Extended Follow-up of Treated and Untreated Retinopathy in Incontinentia Pigmenti
Analysis of Peripheral Vascular Changes and Incidence of Retinal Detachment

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Importance
Extended follow-up of treated and untreated retinopathy in incontinentia pigmenti (IP) has not previously been documented, to our knowledge.

Objective
To determine which eyes with IP are at risk for retinal detachment.

Design, Setting, and Participants
Observational cohort study of patients with IP who were retrospectively identified at a tertiary care academic center between 1976 and 2013. Fifty eyes of 25 female participants meeting clinical criteria for IP were followed up for at least 6 months. The last year of follow-up was between 1987 and 2014.

Main Outcomes and Measures
Progression of retinopathy or the development of retinal detachment was assessed with fluorescein angiography, clinical examination, or both.

Results
The median duration of follow-up was 9.3 years (range, 0.5-22.8 years). Over this period, 11 eyes (22%; 95% CI, 11%-33%) developed retinal detachment. The odds of retinal detachment were increased if there was retinal neovascularization (odds ratio, 11.61; 95% CI, 1.34-100.56; \( P = .03 \)) or ischemic optic neuropathy (odds ratio, 5.27; 95% CI, 1.61-17.23; \( P = .006 \)) on initial examination. A bimodal distribution of retinal detachments was observed, with most tractional detachments (7 eyes) occurring by age 2.5 years (median, 1.5 years; range, 14 days-7.0 years) and most rhegmatogenous detachments (4 eyes) occurring in adults (median age, 31.5 years; range, 14.0-47.0 years). Three eyes of young patients (\( \leq 2.5 \) years) developed tractional detachment, despite prophylactic ablation in 4 eyes; only one eye of older patients (\( \geq 14.0 \) years) developed retinal detachment following prophylactic ablation in 6 eyes. Persistent fetal vasculature appears to occur more commonly in IP (14%; 95% CI, 4%-25%) than in the general population.

Conclusions and Relevance
All eyes with retinopathy due to IP should be monitored throughout adulthood for the development of retinal complications. During infancy and early childhood, ophthalmoscopic examination should be performed frequently so that prompt treatment can be initiated if there is progressive disease. Because of the nonrandomized nature of this study, the indications for prophylactic ablation and its success rate remain uncertain. Patients with less than 6 months of follow-up were excluded from the analysis, which could have biased this study cohort toward patients with more severe or less severe disease.
Follow-up of Retinopathy in Incontinentia Pigmenti

Incontinentia pigmenti (IP), also known as Bloch-Sulzberger syndrome, is a rare X-linked dominant disease affecting the eyes, central nervous system, skin, and teeth. Affected infants are typically female because the responsible mutations in nuclear factor-kB essential modulator (NEMO) gene (OMIM 300248) are lethal to males in utero. Initially, infants may manifest a characteristic erythematous vesicular rash. Later, these lesions are replaced with verrucous lesions and, ultimately, pigmented whorls and streaks.

Although the skin findings are the most obvious, the neurologic and ophthalmic manifestations are the most medically important. Neurologic disease from vasoocclusions can include seizures, paralysis, and mental retardation. Ophthalmic manifestations are reported in approximately 35% of patients, and approximately 20% will develop vision-threatening disease. Patients are initially seen with peripheral ischemia from vasoocclusion in the retina and subsequent peripheral neovascularization. However, when vision loss occurs, it usually develops as a result of tractional retinal detachment secondary to contraction of fibrovascular tissue or rhegmatogenous detachment related to the development of holes in atrophic, avascular retina. Less commonly, vision loss can result from vitreous hemorrhage, retinal arterial occlusion, ischemic optic neuropathy, or occipital lobe infarction in the brain.

Based on similarities to retinopathy of prematurity, many physicians recommend ablation to peripheral ischemic retina in IP, with the intent to halt fibrovascular proliferation and prevent retinal detachment. Although prophylactic ablation appears to have been successful in a few IP cases, some eyes with proliferative retinopathy maintain a stable or improved course with observation alone. Extensive photocoagulation or cryotherapy, by themselves, can be associated with cicatrical changes such as epiretinal membrane or proliferative vitreoretinopathy. Furthermore, retinal tears can develop at the edge of previously treated retina and lead to retinal detachment.

