Electrophysiological characterisation and monitoring in the management of birdshot chorioretinopathy

G E Holder, A G Robson, C Pavesio, E M Graham

Aims: To characterise patients with birdshot chorioretinopathy (BCR) clinically and electrophysiologically in order to monitor changes in retinal function before and after treatment with corticosteroids and/or immunosuppression.

Methods: 18 patients with BCR were characterised clinically and electrophysiologically. Serial studies were performed on 14 patients in order to monitor changes in retinal function before and after treatment with corticosteroids and/or immunosuppression.

Results: Most patients presented with characteristic subretinal pale spots, were HLA-A29 positive, and had diverse signs of ocular inflammation. Various electrophysiological abnormalities were present. Moderately severe bilateral pattern electroretinogram (PERG) abnormalities at presentation were common, reflecting macular dysfunction. Cone mediated 30 Hz flicker electroretinograms (ERGs) were consistently delayed before treatment, and were the most sensitive parameter of retinal dysfunction. Scotopic maximal ERG responses were abnormal in 13 patients; 10 had an electronegative maximal ERG or a reduced b:a ratio in one or both eyes. Single flash photopic ERGs were less often and less severely affected. Photopic ON and OFF ERG responses often revealed predominant ON response b-wave abnormalities with relative OFF response preservation. ERGs improved in treated cases, sometimes preceding clinical signs of recovery. Pattern ERG improvements occurred, possibly reflecting the resolution of macular oedema.

Conclusions: The ERG data confirm that BCR frequently affects inner retinal function of cone and rod systems. Clinical features were not reliable indicators of functional deterioration or recovery. Objective electrophysiological assessment of retinal function demonstrated improvement following treatment and provides a reliable method of monitoring treatment efficacy, enabling management decisions to be taken with greater confidence and allowing early initiation or modification of treatment.

METHODS

A cohort of 18 patients with BCR is described. All were clinically ascertained (table 1) and received electrophysiological assessment. This incorporated full field ERGs in order to monitor generalised retinal function and pattern electroretinogram (PERG) to assess macular function. Many patients also had electro-oculogram (EOG) recording to examine the function of the retinal pigment epithelium/photoreceptor complex, and ON and OFF response ERG recording separately to examine the function of the photopic ON and OFF pathways.

Abbreviations: BCR, birdshot chorioretinopathy; CMO, cystoid macular oedema; EOG, electro-oculogram; ERG, electroretinogram; PERG, pattern electroretinogram; VA, visual acuity
<table>
<thead>
<tr>
<th>Patient</th>
<th>VA</th>
<th>Visual distortion</th>
<th>Floaters</th>
<th>Photopsiae</th>
<th>Nyctalopia</th>
<th>Field loss</th>
<th>Colour vision</th>
<th>Pale spots</th>
<th>HLA-A29</th>
<th>Vitritis</th>
<th>Vasculitis</th>
<th>Pale disc</th>
<th>Disc oedema</th>
<th>CMO</th>
<th>Blood vessel attenuation</th>
<th>Other features</th>
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<td>LE affected 2 years before RE. Mid-peripheral chorioretinal atrophy and pigmentary changes</td>
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</tbody>
</table>

The presence of abnormality is marked by a cross (+) and refers to right (upper half of row) and left (lower half of row) eyes. NA, not available.
The full field ERG protocol incorporated the ISCEV standard rod specific and maximal ERGs, both recorded under dark adaptation, and the photopic 30 Hz flicker and single flash ERGs, both recorded after a standard period and intensity of light adaptation. All eyes were dilated before full field testing using tropicamide (1%) and/or phenylephrine hydrochloride (2.5%). ISCEV standard pattern ERGs were performed without mydriasis; EOGs were also recorded to ISCEV standard.

Long duration photopic stimulation was used to record ON and OFF ERG responses using previously described techniques. In brief, an amber stimulus of 120 ms or 200 ms duration (luminance 560 cd/m²) was presented upon a bright green background (luminance 160 cd/m²) close to peak rod spectral sensitivity and thus suitable to suppress rod function. Colour contrast sensitivity was measured psychophysically in all patients by determining thresholds along isoluminant protan, deutan, and tritan colour confusion axes using the Arden colour contrast sensitivity system.

