Corneal Limbal Stem Cell Deficiency in Children with Stevens–Johnson Syndrome

SE HYUN CHOI, MEE KUM KIM, AND JOO YOUN OH

• PURPOSE: To determine the incidence of corneal limbal stem cell deficiency (LSCD) as chronic ocular sequelae in children with Stevens–Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) and analyze the factors associated with LSCD development.
• DESIGN: Retrospective case series.
• METHODS: Medical records were reviewed of pediatric patients who had been admitted to Seoul National University Hospital with SJS/TEN and who were diagnosed as having acute ocular involvement. For each record, the following data were collected: demographic information, underlying diseases, causative agents, acute systemic and ocular manifestations, systemic and ocular treatments, chronic ocular complications including LSCD, and visual acuities.
• RESULTS: Of 19 children with SJS/TEN, LSCD developed in 6 (32%) patients at a mean of 12.3 ± 21.3 months after the onset of SJS/TEN (median 3.5 months). Severity of acute systemic involvement including elevation of liver enzyme levels and serum C-reactive protein levels was significantly correlated with the development of LSCD ($P = .0038$) and chronic ocular complications ($P = .0044$). The presence of corneal epithelial defect necessitating the use of therapeutic contact lenses in the acute phase was also associated significantly with LSCD development. Combined penetrating keratoplasty and limbal allograft were performed in 3 of 6 LSCD patients, and grafts failed in 2 (67%) patients because of infection. At the last follow-up, visual acuities were significantly poorer in patients with LSCD compared with those without LSCD ($P = .0055$).
• CONCLUSIONS: Corneal LSCD occurred in 32% of pediatric patients with SJS/TEN, leading to poor visual outcome. Severity of acute systemic involvement was significantly associated with the development of LSCD and chronic ocular complications. (Am J Ophthalmol 2019;199:1–8. © 2018 Elsevier Inc. All rights reserved.)

AJO.com Supplemental Material available at AJO.com.

Accepted for publication Oct 13, 2018.

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STEVENS–JOHNSON SYNDROME (SJS) AND TOXIC epidermal necrolysis (TEN) are acute immune-mediated disorders of the skin and mucous membrane caused by an idiosyncratic hypersensitivity reaction to systemic medications or infections.[1] SJS/TEN are rare diseases with an estimated annual incidence of 0.4 to 7 per million population,[1,2] and the mortality rate of SJS/TEN is low (0-25%).[3,4] However, patients who survive an episode of SJS/TEN frequently develop delayed sequelae. Chronic ocular sequelae are one of the most debilitating long-term complications.[5,6]

Children with SJS/TEN have higher ocular and visual morbidities compared with adults.[7,8] Chronic ocular complications after childhood SJS/TEN have been reported to occur in 12% to 75% of patients.[5,8–11] The long-term visual impairment in SJS/TEN is largely associated with corneal damage, ranging from dry eye–related keratopathy to limbal stem cell deficiency (LSCD).[8–11] In particular, LSCD is one of the most severe complications in patients with SJS/TEN and the primary cause of permanent vision loss, because limbal stem cells do not regenerate and the outcome of limbal allotransplantation is poor in patients with SJS/TEN.[12]

Several recent studies have reported on the characteristics of acute and chronic ocular manifestations of SJS/TEN in the pediatric population.[7,8,10] Few studies, however, investigated prognostic factors associated with chronic ocular complications, such as LSCD. We examined the incidence of LSCD in children with SJS/TEN and analyzed the factors affecting the development of LSCD. We also adapted the scoring systems previously designed to grade the severity of acute systemic, acute ocular, and chronic ocular manifestations of SJS/TEN.[13,14] By using the scoring systems we evaluated the effects of acute systemic and ocular involvements on the development of LSCD and chronic ocular complications.

METHODS

• STUDY DESIGN AND SUBJECTS: This study is a retrospective case series of patients <16 years of age who were admitted to Seoul National University Children's Hospital because of SJS/TEN between 2003 and 2017 and who were diagnosed with acute ocular involvement. The review of medical charts was approved by the Institutional Review Board of Seoul National University Hospital (1801-062-915).

