Clinical Variations in Assessment of Bull’s-eye Maculopathy

Malaika M. Kurz-Levin, MD; Anthony S. Halfyard, PhD; Catey Bunce, MSc; Alan C. Bird, MD; Graham E. Holder, PhD

Objectives: To evaluate the phenotypic variation in bull’s-eye maculopathy and seek possible correlations between functional loss and clinical appearance.

Methods: From January 1, 1999, to September 30, 2000, we prospectively examined patients with bull’s-eye lesions. Age of onset, duration of symptoms, visual acuity, clinical appearance, and autofluorescence images were recorded, the area of atrophy measured, and electrophysiologic investigations performed.

Results: Forty-seven patients, including 6 sibling pairs, met the study entry criteria. On the basis of autofluorescence imaging, 3 distinct groups were identified. Group 1 showed a distinct ring of increased autofluorescence surrounding an area of decreased autofluorescence. In group 2, the ring of increased autofluorescence was not present. Group 3 displayed a speckled appearance within the affected area. All patients had evidence of central sparing in an area of centrally increased autofluorescence. There was significant correlation with the age of onset, visual acuity, and duration of disease. Electrophysiologic tests revealed that 28 patients had macular dysfunction only, 14 had cone-rod dystrophy, 3 had rod-cone dystrophy, and only 2 (monozygotic twins) had cone dystrophy. The correlation between electrophysiologic and autofluorescence data was poor. The sibling pairs had concordant autofluorescence appearance, but electrophysiologic grouping differed in 2 pairs.

Conclusions: Bull’s-eye maculopathy represents a heterogeneous group of disorders. The clinical appearance was not helpful in assessing the degree of retinal dysfunction. The difference in qualitative characteristics of functional loss between siblings implies that these attributes do not necessarily reflect the influence of the primary mutation.

Arch Ophthalmol. 2002;120:567-575

Kearns and Hollenhorst introduced the term bull’s-eye maculopathy (BEM) in 1966 to describe the characteristic clinical appearance of chloroquine retinopathy. In 1971, Deutman used the term to describe similar lesions in patients with inherited retinal dystrophies initially characterized by a central red spot surrounded by a ring of atrophic pigment epithelium or pigment epithelial mottling. The ring of atrophy may vary in degrees of eccentricity from the fovea. It is considered distinct from Stargardt maculopathy in which the atrophy is physically discontinuous, as best demonstrated by autofluorescence imaging. Bull’s-eye lesions in retinal dystrophies have since been reported in cone dystrophy (CD), cone-rod dystrophy (CRD), and rod-cone dystrophy (RCD). Furthermore, Deutman described simplex cases of BEM with loss of central vision but a normal full-field electroretinogram (ERG). Similar changes have been described in dominant pedigrees.

The mechanisms by which the degeneration occurs in this striking distribution are not well understood. The appearance may correspond to the pattern of lipofuscin accumulation in the cells of the retinal pigment epithelium (RPE), which in healthy subjects is highest at the posterior pole and shows a depression at the fovea, thus explaining the annular pattern and central sparing. Furthermore, the small area of central sparing was postulated as being due to a photoprotective effect of the high foveal concentration of luteal pigment. The initially spared center usually becomes involved during the disease, at which point the diagnosis of BEM can no longer be made. This study aims to describe the phenotype of patients with BEM to determine whether the nature of functional loss can be correlated with the clinical appearance of the fundus.

RESULTS

Forty-seven patients (30 women and 17 men) fulfilled the study entry criteria. In
PATIENTS AND METHODS

All patients with a bull’s-eye lesion at the macula examined from January 1, 1999, to September 30, 2000, were included in this prospective study after providing informed consent. Patients were excluded if any evidence of additional retinal abnormalities were present, such as intraretinal pigmentation in a bone-spicule pattern or white-yellow deep retinal flecks and discontinuous atrophy suggestive of Stargardt macular dystrophy–fundus flavimaculatus (SMD-FFM). The possibility of toxicity was ruled out in all patients. The diagnosis of BEM was based on the presence of a ring of RPE pallor or pigment epithelial mottling around the fovea. The diagnosis was sustained only if there appeared to be central sparing. These changes were initially identified by ophthalmoscopy and confirmed by autofluorescence imaging with the confocal scanning laser ophthalmoscope (cSLO) (Zeiss Prototype; Carl Zeiss Inc, Oberkochen, Germany) (Figure 1), using previously published techniques.46 Patients in whom a mutation in a gene known to cause retinal dystrophy was identified were not included; reports of these patients have been previously published.10,11 Patient demographics (age, sex, age of onset, age at initial examination, duration of disease, best-corrected visual acuity, fundus appearance on slitlamp biomicroscopy) were recorded and the mode of inheritance noted. Visual acuity was measured using a Snellen chart. Color fundus photographs and fundus autofluorescence images were obtained and electrophysiologic investigations undertaken. The area of pigment epithelial atrophy, defined as the area of decreased autofluorescence as assessed on the cSLO, was measured on computer image using Adobe Photoshop (Adobe Systems Inc, San Jose, Calif), the number of square pixels being converted into square degrees. Age of onset was defined as the age at which the first symptoms were noticed. Duration of the disease was calculated as the difference between the age of onset of symptoms and the age at examination.

