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# Ocular manifestations in acute stage Stevens-Johnson syndrome/toxic epidermal necrolysis - A retrospective study in a tertiary hospital in South India

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## Abstract:

**PURPOSE:** To describe the ocular manifestations in the acute stage of Stevens-Johnson syndrome/toxic epidermal necrolysis.

**MATERIALS AND METHODS:** We reviewed all the medical records of patients diagnosed with Stevens-Johnson syndrome/toxic epidermal necrolysis and erythema multiforme between 2012 and 2019. Demographics, ophthalmic manifestations, and the treatment given systemically and locally were reviewed and analyzed.

**RESULTS:** We had forty-five patients admitted to our hospital between Jan 2012 to Dec 2019 with SJS/TEN as a diagnosis. Twenty-six (57.5%) of them were females, and 19(42.2%) were males. The mean age was 27.5 years. Forty (88.9%) of our cases were diagnosed as Stevens-Johnson syndrome, and five (11.9%) as toxic epidermal necrolysis. We found antiepileptics as a triggering agent in thirteen cases (28.8%). Fever (84.4%) and mucosal lesions (86.7%) were the most common presenting symptom. We found ocular symptoms in only 22 (48.9%) patients. The treating physicians referred only thirty-one cases to the ophthalmologist, out of which 22 cases were referred within three days of admission. The most common ocular involvement was conjunctival congestion (69%). Ocular grading showed that mild grade included 42.9%, moderate grade 28.6%, and severe grade 28.6% of the cases. The ocular treatment involved medical management with lubricating drops (100%), topical steroids (58.6%), and topical antibiotics (68.9%). Five individuals with a severe grade of ocular involvement underwent amniotic membrane transplantation.

**CONCLUSION:** Ocular examination and grading are essential in the acute stage of SJS/TEN. It helps the ophthalmologist recognize the sentinel findings and institute appropriate treatment in the acute stage as early as possible.

## Keywords:

Acute stage, Amniotic membrane, Conjunctivitis, Ocular grading, Ocular manifestations, Stevens-Johnson syndrome, Toxic epidermal necrolysis

## Introduction

Stevens-Johnson syndrome (SJS) was first described in 1922 as a life-threatening autoimmune disease associated with blisters on skin and mucus membrane and has since remained a disease of poor understanding of

etiology and management. Multiple studies have evaluated the etiology, which shows that the disease remains a challenge to the medical fraternity.<sup>[1]</sup>

There have been various drugs, microorganisms, and genetic susceptibility

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implicated in the etiology of the SJS. There have been cases where an external trigger has not been identified in the etiology.<sup>[1-4]</sup> The treatment, too, remains as varied as its etiology. Some studies propose systemic steroid use, while some contradict the use of steroids. The effect of systemic steroids and immunomodulatory drugs on ocular manifestations also remains equivocal.<sup>[1,2]</sup>

The ocular manifestations have been reported in 50%–81% of the in-patients, and the common ocular involvement in the acute stage includes conjunctivitis, subconjunctival hemorrhage, and lid margin ulceration.<sup>[3]</sup> Ankyloblepharon, limbal stem cell deficiency, corneal vascularization, and dry eye are reported in the late stages of the disease.<sup>[4]</sup> The proportion of patients with long-term complications also varies; while Di Pascuale *et al.* reported a 71% occurrence of symblepharon, Chang *et al.* reported only 6.6% of the occurrence of symblepharon.<sup>[5,6]</sup> This variation has been attributed to access to ocular treatment in the acute stages of the disease. Thus experts have emphasized the need for ophthalmologists to be part of the primary team involved in the management to reduce long-term ocular morbidity.<sup>[7-9]</sup>

Ocular condition management involves medical treatment with lubricants, antibiotics, forniceal sweeping, topical steroids, and surgical management with amniotic membrane transplantation (AMT).<sup>[10]</sup>

We aimed to study the demographic patterns and the ocular manifestation in the acute stage of the disease and their proportion of involvement in a tertiary hospital in south India. This would lead us to understand the disease better and emphasize the need for an ophthalmologist to be part of the primary treating team managing the SJS and toxic epidermal necrolysis (TEN).

## Materials and Methods

After obtaining the ethical committee clearance from our Institutional Review Board (RAMAIAH MEDICAL COLLEGE MSRMC/EC/AP-07/03-2020), we conducted a retrospective observational study. We reviewed all the medical records of individuals admitted to the hospital from 2012 to 2019 with SJS and TEN's diagnosis. The patient consent is waived by IRB.

