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Diagnostic criteria for limbal stem cell deficiency prior to surgical intervention - A systematic literature review and analysis

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Abstract

An accurate diagnosis of limbal stem cell deficiency (LSCD) is the premise of an appropriate treatment. However, there is no consensus about the diagnostic criteria for LSCD. We performed a systematic literature search of the peer-reviewed articles on PubMed, Medline, and Ovid to investigate how LSCD was diagnosed prior to surgical intervention. The methods used to diagnose LSCD were collected including clinical presentation, impression cytology (IC) and in vivo confocal microscopy (IVCM). Among 131 eligible studies (4054 eyes), 26 studies (459 eyes, 11.3%) did not mention the diagnostic criteria. In the remaining 105 studies, the diagnosis of LSCD was made on the basis of clinical exam alone in 2398 eyes (62.9%), and additional diagnostic tests were used in 1047 (25.8%) eyes. IC was used in 981 eyes (24.2%), IVCM was used in 29 eyes (0.7%), and both IC and IVCM were used in 37 eyes (0.9%). Our findings suggest that only a small portion of patients underwent a diagnostic test to confirm the diagnosis of LSCD. Treating physicians should be aware of the limitations of clinical examination in diagnosing LSCD and perform a diagnostic test whenever possible before surgical intervention.

Keywords

Limbal stem cell deficiency; limbal stem cells; diagnosis; impression cytology; in vivo laser scanning confocal microscopy; imaging

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Disclosure

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I. Introduction

Limbal stem cells (LSCs) are responsible for the regeneration of corneal epithelial cells and the maintenance of the integrity and transparency of the cornea. [110] Destruction of the LSCs, the stem cell niche, or both, leads to LSC dysfunction and deficiency. Limbal stem cell deficiency (LSCD) results in delayed epithelial wound healing, recurrent epithelial erosions, and loss of vision.

There is no consensus about the diagnostic criteria for LSCD. [66] The ocular symptoms of LSCD, such as photophobia, recurrent episodes of ocular pain, foreign body sensation, tearing and decreased vision, are usually nonspecific and have limited diagnostic value. The typical clinical signs include late fluorescein staining in a vortex pattern, recurrent/persistent epithelial defects, fibrovascular pannus, and the absence of palisades of Vogt; however, these clinical presentations are not specific to LSCD. In complex eyes with other comorbidities, signs of other diseases such as corneal neovascularization, dry eye, and subepithelial scarring might be mistaken as severe LSCD. [65]

Tests have been developed to confirm the diagnosis of LSCD. The presence of goblet cells or conjunctiva-derived cells in the corneal epithelium, which is a sign of LSCD, can be detected by impression cytology (IC) for confirming an LSCD diagnosis.[35,137] More recently, in vivo confocal microscopy (IVCM) has been used to detect cellular morphologic changes or goblet cells on the cornea.[68,81,92]

Surgical interventions, either limbal transplantation or keratoprosthesis, can restore vision in eyes with severe LSCD that do not respond well to medical treatment. In the cases of allogeneic LSC transplantation, systemic immunosuppression is required and poses systemic, potentially life-threatening, side effects. Therefore, an accurate diagnosis and classification of LSCD are necessary for the selection of an appropriate treatment. Here we report the findings of a systematic review and analysis of the published peer-reviewed literatures that assessed how LSCD was diagnosed in patients who underwent surgical intervention for the condition.

II. Methods

A. Eligibility Criteria

Original papers that reported surgical outcomes of LSCD in more than 5 eyes were included. Literature reviews, animal studies, laboratory studies, correspondence, notes, editorials and conference abstracts were excluded. If our searches identified multiple reports from the same authors and the same institutions, these reports were assessed and grouped according to the study duration, surgery type, donor source, and patient information; only the most recent studies with updated data, larger populations and longer follow-up were included to avoid redundant studies reporting outcomes at different time points from an overlapping group of patients. In a few studies, IC was selectively performed in only a small portion of the patients. The number of eyes that were reported as having undergone IC was counted as having the adjuvant test. The eligibility of included studies were evaluated by two authors

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(Q.L. and T.C.) independently. In cases of disagreement, a third author (S.D.) participated in the discussion until the consensus was reached.

