig. 4 for both controls and CSC patients. Because the curves include all the raw data, the upper limit of the shaded control range is the best normal and the lower limit is the worst normal. Figure 4(a) shows that the static perimetry thresholds of CSC patients generally complied with age-matched controls. In contrast, the TMP results (Fig. 4b) showed marked reductions in sensitivity in all CSC cases. Two trends can be seen in the TMP curves (Fig. 4b). One shows a localized depression in a few points to the right side of the curve, whereas the second suggests a more generalized depression over all the data set.

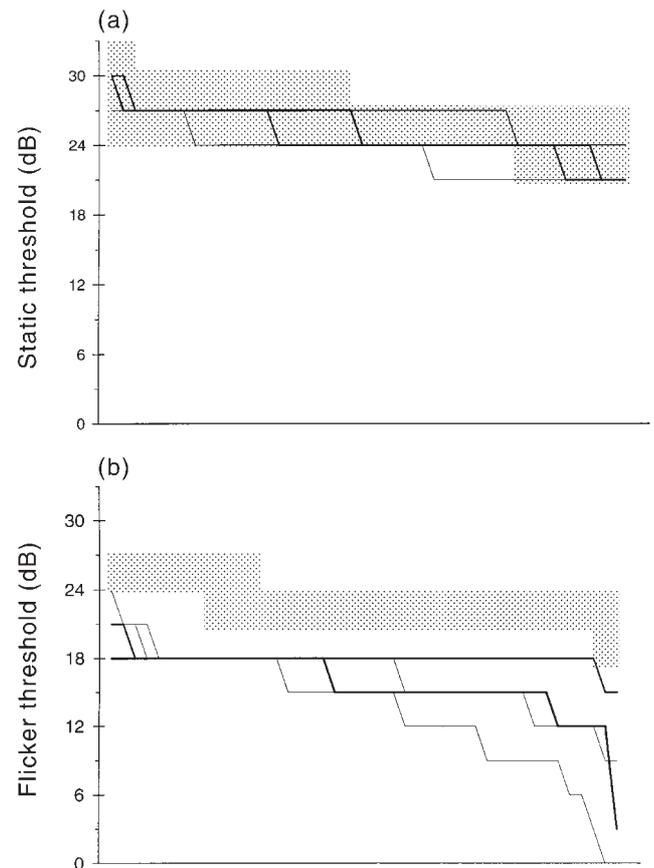


Figure 4. Linear histograms (Bébie curves) for normal controls (the shaded region encompasses all normals) and central serous chorioretinopathy (CSC) patients (lines). (a) Static perimetry outcomes. All are within the normal range. (b) Temporal modulation perimetry outcomes. Note how the temporal modulation perimetry results show a generalized depression over most visual field locations and a deep localized scotoma at the few points shown to the right.

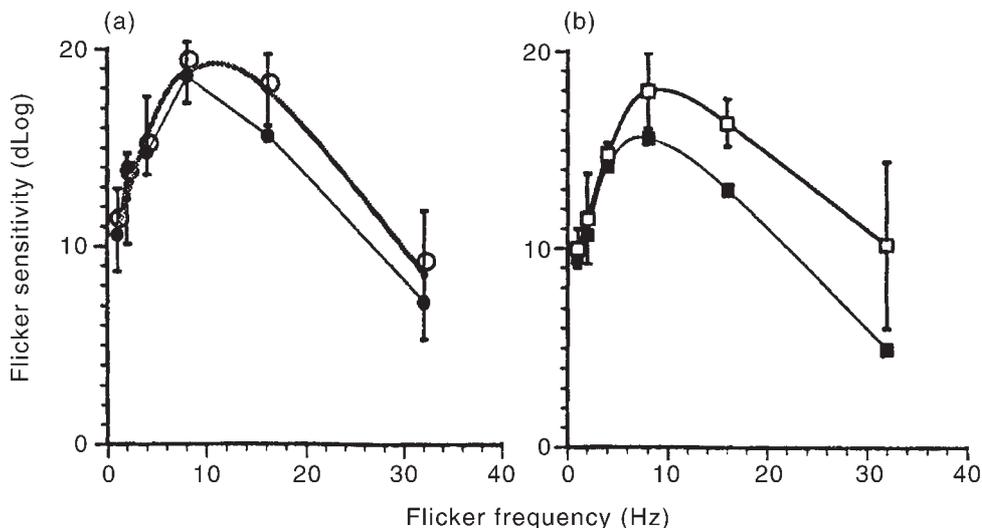


Figure 5. De Lange function measured using a 3° target with foveal fixation (a) and fixation centred over the lesion (b). Open symbols (thin line) indicate results for the normal fellow eye and solid symbols indicate results for the affected eye of case 3. The thick line shows age-matched data.

Figure 5 shows the de Lange function for case 3, who was tested extensively on the laboratory equipment. The nature of the loss appears to be frequency dependent, with the greatest loss being evident at 16 Hz ($P < 0.05$, 0°; $P < 0.01$, 4°). Also, the depth of the loss is greatest directly over the lesion (3.8 dB) compared with that found in the fovea (2.1 dB). It is interesting to note that the depth found with a larger target is not as profound in this patient as that found with the smaller target (3.8 vs 14 dB; compare Fig. 5 with Fig. 3). Moreover, the average depression of this person's Bébie curve (-4.3 dB) is of similar magnitude to that found with the larger target and perhaps it is this aspect of the loss that the larger stimulus has identified. It would suggest that this person's loss has a considerable spatiotemporal component, being most selective for small flickering targets.

