Severity of Familial Isolated Retinitis Pigmentosa Across Different Inheritance Patterns Among an Asian Indian Cohort

Purva Bende, BE; Krupa Natarajan, MS (MLT); Thennarasu Marudhamuthu, MSc (Biostatistics); Jagadeesan Madhavan, MBBS, DO, PhD

ABSTRACT

Purpose: To predict the progression to legal blindness in patients with isolated inherited retinitis pigmentosa.

Methods: This retrospective study evaluated patients with isolated inherited retinitis pigmentosa for age at onset, duration of the disease, and best-corrected visual acuity in an Asian Indian cohort. The Mann–Whitney U test was used to analyze the variables.

Results: Of 134 patients evaluated, 72% were autosomal recessive, 17% were autosomal dominant, and 11% were X-linked recessive pedigrees. Median age at onset was 8 years for X-linked recessive, 11 years for autosomal recessive, and 21 years for autosomal dominant disease, which was statistically significant. The refractive error due to axial myopia was significantly high in X-linked recessive (-3.50 diopter sphere) compared to autosomal recessive (-1 diopter sphere) and autosomal dominant (0.00 diopter sphere) cases ($P < .000$). Legal blindness occurred in 50% of X-linked recessive and autosomal recessive cases but in only 32% of autosomal dominant cases.

Conclusion: Identifying the gene defects involved in this cohort will help understand the phenotype variability.


INTRODUCTION

Retinitis pigmentosa is a degenerative retinal disease that is one of the leading causes of blindness among genetic eye diseases. Inherited retinal degenerative disorders result in progressive visual loss due to decreased function and aberrant structure of the retina. Patients may present with defective central vision, night vision, peripheral vision, and color vision. The disease occurs in isolation or associated with other systemic conditions to present as a syndrome. It has extensive genotype and phenotype variability. The type of retinal degeneration varies with the site of retinal involvement, inheritance pattern, and disease progression, with a few unique phenotype characteristics. Retinal degeneration might result due to a defect in many genes or a single gene (allelic heterogeneity). Thus, this highly heterogeneous and pleomorphic disease has considerable overlap in genotype and phenotype characteristics, which makes molecular and clinical understanding of disease progression difficult.

Genetically, the disease has autosomal dominant,
autosomal recessive, and X-linked recessive modes of inheritance. Previous studies have correlated the phenotype variability with the inheritance pattern.3-5 This retrospective study aimed to understand the severity of the disease based on the inheritance pattern in familial isolated retinitis pigmentosa (non-syndromic retinitis pigmentosa) to predict the progression to legal blindness in patients for better clinical management in an Asian Indian cohort.

PATIENTS AND METHODS

The study was done at the Medical and Vision Research Foundation in Chennai, India. The patients were all Asian Indians from the Indian subcontinent. After institutional ethical clearance, case files of 134 patients with isolated retinitis pigmentosa with well-characterized inheritance pattern were retrospectively evaluated.

The patients were evaluated by slit-lamp biomicroscopy, indirect ophthalmoscopic examination, electroretinogram assessment, static perimetry, and optical coherence tomography whenever required. Patients with X-linked recessive, autosomal recessive, and autosomal dominant inheritance were evaluated for age at onset (age at which the symptoms of defective vision were first noticed), duration of the disease, and visual acuity after refractive error correction.

All continuous data were presented by median with interquartile range and analyzed by Mann–Whitney U test. The analysis was performed using SPSS version 14.0 software (SPSS, Inc., Chicago, IL). A P value less than .05 was considered significant.

RESULTS

Of the 134 patient files evaluated, 72% were autosomal recessive, 17% were autosomal dominant, and 11% were X-linked recessive pedigrees. The patients presented with symptoms of defective straight vision, night vision, peripheral vision, or color vision. The median age at onset of the disease was 8 years for X-linked recessive, 11 years for autosomal recessive, and 21 years for autosomal dominant disease with statistical significance (autosomal dominant vs autosomal recessive: \( P = .009 \); autosomal dominant vs X-linked recessive: \( P = .002 \); autosomal recessive vs X-linked recessive: \( P = .110 \)). The refractive error due to axial myopia was significantly high in X-linked recessive (-3.50 diopter sphere) compared to autosomal recessive (-1 diopter sphere) and autosomal dominant (0.00 diopter sphere) cases (\( P < .000 \)). Overall, there was no statistical significance with visual acuity at the time of examination across inheritance.