All patients underwent electrophysiologic investigations according to the protocols recommended by the International Society for Clinical Electrophysiology of Vision.17-20 Full-field ERGs, electro-oculogram, pattern ERG (PERG), focal ERG, and color-contrast sensitivity measurement were performed. The patients were classified as having macular dystrophy (MD) if the results of PERG were abnormal but there was no ERG evidence of generalized photoreceptor dysfunction. Additionally, if the cone ERG was exclusively affected, the condition was designated as CD; if cone ERGs were more affected than rod ERGs compared with normal, the diagnosis of CRD was made, but if rod ERGs were more affected than cone ERGs, the diagnosis of RCD was made, thus categorizing them into 4 groups (MD, CD, CRD, and RCD).

The patients were divided into 3 cSLO groups. Group 1 showed a distinct ring of increased autofluorescence surrounding an area of decreased autofluorescence. In group 2, the ring of increased autofluorescence was not present. Group 3 displayed a speckled appearance within the affected area. All patients had an area of centrally increased autofluorescence as evidence of central sparing. Patients were categorized as having mild (visual acuity, 6/6-6/12), moderate (6/18-6/36), or severe visual loss (vision worse than 6/36). We subdivided the patients into mild PERG P50 amplitude abnormality (>1.2 µV), moderate (0.5-1.2 µV), severe (>0.5 µV), and undetectable. The ethics committee of Moorfields Eye Hospital, London, England, approved the study. Each patient gave informed consent.

Because of nonnormality, the Kruskal-Wallis test was used to assess whether the patients in the 3 different cSLO image groups and those in the 4 electrophysiologic groups differed significantly with regard to age of onset and duration of disease. If the Kruskal-Wallis test was statistically significant for cSLO groups, we used the rank sum tests to determine differences among groups. Because of the small numbers of patients in some of the categories, this was not repeated for the electrophysiologic groupings and descriptive results are presented. The Kruskal-Wallis test was also used when testing for an association between visual acuity and area of atrophy. The Fisher exact test was applied when comparing categorical variables between the cSLO groups and the electrophysiologic groups, such as the distribution of the electrophysiologic findings and visual acuity, and when assessing any association between visual acuity and PERG P50 component amplitude. The Spearman rank sum correlation coefficient was applied when assessing the association between duration of illness and area of atrophy.

The findings concerning age of onset, duration of disease, and visual acuity were grouped according to the 3 different cSLO appearances and the 4 different electrophysiologic results (Table 1) (Figure 2 and Figure 3). There was strong evidence of a difference between cSLO groups concerning the age of onset (P = .01). The difference was most pronounced when comparing patients in group 1 with those in group 3 (P = .002), whereas the age of onset of subjects in group 1 was not statistically significantly different from those in group 2 (P = .19) or between group 2 and group 3 (P = .09). There was strong evidence of an association between the duration of disease and the cSLO groups (P = .03). Rank sum testing revealed that the patients in cSLO group 3 had a statistically significantly shorter duration of disease (P = .008) than those in cSLO group 1. There was strong evidence of an association between visual acuity and cSLO grouping (P = .006), with patients in cSLO group 3 tend-
ing to have better visual acuity (P = .001 for group 1 and group 2). There was no evidence of an association between the area of pigment epithelial atrophy and either visual acuity or duration of disease.