Some patients had follow up recordings over varying time scales. The alterations in electrophysiology are described.

RESULTS

The incidence of the common symptoms and signs found on examination of the 18 patients is shown in table 1. The constellation of symptoms varied between patients but could include floaters (12 cases), field loss (10 cases), visual distortion (nine cases) and/or visual acuity loss (seven cases), photopsiae (nine cases), colour vision problems (nine cases) and nyctalopia (seven cases). The characteristic hypochromic birdshot lesions were seen in 15/18 patients at presentation. Sixteen patients had signs of vitritis and 15 had signs of vasculitis and/or vessel attenuation. Other signs varied but often included disc pallor, disc oedema and CMO. HLA-A29 status was not ascertained in two clinically definite patients (cases 12 and 13); all others were HLA-A29 positive.

The electrophysiological findings in 18 patients are summarised in table 2. The initial electrophysiological abnormalities were usually bilateral but interocular asymmetries were often observed; only one patient with very mild disease had unilateral abnormalities (case 12). Photopic cone flicker ERGs were consistently delayed in at least one eye of all patients. Single flash photopic ERGs were less often and less severely affected. Photopic ON and OFF ERG responses in 12/13 patients revealed predominant ON b-wave abnormalities with relative (10 patients) or complete (two patients) preservation of the OFF d-wave. Scotopic maximal ERG responses were abnormal in 13 patients; six had (electro) negative maximal ERG responses, or a reduced b:a ratio in both eyes, and a further four showed unilateral b-wave reduction. One patient with a 15 year history (case 7) had an electronegative maximal ERG with a subnormal a-wave, in keeping with a degree of additional photoreceptor loss.

Eight out of 12 cases showed improvement in clinical signs following systemic treatment with steroids and/or immuno-suppressives (table 3). Inflammatory signs such as vitritis and vasculitis often improved initially but rebound inflammation occurred in six cases as high dose systemic medication was tapered (cases 3, 6, 10, 13, 14, and 18). Two of the patients who did not improve had treatment withdrawn after...
### Table 3  Summary of ERG monitoring and follow up in the 18 patients; nine of 10 patients showed improvement in full field ERGs following systemic treatment

