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Retinal Dysfunction in Central Serous Retinopathy

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Summary
Patients with acute and chronic central serous retinopathy (CSR) were studied by psychophysical and photochemical means to establish the extent of visual depression and to investigate the basis of rod dysfunction in this disorder. In acute disease with serous detachment of the retina, the loss of sensitivity attains 3 log units and parallels the height of retinal elevation as does its recovery with resolution of the episode. Immediately after resolution, there is a residual 0.5 log unit threshold elevation. In chronic disease, marked loss of function exists over areas of abnormal retinal pigment epithelium in the absence of clinically detectable serous detachment. Although rhodopsin levels are low in both acute and chronic CSR, this relative lack of visual pigment does not totally account for the functional deficits in either situation.

Central serous retinopathy (CSR) is a relatively common disorder generally affecting healthy young to middle aged males. It is most often recognised in its well characterised, simple form, with acute detachment of the neurosensory retina from the underlying retinal pigment epithelium (RPE).[1] In such cases, the source of the fluid is indicated as either a pinpoint leak or RPE detachment by fluorescein angiography.[1] Spontaneous resolution occurs in most individuals with clinical flattening of the retina after an average duration of four months.[2] Approximately one-third of individuals suffer recurrent episodes and a similar number show evidence of previous CSR on initial presentation.[2] Persistent or permanent visual deficits are detected in only a small percentage of patients.[2,3]

Another fundus appearance is characterised by multifocal areas of involvement with angiographically evident patches of hyperfluorescence at the level of the RPE. Some of these foci represent transmission defects alone, but others suggest the chronic passage of fluid across the RPE towards the neuroretina. While it is possible that this different appearance represents a separate disease entity, most clinicians now recognise a continuum of disease and accept the multifocal variety as an advanced stage of CSR. Referred to by a variety of names, this picture of widespread, often gravity-determined patches of abnormal RPE is believed to represent the cumulative effects of chronic and recurrent disease in those individuals.[4–7]

Despite ample opportunity to study the natural disease as well as attempts to devise an animal model,[8] no convincing pathogenetic mechanism has been established. Over the years, certain mechanisms have been proposed and others discarded. Current thoughts include defective function of the RPE which allows movement of fluid from the choroid toward the retina,[9] and alternatively, abnormal active transport by the RPE into the subretinal space.[10]

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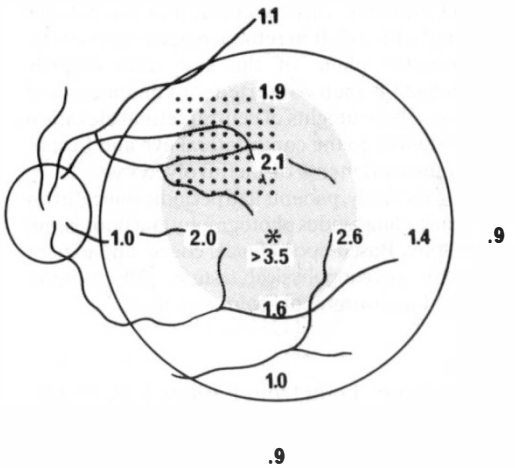

Fig. 1a. *Retinal drawing, Patient 1, showing area of serous detachment (stippled area), threshold elevation in log units (numerals) at 12 retinal foci and region across which fine matrix perimetry was performed (square of dots). Greatest elevation of threshold corresponds to area of serous detachment. (Fovea marked by asterisk.)*

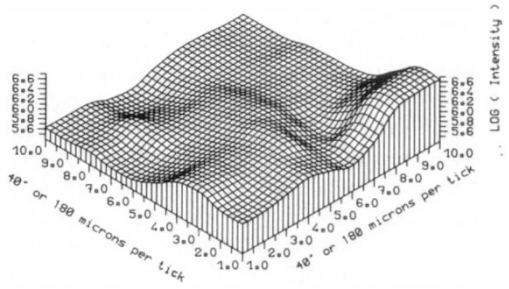

Fig. 1b. *Three dimensional contour plot of fine matrix perimetry in Patient 1. The 7×7 degree retinal test area is designated by square of dots in Fig. 1a. Elevation of threshold above normal is represented by height above baseline. Area of greatest threshold elevation corresponds to retinal location nearest centre of serous detachment. (Normal threshold is 4 log units.)*

