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Major review

The iridocorneal endothelial syndrome

Luis Silva, MD[a,*], *Ahmad Najafi, MD*[a], *Yanin Suwan, MD*[a,b], *Chaiwat Teekhasaenee, MD*[b], *Robert Ritch, MD*[a]

[a] *Einhorn Clinical Research Center, The New York Eye and Ear Infirmary of Mount Sinai, New York, New York, USA*
[b] *Department of Ophthalmology, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand*

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ABSTRACT

The iridocorneal endothelial syndrome represents a unique group of ocular pathologies (Chandler syndrome, progressive iris atrophy, and Cogan-Reese syndrome) characterized by the proliferation of corneal endothelial cells that migrate toward the iridocorneal angle and iris surface causing, to a degree varying according to the subtype, corneal edema and decompensation and secondary glaucoma, whether by obstructing the angle or producing peripheral anterior synechiae by contraction of the basement membrane of the migrating cells over the surface of the iris. A triggering factor, possibly viral, induces the corneal endothelial cells to proliferate and behave like epithelial cells. Diagnosis is made based on typical ocular findings on the cornea and iris. Iridocorneal endothelial syndrome is more frequent in young women, with unilateral involvement in most cases. *In vivo* confocal microscopy is an excellent diagnostic tool, especially in borderline presentations like early cases of Chandler syndrome, which affects the cornea predominantly. Typical clinical management consists of treating the corneal edema and decompensation, where endothelial keratoplasty techniques have replaced in many cases the need for a penetrating keratoplasty and treating the secondary glaucoma, which usually requires surgical intervention.

1. Introduction

The iridocorneal endothelial syndrome (ICE) consists of a group of ocular disorders in which the common denominator is the proliferation of corneal endothelial cells (CECs) that migrate toward the iridocorneal angle and onto the iris. ICE is frequently associated with glaucoma, whether by obstruction of the angle by the proliferating cells or by contraction of their basement membrane over the iris, which pulls the iris peripherally and may form peripheral anterior synechiae (PAS). The proliferation of these cells also predisposes to corneal edema and decompensation.

The condition comprises 3 clinical variants: Chandler syndrome (CS), progressive iris atrophy (PIA), and Cogan-Reese syndrome (CRS). In 1903, Harms described a glaucoma associated with essential iris atrophy.[39,92] In 1956, Chandler described a similar syndrome, where the iris atrophy was milder, and corneal signs predominated.[14] Later, Cogan and

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* Corresponding author: Luis Silva, MD, Einhorn Clinical Research Center, 310 E 14th Street, South Building, Suite 304, New York, NY 10003, USA.
E-mail address: lsilva@nyee.edu (L. Silva).
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Reese presented a syndrome similar to that previously reported, but with pigmented nodules on the anterior surface of the iris.[20,92,95] In certain cases, signs from the 3 clinical variants may overlap (mixed forms).[41]

2. Chandler syndrome

2.1. *Clinical findings/presentation/features*

CS is characterized by unilateral (usually) decreased vision, corneal edema, epithelial bullae, hammered silver appearance of the corneal endothelium (Fig. 1A), normal intraocular pressure (IOP) at presentation, and mild iris atrophy.[14] The cobblestone or hammered silver appearance of the abnormal endothelium, which results from the reflection of light from the posterior surface of the endothelial cells rather than from an abnormal Descemet membrane, may be seen in any of the ICE syndrome variants.

All 3 variations of ICE syndrome may develop iridocorneal adhesions, but CS has less iris involvement. The pupil frequently shows corectopia. When the diagnosis is made in later stages, iris anomalies may be more pronounced, and areas of atrophy may be observed, but usually never lead to a full-thickness iris hole[84] (Fig. 1B). CS can rarely present with ectopic Descemet membrane over the lens capsule that can be mistaken for anterior lens capsule during capsulorrhexis.[8]

Specular microscopy shows the ICE cells with typical dark-light reversal pattern. The cell surface is dark instead of light, often with a central, hyperreflective nucleus, and the intercellular junctions are light instead of dark.[44] Four patterns of ICE cell distribution have been described on the cornea. In "total ICE" the normal endothelium is completely replaced by ICE cells. In "subtotal ICE (+)" the ICE cells replace a variable portion of the endothelium, and the remainder is composed of small cells, whereas in "subtotal ICE (−)," the ICE cells replace a variable portion of the endothelium, but the remaining is composed of enlarged cells. Finally, "disseminated ICE" denotes ICE cells scattered individually or in small clusters among the mosaic of normal endothelial cells.[67,89]

In the clinically uninvolved eye, subclinical endothelial changes including increased pleomorphism (decreased hexagonal percentage), and a relatively high coefficient of cell area variations can be observed.[72,73] The total number of endothelial cells does not show a statistically significant change compared to normal. Although specular microscopy can provide the status of the corneal endothelium, it poorly predicts clinical prognosis and cannot replace close scrutiny for early detection and management of elevated IOP.[70]

When corneal edema precludes visualization of the corneal endothelium, confocal microscopy has been shown to be superior to specular microscopy.[19,61,88] In the setting of corneal edema, the specular microscope cannot adequately visualize the endothelial changes. In contrast, confocal microscopy can still reveal epithelioid endothelial cells with hyperreflective nuclei, with preservation of the tissue organization of the corneal endothelium and absence of inflammatory cells (Fig. 1C).[36,61] Confocal microscopy shows 2 distinct patterns of changes in the epithelioid-like endothelial cells in ICE syndrome: (1) relatively regular size and shape and conserving a pattern similar to normal endothelial cells, with loss of normal hexagonality and prominent uniform "cobblestone-like" nuclei occupying the central area of the cells and (2) endothelial cells more irregular in size and shape, with hyperreflective diversely shaped nuclei adjacent to the boundaries of the cells. The stromal nerves appear to be thicker (pseudothickening) compared to the noninvolved side.[63]

