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Changes In Different Structures of Eyeball in Ice Syndrome : A Review Study

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ABSTRACT

ICE syndrome (iris corneal endothelium syndrome) is a rare condition that affects the irregular corneal endothelium, which can cause varying degrees of glaucoma.

The proliferative and structural abnormalities of the corneal endothelium, the increasing constriction of the iridocorneal angle, and iris abnormalities such atrophy, correctopia, and polycoria are the hallmarks of the ICE syndrome.

A Narrative review was done to review the articles available on PubMed, Google Scholar, Medline, Publon, Orcid, Healthstar, and others related to ICE syndrome. Peer-reviewed articles/ studies were referred to ascertain the available screening tests, risk factors, physiological parameters, and diagnosis of glaucoma on the basis of ICE, chandler's syndrome, progressive iris atrophy and management options for ICE syndrome.

This review study provides an overview of the ICE syndrome's complications, ocular examination, causes and about management options. Thus, the assessment can be easily done by full ophthalmic workup, with vision assessment of refractive error, slit lamp examination, intraocular pressure measurement, and fundus examination. In Gonioscopy findings we will get PAS usually extending to or beyond the schwalbe line.

It is yet unknown what factors underlie corneal endothelial changes and are the primary causes of ICE syndrome. A viral aetiology has been proposed, particularly Epstein virus and Herpes simplex virus.

The initial step in treating corneal oedema is to lower the intraocular pressure inside the eye.

Keywords : Specular microscopy, Anterior segment OCT, Gonioscopy, Correctopia, Polycoria

I. INTRODUCTION

ICE syndrome (iris corneal endothelium syndrome) is a rare condition that affects the irregular corneal endothelium, which can cause varying degrees of glaucoma. Eagle and Yanoff coined the term "ICE syndrome" to refer to a group of conditions marked by primary corneal endothelial abnormalities and membrane formation at the corneal angle and on the anterior surface of the iris. Without pupil block, this can result in secondary angle-closure glaucoma.[1–5]

Approximately 85% of people with ICE syndrome have glaucoma. And females between the ages of 23 and 46 are the demographic most commonly affected by this condition. People do not initially exhibit any severe glaucoma symptoms, but with time, the majority of patients in this syndrome develop glaucoma.

This syndrome is diagnosed using a variety of diagnostic techniques. Specular microscopy and confocal microscopy are used to diagnose corneal changes. Angle depth, gonioscopy angles, and intraocular pressure measured during field tests are used to detect glaucoma. UBM's diagnosis of any nodules determines whether there has been any change in Iris.

Clinical variants of ICE Syndrome: [2]

Based on changes in the iris-

1. Chandler syndrome
2. Essential /Progressive Iris atrophy
3. Iris Nevus / Cogan Reese syndrome.[6]

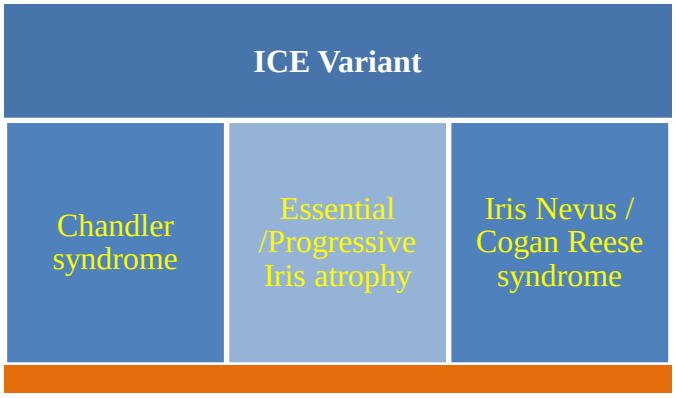

Fig 1: Clinical variants of ICE Syndrome

1. Chandler Syndrome:

The most prevalent form of ICE Syndrome is Chandler Syndrome. The corneal endothelial dysfunction and corneal oedema are the most noticeable symptoms of Chandler syndrome.[7]

Similar to fox dystrophy, the endothelium in this condition exhibits changed behaviour and takes on the appearance of hammered silver. When the endothelium exhibits abnormal behaviour, the pumping system malfunctions and fluid builds up in the cornea, leading to corneal oedema and reduced vision.

Contraction of this membrane causes abnormalities in the iris (corectopia of the eye), which can occur simultaneously with abnormal endothelial cells migrating as a membrane over nearby tissues including the trabecular meshwork and iris. Additionally, iridotrabeculate synechiae impede the trabecular meshwork's water outflow, which results in secondary glaucoma.