0002-9394/$36.00
https://doi.org/10.1016/j.ajo.2018.10.016

TABLE 1. Patient Demographics and Clinical Characteristics

	Total (n = 19)	No LSCD (n = 13)	LSCD (n = 6)	*P* Value
Age at onset (years)				
Mean ± SD	6.7 ± 4.7	6.0 ± 4.7	8.3 ± 4.7	.2035
Range	0.2–16.3	0.2–16.3	5.7–12.6	
Gender, n (%)				
Male	13 (68)	10 (77)	3 (50)	.3201
Female	6 (32)	3 (23)	3 (50)	
Duration of admission (days)				
Mean ± SD	40.4 ± 68.2	18.1 ± 8.7	88.8 ± 111.6	.0281
Range	4 weeks to 293	7–39	13–293	
Duration of follow-up (months)				
Mean ± SD	50.1 ± 50.0	38.4 ± 45.7	75.4 ± 53.6	.0577
Range	4 wks to 162.5	0.9–162.5	19.6–155.8	
Diagnosis, n (%)				
SJS	13 (68)	9 (69)	4 (67)	>.9999
TEN	6 (32)	4 (31)	2 (33)	
Underlying diseases, n (%)				
None	13 (68)	8 (62)	5 (83)	
Seizure disorder	2 (11)	2 (15)	0 (0)	
Leukemia	1 (5)	1 (8)	0 (0)	
Nephritis	1 (5)	1 (8)	0 (0)	
Depression	1 (5)	1 (8)	0 (0)	
JRA	1 (5)	0 (0)	1 (17)	
Causative drug (antibiotics), n (%)	13 (68)	8 (62)	5 (83)	.6047
β-Lactam	10 (53)	6 (46)	4 (67)	
Glycopeptides	1 (5)	1 (8)	0 (0)	
Macrolides	1 (5)	0 (0)	1 (17)	
Combined[a]	1 (5)	1 (8)	0 (0)	
Causative drug (others), n (%)				
Antiseizure drug	3 (16)	3 (23)	0 (0)	
NSAIDs	1 (5)	1 (8)	0 (0)	
ACE inhibitor	1 (5)	1 (8)	0 (0)	
DMARDs	1 (5)	0 (0)	1 (17)	

ACE = angiotensin-converting enzyme; DMARDs = disease-modifying anti-rheumatic drugs; JRA = juvenile rheumatoid arthritis; LSCD = limbal stem cell deficiency; NSAID = nonsteroidal anti-inflammatory drug; SD = standard deviation; SJS = Stevens–Johnson syndrome; TEN = toxic epidermal necrolysis.

[a]Macrolides plus β-lactam plus aminoglycoside.

Patient inclusion criteria were: (1) patients <16 years of age; (2) patients who visited our hospital immediately after the disease onset, underwent thorough systemic evaluation, and who were diagnosed with SJS/TEN by a physician or a dermatologist; (3) patients who were found to have ocular involvement by an ophthalmologist within 2 weeks of the appearance of skin lesions and who were treated according to our standard protocol; (4) patients without a history of ocular disorder or surgery before the onset of SJS/TEN; and (5) patients who were followed up by corneal specialists (O.J.Y., K.M.K.) for >4 weeks after SJS onset.

The acute ocular management protocol used for patients was as follows: (1) supportive care with instillation of preservative-free artificial tears every 2 hours and topical levofloxacin 0.5% (Cravit, Santen Pharmaceutical, Osaka, Japan) 4 times a day in all patients; (2) administration of topical prednisolone acetate 1% (Pred forte, Allergan, Irvine, CA, USA) 4 times a day in patients except for those with concurrent infectious keratitis; (3) mechanical lysis of adhesions, forniceal sweeping, and conjunctival membrane peeling, if any, on a daily basis; (4) application of bandage contact lenses in cases with corneal epithelial defects; and (5) prompt amniotic membrane transplantation within 10 days to cover the entire ocular surface and eyelid margins[15–18] in patients where corneal and conjunctival epithelial defects persisted and symblepharon progressed despite the aforementioned treatments.