In vivo confocal microscopy has also shown changes in other layers of the cornea in eyes with ICE syndrome, although it is generally considered to be an endothelial disorder. These include varying degrees of changes of the corneal stroma, pseudoprominent corneal nerves, and bizarre syncytia of keratocytes.[35] Its superior resolution, ability to analyze all cellular layers of the cornea even in the presence of edema and scar, and static and dynamic capabilities of its scan make confocal microscopy an invaluable test to differentiate different diseased states of the cornea and provides a tissue-based diagnosis more feasible in cases of vague clinical presentations.[34,35,72]

Ultrasound biomicroscopy and anterior segment optical coherence tomography may also be used to assess the angles in cases of ICE syndrome with accompanying corneal edema.[103]

2.2. *Differential diagnosis*

2.2.1. *Posterior polymorphous corneal dystrophy*

Posterior polymorphous corneal dystrophy (PPCD—also abbreviated as PPMD) is a corneal endothelial disorder, typically

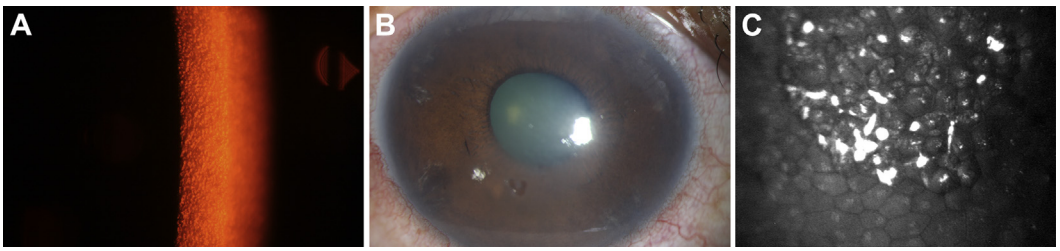

Fig. 1 – Chandler syndrome (CS). A: Specular microscopy of an eye with CS demonstrating orange skin or hammered silver appearance of the endothelium. The photograph was taken with a Haag Streit Eisner lens. B: Slit lamp photograph of an eye with CS reveals central bullous keratopathy, corectopia, ectropion uvea, and scattering iris atrophy. C: Confocal microscopy demonstrating characteristic groups of epithelial-like endothelial cells containing prominent hyperreflective nuclei in an eye with iridocorneal endothelial syndrome.

bilateral, transmitted as an autosomal dominant trait, although isolated unilateral cases have been described as *de novo* mutations (Fig. 2A).[22,87,99] Once considered to be differentiating features between PPCD and ICE syndrome, bilateral involvement, age at presentation, and presence of epithelial-like endothelial cells are no longer so[5]; however, ICE syndrome is typically unilateral, does not have a hereditary pattern, and affects more frequently young women. PPCD is usually bilateral and includes vesicles, banding, or Descemet membrane opacities at the level of the endothelium.[19] Using endothelial specular microscopy, isolated ICE tissue ("ICE-bergs") and PPCD vesicles may appear to be analogous. An ICE-berg consists of a nest of ICE cells surrounded by a thin dark edge, lying within the endothelium and distorting cells adjacent to it, whereas a PPCD vesicle is a pit delineated by a thick, dark border and lying anterior to endothelial cells without distorting them (Fig. 2B). Endothelial cells are recognizable as such in both conditions, but in ICE they are commonly much smaller, whereas in PPCD, they are almost always larger than normal.[60]

In ICE syndrome the anterior banded and posterior nonbanded Descemet membrane are normal, whereas only the anterior banded layer is normal in PPCD, suggesting that an insult occurred after 5 months of gestation when the development of anterior Descemet membrane is complete.[60] *In vivo* confocal microscopy has shown its ability to differentiate different diseased corneal states when corneal edema precludes thorough slit lamp examination of the corneal layers.[35] Regardless, confocal microscopy may be misleading in the diagnosis of corneal disease even in the presence of clinical features in which only a strong family phenotype history can lead to proper diagnosis.[59]

2.2.2. *Fuchs endothelial dystrophy*

This bilateral disorder, characterized by endothelial excrescences called guttae and corneal edema, usually occurs without known inheritance pattern, although some cases with autosomal dominance inheritance have been reported.[99] It does not have abnormalities at the iridocorneal angle or iris. In the presence of corneal edema precluding the evaluation of these structures by gonioscopy, ultrasound biomicroscopy or anterior segment optical coherence tomography may be useful to rule out the presence of PAS. Again, *in vivo* confocal microscopy may differentiate both entities. It will identify the presence of the "ICE cells" on the corneal endothelium in ICE syndrome and the hyporeflective nuclei in Fuchs endothelial dystrophy.[88]

3. Progressive iris atrophy

3.1. *Clinical findings/presentation/features*

PIA is a slowly progressive disease.[94] The initial clinical event is usually the formation of focal PAS. Endothelial proliferation may contribute to the formation of focal synechiae in a previously open angle.[29] There is an extreme variation in the clinical appearance of the cornea. The change in its posterior aspect is often the only corneal abnormality, but other cases also show corneal edema.

Iris changes are usually seen late in the course of disease by developing corectopia and areas of stromal thinning. The pupil is typically dragged toward a prominent PAS with corresponding ectropion uveae.[13] The iris is stretched on the side opposite to the direction of pupillary distortion and develops stromal atrophy and hole formation, called a "stretch hole"[83] (Fig. 3A). Progressive synechia formation and pupillary displacement related to membrane shrinkage put tension on the iris. Ultimately, with increasing synechial closure, tension on the stroma increases, stromal collagen and vessels give way, and iris atrophy and full-thickness hole formation result (Fig. 3B).