The exact cause of Chandler syndrome is unknown. Some researchers suspect that inflammation or chronic viral infections may be the root of the disease. HSV (herpes simplex virus) DNA was detected by the polymerase chain reaction of corneal specimens from ICE syndrome.[8]

2. Essential/Progressive Iris Atrophy:

It is an extremely uncommon, progressive condition that causes pupillary displacement, iris atrophy, or distorted areas of the iris hole.

Most frequently, just one eye is affected by this condition, and it progresses gradually over time. A portion of the iris is adhered to the cornea's PAS (peripheral anterior cornea). Secondary glaucoma and visual loss might result from the drainage angle's subsequent closure. The displacement or distortion of the pupil, the patchy area of the iris, and the iris hole are the three basic signs of essential iris atrophy.[9-11]

3. Iris nevus or Cogan-Reese syndrome:

This variant of ICE syndrome is characterized by its unique iris findings. The anterior surface of the iris has a tan, drooping nodule, or diffuse pigmented lesion. However, iris atrophy is rare in these particular patients.[12-14]

ETIOLOGY

The true etiology of ICE syndrome is not well understood.[15,16] The unusual epithelial-like activity of the cornea has been attributed to a low-grade inflammation at the level of the corneal endothelium caused by an underlying viral infection with Epstein-Barr virus (EBV) or Herpes simplex virus (HSV). [17,18] When compared to healthy controls, ocular endothelial cells from patients with the ICE syndrome had higher percentages of HSV DNA, according to PCR testing. [18]

SIGNS AND SYMPTOMS

Signs:

- Unilateral Glaucoma
- Appearance of silver struck by the mallet of the corneal endothelium
- Chandler's syndrome: abnormal corneal endothelium
- Cogan Rees syndrome: Nodules on iris
- Abnormal Iris Atrophy: Correctopia, Stretch and melt holes
- Abnormal Corneal endothelial cells
- PAS formation in the angle

Symptoms:

- Asymptomatic in the early stages
- Severe loss of vision in untreated glaucoma.[19]

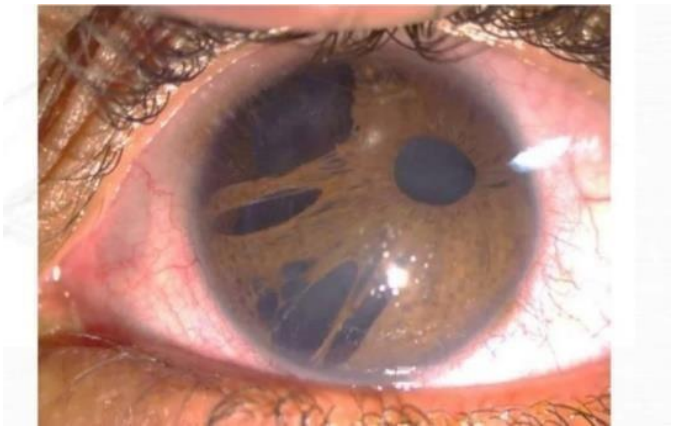

Fig 2: Progressive optic atrophy. (Courtesy from De Maria et al.)

PATHOPHYSIOLOGY:

The corneal endothelium is known to develop abnormally in ICE syndrome. On the inner surface of the cornea, a monolayer of distinct hexagonal cells compensates the corneal endothelium.

The neural crest is the embryological source of corneal endothelial cells. They are post-mitotic and do not divide normally at postnatal age. The density of corneal endothelial cells is approximately 3000 cells/mm2 in adulthood and gradually declines with ageing. By controlling the flow of liquids, nutrients, and solutes between the aqueous humour and the corneal structure, the corneal endothelium actively maintains the transparency of the cornea.

According to many studies in which many hypotheses have been made about the pathology of ICE Syndrome, the result of all these cellular changes is that the abnormal endothelial cells of ICE Syndrome move posteriorly across the Schwalbe line and the iridocorneal angle. It means to block and enter the anterior chamber. Cover the iris. They form an abnormal basement membrane, which eventually contracts, causing abnormal pupil shape, atrophic damage to the iris, and the formation of adhesions between adjacent structures. [20]

High PAS leads to secondary angle-closure glaucoma. However, it can happen without obvious symptoms

because the invading corneal endothelium has the ability to functionally narrow the angle without contracting. Because it might be challenging to see the fibrous vasculature that obstructs the atrioventricular flow by corneoscopy, individuals may initially present with what seems to be open-angle glaucoma. [21]

Prevalence of Glaucoma in ICE syndrome

As per one article study which was done by Chandan P, Rao HL et al.[22] the prevalence of glaucoma in ICE syndrome was reported to be 46-82%, and in this article, the prevalence of glaucoma was 73%.