B. Data Collection

The data about the diagnostic methods used to diagnose LSCD that were collected included clinical findings, IC and its results (e.g., the presence of goblet cells, epithelial morphology, and epithelial biomarkers), and IVCM and its results. The study type and the authors' affiliation were also collected to address the global distribution of surgical interventions for LSCD.

III. Results

A total of 131 studies (3818 subjects and 4054 eyes) met the inclusion criteria and were included in the analysis (Figure 1). Surgical treatment of LSCD had been offered at 66 eye centers in 23 countries in Europe, Asia, North America and South America (Table 1). Of the 131 studies, 5 were uncontrolled clinical trials,[18,41,61,112,157] 29 were prospective studies,[3,13,17,28,34,46,47,63,71,72,74,75,80,96,99,102,103,108,111,113,120,124,128,129,135,136,143,145,156] and [73] were retrospective studies.[1,2,5,7–12,14–16,20,24–26,31,32,38–40,42,44,45,48,50–53,56,59,60,62,64,69,70,76,77,82–90,94,97,98,105,107,115,117–119,121,122,125–127] In the remaining 24 studies,[6,29,36,37,43,49,54,55,58,73,79,87,95,104,106,116,123,142,144,147,148,150,151,155] the study type could not be determined from the information provided in the papers.

Twenty-six studies did not mention the diagnostic criteria used in the evaluation of 433 subjects (459 eyes, 11.3%). The clinical presentations were used as one criterion for LSCD in the remaining 105 studies (3595 eyes, 88.7%) that specified their diagnostic criteria. These presentations included late fluorescein staining (either vortex staining or punctate staining), lusterless corneal epithelium or loss of corneal epithelial transparency, epithelial irregularity, recurrent/persistent epithelial defects, superficial neovascularization, fibrovascular pannus, the absence of palisades of Vogt, symblepharon, corneal stroma opacity or scarring, and chronic ocular surface inflammation.

Clinical findings alone without adjuvant tests were used for the diagnosis in 2398 subjects (2548 eyes, 62.9%). A diagnostic test was used in 987 subjects (1047 eyes, 25.8%). The diagnosis was confirmed by IC in 981 eyes (24.2%), by IVCM in 29 eyes (0.7%), and by both IC and IVCM in 37 eyes (0.9%) (Table 1).

Of the 42 studies that employed IC as a diagnostic test, 22 studies (605 eyes) reported the presence of goblet cells on the cornea as the evidence of conjunctivalization of the corneal surface [6,9,28,41,46,59,69,96,98,102,103,105,113,120–122,129,136,138,149–151] Immunohistochemical staining to identify cytokeratin profiles was used in 5 studies (76 eyes);[29,63,79,106,135] studies, K3 and K19 were used as the biomarkers of corneal epithelial cells and conjunctival epithelial cells, respectively. The determination of cellular morphology (e.g., the shape and size of the cells, the nucleus size, and the nucleus-cytoplasm alteration) and cytoplasm staining pattern were used as diagnostic criteria in 3 studies (59 eyes). [51,71,72] The remaining

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12 studies (278 eyes) mentioned the use of IC but did not describe the details of the method used to confirm conjunctivalization of the corneal surface.[5,7,8,64,70,76,77,98,131,133,142,157]

IVCM was used in only 4 studies (66 eyes), all of which were performed by institutions in Europe. The presence of conjunctival-like or mixed epithelial cell phenotype in the central cornea was used as the supporting evidence in 3 studies, [41,108,126] and the detection of goblet cells on the cornea was used to confirm the LSCD diagnosis in 1 study.[97]