In contrast, there is a less common type of iris atrophy called a "melting hole" in which surrounding iris is not stretched (Fig. 3C). This type of hole has been demonstrated as the result of an ischemic process by fluorescein angiography.[94] The iris pattern remains normal except in the sites of atrophy. Heterochromia usually does not occur, and ectropion uveae is rare.[92] As mentioned previously, anterior segment optical coherence tomography may be used to visualize and precisely document iris atrophy and iridocorneal synechiae resulting from ICE syndrome.[32]

3.2. *Differential diagnosis*

3.2.1. *Cogan-Reese syndrome*

In CRS a diffuse proliferation of corneal endothelium involving most of the iris and anterior chamber angle does not result in marked pupillary displacement. The diffuse

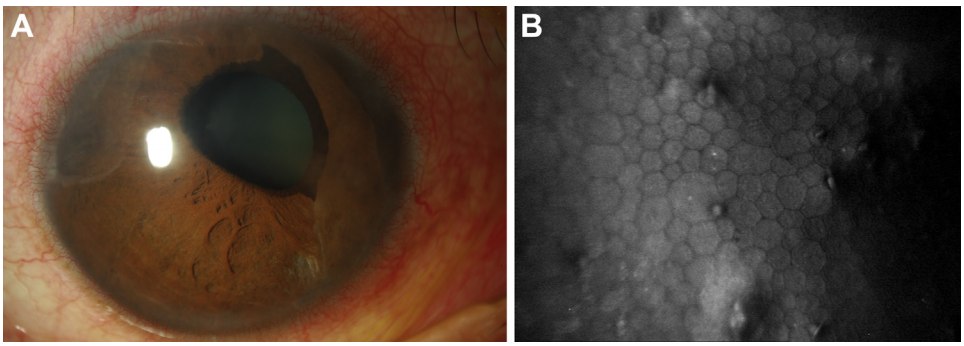

Fig. 2 – Posterior polymorphous dystrophy (PPCD). *A*: An eye with familial PPCD showing translucent iris membrane obscuring iris crypts and collarette, ectropion uvea, corectopia, peripheral anterior synechiae, and iris atrophy. *B*: Confocal microscopy of an eye with PPCD revealing characteristic endothelial vesicular lesions.

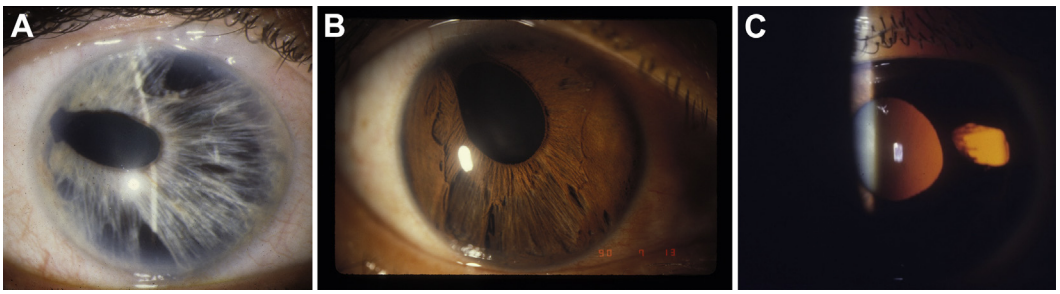

Fig. 3 – Progressive iris atrophy (PIA). A: Slit lamp photograph of an eye with PIA showing ectropion uveae, corectopia, iris atrophy, and stretching holes. The eye has a superior bleb with a peripheral iridectomy. B: Slit lamp photograph of an eye with PIA shows superior peripheral anterior synechiae leading to ectropion uvea, corectopia, and iris atrophy. The atrophy occurred not only superficially exposing the posterior iris but also deeply resulting in full-thickness iris holes. C: Slit lamp photograph of an eye with PIA and melting hole.

endothelialization tends to distribute tension uniformly on the iris; therefore, iris atrophy and hole formation are less likely to occur.[29] In contrast, focal endothelial proliferation, as in PIA, leads to synechia formation, pupillary displacement, and greater incidence of hole formation.

3.2.2. *Chandler syndrome*

Iris abnormalities may be overshadowed by corneal edema; however, as stated previously, areas of atrophy can be observed in later stages in CS, but usually never lead to a full-thickness iris hole as in PIA.[84]

3.2.3. *Axenfeld-Rieger syndrome*

A bilateral, congenital, autosomal dominant disorder in most cases, but also may occur sporadically, that includes iris abnormalities such as corectopia, polycoria, and iridocorneal attachments to a posterior embryotoxon[50] (Figs. 4A and 4B). It does not have corneal endothelial changes, in contrast with ICE syndrome.[93]

Histopathologically, both ICE syndromes and Axenfeld-Rieger syndrome (ARS) include a monolayer of endothelial-like cells, with a Descemet-like membrane that extends from the cornea, across the anterior chamber angle, and over the anterior surface of the iris.[90] Although in ICE syndrome, the membrane is acquired after birth, in ARS, it is thought that the membrane is derived, not from abnormal corneal endothelium, but from retention of the primordial endothelial layer lining the anterior chamber during gestation. Hence, it is a congenital disorder, as opposed to ICE syndrome.[91] A striking difference between both entities is the presence of a posterior embryotoxon with iris strands in ARS. In ICE syndrome, instead of iris strands, there may be PAS to the Schwalbe line or beyond, and a posterior embryotoxon is rarely seen.[94] Additionally, the mechanism of the glaucoma differs in the 2 conditions. The membrane over the trabecular meshwork or PAS causes the secondary glaucoma in ICE syndrome, whereas maldevelopment of the trabecular meshwork and Schlemm canal, and not the associated iris strands, causes the secondary glaucoma in ARS.[91]

3.2.4. *Aniridia*

Aniridia is a bilateral congenital disease that may be confused with late stage PIA. If corneal clouding is present, it is usually caused by a pannus due to a limbal stem cell deficiency and not by endothelial cell dysfunction. It is often associated with other congenital ocular malformations, including optic nerve hypoplasia, and patients usually have poor vision and nystagmus.[84] ICE syndrome is not congenital. It is acquired. There have been sporadic, extremely rare reports in children, most of them diagnosed after 10 years of age.[6,75,85]

