Risk Factors for Posterior Subcapsular Cataract in Retinitis Pigmentosa

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PURPOSE. Posterior subcapsular cataract (PSC) is a frequent complication in patients with retinitis pigmentosa (RP). The risk factors for PSC formation in RP are largely unknown. The purpose of this study was to investigate the risk factors for PSC.

METHODS. We retrospectively studied a total of 322 eyes of 173 patients who were diagnosed with typical RP compared to those without PSC (P = 0.0003, P = 0.0004, respectively). When the aqueous flare values were assessed continuously, each 1-log-transformed increase in flare levels was associated with an elevation of the likelihood of having PSC after multivariable adjustment (odds ratio: 1.71; 95% confidence interval: 1.05–2.77). There were no significant associations of the other possible risk factors with PSC.

RESULTS. The geometric mean values of aqueous flare and mean values of visual acuity were significantly higher for the RP patients with PSC compared to those without PSC (P = 0.0003, P = 0.0004, respectively). When the aqueous flare values were assessed continuously, each 1-log-transformed increase in flare levels was associated with an elevation of the likelihood of having PSC after multivariable adjustment (odds ratio: 1.71; 95% confidence interval: 1.05–2.77). There were no significant associations of the other possible risk factors with PSC.

CONCLUSIONS. Our analysis demonstrated that elevated aqueous flare is a significant risk factor for PSC formation. This result might provide insights into the association of inflammation and the pathogenesis of PSC formation in RP.

Keywords: posterior subcapsular cataract, retinitis pigmentosa, intraocular inflammation

Retinitis pigmentosa (RP) is a group of inherited retinal degeneration diseases resulting from photoreceptor cell death, and over 1.5 million individuals suffer from RP.1 Together with progressive rod and cone degeneration, cases of RP are frequently associated with posterior subcapsular cataract (PSC). PSC is the most common morphologic category in individuals with RP (41%–53% frequency).2–4 In our previous study, PSC was associated with over 60% of RP patients who underwent cataract surgery.5 PSCs also debilitate central vision, as well as macular complications such as cystoid macular edema (CME) and epiretinal membrane (ERM).6–9

It has been reported that several factors (i.e., diabetes mellitus, hypertension, dyslipidemia, high myopia, asthma, history of steroid intake, and intraocular inflammation) could pose a risk of the development of PSCs.10–11 However, the mechanisms underlying PSC formation in RP have not been identified. In the present study, we investigated possible risk factors for PSC formation, and our findings suggest an etiology of PSC in RP patients.

METHODS

Study Design and Ethics Statement

We retrospectively reviewed the records of patients with RP and obtained their examination results, including visual and systemic parameters. The aqueous flare was consecutively measured in RP patients who were referred to Kyushu University Hospital in 2012 and 2013. We analyzed the results of each patient’s slit-lamp examination conducted on the same day that the patient’s questionnaire responses and aqueous flare measurements were obtained for the detection of PSCs.

This study was approved by the Institutional Review Board of Kyushu University Hospital (Fukuoka, Japan) and was conducted in accord with the principles of the Declaration of Helsinki on Biomedical Research Involving Human Subjects. The review board waived the need for written informed consent because the study design was a retrospective chart review.

Patients

Patients were recruited from Kyushu University Hospital in 2012 and 2013. 173 patients with a diagnosis of typical RP underwent an ophthalmic examination, including the measurement of aqueous flare. The eyes of patients who had a history of other ocular diseases or intraocular surgery (e.g., cataract surgery) and those who had received treatments that were shown to affect aqueous flare values (e.g., topical steroid, topical dorzolamide, or oral acetazolamide) were excluded. After these exclusions, a total of 322 eyes of the original 173 patients were enrolled. The methods used for the comprehensive eye examinations were as described.12
The diagnosis of typical RP was based on a history of night blindness, visual field constriction and/or ring scotoma, and markedly reduced or nonrecordable a- and b-wave amplitudes on electroretinography testing, in addition to ophthalmoscopic findings (e.g., bone spicule-like pigment clumping in the midperipheral and peripheral retina and attenuation of retinal vessels).

**Laser Flare Photometry**

The aqueous flare was measured with a Kowa FM-600 laser flare meter (Kowa, Nagoya, Japan) as described in our previous studies.12,13 Flare values were obtained 30 minutes after pupillary dilation with 0.5% tropicamide and 5% phenylephrine hydrochloride. Five measurements were taken and averaged in each eye. The results are expressed as photon counts per millisecond (pc/ms).