Systemic treatments, including systemic corticosteroids (daily intravenous infusion of 30 mg/kg methylprednisolone for 3 consecutive days) and intravenous immunoglobulin,

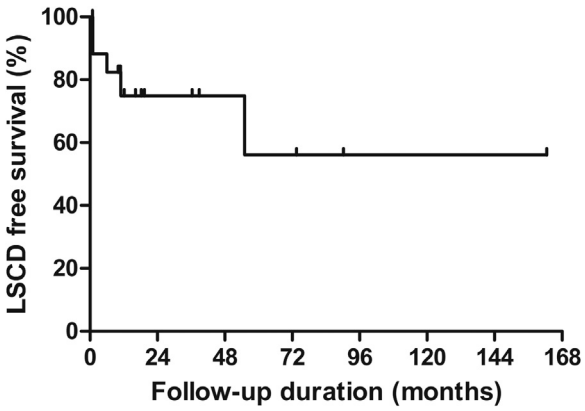

FIGURE 1. The survival curve for limbal stem cell deficiency (LSCD) development in children with Stevens–Johnson syndrome/toxic epidermal necrolysis. LSCD developed in 31.6% of patients at a median of 3.5 months after the onset of Stevens–Johnson syndrome/toxic epidermal necrolysis.

were administered following the decision of a physician based on the systemic condition of a patient.

After hospital discharge, all patients were examined for their ocular conditions within a month and followed up at 3-month intervals for ≥1 year if there was no ocular involvement. Patients with ocular involvement were followed up as necessary depending on each patient's ocular status.

• **DATA COLLECTION AND ANALYSIS:** The following data were collected from the medical record: demographic and clinical information of patients (age, gender, medical and family history), causative agents implicated in SJS/TEN development, acute systemic and ocular manifestations, chronic ocular complications including LSCD, systemic and ocular treatments, durations of admission and follow-up, interval to LSCD development, and best-corrected visual acuities (BCVAs).

Severity of systemic manifestations in the acute stage was determined using acute systemic involvement score (ASS) on a scale of 0 to 16. The ASS is a sum of scores for the presence of erythema blisters, high fever, respiratory disturbance, total necrosis of epidermis, liver dysfunction, anemia, serum C-reactive protein elevation, kidney dysfunction, and pneumonia as suggested by Kim and associates.[14] Each variable of ASS was selected based on the severity of illness score for TEN and Japanese acute systemic index score by the Japanese Research Committee on Severe Cutaneous Adverse Reaction.[14,19] Acute ocular manifestations were graded on a scale of 0 to 3 using the acute ocular involvement score (AOS) as previously described[14]: score 0 (no involvement), score 1 (conjunctival hyperemia), score 2 (either conjunctival pseudomembrane or corneal epithelial erosion), and score 3 (both conjunctival pseudomembrane and corneal epithelial erosion).

The severity of chronic ocular complications was decided at the final follow-up of each patient according to the chronic ocular surface complications score (COCS) on a scale of 0 to 15. The COCS is a grading system that is designed to evaluate chronic ocular manifestations in patients with SJS, and it represents a sum of scores for conjunctival hyperemia, decreased tear volume (Schirmer test ≤1 mm/min), eyelid involvement, corneal involvement, limbal deficiency, and symblepharon formation.[13,14]

LSCD was diagnosed in the chronic phase of SJS/TEN by corneal specialists (O.J.Y., K.M.K.) based on the following clinical features: a loss of limbal palisades of Vogt,[20] irregular staining of the limbal and corneal epithelium with fluorescein, and the presence of superficial neovascularization of the cornea involving the limbus.

Patients were divided into 2 groups based on the development of LSCD, and each factor was compared between the 2 groups. The worst eye of each patient was chosen for analysis because all patients had bilateral ocular involvement.

• **STATISTICAL ANALYSIS:** GraphPad Software (GraphPad Prism, La Jolla, CA, USA) was used for statistical analysis. A nonparametric Mann–Whitney *U* test was used to compare quantitative variables between the 2 groups, and the Pearson χ^2 test was used to compare qualitative variables. Pearson *r* coefficient with a 2-tailed *P* value was calculated to assess the correlation between 2 variables. Data were presented as the mean ± standard deviation or median and interquartile range. Differences were considered statistically significant at $P < .05$.

