Iridocorneal Endothelial Syndrome in Thai Patients

Clinical Variations

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Objective: To evaluate the spectrum of iridocorneal endothelial syndrome, to our knowledge, never studied previously in Orientals.

Methods: From 1986 to 1998, we examined 60 consecutive patients (20 men, 40 women) with characteristic signs of iridocorneal endothelial syndrome and compared the clinical manifestations to those reported in white patients.

Results: Cogan-Reese syndrome (CRS) was most common (38 patients), while 14 patients had Chandler syndrome (CS), and 8 had progressive iris atrophy. Three patients initially classified as having CS and 1 as having progressive iris atrophy progressed to CRS. Glaucoma occurred in 46 patients (76.7%), most commonly in patients with progressive iris atrophy or CRS. Ten patients had slow progression of disease during the follow-up period of up to 12 years. Three patients (2 with CRS, 1 with CS) had asymptomatic localized islands of “hammered-silver” appearance and 11 (8 with CRS, 2 with CS, and 1 with progressive iris atrophy) had subclinical abnormal endothelium in the contralateral eyes. A translucent membrane was commonly seen on the brown iris surface. Total endothelial involvement was present in 49 patients, while 6 (4 with CRS, 2 with CS) had focal endothelial abnormalities with sharp demarcation from adjacent normal endothelium.

Conclusions: Iridocorneal endothelial syndrome occurs in Orientals. Cogan-Reese endothelial syndrome is the most common form and is strongly associated with glaucoma. Although several clinical manifestations were similar between whites and Orientals (mean age of onset, sex predilection, iris changes, peripheral anterior synechiae formation, or corneal edema), CRS was most prevalent; a translucent membrane were more noticeable in Orientals.

PATIENTS AND METHODS

All 60 consecutive patients (20 men, 40 women) with clinical signs of ICE syndrome seen in the Department of Ophthalmology, Ramathibodi Hospital, Bangkok, Thailand, between July 1, 1986, and August 31, 1998, underwent complete ocular examination, including specular microscopy. Patients who had a history of ocular trauma or uveitis were excluded from the study. The diagnosis of ICE syndrome was made by the presence of a typical “hammered-silver” appearance of the posterior corneal surface (Figure 1), or corneal edema that precluded visualization of the posterior cornea, and characteristic iris stromal abnormalities. The patients were classified into 3 clinical variations based on iris changes.9 Chandler syndrome was diagnosed if there was minimal or mild stromal atrophy (Figure 2). Patients with extensive iris stromal atrophy and distortion with stretch and melting holes were diagnosed as having PIA (Figure 3). Those with iris nodules with any degree of iris stromal atrophy were diagnosed as having CRS (Figure 4).

Bilateral corneal endothelial photography was performed in 49 patients with sufficient corneal clarity using a specular microscope (model CSP 580; Konan, Tokyo, Japan). In addition, anterior segment and anterior chamber angle photography were performed periodically.

Complete slitlamp biomicroscopy, applanation tonometry, gonioscopy, and dilated ophthalmoscopy were performed to determine corneal edema, iris changes, intraocular pressure (IOP), and the extent of PAS. In some patients, severe corneal edema obviated assessment of PAS and performance of specular microscopy. The extent of PAS present on gonioscopy was graded as absent, mild (<90°), moderate (90°-180°), or extensive (>180°). Automated perimetry was performed in patients with sufficient visual acuity and corneal clarity. Because most of the patients had already been treated with antiglaucoma medications when first seen, initial pretreatment IOPs were unavailable. Previous and follow-up filtering surgical procedures or penetrating keratoplasty were recorded. Initial symptoms, age of onset, and medical and family histories were also recorded.

Fifty-one patients were followed up for 6 months to 12 years (mean ± SD duration of follow-up, 3.9 ± 3.1 years), while 9 patients were seen only on a single visit. Informed consent was obtained when indicated for diagnostic procedures and intervention. We compared our findings with those of similar referral-based white populations.7,9

Initial complaints consisted of blurred vision, haloes, ocular pain and/or redness, or abnormal pupils. Originally 34 patients were diagnosed as having CRS, 17 as having CS, and 9 as having PIA. Three of the patients with CS and 1 with PIA developed iris nodules during follow-up and progressed to CRS. The final distribution for analysis was 38 patients with CRS, 14 with CS, and 8 with

PIA. Patients in the 3 groups were similar to each other in age distribution (P = .34, analysis of variance) (Table 2).

CORNEAL FINDINGS

A characteristic hammered-silver appearance of the posterior corneal surface was observed in all patients except for 11 who had corneal edema obscuring visualization. Specular microscopy revealed characteristic rounding of the endothelial cells and pleomorphism with intracel-
ular dark areas. Forty-three patients had generalized endothelial abnormalities, while 6 (4 with CRS, 2 with CS) had localized islands of endothelial abnormalities with an abrupt demarcated border separating the adjacent normal areas of endothelium.