We collected demographic data, including age and gender. The systemic symptoms such as fever, mucosal involvement, skin involvement, and genital involvement were recorded. The triggering drug was identified, and any other systemic associations were noted. Ocular findings, including visual acuity, lid margin findings, conjunctival, and corneal involvement, were recorded.

As it was a retrospective study and examinations were done by multiple ophthalmologists, the recorded findings varied. Conjunctival involvement was noted as conjunctivitis if terms of "redness," "congestion," "conjunctivitis," "follicles," or "papillae" were recorded in the case sheet. If "membrane" or "pseudomembrane" was documented, it was considered as membranous conjunctivitis. If corneal involvement was not mentioned or written as normal, corneal involvement was noted as nil. We recorded corneal involvement for those cases where the corneal examination was recorded as corneal epithelial defects or haze. They were graded into mild, moderate, and severe based on the first ophthalmic documentation.

The ophthalmic treatment instituted was recorded, which could be either medical or surgical interventions. The surgical intervention included AMT with suture fixation. All patients underwent an ophthalmic examination as soon as the physician referred them, and after the first examination, each patient was examined either daily or on alternate days based on the severity of ocular involvement.

A study by Chow *et al.* revealed that the ocular manifestation amongst the cases of SJS/TEN is 53%.<sup>[11]</sup> Based on the study's findings with an absolute precision of 20% and desired confidence interval of 95%, it was estimated that 24 patients need to be enrolled in this study. On review of the medical records, we found that over 7 years, the number of patients admitted with the diagnosis of SJS/TEN was 45, and we included all of them as it was a retrospective study and we expected some data to be missing in some patients. We expressed the quantitative factors in terms of mean and standard deviation (SD) or median with interval range. We presented the qualitative parameters relating to visual acuity, the grade of ocular involvement, and management as percentages. Differences in mean values were tested for statistical differences by Student's *t*-test or by an appropriate nonparametric test of significance. Any association between the factors was studied by Chi-square or Fischer's test of significance. Data were analyzed using SPSS for Windows, Version 16.0. Chicago, SPSS Inc. Released 2008.

## Results

We had 45 in-patients over 7 years from January 2012 to December 2019. The mean age of patients was 27.5 years with an SD of 18.8 (range 1–74 years). Twenty-six of them (57.5%) were females, and 19 males (42.2%) with a female to male ratio of 1.37:1. The mean age among females was 29.8 years (SD 19.5), while in males, it was 24 years (SD 17.9). The mortality rate in our patients was 6.6% (3 cases).

Twenty-seven cases (64.3%) had no seizure disorder, and 15 (30%) patients had a known history of seizure disorder and were on antiepileptics. In 3 cases, data was missing. Twenty-eight individuals (62.2%) did not have any associated systemic disease, while three patients (6.7%) had rheumatoid arthritis and were on immunosuppressive drugs. Three cases were diagnosed as sepsis, and ten patients had multiple systemic disorders such as carcinoma, cardiovascular disease, and stroke.

The admission diagnosis included 40 (88.9%) SJS and 5 (11.1%) of TEN. We did not find any case documented as SJS-TEN overlap syndrome in the medical records. Of the total cases, 23 (52.1%) needed Intensive Care Unit (ICU) admission, and the remaining were managed in the ward.

When we analyzed the etiological factors, the history of drug intake was recorded as a trigger in 42 cases, and the remaining patients ( $n = 3$ ) did not give any account of drug intake. The cause remained unidentified. It could have been a viral or any infective etiology, which was not proven. The triggering drugs identified are shown in Table 1. Antiepileptics were the most common triggering drugs followed by antibiotics. Antiepileptics included phenytoin, which was seen in 11 (84.6%), and the remaining were due to carbamazepine 2 (15.4%). Antibiotics included fluoroquinolones and cephalosporins, whereas analgesics included ibuprofen. When we compared the age with the drugs involved, we found that below 20 years, antibiotics and analgesics were the most common trigger drugs and accounted for 65% of the cases, while in the age group 41–60 years, phenytoin accounted for 57.1% of the cases. In the age

**Table 1: Triggering drugs identified in Stevens Johns syndrome/toxic epidermal necrolysis**

Drug	Cases (%)
Antiepileptics	13 (28.8)
Phenytoin	11
Carbamazepine	2
Antibiotic and analgesic (ibuprofen and multiple antibiotics- fluoroquinolones/cephalosporins)	10 (22.2)
Analgesic alone (ibuprofen)	5 (11.1)
Antibiotic alone	6 (13.3)
Fluoroquinolone	3
Cephalosporins	3
Methotrexate	2 (4.4)
Indian traditional medicine	3 (6.7)
Unknown drug	3 (6.7)

