Journal of Experimental and Clinical Medicine
https://dergipark.org.tr/omujecm

Review Article

J Exp Clin Med
2025; 42(2): 212-218
doi: 10.52142/omujecm.42.2.16

A comprehensive review on Chandler's syndrome: Pathophysiology, diagnosis, management, and future perspectives

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Received: 17.12.2024 • **Accepted/Published Online:** 27.06.2024 • **Final Version:** 30.06.2025

Abstract

Chandler's Syndrome, a rare subtype of the iridocorneal endothelial (ICE) syndrome spectrum, is marked by corneal endothelial abnormalities, iris atrophy, and secondary glaucoma. This narrative review synthesizes current evidence on its clinical features, pathophysiological mechanisms, diagnostic modalities, and therapeutic approaches. Predominantly affecting middle-aged Caucasian women, Chandler's Syndrome typically presents unilaterally with corneal edema, visual impairment, and subtle iris alterations. Aberrant endothelial cell proliferation and migration lead to peripheral anterior synechiae (PAS), intraocular pressure (IOP) elevation, and progressive corneal decompensation. While the etiology remains incompletely understood, herpes simplex virus (HSV) and Epstein–Barr virus (EBV) have been postulated as potential viral triggers. Morphological changes, including endothelial cell metaplasia and ectopic membrane formation, further impair aqueous humor outflow and corneal transparency. Diagnosis relies on slit-lamp biomicroscopy, specular and confocal microscopy, and ultrasound biomicroscopy (UBM). Accurate differentiation from posterior polymorphous corneal dystrophy (PPCD) and Fuchs' endothelial dystrophy is critical. Management strategies encompass pharmacological IOP control and surgical interventions such as trabeculectomy, glaucoma drainage devices, Descemet stripping endothelial keratoplasty (DSEK), or penetrating keratoplasty (PK). Literature for this review was identified through PubMed, Scopus, and Google Scholar using relevant search terms, with inclusion based on clinical applicability and peer-reviewed validity. Future studies should prioritize elucidation of viral involvement and endothelial pathobiology to guide targeted therapeutic innovations.

Keywords: Chandler syndrome, corneal diseases, Iridocorneal endothelial syndrome, ultrasound biomicroscopy, keratoplasty

1. Introduction

Chandler's Syndrome, a rare variant of iridocorneal endothelial (ICE) syndrome, is characterized by corneal endothelial abnormalities in conjunction with angle and iris changes (1). First described by Chandler in 1956, it is now classified among the three distinct clinical subtypes of ICE syndrome, alongside Essential Iris Atrophy and Cogan-Reese Syndrome (2,3). ICE syndrome constitutes a non-hereditary, proliferative endotheliopathy marked by peripheral anterior synechiae (PAS), elevated intraocular pressure (IOP), and progressive endothelial decompensation (4). Essential Iris Atrophy, in particular, manifests with significant iris alterations, including pupil distortion and stromal thinning, frequently leading to secondary glaucoma due to progressive angle closure (5,6).

ICE syndrome is typically sporadic and predominantly affects Caucasian women aged 20 to 50 years (7). Chandler's Syndrome accounts for approximately 50% of ICE cases and is often associated with prominent corneal edema and comparatively milder iris changes relative to the other subtypes (8). Although the underlying etiology remains undetermined, a viral hypothesis has gained traction, with herpes simplex virus (HSV) and Epstein–Barr virus (EBV) implicated in its pathogenesis. Elevated HSV DNA levels detected in corneal endothelial specimens from affected individuals support this association (9).

Early diagnosis of Chandler's Syndrome is challenging due to minimal iris involvement and variable IOP elevation in the initial stages (8). Differentiation from conditions such as posterior polymorphous corneal dystrophy (PPCD) is critical, given PPCD's typical bilateral, hereditary presentation versus the sporadic, unilateral nature of Chandler's Syndrome (10). Histopathological findings often reveal endothelial cells exhibiting epithelial-like morphology, consistent with aberrant differentiation potentially triggered by viral agents (11).

