Objective: To describe the clinical features and outcomes of a large group of patients with a spectrum of clinical appearances and diagnosed as having punctate inner choroidopathy (PIC).

Methods: In a retrospective consecutive case series, patients seen during a 16-year period at Moorfields Eye Hospital who were diagnosed as having PIC and had a minimum of 12 months' follow-up were included. Patients were classified as having typical PIC or atypical PIC (larger, presumed ocular histoplasmosis syndrome–like lesions). Main outcome measures included development of choroidal neovascularization, development of new PIC lesions, and final visual acuity.

Results: A total of 136 patients (271 eyes) were included. The average age was 32 years, 126 patients (93%) were female, and the mean refraction was −4.6 diopters. The overall mean follow-up was 6.2 years. Among 63 normal fellow eyes, 56 (88%) remained unchanged, 3 (5%) developed PIC lesions, and 4 (6%) developed choroidal neovascularization. Eyes with PIC lesions remained unchanged in 49 of 74 cases (66%), with 9 (12%) developing new PIC lesions and 16 (22%) developing choroidal neovascular membrane. In eyes with choroidal neovascularization, the mean logMAR visual acuity was 0.63 at study entry, 0.63 at 12 months, 0.61 at 2 years, and 0.71 at final review (mean, 6.1 years). Overall, 40 eyes with PIC-related choroidal neovascular membrane (26%) had final visual acuity less than 6/60. No differences were observed between typical and atypical PIC eyes in any of the outcome measures or in any of the subgroup analyses.

Conclusions: Punctate inner choroidopathy–related choroidal neovascularization was not visually benign. No differences were observed between eyes with typical and atypical choroidal lesions, supporting the notion that they represent a spectrum of a single disease, PIC.

THE TERM PUNCTATE INNER choroidopathy (PIC) was first used by Watzke et al in 1984 to describe findings in a group of 10 patients with multifocal, well-circumscribed, usually small choroidal lesions. These lesions were said to variably evolve into hypopigmented scars, pigmented scars, or hyperplastic fibrotic scars as a result of choroidal neovascularization (CNV). Watzke and colleagues commented that the scars resembled those found in presumed ocular histoplasmosis syndrome (POHS). Histoplasmin skin test results, however, were negative in the 7 cases that underwent testing. In contrast to POHS, the evolution of PIC lesions was symptomatic and the disease tended to affect younger, myopic women. Earlier articles by François et al, Doran and Hamilton, and Miller et al probably described the same disease under different names.

Eyes with a clinical appearance identical to that of POHS are often observed in non–Histoplasma-endemic areas. These eyes have been variably labeled as having POHS, multifocal inner choroiditis, recurrent multifocal choroiditis, pseudo-POHS, disseminated inner choroiditis, or multifocal choroidopathy. Such eyes commonly develop recurrent symptomatic choroiditis, similar to eyes with smaller, more typical PIC lesions. As a result, it has become commonplace to label eyes with multifocal choroidal lesions in the absence of other signs of uveitis (and in the absence of another diagnosis) as having PIC. We describe the clinical features and outcomes of a large group of patients thus diagnosed with PIC.

METHODS

All patients seen during a 16-year period at Moorfields Eye Hospital, London, England, and diagnosed as having PIC were eligible for inclusion in our study. Cases were identified by searching a computerized database of clinical diagnoses as well as a personal database of diagnoses maintained by one of us (J.D.). All rec-
Punctate inner choroidopathy was defined as the presence of multifocal, pale, atrophic lesions at the level of the retinal pigment epithelium and inner choroid in the absence of any sign of inflammation elsewhere in the eye (ie, vitritis, pars planitis, anterior chamber cells, or anterior synechiae). Necessary for the diagnosis for the purpose of this study were an absence of systemic disease known to be associated with choroiditis and no exposure to *Histoplasma*-endemic regions of the world. Choroidal neovascularization in the absence of such lesions was not sufficient for the diagnosis. Eyes with pathologic myopia were excluded. Lesion location could be anywhere in the post-equatorial fundus. A lesion size less than one-fourth the disc diameter was not necessary for the diagnosis.

