Prevalence of Chronic Ocular Complications in Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis

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INTRODUCTION

The aim of this study is to identify the proportion of patients who develop long-term ophthalmic complications regardless of acute ocular involvement and treatment. The study was conducted in Cape Town, South Africa and most of the study participants were indigenous black African and mixed-race patients. Most came from areas in Cape Town with low socioeconomic circumstances and a high prevalence of HIV. Owing to high incidence of HIV infection and the use of nevirapine, the Groote Schuur Hospital in Cape Town is experiencing a surge in the amount of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) admissions. This has added to the general incidence of SJS and TEN from other medications. The Dermatology Department at the Groote Schuur Hospital has since the rollout of anti-retroviral medication in the early 2000’s experienced an increase of 95% of SJS or TEN admissions.

No other studies have compared chronic ocular complications on HIV-positive and HIV-negative patients resulting from SJS and TEN.
and TEN. A secondary aim was to see if HIV infection affects the long-term outcomes of ocular complications resulting from SJS and TEN.

The extent and severity of chronic ocular manifestations were graded. Clinical involvements of the external ocular structures were graded according to the new grading system formulated by Sotozono et al.¹

**METHODS**

Patients with a confirmed dermatological diagnosis of SJS and TEN were recruited from a database from the Department of Dermatology. A total of 54 consecutive living patients diagnosed between January 2003 and November 2009 were recruited for the study.

Participants included patients with a dermatological diagnosis of SJS or TEN that were admitted and treated for their dermatological disease at a tertiary hospital with a follow-up of 6 months or longer. In addition, both eyes of patients were included, even if there was no clinical evidence of involvement. Patients were excluded if they had any previous eyelid or ocular surface surgery or refused recruitment.

Ethical approval was granted by the University Ethics Committee.

The medical history, ophthalmic examination findings, HIV status and CD4 count of each patient, as well as their medical history, was captured on an itemized data collection form. The degree of involvement was classified into 13 components of three categories: Corneal (Table 1), conjunctival and eyelid complications (Table 2).

A score of 0-3 reflected increasing severity, with 0 representing no involvement.

Tear break-up times were measured for each eye, and the tear film stability was assessed. Each eye was graded, and a score representing the total of the sub-scores was assigned. This severity score could therefore range from 0 to 39, with 39 representing the worst affected.

Data were analysed using Stata version 11.1 (StataCorp LP, 4905 Lakeway Drive College Station, TX 77845 USA). Normality of the data was estimated using the Shapiro-Wilk test. Medians, ranges and interquartile ranges (IQR) were estimated for nonnormally distributed variables. Proportions and 95% confidence intervals (CIs) were estimated adjusting for clustering by patient where both eyes were analysed. The nonparametric Wilcoxon rank sum (Mann-Whitney) test was used to compare two medians, and the Kruskal-Wallis test was used when three or more medians were compared, because the

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**Table 1: Corneal complications**

| Severity of superficial punctuate keratopathy | Staining of <1/3 of the corneal surface
| Staining of >1/3 but <2/3 of corneal surface | Staining of >2/3 of the corneal surface
| Corneal epithelial defect | Epithelial defect involving <1/4 of the corneal surface
| Epithelial defect involving >1/4 but <1/2 of the corneal surface | Epithelial defect involving >1/2 of the corneal surface
| Loss of the POV | Loss of <1/2 of the circumference of the POV
| Loss of >1/2 of the circumference of the POV | Total loss of the circumference of the POV

**Conjunctivalization**

| Conjunctivalization involving <1/4 of the corneal surface
| Conjunctivalization involving >1/4 but <1/2 of the corneal surface
| Conjunctivalization involving >1/2 of the corneal surface

**Corneal neovascularization**

| Neovascularization confined to the corneal periphery
| Neovascularization extending up to the pupil margin
| Neovascularization extending beyond the pupil margin into the central cornea

**Corneal opacification**

| Partial obscuration of iris details
| Iris details poorly seen with pupil margin just visible
| Complete obscuration of iris and pupil details

**Corneal keratinization**

| Keratinization involving <1/4 of the corneal surface
| Keratinization involving >1/4 to 1/2 of the corneal surface
| Keratinization involving >1/2 of the corneal surface