Individuals suffering from CSR experience a number of familiar visual symptoms. In addition to decreased central acuity, distortion, micropsia and altered colour perception, patients commonly note a relative scotoma and delayed recovery after light exposure. Aspects of cone dysfunction in CSR have previously been investigated.[11] We have chosen to measure the functional deficits in rod function in CSR. In this study, combined testing of anatomic, psychophysical, and photochemical parameters has been employed in order to measure the functional loss in acute and chronic disease, to assess the correlation between visual deficit and the height of serous detachment, and to define the role of rhodopsin deficiency as a cause of loss of sensitivity in CSR.

Patients

Patients included in our study were recruited from the Retinal Diagnostic Department at Moorfields Eye Hospital. The criteria for entry into the study included the following: fundus and angiographic changes typical of CSR, age at onset of symptoms of 60 years or less, corrected acuity of 6/12 or better and the absence of other ocular conditions which might influence results. No patients demonstrated large RPE detachments and no eyes studied had received previous photocoagulation.

For the purpose of identifying mechanisms of visual dysfunction in CSR, we studied patients who by history, fundus appearance and angiographic characteristics could be classified into one of two categories. In the first were individuals who suffered acute symptoms and demonstrated serous detachment with either a spot leak or a pigment epithelial detachment. The second category consisted of those with no evident subretinal fluid or active leakage, but with multiple areas of hyperfluorescence at the level of the RPE.

There were five patients in each of our groups. Few of our acute patients had evidence of prior episodes of CSR in either eye. The chronic patients described stable if reduced acuity on a long term basis and were often aware of long standing scotomas; some had been observed in the past to have acute CSR in the same or opposite eye.

Methods

Thorough clinical examiantion and fundus photography including fluorescein angiography were performed to define serous detachment and RPE

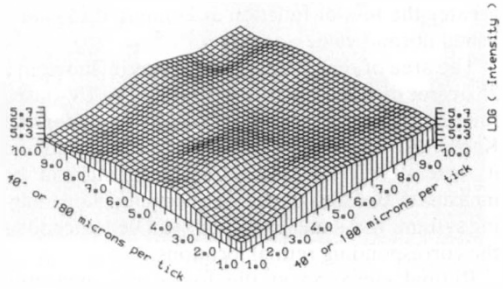

Fig. 1c. *Fine matrix perimetry in Patient 1 six weeks later, over the same retinal area as Fig. 1b.*

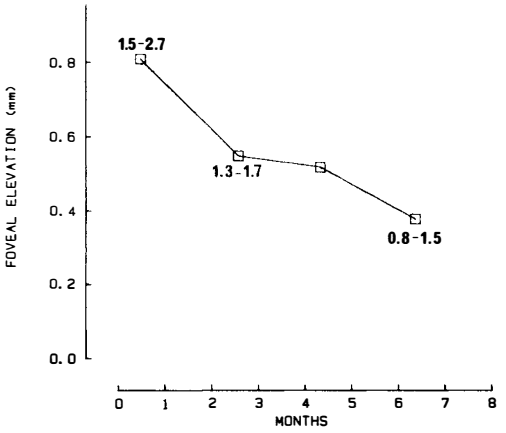

Fig. 2. *Foveal elevation (in millimeters) in Patient 1 measured by an optometer technique over a six month period of observation. The numbers represent range of threshold elevation within the serous detachment at corresponding stages in the disease.*

changes. Goldmann visual fields were used to identify areas most suitable for further investigation.

The following examination techniques were then utilised to assess visual function in these areas:

Dark adaptation and static perimetry were carried out in the areas of reduced retinal function as well as in neighbouring unaffected regions, using an automated modified Lister perimeter as described by Ernst and co-workers.[12] In this technique, red and green LEDs are employed as stimuli which allows separation of the relative contributions of cones and rods. Results are expressed in log unit elevation of threshold above normal.

Fine matrix perimetry was performed using apparatus recently designed by Fitzke.[13] This technique uses a television screen to present pulsed blue stimuli, each of which subtends 10 minutes of arc, under scotopic conditions. Sensitivity is tested at one hundred positions within a 7×7 degree test field. Subsequent processing of the data produces a three-dimensional representation of rod thresholds wherein the higher the elevation from baseline, the greater the loss of function as compared to established normal values.

