Limbal Stem Cell Deficiency :Presentation, Diagnosis and Management

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The human corneal surface epithelium is continuously repopulated by the limbal stem cells (LSCs). The stem cells in the limbusthat are vital for re-population of the corneal epithelium and to the barrier function of the limbus. . Limbal stem cell deficiency (LSCD) is characterized by a loss or deficiency of the stem cells in the limbus. When these stem cells are lost, the corneal epithelium is unable to repair and renew itself. This results in epithelial breakdown and persistent epithelial defects, corneal conjunctivalization and neovascularization, corneal scarring, and chronic inflammation. All of these contribute to loss of corneal clarity, potential vision loss, chronic pain, photophobia, and keratoplasty failure.There are many causes of limbal stem cell deficiency and it is important to know how to recognize them and how to intervene. Although LSCD can be detected clinically, laboratory tests are necessary to confirm the diagnosis and monitor the disease progression. This article concisely reviews the clinical presentation, techniques for diagnosis and management of limbal stem cell deficiency disorders.

Etiology

The etiologies can be genetic, acquired, or idiopathic.

Genetic:

Limbal stem cell deficiency has been associated with PAX6 gene mutations, which are also implicated in aniridia and Peter's Anomaly.

Acquired:

Inflammatory

Steven-Johnsons Syndrome (SJS), ocular cicatricialpemphigoid, and graft versus host disease.Chronic ocular allergy such as VKC and Neurotrophickeratopathy.

Infectious:

Herpes keratitis and trachoma.

Traumatic/Iatrogenic:

Acquired causes also include trauma from chemical or thermal burns, and prior ocular surgeries or cryotherapies at the limbus. Radiation and chemotherapy are other potential causes, and systemic as well as topical chemotherapeutic medications may be sufficient to cause deficiency. LSCD has also been seen with benzalkonium chloride toxicity with glaucoma medications and Inappropriate contact lens use.

Tumors/Overgrowth of Other Tissue:

Ocular surface tumors and Pterygium are a known cause of LSCD.

CLINICAL PRESENTATION

History:

Pain resulting from recurrent erosions and decreased vision.

Other symptoms:

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Contact lens intolerance, photophobia, tearing, and blepharospasm. A patient with LSCD from chemical burn or trauma will give a history of such an event.

Physical examination

Recurrent epithelial erosions leads to chronic keratitits, scarring, and calcification if untreated. Delayed wound healing and corneal neovascularization eventually leads to a process called conjunctivalization occurs. The corneal surface will be covered by conjnuctiva-like epithelium that undergoes transformation into a cornea-like epithelium with loss of goblet cells, a process termed conjunctival transdifferentiation. Patients usually suffer from recurrent erosions and decreased vision as a result of an irregular optical interface, weak tensile strength, and an incompetent barrier function.

Signs

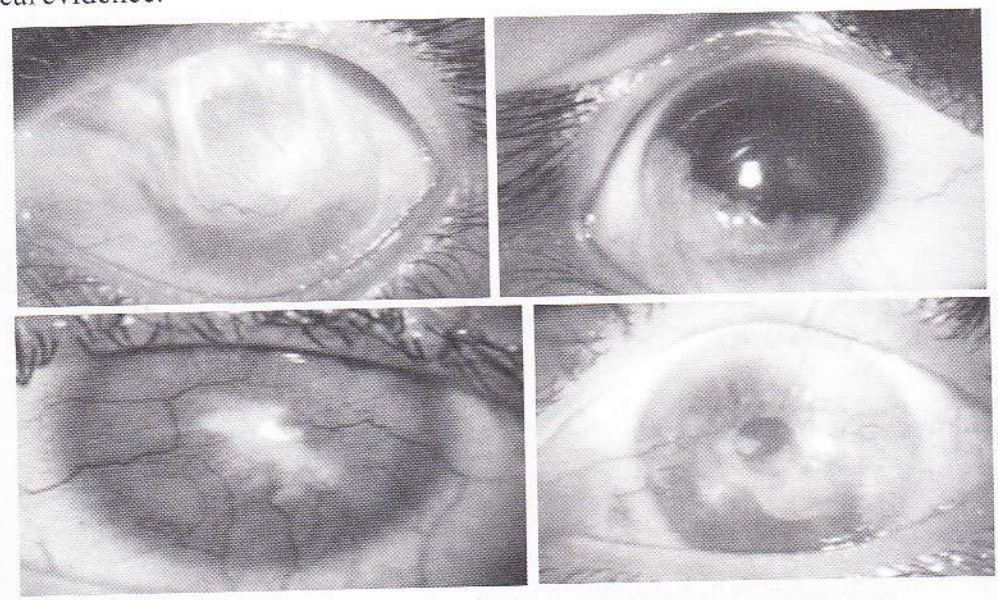
Progressive epitheliopathy with hazy, translucent epithelium extending centrally from the limbus, most commonly from the superior limbus. Epithelial staining, from punctate changes to more confluent staining, is broadest adjacent to the involved limbus and extends centripetally into the cornea to varying degrees in a whorl shape. Patients often have evidence of mild to moderate tear film dysfunction, superficial and deep vascularization, persistent epithelial defects leading to ulceration, melting, and perforation, fibrovascular pannus, and finally scarring, keratinization, and calcification.