POV: Pâsaudes of Vogt

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**Table 2: Conjunctival and eyelid complications**

| Conjunctival complications |
| Conjunctival hyperemia |
| Mild or sectoral engorgement of the conjunctival vessels
| Moderate or diffuse engorgement of the conjunctival vessels
| Severe hyperemia or significant engorgement of the conjunctival vessels

| Symblepharon formation |
| Symblepharon formation only involving the conjunctival surface
| Symblepharon formation involving <1/2 of the corneal surface
| Symblepharon formation involving >1/2 of the corneal surface

**Eyelid complications**

| Trichiasis: Total area of the upper and lower eyelids combined |
| Trichiasis involving <1/4 of the lid margin
| Trichiasis involving >1/4 and <1/2 of the lid margin
| Trichiasis involving >1/2 of the lid margin

| Mucocutaneous junction involvement |
| Mild irregularity of the mucocutaneous junction
| Moderate irregularity of the mucocutaneous junction
| Severe irregularity of the mucocutaneous junction

| Meibomian gland involvement |
| Yellowish-white oily fluid expressed
| Thick cheesy material expressed
| Inability to express any fluid

| Punctal involvement |
| Iatrogenic punctal occlusion (e.g., punctal plugs or sutures)
| Either superior or inferior puncta occluded by scarring
| Both superior and inferior puncta occluded by scarring

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Data for eyes were clustered by patients. Somers-D P values were used. The nonparametric Spearman’s correlation coefficient was used to estimate the relationship between two scores.
RESULTS

A total of 108 eyes of 54 patients were included in the study. There were 28 males and 26 females. The median age at diagnosis was 37 years and ranged between 12 and 74 years, the IQR was 26–47. Medications were the cause in all cases. The most common associated drugs were: Antibiotics (28%), anti-retroviral (34%) and anti-epileptic (22%) medications. Thirty-two (59.3%) patients were HIV-positive, with CD4 counts ranging between 6 and 521 (median 171.5 and IQR of 112–202) at the time of dermatological diagnosis.

Only six patients (11%) needed initial consultation and treatment by an ophthalmologist in the acute phase because of epithelial or conjunctival defects. However, 6 months or more after the initial presentation, 48 (89%) patients had developed chronic ocular complications.

Of the seven components of corneal complications, the loss of palisades of Vogt (POV) was the most common (85.2% [95% CI 75.4–95.0]). In most cases, loss of more than half of the circumference of the POV was noted. Superficial punctate keratopathy (SPK) was present in 81.2% of cases and could most likely be attributed to the instability of the tear film.

Among the six components of conjunctival and eyelid complications, mild mucocutaneous junction abnormalities were the most common, with 79.6% (95% CI 68.5–90.7) of patients affected, followed by mild conjunctival hyperemia at 40.7% (95% CI 31.5–50.6). Nine patients (17%) in the cohort had moderate to severe lid complications, which included trichiasis and mucocutaneous junction abnormalities. These patients’ severity scores ranged between 19 and 29 and were the worst affected visually, with visual acuities ranging from 6/24 to counting fingers. These nine patients had extensive corneal opacification, which accounted for the low final visual acuity. Even though, there was no statistically significant (P = 0.07, Spearman’s rho = 0.8) correlation between the extent of corneal complications and the eyelid abnormalities, there was clinical significance between the extent of eyelid complications and corneal opacification.

The overall severity scores ranged between 0 and 29, the median score was 9, and the IQR was 2.0–2.5. Despite the high percentage of chronic ocular complications, most patients had good Snellen visual acuities ranging from 6/6 to 6/18, with an average visual acuity of 6/13.4. The average visual acuity of the six patients who were assessed by an ophthalmologist for their acute ocular complications was 6/12.1. The average visual acuity of the patients who were not assessed by an ophthalmologist in the acute stages was 6/11.4 and was not statistically significant (P = 0.045).

The severity scores were worse in females compared with males medians and IQRs 3.5 (2.0–8.0) compared with 4.5 (3.0–11.0) respectively, but these differences were not statistically significant (Wilcoxon rank sum test z = −2.33, Somers-D P = 0.09).

There was no statistically significant difference between severity scores between HIV-positive and HIV-negative patients (Wilcoxon rank sum test z = −0.87, Somers-D P = 0.54). Further, by restricting the analysis to only HIV-infected patients, no statistically significant difference was found in severity scores by CD4 category (<200, 200–349, 350+, Kruskal–Wallis Chi-squared test = 1.09 with 2 d.f. Somers-D P = 0.4).

