



IRIDOCORNEAL ENDOTHELIAL SYNDROME



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IRIDOCORNEAL ENDOTHELIAL SYNDROME

The iridocorneal endothelial (ICE) syndrome takes many clinical forms but includes some combination of:

1. Iris atrophy
2. Corneal edema
3. Secondary angle-closure glaucoma without pupillary block.

This syndrome is caused by an abnormal corneal endothelium that forms a membrane over the anterior surface of the iris and the angle structure which contracts and distorts the iris and closes the angle.

HISTOPATHOLOGY

1. Histopathologic examination of eyes affected by the ICE syndrome reveals a thin, abnormal corneal endothelium and Descemet's membrane separated by a thick accumulation of collagen.
2. These tissues form a multilayered membrane that covers the angle and extends onto the anterior surface of the iris.
3. The endothelial cells develop the epithelial-like characteristics of desmosomes, microvilli, tonofilaments (contractile elements), and proliferation – none of which occur in normal corneal endothelium. Other endothelial cells showed filopodium and cytoplasmic actin filaments suggesting migration.
4. Metaplasia of endothelium into cells with epithelial characteristics occurs due to an unknown trigger.
5. Another observation was a multilayered collagenous membrane posterior to the normal prenatal and postnatal layers of the collagenous structures of the Descemet membrane.
6. Clinically seen as 'beaten silver' appearance of endothelium on slit-lamp examination; a loss of the normal, regular endothelial mosaic on specular reflection; and alterations in the size and shape of endothelial cells on specular microscopy.
7. The size and shape of endothelial cells show great variation – some may be necrotic, and the findings are often patchy in the early stages of the condition.
8. Light microscopy of the iris in ICE syndrome shows a cellular membrane on the anterior surface of the iris referred as retrocorneal membrane that is continuous with that seen over the anterior chamber angle in the quadrant toward which the pupil is distorted.

PATHOGENESIS

1. The most commonly accepted theory - the defect is in the corneal endothelium, whose dysfunction results in corneal edema. The corneal endothelium in this condition elaborates a membrane (Campbell) which causes a secondary angle closure.
2. When the membrane contracts, it forms PAS leading to glaucoma, as well as iris defects such as corectopia, 'stretch holes', and iris nodules. Ischemia may be a secondary producing 'melt holes.'
3. A few investigators postulate that there is an abnormal proliferation of neural crest cells or a fetal crest of epithelial cells. Other authorities suggest the endothelium proliferates because of inflammation.
4. Electron micrographic, immunohistochemical, and serologic studies have suggested HSV and, in another laboratory, EBV. The viral might explain the unilaterality of this syndrome in the vast majority of patients.
5. Changes in the Lens - in rare cases, the retrocorneal membrane of the ICE syndrome may grow over the anterior lens surface, simulating the anterior lens capsule, which can create confusion when

performing a capsulorrhexis during cataract surgery. This retrocorneal membrane can also appear on the anterior surface of an intraocular lens implant.

CLINICAL PRESENTATION

1. The PAS are more extensive in the quadrant toward which the pupil is displaced.
2. The iris in the opposite quadrant has thinner stroma and full-thickness holes in some cases.
3. In the Cogan-Reese syndrome, pigmented lesions project anteriorly from the iris surface and are surrounded by the multilayered membrane. The nodules are actually small portions of iris stroma that have been pinched off by the membrane.
4. Within the spectrum of the ICE syndrome there are three well characterized clinical entities –
 - i) Progressive iris atrophy
 - ii) Chandler's syndrome
 - iii) Cogan-reese syndrome
 - iv) Variety of intermediate forms.
5. All of the variants of this syndrome appear in early to mid-adult life, occur in whites>blacks, affect women>men.
6. The patients are seen after noticing a change in the appearance of their iris or pupil, a disturbance in their vision, or mild ocular discomfort.
7. There are a few reports of familial cases, in most individuals the medical and family histories are unrevealing. The ICE almost always involves one eye, although the fellow eye may have subclinical abnormalities of the iris or corneal endothelium. A few reports of individuals with bilateral involvement have been well documented.
8. Some degree of corneal endothelial abnormality is seen on slit-lamp examination in most patients with abnormal specular microscopy in all.

Major Clinical Variations	Characteristic Features
Progressive iris atrophy	corectopia, atrophy, hole formation
Chandler syndrome	corneal edema, often at normal IOP
Cogan-Reese syndrome	Nodular, pigmented lesions of the iris are the hallmark and may be seen with the entire spectrum of corneal and other iris defects

PROGRESSIVE (ESSENTIAL) IRIS ATROPHY

1. The clinical picture is dominated by **corectopia and progressive dissolution of the iris**.
2. The iris dissolution begins as a patchy disappearance of the stroma and progresses to full-thickness holes.
3. Some of the holes occur in quadrants away from the direction of pupillary displacement and are caused by traction ('stretch holes'). Other holes occur without corectopia and are ischemic in nature ('melt holes'), as demonstrated on fluorescein angiography of the iris.
4. Broad patchy PAS form attachments anterior to Schwalbe's line. The synechiae lift the iris off the surface of the lens, and also produce ectopion uveae and corectopia.
5. Depending on the distribution of the synechiae, the pupil can be displaced to one side or pulled into a pear, oval, or slit shape.
6. As the PAS become more extensive, IOP rises. The severity of the glaucoma is related to the extent of the synechiae.