Baseline demographic data including age, sex, and place of residence were collected. Evaluated ocular features included refraction, visual acuity (VA), and fundus appearance. In all eyes, PIC lesions were counted (<5, 5-10, 11-20, and >20) and distribution was assessed (predominantly posterior pole, predominantly peripheral, and mixed). The size of the lesions was graded (all less than or equal to one-fourth the disc diameter, most less than or equal to one-fourth the disc diameter, most larger than one-fourth the disc diameter, and all larger than one-fourth the disc diameter). The presence or absence of peripapillary PIC lesions was recorded.

Following grading of fundus photographs by two of us (R.W.E. and J.W.), patients were divided into 1 of 2 groups: typical PIC or atypical PIC. Typical PIC eyes were defined as those with small lesions (less than or equal to one-fourth the disc diameter) predominantly confined to within the arcades and generally not peripapillary in distribution (Figure 1A). Atypical PIC eyes were those with larger lesions distributed both within and outside the arcades and often appearing in a peripapillary location (similar to the POHS phenotype) (Figure 1B). If a patient had typical PIC in one eye and atypical PIC in the other, that patient was regarded as having atypical PIC.

The clinical course and visual outcome were recorded for all eyes. Particularly noted were the development of new PIC lesions, the development of new CNV, and VA at all visits. Symptomatic ocular inflammation was specifically noted if documented. Any treatment received for the ocular disease was recorded, particularly treatment for CNV or choroiditis. Efforts made to determine the cause of visual loss (if relevant).

The VAs were measured using Snellen charts and were converted to logMAR equivalents for the purpose of analysis using the formula logMAR = −log(Snellen fraction).

Additional clinical and follow-up data were gathered for eyes with PIC-related CNV. Choroidal neovascularization was defined in 2 ways. Active CNV featured an elevated subretinal lesion arising from a PIC lesion and associated with subretinal fluid, subretinal hemorrhage, and/or leak beyond the boundaries of the lesion on fluorescein angiography. Inactive CNV consisted of an elevated, fibrotic, subretinal lesion arising from a PIC lesion, with no subretinal hemorrhage or fluid and with fluorescein staining confined to the fibrotic lesion on fluorescein angiography. Details of the treatment used for the neovascular membrane (if any) were collected. End points recorded for the eyes with CNV were VA at 1 year and 2 years following the initial visit and final VA. Natural history was compared with the outcomes of different treatment modalities.

Many eyes evolved during the follow-up period. For instance, an eye with PIC lesions could develop CNV. Such an eye would be included in the presentation of CNV visual outcomes provided that 12 months’ follow-up data were available from the date the eye entered the new group.

Statistical analysis was performed using 2-tailed Fisher exact test for comparing categorical variables and using t test for comparing continuous variables.

A total of 214 patients were entered into the database with the diagnosis of PIC. Seventy-eight were excluded. Reasons for exclusion were as follows: 24 cases had no notes available; 28 had inadequate follow-up; 5 had questionable diagnoses; and 21 had alternative diagnoses (7 with pathologic myopia, 6 with multifocal choroiditis with panuveitis, 5 with POHS, and 1 each with age-related macular degeneration, sarcoidosis, and idiopathic CNV). This left a total of 136 patients.

**DEMOGRAPHIC CHARACTERISTICS**

Of the 136 patients, 126 (93%) were female. The average age at the initial visit was 32 years (range, 16-64 years). The mean spherical equivalent refraction was −4.6 diopters (D) (range, −14 to +4 D), with 16% being emmetropic or hypermetropic. The mean follow-up was 6.2 years.

Among 113 patients, 60 (53%) were classified as having typical PIC and 53 (47%) as having atypical PIC.
Twenty-three patients could not be classified as no photographs were available for review. There were no differences in demographic data between the typical and atypical groups (95% vs 91% female, respectively; mean age, 32 vs 33 years, respectively; and mean refraction, −4.7 vs −4.6 D, respectively).

**UNILATERAL VS BILATERAL DISEASE**

Sixty-four patients (47%) had unilateral disease at baseline, with 49 having PIC lesions and CNV in the affected eye and 15 having PIC lesions only (at the initial visit) in the affected eye. The average follow-up for this group was 5.3 years (range, 1-22 years). Only 7 developed disease in their normal eye (3 developed PIC lesions and 4 developed CNV). Of the 15 patients with unilateral PIC lesions, 8 remained unchanged, 4 developed CNV in the affected eye, and 3 developed new PIC lesions in the affected eye. One patient was monocular.