Most of the affected patients were female in the adult age group between the ages of 23 to 46years age.

ICE syndrome was unilateral in 90% of patients. Bilateral involvement was found to occur in only 10% of subjects.[23]

In one article done by HC Laganowski, MG Kerr Muir, and RA Hitchings In 50% of patients, ICE syndrome was found to appear most frequently in mutants in which abnormal cells affect the entire posterior surface of the cornea.[23,24]

Clinical Diagnosis

The corneal endothelium exhibits proliferative and structural abnormalities, the iridocorneal angle gradually becomes blocked, and the iris exhibits abnormalities such as atrophy, correctopia, and polycoria. The most frequent causes of vision loss in these patients as a result of these alterations are secondary glaucoma and corneal decompensation.

Patients with ICE syndrome may initially appear with blurry vision, iris abnormalities, or monocular pain (caused by corneal oedema or increased IOP from angle closure). Full ophthalmic workups with fundus examinations, slit lamp examinations, intraocular pressure measurements, and visual assessments of refractive error can all be used to quickly perform the assessment. [25]

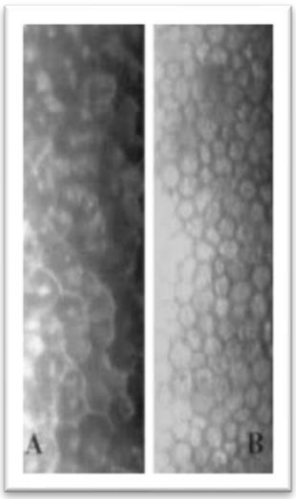

Fig 3: Corneal Endothelium in Specular Microscopy [Courtesy from webpage]
A: In ICE Syndrome
B: In Normal Eye

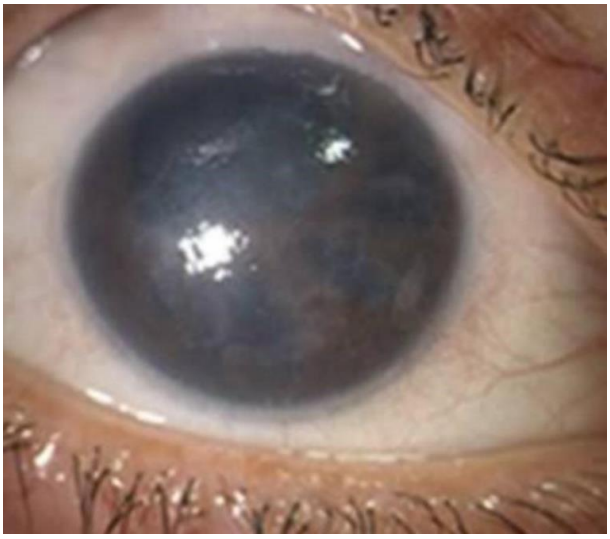

Fig 4 : ICE Syndrome (Corneal Edema with Iris Atrophy) [Courtesy from Marta Sacchetti et al.]

In Gonioscopy findings we will get PAS usually extending to or beyond the Schwalbe line.

We can use specular microscopy to distinguish between these two states. The ICE cell is a dark area with a bright center spot and a bright border. These are generally larger than normal endothelial cells and occur in areas where the cornea appears to have a hammered, silvery appearance. These cells are

regarded as pathognomonic of ICE syndrome and are termed “ICE cells” along with the tissue they form termed “ICE tissue”.

The four basic patterns of ICE cells are explained by previous authors. Recent findings using an in vivo confocal microscope highlighted two major patterns of aberrant "epithelial-like" endothelium. Both are characterized by a clear hyper-reflex nucleus and a loss of regularity in cell size and shape. 5-10 stromal nerve fibers of the affected eye were abnormally thick and distorted. Especially for edematous corneas, it is advisable to look for these signs to facilitate diagnosis. (26)

We can also do an Anterior segment Oct to get the exact corneal edema findings. We can do UBM for getting information about nodules or the structure of Iris which may be the cause of High intraocular pressure.

DIAGNOSTIC TESTS FOR ICE SYNDROME

1. Specular microscopy:

This is the important diagnostic test which has been done for the diagnosis of ICE syndrome is specular microscopy. In ICE syndrome endothelial cells are dark areas with a light central spot and a light peripheral zone. These are generally larger (polymorphism) than normal endothelial cells with a loss of hexagonal margins.

2. Tonometry:

Tonometry is done to get the value of the intraocular pressure of the eyeball. If we are getting high pressure then it is again tried with the standard method (GAT).

