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Updates on congenital hereditary endothelial dystrophy

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Abstract:

Congenital hereditary endothelial dystrophy (CHED) is a rare genetic corneal disorder causing progressive cornea clouding and significant visual impairment. CHED remains a leading indication for pediatric corneal transplantation despite its infrequency, particularly in regions with high consanguinity rates like Southeast Asia. Identifying the Solute Carrier Family 4 Member 11 (SLC4A11) gene as the genetic basis of CHED has led to the discovery of it's various genetic variations. However, a comprehensive understanding of its clinical-genetic correlation, pathophysiology, and optimal management is ongoing. This review aims to consolidate current knowledge about CHED, covering its genetic origins, pathophysiological mechanisms, clinical presentation, and management strategies. Surgical intervention, such as penetrating keratoplasty (PK), Descemet stripping automated endothelial keratoplasty (DSAEK), and Descemet membrane endothelial keratoplasty (DMEK), remains the primary treatment. DSAEK and DMEK offer advantages over PK, including quicker visual recovery, reduced complications, and longer graft survival, especially in the pediatric age group. The timing of surgical interventions depends on disease severity, age at presentation, comorbidities, and visual potential. Elevated oxidative stress in CHED corneal tissue suggests potential benefits from anti-inflammatory drugs to rescue mutated endothelial cells. Considering the limitations of corneal graft surgeries, exploring novel gene-based molecular therapies are essential for future management. Early diagnosis, appropriate surgical interventions, amblyopia control, and genetic counseling for predictive analysis are pivotal for optimizing CHED management. A multidisciplinary approach involving ophthalmologists, researchers, and genetic counselors is essential for precise diagnosis and optimal care for CHED patients.

Keywords:

Congenital hereditary endothelial dystrophy, corneal endothelial dystrophies in childhood, Solute Carrier Family 4 Member 11 (SLC4A11)

Introduction

Congenital hereditary endothelial dystrophy (CHED) represents a rare form of corneal endothelial dystrophy seen in early infancy or neonatal age and is presented with bilateral symmetrical, slowly progressive corneal cloudiness.[1] Because of its rarity, there is a lack of comprehensive global prevalence data for CHED. However, it is relatively more prevalent in populations with a history of consanguineous marriages.

In addition, in countries such as India and those in the Middle East, CHED is a commonly encountered indication for corneal transplant procedures.[2] CHED was first described by Laurence (1863) as "corneitis interstitialis in utero" and was initially classified as a variant of intrauterine interstitial keratitis and subsequently as stromal dystrophy.[3] In 1960, Maumenee[4] hypothesized that CHED results from a primary dysfunction of the corneal endothelium. Histopathology and electron microscopy data from different studies later confirmed this theory.[5]

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Genetics

Initially, CHED comprised two genetic variants: CHED1 (autosomal dominant) and CHED2 (autosomal recessive) linked to a 2.7 centimorgan (cM) interval within large 30 cM posterior polymorphous corneal dystrophy (PPCD) locus on chromosome 20. Later studies excluded CHED2 from the region containing CHED1 and positioned it between two markers D20S113 and D20S882 at 8 cM interval on chromosome 20p13.[6] Eventually, in a study by Vithana *et al*., CHED2 locus was delineated to a 2.2 Mb region comprising 30 genes and among them, Solute Carrier Family 4 Member 11 (SLC4A11) was identified as the prospective candidate gene for CHED2[7] [Figure 1]. In the present International Classification of Corneal Dystrophies (IC3D),[8] CHED1 has been excluded and reclassified as a type of PPCD or posterior polymorphous dystrophy (PPMD) while CHED2 is referred as CHED.

More than 100 variations in SLC4A11 have been identified as the genetic cause for CHED.[9] These variations are typically inherited in an autosomal recessive pattern and manifest in affected individuals either in a homozygous or compound heterozygous state. These variations include missense, indels, splice-site, nonsense, and frameshift variations, distributed across the entire structure of SLC4A11. Supplementary Table 1 lists the chronological identification of these variations in different studies.[7,9-32] The pathogenic nature of these identified variations was established based on their exclusive presence in affected members and absence from a large number of ethnic healthy control screened, followed by *in silico* and *in vitro* analysis in few studies. Many of these SLC4A11 variations seem to affect protein folding, and their localization.[33] In addition, experiments with SLC4A11 knockout (KO) mice presenting CHED phenotype have affirmed SLC4A11's role in CHED development.[34] Overall, the involvement of SLC4A11 variations in the CHED phenotype has been firmly established, and the range of these variations continue to expand.

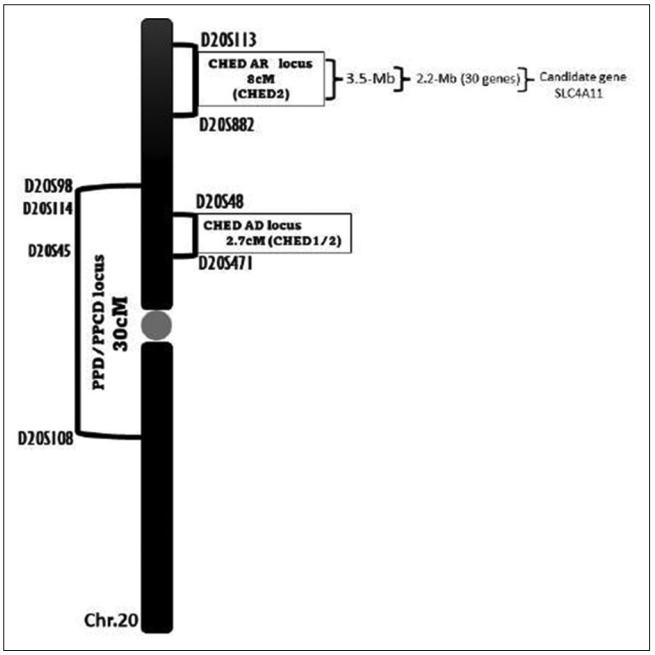

Figure 1: Congenital hereditary endothelial dystrophy 1 (CHED1) autosomal dominant and CHED2 autosomal recessive initially linked to a 2.7 centimorgan (cM) interval on chromosome 20. CHED 2 locus was excluded later and positioned between markers D20S113 and D20S882 within an 8 cM interval on chr. 20p13, and further delineated to identify Solute Carrier Family 4 Member 11 as a candidate gene