RESULTS

• **DEMOGRAPHICS AND CLINICAL CHARACTERISTICS:** Of the 32 patients with SJS/TEN who were <16 years of age who visited Seoul National University Children's Hospital, 19 patients (38 eyes) met the inclusion criteria for this study. Thirteen patients (68%) had SJS and 6 (32%) had TEN. All patients were of Korean ethnicity. Demographics and clinical characteristics of patients are summarized in Table 1. The mean age at onset of SJS/TEN was 6.7 years (range 2 months to 16 years). There was a male predominance at a ratio of 2.2:1. The mean duration of hospital admission in the acute stage was 40.4 days (range 7-293 days). The median follow-up duration was 35.8 months (range 4 weeks to 162.5 months). One patient was followed up for 4 weeks, but the other 18 patients were followed up for >10 months (Supplemental Table 1; supplemental material available at AJO.com). Thirteen patients (68%) had no medical history, but 6 (32%) had underlying diseases, including seizure disorde (n = 2), leukemia (n = 1), nephritis (n = 1), major depressive disorder (n = 1), and juvenile

TABLE 2. Comparison of the Severity of Acute Systemic Involvement Between Patients With and Without LSCD

	Total (n = 19)	No LSCD (n = 13)	LSCD (n = 6)	*P* Value
Total score, mean ± SD	8.2 ± 2.3	7.2 ± 1.9	10.3 ± 1.5	.0038
Erythema (0-4), 1 point for oral erosive lesions with bloody scales, 1 point for labial erosive lesions with bloody scales, 1 point for oral or labial erosive lesions only, 1 point for genital involvement, mean ± SD	2.6 ± 0.6	2.5 ± 0.7	2.8 ± 0.4	.5573
Blisters (0-3), 1 point for >30% of total body surface area, 1 point for 10-30% of total body surface area, 1 point for ≤0-30% of total body surface area, mean ± SD	1.9 ± 1.0	1.8 ± 1.0	2.2 ± 1.0	.4118
High fever (≥38°C), n (%)	19 (100)	13 (100)	6 (100)	>.9999
Respiratory disturbance, n (%)	5 (26)	3 (23)	2 (33)	>.9999
Total necrosis of epidermidis, n (%)	3 (16)	2 (15)	1 (17)	>.9999
Liver dysfunction (0-2), 2 points for ALT or AST >100 and 1 point for 40 < ALT ≤ 100 or 40 < AST ≤ 100, mean ± SD	0.7 ± 0.8	0.4 ± 0.7	1.5 ± 0.5	.0051
Anemia (hemoglobin <10 g/dL), n (%)	2 (11)	1 (8)	1 (17)	>.9999
Pneumonia (infiltration in chest radiograph), n (%)	4 (21)	1 (8)	3 (50)	.0709
Kidney dysfunction (serum BUN >10 mmol/L), n (%)	10 (53)	6 (46)	4 (67)	.6285
CRP elevation (serum CRP ≥5 mg/dL), n (%)	13 (68)	7 (54)	6 (100)	.0442

ALT = alanine aminotransferase; AST = aspartate transaminase; BUN = blood urea nitrogen; CRP = C-reactive protein; LSCD = limbal stem cell deficiency; SD = standard deviation.

rheumatoid arthritis (n = 1). Oral drugs were the causative agents in all patients (Table 1). Antibiotics were the most common drug class responsible for SJS/TEN (n = 13, 68%), followed by antiseizure medications (n = 3), nonsteroidal anti-inflammatory drugs (n = 1), angiotensin-converting enzyme inhibitors (n = 1), and disease-modifying antirheumatic drugs (n = 1).

• **INCIDENCE OF LSCD:** LSCD developed in 6 of 19 patients (32%) at a median of 3.5 months (interquartile range 1-11 months) after the onset of SJS/TEN (Figure 1). To identify the factor(s) associated with LSCD development, each variable was compared between patients who developed LSCD (LSCD group) and those who did not (no LSCD group). The length of hospital stay in the acute phase was significantly longer in LSCD group compared with the no LSCD group (40.4 ± 68.2 vs 18.1 ± 8.7 days, $P = .0281$) (Table 1), an indication that acute systemic condition was poorer in patients of LSCD group. Otherwise, there was no significant difference in variables, such as age, gender, underlying diseases, or causative drugs between the 2 groups.

• **ASSOCIATION OF ACUTE SYSTEMIC OR OCULAR MANIFESTATIONS WITH LSCD DEVELOPMENT:** Severity of acute systemic manifestations, a measure of acute systemic involvement in SJS/TEN, was significantly associated with the development of LSCD. The ASS was significantly higher in the LSCD group than in the no LSCD group (10.3 ± 1.5 vs 7.2 ± 1.9 scores, $P = .0038$) (Table 2). This result is in line with longer hospital stays of patients with SJS/TEN in the LSCD group as shown in Table 1. Among the individual components of ASS, liver dysfunction score and serum C-reactive protein elevation (>5 mg/dL) were factors that were significantly associated with LSCD development ($P = .0051$ and $P = .0442$, respectively) (Table 2). In addition, the severity of acute systemic manifestations significantly influenced the development of chronic ocular complications, as indicated by a significant, positive correlation between ASS and COCS values ($R^2 = 0.3874$, $P = .0044$) (Figure 2).