While ICE syndrome is predominantly unilateral, bilateral involvement has been reported in up to 10% of cases. These bilateral or atypical presentations, including rare occurrences in male patients, challenge the conventional understanding of strict unilaterality (12–20). In Asian populations, structural predispositions—such as narrower anterior chamber angles—

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heighten the risk of primary angle-closure glaucoma (PACG) in the contralateral eye, underscoring the need for vigilant bilateral assessment, particularly among older individuals (21–25).

Current management of Chandler's Syndrome emphasizes IOP regulation and corneal preservation. Surgical options, including penetrating keratoplasty, may be considered in advanced disease, though outcomes are often compromised by graft failure and ongoing endothelial dysfunction (26). Ongoing progress in surgical techniques and exploration of targeted therapies remain essential to improving long-term prognosis. This narrative review consolidates contemporary knowledge on the pathophysiology, clinical spectrum, diagnostic challenges, and therapeutic strategies associated with Chandler's Syndrome. By bridging established clinical data with emerging research, this review aims to assist clinicians in the recognition and comprehensive management of this rare ocular condition, while highlighting key priorities for future investigation.

2. Methodology

This review was conducted using a narrative approach to synthesize and interpret current literature on Chandler's Syndrome, a subtype of iridocorneal endothelial (ICE) syndrome. A comprehensive literature search was performed using electronic databases including PubMed, Scopus, and Google Scholar. The search strategy incorporated a combination of keywords such as "Chandler's Syndrome," "iridocorneal endothelial syndrome," "ICE syndrome," "corneal edema," "glaucoma," "endothelial cell transformation," and "Descemet's membrane." Boolean operators (AND/OR) were used to optimize search combinations.

Articles published in English up to April 2025 were considered for inclusion. Priority was given to peer-reviewed original research articles, clinical studies, review papers, and histopathological reports that provided insight into the epidemiology, pathophysiology, clinical manifestations, diagnostic imaging, and management of Chandler's Syndrome. Case reports, conference abstracts, editorials, and non-English language publications were excluded unless they contributed unique or illustrative information on rare features or variants. Reference lists of key articles were manually screened to identify additional relevant studies.

3. Clinical Manifestations

Chandler's Syndrome typically manifests as unilateral visual disturbances resulting from corneal endothelial dysfunction. Affected individuals often report morning visual haze, reduced visual acuity, and perception of halos, symptoms that are especially prominent upon awakening due to nocturnal corneal fluid accumulation and subsequent light scatter (14, 27–29). These visual phenomena are primarily attributable to corneal edema, with secondary glaucoma playing a lesser role in the initial symptomatic phase. Clinical evaluation reveals subtle iris alterations, which may complicate early diagnosis. Some patients present with changes in pupil morphology, including corectopia, warranting further ophthalmologic assessment (29).

Although mild iris atrophy may be observed, classic features such as full-thickness iris holes—typical of other ICE variants—are infrequently encountered in Chandler's Syndrome (2). The pupils generally retain a round or mildly oval configuration in this subtype. Considerable phenotypic variability characterizes the syndrome. Although classically unilateral, bilateral but asymmetrical involvement has been reported, with one study documenting only two bilateral cases among 21 individuals with ICE syndrome (30). Rarely, overlapping features of two ICE subtypes may coexist within the same patient, further complicating clinical classification and subtype distinction. Slit-lamp biomicroscopy typically reveals key features, including a "hammered-silver" endothelial appearance (Fig.1.) and peripheral anterior synechiae (PAS) (Fig.2.) (8,31). Additional findings may include corneal guttae and stromal iris atrophy, both of which contribute to elevated intraocular pressure over time.