SLC4A11 variations are associated with a small subset of Fuchs endothelial corneal dystrophy (FECD) patients. In a study of 89 FECD patients, four had SLC4A11 variations, and a similar pattern was observed in 7 out of 192 late-onset FECD cases.[14,19] In addition, CHED carrier parents displayed milder FECD symptoms in few studies, indicating the contribution of one copy of the SLC4A11 mutant allele to a less severe FECD phenotype.[25]

SLC4A11 variations are also linked to Harboyan syndrome, a condition resembling CHED and featuring neurosensory hearing loss.[35] In a cohort of 21 Iranian patients, 16 exhibited symptoms of corneal dystrophy with perceptive deafness, while four had CD without deafness referring CHED cases. Notably, in one CHED patient having the absence of SLC4A11 variation, a novel variation in multiple PDZ domain protein (MPDZ) was discovered, suggesting its potential involvement in the CHED phenotype.[24] Considering this, several CHED cases where SLC4A11 variations remain undiscovered the MPDZ involvement needs to be explored.

Developmental Origin

The embryonic development of anterior segment comprises of separation of the lens vesicle from the surface ectoderm, followed by the three waves of neural crest cell migration starting from 6 to 8 weeks of gestation to form the corneal endothelium and trabecular meshwork, corneal stroma, and iris stroma in wave 1, 2, and 3, respectively. After 12 weeks of gestation, the corneal endothelium produces Descemet membrane (DM) composed of an anterior banded zone, produced before the 5th month of gestation and a posterior nonbanded zone produced later. CHED, which characteristically has a normal anterior banded zone and an abnormal posterior nonbanded zone, is postulated to arise from an abnormality in neural crest cell terminal differentiation, manifested by degeneration of corneal endothelial cells after the synthesis of a normal anterior banded zone in the 5th month of gestation.[36]

Pathophysiology

Although the genetic basis for majority of CHED is known due to the SLC4A11 gene, its pathophysiology is still explorative. The exact function of SLC4A11 in human cornea is not yet clear. The initial *in vitro* studies on SLC4A11 indicated its role in Na+ and H+ (or OH−) transport and NH4+ permeability. Other studies showed that it can also enhance cellular water permeability, acting as an aquaporin.[37] On the other hand, the borate transporter activity of SLC4A11 is controversial.[38] The more likely role of SLC4A11 in corneal endothelial cells is to regulate the transport of fluid and electrolytes and modulate intracellular pH, volume, and membrane potential in cornea. Variations in the SLC4A11 gene lead to reduced activity or quantity or availability of the SLC4A11 protein, which disrupts the normal ion and water balance in the cornea resulting the accumulation of excess fluid in the corneal stroma, leading to corneal edema and opacification.

Oxidative stress in congenital hereditary endothelial dystrophy

Oxidative stress has been found to exert an important role in degeneration and apoptosis of corneal endothelial cells. Corneal endothelium in general is more prone to oxidative stress due to high exposure to sunlight, increased metabolic activity and postmitotic arrest.[39,40] Most of the *SLC4A11* variations associated with CHED makes the protein incapable of transit from endoplasmic reticulum (ER) to its location at the cell surface.

Cytoplasmic retention of mutated SLC4A11 protein results in higher levels of reactive oxygen species (ROS) and increase cellular stress. Guha *et al*. showed that si-RNA mediated SLC4A11 knockdown in a human corneal endothelial cell line result in elevated ROS levels, changes in mitochondrial membrane potential, and a compromised nuclear factor erythroid 2-related factor 2 (NRF2) driven antioxidant signalling pathway. Intriguingly, CHED corneal tissue specimens collected from patients also displayed indications of oxidative stress and a diminished NRF2-mediated antioxidant response.[41] These suggest a possibly increased oxidative environment in aqueous humour and corneal tissues of CHED patients. HEK293 cells expressing mutant SLC4A11 has also been found to be more prone to oxidative insults with increased generation of ROS and reduced mitochondrial activity. Recent studies using CHED model of SLC4A11 KO mice have revealed that glutamine-induced mitochondrial dysfunction plays a substantial role in causing oxidative stress, impaired lysosomal function, aberrant autophagy, and cell death in corneal endothelial cells along with ER stress.[42] In another study employing a SLC4A11 KO mouse model unveiled that within the corneal endothelium of these mice, autophagy was activated but exhibited dysfunction, leading to abnormal autophagy flux, impaired lysosomal function, along with reduced TFEB (transcription factor EB) nuclear translocation as a contributing factor for it.[43]

To relieve the stress that occurs due to retainment of misfolded SLC4A11 in the ER, attempts have been made to ameliorate folding defects using nonsteroidal anti-inflammatory drugs (NSAIDs) as a therapeutic approach. A study by Chiu *et al*.[44] conducted a high throughput assay and identified Glafenine and perhaps other NSAIDs in rescuing trafficking defects of some SLC4A11 mutants. In another study, several commonly available ophthalmic NSAIDs were tested in HEK293 cells expressing various variants of SLC4A11. Using bioluminescence resonance energy transfer assay, it was found that treatment of ophthalmic NSAID like nepafenac at concentration 64 μM and diclofenac at concentration 0.6–1 μM significantly increased surface abundance of protein in most of the tested SLC4A11 mutants and enhanced water flux activity in mutants like SLC4A11-G709E and SLC4A11-E143K.[45] Therefore, ophthalmic NSAIDs in the form of eye drops hold potential for useful therapy to treat CHED patients.

Histopathology

Light microscopy

Histopathological studies of corneal buttons of CHED collected posttransplantation show all the corneal layers involvement. The stratified squamous epithelium of the cornea exhibits diffuse edema, predominantly in the basal cells, where it manifests as hydropic degeneration characterized by the accumulation of fluid within the cells, resulting in cytoplasmic vacuolation. In the late stage of CHED, this edema leads to subepithelial bullae formation. Bowman membrane (BM) is initially intact, but when edema progresses, it either breaks or gets fragmented. At the stromal level, changes that appear due to edema results in reduced staining (less pink color in hematoxylin and Eosin stain) and there is a partial or complete loss of lamellar arrangement of collagen fibers depending on the early or late stage of CHED. DM appears intact, thickened, and laminated on histopathology due to abnormal and accelerated secretion by the scarce, irregular, degenerated, atrophic, and/or multinucleated endothelial cells[46] [Figure 2].