In a large cohort of 50 eyes, we document angiographic and ophthalmoscopic changes over a prolonged period in treated and untreated retinopathy in IP. We identify factors associated with the development of retinal detachment and propose recommendations for ophthalmic screening in patients with IP.

Methods

Study Design and Sampling

Approval from the Johns Hopkins Hospital Institutional Review Board Ethics Committee was obtained for the study. Written informed consent was obtained from participants. This was an observational cohort study. All individuals with a clinical diagnosis of IP were retrospectively identified from the patient panel of the lead investigator (M.F.G.) at Wilmer Eye Institute, with an initial visit between 1976 and 2013. The diagnosis of IP was based on previously published criteria. In 8 patients, there was a history of IP in a first-degree female relative, along with supportive skin findings, history of miscarriages, or retinal disease. If no first-degree relative was affected, participants fulfilled at least 1 major criterion (typical neonatal rash, typical truncal hyperpigmentation, or linear hairless lesions). All patients were evaluated by a dermatologist or a geneticist, who performed a skin biopsy (8 patients) or genetic testing (3 patients) if the diagnosis was in question. Patients were followed up for a minimum of 6 months. The last year of follow-up was between 1987 and 2014. Those with follow-up of less than 6 months were excluded from the study. In addition, patients without a sufficiently well-documented baseline peripheral retinal examination were excluded.

Fifty eyes of 25 female patients with IP were included in our analysis. In 3 eyes, there was no view to the posterior pole owing to a retrolental membrane or retinal detachment. One eye had been enucleated before presentation to Wilmer Eye Institute. These 4 eyes were excluded from statistical analysis when evaluating factors associated with retinal detachment. B-scan ultrasonography was performed on all eyes without a view to the fundus to confirm posterior pole pathology.

Treatment with ablative therapy was left to the discretion of the treating retinal specialist (C.J.C., I.C.H., and M.F.G.). Eyes that demonstrated nonperfusion with documented progressive neovascularization were typically treated with scatter photocoagulation or cryotherapy to nonperfused areas. Eyes with vitreous hemorrhage resulting from active neovascularization were also usually treated. Flat neovascularization generally was not treated unless there was clear progression at successive examinations (ie, progressive neovascularization, development of definite traction, or vitreous hemorrhage). Treatment of retinal detachment was also left to the discretion of the treating retinal specialist (scleral buckling in 2 patients and pars plana vitrectomy in 3 patients).

Examination and Testing

Participants underwent a complete eye examination by one of the study investigators (C.J.C., I.C.H., or M.F.G.) at baseline and at each subsequent visit. Color photographs with a 30° fundus camera, a widefield digital imaging system (RetCam; Clarity Medical Systems), or a widefield camera (200Tx; Optos PLC) were obtained whenever possible. All but 2 participants had a full evaluation with fundus photographs and fluorescein angiography on at least 1 visit. Of 15 children younger than 2 years, 11 were evaluated and photographed using general anesthesia. Fluorescein angiography and detailed retinal drawings were used to document nonperfusion, neovascularization, traction, vitreous hemorrhage, retinal breaks, and presence of retinal detachment. Based on the findings from fluorescein angiogram and review of retinal drawings, the number of quadrants of nonperfusion was graded from 0 to 4 at the initial visit and at the last follow-up visit.

Statistical Analysis

Fisher exact test was used to compare characteristics between the participants who did vs did not develop retinal detachment using 2-sided significance testing. Nonnormally distributed variables were analyzed with Wilcoxon signed rank test.
test using 2-sided significance testing. Factors associated with retinal detachment were assessed using logistic regression models. The generalized estimating equation approach was used to account for intereye dependencies. Statistical analysis was performed using commercially available software (SAS, version 9.2; SAS Institute Inc).

## Results

Forty-two female patients were evaluated for inclusion in this study. Because of insufficient follow-up (<6 months) or insufficient documentation of the peripheral retinal examination, 17 patients were excluded from the study. There was no statistically significant difference between the baseline characteristics of enrolled and excluded patients (eTable 1 in the Supplement).

### Patient Characteristics Associated With Retinal Detachment

Twenty-five participants were enrolled in the study. Their median age at the first documented retinal evaluation was 0.9 years, and the median age at the last retinal examination was 14.4 years (eTable 2 in the Supplement). The median duration of follow-up was 9.3 years (range, 0.5-22.8 years). There was no significant difference in the age at presentation or the duration of follow-up between the groups that did vs did not develop retinal detachment.