3.2.5. *Iridoschisis*

This condition, characterized by progressive separation and dissolution of the anterior layers of the iris stroma, is usually

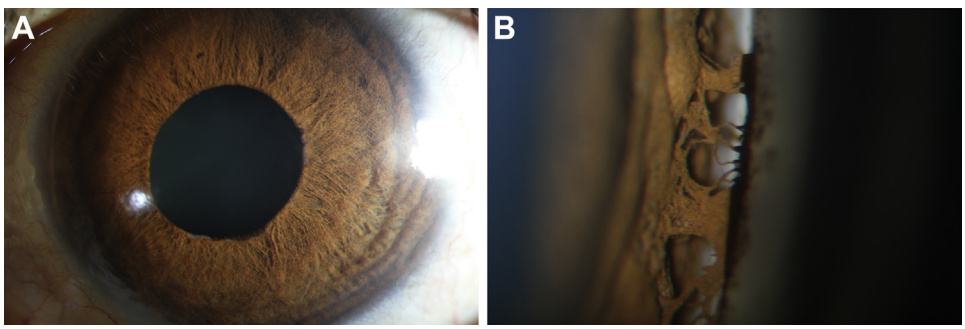

Fig. 4 – Axenfeld-Rieger syndrome (ARS): A: An eye with ARS and iris hypoplasia showing generalized exposure of iris stroma, absent collarette, corectopia, and limited ectropion uvea. B: Gonioscopy of an eye with ARS demonstrating characteristic iris strands attached to Schwalbe line.

bilateral and tends to occur in the elderly.[92] PIA is usually unilateral and manifests in young to middle adulthood.

4. Cogan-Reese syndrome

4.1. *Clinical findings/presentation/features*

The CRS has characteristic pigmented nodules on the iris and loss of normal iris architecture (Figs. 5A and 5B). The nodules may begin as a sparse number of fine, light tan, or yellow protuberances on the iris surface. The underlying iris stroma in the region of the nodules has a characteristic matted appearance with loss of normal iris crypts.[92] Iris nodules in eyes with CRS are typically discrete, round or flat, irregular, hyperpigmented lesions. They occur only over the area of translucent membrane and are not present elsewhere on the iris surface.[96] Scheie and Yanoff described 2 types of pigmented nodules on the iris in CRS.[86] One of these appears as fine, pedunculated nodules on the iris surface. The second type has been described as a matted appearance on the stroma of the iris with a velvety whorl-like surface and loss of iris crypts. The 2 types of iris lesions may rarely coexist in the same eye.[86] Transmission electron microscopy reveals iris nodules composed of polyhedral-to-fusiform melanocytic cells showing surface microvilli and long, delicate interweaving dendritic-like processes, covering long, stout branching processes that appeared to represent the underlying stromal cells of the iris.[92]

The migrating ICE cells may represent either a subgroup of endothelial cells derived from neural crest tissue that are proliferating abnormally[9] or metaplastic endothelium.[66] The typical corneal endothelial abnormality is a hammered silver appearance of the posterior corneal surface. This abnormal endothelium in CRS has greater ability to proliferate and migrate over anterior chamber and anterior iris surface. This may explain why iris features are found more commonly in patients with CRS or PIA than CS, leading to more frequent and advanced iris abnormalities and secondary glaucoma.[2] A translucent membrane obscuring iris crypts with a distinct border is more noticeable in darkly pigmented irides.[96] This membrane and characteristic iris matting may be responsible for the development of iris nodules by pinching off portions of the iris stroma.[29] Teekhasaenee and Ritch reported CRS in Asian eyes, more frequently in dark brown irides. Darker irides contain more melanin pigment granules in the superficial stromal melanocytes than do lighter irides.[96] It seems that the higher the amount of melanin in the iris favors the higher incidence of nodules.

In CRS, the cornea is usually clear initially and may develop edema during follow-up. Corneal edema is most often mild to moderate.

There is a loss of the normal iris pattern due to changes in the iris stroma and PAS. The iris tends to have a smooth appearance with fewer iris crypts and decreased pupillary ruff. Circular folds parallel with the pupillary border become less distinct.[86] CRS and PIA produce more severe pupil distortion than CS. The pupils generally deviate toward the site of membrane and PAS. The prevalence and severity of iris atrophy in CRS are in between CS and PIA.[95] Corectopia is moderate to severe in PIA and CRS.[95] Usually, there are no full-thickness holes or ectropion uveae at the pupillary border.[27] Iris heterochromia is characteristic, and the affected eye is the one with the darker iris. Except for the synechiae, no abnormality of the angle is seen (Fig. 5C).[86]

Advancement of the ICE cells over the iris can be measured by noting the topographical progression of the nodules over the iris and loss of normal iris architecture.[97] Transformation between each entity (from CS or PIA to CRS, from PIA to CRS and end up with CS) has been reported.[23,95] The nodules may occur late in the course of disease, which cases having been followed as PIA for many years before the appearance of the nodules.[95]

The most frequent complaints in CRS are changes in the shape and size of the pupil similar to PIA, which patients may describe as a distorted pupil, a second pupil, or a dark spot on the iris.[92,95] In a few cases the condition is diagnosed during a routine ocular examination for an unrelated matter.[92]

4.2. *Differential diagnosis*

4.2.1. *Progressive iris atrophy*

The iris pattern in PIA remains normal except at the site of atrophy. CRS shows effacement of the normal pattern of the iris surface.[29] Iris heterochromia and ectropion uveae are rare. Hole formation is not a diagnostic fundamental feature since it can occasionally be found in CRS.[86]