Transmission electron microscopy

Multiple layers of basement membrane-like material on the posterior part of the DM, degeneration of endothelial cells with many vacuoles, and stromal thickening with severe disorganization and disruption of the lamellar pattern can be noted.[47,48] The changes in the epithelial layer are secondary to chronic corneal edema. The epithelium thickens in CHED, increases

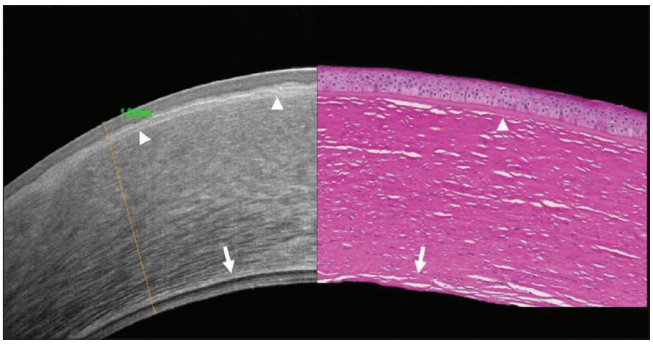

Figure 2: Histopathological image of hematoxylin and eosin stained corneal button of congenital hereditary endothelial dystrophy patient, post penetrating keratoplasty (right) and comparison to its anterior segment optical coherence tomography image (left). Image showing involvement of all layers with fragmentation noted at the Bowman membrane (white arrow head) and thickened Descemet membrane (white arrow)

from 5 to 15 cell layers. Intracellular or intercellular edema occurs, especially in the basal epithelium.[49] Due to the presence of fluid clefts and vacuoles, the basal epithelium tends to separate from the underlying BM which in turn shows irregularity due to areas of partial loss and disruption along with surrounding areas of thickening. Stroma might have homogeneous granular materials with fluid pockets between the stromal collagen fibrils, resulting in marked thickening of the stroma and severely disorganized lamella. This causes abnormal refraction of light leading to a ground-glass appearance. Stromal inflammation and vascularization are usually not found. There is often a reduced endothelial density in the central cornea, while the peripheral cornea in CHED has a relatively normal density and appearance. In the transition zone, cells are irregularly shaped, with pleomorphism and polymegethism. The characteristic endothelial hexagonal pattern is disrupted in CHED, and there may be the presence of multinucleated cells. However, unlike Fuchs' dystrophy, CHED does not exhibit guttae.

Clinical Presentation

CHED is characterized by bilateral diffuse, noninflammatory corneal cloudiness with edema. In general, a family history may be positive for CHED, and consanguineous parents increase a neonate's risk of being born with it. The clinical picture can vary from mild haziness to a moderately severe, diffuse, homogeneous, gray-white, ground-glass appearance that involves the entire cornea from limbus to limbus. Corneal clouding is typically present at birth or within the neonatal period. Corneal opacification is usually dense at the time of diagnosis and generally stationary but may show slow progression with the development of secondary changes. There is no associated photophobia or epiphora. Nystagmus is commonly present, presumably due to severe corneal opacification at an early age.[50,51] Subepithelial amyloid deposits resembling gelatinous drop-like dystrophy have been reported in CHED2.[52] Painful epithelial erosion rarely occurs in CHED. Fine epithelial edema creates a roughened corneal surface and distorted light reflex. Corneal sensation remains intact. The corneal thickness increases 2-3 times than usual, but the corneal diameter remains unchanged. The intraocular pressure may show a falsely high value due to the enlarged corneal thickness. DM is generally thickened with the changes in the composition [Figure 2].

Congenital Corneal Opacity and Differential Diagnosis

Cases of CHED can easily be mistaken for conditions that present as congenital corneal opacity (CCO). These may result from hereditary, developmental, infectious, or metabolic causes. They can be bilateral and seen in isolation or association with other ocular or systemic abnormalities. The prevalence of CCO is approximately 3:100,000 new-borns, increasing to 6:100,000 if congenital glaucoma is included.[53] Conventionally, these have been classified by the mnemonic "STUMPED."[54] However, this classification did not give much perspective regarding pathogenesis, surgical intervention, and prognosis. Nischal *et al*. proposed another classification where CCO can be primary or secondary.[55] Primary CCO consists of corneal dystrophies and choristomas presenting at birth while secondary CCO includes kerato-irido-lenticular dysgenesis or other causes such as infection, iatrogenic, or developmental anomalies. It is very important for an ophthalmologist to diagnose these conditions accurately, predict the natural history of the disorder, look for associated ocular and systemic abnormalities, provide genetic counseling, and promptly begin appropriate medical or surgical therapy. Timely and prompt intervention is essential to prevent the development of amblyopia resulting from visual deprivation in these conditions.

Most CCO can be differentiated from CHED due to their characteristic clinical presentation; however, in certain CCO conditions, a thorough knowledge of the pathogenesis, clinical presentation and aid from diagnostics and histopathology might be needed to differentiate them. Some of the common mimickers include primary congenital glaucoma (PCG), corneal changes due to birth trauma, X-linked endothelial corneal dystrophy (XECD), PPMD, congenital hereditary stromal dystrophy (CHSD), and mucopolysaccharidosis (MPS) [Figure 3]. Examining specific parameters can provide valuable insight for differentiation among birth trauma, congenital glaucoma, and CHED [Table 1].