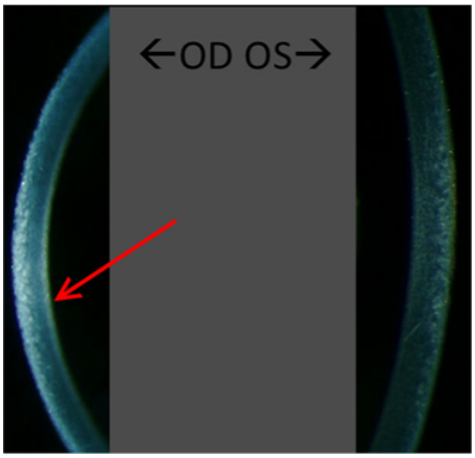

Fig. 1. Slit-lamp photograph showing the characteristic "hammered silver" appearance of the corneal endothelium in Chandler's Syndrome (33)

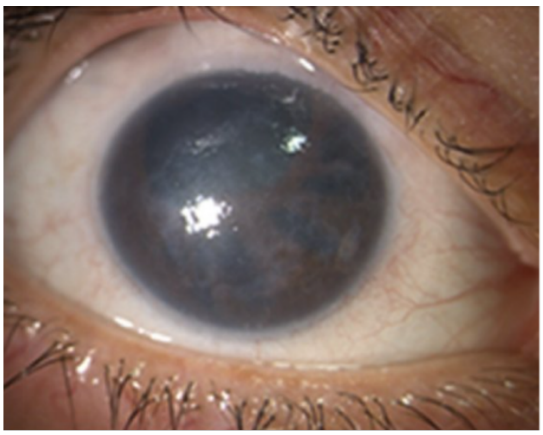

Fig. 2. Moderate corneal edema, polycoria, and peripheral anterior synechiae in a patient with Chandler's Syndrome (40)

Table 1. Comparative analysis of corneal manifestations: Chandlers syndrome vs. ICE subtypes

Chandler's Syndrome	ICE Subtypes
Primary corneal edema with "hammered silver" or "beaten bronze" endothelial appearance (32)	Less prominent corneal edema, may develop secondary to elevated IOP (33)
Bullous keratopathy and corneal endothelial decompensation as predominant features (32)	Corneal changes typically secondary to iris and angle abnormalities (34)
Microcystic edema even at normal intraocular pressures (33)	Corneal pathology usually associated with advanced glaucomatous damage (34)
Corneal thickness increases with decreased endothelial cell density and hexagonal cell ratio (32)	Corneal involvement less severe and often follows iris manifestations (34)

Table 2. Comparative analysis of iris and pupillary abnormalities: Chandlers syndrome vs. ICE subtypes

Chandler's Syndrome	ICE Subtypes
Mild to absent iris changes, minimal iris atrophy (32, 33)	Severe corectopia, iris hole formation, polycoria, ectropion uveae (33)
Minimal pupillary distortion or displacement (33)	Multiple pedunculated nodules on anterior iris surface, heterochromia (35)
Iris findings less common, majority of patients show no iris changes (33)	Robust and progressive iris findings over time (33)
Preservation of iris architecture in early stages (36)	Tan pedunculated nodules with adjacent iris atrophy, ectropion uveae (37)

Table 3. Comparative analysis of glaucomatous manifestations: Chandlers syndrome vs. ICE subtypes

Chandler's Syndrome	ICE Subtypes
Elevated intraocular pressure often presenting feature (36)	Glaucoma development through extensive synechial angle closure (34)
May present with normal pressures initially due to corneal pump dysfunction (33)	Pressure elevation typically follows iris and angle structural changes (35)
Glaucomatous damage may be masked by corneal edema (36)	Visual field defects often correlate with extent of iris atrophy (34)