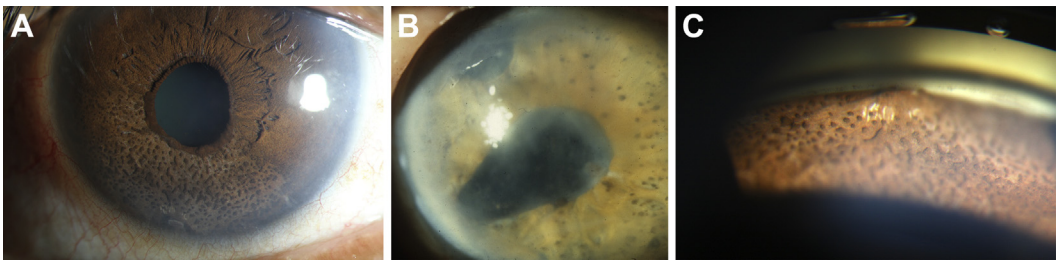

Fig. 5 – Cogan-Reese syndrome (CRS): *A*: Slit lamp photograph of an eye with CRS sectorial (4–9 o'clock positions) iris changes showing characteristic iris nodules, loss of iris crypts and collarette, hypochromia, ectropion uvea, and corectopia. *B*: Another eye with CRS showing typical iris nodules, corectopia, and corneal edema. There is a peripheral iridectomy at 11 o'clock. *C*: Gonioscopy of the eye revealing characteristic iris nodules in the angle, scattering pigmentation of the Schwalbe line, and localized peripheral anterior synechiae with associated early iris atrophy.

4.2.2. *Tapioca melanoma*

This rare entity presents as multiple nodules on the iris that resemble tapioca pudding or frog's eggs.[86] The nodules are small; some are pedunculated, hypopigmented or nonpigmented, multifocal, or confined to one sector, with significant vascularity within the affected area. Iris nodules in CRS are typically hyperpigmented. PAS and iris atrophy typical of CRS do not occur in tapioca melanoma, although the angle can fill with tumor.[86]

4.2.3. *Diffuse malignant melanoma of iris*

The iris tends to have a thicker, darker surface with little or no distortion of the pupillary margin. PAS and glaucoma are rare but do occur. Distortion of the pupillary margin, the presence of PAS, and the velvety or amorphous iris surface, often with fine nodules are indicative of CRS rather than of diffuse iris malignant melanoma.[86] Ring melanoma of the ciliary body and iris can present with signs of ICE syndrome and must be in differential diagnosis of unilateral anterior segment abnormalities and refractory glaucoma.[64]

4.2.4. *Oculodermal melanocytosis*

In rare cases, iris mammillations may be seen associated with iris hyperpigmentation in patients with oculodermal melanocytosis. These are described as smooth and small nodular formations with homogeneous distribution over the iris.[78] Diffuse malignant melanoma of the iris in a nevus of Ota may also simulate CRS, but ipsilateral hyperpigmentation of lids, conjunctiva, sclera, and the fundus help to differentiate the entity (Fig. 6). A history of congenital heterochromia and lid hyperpigmentation may be helpful diagnostically.[92]

4.2.5. *Neurofibromatosis*

The Lisch nodules of neurofibromatosis are flat, larger, lighter colored, and less sharply demarcated from the surrounding stroma (Fig. 7). Pupillary distortion and PAS do not occur.[86]

4.2.6. *Miscellaneous*

Iris melanocytoma can present with signs of CRS, and histopathologic evaluation is needed for proper diagnosis.[38] Iris metastasis from non–small-cell lung cancer can also mimic the clinical appearance of CRS.[40] The presence of intraocular inflammation may help differentiate the iris nodules that may be seen in sarcoidosis.[84]

5. Histopathology of ICE syndrome

Light microscopy shows the abnormal endothelial cells to be taller than the adjacent normal cells and to have a multilayer organization. Microvilli, a feature of epithelial cells, are found on the surface of the abnormal cells.[65] The tall and conical shape of ICE cells explains the specular microscopic appearance of the light-dark reversal pattern seen in ICE syndrome.[66] ICE cells located in the vicinity of normal CECs are nonmotile and have high metabolic activity, which may play a role in damaging nearby endothelial cells through a toxic effect.[67]

An immunohistochemical study of ICE syndrome samples taken following Descemet stripping automated endothelial keratoplasty (DSAEK) showed multilayered endothelial cells, thickened Descemet membranes, and positive staining for cytokeratins AE1/3 and MAK6, which differentiated it from PPCD, which also has wide-spaced collagen fibers in Descemet membrane.[11] Immunohistochemical staining has shown markers for multilayered epithelial surfaces, AE1 (normally stains conjunctiva and corneal epithelium) and AE3 (normally only conjunctiva), as well as vimentin (normally seen in mesenchymally derived cells, e.g., endothelial cells).[43] An immunofluorescence study of epithelial-like cells in ICE syndrome has shown the presence of vimentin and anti-endothelial antibody 2B4.14.1, which is strong evidence of endothelial metaplasia as the source of ICE cells.[46] The presence of vimentin, a 53kD intermediate cytoskeletal filament and marker of mesenchymally derived cells (e.g., corneal endothelium), strongly suggests CECs as the origin of ICE cells.[55] Accumulation of collagen type VIII in the posterior nonbanded wide-spaced collagen layer of Descemet membrane was a pathologic finding of the diseased cornea compared to normal ones, forming a posterior collagenous layer in Fuchs endothelial dystrophy and ICE syndrome. In the latter, the posterior collagenous layer consisted of 2 layers, the anterior layer containing mostly wide-spaced collagen and the posterior mostly microfibrils.[69] Transforming growth factor beta, a pleiotropic cytokine involved in various aspects of

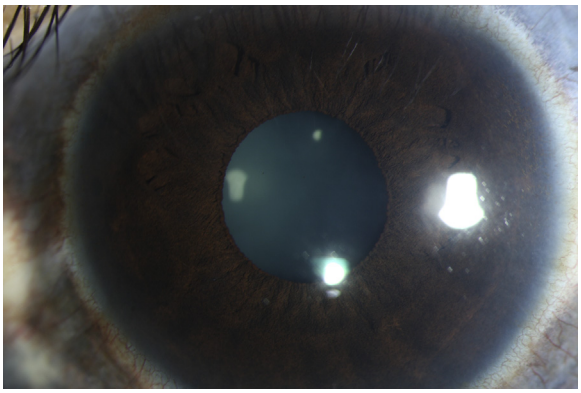

Fig. 6 – Oculodermal melanocytosis (ODM): An eye with ODM showing hyperpigmentation of the iris and episclera and prominent pupillary ruffs.