**Definition of PSC**

The presence of PSC was defined as a Lens Opacification Classification System III score ≥1.14 Two ophthalmologists determined the presence of PSCs with the aid of a slit-lamp biomicroscope after dilation with tropicamide 1% and phenylephrine 2.5%. We collected the data including slit-lamp biomicroscope after dilation with tropicamide 1% and phenylephrine 2.5%. We considered the following possible risk factors for PSC: age, sex, hypertension, diabetes mellitus, high myopia, asthma, history of steroid intake, and aqueous flare. We estimated the age- and sex-adjusted and multivariable-adjusted odds ratio (OR) and 95% confidence interval (CI) of each potential risk factor by using a logistic regression analysis. We then examined the linear relationship between aqueous flare values by dividing the patients’ eyes into four groups based on the quartile level of the aqueous flares: Quartile 1, flare <5.8 pc/ms; Quartile 2, flare 5.8 to 8.1 pc/ms; Quartile 3, flare 8.2 to 11.9 pc/ms; and Quartile 4, flare >11.9 pc/ms.15 All of the statistical analyses were performed with SAS software, version 9.3 (SAS Institute, Cary, NC, USA). Two-sided P values <0.05 were considered significant.

**Statistical Analysis**

We determined the frequency of PSCs and then analyzed the risk factors for PSC. We considered the following eight possible risk factors for PSC: age, sex, hypertension, diabetes mellitus, high myopia, asthma, history of steroid intake, and aqueous flare. Age and aqueous flare were treated as continuous variables, and the others as categorical variables. Information on hypertension, diabetes, asthma, and history of steroid intake was obtained using a questionnaire by trained doctors at the initial examination on the same day as the PSC detection. High myopia was diagnosed on the basis of a refractive error of ≤−6.0 diopter (D). Each categorical variable was coded as either 1 or 0 depending on the presence or absence of the factor.

The aqueous flare values were treated as a continuous variable and were transformed into logarithms to improve the skewed distribution. Mean values were compared by using Student’s t-test, and frequencies were compared by using the χ² test and Fisher’s exact test. The Wilcoxon rank-sum test was used to compare aqueous flare values. VA, visual acuity; logMAR, logarithm of the minimal angle of resolution; AD, autosomal dominant; AR, autosomal recessive.

**RESULTS**

Using the total of 322 eyes of 173 patients with RP we compared the demographic data between the patients with PSC and those without PSC. Among 173 patients, there were 149 patients whose bilateral eyes were included, 61 with bilateral PSC (40.9%), and 10 with unilateral PSC (6.7%). The geometric mean values of aqueous flare and the mean values of visual acuity were significantly higher for the RP patients with PSC compared to those without PSC (P = 0.0003, P = 0.0004, respectively; Table 1).

We considered the following possible risk factors for PSC: age, sex, hypertension, diabetes mellitus, high myopia, asthma, history of steroid intake, and aqueous flare. When the aqueous flare values were assessed continuously, each 1-log-transformed increase in flare levels was associated with an elevation of the likelihood of having PSC after multivariable adjustment (OR: 1.71; 95% CI: 1.05–2.77; Table 2). There were no significant associations of the other possible risk factors with PSC.

We divided the data of the patients’ eyes into quartiles based on the aqueous flare values (Figure). Given the association of PSC with age and gender, we adjusted for these variables to exclude the confounding effects. The eyes in the third and highest quartile of aqueous flare had significantly...
and this result is in accordance with previous studies. Revealed that the frequency of PSC in RP patients was 44.4%, suggesting the involvement of inflammation in the formation of PSC. Along with progressive rod and cone degeneration, cases of RP are frequently associated with PSC and macular complications such as ERM and CME. Merin and Auerbach reported that the frequency of PSC was 41%, and Pruett showed that the rate of cataracts in typical RP is 46.4%; 93.6% of these were PSCs. PSC is the most frequent disease among RP complications and leads to a loss of central vision. Our present analysis suggests the involvement of inflammation in the formation of PSC in RP.

Along with progressive rod and cone degeneration, cases of RP are frequently associated with PSC and macular complications such as ERM and CME. Merin and Auerbach reported that the frequency of PSC was 41%, and Pruett showed that the rate of cataracts in typical RP is 46.4%; 93.6% of these were PSCs. PSC is the most frequent disease among RP complications and leads to a loss of central vision. Our present analysis revealed that the frequency of PSC in RP patients was 44.4%, and this result is in accordance with previous studies.

To our knowledge, this is the first study to investigate the risk factors for PSC in RP patients. Our findings demonstrated that the presence of PSC is significantly correlated with elevated aqueous flare independent of potential confounding factors, suggesting the involvement of inflammation in the formation of PSC in RP.