Primary congenital glaucoma

PCG is generally discovered at birth or in the 1st months of life. The classic triad of epiphora, photophobia,

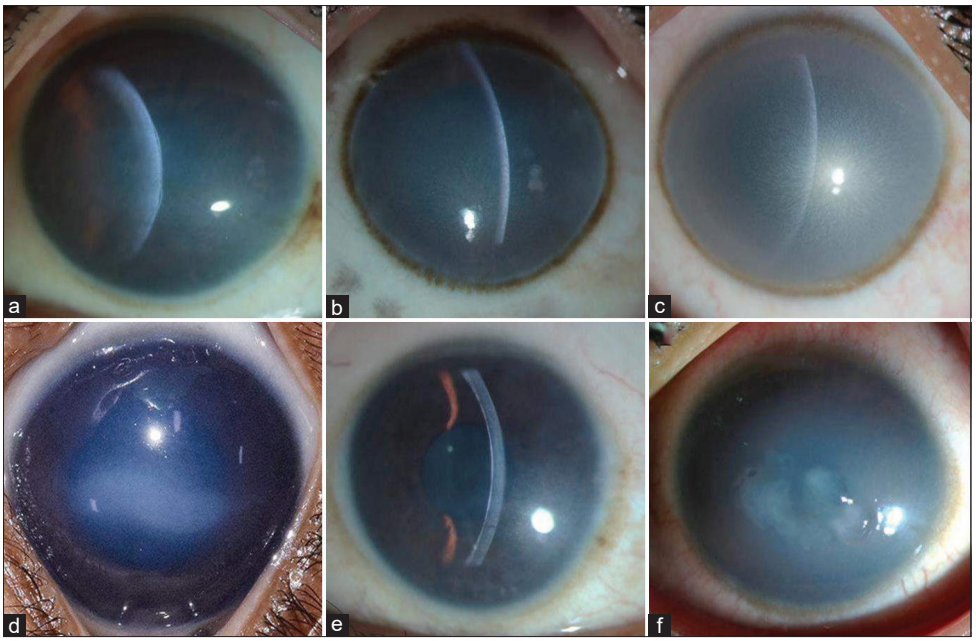

Figure 3: Slit lamp photographs. (a) Congenital hereditary endothelial dystrophy (CHED) with grey-white ground glass corneal opacity, (b) mucopolysaccharidosis Type IH (Hurler's syndrome) with normal corneal thickness as seen on the slit beam, (c) Congenital hereditary stromal dystrophy with corneal opacity and a normal epithelium, (d) Primary congenital glaucoma with large horizontal corneal diameter and presence of Haab's stria, (e) Posterior polymorphous corneal dystrophy (PPCD) showing thickening and opacity at Descemet membrane and endothelial layer, (f) CHED with large central epithelial bulla

Table 1: Differentiating points between corneal changes due to birth trauma, congenital glaucoma, and CHED

Birth trauma	Congenital glaucoma	CHED
Normal IOP	High IOP	Usually, normal IOP
Normal corneal diameter	Large corneal diameter with buphthalmos	Normal corneal diameter
Corneal edema in the immediate postpartum period	Corneal edema weeks or months after birth	Corneal edema since birth/ immediate neonatal period
Vertical or oblique tears in DM	Horizontal or concentric to limbal tears	-
Left eye predominantly affected	No preference	Usually, bilateral
Usually, no photophobia	Photophobia	-

CHED=Congenital hereditary endothelial dystrophy, IOP=Intraocular pressure, DM=Descemet membrane

and blepharospasm is most common presentation of PCG. Characteristic signs of PCG include bluish corneal discoloration, Haab's striae, increased corneal diameter (megalocornea), limbal stretching, blue sclera due to pan ocular enlargement, buphthalmos, elevated intra ocular pressure (IOP), and optic nerve head changes.[56]

X-linked endothelial corneal dystrophy

XECD is very rare form of X-linked posterior CD,[57] affecting predominantly males. Females are generally asymptomatic with endothelial changes similar to moon craters seen on retro-illumination. In addition to these features, males can present with congenital corneal cloudiness that later progresses to sub-epithelial band keratopathy with or without nystagmus and reduced visual acuity. IOP is usually normal and there is no evidence of peripheral irido-corneal adhesions, unlike PPCD or CHED. DM may occasionally show presence of small excavation/pits, besides having an abnormal anterior banded zone with the absence of a posterior non-banded zone.

Posterior polymorphous corneal dystrophy

PPCD is an autosomal dominant disorder, generally asymptomatic, slowly progressive, and usually bilateral but asymmetric. It involves the epithelization of endothelial cells. Manifestations of this condition can be highly variable. It can present rarely as congenital corneal clouding; however, most patients are asymptomatic, presenting as an incidental finding.[58] Slit-lamp findings include opacities of DM and endothelium with a characteristic vesicular, band-like or diffuse pattern.

Congenital hereditary stromal dystrophy

CHSD is a rare, autosomal dominant inheritance with diffuse cornea clouding from limbus to limbus, with flake-like opacities in the stroma. There is no vascularization or staining of the cornea. Pachymetry demonstrates increased stromal thickness. Epithelium and endothelium are normal, as seen by electron microscopy and confocal microscopy, although an absence of anterior banded zone of DM has been reported.[8]

Mucopolysaccharidosis

MPS are the heterogeneous group of lysosomal storage disorders caused by the intra and extracellular abnormal glycosaminoglycans accumulation. These may present with corneal opacity in the neonatal or later period. In some types, corneal opacity develops within a few weeks to months of birth, raising the differential for congenital glaucoma and CHED. These include the MPS IH [Hurler's Syndrome – Figure 4b-d], MPS IS (Scheie Syndrome), and some cases of MPS VI (Maroteaux-Lamy Syndrome). One must look for systemic features like – dwarfism, facial, skeletal abnormalities, hepatosplenomegaly or mental retardation for differential diagnosis. Further, diagnosis can be confirmed by measuring the affected enzyme in peripheral leukocytes, cultured dermal fibroblasts, or amniotic cells.[59] Other metabolic conditions that can also have an early presentation of corneal cloudiness include GM1 gangliosidosis Type I, mucolipidosis Type IV, and mild opacity in Type II.[60]

Investigations

Pachymetry

CHED cases show 2–3 times increase in corneal thickness compared to age-related normal corneas. Grading the corneal haze in cases of CHED has always been subjective due to less objective methods available.

Slit-lamp evaluation

Subjective grading of the corneal cloudiness can be done based-on slit-lamp examination. The cornea shows ground glass appearance with slit beam indicating increased corneal thickness [Figure 4a]. A study by Ramappa *et al*.[61] graded corneal clouding in CHED based on the visibility of iris structures and presence or absence of anterior stromal scarring, referred to as Mild – where minimal corneal cloudiness did not obscure iris details, Moderate – where obscured iris details were obscured but pupillary silhouette remained visible, and severe - where both iris and pupillary details were obscured. Furthermore, this grading[62] conventionally has been done as:

- Grade 0-No haze
- Grade 1-Iris details visible (mild)
- Grade 2-Pupil margin visible; iris details not visible (moderate)
- Grade 3-Pupil margin not visible (severe)
- Grade 4-Opaque cornea.