A total of 72 patients had bilateral disease at the initial visit: 26 had bilateral CNV, 10 had PIC lesions in both eyes, and 36 had CNV in one eye and PIC lesions in the absence of CNV in the other eye. Twelve patients developed CNV in an eye with PIC lesions and 4 developed new PIC lesions. The mean follow-up for this group was 6.9 years (range, 1-21 years) (Table 1).

Presented in another way, 85 patients initially had unilateral choroidal neovascular membrane (CNVM). Among these patients, 36 had PIC lesions in the fellow eye and 49 did not. Thirteen of the fellow eyes (15%) were observed to develop CNV. Normal fellow eyes eventually developed CNVM in 3 of 49 cases (6%), and fellow eyes with PIC lesions developed CNVM in 10 of 36 cases (28%) (P=.01). The PIC lesions were therefore a risk factor for CNVM development in fellow eyes.

Thirty patients were symptomatic for choroidal inflammation at some stage during their clinical course. There was a trend for those with symptomatic choroiditis to have smaller choroidal lesions (17 with typical PIC vs 7 with atypical PIC; P=.06). Photopsia and blurred vision were the most common symptoms.

Five eyes of 5 patients were diagnosed clinically with acute zonal occult outer retinopathy, although the diagnostic criteria were not rigorous and none were confirmed with electrophysiological testing.

**VISUAL ACUITY OUTCOMES**

A total of 271 eyes of 136 patients were included in the study. Overall, final VA was 6/12 or better in 178 eyes (66%) and less than 6/60 in 41 eyes (15%). Four of the 136 patients (3%) had VA less than 6/60 bilaterally as a result of PIC or PIC-related CNVM. The reason for vision loss could be determined in 138 eyes: CNV in 119 eyes, PIC lesions in the absence of CNVM in 17 eyes, and epiretinal membrane in 2 eyes.
Normal Fellow Eyes

There were 63 normal fellow eyes. There was no change in VA in this group. The median VA at baseline and at final review was 6/6. The change in mean logMAR VA from baseline was 0.04 (approximately equivalent to 2 Early Treatment Diabetic Retinopathy Study letters). The development of PIC lesions in the absence of CNV was not visually significant. However, CNV development was associated with a decrease in VA from 6/6 to counting fingers in 1 eye (for the other 3 eyes that developed CNV, 1 remained at 6/6, 1 decreased to 6/9, and 1 decreased to 6/12) (Table 2).

Eyes With PIC Lesions Only

A total of 74 eyes of 63 patients had PIC lesions only at baseline. The average follow-up for these eyes was 4.5 years (range, 107 days to 14 years). Outcomes for these eyes are presented in Table 2 and Table 3. No differences were observed between eyes of patients with typical PIC or atypical PIC. Overall, 49 eyes (66%) remained unchanged, 9 (12%) developed new PIC lesions (Figure 2), and 16 (22%) developed CNVM (Figure 3). The mean time to diagnosis of CNVM was 3.8 years (range, 107 days to 12 years).

Of the 12% of eyes that developed new PIC lesions, the mean time to appearance of new lesions was 2.6 years (range, 1-6 years). Four of these 9 eyes were symptomatic for ocular inflammation when the new PIC lesions were noted, and the new PIC lesions were noted incidentally at follow-up in the remaining 5 eyes. The VA data for the PIC eyes are presented in Table 2. Of the 16 eyes in the group with PIC that developed CNVM, 8 (50%) had final VA of 6/12 or better and 4 (25%) had final VA less than 6/60.