IV. Discussion

The transplantation of either limbal tissues or cultivated LSCs has been the surgical intervention of choice for severe to total LSCD for more than three decades; however, there is a lack of consensus in the diagnostic criteria for LSCD, as shown in the present systematic review. Most of the clinical signs used in all studies are not pathognomonic for LSCD. Presence of corneal neovascularization, symblepharon, ocular surface inflammation, absence of palisade of Vogt, or persistent epithelial defect does not necessary indicate LSCD. Other conditions might be misdiagnosed as LSCD.[65,92]

Impression cytology is considered a standard method to confirm the diagnosis of LSCD, either by detecting goblet cells on the corneal surface or by identifying specific cytokeratin of the conjunctiva. [91,100,109] Although the detection of goblet cells on the cornea has high specificity in the diagnosis of LSCD, its sensitivity is quite low, ranging from 13.8%-59%. [68,91,114]Detection of biomarkers of conjunctival epithelial cells such as K7 and K13 using immunohistochemistry or RT-PCR has a similar specificity but the sensitivity is 28%-48% higher than the detection of goblet cells. [100,101,109,114] The protocol to detect biomarkers of conjunctival epithelial cells varied among different centers, however, and a standardized protocol is lacking. In addition, it is time-consuming and requires laboratory support. Additional work still is needed to make this method feasible in clinical practice.

In vivo laser scanning confocal microscopy is an in vivo imaging technique to visualize the microstructures of ocular surface tissues at the single-cell level. This method has many advantages over IC, including noninvasiveness, real-time results, and good repeatability. Apart from the presence of either goblet cells or conjunctival-like epithelial cells on the cornea, the alterations of cellular morphology, basal epithelial density, epithelial thickness and subbasal nerve plexus have also been shown to be good parameters for the diagnosis of LSCD.[19,21,22,27] IVCM has been confirmed to have a high degree of concordance with IC [30,68,92] and has been applied in many clinical studies on LSCD; [33,81,92] however, our review shows that only 4 investigations (66 eyes) used IVCM as a confirmatory test in the diagnosis of LSCD before surgical intervention. This might be due to the limitation of IVCM, which is time-consuming and technically challenging, especially when the examination is performed at the limbal area. Moreover, a small sampling area is also a big limitation that impedes its application in the clinical practice. Therefore, recent studies have investigated whether anterior-segment OCT might be another feasible imaging technique to diagnose LSCD. [4,67,78,93,154]

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Clinical findings alone are insufficient to make the diagnosis and stage the severity of the disease, particularly in complicated cases, because the clinical signs used to diagnose LSCD are not pathognomonic. [66] Residual normal limbal epithelial cells have been detected in eyes with clinical signs of total LSCD. [23] In addition, we recently reported a case of corneal neovascularization misdiagnosed as total LSCD.[65] This highlights the subjective nature of the interpretation of clinical findings. Therefore, the diagnosis based only on clinical presentation may be inaccurate or even incorrect in some cases. Additional efforts should be made to perform the diagnostic tests prior to surgical intervention to maximize the outcome of treatment and reduce risks to the patient.

The current study found that confirmatory testing, i.e., IC, IVCM, or both, was used in the diagnosis of LSCD in only 25.8% of eyes prior to surgical treatment. A previous review reported that only 39% of the interventional studies on LSCD published from 2003 to 2013 used an additional diagnostic method to confirm the diagnosis.[57] The current study, which includes all surgical interventional studies published prior to December of 2018, shows an even lower prevalence of the use of confirmatory tests. Low utilization of diagnostic testing might be from a lack of laboratory support or unavailability of equipment to perform the tests. Limited access to alternative diagnostic methods is likely the major reason for reliance on clinical diagnosis in practice. In addition, a lack of consensus on the diagnostic criteria for LSCD and poor understanding of the limitations of clinical findings in its diagnosis, also contribute to low utilization of a diagnostic test. Clinicians should recognized the limitation of clinical diagnosis and make efforts to obtain confirmatory diagnostic tests whenever possible.