<table>
<thead>
<tr>
<th>Case</th>
<th>EDD visits</th>
<th>Treatment</th>
<th>VA before treatment</th>
<th>VA after treatment</th>
<th>PERRG P50 changes</th>
<th>Full field ERG changes</th>
<th>Clinical changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5 (19)</td>
<td>Oral prednisolone</td>
<td>6/9</td>
<td>6/6</td>
<td>See text</td>
<td>See text</td>
<td>Developed pale discs, vessel sheathing and early lens opacities over 2 years following treatment. VA stable</td>
</tr>
<tr>
<td>2</td>
<td>4 (16)</td>
<td>Oral prednisolone</td>
<td>6/9</td>
<td>6/12</td>
<td>See text</td>
<td>See text</td>
<td>Mild clinical improvement</td>
</tr>
<tr>
<td>3</td>
<td>11 (43)</td>
<td>Oral prednisolone and cyclosporin</td>
<td>6/6</td>
<td>6/5</td>
<td>See text</td>
<td>See text</td>
<td>Treatment improved inflammatory signs but had little impact on VA or CMO. Subjectively and clinically stable. Prednisolone withdrawn due to systemic complications. Gradual mild worsening of VA over 4 years, vascular sheathing</td>
</tr>
<tr>
<td>4</td>
<td>10 (82)</td>
<td>Oral prednisolone (1 course)</td>
<td>6/9</td>
<td>6/6</td>
<td>Initial deterioration then some fluctuation</td>
<td>Deterioration</td>
<td>Mild subjective worsening of vision LE &gt; RE. Pale spots manifest 2.5 years after presentation</td>
</tr>
<tr>
<td>5</td>
<td>5 (70)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Deterioration</td>
<td>Deterioration RE</td>
<td>Subjective improvement in VA. Vasculitis and CMO improved but recurrent inflammation and epiretinal membranes developed as medication was tapered</td>
</tr>
<tr>
<td>6</td>
<td>3 (13)</td>
<td>Oral prednisolone and azathioprine</td>
<td>6/9</td>
<td>6/6</td>
<td>Marked improvement both eyes followed by deterioration as medication was reduced</td>
<td>Improved following treatment but mild deterioration as medication was tapered</td>
<td>Increasing annular scotoma and extensive chorioretinal degeneration over 15 years with sparing of central maculae, now stable</td>
</tr>
<tr>
<td>7</td>
<td>3 (16 years)</td>
<td>Oral prednisolone</td>
<td>6/6</td>
<td>6/6</td>
<td>Subnormal 15 years earlier: Undetectable over the past 16 months</td>
<td>Profound deterioration over 15 years but stable over the past 16 months</td>
<td>Orbital floor injections initially reduced ocular inflammation and peripheritis but RE VA suddenly fell to 6/60. Marked bilateral improvement in vitritis, CMO, and VA on systemic steroids</td>
</tr>
<tr>
<td>8</td>
<td>4 (67)</td>
<td>Orbital floor injections of triamcinolone then oral prednisolone</td>
<td>6/60</td>
<td>6/24</td>
<td>Subnormal but stable with orbital floor injections. Marked improvement with oral prednisolone, associated with reduced CMO</td>
<td>Slight deterioration while being treated with orbital floor injections. Marked improvement with oral prednisolone</td>
<td>Moderate subjective improvement in VA. Development of vitreous and CMO but stable over past 18 months</td>
</tr>
<tr>
<td>9</td>
<td>3 (18)</td>
<td>Not treated</td>
<td>—</td>
<td>—</td>
<td>Improved</td>
<td>Stable</td>
<td>Mild subjective worsening of vision. Disc oedema and vasculitis improved without treatment. Developed inferior bilateral atrophic scars</td>
</tr>
<tr>
<td>10</td>
<td>4 (33)</td>
<td>Oral prednisolone and cyclosporin</td>
<td>6/9</td>
<td>6/5</td>
<td>Subnormal but stable in the presence of persistent CMO</td>
<td>Improved initially, then deterioration as treatment was tapered</td>
<td>Improvement in VA within 2 weeks but with persistent CMO. Inflammatory signs became quiescent but recurred when medication was tapered. Increasing steroids controlled rebound inflammation but disc pallor slowly worsening</td>
</tr>
<tr>
<td>11</td>
<td>1</td>
<td>Not treated</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Mild deterioration in VA over 34 months, Development photopsias in LE, otherwise stable. Worsening VA over 3 years. Clinically stable over 10 months</td>
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<tr>
<td>12</td>
<td>1</td>
<td>Topical Betamethasone</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>VA stable over 15 months but fluctuating signs including CMO, floaters, and mild perceptual disturbance as cyclosporin was tapered. Essentially stable over following 18 months on low dose cyclosporin</td>
</tr>
<tr>
<td>13</td>
<td>3 (38)</td>
<td>Oral prednisolone and cyclosporin</td>
<td>6/12</td>
<td>6/9</td>
<td>Improvement associated with reduced CMO</td>
<td>Improved</td>
<td>Gradual deterioration in VA over 3 years. Clearer vitreous following high dose therapy but fresh BCR lesions on right and worsening of vitritis as medication was tapered. Right macula developed RPE changes, posterior vitreous detachment LE</td>
</tr>
<tr>
<td>14</td>
<td>1</td>
<td>Oral prednisolone and cyclosporin</td>
<td>6/5</td>
<td>6/6</td>
<td>—</td>
<td>—</td>
<td>Gradual improvement in VA and colour vision and slight reduction in vitritis over 2 years. Intraocular bleeding associated with high BP. Slight reduction in VA but clinically stable for 2 years since therapy ceased</td>
</tr>
<tr>
<td>15</td>
<td>3 (36)</td>
<td>Oral prednisolone</td>
<td>6/18</td>
<td>6/12</td>
<td>Undetectable</td>
<td>Deterioration since medication was tapered</td>
<td>Marked improvement in VA and colour vision and slight reduction in vitritis over 2 years. Intraocular bleeding associated with high BP. Slight reduction in VA but clinically stable for 2 years since therapy ceased. Prednisolone withdrawn due to raised BP (no subjective improvement). Periocular depot steroids initially resulted in reduced floaters and vitritis but recurrence of vitritis 2 years later</td>
</tr>
<tr>
<td>16</td>
<td>1</td>
<td>Oral prednisolone (1 course) Depot steroids</td>
<td>6/9</td>
<td>6/9</td>
<td>—</td>
<td>—</td>
<td>Marked improvement in VA and colour vision and slight reduction in vitritis over 2 years. Intraocular bleeding associated with high BP. Slight reduction in VA but clinically stable for 2 years since therapy ceased. Prednisolone withdrawn due to raised BP (no subjective improvement). Periocular depot steroids initially resulted in reduced floaters and vitritis but recurrence of vitritis 2 years later</td>
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<tr>
<td>17</td>
<td>3 (71)</td>
<td>Systemic treatment refused by patient Orbital floor steroids</td>
<td>—</td>
<td>—</td>
<td>Stable</td>
<td>Significant ERG deterioration</td>
<td>Fluctuating VA over 8 years and increased photopsiae. Reported visual disturbances on eye closure. Developed multiple atrophic RPE lesions, macular and peripheral retinal thickening, vasculitis and vascular attenuation</td>
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<tr>
<td>18</td>
<td>3 (11)</td>
<td>Oral prednisolone</td>
<td>6/9</td>
<td>6/6</td>
<td>Improved</td>
<td>Mild improvement</td>
<td>Marked improvement in VA and colour vision and slight reduction in vitritis over 2 years. Intraocular bleeding associated with high BP. Slight reduction in VA but clinically stable for 2 years since therapy ceased. Prednisolone withdrawn due to raised BP (no subjective improvement). Periocular depot steroids initially resulted in reduced floaters and vitritis but recurrence of vitritis 2 years later</td>
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</table>
bilateral PERG abnormalities were present in 14 patients; in four the abnormality was unilateral.