The diagnosis of Chandler's Syndrome (CS) is frequently delayed due to its characteristically subtle iris changes, which lack the pronounced features observed in progressive iris atrophy or Cogan-Reese syndrome, such as iris holes or nodular formations (32, 38). These mild signs—most commonly corectopia or stromal thinning—are often overlooked during routine slit-lamp evaluations, especially in the early stages of disease (33). Diagnostic uncertainty is further compounded by the typically modest intraocular pressure (IOP) elevations observed in CS. Median IOP values are generally lower than those associated with other ICE subtypes, which may contribute to delayed recognition of glaucomatous progression (38). Moreover, corneal edema—a hallmark clinical feature of CS—does not consistently correlate with IOP levels, potentially leading to underestimation of disease severity and the risk of secondary glaucoma (33, 38). In atypical presentations, including bilateral cases, CS may be misdiagnosed as other ocular conditions such as Fuchs' endothelial dystrophy, herpetic keratouveitis, or developmental anomalies like Axenfeld-Rieger syndrome, further complicating clinical classification (32, 34). These diagnostic challenges highlight the importance of adjunctive imaging modalities. Techniques such as specular and confocal microscopy, along with ultrasound biomicroscopy, are instrumental in detecting endothelial abnormalities and angle membranes that may not be evident with standard examination methods (39).

4. Pathophysiology

The central pathogenic mechanism in Chandler's Syndrome (CS) involves aberrant behavior of corneal endothelial cells, which undergo epithelial-like transformation (33, 40). Transmission electron microscopy has revealed that these transformed endothelial cells develop desmosomes, microvilli, and intracytoplasmic filaments (40, 41). These phenotypically altered cells migrate posteriorly beyond Schwalbe's line, forming a contractile basement membrane that encroaches upon the trabecular meshwork and iris (33, 40), leading to peripheral anterior synechiae (PAS) and secondary angle-closure glaucoma. In contrast to congenital corneal dystrophies, CS is characterized by postnatally acquired endothelial changes, with prenatal Descemet's membrane appearing histologically normal (42). This observation supports a non-congenital pathogenesis that distinguishes CS from conditions such as posterior polymorphous dystrophy (44). Two prevailing hypotheses attempt to explain PAS development in CS: the "Spontaneous Hole Formation Theory," which posits that iris holes facilitate synechiae formation (5, 44), and the "PAS-First Theory," suggesting that PAS formation leads to subsequent pupil distortion (6, 45). Both models attribute anterior segment remodeling to endothelial degeneration and ectopic membrane proliferation (46).

Ultrastructural variability among CS specimens has been noted. Some studies describe attenuated endothelial cells lacking epithelial features (10), whereas others report keratin-positive, filament-rich cells with epithelial-like morphology (41). These findings blur the boundary between CS and posterior polymorphous corneal dystrophy (PPMD) (10, 47). Immunohistochemically, affected endothelial cells stain positively for cytokeratins K7 and KL1 (48), but are negative for glial, vascular, and neuroendocrine markers (49, 50). Early disease stages are characterized by enhanced barrier function and tight junction formation (51), while advanced stages show endothelial necrosis, intercellular gaps, and marked morphometric irregularity (9). A fibrous layer developing

between Descemet's membrane and the endothelium further contributes to corneal opacity and progressive vision impairment. Although CS may clinically resemble Fuchs' endothelial dystrophy, its unilateral presentation and lack of hereditary transmission aid in its distinction (52, 53). Additional ultrastructural markers identified in CS include liposomal junctions and pigment granules (54).

5. Corneal and Iris Endothelial Alterations

Endothelial cell metaplasia in CS results in abnormal collagen synthesis and the formation of a fibrotic, retro-Descemet membrane (55–57). These structural changes contribute to Descemet's membrane lamination, thickening, and progressive corneal decompensation (58). Affected endothelial cells display dynamic, motile phenotypes—characterized by microvilli, ruffled borders, and elongated filopodia—that may reflect a maladaptive reparative response (54, 56, 59). On the iris surface, these ectopic endothelial cells distort anterior segment architecture, thereby facilitating PAS formation and angle narrowing. Resultant obstruction of aqueous humor outflow and elevated intraocular pressure (IOP) contribute to glaucomatous optic neuropathy, in line with the clinical trajectory observed in other ICE syndrome variants (56).