Corneal edema was present at the initial visit in 22 patients and was most common in CS (8 patients [57.1%]) (Table 2). Two patients with CRS and 1 with PIA developed corneal edema during follow-up. Eight patients required penetrating keratoplasty.

**IRIS FINDINGS**

A translucent membrane with a distinct border was commonly visible on the anterior iris surface obscuring the iris crypts. The iris surface underneath the membrane appeared indistinct compared with the darker adjacent area (Figure 2).

Corectopia was present in 59 patients (13 with CS, 38 with CRS, and 8 with PIA). Patients with CS had slight pupil deviation while those with CRS and PIA had more severe displacement. The pupils generally deviated toward the site of the membrane and adjacent PAS. Ectropion uvea was present in 42 patients (5 with CS, 30 with CRS, and 7 with PIA). Its location usually corresponded to the direction of corectopia.

Iris stromal atrophy was mild or minimal in patients with CS and extensive in patients with PIA. Polycoria was present in all patients with PIA and 5 patients with CRS. The iris holes were usually opposite the direction of the corectopia.

Iris nodules in eyes with CRS were typically round or flat, irregular, hyperpigmented lesions and never pedunculated. They occurred in clusters within the area encompassed by the translucent membrane on the iris surface. The nodules were not present elsewhere on the iris surface.

**ANTERIOR CHAMBER ANGLE FINDINGS**

Peripheral anterior synechiae were observed in 56 patients at the initial visit. Two patients with CS did not have PAS and 2 with CRS had corneal edema obscuring the view. The synechiae were broad and extended anteriorly to the Schwalbe line and were visible with conventional slitlamp examination. Peripheral anterior synechiae in patients with focal endothelial abnormality occurred in areas adjacent to the abnormal endothelium. Peripheral anterior synechiae more than 180° in extent occurred more frequently in patients with CRS (22 patients) and PIA (5 patients) than in patients with CS (4 patients) (Table 3).

**GLAUCOMA**

Elevated IOP with or without glaucomatous cupping and/or visual field damage occurred in 46 patients. One patient with CS and focal endothelial changes slowly developed progressive PAS from less than 90° to greater than 180° during the 11 years of follow-up. Iris nodules developed at year 4 and elevated IOP at year 11.

Among patients with elevated IOP, the condition of 14 was controlled medically and 32 required filtering sur-

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**Table 2. Patient Characteristics**

<table>
<thead>
<tr>
<th>ICE Syndrome Subgroup*</th>
<th>Mean ± SD Age of Onset (Age Range), y</th>
<th>No. (%) of Patients at Final Follow-up</th>
<th>No. Who Underwent Penetrating Keratoplasty</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>With Glaucoma</td>
<td>With Corneal Edema</td>
</tr>
<tr>
<td>CS (n = 14)</td>
<td>47.6 ± 8.7 (30-59)</td>
<td>8 (57.1)</td>
<td>8 (57.1)</td>
</tr>
<tr>
<td>CRS (n = 38)</td>
<td>42.4 ± 12.2 (24-70)</td>
<td>32 (84.2)</td>
<td>13 (34.2)</td>
</tr>
<tr>
<td>PIA (n = 8)</td>
<td>45.4 ± 15.1 (27-67)</td>
<td>6 (75.0)</td>
<td>4 (50.0)</td>
</tr>
<tr>
<td>Total (N = 60)</td>
<td>43.7 ± 12.3 (24-70)</td>
<td>46 (76.7)</td>
<td>25 (41.7)</td>
</tr>
</tbody>
</table>

*ICE indicates iridocorneal endothelial; CS, Chandler syndrome; CRS, Cogan-Reese syndrome; and PIA, progressive iris atrophy.
gery. Patients with CRS needed filtering surgery more often than those with CS or PIA.

Automated perimetry performed in 37 patients with sufficient visual acuity and corneal clarity revealed intact visual fields in 21 and typical glaucomatosus damage in 16. Visual field defects occurred most frequently in patients with CRS (36.8%) and less frequently in patients with CS (14.3%).

TABLE 3. Peripheral Anterior Synechiae (PAS)

<table>
<thead>
<tr>
<th>ICE Syndrome Subgroup</th>
<th>Absent</th>
<th>&lt;90°</th>
<th>90°-180°</th>
<th>&gt;180°</th>
<th>No View</th>
</tr>
</thead>
<tbody>
<tr>
<td>CS (n = 38)</td>
<td>0 (0)</td>
<td>8 (21.0)</td>
<td>6 (15.8)</td>
<td>22 (57.9)</td>
<td>2 (5.3)</td>
</tr>
<tr>
<td>CRS (n = 28)</td>
<td>0 (0)</td>
<td>1 (12.5)</td>
<td>2 (25.0)</td>
<td>5 (62.5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>PIA (n = 8)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

*ICE indicates iridocorneal endothelial; CS, Chandler syndrome; CRS, Cogan-Reese syndrome; and PIA, progressive iris atrophy.
†Due to rounding, values do not total 100%.