**Table 2: Age-wise (years) triggering drugs for Stevens Johns syndrome/toxic epidermal necrolysis**

Age (years)	Antiepileptics (%)	Antibiotic and analgesic (%)	Indian traditional medicine (%)	Methotrexate (%)	Unknown (%)
1-20	3 (15)	13 (65)	2 (10)	0	2 (10)
21-40	5 (41.6)	5 (41.6)	1 (9)	0	1 (9)
41-60	4 (57.1)	2 (28.6)	0	1 (14.3)	0
>60	1 (33.3)	1 (33.3)	0	1 (33.3)	0

group 21–40 years and above 60 years, it was various drugs, and no single drug had a higher occurrence. The age-wise triggering drug has been shown in Table 2.

The presenting symptoms of the patients have been shown in Table 3. Mucosal lesions (86.7%) and fever (84.4%) were the most common complaint amongst the patients. Upon systemic examination, maculopapular rashes were the most common finding and were found in 30 (66.7%) cases, followed by bullae and hyperpigmentation. Genital lesions were seen in only 15 (33.3%) of the cases. Palms and soles were affected in 9 (20%) of the patients. There was no relation between the occurrence and severity of ocular involvement with genital ( $P = 0.655$ , Fischer's exact test) or buccal mucosal involvement.

Thirty-one patients (68.9%) were referred to an ophthalmologist, and the day of referral varied from 1 to 12 days after admission. Twenty-two cases (74.2%) were seen within 3 days. Of the 31 cases, only 29 patients had a documented ocular finding, and in two patients, data was missing. Ophthalmic involvement is shown in Table 4.

Twenty-seven patients had symmetrical ocular involvement, while two patients had asymmetric involvement. The conjunctival signs included congestion (39 eyes-67.2%), membranous conjunctivitis (12 eyes-20.6%), epithelial defect (10 eyes-17.2%), forniceal foreshortening (2 eyes-3.4%).

The most common corneal involvement was an epithelial defect, which was <3 mm. When corneal involvement was present, we found that all patients were referred by the physician within 3 days, probably due to increased pain.

The ocular disease severity was graded according to the available findings using a grading system, as suggested by Gregory<sup>[12]</sup> shown in Table 5. We included both severe and extremely severe grades suggested by Gregory *et al.* as a severe grade. Mild and moderate cases accounted for 71.4%. Visual acuity at presentation was compared to the severity of ocular involvement and was found to be unrelated, with 77%–83% in each group having a visual acuity greater than Counting fingers 6 meters on the bedside.

Four patients (out of 24) with SJS had severe grades, and only two patients (out of five) with TEN had severe

involvement. Only one individual who died had an ocular examination and was found to have a mild grade of ocular involvement. Of those who required ICU admission, 13 patients had mild to moderate ocular involvement, and five had severe involvement. However, when we analyzed severe grades, we found that 5 (83.3%) needed ICU treatment and only one was treated in ward.

The day of examination did not affect the detection of lid involvement. When seen within 3 days, 45.5% (10/22) had lid involvement, while, when seen after 4 days, 57.1% (4/7) had lid involvement, which was not statistically significant ( $P = 1$ , Fisher's exact test).

Systemic treatment analysis showed that 37 patients (82.2%) received systemic steroids, of which intravenous (IV) betamethasone was given in 22 (48.9%) of the individuals, IV hydrocortisone in 6 (13.3%), oral prednisolone in 8 (17.8%) and one case received IV methylprednisolone.

Seventeen of the individuals (80.9%) with ocular involvement were started on topical steroids, and

20 patients were started on topical antibiotics, which included chloramphenicol, tobramycin, and azithromycin drops. Cyclosporine was started in 5 patients, and these were the patients with severe grade. All the 29 patients who were examined were treated with lubricating eye drops.

Six individuals with severe grades were advised AMT, but only five individuals consented and underwent AMT. We followed all the patients who underwent AMT regularly as they were under the care of an ophthalmologist. Four of them had a mild dry eye, and three of them developed lid margin keratinization after 6 months, which required further treatment, but none had ocular surface keratinization. Best-corrected visual acuity was maintained in all of them above 6/12. The follow-up of these patients has been shown in Table 6. The patients with mild and moderate ocular involvement grades were lost for follow-up as these patients were not under the direct care of an ophthalmologist.