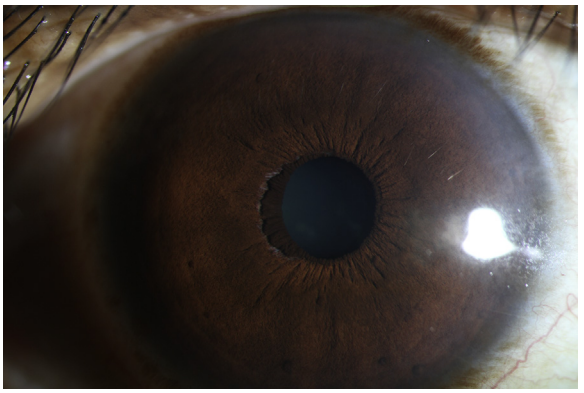

Fig. 7 – Neurofibromatosis: A slit lamp photograph of an eye with neurofibromatosis type 1 showing multiple Lisch's nodules and congenital ectropion uvea.

tissue development, maintenance, and pathology, caused similar changes to ICE syndrome when injected into a rat eye model, such as transforming endothelial cells, matrix deposition, and PAS formation, causing glaucoma.[82]

Light and electron microscopy in PIA revealed endothelium and abnormal basement membrane on the surface of the trabecular meshwork and peripheral iris deep to synechiae in over half the cases, indicating that endothelial proliferation occurred before synechial closure.[29]

In CRS, the anterior iris is thickened focally by an increased number of benign-appearing melanocytic cells.[28] The nodules are composed of iris stromal melanocytes that project through a fenestra in the abnormal basement membrane laid down by the migrating endothelium.[89] The iris nodules are found only in the endothelialized portion of the iris.[30] Scanning electron microscopy shows a continuous sheet of irregular polygonal endothelial cells on the anterior iris surface. The endothelial cells have scattered cilia and numerous microvilli. Transmission electron microscopy confirmed the endothelial nature of the cells covering the anterior iris surface. Two distinct populations of melanocytic cells are observed in the iris stroma.[30]

6. Epidemiology/associations

ICE syndrome is considered rare and is acquired and sporadic. It is typically unilateral and affects middle-aged patients (more often women, between the second and fourth to fifth decades of life).[84,92] There are, however, exceptions to the rule. It has been rarely reported bilaterally.[24,37,42,49,71] ICE syndrome has also been reported in younger patients,[6,75] such as a CS in an 11-year-old girl.[85] As pediatric cases with ICE syndrome are an exception rather than the rule, careful differential diagnosis should be made with other entities resembling ICE syndrome in children, such as PPCD, ARS, or chronic uveitis causing iris atrophy and PAS. Specular microscopy and/or *in vivo* confocal microscopy must be part of the evaluation in these cases, searching for evidence of the typical ICE cells.

There have been some isolated cases of ICE syndrome reported to be associated with other conditions, such as a bilateral CS in a male with concomitant fingerprint dystrophy-like epithelial changes[7] or ICE syndrome with ipsilateral sensorineural hearing loss[47]; however, no definite association can be established based on these single case reports.

Among the 3 variants of ICE syndrome, CS has been described as the most frequent in whites.[92,95] In Asians, CRS was reported as the most common form and is strongly associated with glaucoma.[96] PIA predominantly affects women with a reported male to female ratio ranging from 1:2[92] to 1:5.[27] In a retrospective study from 203 Indian subjects, PIA was the most common clinical variant (52%), followed by CS (39%) and CRS (9%).[15] The discrepancy in the most common ICE syndrome variant among different studies is highly suggestive of ethnic differences and susceptibilities.

7. Etiology/pathogenesis

CECs do not divide after birth.[84,102] They stay arrested in the G-1 phase of mitosis by the 120 and 165 mm stages of development,[100] thanks to the presence of inhibitors of cyclin-dependent kinases. A triggering factor causes the endothelial cells to lose control of the cellular cycle. By downregulation of the expression of the inhibitors of the cyclin-dependent kinases, the endothelial cells may proliferate and behave like epithelial cells, with no malignant transformation.[81]

The most accepted pathogenesis of the ICE syndrome is a viral infection. The fact that it is usually unilateral may be explained by the development of antibodies, which would prevent damage to the contralateral eye in the vast majority of cases. *Herpes simplex* viral DNA has been reportedly recovered from the cornea of ICE patients,[3] but its pathological role is still speculative. Others have shown that Epstein-Barr virus may also play a role in the disease development.[98]

According to the membrane theory of Campbell, the disease begins as an abnormality of the corneal endothelium, which leads to formation of a membrane across portions of the anterior chamber angle and anterior surface of the iris. Contraction of the membrane leads to PAS and iris changes.[13,92] This hypothesis has been supported by histological, electron microscopy, and immunohistochemistry studies, confirming the presence of endothelial cells with unique characteristics of epithelial cells (see histopathology section). Patel and colleagues described the clinicopathologic features of 9 patients with CS. They found extension of the endothelial cell layer and Descemet membrane over the trabecular meshwork in 2 trabeculectomy specimens and onto the anterior surface of the iris in 4 specimens.[76]

Alternatively, Bahn and colleagues proposed the hypothesis that the ICE syndrome to be the result of an altered proliferation of neural crest cells[9] from which CECs derive. This would not explain why this condition typically presents as an acquired condition in early adulthood.

