ORIGINAL ARTICLE

Ocular manifestations and outcome of treatment of Stevens-Johnson Syndrome: experience at a Nigerian University Teaching Hospital

Chuka M **OKOSA**[1]
Chinedu C **ANAJEKWU**[2]
Ugochukwu V **EKPE**[1]

[1]*Department of Ophthalmology Guinness Eye Centre Nnamdi Azikiwe University Teaching Hospital Onitsha Anambra State, NIGERIA*

[2]*St Charles' Borromeo Hospital Onitsha Anambra State, NIGERIA*

Author for Correspondence
Michael Chuka **Okosa**
Department of Ophthalmology
Guinness Eye Centre
Nnamdi Azikiwe University
Teaching Hospital Onitsha
Anambra State, NIGERIA

Email: chukamokosa@yahoo.com
Phone: +24-803-714-4605

Received: October 6th, 2012
Accepted: June 30th, 2013

ABSTRACT

Background: Stevens-Johnson Syndrome (SJS) is an immune-based reaction, usually to drugs, resulting in muco-cutaneous eruptions that lead to sores that heal with variable degrees of scarifications. Ocular surface and adnexal inflammation and cicatrisation occur, resulting in degrees of ocular motility, tear-function, and visual defects. Documentation of this disease is abundant in West Africa but reports on the management of the ocular complication deployed and their outcome are scarce.

Objective: The objective of this paper is to document our experience of the eye complications of this disease at a tertiary eye center in Nigeria, management deployed, and outcomes of the treatment.

Methodology: This is a retrospective study of seven patients with SJS who presented between 2006 and 2010 at Guinness Eye Center Onitsha evaluated by principal investigator (OMC) and other members of the team (ACC and EVU). Relevant data were extracted from clinical history, physical, ocular examinations and laboratory studies done, treatment administered, with the outcomes.

Results: Commonest precipitating factors were anti-malarial medications used in self-treatment, and bought as over the counter drugs. Full blood count, urinalysis and HIV tests were all normal. Management included medication in all and surgery in three.

Eventual adnexal and ocular surface cicatrisation depended on how early the patient presented to hospital. Final visual acuity depended on presenting visual acuity, how early in the disease patients presented, degree of inflammation and the degree of ocular surface cicatrisation.

Conclusion: Ocular involvement in SJS results in widely differing degrees of ocular disability. Management involves medications and surgery. Treatment of severe cicatrisation gave disappointing visual results.

Keywords*: Cicatrisation, conjunctival congestion, medications, outcome, surgery*

INTRODUCTION

Stevens-Johnson Syndrome (SJS) is muco-cutaneous expression of immune-based reaction first described in 1922.[1,2] Implicated causes include therapeutic agents, micro-organisms, malignancies and radiation treatment.[3,4, 5,6] All age groups are affected, and degrees of manifestation vary, leading to different names.[1,7,8,9] SJS is a multi-systemic illness with onset characterized by headaches, malaise, fever, arthralgia and upper respiratory tract symptoms, occurring a few days to weeks after exposure.[8] It manifests as rash-like lesions, areas of necrosis on the skin

and mucous membrane of the gastro-intestinal, respiratory, oro-genital systems and eyes.[1,2]

Mucous membrane lesions heal by cicatrisation, stricture formation and varying degrees of disability, consequently.[1] This affects the eyelid, conjunctiva and cornea resulting in anatomic distortions, functional disability or even blindness.[10,11] Although skin biopsy may be helpful in diagnosis, the disease is usually diagnosed based on clinical criteria as there is no single diagnostic laboratory test.[12,13] Also, in some racial groups, some genetic markers have been described as being risk factors to SJS/TEN if certain drugs are used, but in general it appears there is no way of predicting with any degree of certainty who is at risk.[14,15,16]

The investigators were intrigued by this disease on its first presentation in 2006 of a patient with severe visual disability from this disease at Guinness Eye Centre Onitsha. We were unable to access data that focused on treatment of his stage of the disease and the outcome, to answer his questions. Subsequent cases presenting in later years, though few, were carefully documented. These cases were the subject of this retrospective study.

The objective of this report is to present manifestations, ocular complications, treatment administered and their outcomes, in patients who presented to Guinness Eye Centre Onitsha from 2006 to 2010 with SJS. The report aims at contributing to the knowledge base in this frequently visually devastating disease for better management of the condition.