ELECTROPHYSIOLOGIC FINDINGS

The electrophysiologic findings are given in Table 2, with grouped clinical data in Table 1. Macular dystrophy (abnormal PERG, normal ERG, and normal electro-oculogram) was present in 28 patients (60%), CRD in 14 (30%), and RCD in 3 (6%). Only 2 patients (4%), who were monozygotic twins, had CD. Two patients with central cone and peripheral rod involvement but normal peripheral cone function were labeled as having CRD (patients 25 and 27). Patient 23 showed equally affected full-field cone and rod ERGs, but a nondetectable PERG, and was also designated as having CRD. Pa-

<table>
<thead>
<tr>
<th>Variable</th>
<th>cSLO Group 1 (n = 21)</th>
<th>cSLO Group 2 (n = 16)</th>
<th>cSLO Group 3 (n = 8)</th>
<th>MD Group (n = 28)</th>
<th>CRD Group (n = 14)</th>
<th>RCD Group‡ (n = 3)</th>
<th>CD Group‡ (n = 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age of onset, y</td>
<td>20 (18-27)</td>
<td>27.5 (17.0-43.5)</td>
<td>43.5 (32.0-45.5)</td>
<td>28 (19-45)</td>
<td>20.5 (15-30)</td>
<td>33, 49, 54</td>
<td>27, 23</td>
</tr>
<tr>
<td>Median duration of disease, y</td>
<td>7 (4-17)</td>
<td>7 (1.5-14.5)</td>
<td>2 (2-6)</td>
<td>5.5 (2.5-10)</td>
<td>7.5 (1-22)</td>
<td>2, 4, 5</td>
<td>7, 11</td>
</tr>
<tr>
<td>Median visual acuity</td>
<td>6/36 (6/6-1/60)</td>
<td>6/60 (6/6-3/60)</td>
<td>6/9 (6/6-6/36)</td>
<td>6/24, 6/36† (6/6-3/60)</td>
<td>6/36, 6/60† (6/6-1/60)</td>
<td>6/5, 6/60, 6/6</td>
<td>6/60, 1/60</td>
</tr>
</tbody>
</table>

Table 1. Age of Onset, Duration of Disease, and Visual Acuity OD of All Patients With Bull’s-eye Maculopathy*

* cSLO indicates confocal scanning laser ophthalmoscope; MD, macular dystrophy; CRD, cone-rod dystrophy; RCD, rod-cone dystrophy; and CD, cone dystrophy. Two patients in the cSLO groups did not undergo autofluorescent imaging.
† Two middle values are presented rather than taking the arithmetic mean of 2 visual acuities.
‡ Data are given for each participant in the group.

Figure 1. Color photographs and autofluorescence images of patient 20, aged 31 years, with a bilateral bull’s-eye lesion; visual acuity with each eye was 6/9. The confocal scanning laser ophthalmoscope images show decreased perifoveal autofluorescence, corresponding to the retinal pigment epithelial atrophy bordered centrally and peripherally by increased autofluorescence.
tient 12 was labeled as having MD since the photopic single-flash ERG was unaffected, despite a mildly subnormal 30-Hz flicker response. Three patients had a negative scotopic maximal ERG waveform with a-wave preservation and relative b-wave loss (patients 6, 28, and 29). The 2 patients with CD (patients 16 and 17)
showed a reduced b/a ratio in the photopic ERG. The on and off systems were separately tested in 15 patients using a 200-millisecond amber stimulus on a green background; reduction of the on b-wave occurred in 3 cases (patients 16, 17, and 18). These patients appear to have a postphototransduction cone on-system abnormality.

We found strong evidence of an association between the different electrophysiology groups and the age at onset (P = .05), with a tendency for patients to develop RCD later in life than the other categories (Table 1). There was little evidence of association between the electrophysiology groups and the duration of disease (P = .60), visual acuity (P = .70), or area of atrophy as measured on the cSLO image (P = .60). However, our power to detect any association is weak owing to the small numbers in some of the groups. There was a

---

Figure 3. Examples of the 4 different electrophysiologic phenotypes. Note that the pattern electroretinogram (PERG) is markedly abnormal in all 4 patients, with patient B showing the least number of PERG abnormalities. A, Disease confined to the macula; normal electroretinograms but undetectable PERG P50 component. B, Generalized retinal dysfunction involving both rod and cone systems; the rod system is more affected than the cone system, with the latter findings falling only just outside the normal range. C, Generalized retinal dysfunction involving both rod and cone systems; the cone system is more affected than the rod system showing profound amplitude and implicit time changes. D, Dysfunction confined to the cone system.
A strong association between the electrophysiology and the PERG P50 component amplitude \( (P = .006) \), with almost all CRD patients having a nondetectable PERG compared with 17 of 28 patients with MD alone. Assessing the distribution of the PERG results among the 3 cSLO groups, we found borderline evidence of a difference \( (P = .06) \) (Table 4). However, there was a statistically significant association between visual acuity and PERG: eyes with a severely reduced PERG had markedly reduced visual acuity (Table 5).
SIBLING COMPARISON