6. Viral Etiology

Polymerase chain reaction (PCR)-based studies have identified herpes simplex virus (HSV) DNA in up to 64% of corneal endothelial specimens from ICE syndrome patients, including those with CS, when compared to control samples (40, 60). HSV DNA has also been detected in aqueous humor, providing further support for viral involvement in the pathogenesis of corneal endothelial metaplasia (60). Electron microscopy corroborates these findings, revealing epithelial-like endothelial features such as desmosomes and microvilli—hallmarks of virus-induced cellular reprogramming (40). While Epstein-Barr virus (EBV) and varicella-zoster virus (VZV) have also been sporadically linked to CS (40, 43, 61), their exact pathogenic roles remain unclear. The typically unilateral and sporadic presentation of CS aligns with a hypothesis of postnatal viral acquisition (40). Despite ongoing speculation regarding viral etiology, no randomized controlled trials have demonstrated therapeutic benefit from antiviral agents in CS. Consequently, antiviral therapy remains investigational at this stage (43).

7. Diagnostic tools and their specific detection capabilities

The diagnosis of Chandler's Syndrome relies on a combination of clinical examination and targeted diagnostic modalities. Slit-lamp biomicroscopy typically reveals diffuse or microcystic corneal edema, which may be present even in the setting of normal intraocular pressure. A hallmark feature is the characteristic "hammered silver" or "beaten bronze" appearance of the corneal endothelium, reflecting abnormal cellular morphology (33, 36). Corectopia, though often subtle, may also be noted. Gonioscopic evaluation is critical, demonstrating broad-based peripheral anterior synechiae (PAS) that extend above Schwalbe's line—considered pathognomonic for ICE syndrome—as well as membrane formation obscuring angle structures (33, 36, 39). Tonometric assessment reveals variable intraocular pressure elevation; although pressure may remain within normal limits during early disease, progressive endothelial dysfunction and angle compromise frequently result in secondary glaucoma (36, 40). These findings underscore the importance of comprehensive anterior segment evaluation in patients presenting with unexplained unilateral corneal edema and iris abnormalities.

Functional and structural assessments play a critical role in evaluating glaucomatous progression in Chandler's Syndrome. Visual field testing may reveal early functional deficits, typically presenting as mild generalized constriction or superior nasal field defects, consistent with glaucomatous optic neuropathy. These changes, though sometimes subtle, provide important evidence of optic nerve compromise (36, 62). Optical coherence tomography (OCT) complements these findings by offering high-resolution structural imaging of the optic nerve head. It enables precise evaluation of optic disc cupping and retinal nerve fiber layer thinning, both of which are indicative of glaucomatous damage (62). Together, these modalities support early detection and longitudinal monitoring of glaucoma in the context of Chandler's Syndrome.

Advancements in ocular imaging technologies have significantly enhanced the diagnostic precision and disease monitoring of Chandler's Syndrome. Techniques such as specular microscopy, confocal microscopy, and ultrasound biomicroscopy (UBM) allow detailed visualization of endothelial abnormalities and anterior segment changes not evident on routine examination (Table 4).

Table 4. Advanced imaging technologies

Diagnostic Tool	Specific Findings in Chandler's Syndrome
Specular Microscopy	Reduced corneal endothelial cell density; light-dark reversal characteristic of ICE; dysmorphic endothelium; "epithelium-like" transformation of corneal endothelium (62, 63).
Confocal Microscopy	"Epithelium-like" transformation of corneal endothelium; irregularly shaped cells with hyperreflective nuclei; ICE-cells visualization on corneal endothelium (39, 40, 64).
Ultrasound Biomicroscopy (UBM)	Membrane extending from corneal endothelium to anterior iris surface causing traction; structural changes of anterior chamber angle; bridge-shaped synechiae; membrane-like mounds in iridocorneal angle (39, 40, 65).
Anterior Segment OCT (AS-OCT)	ICE membrane visualization; differentiation between true PAS and iridocorneal touch; assessment of trabecular meshwork involvement; increased lens vault (66, 67).
Pachymetry	Corneal thickness measurements to assess edema severity (63).