However, AOS, a measure of acute ocular manifestations in SJS/TEN, was not significantly different between the LSCD and no LSCD groups ($P = .1970$). Similarly, no significant correlation was observed between AOS and COCS values (Figure 2).

• **EFFECTS OF ACUTE SYSTEMIC AND OCULAR TREATMENTS ON LSCD DEVELOPMENT:** Systemic treatment modalities in the acute phase of SJS/TEN (supportive care only, systemic corticosteroids, intravenous immunoglobulin, or combined therapy) did not have significant effects on the development of LSCD (Table 3).

As for ocular treatments, the use of therapeutic contact lenses in the acute stage was more common in the LSCD group than in the no LSCD group ($P = .0043$) (Table 3).

• **VISUAL AND OCULAR OUTCOME:** Overall, 75% of children with ocular SJS/TEN achieved a Snellen BCVA of 20/40 or better at the final follow-up, of which 25% had a BCVA of 20/20 or better (Figure 3). However, it was evident that the visual outcome was poor in patients with LSCD. The final BCVA was significantly lower in patients with LSCD compared with those without LSCD (1.33 ± 1.52

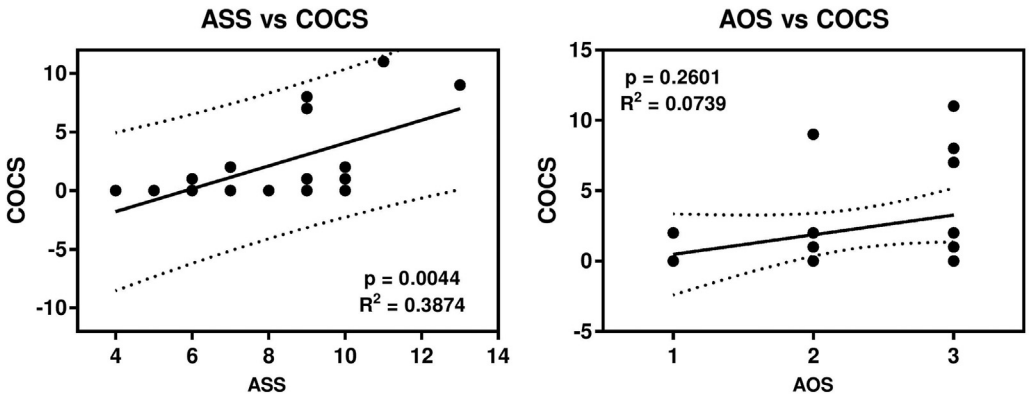

FIGURE 2. Correlation of chronic ocular complications with acute systemic or ocular manifestations. (Left) There was a significant positive correlation between acute systemic involvement score (ASS) and chronic ocular surface complications score (COCS). (Right) No significant correlation was observed between acute ocular involvement score (AOS) and COCS values. ASS and AOS were used as measures of acute systemic and ocular involvements in Stevens–Johnson syndrome/toxic epidermal necrolysis. COCS was used to grade the severity of chronic ocular sequelae in patients with Stevens–Johnson syndrome/toxic epidermal necrolysis.

TABLE 3. Systemic and Ocular Treatments

	Total (n = 19)	No LSCD (n = 13)	LSCD (n = 6)	*P* Value
Systemic treatment, n (%)				
Supportive care alone	2 (11)	2 (15)	0 (0)	
Conventional steroid	2 (11)	1 (8)	1 (17)	
IVIG	8 (42)	6 (46)	2 (33)	
Steroid plus IVIG	7 (37)	4 (31)	3 (50)	
Ocular treatment, n (%)				
Topical steroid	16 (84)	10 (77)	6 (100)	.1997
Bandage contact lens	7 (37)	2 (15)	5 (83)	.0043
Membrane peeling	11 (58)	6 (46)	5 (83)	.1271
Early AMT	3 (16)	1 (8)	2 (33)	.1542
Late AMT	4 (21)	0 (0)	4 (67)	.0039
PKP	3 (16)	0 (0)	3 (50)	.0206
Limbal transplantation	3 (16)	0 (0)	3 (50)	.0206
Fornix reconstruction	4 (21)	1 (8)	3 (50)	.0709