DISCUSSION

These cases indicate that small (0.5°) flickering perimetric targets are better suited than are steady state targets for the detection and definition of scotomata caused by CSC. The significant increase in pattern defect in the presence of a near normal mean defect reflects the localized nature of the losses. Although small losses are found with a steady state target, these are often not significantly different from the normal range. However, in all cases, the scotoma appears deeper and larger with flicker, such that they are significantly outside the normal range, making them clinically easier to detect. The depth and extent of the flicker-defined scotomata also seems to correlate with serous elevation.

The de Lange curve result for case 3 is in general agreement with that reported by Mayer, who found the most significant losses of sensitivity at 10–14 Hz in ARMD

patients.¹³ Additionally, we show greater losses are found using small (0.5°) localized targets compared with the larger (2.8°) ones adopted by that study. These differences most likely reflect the different target size, but it should be noted that with the de Lange testing there is no local luminance increment from the background adapting level, whereas there is for the TMP target. If this luminance increment influences the outcome, it is difficult to explain why the losses would be greater in its presence, as it should make the stimulus more visible. Additionally, the excellent FP rates indicate the subjects were responding to the flicker percept. Assuming the difference were due to target size, this may reflect the localized nature of the functional impairment in CSC. In this case, any target larger than the lesion will sample impaired as well as healthy retina, thus reducing the apparent loss, whereas a smaller target will fall within the lesion and reflect the full extent of the functional impairment. Alternatively, it is possible that the larger test targets may be identifying a different type of deficit being a more generalized loss. This possibility is supported by the appearance of the Bébie curves, which indicate that most data points derived by TMP are outside the normal range, not just those within the scotoma. This finding suggests that CSC not only causes a deep localized loss, but also a surrounding generalized depression of some 2–5 dB.

The two cases after recovery show different outcomes that may be related to duration of the disease. The case that resolved in 4 weeks enjoyed complete recovery of flicker sensitivity, whereas the case that lasted 2 years suffered a permanent deficit in flicker sensitivity. The latter finding may reflect retinal pigment epithelium (RPE) or photoreceptor dysfunction or death caused by prolonged separation of these layers. Chuang *et al.* have demonstrated a reduced level of rhodopsin in CSC patients following

recovery and have shown that the loss of visual function is consistent with reduced rhodopsin levels.¹⁶ Similarly, after repeated CSC, RPE damage can often be visualized ophthalmoscopically.

Mechanism of loss

The primary pathology in CSC is most likely in the choroid,²⁰ but the site of interruption to vision is at the RPE–photoreceptor complex.²¹ The normal retinal structure is interrupted by serous fluid in the subretinal space, which causes the neuroretina to detach from the RPE.²² Although the RPE–photoreceptor complex is disrupted, the inner layers of the retina are structurally unaffected and so they should retain their capacity for gross function, as is evidenced by the normal static perimetry result and only slightly reduced visual acuity. However, separation of the RPE and photoreceptors is sufficient to cause a localized loss of flicker sensitivity.

Steinberg notes that the RPE–photoreceptor complex has an extremely high metabolic rate, with nutrition derived from the choriocapillaris.²³ He suggests that the loss of apposition between the neural retina and choriocapillaris (as in serous elevation) will lead to a mild hypoxic state affecting photoreceptor metabolism.²³ More importantly, an increase in metabolic demand due to flickering lights has been well established.²⁴ Given that serous elevation interferes with photoreceptor metabolism, then it is possible that the retina cannot respond appropriately, at a local level, to the metabolic challenge that flicker stimulation provides. This theory explains the localized losses of flicker sensitivity in the context of the known pathophysiology of CSC. In contrast, Mayer has argued that flicker losses found in ARMD reflect selective ganglion cell pathway dysfunction (M-cells) possibly due to involvement of the photoreceptors or other components that connect to such cells.¹⁰ Any selective involvement of pathways could reflect the metabolic demands of these pathways, as the nature of the loss is directed at cells that require high metabolic loads when stimulated by flickering targets. However, we disagree with this notion because the spatio-temporal characteristics of our losses (mid to high frequency, small spots) are inconsistent with abnormal magno-cellular function.

Implications

Our results support the findings of others in CSC who report either deficits in temporal function or localized scotomata with perimetric techniques.^{16,25} Our findings also support and extend those of other investigators who report abnormal flicker sensitivity with maculopathy.^{8–11} An additional implication of our finding is that TMP can demonstrate localized loss of visual function in CSC that is greater than that found using laboratory based equipment. Most

importantly, TMP is easily applicable to the clinical setting. Thus, in the event a demonstration of retinal dysfunction in CSC is required, then TMP could be used. It is possible that TMP may prove to be similarly valuable with other causes of oedematous maculopathy.

Conclusions

The present paper demonstrates that TMP detects a loss of flicker sensitivity in patients with CSC. Deeper and more clearly defined scotomata are found with a flickering stimulus compared with a steady state one. The duration of the disease may be important for recovery of flicker sensitivity. Temporal modulation perimetry is a reliable test with a short test-time that may be clinically useful. We do not foresee TMP being valuable for the diagnosis of CSC, because this is readily done with fluorescein angiography. However, if fluorescein angiography is not available or cannot be performed (e.g. in pregnancy), then TMP may provide useful information.

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