The subjective corneal grading into mild, moderate, and severe types is shown in Figure 5.

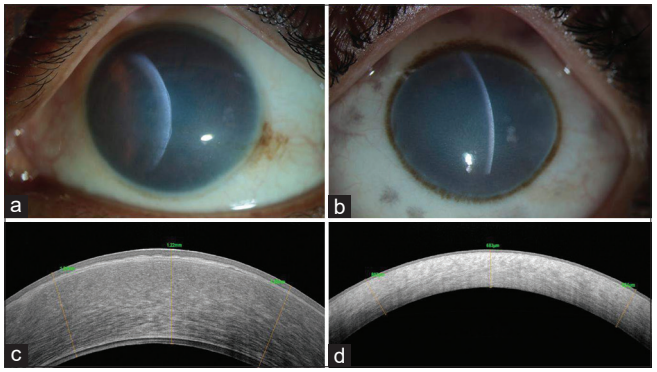

Figure 4: Shows the slit-lamp biomicroscopy photographs. (a) Congenital hereditary endothelial dystrophy (CHED) with the ground-glass appearance of the cornea with the slit beam suggestive of increased corneal thickness, (b) Mucopolysaccharidosis Type IH (Hurler's Syndrome) with corneal cloudiness with slit beam suggesting a normal corneal thickness, (c) Anterior segment optical coherence tomography showing CHED with a thickened epithelial layer with underlying irregular Bowman membrane, increased stromal thickness, and abnormally thickened Descemet membrane, (d) Hurler's syndrome with a thickened corneal stromal layers and hyperreflective stroma

Densitometry using Scheimpflug imaging

Corneal densitometry uses the Scheimpflug imaging principle to measure the reflectance. The reflectance measures the light reflected back from a surface or film. Using this principle with the Pentacam (Oculus), one can measure or quantify the reflectance or backscatter of the cornea.[63] The uniform organization of collagen fibers is responsible for a normal cornea to be optically transparent. However, any imbalance can lead to cornea swelling, which can be reflected as an increase in the reflectance of the cornea on Scheimpflug imaging [Figure 5]. The densitometry values show a remarkable difference compared to the post-surgical value in these cases. Thus, the densitometry measurement standardizes from 0 to 100 grayscale units, defining a minimum light scatter of

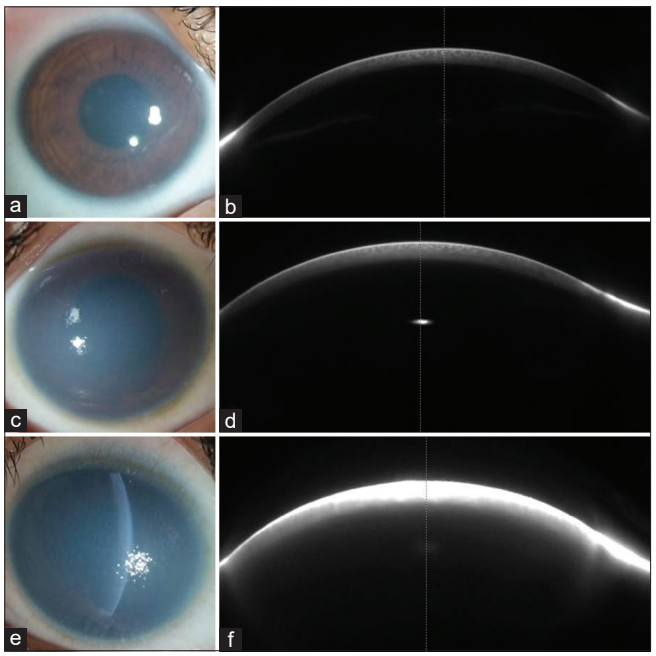

Figure 5: Subjective grading of corneal cloudiness into (a), mild (c), moderate (e) severe; with corresponding densitometry shown, respectively, in images labelled as (b, d and f)

0 (maximum transparency) and a maximum light scatter of 100 (minimum transparency).

Anterior segment optical coherence tomography

Anterior segment optical coherence tomography (AS-OCT) in CHED shows a generalized increase in corneal thickness [Figure 4c]. There is a thickened epithelial layer with an underlying irregular BM, increased stromal thickness, and abnormally thickened and hypo-reflective DM. Light backscattering can also be studied using AS-OCT to estimate corneal transparency objectively.[64]

Management

It has always been a challenge to decide the most appropriate strategy to deal with the corneal cloudiness in CHED. Due to a lack of a definitive conservative approach, the current definitive treatment modality available includes the various forms of corneal transplantation, with their various limitations and challenges related to the long-term well-being of CHED affected children. The options for providing a clear optical axis in these children include conventional full-thickness penetrating keratoplasty (PK),[65] Descemet stripping automated endothelial keratoplasty (DSAEK),[66] and DM endothelial keratoplasty (DMEK).[67]

Penetrating keratoplasty

PK has long been the standard of treatment for children with CHED, but the decision to proceed with PK is complex owing to the challenges of pediatric PK and the threat of amblyopia. Pediatric PK presents unique preoperative, intraoperative, and postoperative issues that must be addressed. Preoperatively, the timing and risk-benefit ratio of surgery must be considered. Assessment of the degree of visual impairment is difficult in the preverbal child, and some children with mild CHED may have reasonably good vision without surgical intervention.[68] The correct timing for surgical intervention is still unclear. Sajjadi *et al*.[69] have recommended waiting until strabismus or nystagmus develops before attempting surgical intervention in CHED. Others have suggested earlier intervention, as a delay in surgery increases the risk of amblyopia to set in. Thus, it is a trade-off between amblyopia prevention versus attempt to gain better graft survival.[70,71] Considering the timing of surgical intervention in CHED, there is a trend toward early intervention.