AMT = amniotic membrane transplantation; IVIG = intravenous immunoglobulin; LSCD = limbal stem cell deficiency; PKP = penetrating keratoplasty.

vs 0.05 ± 0.09 logMAR visual acuities, $P = .0055$) (Figure 3). Forty percent of eyes in patients with LSCD had a BCVA less than 20/200, whereas all eyes in the no LSCD group maintained a visual acuity of 20/40 or better (Figure 3). In addition, chronic ocular complications were more severe in the LSCD group than in the no LSCD group as indicated by higher COCS in the LSCD vs the no LSCD group (6.33 ± 3.98 vs 0.46 ± 0.78 scores, $P = .0013$) (Table 4). Although not statistically significant, the number of patients requiring fornix reconstruction was higher in the LSCD group than in the no LSCD group ($P = .0709$).

• **SURGICAL OUTCOME OF LSCD:** Penetrating keratoplasty combined with limbal allograft was performed in 3 of 6 patients with LSCD at a mean of 46.3 ± 14.4 months after the onset of SJS/TEN (Table 3). The graft infection occurred in all 3 patients (*Corynebacterium*, *Bacillus*, and *Candida parapsilosis*) at a mean of 4.33 ± 1.53 months after surgery (Figure 4), and the graft failure developed in 2 (67%) patients. The median survival time of the grafts was 4 months.

DISCUSSION

AS THE SURVIVAL OF PATIENTS WITH SJS/TEN HAS increased with the improvement of supportive care, chronic complications have emerged as significant problems that lead to deterioration of quality of life in patients with SJS/TEN. One of the most disabling complications is chronic ocular sequelae in the eyelids, conjunctiva, or cornea.[9,21] In particular, corneal vascularization and keratinization, the hallmark of LSCD, are directly associated with irreversible vision loss.

The pathogenesis of LSCD in SJS/TEN involves destruction of limbal stem cells caused by chronic ocular surface inflammation and replacement of the corneal epithelium by abnormal conjunctival tissue. For treatment of LSCD, limbal transplantation using the contralateral healthy eye (autografts) or allogeneic donor eye (allografts) is used.[22,23] Limbal autografts, however, are not possible because both eyes are involved in SJS/TEN. The outcome of limbal allografts is poor because of a high rejection rate despite long-term immunosuppression.[24] In addition, infection to the cornea is a frequent complication in patients with SJS/TEN with LSCD and results in poor visual outcome.[25] Therefore, the prediction and

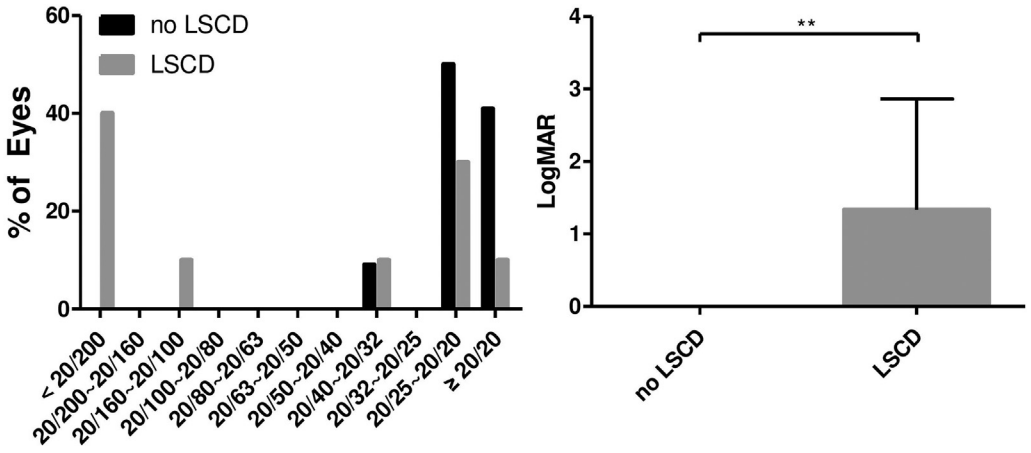

FIGURE 3. The visual outcome in patients with Stevens–Johnson syndrome/toxic epidermal necrolysis with and without limbal stem cell deficiency (LSCD). (Left) Distribution of number of eyes according to best-corrected visual acuity as measured with the Snellen chart at the final follow-up. (Right) The logMAR visual acuity in patients with LSCD vs those without LSCD.