Symptoms

Eye pain and blurry vision , Eye irritation, contact lens intolerance, and blurred or decreased vision were the most common symptoms in one study.

Clinical diagnosis

A diagnosis of limbal stem cell deficiency requires both clinical signs and symptoms of the disease along with cytological evidence.

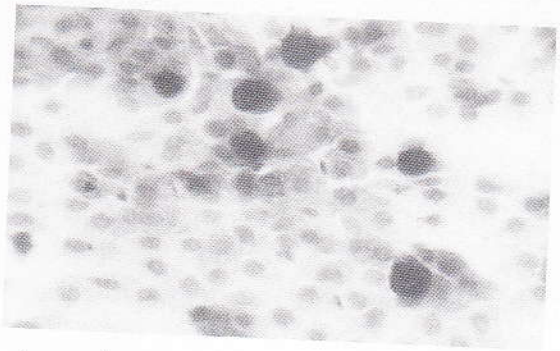


Diagnosis of limbal stem cell deficiency

LSCD can be detected clinically based on the presentation described above. Laboratory tests are necessary to confirm the diagnosis of LSCD and monitor success of surgical interventions. In this section, impression

cytology and in vivo confocal microscopy are discussed.

Impression cytology



Impression cytology has been the gold standard diagnostic test for LSCD.. It is therefore, ideal to study superficial cells, the epithelial morphology and goblet cells.The epithelial morphology alone cannot distinguish conjunctial epithelial cells from corneal epithelial cells.Immunocytochemistry on impression cytology specimens could identify the specific cytokeratin and hence the type of epithelium

In vivo laser scanning confocal microscopy

In vivo laser scanning confocal microscopy (IVCM) provides high-resolution images of the ocular surface at the cellular level. Recently, IVCM has been used to study corneal and limbal microstructures.Thereare significant microstructural changes in LSCD. Vera et al. reported corneal epithelial abnormalities and absence of the subbasal nerve plexus in patients with chronic Stevens-Johnson syndrome, toxic epidermal necrolysis and LSCD. Recently, microstructural changes have been detected in the cornea and limbus in LSCD compared to normal controls.36 In this study, patients are classified into 3 stages of LSCD: early, intermediate, late stage based on clinical presentation and evaluated the corneal and limbal epithelium changes on confocal microscopy. Significant microstructural changes in the corneal and limbal epithelium are seen even in the early stage of LSCD. The corneal epithelial cells in LSCD have less distinct borders and have prominent nuclei. The size of basal epithelial cells increases. Epithelial cells in the deeper layers become affected in more advanced stage of LSCD. In the late stage, epithelial cells show significant metaplasia and there is neovascularization. Compared with the healthy control subjects, eyes with early stage LSCD have an average of 38% reduction in basal epithelial cell density and a 58% reduction in subbasal nerve density. The limbal epithelium also shows similar changes and there is an absence of palisades of Vogt. A combination of morphological changes in the corneal epithelium, and a significant reduction in both basal epithelial cell density and subbasal nerve density might be the early signs of LSCD.

Detection of goblet cells in the corneal epithelium of patients with LSCD has been reported.However, there is inconsistency regarding the morphological features of goblet cells on the confocal images

MANAGEMENT

Medical management of limbal stem cell deficiency-Optimization of ocular surface health is the first step in the management of LSCD. Often, there are constant insults to the corneal epithelium from multiple concurrent external disorders such as dry eyes, ocular surface inflammation, soft contact lens, and drug toxicity from multiple eye medications the transplanted limbalgraft.Dry eyes can be treated with frequent preservative-free artificial tears, punctual occlusion, and topical cyclosporine. Long term preservative free topical cortical steroids might be necessary to control ocular surface inflammation as in chemical burns and Stevens-Johnson syndrome. In the case of LSCD due to contact lens wear, complete cessation of the wear is necessary and topical corticosteroids may facilitate the recovery.Fluid-ventilated, gas-permeable scleral contact lenses are valuable in the management of severe ocular surface disease. Scleral lenses also promote healing of PED refractory to other treatments and prevent PED recurrence.