The area of serous detachment was included in a 25 degree diameter test area evaluated by TV-based fundus reflectometry as described by Faulkner and Kemp.[14] In this technique, levels of rhodopsin and its rate of regeneration after bleaching can be measured. Because the technique includes an imaging system, these measurements can be matched to the corresponding retinal locations.

Retinal elevation at the fovea was measured untilising an optometer method recently developed by Fitzke, Holden, and Sheen.[15] Based upon the Scheiner principle, this apparatus uses the defocus associated with a shift in retinal image to refract the photoreceptor plane of the eye. The dioptric measurement is then converted into millimeters of elevation. These heights of central retinal elevation were compared to the contralateral eye and to subsequent measurements of the involved eye.

During the study, patients had periodic clinical evaluations including fundus photography and fluorescein angiography. Based upon clinical course and patient availability, psychopohysical testing, reflectometry and height measurements were repeated.

Results

Acute patients: Data from Patient 1 are representative of the relationship between threshold elevation and height of serous detachment in acute CSR with serous detachment. Static perimetry and fine matrix perimetry demonstrated a marked elevation in threshold in the area of serous detachment, with greater than 3.5 log units loss of sensitivity near the fovea (Fig. 1a). The topographic detail provided by the fine matrix technique indicates an increasing loss of sensitivity approaching the centre of the serous detachment (Fig. 1b). This almost certainly relates to the height of serous detachment as well. As resolution occurred, recovery of sensitivity initially occurred in the most severely affected area (Fig. 1c). With time, a correlation was demonstrated between foveal elevation and sensitivity, as the retina flattened (Fig. 2). Thus, there is a parallel between the height of retinal elevation and sensitivity not only across the retina at a single stage in the disease, but also with resolution and flattening of the retina.

Fundus reflectometry was performed during the period of serous elevation of the retina in Patient 2, who demonstrated more than 3.5 log units elevation of threshold in the area of detachment (Fig. 3a). Rhodopsin was deficient in this region, but not entirely absent, and was normal elsewhere (Fig. 3b). Approximately 30 per cent normal levels of rhodopsin were recorded in the area of serous detachment.

In Patient 3, these parameters were recorded during spontaneous resolution of acute CSR. Rod thresholds initially elevated by 3.5 log units returned to within approximately 0.5 log unit of normal within three

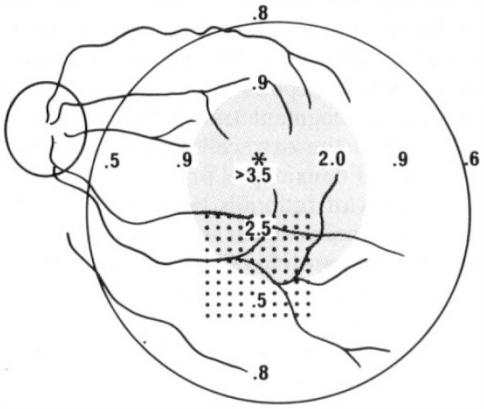

Fig. 3a. *Retinal drawing (Patient 2) showing serous detachment (stippled area), threshold elevation in log units and area tested by fine matrix perimetry (square of dots). Greatest elevation of threshold is within the area of detachment. Large circle outlines the 25 degree retinal area in which rhodopsin was measured.*

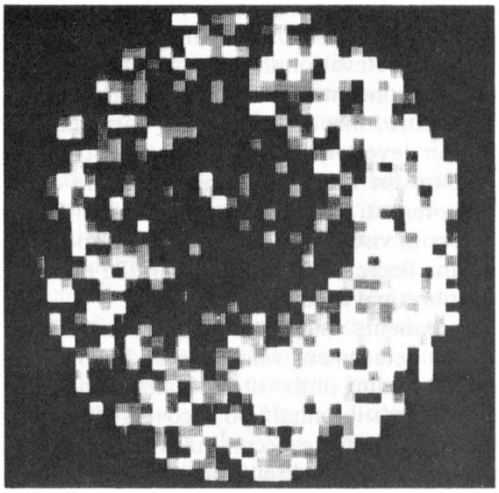

Fig. 3b. *Digitised, averaged fundus reflectometry data (Patient 2) from 25 degree area encircled in Fig. 3a. Each pixel or rectangle represents approximately 1 degree square of retina. Relative rhodopsin is represented on a brightness scale: levels within the area of serous detachment are 30 per cent of normal.*

weeks after clinical resolution of serous detachment was noted. Height measurements documented reapposition of retina to RPE. Fundus reflectometry performed at this stage revealed that rhodopsin levels were 20 per cent of normal in the area of previous detachment.