## Discussion

Ocular manifestations in the acute stage of SJS/TEN may vary and may not correlate with the late-stage complications, but if they are not recognized and treated appropriately by an ophthalmologist, it may result in ocular morbidity.<sup>[6,7,13]</sup> Hansen *et al.* in their study suggested that 50%–80% of the patients have acute ocular involvement, while 30%–50% of the initial cases continue to develop chronic ocular disease.<sup>[14]</sup> Hence it becomes important for the ophthalmologist to be part of the primary team managing the acute condition to identify and alleviate ocular involvement.

The mean age in our study was 27.5 years (SD 18.8), while many other studies showed a higher mean age of

**Table 3: Presenting symptoms in Stevens Johns syndrome/toxic epidermal necrolysis**

Symptoms	Cases (%)
Fever	38 (84.4)
Skin rashes	35 (77.8)
Mucosal lesions	39 (86.7)
Eye complaints (discharge, red-eye)	22 (48.9)

**Table 4: Ocular findings in Stevens Johns syndrome/toxic epidermal necrolysis**

Ocular findings	Cases (%)
Eye discharge	18 (65.5)
Lid involvement (erosions/keratinisation)	15 (51.7)
Conjunctival involvement	19 (69)
Corneal erosions	4 (13)

**Table 5: Grading of ocular involvement and visual acuity at presentation of Stevens Johns syndrome/toxic epidermal necrolysis**

Grade (Gregory <i>et al.</i> ) <sup>[12]</sup>	Cases (%)	Cases (%) with visual acuity > counting finger 6 m (bedside)
Mild: Conjunctival congestion	9 (42.9)	7 (77.8)
Moderate: Lid margin defect < 1/3 conjunctival epithelial defect < 1 cm	6 (28.6)	5 (83.3)
Severe: Lid margin defect > 1/3 defect, conjunctival staining > 1 cm, corneal punctate staining and epithelial defect	6 (28.6)	5 (83.3)

**Table 6: One year follow up of patients who underwent amniotic membrane transplantation**

Case	BCVA		Lid margin keratinization	Symblepharon	Ocular surface keratinization	Dry eye	Corneal vascularisation
	RE	LE					
1	6/12	6/9	+	-	-	+	-
2	6/6	6/6	-	-	-	-	-
3	6/9	6/36	-	-	-	+	+
4	6/12	6/9	+	-	-	+	-
5	6/9	6/9	+	-	-	+	-

BCVA=Best corrected visual acuity, RE=Right eye, LE=Left eye, + (present), - (absent)

41–52 years.<sup>[3,11]</sup> This dissimilarity may be because we included all the patients with ages ranging from 1 to 74 years. We saw a female preponderance with a female to male ratio of 1.37:1. Jongkhajornpong *et al.* also reported a similar finding in their study,<sup>[4]</sup> but other studies showed a male preponderance,<sup>[15]</sup> indicating that there might not be any gender predilection.<sup>[13]</sup>

Studies show that SJS accounts for 56%–73% of the cases, and TEN varies from 16% to 25% of all the patients requiring admission. Our study found that SJS accounted for 88.9% of the patients and TEN for 11.1% of the cases. The majority of the cases were SJS, and a relatively small proportion was contributed by TEN. We did not have any case of SJS/TEN overlap as they were not documented in the medical records. This could also be the reason for a higher proportion of SJS.

Studies have shown that antiepileptics and antibiotics are the most common triggers.<sup>[8]</sup> In our study, too, we found a similar association. However, we found that below 20 years of age, antibiotics were the most common triggering drugs and accounted for one-third of the cases, and amongst antibiotics; fluoroquinolones, and cephalosporins were commonly reported. In contrast, other studies have reported sulphonamides and clotrimazole as the most common antibiotics.<sup>[12,15]</sup> This variance could be due to the reduced use of sulphonamides by general practitioners. In the 40–60 years age group, antiepileptics were the most commonly reported triggers, with phenytoin accounting for over eighty percent of the cases.

Fever (84.4%) and mucosal lesions (86.7%) were the common systemic symptoms patients presented with, while ocular complaints were reported in only 48.9% of the patients. The primary treating physicians referred only 68.8% of the patients to ophthalmologists.

This is probably due to emphasis on life-saving measures in the acute stage or the primary physician's inability to recognize any involvement of the eye and thus failed to recognize the need for ophthalmology referral. We need to address this, as some ocular signs can be subtle and require an ophthalmologist to examine to identify them. The day of referral varied from 1 to 12 days, and of them, 74.2% were referred within 3 days. Nearly one-third of the patients were referred after 4 days. This needs to be considered a significant limitation in the comprehensive management of these patients. The primary physician needs to be aware that an early ophthalmology referral will result in an early ocular treatment institution. Kohanim *et al.* emphasize that the windows of opportunity should not be missed to provide the patient with the best possible treatment.<sup>[3]</sup>

Our study found that those with severe ocular involvement had a higher proportion (83.3%) of patients requiring ICU treatment, thus indicating that those with severe ocular involvement also had a severe systemic involvement warranting an ICU treatment. Though this was not statistically significant due to few case numbers, the treating physician needs to be aware of the need for ocular examination in patients admitted to the ICU and request an ophthalmologist referral at the earliest in all those admitted to the ICU.