We evaluated the neurologic status of all participants to determine whether the development of seizures, strokes, or any other major neurologic disease (developmental delay, white matter lesions, or microcephaly) was associated with retinal detachment. There was a trend toward the development of retinal detachment in participants with neurologic disease ($P = .08$) (eTable 2 in the Supplement). Of 6 young participants with tractional detachments (age at detachment, ≤2.5 years), 3 were initially seen with concomitant neurologic disease (eTable 3 in the Supplement).

### Clinical Risk Factors for Retinal Detachment in Each Eye

We asked whether specific clinical characteristics for each eye were associated with the development of retinal detachment. Of 46 eyes that provided sufficient view for retinal evaluation and grading, the presence of retinal neovascularization (odds ratio, 11.61; 95% CI, 1.34-100.56; $P = .03$) or ischemic optic neuropathy (defined as disc pallor with associated afferent pupilary defect) (odds ratio, 5.27; 95% CI, 1.61-17.23; $P = .006$) on initial examination was associated with increased odds of retinal detachment in a univariate model (Table). There was a trend toward retinal detachment in eyes with peripheral nonperfusion on initial examination (odds ratio, 7.79; 95% CI, 0.83-73.63; $P = .07$). The numbers of patients with arterial occlusion and vitreous hemorrhage were too small to perform logistic regression. Because of the small sample size, this study was not powered to detect how risk factors may be dependent on one another. Therefore, multivariable analysis was not included herein.

### Outcomes of Eyes Treated With Prophylactic Ablation

Having identified retinal neovascularization as a risk factor associated with subsequent retinal detachment, we then evaluated whether prophylactic ablation prevented retinal detachment. Of 50 eyes studied, 10 were treated with prophylactic ablation to nonperfused retina. One eye was treated with cryotherapy, and the remaining 9 eyes were treated with laser photocoagulation (eTable 4 in the Supplement). Eight treated eyes had angiographic evidence of leakage from neovascularization before initiation of ablative therapy, and 2 eyes treated by an outside physician demonstrated nonperfusion but no angiographic leakage before treatment. Of the eyes in the youngest group that received prophylactic ablation (age at treatment, 1 month to 2 years), 3 of 4 eyes developed subsequent tractional detachment. When evaluating the combined eyes of teenagers (age at treatment, 13-17 years) and adults (age at treatment, 46 and 47 years) that received prophylactic ablation laser therapy, 1 of 6 developed subsequent rhegmatogenous detachment, and 5 did not.

### Table. Factors Associated With the Development of Retinal Detachment in Eyes With Incontinentia Pigmenti

<table>
<thead>
<tr>
<th>Clinical Finding</th>
<th>Eyes, No. (%)</th>
<th>Odds Ratio (95% CI)</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of peripheral nonperfusion on initial exam</td>
<td>25/46 (54.3)$^b$</td>
<td>7.79 (0.83-73.63)</td>
<td>.07</td>
</tr>
<tr>
<td>Progression of peripheral nonperfusion on follow-up</td>
<td>8/45 (17.7)$^b$</td>
<td>2.39 (0.48-11.75)</td>
<td>.28</td>
</tr>
<tr>
<td>Presence of retinal neovascularization on initial exam</td>
<td>19/46 (41.3)$^b$</td>
<td>11.61 (1.34-100.56)</td>
<td>.03</td>
</tr>
<tr>
<td>Ischemic optic neuropathy on initial examination</td>
<td>8/46 (17.4)$^b$</td>
<td>5.27 (1.61-17.23)</td>
<td>.006</td>
</tr>
<tr>
<td>Branch retinal artery</td>
<td>2/46 (4.3)$^b$</td>
<td>4.04 (0.99-16.61)</td>
<td>.05</td>
</tr>
<tr>
<td>Presence of vitreous hemorrhage at any time</td>
<td>3/46 (6.5)$^b$</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

Abbreviation: NA, not applicable.

$^a$ Five eyes could not be examined and included in analysis because 4 eyes provided no view to the posterior pole on initial presentation and there was subsequent funnel retinal detachment in one eye on follow-up.