**COMMENT**

An endothelial abnormality is believed to be the primary event of the pathogenesis of the ICE syndrome accounting for all aspects of the disease. The abnormal endothelial cells may either derive from neural crest tissue or represent an epithelial-like metaplastic transformation. The abnormal endothelium leads both to corneal edema and to the proliferation of the corneal endothelium and Descemet membrane across the anterior chamber angle and onto the iris surface. Contrac-

tion of this membrane results in PAS formation with associated glaucoma, corectopia, and ectropion uveae. Stretching of the iris in the opposite direction to the corectopia accounts for iris atrophy and hole formation. In addition, this membrane may be responsible for the development of iris nodules, possibly by pinching off portions of the iris stroma.

In our patients, CRS occurred most frequently. In dark brown irides, the endothelial Descemet membrane was clinically discernible using slitlamp biomicroscopy. The iris surface structure and crypts were obscured by the membrane and the covered areas appeared hypochromic compared with the adjacent areas with an abrupt junction. To our knowledge, this finding has not been previously noted. As mentioned earlier, the iris nodules histologically are areas of iris stroma containing pigmented melanocytes extruding through the holes in the membrane. Darker irides contain more melanin pigment granules in the superficial stromal melanocytes than do lighter irides. More densely pigmented iris stroma may be more easily visible clinically.

Eyes with CS, the most common form of ICE syndrome in the white population, tend to have a lower IOP and a greater tendency to develop corneal edema than eyes with CRS or PIA. Our patients with CS also developed corneal edema more frequently than those with CRS or PIA.

Because the reported series were studied in glaucoma clinics, there could have been referral bias. Although PIA is more readily diagnosed than the CS or CRS, it has the lowest prevalence in both our study and the study of Wilson and Shields. The study of Shields et al was a retrospective study and classification criteria then had not been definitively established. They divided the syndrome into only 2 entities—CS (55) and PIA (27)—noting in their “Discussion” section that among the total 82 patients, 9 were noted to have iris nevus-CRS.

Although the ICE syndrome has been described as a unilateral condition, subclinical mild to moderate pleomorphism of the corneal endothelium in the contralat-
eral eye was present in 14 of our patients. Three had characteristic islands of endothelial abnormalities with an abrupt junction from adjacent endothelium. Subclinical endothelial abnormalities in the contralateral eye or patients with bilateral involvement have been reported. It remains unanswered whether these endothelial changes represent preexisting abnormalities that will lead to development of the disease or whether ICE is a bilateral disease.

Two patients had ocular hypertension and papillitis in the contralateral eye in the absence of PAS or of endothelial or iris abnormalities. One of our patients with PIA who did not have glaucoma developed an ipsilateral idiopathic macular hole. Because the ocular changes were inconsistent, no association could be made and they may merely represent coincidental findings.

Partial or focal corneal involvement with an abrupt junction between the normal endothelial and ICE cells has been described. Wilson and Shields examined 12 patients with focal endothelial involvement and found no correlation between the location of the focal endothelial abnormalities and the PAS. Six patients (4 with CRS, 2 with CS) of our patients had focal endothelial changes with a demarcating junction. However, they developed PAS with corresponding corectopia and ectropion uvea only in the areas adjacent to the abnormal endothelium.

Reports of prevalence of glaucoma in eyes with ICE syndrome range from 46% to 82%. The prevalence of elevated IOP was similar in CS and PIA and higher in CRS. However, another study reported the greatest prevalence of IOP elevation in CS. Although glaucoma in CS was reported to be less severe and easier to manage by most investigators, another study did not confirm this finding.

Glaucoma occurred in 46 (76.7%) of our 60 patients. Cogan-Reese syndrome and PIA appeared to have more extensive PAS formation and glaucoma than CS. Visual field defects occurred most frequently in CRS (36.8%) and a greater proportion of patients with CRS required filtering surgery.

A study reported the success of additional surgery in ICE syndrome to be comparable to those of initial surgery in patients with primary open-angle glaucoma. Early surgical intervention after IOP has been normalized as much as possible with medicine has been suggested. However, 1 of our patients developed an extensive change of the iris following an uncomplicated trabeculectomy. It is possible that surgical trauma may aggravate the disease.