3. Gonioscopy:

Peripheral anterior synechiae, usually extended to or beyond the schwalbe line is a common variation of ICE syndrome.

4. Fundus photo: In ICE syndrome, a Stereo disc photograph is done to assess the cup disc ratio and see for any disc damage, and that damage is correlated with vision, disc damage, and field damage.

5. HVF: This is the standard method for Visual field assessment. This helps to see the visual field loss and that is correlated to glaucomatous changes or disc damage.

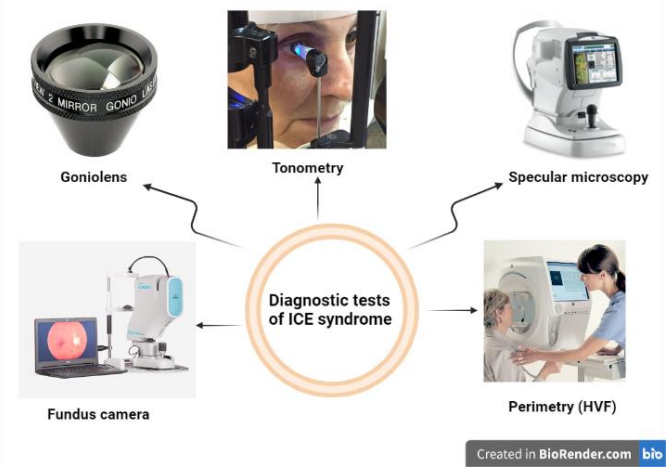

Fig 4: Various diagnostic test of ICE syndrome

Table 1: Reliability of various instruments in ICE syndrome associated with glaucoma.

Instruments name	Parameters measured	Reliability in ICE syndrome
Tonometry	Get the value of the intraocular pressure of the eyeball	Gives the idea of glaucomatous changes
Gonioscopy	Get the value of angle of anterior chamber	Gives the idea of synechiae and/or angle closure glaucoma
Specular microscopy	Visualize and analyze the corneal endothelium	Gives the idea of corneal endothelium conditions (polymorphism & polymegathism)
Fundus camera	Measures the cup disc ratio and disc conditions	Gives the idea of glaucomatous disc cupping
Perimetry	Measures the visual field extension	Gives the idea of visual field i.e. correlated to

		glaucomatous changes or disc damage

II. DIFFERENTIAL DIAGNOSIS OF ICE SYNDROME

1. Posterior polymorphous Dystrophy (PPMD)
2. Fuch's Endothelial dystrophy
3. Peters Anomaly
4. Axenfeld rieger syndrome
5. Iridoschisis
6. Diffuse malignant melanoma of iris
7. Neurofibromatosis
8. Miscellaneous

1. Posterior polymorphous Dystrophy (PPMD):

It is a bilateral, familial disorder of the corneal endothelium. It typically remains asymptomatic until adulthood. The inheritance pattern is usually autosomal dominant.[27-29] There is no race or sex prediction in this condition.

In this condition in the cornea, there will be an appearance of vesicles on the posterior aspect of the cornea at the level of the descemet's membrane. That may be present in linear or groups surrounded by grey haze.

In slit lamp, biomicroscopy, and Specular microscopy two patterns of endothelial are seen. In one there is a localized vascular and 2. Band-like patterns were seen. In the Anterior chamber, there will be broad PAS and anterior Synachae will be seen beyond the Schwalbe line.

2. Fuch's Endothelial dystrophy:

It is a bilateral disorder occurring more commonly in females with onset between 40 to 70 years of age. In this condition, there is a strong familial tendency and an autosomal dominant inheritance pattern has been described.[30]

In Specular microscopy there will be corneal guttata will be seen which is increasing with age. In a slit lamp, the corneal will look the same as ICE syndrome as like beaten silver appearance.

There are no Iris changes in this type of condition. There is a high incidence of Glaucoma in this type of patient due to the high incidence of Axial hypermetropia.

Generally, glaucoma is not present in Fuch's Endothelial dystrophy. If treatment is given that is for reduction of IOP

3. Peters Anomaly:

It is present since birth. It is generally characterized by a central defect in the desert membrane and endothelium with thinning and opacity of the corneal stroma. It may be associated with cataracts and Axenfeld Rieger syndrome. But this condition has many systemic associations. It is multiple malformation syndrome as eye and other extraocular defects including Cleft palate, congenital heart defect, developmental delay, and cleft lip.

4. Axenfeld Rieger syndrome:

Axenfeld anomaly refers to the presence of Posterior embryoxoton on the cornea. Rieger anomaly includes peripheral abnormalities with additional changes of the iris like Correctopia, polycoria, and hole formation. Rieger syndrome includes ocular anomalies with the systemic developmental defect.