Nine out of 10 patients who had serial electrophysiology showed significant improvement in full field ERGs following systemic treatment with steroids and/or immunosuppressives (table 3). The most sensitive electrophysiological parameter was the implicit time of the 30 Hz flicker ERG (fig 1). Pattern ERG abnormalities improved bilaterally in 6/9 cases and unilaterally in 2/9 cases following systemic treatment with corticosteroids and/or immunosuppression, possibly reflecting reduced macular oedema (table 3). Increases in PERG P50 amplitude were associated with better visual acuity in all but two cases.

One patient refused systemic treatment, only consenting to intermittent sub-Tenon’s steroid injections. Initially, there was only a mildly subnormal maximal ERG response in one eye, with 30 Hz flicker ERG abnormalities in both eyes (case 17). Over a 5 year period there was marked ERG deterioration, with the development of an electronegative maximal ERG response in both eyes and increased abnormality of the flicker responses. The patient retained reasonably good acuity but the fundus appearance deteriorated (table 3). In case 8, orbital floor injections improved clinical signs of inflammation but ERGs showed deterioration over the same period. This patient consented to systemic treatment only when visual acuity dropped precipitously in one eye. Oral steroids produced marked bilateral improvement; vitritis and CMO was reduced, visual acuity improved, and ERGs showed significant recovery.

Full field ERG or pattern ERG abnormality did not always correspond to the severity of clinical signs and symptoms, both of which could remain stable during periods of profound ERG deterioration (cases 1 and 2). Visual acuity and pattern ERGs could not be used to monitor treatment efficacy.

![Figure 1](image1.png)

**Figure 1** Histogram showing magnitude of implicit time improvement in 30 Hz flicker ERGs in right (open bars) and left (solid bars) eyes following systemic treatment in nine patients who were monitored longitudinally.

![Figure 2](image2.png)

**Figure 2** Pretreatment and post-treatment ERGs (case 1, right eye). Mildly electronegative ERGs showed slight deterioration over 2 months. Steroid therapy was commenced and full field ERGs normalised over the following months. Pattern ERGs remained subnormal. See text for further details.

A single course of therapy because of systemic complications (cases 4 and 16). There was mild unilateral deterioration of visual acuity in two treated cases associated with retinal pigment epithelium (RPE) changes at the macula (case 14) or persistent CMO (case 2). Following systemic treatment, Snellen visual acuity improved by two lines (five eyes), one line (11 eyes) or remained stable (six eyes).