Chronic patients In patients designated as chronic, significant elevation in threshold was present in the absence of detectable retinal separation from the RPE or active fluorescein leakage. As demonstrated in Patient 4, threshold elevations of up to 3.5 log units or more above normal could be measured over wide regions of abnormal RPE (Fig. 4a). The reflectometry data relate to loss of sensitivity in a manner similar to that obtained in

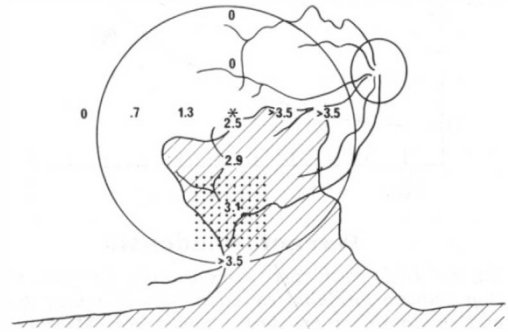

Fig. 4a. *Retinal drawing (Patient 4) showing large area of abnormal RPE in chronic CSR. Threshold elevation in some areas of affected region exceeds 3.5 log units.*

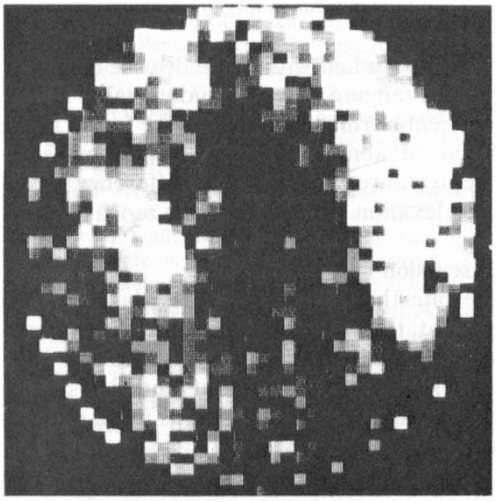

Fig. 4b. *Relative rhodopsin content (Patient 4) within area encircled in Fig. 4a. In the area of abnormal RPE, visual pigment values range from undetectable to 30 per cent normal.*

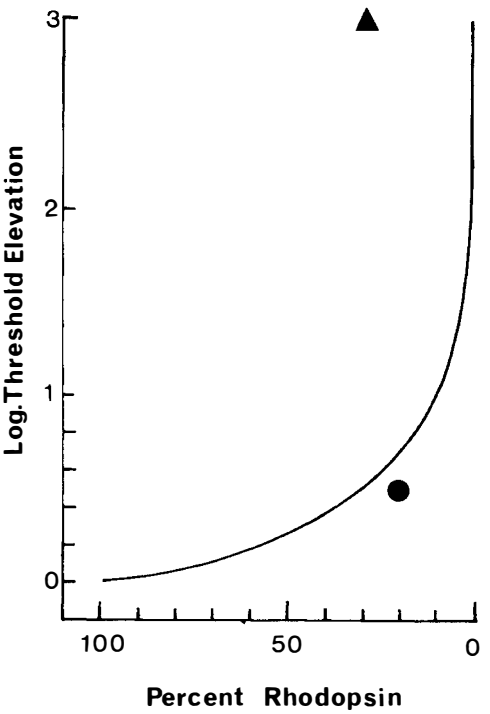

Fig. 5. *Light catch curve demonstrating the relationship between threshold elevation (loss of sensitivity) and rhodopsin in the dark adapted eye. Measured rhodopsin levels (30 per cent normal) in a patient with acute CSR cannot account for the 3 log unit threshold elevation (triangle). After resolution of serous detachment, 20 per cent rhodopsin with 0.5 log unit threshold elevation approximates the light catch curve (circle) and can explain residual loss of function.*

patients studied with acute disease (Fig. 4b). Values ranging between undetectable and 30 per cent normal rhodopsin were found in the areas of abnormal RPE. Height measurements showed no significant difference in retinal elevation in these areas on repeat testing.