Intraoperative challenges in PK for CHED in younger age groups include managing the low scleral rigidity and the tendency for anterior rotation of the lens-iris diaphragm that predisposes to shallowing of the anterior chamber, peripheral anterior synechiae (PAS) formation, iris incarceration in the wound, endothelial trauma, glaucoma, and expulsion of intraocular contents due to an "open to sky" procedure. Furthermore, there is a high demand for postoperative care. Pediatric patients have a tendency for a rapid and severe inflammatory response, predisposing to graft rejection, PAS formation, glaucoma, and cataract.[72] Robust wound healing may result in corneal neovascularization, uneven contraction of tissue, early loosening of sutures, irregular astigmatism, overriding of graft tissue with poor epithelialization, and ulceration. Frequent, often monthly, examinations under anesthesia and vigilant parental or caregiver observation for signs of rejection are important for early detection of graft rejection and suture-related complications. In addition, after surgery, a full-thickness corneal wound is at higher risk of traumatic rupture in children than adults, given the unpredictable nature of their daily activities. For these reasons, surgery has often been avoided or delayed for as long as possible, not only in eyes with severe anterior segment abnormalities (e.g., Peter's anomaly) but also in eyes with relatively normal anatomy, such as those affected by CHED.[73]

A retrospective study comparing data of PK done between the years of 1978 and 2013 at the Royal Victoria eye and ear hospital, reported a poor outcome in the Irish cohort with a mean graft survival rate of 36% after a follow-up of 101 months.[74] However, earlier studies have shown a better graft survival rate in cases undergoing pediatric PK in CHED,[74-77] as shown in Table 2.

Descemet stripping automated endothelial keratoplasty

In DSAEK, the surgeon uses a "closed-system" technique throughout the procedure and performs all manoeuvres through a short, clear cornea tunnel. Vision-threatening intraoperative complications, particularly suprachoroidal haemorrhage, are extremely rare and more easily manageable.[78,79] Also, the structural integrity of the globe is maintained closer to the natural state, and postoperative wound dehiscence is less frequent and, in any case, unlikely to compromise visual outcome. Today, DSAEK has become the treatment of choice in adults as well as children, with corneal endothelial disease of various origins (Fuchs dystrophy, postsurgical endothelial decompensation, graft failure). The benefits of endothelial transplantation procedures such as DSAEK over conventional PKP include faster visual rehabilitation,[80] fewer sutures related complications, and a structurally stronger globe. These benefits are especially desirable in the pediatric age group. The main challenge in DSAEK is due to difficult DM removal and poor view. Some surgeons modify the DSAEK procedure for patients with CHED and elect not to strip the DM of the infant host and instead directly attach the donor graft to the posterior surface

Table 2: Comparative summary of the results of penetrating keratoplasty in patients with congenital hereditary endothelial dystrophy (adapted from AlArrayedh *et al.*)[74]

Studies	Number of patients/ eyes	Age at surgery	Follow-up period/graft clarity rates	2-year graft survival rate (%)	Percentage postoperative VA ≥20/80
Kirkness *et al.*[75]	20/31	Mean 13.5 (2 months–60 years) Median between 10 and 15 years	39 months/84%	-	77
Sajjadi *et al.*[69]	21/37	Mean 9.5 (2–30 years)	36 months/92%	-	78
Al-Rajhi and Wagoner[71]	40/56	Mean 11.8±7.7 years (2 months–35 years)	37.1±34.2 months/62.5%	72	21
Schaumberg *et al.*[70]	9/16	Mean 42.3±35.7 months (3–120 months)	70.6±73.4 months/69%	71	25
Javadi *et al.*[76]	15/24	Mean 8.1±2.5 years (3.5–12 years)	35.5±36.2 months/79.1%	88	52.6
Özdemir *et al.*[77]	24/47	Mean 26.4±3.1 years (15–46 years)	101±39 months/78.7%	89.3	83
	11/18	Mean 7.6±3.1 years (2–12 years)	59.7±27 months/50%	61.1	28
AlArrayedh H *et al.*[74]	14/24	Mean 22.9 (5–52 years)	101 months	37.50	17

of the cornea. This method is associated with overall good long-term outcomes.[81,82] One case series has suggested steps to ensure intraoperative adhesion, such as a 15-min corneal massage, large anterior chamber air bubble, possible venting incision, and additional days with postoperative eye shield.[83,84] A case series reported the outcomes of DSAEK performed in 30 phakic eyes of 16 pediatric patients with CHED in different age groups.[85] The visual outcomes of this case series were encouraging. The average BCVA was logMAR 0.32 in the infant group and logMAR 0.54 in the child group. The postoperative BCVA in 33% of eyes in the child group and 86% of eyes in the infant group had achieved logMAR 0.4 or better. Patients in the infant group had statistically better results regarding postoperative BCVA than those in the child group, possibly due to relieving form deprivation and beginning amblyopia treatment at a younger age.

A recent study by Ramappa *et al.*[61] compared the paediatric DSAEKs performed between 2008 and 2020. CHED, the most common indication for pediatric DSAEK, had a long-term graft survival probability of 97%, 95%, 90%, and 90% at 1, 3, 5, and 7 years, respectively. This suggests that CHED with no prior interventions is likely to influence long-term graft survival positively. In conclusion, DSAEK provides superior long-term clinical outcomes with low complication rates suggesting that it is safe and effective surgical alternative in children with corneal endothelial disease.

Descemet membrane endothelial keratoplasty

This is another EK procedure, where the graft is prepared by manually stripping the DM from the donor cornea. The graft is extremely fragile and thin, has a propensity to rolls up and can be inserted via a smaller incision than used in DSAEK. Contrary to DSAEK, the DMEK graft has no stromal layer, which avoids incompatible convergence of the host and donor stromal fibers. Also, DMEK has shown to provide better results and less long-term graft rejection as compared to DSAEK and PK.[86-88] However, there are very few reports of outcomes of DMEK in cases of CHED. A retrospective study by Saad *et al.*,[89] compared DMEK performed in 14 eyes of CHED, showing that 13/14 eyes maintained a clear cornea at final follow-up (mean, 16.9 ± 8.1 months). Following surgery, corrected distance visual acuity improved from 0.9 ± 0.3 log MAR (Snellen 20/158) to 0.4 ± 0.2 (20/50). Thus, DMEK provided good visual outcome. However, the procedure is surgically demanding and more challenging to manage among infants.