Several factors (i.e., diabetes mellitus, hypertension, high myopia, asthmatic, history of steroid intake, and intraocular inflammation) could pose a risk for the development of PSC. The etiology and formation of PSCs vary according to the cause of PSC. In the present study, no significant effects of these risk factors on PSC formation were revealed, except for the aqueous flare value (a sensitive marker of intraocular inflammation). We suspect that PSC in RP is independently composed based on the process of these mechanisms, except for intraocular inflammation.

Al-Ghoul et al. showed that in the Royal College of Surgeon (RCS) rat, a model for inherited retinal degeneration, PSCs morphologically appear as a proliferation of dysplastic bladder-like fibers or Wedl cells in the meridional region of the lens that subsequently migrate and aggregate at the posterior pole. Joy and Al-Ghoul also suggested that proinflammatory cytokines are potential initiating factors in aberrant fiber-end migration and subsequent PSC formation in RCS rats. Moreover, Gwon et al. revealed that inflammation induced by an intravitreal injection of Concanavalin A, a nonspecific inflammatory agent, was associated with PSC formation in rabbit. We previously showed that proinflammatory cytokines/chemokines such as interleukin (IL)-1α, IL-6, IL-8, and interferon-γ are elevated in the vitreous of RP patients compared to the vitreous of patients with idiopathic ERM. We also demonstrated that aqueous flare values are increased in patients with RP compared to normal subjects, supporting the association between inflammation and RP. On the basis of these findings, it is apparent that chronic inflammation in RP may contribute to fiber growth at posterior ends.

This study is significant because of its relatively large sample size, but there are some limitations that should be discussed. First, although potential confounders were included in our analyses, we cannot rule out the possibility of unknown confounding factors for the development of PSC. Second, our findings were based on a single measurement of aqueous flare that might not capture various ranges of inflammation in RP patients. Moreover, because of the cross-sectional nature of our study, it is difficult to define the causal relationship between confounding factors, in particular for inflammation, and PSC. Further studies including prospective investigations are needed to clarify this association. Last, there is a possibility that we could not detect subtle PSCs at an early stage, which could have caused an underestimation of the role of inflammation in PSC formation.

In conclusion, the results of our analysis revealed that elevated aqueous flare is a significant risk factor for PSC formation. This result might provide insights into the association of inflammation and the pathogenesis of PSC formation in RP.

TABLE 2. Age- and Sex-Adjusted and Multivariable-Adjusted ORs of Risk Factors for PSC in Eyes With RP

<table>
<thead>
<tr>
<th>Variable</th>
<th>Age- and Sex-Adjusted OR (95% CI)</th>
<th>P Value</th>
<th>Multivariable-Adjusted OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, per 1 year</td>
<td>1.01 (0.996–1.03)</td>
<td>0.167</td>
<td>1.00 (0.99–1.02)</td>
<td>0.175</td>
</tr>
<tr>
<td>Sex, female</td>
<td>0.81 (0.52–1.26)</td>
<td>0.346</td>
<td>0.85 (0.51–1.41)</td>
<td>0.524</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.68 (0.37–1.28)</td>
<td>0.232</td>
<td>0.85 (0.44–1.64)</td>
<td>0.618</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.74 (0.20–2.74)</td>
<td>0.650</td>
<td>0.78 (0.20–3.05)</td>
<td>0.718</td>
</tr>
<tr>
<td>Asthma</td>
<td>2.92 (0.58–14.85)</td>
<td>0.196</td>
<td>2.40 (0.46–12.54)</td>
<td>0.301</td>
</tr>
<tr>
<td>Steroid intake</td>
<td>0.14 (0.003–6.02)</td>
<td>0.305</td>
<td>0.28 (0.56–3.79)</td>
<td>0.507</td>
</tr>
<tr>
<td>Myopia</td>
<td>0.87 (0.36–2.10)</td>
<td>0.763</td>
<td>1.45 (0.56–3.79)</td>
<td>0.445</td>
</tr>
<tr>
<td>Flare, per 1-log-increase</td>
<td>1.79 (1.14–2.82)</td>
<td>0.012</td>
<td>1.71 (1.05–2.77)</td>
<td>0.031</td>
</tr>
</tbody>
</table>

Multivariable adjustment was made for age, sex, hypertension, diabetes, asthma, steroid intake, myopia, and flare.

**DISCUSSION**

Figure. Multivariable-adjusted ORs for PSC according to the flare quartile levels in RP patients (\(P < 0.05\) versus Quartile 1; \(P\) for trend <0.05). Flare levels were divided as follows: Quartile 1, flare <5.8 pc/ms; Quartile 2, flare 5.8 to 8.1 pc/ms; Quartile 3, flare 8.2 to 11.9 pc/ms; and Quartile 4, flare >11.9 pc/ms.
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**References**