8. Management and Treatment

The initial therapeutic approach in Chandler's Syndrome emphasizes intraocular pressure (IOP) reduction and symptomatic relief, particularly for morning visual haze. Topical hypertonic saline may offer temporary corneal deturgescence, thereby improving visual clarity. First-line pharmacologic agents typically include aqueous humor suppressants, such as beta-blockers (e.g., timolol) and carbonic anhydrase inhibitors (e.g., dorzolamide). While effective in lowering IOP, these agents should be prescribed cautiously, as they may exacerbate underlying corneal edema.

Prostaglandin analogs are generally avoided due to their potential to reactivate latent herpesviruses, a concern supported by virologic hypotheses in Chandler's Syndrome pathogenesis (29). The application of Minimally Invasive Glaucoma Surgery (MIGS) in Chandler's syndrome remains largely unexplored in published literature. Available evidence suggests that Schlemm's canal-based procedures, including Trabectome and iStent devices, are not feasible in most ICE syndrome patients due to continued endothelial membrane proliferation that compromises long-term efficacy (68). Future research should focus on developing novel surgical approaches specifically designed for the unique challenges presented by ICE syndrome variants, as conventional MIGS techniques remain unsuitable for this patient population.

Management of secondary angle-closure glaucoma presents particular challenges, especially in patients with high lens vault and shallow anterior chambers. In such anatomical contexts, phacoemulsification may mitigate non-pupillary block mechanisms that contribute to angle narrowing. Clinical evidence indicates that patients with greater lens vaults experience more substantial postoperative IOP reduction, thereby supporting early lens extraction as a viable strategy in select cases (70-72).

Table 5. Treatment summary

Category	Mild Disease	Moderate Disease	Severe/Refractory Disease
Corneal Edema Management	Topical hypertonic saline drops and ointments (33).	Combination therapy with aqueous suppressants (33).	Endothelial keratoplasty (DSEK/DSAEK) (69).
IOP control	Beta blockers, alpha agonists, carbonic anhydrase inhibitors (33, 40).	Combination topical therapy (40).	Trabeculectomy with antifibrotic agents (33, 68).
Surgical Intervention	Medical management (40).	Trabeculectomy with mitomycin-C (33).	Glaucoma drainage devices (tube shunts) (33, 68).

9. Conclusion

Chandler's Syndrome, a rare and under-recognized variant of the iridocorneal endothelial (ICE) syndrome spectrum, presents distinct diagnostic and management challenges due to its subtle clinical features and progressive nature. Characterized by abnormal endothelial cell behavior, anterior segment remodeling, and secondary glaucoma, its pathophysiology implicates both cellular metaplasia and possible viral triggers. Advances in imaging modalities and surgical techniques have enhanced diagnostic accuracy and therapeutic outcomes; however, delayed diagnosis and treatment failure remain common. Current management remains largely supportive, with no definitive therapies targeting the underlying endothelial dysfunction. Ongoing research into the molecular and virologic basis of the disease is essential to inform targeted interventions. Early recognition, individualized management strategies, and long-term monitoring are critical to preserving visual function and quality of life in affected patients. This review underscores the need for increased clinical awareness and interdisciplinary collaboration to optimize outcomes in this complex and visually debilitating disorder.

Conflict of interest

The authors declared no conflict of interest.

Funding

No funding was used for the study.

Acknowledgments

None to declare.

Authors' contributions

Concept: M.V.K., G.U., Design: M.V.K., G.U., Data Collection or Processing: G.U., M.V.K., A.R., L.K.K., Y.S.R., Analysis or Interpretation: G.U., M.V.K., A.R., L.K.K., Y.S.R., Literature Search: G.U., M.V.K., A.R., L.K.K., Y.S.R., Writing: G.U., M.V.K., A.R., L.K.K., Y.S.R.

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