METHODOLOGY

This is a retrospective descriptive study of seven patients diagnosed with SJS seen by the authors from January 2006 to December 2010 at Guinness Eye Centre Onitsha, Nigeria. All the affected patients were examined by the principal investigator and at least one other member of the team, at presentation and subsequent follow-up. Scores allotted to severity of various ocular effects were given in agreement by the investigators.

Tear film deficiency was assessed using value of marginal tear strip with aid of moistened fluorescein strip staining of the lower bulbar conjunctiva. Diagnosis was clinical, based on the skin lesions. Amateur illustrative photographs were taken with patients' consent for documentation and follow-up purposes at the time of presentation. All treatments were with full and informed consent of the patients and their relatives and signed consents for all surgical procedures. Follow-up period varied from 18 months to three years. Laboratory studies, done included full blood count, dipstick urinalysis and HIV screening.

RESULTS

Patients with SJS were 7 out of 83,200 newly registered patients presenting to the Centre at the study period - an incidence of 0.0084%. They were three males and four females, and were all in the age range 21-30 years. Three of them were students; one was a musician, one an apprentice trader, one on national youth service and one a lawyer.

Onset was within 3–4 days after exposure to the provoking substance, in all cases, as depicted in Table 1, but overdose did not seem to have been implicated in any of the cases. None had any known systemic allergy or previous reactions to drugs. They were also unable to volunteer if they had used the suspected drugs on a previous occasion.

Presenting complaints were conjunctival congestion, watering, grittiness/soreness and defective vision in all of them; photophobia in 6 (85.7%); symblepharon in 3 (42.9%); and double vision in 1 (14.3%). Both eyes of each patient had about the same severity of ocular effects depicted in Table 2, required the same treatment - medical or surgical; final visual outcomes were identical as shown in Table 3.

Table 1. Showing the provoking substances among patients with SJS and severity of ocular morbidity

Provoking Substances	No. of Patients	Severity of Ocular Morbidity
Camoquine	1	++
Maloxine from patent medicine seller	1	++
Mepacrine from patent medicine seller	1	++++
Unknown antibiotic + anti-malarial mixture from a pharmacist for a febrile illness with malaise	1	++
Farm activity	1	+++
Co-trimoxazole / prednisolone combination for toxoplasmic chorio-retinitis from ophthalmologist	1	+
Unknown mixture of drug from patent medicine stores for febrile illness	1	++
TOTAL	**7**	

Scores (+) awarded for: presence of inflammation (+), ocular motility defect (+), visual acuity defect-less than 6/18 (+) and dry eyes as evaluated by marginal tear strip and fluorescein staining (+)

Table 2. Findings observed in the eyes of seven patients presenting with SJS

Ocular Signs	No. of Eyes
Conjunctival congestion	7 (100%)
Conjunctival scarring	5 (71.4%)
Conjunctival keratinization	3 (42.9%)
Corneal ulcer/infiltration	3 (42.9%)
Corneal scar	2 (28.6%)
Adherent leukoma	2 (28.6%)
Pannus/pseudopterygium	3 (42.9%)
Symblepharon	4 (57.1%)
Mechanical ptosis	4 (57.1%)
Fusion of upper and lower eyelids together	1 (14.3%)
Dry eye condition	6* (85.7%)

**N/B: One patient had fused lids and tear meniscus could not be evaluated.*

The appropriate medical treatment was topical betametazone-neomycin in all seven, hypromellose in 6 (85.7%), chloramphenicol in 3 (42.9%) and oral prednisolone in 1 (14.3%).

Table 3. Depicting visual acuity at presentation and at 6 months after intervention in 14 eyes affected by SJS

Visual Acuity	At Presentation	At 6 months After Intervention
6/18 or better	6 (42%)	6 (42%)
Less than6/18 up to 6/60	0 (0.0%)	0 (0.0%)
Less than 6/60 up to 3/60	0 (0.0%)	5 (35.7%)
Less than 3/60 up to 1/60	6 (42%)	1 (7.1%)
Less than 1/60 up to perception of light	2 (14.3%)	2 (14.3%)
No perception of light	0 (0.0%)	0 (0.0%)

Number and percentage represent Eyes
The single determinant to final visual acuity appears to be presenting visual acuity

Surgical procedure carried out to correct anatomical distortion causing functional defect in the affected eyes were 'rodding' in 4 (28.6%), symblepharon division 4 (28%), pannus / pseudopterygium separation / excisionin 4(28.6%), blepharoplasty 2(14.3%), and fornices reformation 2(14.3%).