Surgical management of limbal stem cell deficiency-Unilateral or bilateral partial LSCD may only require observation if the patient is asymptomatic. Repeated mechanical debridement known as the sequential sector conjunctival epitheliectomy, amniotic membrane transplantation, and ipsilateral limbal translocation to an area of LSCD are suggested as an early therapeutic option. Amniotic membrane promotes epithelialization and reduces angiogenesis and inflammation. It preserves and maintains the epithelial progenitor cells and thus can be used instead of limbal transplantation in the management of partial LSCD. Total unilateral LSCD requires a conjunctival limbal autograft which may be harvested from the healthy fellow eye. Recently, a technique called "simple limbal epithelial transplantation" was described. Direct transplantation of the 2 × 2 mm piece of healthy limbal donor is cut into pieces and secured on amniotic membrane using fibrin glue without ex vivo cultivation can successfully reconstruct the ocular surface after pannus excision. In total bilateral LSCD, limbal stem cell transplantation from allogeneic tissue is necessary. Allogeneic tissues may be obtained from a cadaveric or a living-related donor and transplanted to the ocular surface directly. Alternatively, transplantation of the cell sheet after cultivation can also achieve success. Allografts require prolonged systemic immunosuppression and the long-term survival of allograft is worse than that of autologous transplantation. Keratoprosthesis can be used as an alternative to allograft transplantation to avoid immunosuppression. The Boston type 1 keratoprosthesis can achieve an excellent visual outcome in eyes with LSCD secondary to non-immnumological disorders if there is adequate tear function. Bandage contact lens, conjunctival graft or oral mucosal graft might be necessary to stabilize the ocular surface. The osteo-odontokeratoprosthesis and the Boston type 2 keratoprosthesis are reserved for total LSCD with minimal or no tear function.

Amniotic Membrane Transplantation-Amniotic membrane transplantation (AMT) was first used by Kim and Tseng for corneal surface reconstruction in a rabbit model of total limbal deficiency. Tsubota et al later described use of amniotic membrane with limbal allograft transplantation in patients with ocular cicatricialpemphigoid and Stevensen-Johnson Syndrome. The procedure has been used to create a limbal barrier in pterygium surgery and for conjunctival surface reconstruction following excision of tumours, scars and symblepharon.The amniotic membrane is a thick basement membrane and avascular stromal matrix. Lee and Tseng theorise that these features are crucial to successful transplantation.

Tseng et al demonstrated that in eyes with chemical burns (n=14); Stevensen Johnson Syndrome, toxic epidermal necrolysis or pseudopem-phigoid (n=5); contact lens induced keratopathy (n=3); aniridia (n=3); multiple surgical procedures (n=2); atopy (n=2); and unknown cause (n=2), all amniotic membrane covered eyes (except for two eyes with atopy) showed rapid epithelialisation (2-4 weeks) and reduced inflammation, vascularisation and scarring. For the mean follow up of 15.4 months, 25 of 30 eyes showed visual improvement ranging from 1 to 6 lines. Coneal graft rejection occurred in 9 of 14 eyes and reversible early limbal allograft rejection in 3 of 21 eyes. They concluded that AMT alone is sufficient for partial limbal deficiency with superficial involvement and is superior to allo-limbal transplantation (ALT) since it is not necessary to administer cyclosporine.

Lee and Tseng performed AMT in 11 eyes for persistent epithelial defects with ulceration and obtained successful recpithelialisation in 10 of 11 eyes. Ongoing research into the regulatory mechanism of limbal stem cells may open up exciting frontiers leading to an enhancement of our therapeutic armamentarium in successfully managing these disorders.

In summary, diagnosis of LSCD is often clinical. Significant advances have been made to develop noninvasive tests to objectively diagnose LSCD in recent years. Diagnostic tests that can quantify the stem cell function may help to develop a classification system for LSCD, and monitor the progress of the disease and treatment outcomes. The management of LSCD remains challenging. Many medical and surgical options are available to rehabilitate the ocular surface. When judiciously used, successful outcomes can be achieved in a majority of cases.