ARS is an inherited autosomal dominant trait. It is a present bilateral developmental disorder of the eyes with no gender prediction.

5. Iridoschisis:

This condition, characterized by progressive separation and dissolution of the anterior layers of the iris stroma, is usually bilateral, and tend to occur in the elderly.[31] PIA is usually unilateral, and manifests in young to middle adulthood.

6. Diffuse malignant melanoma of iris:

The iris tends to have a thicker, darker surface with little or no distortion of the pupillary margin. Peripheral anterior synechiae 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.[32]

7. Neurofibromatosis:

The Lisch nodules of neurofibromatosis are flat, larger, lighter colored, and less sharply demarcated from the surrounding stroma. Pupillary distortion and PAS do not occur.[32]

8. Miscellaneous:

Iris melanocytoma can present with signs of CRS, and histopathologic evaluation is needed for proper diagnosis.[33] Iris metastasis from non-small cell lung cancer can also mimic the clinical appearance of CRS.[34] The presence of intraocular inflammation may help differentiate the iris nodules that may be seen in sarcoidosis.[35]

Clinical features:

Cornea shows prominent anteriorly displaced Schwalbe's line. It may just involve the temporal quadrant. The anterior chamber angle is open with few strands bridging the angle from the peripheral iris to the Schwalbe line. The iridocorneal adhesion will be similar in color and texture. Iris has marked atrophy, polycoria band Correctopia. Developmental defects include deformities of teeth and facial bones such as Microdontia and Hypodontia.

Management of ICE syndrome:

Patients with ICE syndrome require treatment for Corneal edema and associated Glaucoma.

In the early stages, drugs that reduce aqueous production are used. Aqueous facilitators are of no use, as the TM is affected. However other pathways may still be targeted.

Prostaglandins may not be advocated, as there is a school of thought that believes the HSV / Epstein Barr virus to be an etiological factor. There have been no reported cases of reactivation of the viral infection.

When the IOP can no longer be controlled medically, surgical intervention is indicated. Laser trabeculoplasty is not effective for this disease, as the angle is affected.

Filtering surgery is reasonably successful, though late failures have occurred because of endothelialization of the filtering bleb & the fact that the surgery is done on relatively young adults, where fibroblastic proliferation is common. . Glaucoma drainage devICE surgery is the surgery of choICE & has proven to be more effective.

Filtering with antimetabolites is successful although late failure may occur because of endothelialization of the filtering bleb. When medical treatment or conventional Filtration surgery is failed then glaucoma drainage is implanted. It appears an effective method for lowering IOP.

Corneal edema can be controlled by the use of Hypertonic saline solutions and soft contact lenses. Irreversible chronic corneal edema requires Penetrating Keratoplasty once if the glaucoma is controlled.[36-37]

Prognosis:

Visual prognosis is better in the ICE syndrome if Glaucomatous changes can be controlled initially. If corneal conditions are not controlled even after controlling IOP then after PK/DSEK visual prognosis is also better if the host body's reaction to the grafting is in the normal range.

After all, I can say we can get approx 70 percent of vision can be saved in this syndrome.

III.CONCLUSION

This review study highlights the complexities associated with managing patients with ICE syndrome. I reached on conclusion that In ICE syndrome there is corneal edema and different level of Iris changes are present. It is generally present in one eye rarely in both eyes are more affected by this condition in comparison to males. Initially, there are no glaucomatous changes in the eyes but after some time 85 % of the patients are diagnosed with ICE syndrome glaucoma.

Corneal edema is tried to control by controlling the eye pressure of the eyeball if not controlled then corneal transplantation is done when IOP is under-controlled. And Glaucoma condition is tried to

control with Topical AGMs, if not controlled then filtration surgery is done. In many patients after Filtration surgery, (Trabeculectomy) if it is not controlled then Valve Implantation is done to control the glaucomatous changes. This study helps to guide the patient and clinician as to which future interventions are chosen.

Abbreviation

- PIA: Progressive iris atrophy
- ICE syndrome: Iridocorneal Endothelial Syndrome
- AGM : Antiglaucoma medication
- GAT: Goldman Applanation tonometer
- PPMD: Posterior polymorphous Dystrophy
- IOP: Intraocular pressure
- PAS: Peripheral Anterior Synachae
- TM: Trabecular meshwork
- HSV: Herpes simplex virus
- ARS : Axenfeld Rieger syndrome
- PK: Penetrating Keratoplasty
- DSEK: Desmet's Membrane Endothelial Keratoplasty

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