Table 3. Primary Outcomes in Eyes With Punctate Inner Choroidopathy Lesions at Baseline

<table>
<thead>
<tr>
<th>End Point</th>
<th>PIC Lesions (n=74)b</th>
<th>Typical PIC (n=36)</th>
<th>Atypical PIC (n=24)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No change</td>
<td>49 (66)</td>
<td>25 (69)</td>
<td>15 (63)</td>
<td>.55</td>
</tr>
<tr>
<td>New PIC lesion</td>
<td>9 (12)</td>
<td>4 (11)</td>
<td>4 (17)</td>
<td>.74</td>
</tr>
<tr>
<td>CNVM</td>
<td>16 (22)</td>
<td>7 (19)</td>
<td>5 (21)</td>
<td>&gt;.99</td>
</tr>
</tbody>
</table>

Abbreviations: CNVM, choroidal neovascular membrane; PIC, punctate inner choroidopathy.

a The mean follow-up was 4.5 years.

b In 14 eyes, no photographic grading of phenotype was possible.

Figure 2. Evolution of punctate inner choroidopathy lesions over a 4-year period, shown in August 2002 (A), March 2004 (B), and August 2006 (C). Progression was observed in 12% of eyes with punctate inner choroidopathy lesions.

Figure 3. Progression of choroidal neovascularization in an eye with punctate inner choroidopathy lesions. Twenty-two percent of eyes with punctate inner choroidopathy lesions developed de novo choroidal neovascular membrane.
Eyes With PIC-Related CNVM

A total of 153 eyes of 117 patients had PIC-related CNVM. The mean follow-up was 5.9 years (range, 1-21 years), with 100% having 12-month VA data and 88% having 2-year data. Visual outcomes of this group are summarized in Table 4. Among the 153 eyes, final VA was less than 6/12 in 87 (57%) and less than 6/60 in 40 (26%). Also shown in Table 4 are data for typical PIC eyes vs atypical PIC eyes. No significant differences were observed between the typical and atypical PIC eyes.

Active CNVM (ie, signs of subretinal fluid, hemorrhage, or angiographic leak beyond the margins of the neovascular lesion) and inactive CNVM (fibrotic lesions) are compared in Table 5. Mean VA at 2 years remained essentially unchanged in both groups when compared with baseline. However, active CNVM as compared with inactive CNVM had a more variable course, with a trend to a greater incidence of visual loss at 2 years (doubling of the visual angle, 25% vs 16%, respectively; P = .36) and a greater incidence of visual gain (halving of the visual angle, 35% vs 13%, respectively; P = .01).

Outcomes of treated active CNVM are presented in Table 5 (no inactive CNVM eyes received treatment). The final mean VA was similar across all CNVM groups (6/28-6/34) regardless of mean baseline vision, treatment received, or CNVM activity. Baseline vision was not consistent across treatment groups, with eyes having argon laser treatment (all with nonsubfoveal CNVM) faring significantly better and eyes undergoing submacular surgery faring significantly worse. Prevalence of significant vision loss was similar in all groups (it appeared lower in those receiving submacular surgery; however, the numbers were small). No patients were treated with anti–vascular endothelial growth factor agents.

Here we present the largest series to date of patients diagnosed as having PIC. Our study includes all eyes with multifocal choroidal lesions in the absence of vitreous or anterior chamber inflammation (also in the absence of systemic disease known to cause choroiditis and of exposure to Histoplasma-endemic areas). We recognize that many clinicians may not consider the eyes described as having atypical PIC in this article to represent this disease at all. In support of our pooled classification, we could not identify any significant differences between eyes described as having typical PIC and those described as having atypical PIC. However, patients from Histoplasma-endemic areas and those with other recognized disease entities associated with multifocal choroiditis were specifically excluded from this study—these represent specific entities with known, differing etiologies. It is our view that typical and atypical PIC should be considered a spectrum of a single disease, PIC (a form of multifocal choroiditis), until differing etiologies can be demonstrated.

### Table 4. Visual Outcomes of Punctate Inner Choroidopathy–Related Choroidal Neovascularization at 12 Months, 24 Months, and Final Review

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline VA, logMAR</th>
<th>12-mo Follow-up VA, logMAR</th>
<th>24-mo Follow-up VA, logMAR</th>
<th>Final Review VA, logMAR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No./Mean</td>
<td>Doubling Visual Angle, No. (%)</td>
<td>Halving Visual Angle, No. (%)</td>
<td>No./Mean</td>
</tr>
<tr>
<td>All CNVM</td>
<td>153</td>
<td>0.63</td>
<td>35 (23)</td>
<td>34 (22)</td>
</tr>
<tr>
<td>Typical PIC</td>
<td>65</td>
<td>0.59</td>
<td>11 (17)</td>
<td>11 (17)</td>
</tr>
<tr>
<td>Atypical PIC</td>
<td>62</td>
<td>0.66</td>
<td>18 (29)</td>
<td>13 (21)</td>
</tr>
</tbody>
</table>