DISCUSSION

Stevens-Johnson Syndrome and TEN are complex immunological syndromes that is characterized by mucocutaneous blistering of the skin and at least two mucous membranes.1 Both are part of the same disease entity and differ only in severity. A typical lesion has the appearance of a target; this is considered pathognomonic.2 Males are affected more than females, and it can occur at any age.3 The disease is thought to be either a delayed hypersensitivity reaction to certain medications or a response to epithelial cell antigens modified by drug exposure.4 Genetic predisposition may also play a part due to a genetically determined enzyme deficiency for the metabolites of certain medicines.5

According to certain studies, 27–80% of cases progress to severe ocular disease during the acute dermatological disease. Ocular complications of SJS and TEN during the acute phase include conjunctival chemosis, conjunctival and corneal epithelial defects, corneal ulceration, corneal perforation, endophthalmitis, and membrane formation.

It is not clear whether early intervention in the acute stages of SJS and TEN will limit ocular complications in the future. Further, it is not known why patients who have no ocular involvement in the acute stages of SJS or TEN develop chronic ocular complications after the dermatological disease has ceased.

Treatment of acute ocular manifestations usually begins with an aggressive lubrication of the ocular surface. Most ophthalmologists use topical steroids, antibiotics, and symblepharon lysis as a part due to a genetically determined enzyme deficiency for the metabolites of certain medicines.6

External ocular complications due to SJS and TEN are associated with severe visual morbidity. Around 27–80% of hospitalized patients with SJS and TEN develop acute ocular complications.1 According to De Rojas et al. chronic complications occur in 35% of patients with SJS and TEN.7 There has been no standardized method for the classification of chronic complications of SJS and TEN, and each publication in the literature used its own classification system. This might have led to an under-estimation of true chronic complications, as almost 90% of patients examined in our study had chronic complications. We found the classification used by Sotozono et al. useful in the analysis
of our results. However, we added tear break-up time to the classification for comparison with other studies.\textsuperscript{3}

This study confirmed previous findings that the severity of acute external ocular complications does not predict chronic complications.\textsuperscript{4} Of the 11% of patients in our study that had an initial ophthalmological assessment, all had chronic complications but were not necessarily the worst affected of all participants. Our study thus confirms that acute ocular involvement may give rise to significant chronic complications, but it should only be regarded as a risk factor.\textsuperscript{5,6}

All patients received preserved lubrication during the acute phase of their treatment. It is possible that preservatives may cause ocular surface damage and consequently may have increased the incidence of chronic complications.\textsuperscript{7,8}

This is the first study of its kind that has compared the outcomes of patients who were HIV-positive and HIV-negative in Africa. As HIV-positive patients have a high prevalence of dry eye syndrome, it was not surprising that 81% of patients in this study had SPK secondary to tear film instability.\textsuperscript{9} This proportion was higher than previously reported.\textsuperscript{10} We found there was no statistically significant difference between tear break-up times between HIV-positive and HIV-negative patients ($P = 0.98$).

The management of chronic ocular complications due to SJS and TEN should be directed at minimizing ocular surface inflammation. The visual rehabilitation in patients with severe ocular involvement resulting from chronic complications is difficult and often frustrating for both the patient and the ophthalmologist.

The study has several weaknesses. Only 54 patients were recruited for the study. Several patients were deceased from their complications of HIV infection, which might have caused a gross underestimation of complications.

The fact that patients were seen prospectively and the data were not collected from case notes makes the recording of data objective and more accurate. All patients that were examined were seen by only one ophthalmologist to standardize the recording of the chronic complications. However, this is one of the largest series of its kind at a single unit.

We suggest that all patients with SJS and TEN should be on long-term lubrication as most will suffer from dry eye syndrome. All patients should have an ophthalmological assessment to initiate chronic medication if indicated; however, unless eyelids are severely damaged, specialist ophthalmological intervention is unnecessary. Eyelid damage causes corneal opacification and is the main cause of visual acuity loss. Further, a standardized classification system should be adopted for clinical use and to standardize future studies.

Continued research is necessary into treatment of the acute stages of the disease to prevent long-term complications.

We conclude that most patients will suffer from a wide variety of chronic ocular complications following SJS and TEN. Most complications are ocular surface abnormalities and not necessarily vision-threatening complications. The loss of Vogt’s palisades and dry eye syndrome with SPK were the most common complications. Poorer visual outcomes can be expected if there are severe eyelid complications. HIV status and low CD4 count were not a risk factor for more severe outcomes. All patients with SJS or TEN should have an ophthalmological evaluation regardless of initial monocular involvement.

**REFERENCES**


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