Comparing the duration of the disease and the progression to legal blindness based on visual acuity, 50% of patients with X-linked recessive retinitis pigmentosa became legally blind within 35 years of disease duration and 50% of patients with autosomal recessive retinitis pigmentosa attained legal blindness at a duration of more than 40 years. Only 32% of patients with autosomal dominant retinitis pigmentosa became blind within 15 years and no additional cases of blindness were found after 15 years (Table 1).

DISCUSSION

Understanding disease progression in retinitis pigmentosa is important to plan for genetic and

<table>
<thead>
<tr>
<th>Disease Duration</th>
<th>X-Linked Recessive</th>
<th>Autosomal Recessive</th>
<th>Autosomal Dominant</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
</tr>
<tr>
<td>Up to 5 years</td>
<td>1/13</td>
<td>7.6</td>
<td>16/96</td>
</tr>
<tr>
<td>Up to 10 years</td>
<td>2/13</td>
<td>15.3</td>
<td>27/96</td>
</tr>
<tr>
<td>Up to 15 years</td>
<td>2/13</td>
<td>15.3</td>
<td>31/96</td>
</tr>
<tr>
<td>Up to 20 years</td>
<td>3/13</td>
<td>23.0</td>
<td>39/96</td>
</tr>
<tr>
<td>Up to 25 years</td>
<td>4/13</td>
<td>30.7</td>
<td>42/96</td>
</tr>
<tr>
<td>Up to 30 years</td>
<td>5/13</td>
<td>38.4</td>
<td>45/96</td>
</tr>
<tr>
<td>Up to 35 years</td>
<td>7/13</td>
<td><em>53.8</em></td>
<td>45/96</td>
</tr>
<tr>
<td>Up to 40 years</td>
<td>8/13</td>
<td>61.5</td>
<td>47/96</td>
</tr>
<tr>
<td>&gt; 41 years</td>
<td>8/13</td>
<td>61.5</td>
<td>48/96</td>
</tr>
</tbody>
</table>

*Bold indicates the number at which half of the patients became legally blind.*
social counseling. Recognizing the age at which patients with retinitis pigmentosa become legally blind will help them in their rehabilitation process. Progression of retinal degeneration is assessed based on the central and peripheral visual defects. Comparatively, central vision provides much useful vision against the peripheral vision.\textsuperscript{6} Severity of visual defects is influenced by the type of gene defect and the genetic/environmental modifiers. Age at onset of the disease could be determined by genetic factors, whereas the genetic and environmental factors may affect the progression of the disease.\textsuperscript{1,7} It has been observed that refractive errors, especially myopia, have been associated with retinitis pigmentosa.\textsuperscript{8} Myopia as a degenerative condition may have an additive effect along with the primary degeneration to cause the disease to progress.

In the current study, nearly 25\% of the patients with autosomal recessive and autosomal dominant retinitis pigmentosa were legally blind within 10 years’ duration of the disease, but it took nearly 20 years for the same number of patients with X-linked recessive disease to become legally blind (Table 1). On looking at the age at onset, X-linked disease starts much earlier, so we would expect the age at legal blindness in patients with X-linked recessive disease to be similar to that of those with autosomal recessive disease. However, with longer duration of the disease, 50\% of patients with X-linked recessive disease became legally blind within 35 years, whereas 50\% of the autosomal recessive cohort took more than 40 years to become legally blind. In autosomal dominant disease, only 32\% of patients became legally blind within 15 years and the rest never became blind regardless of the disease duration (Table 1). Interestingly, myopic error is greater in patients with X-linked recessive disease than the rest of the cohort.

One of the drawbacks of the study is that blindness due to peripheral field loss was not considered because it was not properly documented. Because the genes identified to cause X-linked recessive retinitis pigmentosa are related to ciliary development/maintenance and a set of ciliary genes have been found to cause autosomal recessive retinitis pigmentosa,\textsuperscript{1} we presume that a defect in genes that have an important role in ciliary development/maintenance tends to have a severe phenotype compared to others. Identifying the gene defects involved in these patients will help to understand the phenotype variability.

REFERENCES

7. Sheline CT, Zhou Y, Bai S. Light-induced photoreceptor and RPE degeneration involve zinc toxicity and are attenuated by pyruvate, nicotinamide, or cyclic light. \textit{Mol Vis.} 2010;16:2639-2652.