Overall, these ERG abnormalities indicate a high incidence of inner retinal dysfunction, principally affecting the ON pathways in both rod and cone systems. Moderately severe
reliably; some patients had normal Snellen acuity before treatment and persistent macular oedema following therapy but normalisation of full field ERGs (see below).

Three illustrative cases are described in detail.

**Case 1**
A routine fundus examination by an optometrist showed unsuspected retinal abnormalities in a 55 year old woman. Subsequent close questioning revealed a 2 year history of “floaters,” right eye worse than left. Detailed examination revealed the classic hypochromic lesions of BCR. There were bilateral vitreous cells and mild periphlebitis. VA was 6/9 bilaterally. The patient was HLA-A29 positive. Initial PERGs were bilaterally reduced, consistent with macular dysfunction. Colour contrast sensitivity showed elevation of the tritan threshold in both eyes. ERGs indicated generalised retinal dysfunction affecting the rod and cone systems (R1044, 0.81) with a reduced b:a ratio suggesting dysfunction post phototransduction (figs 2 and 3, 1st columns).

The patient remained asymptomatic, other than the persistent floaters and minimal acuity reduction; 2 months later ERGs showed such severe abnormality that there was a giant a-wave and no b-wave (fig 3, second column). We have been unable to trace any previous report of an ERG abnormality of this nature. On direct questioning the patient admitted to some nyctalopia. Steroid therapy was commenced. Full field ERGs had normalised by 16 months after presentation (fig 3). PERGs improved bilaterally but remained subnormal in the right eye (fig 2). During the same period the patient developed pale discs. The patient was kept on low dose maintenance steroids, and her electrophysiology and visual acuity remained stable 30 months after presentation. Five months later some vessel sheathing and early lens opacities were noted.

**Case 2**
A 56 year old woman presented with photopsiae, “faded” colour perception, blurred vision and floaters in the right eye. VA was 6/9 on the right and 6/6 on the left. Examination revealed pale chorioretinal spots and mild vitritis in the right eye and narrow retinal arterioles bilaterally. HLA-A29 was positive. Colour thresholds showed marginal elevation along the tritan axis but were otherwise normal. ERGs on the right were consistent with generalised retinal dysfunction affecting both rod and cone systems with significant PERG reduction indicating macular involvement. The EOG on the right revealed generalised involvement of the RPE which was disproportionately severe in relation to the degree of photoreceptor involvement. All responses on the left were normal. Four months after presentation faint pale lesions developed in the left eye. Nine months later the patient remained subjectively stable but repeat electrophysiology revealed marked deterioration in ERGs from both eyes, right worse than left, with bilateral macular involvement worse on the right (figs 4 and 5, first column). Visual acuity was 6/9 bilaterally. There was mild bilateral vitritis and vasculitis with right CMO. Treatment with high dose steroids was commenced and subsequently maintained at low levels. The ERG showed rapid improvement (figs 4 and 5, second column) and further recovery was apparent when the patient was re-examined 5 months later (figs 4 and 5, third column). However, the right PERG remained subnormal and right visual acuity reduced to 6/12, probably in relation to persistent CMO.

**Case 3**
A 38 year old man presented with an 18 month history of floaters and “swirling” vision. VA was 6/9 on the right and 6/6 on the left. Colour thresholds were elevated (R>1).
Examination revealed typical BCR lesions, vitreous cells, periphlebitis, mild disc pallor and mild CMO. HLA-A29 was positive.

The 30 Hz cone flicker ERGs were delayed and photopic ERGs showed a low b:a ratio. PERGs were mildly reduced bilaterally in keeping with the CMO (fig 6, month 0). Three months later, VA was 6/12 and 6/9 and the patient reported difficulties in adjusting to dim light. PERGs and colour contrast sensitivity measurements were performed (figs 6 and 8); 30 Hz flicker ERGs remained abnormal with little deterioration (fig 7, months 0–6). Treatment with oral steroids and cyclosporin A had little impact on VA or CMO, but the inflammation became relatively quiescent. PERGs showed no change on the right but there was marked improvement in 30 Hz flicker ERGs bilaterally (fig 7, months 6–9). The improvement in electrophysiology occurred 2–3 weeks before the patient noticed ease of his difficulties in dim light.