All 6 sibling pairs were presumed to have autosomal recessive disease (Table 2 and Table 6). When comparing their autofluorescence images, remarkable concordance was found between the siblings, and they were assigned to the same cSLO group. In contrast, the electrophysiologic results were dissimilar in 2 pairs (patients 10 and 11 and patients 40 and 41). In sibling pair 2 (patients 10 and 11), the older sibling (duration of symptoms 7 years longer than his younger sister) had CRD, whereas the sister had MD only. In sibling pair 6 (patients 40 and 41), the older asymptomatic sister had MD and the younger sibling had RCD on electrophysiologic examination. The PERG was similarly affected in all sibling pairs, although in one pair (patients 26 and 27), there was a quantitative difference with the PERG in the older patient being undetectable, but his younger brother showing a reduced but detectable PERG.

The term bull’s-eye maculopathy refers to the distinctive changes seen on fundus examination, although it may signal the presence of a variety of disorders. This study was undertaken to analyze in detail the phenotype in a large study population with the hope of facilitating a more precise diagnosis. The findings might also contribute to the search for causative genes and phenotype-genotype correlation. Apart from a functional classification based solely on the localization of the retinal dysfunction published by Pinckers et al,20 we are unaware of a previous report addressing this question.

The median duration of symptoms and visual acuity in our study compares with previously published results in BEM.4,13 We acknowledge that the duration of symptoms may not truly reflect the duration of disease, but this is the only viable option in the absence of longitudinal studies.

Autofluorescence imaging of the RPE with the cSLO, as a known method for indirectly assessing the state of the photoreceptor cells, was extremely valuable in confirming the diagnosis but was not helpful in assessing the degree of retinal dysfunction. In some cases, the macular abnormality was very subtle on ophthalmoscopic examination but much more evident on the cSLO image. That all sibling pairs showed a very similar autofluorescence pattern suggests that this may reflect genetic influences, assuming that siblings have the same mutations, particularly as some sibling pairs showed marked differences in age. Given the rarity of the disorder, this is likely to be the case. Despite this absolute concordance in the cSLO image, the electrophysiologic results were discordant in 2 sibling pairs. This finding contrasts markedly with previous observations on intrafamilial variation in SMD-FFM; although siblings with SMD-FFM showed wide variation in age of onset, visual acuity, and clinical appearance, electrophysiologic testing revealed qualitatively similar results. In the present study, the siblings with the longer duration of illness had generalized retinal involvement as opposed to dysfunction confined to the macula. This lack of concordance across sibling pairs in BEM may indicate a progressive disorder, which is important when counseling these patients. Unlike Stargardt disease, it cannot be concluded that normal ERGs at one stage in the disorder imply that peripheral retinal function will remain unaffected. Whether the disorder evolves from localized to generalized disease can be determined by longitudinal recording and larger sibling studies.

The importance of the shorter duration of disease, significantly better visual acuity, and the older age of onset in patients displaying a speckled pattern of RPE atrophy within the bull’s-eye lesion (cSLO group 3) is unclear. That PERGs in this group were not better preserved than in the others, and the fact that one case showed generalized dysfunction, argues against this appearance merely representing earlier disease. Rather than assuming that these patients will develop the typical confluent areas of atrophy and possibly loss of vision, they may represent a distinct phenotype with milder disease.

Although the electrophysiologic characteristics concerning generalized retinal dysfunction did not correlate well with variables such as duration of symptoms, visual acuity, and area of atrophy, most patients with CRD...
has previously been noted in some patients with BEM.24 But rather in the postphototransduction system as photopic ERG found in 2 cases suggests that the dysnormality. When diagnosing CD, not allowing any rod system abnormality. Rather than ascribing this discrepancy to a truly different patient population from previous studies, we may have applied stricter criteria than corrected for any magnification factor when measuring the area of atrophy.27,28 Whether or not the extent of atrophy in the bull's-eye lesion represents different disorders is doubtful. It may reflect the duration of disease, although we found no correlation with the duration of symptoms.