TABLE 4. Comparison of the Severity of Chronic Ocular Surface Complications Between Patients With and Without LSCD

	Total (n = 19)	No LSCD (n = 13)	LSCD (n = 6)	*P* Value
Total, mean ± SD	2.32 ± 3.56	0.46 ± 0.78	6.33 ± 3.98	.0013
Chronic conjunctival hyperemia, n (%)	4 (21)	0 (0)	4 (67)	.0039
Decreased tear volume, Schirmer strip test ≤1 mm/min, n (%)	0 (0)	0 (0)	0 (0)	
Lid involvement (0-3): 1 point for trichiasis, 1 point for distichiasis, and 1 point for severe MGD, mean ± SD	0.47 ± 0.70	0.38 ± 0.65	0.67 ± 0.82	.4416
Corneal involvement (0-3): 1 point for superficial punctate keratitis, 1 point for corneal thinning, and 1 point for corneal opacity, mean ± SD	0.63 ± 1.01	0.08 ± 0.28	1.83 ± 0.98	.0002
Limbal deficiency (0-3), 1 point for partial corneal NV, 1 point for near total corneal NV with PED, 1 point for total conjunctivalization, mean ± SD	0.63 ± 1.26	0	2.00 ± 1.55	
Symblepharon (0-4), 1 point for each quadrant involved, mean ± SD	0.37 ± 1.12	0	1.17 ± 1.83	

LSCD = limbal stem cell deficiency; MGD = meibomian gland dysfunction; NV = neovascularization; PED = persistent epithelial defect; SD = standard deviation; SJS/TEN = Stevens–Johnson syndrome/toxic epidermal necrolysis.

prevention of LSCD are essential to reduce chronic ocular morbidity and avoid permanent visual impairment in patients with SJS/TEN.

In our study, LSCD occurred in 32% of children with SJS/TEN at a median of 3.5 months after an acute episode of the disease. An overall visual outcome was favorable because 75% of our patients achieved a BCVA of greater than 20/40, similar to a previous report.[10] In contrast, the surgical outcome and visual prognosis were unfavorable in patients who developed LSCD. Fifty percent of patients had a final visual acuity of greater than 20/40 in the LSCD group and 40% had less than 20/200, whereas all patients in the no LSCD group achieved a BCVA of greater than 20/40. Risk factors associated with the development of LSCD included severe acute systemic manifestations, longer duration of hospital stay, and the presence of corneal epithelial defect that required a bandage contact lens in the acute phase. These results collectively suggest that the long-term ophthalmologic examination is mandatory for children with SJS/TEN who presented with severe systemic manifestations and large corneal epithelial defects in the acute stage. Given that LSCD can occur in an eye without acute ocular involvement many months after an SJS/TEN attack (Figure 4), it is important to note that all patients with SJS/TEN should be followed up for a possibility of LSCD in the long-term. In this regard, our study is limited by the shorter follow-up period in patients in the no LSCD group: the follow-up period of patients in