Levy and colleagues contemplated the possibility of embryonic ectopia of ocular surface epithelium as the origin of abnormal ICE cells, based on electron microscopy and light and electron microscopic immunohistochemistry, which found CECs morphologically similar to epithelial cells and expressed the same profile of differentiation markers as did normal limbal epithelial cells.[67] Such heterotopia could result from the complex events of ocular anterior segment morphogenesis where corneal epithelia and endothelia are in direct contact with each other momentarily during the infolding of surface ectoderm to form the lens[101]; however, they also postulated that ICE cells could arise from a metaplastic stimulus, from another ocular pathology such as a viral infection, or that even such stimulus might be required for the embryonic ectopia to proliferate.[68]

Before chronic edema develops, the endothelial barrier in the affected eyes is actually more impermeable than that in healthy eyes.[10] This observation supports the hypothesis that the disease pathogenesis may represent reparative activities of the injured endothelial cells following a viral infection or inflammation.[68,84]

8. Glaucoma in ICE syndrome

The reported prevalence of glaucoma in eyes with ICE syndrome ranges from 46% to 82%.[59,94,96,100] Laganowski and

colleagues found glaucoma most commonly in the variants in which abnormal cells involved the entire posterior corneal surface (disseminated ICE and total ICE).[59] The angle obstruction caused by migration of the abnormal endothelial cells and the development of PAS may cause increased IOP and consequent development of glaucoma.[84] Dua and colleagues have described a separation of the lamellae of the pre-Descemet layer or Dua layer at the extreme periphery around the circumference of the cornea to form the collagen core of the trabecular meshwork.[26] They also described the presence of tiny holes in the layer as the lamellae start to separate to merge with trabecular meshwork. These holes, randomly located along the periphery of the cornea, connect the corneal stroma directly with the anterior chamber. It has been hypothesized that they could be involved in the egress of aqueous humor from the eye.[26] Therefore, we postulate that the migration of ICE cells toward the periphery could start affecting the drainage of aqueous humor by occluding these holes, even before reaching the iridocorneal angle.

The severity of glaucoma is significantly worse in CRS and PIA compared to CS,[98,100] which may be explained by the higher prevalence of proliferation of ICE cells over the iridocorneal angle and secondary PAS in these ICE syndrome variants. On the other hand, the severity of corneal edema is higher in CS, which speaks in favor of a greater degree of corneal endothelial abnormality, and likely a decreased ability or severity to invade the anterior chamber angle and iris.[100] Another study, however, reported a higher prevalence of IOP elevation in CS.[59]

In PIA, PAS are nearly always observed. Wide anterior PAS attach to the limbus, almost to the transparent edge of the cornea, and close variable degrees of the angle.[92] The PAS usually have areas of increased pigmentation at their anterior-most portions. A yellowish color is occasionally seen at the interface between synechiae and cornea. On histology, PIA has a membrane extending over the open angle or synechiae onto portions of the anterior iris surface. This membrane resembles Descemet membrane and is covered by a single layer of endothelial cells.[92]

IOP is much more difficult to control in patients with CRS or PIA than those with CS, regardless of the extent of PAS.[100] A greater proportion of patients with CRS (50%) or PIA (75%) compared to CS (40%) required filtering surgery in a series published by Wilson and Shields.[100]

9. Treatment

Treatment in ICE syndrome falls into 3 categories: (1) management of corneal decompensation and its related complications; (2) addressing iris atrophy and its cosmetic and visually significant sequelae; and (3) controlling glaucoma associated with ICE syndrome.

9.1. *Corneal decompensation and its related complications*

Penetrating keratoplasty (PK) has been used to treat corneal features of ICE syndrome, with good results, but repeat surgeries are often needed to keep the cornea clear.[4] When possible, endothelial keratoplasty techniques are preferable options for corneal edema secondary to ICE syndrome.[17,18] DSAEK and Descemet membrane endothelial keratoplasty grew in preference over PK for corneal endothelial disorders, including patients with ICE syndrome.[31,33] Endothelial keratoplasty techniques, however, can be more challenging to perform because of the requirement to work through a small incision, to break the PAS, and the need to correctly position the donor tissue in an eye with iris abnormalities or shallow anterior chamber.[79] Fajgenbaum and colleagues reported poor long-term graft survival after DSAEK because of late endothelial failure at a mean of 18 ± 7 months.[31] Huang and colleagues reported deep lamellar endothelial keratoplasty as a surgical option for phakic patients with ICE syndrome[48]; however, deep lamellar endothelial keratoplasty was widely replaced by DSAEK and Descemet membrane endothelial keratoplasty (the third-generation endothelial keratoplasty procedure, where only an isolated donor Descemet membrane and its endothelial layer are transplanted without any corneal stroma), both superior procedures with more reproducible outcomes. Generally, Descemet membrane endothelial keratoplasty is preferred over DSAEK, as the former has been shown to have superior outcomes, faster recovery, lower risk of rejection, and reduced postoperative hyperopic shift in refraction. DSAEK, however, is still preferable in ICE patients with extensive iris abnormalities or iridocorneal synechiae.

Concomitant presence of epithelial basement membrane dystrophies in ICE syndrome can be addressed by epithelial debridement, which can lead to better visual acuity and corneal regularity in these patients.[52] Triple procedures (phacoemulsification, intraocular lens insertion, and DSAEK) have been successfully applied in CS.[58] PK and DSAEK have been reported as equivalent in terms of graft failure or the need for additional IOP-lowering therapy postkeratoplasty.[80] Quek and colleagues reported in their series a higher graft failure rate in essential iris atrophy compared to CS and CRS (46.7% vs 22.2%, P = .39). It did not reach statistical significance because of the small sample size in each subtype,[80] but the results are expectable because eyes with essential iris atrophy tend to be more aggressive and develop more PAS.