Unlike SMD-FFM, in which a single gene is involved, BEM seems to represent a heterogeneous group of disorders.29 The fact that the disorder can be present in autosomal recessive and autosomal dominant patterns supports this view. Furthermore, although 2 genes have been implicated in transmitting dominant disease,10,11 mutations in these genes do not explain all the dominant bull's-eye dystrophies.

Table 6. Electrophysiologic Findings in Sibling Pairs*

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age at Examination/Onset, y</th>
<th>Duration, y</th>
<th>Visual Acuity OD</th>
<th>Electrophysiologic Diagnosis</th>
<th>Pattern Electroretinogram Reduction</th>
<th>Area of Atrophy, Square Degrees</th>
</tr>
</thead>
<tbody>
<tr>
<td>2*</td>
<td>33/16</td>
<td>17</td>
<td>6/12</td>
<td>MD</td>
<td>Mod</td>
<td>12.5</td>
</tr>
<tr>
<td>3*</td>
<td>24/20</td>
<td>4</td>
<td>6/36</td>
<td>MD</td>
<td>Mod</td>
<td>12.9</td>
</tr>
<tr>
<td>10†</td>
<td>47/20</td>
<td>27</td>
<td>6/36</td>
<td>MD</td>
<td>ND</td>
<td>67.5</td>
</tr>
<tr>
<td>11†</td>
<td>38/18</td>
<td>20</td>
<td>6/60</td>
<td>MD</td>
<td>ND</td>
<td>71.9</td>
</tr>
<tr>
<td>16†</td>
<td>34/27</td>
<td>7</td>
<td>6/80</td>
<td>CD</td>
<td>ND</td>
<td>14.9</td>
</tr>
<tr>
<td>17†</td>
<td>34/23</td>
<td>11</td>
<td>1/60</td>
<td>CD</td>
<td>ND</td>
<td>13.9</td>
</tr>
<tr>
<td>26†</td>
<td>25/21</td>
<td>4</td>
<td>6/24</td>
<td>CRD</td>
<td>ND</td>
<td>10.9†</td>
</tr>
<tr>
<td>27†</td>
<td>15/15</td>
<td>0</td>
<td>6/6</td>
<td>CRD</td>
<td>Mod</td>
<td>3.9</td>
</tr>
<tr>
<td>38†</td>
<td>56/54</td>
<td>2</td>
<td>6/6</td>
<td>MD</td>
<td>ND</td>
<td>32.9†</td>
</tr>
<tr>
<td>39†</td>
<td>48/46</td>
<td>2</td>
<td>6/9</td>
<td>MD</td>
<td>ND</td>
<td>65.6†</td>
</tr>
<tr>
<td>40‡</td>
<td>45/45</td>
<td>0</td>
<td>6/9</td>
<td>MD</td>
<td>Mod</td>
<td>9.8</td>
</tr>
<tr>
<td>41‡</td>
<td>35/33</td>
<td>2</td>
<td>6/5</td>
<td>RCD</td>
<td>Mod</td>
<td>1.5†</td>
</tr>
<tr>
<td>33‡</td>
<td>51/29</td>
<td>22</td>
<td>6/60</td>
<td>CRD</td>
<td>ND</td>
<td>28.6</td>
</tr>
<tr>
<td>34‡</td>
<td>24/15</td>
<td>9</td>
<td>8/36</td>
<td>CRD</td>
<td>ND</td>
<td>44.6</td>
</tr>
</tbody>
</table>

*MD indicates macular dystrophy; mod, moderate; CRD, cone-rod dystrophy; ND, nondetectable; and RCD, rod-cone dystrophy. Superscript numbers 1 through 6 represent sibling pairs; older sibling has lower patient number.
†Area of atrophy difficult to delineate on the confocal scanning laser ophthalmoscope.
‡Patient 34 is the son of patient 33 in this dominant family.
Submitted for publication May 31, 2001; final revision received December 10, 2001; accepted December 21, 2001.

This study was supported by the Macular Disease Society, London, England; the Zürcher Hochschulverein and the EMDO-Stiftung, Zürich, Switzerland (Dr Kurz-Levin); and the Foundation for Fighting Blindness, Baltimore, Md (Dr Halfyard).

Corresponding author and reprints: Graham E. Holder, PhD, Moorfields Eye Hospital, City Road, London EC1V 2PD, England (e-mail: graham.holder@moorfields.nhs.uk).

REFERENCES