$^b$ Four eyes could not be examined and included in analysis because there was no view to the posterior pole on initial presentation.
Clinical Characteristics and Outcomes of Eyes Developing Retinal Detachment
We also examined the clinical characteristics of 11 eyes that developed retinal detachment (eTable 3 in the Supplement). There were 7 eyes with tractional detachment and 4 eyes with rhegmatogenous detachment. Patients with tractional detachment were significantly younger than those with rhegmatogenous detachment. The median age of patients with tractional detachment was 1.5 years (range, 2 weeks to 7.0 years), and the median age of patients with rhegmatogenous detachment was 31.5 years (range, 14.0-47.0 years) ($P = .03$) (Figure 1).

Of 7 eyes with tractional detachment, one eye had successful retinal detachment repair with vitrectomy (eTable 3 in the Supplement). One eye with persistent fetal vasculature (PFV) (diagnosed by clinical examination as a stalk emanating from the disc to the retrolental space) underwent pars plana vitrectomy and lensectomy for coexisting tractional detachment, but it redetached and developed subsequent phthisis. One eye had chronic retinal detachment and underwent enucleation to rule out retinoblastoma before the patient’s initial visit at Wilmer Eye Institute. The remaining 4 eyes with tractional detachment were deemed poor candidates for retinal surgery and did not undergo surgery because of developmental abnormality related to PFV or poor perfusion of the macula and surrounding retina.

The 4 eyes with rhegmatogenous detachment developed atrophic holes at the border of perfused and nonperfused retina. The 2 eyes that underwent surgical repair achieved anatomic success, with complete attachment. The 2 eyes that had laser barricade around localized subretinal fluid had no further progression of their detachments beyond the boundary of laser photocoagulation (eTable 3 in the Supplement).

Report of Cases
Case 3 (Partial Involution of Retinal Neovascularization)

An 8-month-old infant was seen with peripheral nonperfusion and angiographic leakage from peripheral retinal neovascularization superotemporally in the left eye (Figure 2A and B). The fellow eye had a funnel-shaped tractional detachment related to PFV that was deemed inoperable. No treatment was recommended for either eye. Follow-up at age 3 years in the left eye showed a different and milder pattern of leakage, with some areas of reorganization and partial involution of neovascularization (Figure 2C, arrow and asterisk indicate corresponding areas).

Case 7 (Tractional Detachment at 7 Years After Prophylactic Cryotherapy and Laser Photocoagulation)

A 1-month-old infant was seen with a normal macular appearance (Figure 3A) in the right eye; however, peripheral examination demonstrated a preretinal hemorrhage and anterior nonperfusion (Figure 3B, arrowheads delineate transition between perfused and nonperfused retina). At age 2 months, cryotherapy was applied anteriorly to nonperfused retina, and laser photocoagulation was performed.
around the preretinal hemorrhage in the right eye. At age 7 years, the patient was seen with a decrease in visual acuity to 20/200 from her previous best visual acuity of 20/100. A tractional detachment (Figure 3C, asterisk) arising from contraction of temporal preretinal fibrovascular tissue (Figure 3C, arrow) was identified, but no retinal breaks were seen. After pars plana vitrectomy and membrane peeling, the patient recovered to a visual acuity of 20/40 by postoperative month 4, maintaining attachment with stable visual acuity at follow-up 2.5 years later.

Case 17 (Long-term Vascular Remodeling of Peripheral Nonperfused Retina)

A 9-month-old infant was seen with peripheral nonperfusion, large arteriovenous loops, and flat neovascularization temporally in the right eye. The initial angiogram demonstrated leakage from areas of neovascularization adjacent to peripheral nonperfusion (Figure 4A). No treatment was performed at that time. Seventeen years later (Figure 4B), there was regression of peripheral neovascularization (Figure 4A and B, arrowheads and asterisks indicate corresponding areas) and vascularization of previously nonperfused retina (Figure 4A and B, asterisks indicate corresponding areas). In other areas, significant vascular remodeling was observed, with the development of new collaterals (Figure 4C and D, asterisks indicate corresponding areas). No overt neovascularization was seen on follow-up widefield angiography at age 17 years, despite extensive peripheral nonperfusion (Figure 4E).

Discussion

To our knowledge, this is the largest documented cohort of patients with IP with long-term follow-up of retinopathy. We present for the first time to date a large number of patients with treated and untreated retinopathy with detailed angiographic and clinical documentation over time.