Discussion

Despite the lack of complete data on each patient, the similarity of results in individuals one to another within each of the two categories allows us to point out tendencies which will hopefully be confirmed as more patients are studied.

In patients with acute disease, loss of sensitivity is directly proportional to the degree of separation between the photoreceptor outer segments and the RPE. With our current understanding of the physiologic interactions between these adjacent cell layers, it is not difficult to suggest mechanisms to explain this relationship between the height of serous detachment and visual dysfunction. Subretinal fluid would predictably disrupt metabolic systems which depend upon pigment epithelium/outer segment transport and homeostasis within the extracellular space of the outer retina. For example, proteins integral to the transport of retinoids between the RPE and receptor cells such as interphotoreceptor retinal binding protein (IRBP) might be deficient due to dilution by subretinal fluid.[16]

Fundus reflectometry in acute CSR shows a 70 to 80 per cent reduction in rhodopsin concentration in the area of serous detachment with normal values in the surrounding retina. However, the functional loss recorded cannot be attributed to rhodopsin deficiency alone. This is based upon the light catch curve which describes the relationship of absorbed quanta of light to rhodopsin molecules in the dark adapted eye if rhodopsin were fully regenerated[17] (Fig. 5). Under these conditions, threshold elevation should correlate with rhodopsin concentrations in a linear manner. Therefore, in our acute CSR patients, rhodopsin levels of 20 to 30 per cent cannot account for the 3.5 log unit threshold elevation present. Factors other than a quantitative defect in visual pigment must be responsible for the decrease in sensitivity in the presence of subretinal fluid.

In patients with acute CSR associated with serous detachment who have undergone presumed healing of the site of leakage and resolution of the subretinal fluid, recovery of function, though incomplete, occurs quickly. The residual 0.5 log unit threshold elevation with a 20 per cent of normal rhodopsin level obeys the light catch relationship. That is, shortly after flattening of the retina, rhodopsin deficiency can explain the remaining functional deficit. This quantitative deficiency in visual pigment may explain the sometimes prolonged period required for full or near complete recovery of visual function after acute CSR.

Those patients we designated chronic did not manifest frank neurosensory detachment. Not surprisingly, their height measurements were stable. Comparison of the reflectometry data with the expected relationship of the light

catch curve demonstrates that, as in acute CSR, rhodopsin deficiency alone does not explain the loss of sensitivity. A parallel may thus exist between the mechanism of visual loss in the acute, detached, and the chronic, flat stages of CSR. In the chronic setting, RPE dysfunction continues, in keeping with the theory of lowgrade, continuous passage of fluid across the RPE in such patients. The same mechanisms proposed in acute CSR may apply, which contrasts with healed, acute CSR in which overall RPE function is normal.

Clinical implications

In acute CSR, there is marked loss of sensitivity from which patients generally recover with flattening of the retina. This is in accord with the view that CSR resolves without major loss of vision. The magnitude of sensitivity loss we observed in our patients during the active phase of the disease was unexpected but perhaps not too surprising: clinically, there may be a tendency to understate the visual deficit during the period of serous detachment because of the typically good acuity.

Perhaps more significant was the fact that patients with diffuse RPE changes had marked loss of sensitivity over areas of involvement in the absence of overt serous detachment. We have not recorded recovery in any of the patients restudied to date and therefore assume that this is a permanent deficit. Concern for this aspect may be relevant to the management of the disorder. It is generally agreed that the areas of RPE changes are the result of chronic and recurrent CSR and may be a response to the presence of subretinal fluid over months to years. In many patients, the distribution of RPE changes appears to be determined by gravity and, at least initially, to be derived from a specific site.[18] Whatever the mechanism, this process may in time lead to irrecoverable visual loss over large areas of retina. If it is confirmed that such patients are destined to suffer considerable and permanent visual loss, there may be some justification for intervention in those patients who can be shown to be entering this phase of the disease.

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