In patients with multiple previous failed keratoplasties, a keratoprosthesis may be an option to restore vision. In these cases, it is highly recommended that the glaucoma be addressed previously, or planned concomitantly, with the keratoprosthesis surgery, such as a glaucoma drainage device.[21,77]

Recent efforts to treat corneal endothelial diseases such as Fuchs endothelial corneal dystrophy, with positive effects, using topical Rho-associated protein kinase inhibitors, which accelerate the migration and proliferation of residual CECs, thus allowing recovery of the corneal endothelial function and corneal edema.[57] If rho-associated protein kinase inhibitor may improve corneal edema, it could be useful in certain patients with ICE syndrome, assuming there is an acceptable number of normal CECs. As endothelial failure is pathophysiologically different between Fuchs endothelial corneal dystrophy and ICE syndrome, this hypothesis is clearly speculative, and further research would be recommended. Another novel approach, cell-injection therapy involving cultured human CECs into the anterior chamber could be a

promising option to eliminate the ICE cells by previously scraping the diseased CECs and replacing them by healthy ones.[56,74]

9.2. *Iris atrophy and its cosmetic and visually significant sequelae*

The new surgical technique of femtosecond-assisted keratopigmentation has been used with good results to address both the cosmetic as well as the visually significant problems seen in PIA.[1] Iris reconstruction with multipiece endocapsular prosthesis is another alternative to treat patients with ICE syndrome and iris problems.[53]

9.3. *Glaucoma associated with ICE syndrome*

Typically, increased IOP may be initially treated with topical drugs, which may be sufficient to stop glaucomatous progression, especially in early stages. As the main pathophysiologic basis for elevated IOP in ICE syndrome is the presence of an abnormal endothelial membrane covering the trabecular meshwork or PAS, drugs that decrease the production of aqueous humor are preferred. In a large retrospective study by Chandran and colleagues with 223 eyes of 203 subjects with ICE syndrome between 1988 and 2013, 163 eyes (73%) had glaucoma, and 50% were managed medically. Glaucoma surgery was required in 54% of subjects with PIA, 47% of CRS, and 45% of CS.[15]

Glaucoma associated with ICE can be managed successfully with different surgical methods when topical drops are not enough to control IOP or stop progression (including trabeculectomy with antifibrotic agents, glaucoma drainage devices, cyclodestructive procedures, and a combination of the 3), but multiple procedures are generally needed to control the IOP.[25,59] Goniotomy has been used with good long-term results in patients with CS, based on the fact that the obstruction occurs at the pretrabecular level by the overgrowing ICE membrane. Espana and colleagues performed a wider trabecular incision (4 clock hours nasally and 4 clock hours inferiorly), obtaining sustained IOP control even after failed trabeculectomy and drainage implant[30]; however, this surgery could fail if a new membrane would cover the cleft or if new PAS would develop in that area.

Trabeculectomy with mitomycin C has a reasonable intermediate-term success rate in ICE patients[59,62]; however, it has a less favorable outcome compared to juvenile, pigmentary, or primary open-angle glaucoma, likely due to the proliferation of endothelium together with its elaboration of abnormal basement membrane within the filtering blebs.[51] In a retrospective study evaluating the effectiveness of primary trabeculectomy with mitomycin C in glaucoma secondary to ICE syndrome from 16 eyes of 15 subjects between 1991 and 2013, Chandran and colleagues reported 64% complete success rate at 12 months and 33% at 60 months. Qualified success was 82% at 12 months and 69% at 60 months.[16] Glaucoma shunts can also be an alternative to decrease the IOP. Different types have shown efficacy in controlling IOP in patients with ICE syndrome and failed medical treatment or trabeculectomy, though additional procedures/revisions may be necessary.[54] In pseudophakic eyes, we advocate for tube insertion through the ciliary sulcus, which decreases the risk of corneal decompensation by tube-cornea touch (especially in eyes with compromised corneal endothelium, which is quite common in ICE syndrome) and also decreases the risk of iris damage or iris dialysis in eyes with important PAS (also common in ICE syndrome, especially PIA or CRS). Placement of the tube behind the iris could also potentially prevent obstruction of the lumen by ICE membrane migrating from the iridocorneal angle, which has been previously reported.[54] We trim the tube bevel down to decrease the risk of obstruction of the lumen by the posterior surface of the iris whether the tip stays ideally beyond the pupillary margin, or right behind it.

Bucher and colleagues reported the formation of a retrocorneal membrane after Baerveldt shunt implantation in a patient with ICE syndrome, which caused decreased visual acuity and required DSAEK, with a good outcome.[12] This isolated case, however, cannot confirm if ICE syndrome is by itself a risk factor to develop a thick retrocorneal membrane, or if it occurred secondary to the surgical intervention.

Among the microinvasive glaucoma surgeries, the use of the microbypass Xen Gel Stent, a tube composed of a collagen-based gelatin, placed ab interno subconjunctivally by a clear corneal incision, was successful in a patient with ICE syndrome followed up to 6.5 months. Future studies with longer follow-up will be needed to determine its efficacy in glaucoma associated with ICE syndrome.[45]

10. Conclusions

ICE syndrome constitutes a fascinating entity that usually requires participation by both cornea and glaucoma subspecialists. Diagnosis is made based on the typical ocular findings on the cornea and iris that is unilateral in most cases. *In vivo* confocal microscopy may assist in borderline presentations, such as early cases of CS, which affects the cornea predominantly. When corneal edema and decompensation develop, endothelial keratoplasty techniques have largely replaced PK; however, the presence of significant anterior synechiae may pose technical challenges that will still require a PK. Despite the evolution of glaucoma surgery, trabeculectomy with antifibrotics or glaucoma drainage devices remains the mainstay of the surgical treatment of ICE-associated glaucoma. Goniotomy may also be an alternative if there are no extensive PAS.

Although its pathophysiology has been extensively documented, the exact triggering factor involved in the corneal endothelium changes—possibly viral—is still controversial and remains to be elucidated. Further research is needed to provide a better understanding of its etiology, which could offer additional tools to treat, halt progression, or prevent the disease.

11. Method of literature search

We conducted a systematic review of the literature using PubMed databases with the following search terms: “glaucoma,” “iridocorneal endothelial syndrome”, “Chandler syndrome,” “progressive iris atrophy,” “Cogan-Reese syndrome,”

"corneal edema," and "keratoplasty." The articles/abstracts used were written in English, German, or French.

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