V. Conclusion

The diagnosis of LSCD in the vast majority of cases was made solely on clinical findings without a confirmatory diagnostic test prior to surgical intervention. The sensitivity of impression cytology is relatively low, while IVCM is technically challenging and has a small examination area. The reliance on the clinical diagnosis in the majority of clinical practice is probably due to limited access to alternative diagnostic methods. Recognizing the limitations of using only clinical findings in the diagnosis of LSCD and increasing the use of additional tests to confirm the diagnosis are important in improving patient care. A consensus on the diagnosis of LSCD needs to be established.

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VI.

Method of Literature Search

We performed a systematic literature search on PubMed, Medline and Ovid using the following search terms: “limbal stem cell deficiency,” “limbal transplantation,” “cultivated limbal epithelial transplantation,” “simple limbal epithelial transplantation,” “cultivated oral mucosal epithelial transplantation,” “conjunctival limbal autograft,” “conjunctival limbal allograft,” “keratolimbal allograft,” “keratoprosthesis,” and “amniotic membrane.” We also reviewed the references from retrieved studies manually to identify relevant articles. The last search was performed on December 31, 2018. Neither the language filter nor the limitation of publication time was applied to the literature searches. The non-English articles were translated to English to obtain the needed information. Only clinical studies on human that reported surgical outcomes of LSCD in more than five eyes were included. Earlier studies on a smaller population published by the same authors were excluded. If impression cytology is selectively performed in partial participants and the authors did not provide the accurate number of eyes undergoing impression cytology, these studies were excluded, too.

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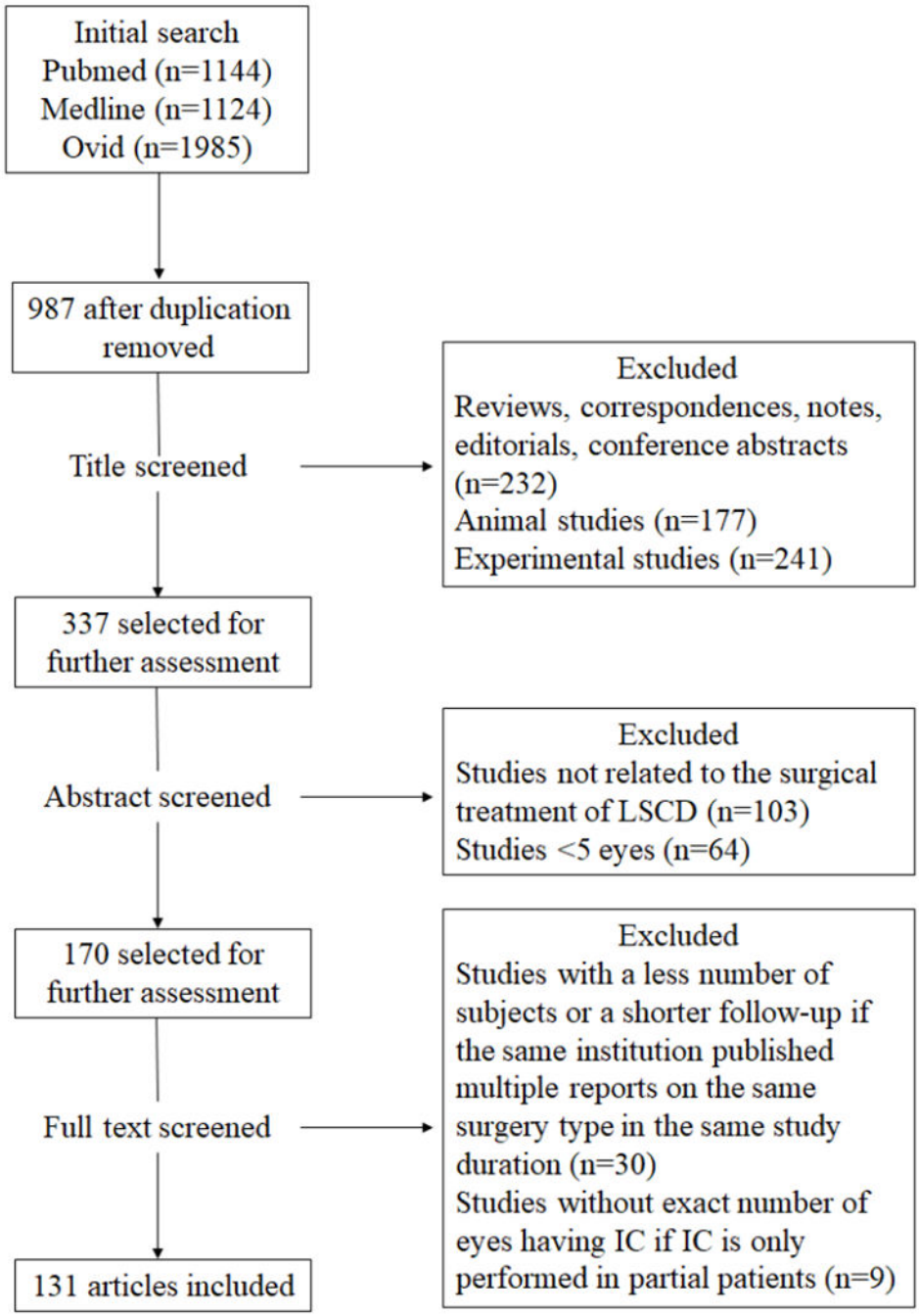