Thus, based on the above studies, we can conclude that while PK can provide a pristine clear graft in cases of CHED, DSAEK outscore PK by offering better long-term outcomes, negligible postoperative complications and expedited visual recovery. A study published by Mehta *et al.*[90] proposed an algorithm by dividing the CHED cases based on anterior segment visibility and presence of secondary corneal changes in deciding the most appropriate medical and or surgical modality for cases of CHED. Considering this, mild cases could see improvements with suitable optical correction, intermittent patching, and potential use of NSAIDs. Moderate cases may find greater benefit from undergoing DSAEK at an early stage, while severe cases with secondary changes such as anterior or posterior scarring and band-shaped keratopathy could benefit from planning a PK.

Although keratoplasty is the mainstay of treatment for patients with CHED, amblyopia management and genetic counselling are also very crucial in the visual rehabilitation of children with CHED. Amblyopia management should be as aggressive as possible with prompt refractive correction and patching therapy directed under the expert guidance of a pediatric ophthalmologist. Without successful treatment of amblyopia, the visual outcome is poor despite a clear medium. Along with this, it is necessary for genetic counseling of the patient and to explain that the risk of having a sibling with CHED is 25% and the risk of the patient having affected offspring is very low provided the patient avoids consanguineous marriages.[53]

Future possibilities in the management

Though surgical intervention of CHED has improved its techniques, and consequently survival rate, these procedures face the challenges of scarcity of donor corneas, allograft rejection, graft failure, post-surgical complications, and recurrence of primary pathology. In this regard, the emerging molecular therapies such as gene therapy or gene editing could be a better alternative. These therapies can resolve the genetic origin of the disease and therefore have the potential to provide a better, reliable, simple, and affordable therapeutic regime.[91] As a genome-editing tool, Clustered regularly interspaced short palindromic repeats-Cas protein (CRISPR-Cas) system provides a suitable therapeutic approach. Its ability to target genome editing and the potential for topical and nonrepetitive administration make it a more suitable technique for treating CDs like CHED. Few *in vitro* and *in vivo* studies have demonstrated the potential of CRISPR in rectifying the genetic foundation of CDs. For example, a Japanese study used CRISPR to correct a common TGFBI (transforming growth factor beta induced) mutation in human corneal cells with no negative effects.[92] Another study used CRISPR to create a new transgenic mouse model of human Lattice CD by incorporating a specific mutation.[93] In another remarkable study, in a mouse model of FECD, viral-mediated delivery of CRISPR was used to knock down a mutant COL8A2 (Collagen Type VIII Alpha 2 Chain) gene, which showed recovery in diseased features.[94] CRISPR as a therapeutic strategy has been evincing hope in a few clinical trials, and its delivery methods are getting rationalized. Recently, new advancement in CRISPR technology has been developed known as exon replacement, which uses CRISPR to replace a specific exon with its counterpart.[95] Such advancement can offer a generalized approach for a personalized gene editing approach. Continuing research to unravel the genetic underpinnings of CHED and adopting a personalized approach to its treatment hold the promise of developing more effective therapies. These efforts could significantly enhance the management of CHED and similar disorders, ultimately benefiting patients by providing tailored and targeted interventions.

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Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consents for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

Data availability statement

The data sets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Conflicts of interest

The authors declare that there are no conflicts of interests of this paper.

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Supplementary Table 1: Chronological list of identified solute carrier family 4 member 11 variations

Variations	AA change	Ethnic origin of patient	Clinical phenotype	References
c. 2264G>A	p.Arg755Gln	Myanmar	CHED2	Vithana *et al*., 2006[7]
c. 1466C>T	p.Ser489Leu	Pakistan	CHED2	
c. 1391G>A	p.Gly464Asp	Pakistan	CHED2	
c. 1813C>T	p.Arg605X	India	CHED2	
c. 353_356delAGAA	Frameshift	India	CHED2	
c2605C>T	p.Arg869Cys	India	CHED2	
IVS15-6_-16 del insggccggccgg	Splice site	India	CHED2	
g. 2943delTTinsA	p. Arg82ArgfsX33	India	CHED2	Jiao *et al*., 2007[10]
g. 3552G>A	p. Ala160Thr	India	CHED2	
g. 8118delCT	p.His568HisfsX177	India	CHED2	
g. 8298C>T	p. Arg605X	India	CHED2	
g. 8379G>T	p. Glu632X	India	CHED2	
g. 9044G>A	p. Arg755Gln	India	CHED2	
g. 9191G>A	p. Arg804His	India	CHED2	
g. 9200delTinsGG	p. Leu807Arg	India	CHED2	
g. 9361C>T	p. Thr833Met	India	CHED2	
g. 9469G>A	p. Arg869His	India	CHED2	
c. 427G>A	p.Glu143Lys	India	CHED2	Ramprasad *et al*., 2007[11]
c. 1156T>C	p.Cys386Arg	India	CHED2	
c. 2263C>T	p.Arg755Trp	India	CHED2	
c. 720G>A	p.Trp240X	UK	CHED2	
c.[2398C>T]+[2437-1G>A]	p.Gln800X and inactivation of splice acceptor site	UK	CHED2	
c. 140delA	p.Tyr47SerfsX69	India	CHED2	Sultana *et al*., 2007[12]
c. 618_619delAG	p.Val208AlafsX38	India	CHED2	
c. 878_889del12	p.Glu293_Glu296del	India	CHED2	
c. 2389_2391delGAT	p.Asp797del	India	CHED2	
c. 1317_1322del6ins8	p.Leu440ValfsX6	India	CHED2	
c. 334C>T	p.Arg112X	India	CHED2	
c.[334C>T]+[1751C>A]	p.Arg112X+Thr584 Lys	India	CHED2	
c. 2407C>T	p.Glu632X	India	CHED2	
c. 625C>T	p.Arg209Trp	India	CHED2	
c. 638C>T	p.Ser213Leu	India	CHED2	
c. 697C>T	p.Arg233Cys	India	CHED2	
c.[1202C>A]+[1418T>G]	p.Thr401Lys+Leu473Arg	India	CHED2	
c. 1751C>A	p.Thr584Lys	India	CHED2	
c. 2318C>T	p.Pro773Leu	India	CHED2	
c. 996+26C_+44Cdel19	Splice site	India	CHED2	
c. 1091-1G>C	Splice site	India	CHED2	
c. 743G>A + c. 1033A>T	p.Ser232Asn+p.Arg329X	Chinese-American	CHED2	Aldave *et al*., 2007[13]
c. 2126G>A	p.Gly709Glu	Chinese	FECD	Vithana *et al*., 2008[14]
c. 2261C>T	p.Thr754Met	Chinese	FECD	
c. 99_100delTC	p.S33SfsX18	Chinese	FECD	
c. 1195G>A	p.Glu399Lys	India	FECD	
c. 867C>T	p.Thr271Met	Saudi Arabia	CHED	Shah *et al*., 2008[15]
c. 473_480del GCTTCGCC	Frameshift	Gipsy (Eastern Europe)	HS	Desir *et al*., 2007[16]
c. 1378_1381delTACGinsA)	p.Tyr460_Ala461delinsThr	Dominican Republic	HS	
c. 1463G>A	p.Arg488Lys	Morocco	HS	
c. 2233_2240dupTATGACAC)+(c. 2528T>C)	p.Thr747ThrfsX6+p. Leu843Pro	South American Indian	HS	
c. 2423_2454del32nt+c. 2528T>C	p.Leu808ArgfsX110+p. Leu843Pro	Netherlands	HS	
c. 637T>C + c. 2566A>G	p.Ser213Pro+p.Met856Val	Sephardi Jewish	HS	
c. 2470G>A	Val824Meth	India	Nonsyndromic CHED	