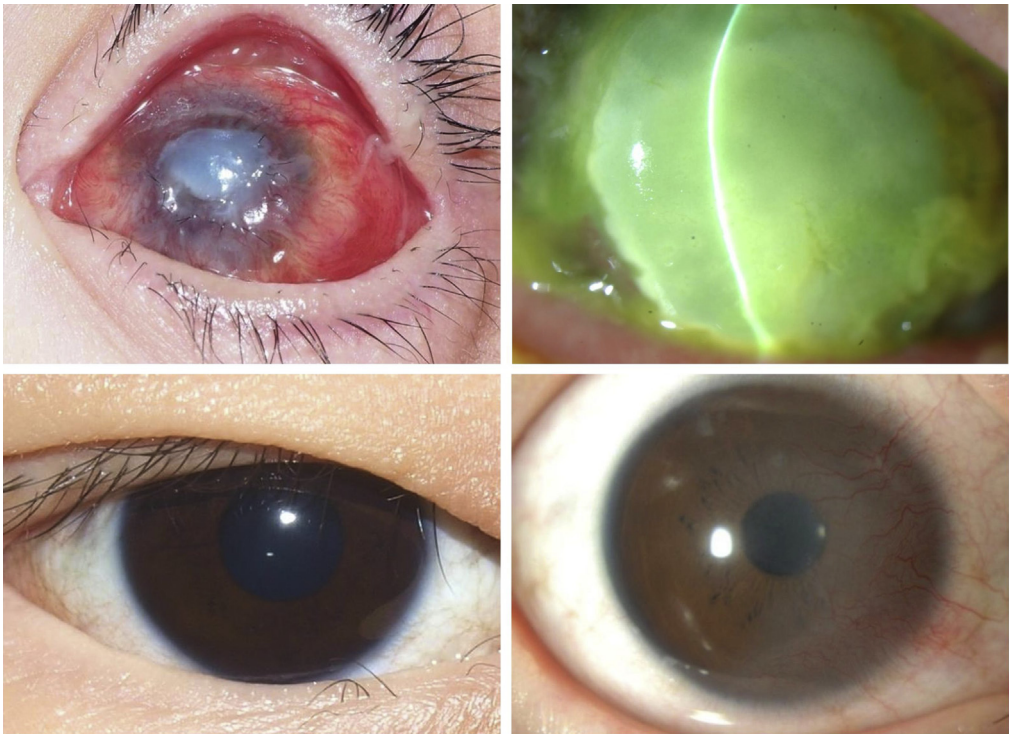

FIGURE 4. Anterior segment photography. (Top) Cases where graft infection developed after penetrating keratoplasty and limbal allotransplantation. The grafts were infected with *Corynebacterium* (top left) and bacillus (top right). (Bottom) A patient who did not have ocular involvement in the acute phase of toxic epidermal necrolysis (bottom left), but who later developed limbal stem cell deficiency at 55 months after the onset of toxic epidermal necrolysis (bottom right).

the no LSCD group (mean 38.4 months) was shorter than in the LSCD group (mean 75.4 months), with borderline significance ($P = .0577$).

There was no significant association between the severity of acute ocular and systemic manifestations ($R^2 = 0.0017, P = .8671$) as assessed by the scoring systems that our group previously adopted (AOS and ASS).[14] Consistent with the result, Morales and associates[26] reported that there was no correlation between the severity of eye involvement and acute systemic condition measured by the SCORe of Toxic Epidermal Necrosis system, another scoring system for the assessment of the severity of acute systemic status. Moreover, in our study, there was no association of AOS with LSCD development or with chronic ocular complications as evaluated by COCS. The results are inconsistent with our previous finding that AOS was significantly correlated with ASS and COCS.[14] This difference is likely related to the inclusion of both adult and pediatric patients in the previous study.[14]

The systemic administration of corticosteroids or immunoglobulin was not effective in preventing LSCD in our patients, which was consistent with previous reports by our group.[7,14] Therefore, more active therapy is needed for patients who are at high risk of chronic ocular complications and LSCD. In this regard, Gregory[27] recently developed a new grading system for the evaluation of acute ocular involvement in SJS/TEN during hospitalization and emphasized the importance of early amniotic membrane transplantation in the first week after the onset of symptoms to prevent significant ocular sequelae in patients with SJS/TEN with severe acute ocular involvement. Recent studies have also shown that timely therapy with prosthetic replacement of the ocular surface ecosystem or mucous membrane grafting during acute SJS helped preserve vision compared with conservative therapy alone.[8,28] Further study is necessary to investigate whether surgical treatment modalities as prosthetic replacement of the ocular surface ecosystem or mucous membrane grafting in an early phase might effectively prevent the development of LSCD and chronic ocular complications.

In conclusion, LSCD occurred in 32% of patients with SJS/TEN who were <16 years of age despite acute management according to the standard protocol. Since the visual prognosis was poor in patients who developed LSCD, frequent follow-up and aggressive management are required to prevent LSCD and subsequent long-term vision impairment in children with SJS/TEN.

FUNDING/SUPPORT: THIS RESEARCH DID NOT RECEIVE ANY SPECIFIC GRANT FROM FUNDING AGENCIES IN THE PUBLIC, COMmercial, or not-for-profit sectors. The following authors indicate no financial support or financial conflict of interest: Se Hyun Choi, Mee Kum Kim, and Joo Youn Oh. All authors attest that they meet the current ICMJE requirements to qualify as authors.

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