Ten of our patients, 5 of whom had glaucoma, had a slow clinical course during follow-up with minimal changes in corneal edema, PAS, and glaucoma. Among the 3 with glaucoma, the conditions of 2 were controlled medically and 3 had undergone trabeculectomy. Nine had total endothelial abnormalities and 1 had focal changes. It seems that the disease becomes latent or goes into remission regardless of the initial severity.

Ten of our patients, 5 of whom had glaucoma, had a slow clinical course during follow-up with minimal changes in corneal edema, PAS, and glaucoma. Among the 3 with glaucoma, the conditions of 2 were controlled medically and 3 had undergone trabeculectomy. Nine had total endothelial abnormalities and 1 had focal changes. It seems that the disease becomes latent or goes into remission regardless of the initial severity.

Table 4. Comparison of ICE Syndrome Between Our Patients and 2 Series of White Patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Source, y</th>
<th>Present Series</th>
<th>Wilson and Shields,9 1989</th>
<th>Shields et al.7 1978</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total No. of patients</td>
<td></td>
<td>60</td>
<td>37</td>
<td>82</td>
</tr>
<tr>
<td>Range of follow-up, y</td>
<td></td>
<td>1-12</td>
<td>1-12</td>
<td>0.1-36</td>
</tr>
<tr>
<td>Single examination, No. of patients</td>
<td></td>
<td>9</td>
<td>18</td>
<td>32</td>
</tr>
<tr>
<td>Age at onset of symptoms, y</td>
<td></td>
<td>43.7</td>
<td>41.5</td>
<td>38.6</td>
</tr>
<tr>
<td>Age range</td>
<td></td>
<td>24-70</td>
<td>19-62</td>
<td>6-58</td>
</tr>
<tr>
<td>Percent female</td>
<td></td>
<td>66.7</td>
<td>62.1</td>
<td>68.3</td>
</tr>
<tr>
<td>Occurrence (% of patients)</td>
<td></td>
<td>CRS (63.3) &gt;CS &gt;PIA</td>
<td>CS (56.8) &gt;CRS = PIA</td>
<td>CS &gt;PIA, CRS†</td>
</tr>
<tr>
<td>Corneal edema, No. (%) of patients</td>
<td></td>
<td>25 (41.7)</td>
<td>14 (37.8)</td>
<td>41 (50)</td>
</tr>
<tr>
<td>Iris changes, No. of patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corectopia</td>
<td></td>
<td>59</td>
<td>27</td>
<td>58</td>
</tr>
<tr>
<td>Ectropion uvea</td>
<td></td>
<td>42</td>
<td>10</td>
<td>23</td>
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<tr>
<td>Polycoria</td>
<td></td>
<td>13</td>
<td>8</td>
<td>20</td>
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<tr>
<td>Glaucoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prevalence, No. (%) of patients</td>
<td></td>
<td>46 (76.7)</td>
<td>NA</td>
<td>63 (76.8)</td>
</tr>
<tr>
<td>Common in</td>
<td></td>
<td>PIA, CRS</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Severe in</td>
<td></td>
<td>CRS, PIA &gt; CS</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>VF defect common in</td>
<td></td>
<td>CRS</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>PAS</td>
<td></td>
<td>56</td>
<td>34</td>
<td>70</td>
</tr>
<tr>
<td>Specular microscopy, No. of patients</td>
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</tr>
<tr>
<td>Total</td>
<td></td>
<td>43</td>
<td>19</td>
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<td>Partial</td>
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<td>6</td>
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<td>Contralateral eyes, No. of patients</td>
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<tr>
<td>Subclinical pleomorphism</td>
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<td>11</td>
<td>NA</td>
<td>†</td>
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<tr>
<td>Focal changes</td>
<td></td>
<td>3</td>
<td>3</td>
<td>NA</td>
</tr>
</tbody>
</table>

* CRS indicates Cogan-Reese syndrome; CS, Chandler syndrome; PIA, progressive iris atrophy; NA, not applicable; VF, visual field; and PAS, peripheral anterior synechiae.
† Total 82: 55 with CS, 27 with PIA. In all patients (CS + PIA), 9 patients also had nodules, ie, CRS was included in these categories.
‡ Two patients had contralateral corneal abnormality but the type was not clarified.
tion of the iris or specular microscopic changes. Herpes simplex viral DNA detection was reported in the ICE syndrome. As in other herpes simplex virus infection, it is possible that our 10 patients are in the inactive or latent stage of the natural course of herpetic diseases.

In summary, ICE syndrome in Oriental eyes, which, to our knowledge, have never been reported in the American literature, does exist. Although most clinical and specular microscopic findings were similar to those reported in whites, a translucent membrane was distinctly noticeable in Oriental eyes with darker (brown) irides, and CRS seemed to be the most common variant with a strong association with glaucoma.

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