Contd...

Supplementary Table 1: Contd...

Variations	AA change	Ethnic origin of patient	Clinical phenotype	References
c. 654(-97)_C.778 (-1488) del698bp	Frame shift	India	CHED2	Hemadevi *et al*., 2008[17]
c. 473_480delGCTTCGCCinsC	p.Arg158ProFSX3	India	CHED2	
c. 806C>T	p.Ala269Val	India	CHED2	
c. 478G>A	p.Ala160Thr	India	CHED2	
c. 1156T>C	p.Cys386Arg	India	CHED2	
c. 374G>A	Arg125His	India	CHED2	
c. 2263C>T	p.Arg755Trp	Saudi Arabia	CHED2	Aldahmesh *et al*., 2009[18]
c. 1253G>A	Gly418Asp	Saudi Arabia	CHED2	
c. 1044+25del19nt	Intronic mutaton	Saudi Arabia	CHED2	
c. 2236C>T	Arg757X	Saudi Arabia	CHED2	
c. 2114+1G>A	Splice site	Saudi Arabia		
c. 501G>C	p.Glu167Asp	Northern European	FECD	Riazuddin *et al*., 2010[19]
c. 845G>C	p.Arg282Pro	Northern European	FECD	
c. 1577A>G	p.Tyr526Cys	Northern European	FECD	
c. 1723G>A	p.Val575Met	Northern European	FECD	
c. 1748G>A	p.Gly583Asp	Northern European	FECD	
c. 2224G>A	p.Gly742Arg	Northern European	FECD	
c. 2500G>A	p.Gly834Ser	Northern European	FECD	
c. 1391G>A	p.Gly464Asp	Pakistan	CHED2	Siddiqui *et al*., 2014[20]
c. 397T>.C	p.Phe133Leu	Mexican	CHED2	
c. 1158C>A	p.Cys386*	Korean	CHED2	Kim *et al*., 2015[21]
c. 1156T>C + c. 1244G>A	p.Cys386Arg+p.Ser415Ala	India	CHED2	Kumawat *et al*., 2016[22]
c. 2528T>C	p.Leu843Pro	Irish	CHED2	Hand *et al*., 2017[23]
c. 150T>A	p.Cys50*	Iranian	CHED2	Moazzeni *et al*., 2020[24]
c. 586G>T	p.Asp196Tyr	Iranian	CHED2	
c. 1217A>T	p.Asp406Val	Iranian	CHED2	
c. 1245delC	p.Ser415ArgfsX15	Iranian	CHED2	
c. 1307C>T	p.Ala436Val	Iranian	CHED2	
c. 1537+1G>C	Splice site	Iranian	CHED2	
c. 1606A>T	p.Ser536Cys	Iranian	CHED2	
c. 2117T>A	p.Ile706Asn	Iranian	CHED2	
c. 2328delT	p.Leu776LeufsX72	Iranian	CHED2	
c. 2519T>C	p.Leu840Pro	Iranian	CHED2	
c. 433G>A	p.Asp129Asn	India	CHED2	Chaurasia *et al*., 2020[25]
c. 9361C>T	p.Thr833Met	India	CHED2	
c. 1249G>A	p.Gly417Arg	India	CHED2	
c. 1813C>T	p.Arg605X	India	CHED2	
c. 2264G>A	p.Arg755Gln	Northern Thailand	HS	Tananuvat *et al*., 2021[26]
c. 1330+1G>T	Splice site	Chinese	CHED	Li *et al*., 2021[27]
c. 2241-2A	Splice site	Pakistan	CHED/progressive HS	Firasat *et al*., 2021[28]
c. 1898-2A	Splice site	Pakistan	CHED/progressive HS	
c. 430C>G	p.Arg128Gly	Pakistan	CHED/progressive HS	
c. 1330+1G>T		Chinese	CHED	Zhang *et al*., 2021[29]
c. 1434_1436del	p.Leu479del	Tunisian	CHED	Chibani *et al*., 2022[30]
c. 1237G>A + c. 698G>T	p.G413R+p.R233L	Chinese	CHED	Liu *et al*., 2022[31]
c. 2024A>C	p.Glu675Ala	Pakistan	CHED	Iqbal *et al*., 2022[9]
c. 2470G>A	p.Val824Met	Pakistan	CHED	
c. 473_480del	p.Arg158fs	Pakistan	CHED	
c. 1487G>T	p.Ser480Ile	India	CHED	Salman *et al*., 2022[32]
c. 620-2A>G	Splice site	India	CHED	

CHED=Congenital hereditary endothelial dystrophy, FECD=Fuchs endothelial corneal dystrophy, HS=Harboyan syndrome