Figure 1.
Flowchart of literatures search on the surgical treatment of LSCD

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Table 1

Diagnostic methods used for the diagnosis of LSCD

Diagnostic Method	Country	Institution	Study	Subjects (%)	Eyes (%)	references
Clinical Examination Only	15+3[a]	41+5[a]	61+6[a]	2398 (62.8%)[b]	2548 (62.9%)[b]	2, 3, 10–13, 15–18, 24, 25, 31, 32, 34, 36–38, 40, 42, 45, 47, 48, 50, 52–54, 59, 62, 69, 73, 75, 80, 82, 84, 85, 87, 89, 95, 99, 107, 111, 112, 115–119, 124–128, 132, 133, 138–145, 147, 152, 153, 155
Confirmatory Diagnostic Tests						
IC only	12+3[a]	20+5[a]	34+6[a]	922 (24.2%)[c]	981 (24.2%)[c]	5–9, 28, 29, 46, 51, 59, 63, 64, 69–72, 76, 77, 79, 96, 98, 102, 103, 105–107, 113, 120–122, 129, 131, 133, 136, 138, 142, 149–151, 157
IVCM only	2	2	2	29 (0.8%)	29 (0.7%)	97, 108
IC+IVCM	1	2	2	36 (0.9%)	37 (0.9%)	41, 135
Unknown	11	21	26	433 (11.3%)	459 (11.3%)	1, 14, 20, 26, 39, 43, 44, 49, 55, 56, 58, 60, 61, 74, 83, 86, 88, 90, 94, 104, 123, 130, 134, 146, 148, 156
Total	23	66	131	3818 (100%)	4054 (100%)	

IC: impression cytology; IVCM: in vivo confocal microscopy

a: In six studies performed at five institutions in three countries, IC was selectively performed in a portion of the patients to confirm the LSCD diagnosis. The diagnoses for the rest of the patients in these studies were based only on clinical findings.

b: The number of subjects and eyes in these six studies in which the diagnoses were based only on clinical examinations and were not been confirmed by IC were included in the category of “clinical examination alone.”

c: The number of subjects and eyes in these six studies in which the diagnoses had been confirmed by IC were included in the category of “clinical examination+IC”.

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