Conjunctivitis was the most common finding in our study, seen in 65% of the cases. Other studies also confirm that conjunctivitis is the most common finding, followed by lid margin abnormalities.<sup>[7,16]</sup> There has been an emphasis on grading ocular findings in the acute stage and treat accordingly with medical or surgical management appropriate to the degree of the involvement. Topical antibiotics are indicated to prevent secondary infection, but we need to take care while choosing the antibiotic after considering the triggering agent. Topical lubricants are necessary to provide symptomatic relief and to reduce symptoms of dry eye.<sup>[12,13]</sup> Topical steroids have been shown to reduce long-term complications if instituted within the 1<sup>st</sup> week of the disease. Topical cyclosporine has also been suggested in some studies to improve the prognosis.<sup>[17]</sup> For severe grades of involvement, AMT has been shown to improve the ocular surface.<sup>[13-15,18]</sup>

In our study, we treated all patients with medical management, and severe cases underwent surgical management. The medical management included lubricants in all patients. Topical antibiotics, steroids, and cyclosporine drops were used only in moderate and severe grades. The grading of the ocular involvement helped us in identifying individuals requiring surgical management. Patients with severe grade underwent AMT with suture fixation within the first 10 days, as soon as the patient was deemed fit for surgery. The treatment protocols had also changed over the years. At the beginning of the study period, in 2012, the surgical management was not done in the acute stage, but after 2013, all patients who had severe grades underwent AMT in the acute stage to preserve the ocular surface. Surgical management was successful in limiting the ocular surface keratinization in all patients. All five individuals who underwent AMT were on regular follow-up. We successfully prevented ocular surface keratinization in all of them, but we encountered lid margin keratinization after 6 months in three of them. Four of the five individuals had mild dry eyes and required artificial tear substitutes. We were able to maintain the best-corrected visual acuity in all the patients. Patients with mild and moderate grades were lost to follow-up. The reasons could be that they were not under direct ophthalmologist

care or did not have any ocular symptoms. However, it is crucial to recognize that these patients require a regular ocular examination to identify long-term complications such as dry eye, lid margin keratinization which can be disturbing, and require treatment if identified early.

Sharma *et al.* described acute stage findings from north India, and in their study, 100% of the cases had eye involvement.<sup>[19]</sup> They reported only mild and moderate ocular involvement. They, too, emphasize that their institute being a super-specialty hospital, the cases were referred to the ophthalmology department earlier. There has not been any study describing the ocular manifestations in the acute stage of SJS/TEN in south India. Ours is the first study to describe these findings from south India. These cases are usually seen in general hospitals and not in specific eye hospitals, as life-saving measures are a priority during acute phase. Our study shows that 68.8% of the patients got an early ophthalmology referral because our institute is a tertiary hospital. We could institute early ophthalmic treatment for these patients with either medical or surgical treatment, depending on their eye condition. If the ophthalmologist is involved in the management only after the acute stage resolution, the window of opportunity is usually lost, and it becomes challenging to treat the complications once they are established. The study emphasizes the need for an ophthalmologist to be part of the treating team in the acute stage of SJS/TEN to recognize the early ocular signs and institute appropriate initial management. The ocular involvement may be variable and not related to the severity of the systemic involvement, and hence the ocular involvement must be graded by an ophthalmologist independent of the systemic involvement. Other studies have also emphasized that no correlation has been found between systemic involvement and ocular involvement severity.<sup>[13,20,21]</sup> Ocular treatment needs to be started simultaneously to the systemic treatment in the acute stage.

This study's limitations were that being a retrospective study, various ophthalmologists were involved in the management and hence recording of findings, and treatment could have occurred in a nonstandardized way.

In conclusion, comprehensive management of the patient in the acute stage of SJS/TEN is crucial in preventing long-term visual morbidity. An ophthalmologist needs to be part of the primary treating team, as early recognition and management of the ocular involvement can avoid many long-term ocular complications. The grading of ocular involvement in the acute stage is a useful tool that helps the ophthalmologist identify the sentinel

signs and helps in deciding about the need for surgical management in patients with severe grades.

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### Conflicts of interest

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

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