Over the following 3 years this patient received episodic treatment with steroids and cyclosporin A. Serial ERGs and colour contrast sensitivity measurements were performed (figs 6, 7, and 8). The 30 Hz flicker ERG implicit time improved with treatment and worsened when treatment was suspended (fig 7). Central vision and visual acuity deteriorated because of worsening CMO. There was significant correlation between PERG P50 amplitude and visual acuity ($r = 0.64$, $p<0.05$) and with colour contrast sensitivity in the right eye along deutan ($r = 0.54$, $p<0.05$) and tritan ($r = 0.56$, $p<0.05$) axes although correlation with protan thresholds just failed to achieve significance ($r = 0.5$, $p<0.1$). PERG and colour thresholds did not correlate with the 30 Hz flicker ERG, suggesting that these colour vision abnormalities relate to fluctuations in macular oedema rather than generalised cone system dysfunction. Colour thresholds in the left eye were mildly elevated and although tritan thresholds became moderately elevated, significant fluctuations were not seen. Over the following 2 years there was a slight exacerbation of inflammatory signs bilaterally, improved with systemic steroids and the patient remains subjectively and clinically stable on low dose maintenance.

**DISCUSSION**

Management decisions in birdshot chorioretinopathy are problematic because of the unpredictable clinical course. Electrophysiological investigation reveals a very high incidence of abnormalities, confirming previous reports, and allows objective assessment of the degree of retinal dysfunction. The functional status of the retina in our patients with BCR could not reliably be inferred either from subjective symptoms or clinical signs, both of which could
remain stable during periods of profound deterioration in electrophysiological function. Visual acuity could not be used to monitor treatment efficacy reliably; some patients had normal Snellen acuity before treatment and some had persistent macular oedema following therapy but normalisation of full field ERGs.

The most sensitive ERG parameter for dysfunction was the 30 Hz cone derived flicker response, abnormal in at least one eye of all patients, consistent with a recent report describing a high incidence of delayed 30 Hz flicker ERGs in BCR22 and in keeping with the presence of retinal inflammatory disease.23 Most patients had pale spots and were HLA-A29 positive. Vitritis was the commonest sign of inflammation, present in all but two patients and vasculitis and/or vessel attenuation...
or vessel attenuation were common signs in the patients mainly at an inner retinal level, 24 a high proportion of study. In addition to the 30 Hz cone flicker ERG, arising tions are supported and extended by the results of the present period.

In case 8, orbital floor injections improved clinical signs of inflammation but ERGs showed deterioration over the same period.

There was significant improvement in retinal function in all but one patient following systemic corticosteroids and/or immunosuppression. Indeed, even very severely abnormal ERGs, such as those in case 1, could normalise. The one exception (case 4) was a diabetic patient in whom treatment was withdrawn after a single course because of systemic complications, and in whom no significant ERG improvement occurred. The observations that normalisation of retinal function could occur following treatment, and that clinical signs were poor indicators of retinal function, has led to the adoption of a treatment strategy in which the ERG data are a vital component of the decision of when to start treatment in BCR and when treatment can be tailed off or altered to a different regime. It is reasonably assumed, when initiating treatment on the basis of an abnormal ERG, that restoration of normal function is beneficial for long term retinal health and survival. Other authors have reached similar conclusions in relation to value of ERG of assessing the efficacy of treatment; the presence of a normal 30 Hz response in BCR following treatment has recently been reported as a good prognostic sign, allowing tapering of immunosuppressive medication without rebound inflammation.25 Pattern ERGs, reflecting macular function, did not always show the same pattern of recovery as full field ERGs; there could be generalised improvement in retinal function shown by full field ERGs, but without a concomitant improvement in visual acuity or colour contrast sensitivity as a result of non-responsive macular oedema.

To conclude, subjective symptoms and clinical signs are poor indicators of generalised retinal function in BCR. Electrophysiological examination provides a method of monitoring the efficacy of treatment, and may facilitate decisions on when to initiate therapy. Normalised retinal function can be achieved in BCR following treatment; it is assumed that this is beneficial to long term retinal health. The data suggest that monitoring of retinal function with electrophysiology after treatment has commenced is likely to improve efficiency of treatment and enable management decisions to be taken with more confidence. It is anticipated that this may lead to improved long term prognosis. A similar approach may be applicable to other retinal inflammatory diseases.

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