Notably, 6 of 42 enrolled and nonenrolled patients (14%; 95% CI, 4%-25%) showed evidence of PFV. Possible explanations for this have been published.24 The high incidence of this rare congenital ocular malformation, in an even rarer systemic disease, suggests that the responsible genetic mutation is causally related (even if indirectly) to the faulty intracocular vascularization that characterizes PFV in IP. The occurrence of PFV in IP indicates that the vasculopathy caused by the responsible NEMO gene is active fetally and that the advanced retinal vasculopathy observed neonatally has undergone substantial evolution during intrauterine life.
Owing to the similarities that IP shares with retinopathy of prematurity, familial exudative vitreoretinopathy, sickle cell disease, and Eales disease, prophylactic ablation has sometimes been advocated for peripheral ischemia or peripheral neovascularization in IP. It remains unclear whether peripheral ablation of ischemia decreases the risk for retinal detachment. In our patients, new collaterals and vascular remodeling at the border of perfused and nonperfused retina could be detected for as long as 17 years after initial presentation. Most important, peripheral nonperfusion and neovascularization can often remain stable and show spontaneous regression over time, similar to retinopathy of prematurity and sickle cell retinopathy. Therefore, leakage from neovascularization may not be an absolute indication for ablation. Prophylactic ablation to nonperfused areas in the youngest children (age at prophylaxis, 1 month to 2 years) failed to prevent retinal detachment in 3 of 4 eyes. In these cases, treatment with laser photocoagulation or cryotherapy may have led to tractional detachment from contraction of fibrovascular tissue, or perhaps these patients had more severe disease and were already at high risk for retinal detachment. Based on the current evidence, it is unclear whether prophylactic ablation prevents retinal detachment later in life. Therefore, we recommend that laser photocoagulation or cryotherapy of nonperfused retina should be limited to patients who show documented progression of neovascularization, progression of vitreous traction, or vitreous hemorrhage at successive visits. In cases where there will be poor follow-up or limited access to ophthalmologic care, there may also be a role for prophylactic ablation.

At present, scant natural history data indicate which eyes are at risk for progression to retinal detachment and when this typically occurs. Participants in this study demonstrated increased risk for retinal detachment when peripheral retinal neovascularization or ischemic optic neuropathy was present on initial presentation. Tractional detachment was typically seen in the youngest patients, as early as 2 weeks (age at detachment, 2 weeks to 2.5 years), and generally these detachments were more severe, with poor surgical prognoses. The detachments that developed later in life were rhegmatogenous, with all 4 occurring at 14 years or older. All such eyes were diagnosed before any macular involvement, and all were successfully treated with either surgical repair or barricade laser. This bimodal age pattern for retinal detachment is similar to that seen in retinopathy of prematurity (Figure 2).

There were several limitations in this nonrandomized study. Given the few eyes that developed retinal detachment, this study may not have been powered to detect meaningful differences between the groups that did vs did not develop retinal detachment. Furthermore, 4 eyes were excluded from statistical analysis because a retrolental membrane limited view to the posterior pole or because the eye was enucleated before presentation. Exclusion of these more severe cases of retinal detachment from the analysis might have caused underestimation of the association of ischemia, neovascularization, and ischemic optic neuropathy with retinal detachment. Although baseline characteristics were not significantly different between enrolled and excluded patients, exclusion of patients with less than 6 months of follow-up could potentially have biased the study cohort toward eyes with more severe or less severe pathology.

Conclusions

To date, no clear recommendations for screening or follow-up have been determined for IP. In our study, retinopathy manifested as early as the first few weeks after birth and
may have been present in utero. Because of the early onset of retinopathy and potential for quick progression to tractional detachment, all infants suspected of having IP should be screened as soon as possible (ideally, within the first 1-2 weeks after birth) to identify peripheral vascular changes. Because the extent of peripheral nonperfusion or neovascularization may be difficult to appreciate clinically, examination should preferably be performed under general anesthesia and with fluorescein angiography, especially if any abnormalities are seen or suspected. The frequency of follow-up should be determined by the severity of retinopathy. Because the rate of retinal detachment decreases beyond age 2 years, we suggest that the follow-up interval may be increased to every 6 to 12 months if the disease becomes stabilized by age 2 years. Given the lifelong risk for retinal detachment, patients with nonperfusion or proliferative retinopathy should be monitored throughout adulthood and be warned of the symptoms of retinal tear or detachment.

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Study concept and design: Chen, Han, Goldberg.

Acquisition, analysis, or interpretation of data: Chen, Han, Goldberg.

Drafting of the manuscript: Chen.

Critical revision of the manuscript for important intellectual content: Chen, Han, Goldberg.

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