7. Elevated IOP may be noted despite open angles when the membrane has covered the angle but not yet contracted to form permanent adhesions.
8. The corneal endothelium may appear normal but more often has the appearance of tiny guttata. The cornea may become edematous when IOP is elevated.

CHANDLER'S SYNDROME

1. Chandler's syndrome is the most common variant of the ICE syndrome.
2. The most prominent features of Chandler's syndrome are **corneal endothelial dysfunction and corneal edema**.
3. The endothelium has a hammered silver appearance that is similar to, but less coarse than, the abnormalities seen in Fuchs' dystrophy.
4. On specular microscopy the endothelial cells appear pleomorphic with dark cytoplasmic areas and loss of the normal hexagonal patterns. Early in the course of the disease specular microscopy demonstrates abnormal and normal endothelial areas which decrease with time.
5. The corneal endothelium becomes so dysfunctional that epithelial edema develops at normal or only slightly elevated IOPs.
6. The iris involvement is generally mild and limited to superficial stromal dissolution. Corectopia is minimal or absent. Peripheral anterior synechiae form, but do not extend as far anteriorly as in progressive iris atrophy. For this reason glaucoma is often mild.

COGAN-REESE SYNDROME

1. The Cogan-Reese, or iris nevus, syndrome is differentiated from progressive iris atrophy and Chandler's syndrome by the occurrence of pigmented lesions of the iris: **pedunculated iris nodules or diffuse pigmented lesions or both**.
2. The nodular lesions that are characteristic of Cogan-Reese syndrome have an ultrastructure similar to that of the underlying stroma of the iris and are always surrounded by the cellular membrane.
3. The pigmented iris lesions may appear years after the other features of the syndrome and then may disappear spontaneously.
4. These are definitively not nevi: instead, they are islands of normal iris pinched by the contracting endothelial membrane. The iris may have any degree of dissolution from mild to severe.
5. The degree of corneal edema and the severity of the angle-closure glaucoma is variable
6. Especially in the early stages, characteristics of both progressive iris atrophy and iris nevus syndrome may be seen in the same iris.

DIFFERENTIAL DIAGNOSIS

1. Posterior polymorphous dystrophy	}	ENDOTHELIAL
2. Fuchs' dystrophy		
3. Iridoschisis	}	DISSOLUTION OF IRIS
4. Aniridia		
5. Rieger's syndrome	}	NODULES
6. Neurofibromatosis 1-Lish nodule		
7. Anterior uveitis with nodules		
8. Malignant melanoma		

The diagnosis is often missed early because the corneal and iris signs may be subtle. Most of the conditions in the differential diagnosis are bilateral, so a unilateral condition should raise the possibility of the ICE syndrome.

MANAGEMENT

- Patients with ICE syndrome may require treatment for corneal edema, the associated glaucoma, or both during the course of the disease.
- Given the unpredictable behavior of the abnormal corneal endothelium, patients with ICE syndrome should be monitored regularly based on signs and symptoms of the disease
- Although specular microscopy can help to diagnose ICE syndrome, the findings do not correlate with the degree of corneal edema or decompensation or with the level of IOP elevation.

MEDICAL MANAGEMENT

1. In the early stages, the glaucoma can often be controlled medically mainly with drugs that reduce aqueous production.
2. If corneal edema produces pain or reduced vision, the patient may be helped by hypertonic solutions or soft contact lenses.
3. In many cases corneal edema is improved if IOP is reduced by medical or surgical therapy.

When the IOP can no longer be controlled medically, surgical intervention is indicated, and a high percentage of patients with the ICE syndrome eventually require surgery.

SURGICAL MANAGEMENT

1. Laser trabeculoplasty offers no help in this condition because most of the angle is covered by a membrane or sealed with synechiae.
2. Short-term success has been reported with a goniotomy procedure.
3. As the entire angle is progressively covered by a membrane or sealed by synechiae, medical therapy or angle surgery eventually fail because of angle closure.
4. Filtering surgery or glaucoma drainage devices are often required
5. Functioning filtering blebs often fail after 2–5 years due to proliferation of a membrane over the internal opening of the sclerostomy/ endothelialization of the bleb, despite the use of antimetabolite therapy (5-FU). Adjunctive mitomycin C has reported intermediate-term success.
6. Repeated filtering procedures, glaucoma drainage-device revision, and cyclodestructive laser may be additional options to lower IOP if previous surgical interventions have failed.
7. In most cases, corneal edema clears after successful filtering surgery; in other cases, edema persists, because of corneal endothelial dysfunction.
8. In corneas with marked dysfunction of the endothelium penetrating keratoplasty is indicated after the glaucoma has been controlled.

FUTURE PROSPECTS

1. The development of therapies can be directed more specifically at the underlying disease process. For example, if the theory of a viral cause proves to be correct, it may allow treatment with antiviral agents.

2. Another approach may be to prevent the growth of the endothelial membrane. An immunotoxin has been described that inhibits the proliferation of human corneal endothelium in tissue culture.
3. Ultimately, the discovery of the stimulus to epithelialization of the corneal endothelium will lead to inhibitors, and possibly prevent this difficult angle-closure disease.

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