**Abbreviations:** CNVM, choroidal neovascular membrane; VA, visual acuity.

### Table 5. Comparison of Visual Outcomes of Active vs Inactive Choroidal Neovascular Membrane

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline VA, logMAR</th>
<th>12-mo Follow-up VA, logMAR</th>
<th>24-mo Follow-up VA, logMAR</th>
<th>Final Review VA, logMAR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No./Mean</td>
<td>Doubling Visual Angle, No. (%)</td>
<td>Halving Visual Angle, No. (%)</td>
<td>No./Mean</td>
</tr>
<tr>
<td>Inactive CNVM</td>
<td>43</td>
<td>0.73</td>
<td>6 (14)</td>
<td>7 (16)</td>
</tr>
<tr>
<td>Active CNVM</td>
<td>110</td>
<td>0.58</td>
<td>29 (26)</td>
<td>28 (23)</td>
</tr>
<tr>
<td>Steroid treatment</td>
<td>35</td>
<td>0.59</td>
<td>11 (31)</td>
<td>13 (37)</td>
</tr>
<tr>
<td>Thermal laser</td>
<td>15</td>
<td>0.25</td>
<td>2 (13)</td>
<td>4 (27)</td>
</tr>
<tr>
<td>Submacular</td>
<td>15</td>
<td>0.95</td>
<td>1 (7)</td>
<td>3 (20)</td>
</tr>
</tbody>
</table>

**Abbreviations:** CNVM, choroidal neovascular membrane; VA, visual acuity.
strated. This disease spectrum may also extend to include the acute zonal ocular outer retinopathy complex of diseases (for more detailed discussion, see the article by Jampol and Becker).}

There is a substantial selection bias in the study population. Not only is there a referral bias to Moorfields Eye Hospital (the largest ophthalmic hospital in Europe), but 12 months of follow-up data were required for inclusion in the study, which likely would have excluded less severe cases such as asymptomatic eyes with normal vision not requiring ongoing care. It is likely, therefore, that the true prognosis in PIC is better than that described here. It is unlikely to be worse.

The observed clinical course of PIC was variable. Normal fellow eyes had an excellent prognosis, with only 1 losing substantial vision due to CNVM. Twenty-two percent of eyes with PIC lesions went on to develop CNVM. The PIC-related CNVM had a somewhat aggressive course. Overall, 26% of eyes observed with PIC-related CNVM had final VA less than 6/60. These outcomes must be viewed in light of the selection bias within the study population but are consistent with other studies. The PIC-related CNVM does not, however, appear to be as aggressive as CNV in age-related macular degeneration—VAs in 43% of eyes remain at 6/12 or better.

It is interesting when observing the effects of CNV treatment on visual outcome to note that the final VA was similar in all groups with CNVM regardless of the treatment they received. However, our study did not include any patients treated with anti–vascular endothelial growth factor therapy. In the series by Chan et al., the 4 patients with PIC treated with 3 bevacizumab injections all improved, and none had VA worse than 6/12 at final review. Caution must be exercised, however, when using anti–vascular endothelial growth factor agents in women of childbearing age.

Normal fellow eyes of patients receiving steroids were significantly more likely to develop CNVM than those in patients without symptomatic choroiditis (19% vs 2%, respectively; P = .04). The indication for the steroids was active PIC, and it was almost certainly the active disease rather than the steroid therapy causing the CNVM. The inflammation is presumably the first step in the series of events that eventually leads to the development of CNVM. A similar selection bias explains why eyes in the group with PIC had a trend toward worse outcomes when they were exposed to immunosuppression. The alternative explanation—that immunosuppression itself resulted in worse outcomes, possibly by exacerbating an underlying infectious cause—is unlikely in our view.

In summary, the clinical outcomes of PIC are described. No differences could be identified between patients with typical and atypical PIC. We believe these should be considered a spectrum of a single disease, PIC (a form of multifocal choroiditis). The PIC-related CNVM was visually significant.

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