Three patients had a final visual acuity of 6/6 and better. They presented early in the disease with presenting visual acuity of 6/18. Three patients who presented with visual acuity of between 3/60 and HM had final visual acuity of 6/60 or less. Details of results as to precipitating substances, presenting features, presenting and final visual acuity is shown in Tables 1 to 3. Simple percentages were used to describe relationship between proportions. Some illustrative pictures in Figures 1 to 3 depict some of the features encountered in two severely affected patients.

Full blood count and erythrocyte sedimentation rate in all the patients were normal. Routine dipstick urinalyses were normal in all seven patients. Proteinuria was

found in one of the female patients at presentation but was absent on repeat test 2weeks later. None of these patients tested positive for HIV using ELISA screening test. Tissue typing was not done because the facilities were not available.

DISCUSSION

Although no data exists about the prevalence of this condition in Nigeria like with most other health indices, SJS/TEN is not common. This report of seven patients among 83,200 hospital eye patients gave a prevalence of 0.008% for the disease and compares with a similar low rate of 1-1.4 in 1million in Europe, and 6 per 1 million people in USA.[17,18] The presented cases may not proportionately represent usual ocular consequences as people with less severe ocular involvement may prefer non-orthodox treatment - a very common health-seeking behavior in Nigeria.[19]

In contrast to the mode of acquiring the disease from prescription of medicine from medical practitioners as reported from different places only one of the seven (14.3%) patients in this series could be linked to such, see Table 1.[3,4,6,14,15] Four of them utilized the common practice of many Nigerians to obtain treatment of disease from non-medical personnel or 'chemist' for reasons which include but not limited to, difficulty in accessing health care, preference, poverty and ignorance.

Onset of the disease in six out of the seven was characterized by symptoms self-diagnosed as malaria - malaise, fever, headaches and rashes. In 5 (71.4%), these symptoms occurred following drug treatment for malaria – quinacrine, amodiaquine, sulphadoxine+pyrimethamine combination. Four of these patients got the disease from self-treatment.

Time of presentation for eye care after onset of the disease varied from seven days (three patients) to four years, but all of them presented with ocular surface inflammation and visual disturbances. The spectrum of ocular and adnexal effects from the acute disease, and its healed sequelae compare with findings by other observers.[2,10,11] All patients in the current study reported acute conjunctival inflammation at the time of occurrence of the disease and those who presented months or years after the acute episode have experienced recurrent conjunctivitis.

On follow-up, all the patients were found to have dry eyes of various degrees indicating damage to tear producing glands, and 5 (71.4%) had severe visual defects due to chronic sequelae. This compares with findings by Haber and his colleagues who found 80% of SJS/TEN patients on admission had acute ophthalmic problems, but contrasts with their rather low 35% chronic sequelae.[20]

In contrast to reports that have associated SJS with HIV positivity in Africa tending to suggest that SJS may be a marker for HIV positivity, none of the affected patients in this series tested positive to ELISA screening test for HIV.[21,22,23,24] Other workers in other places have not described an association between the two conditions.[12,15,16,18] This suggests that any association could be co-incidental, being probably a reflection of the prevalence of HIV positivity in a community.

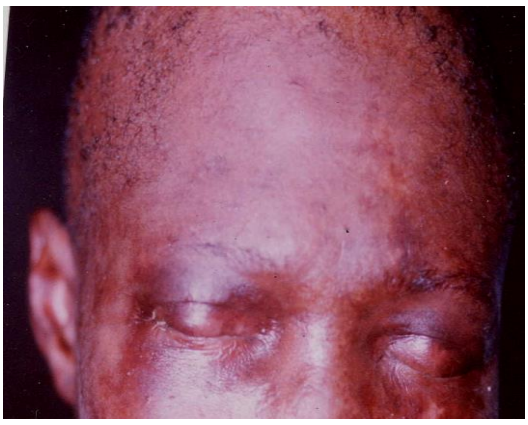
Medical treatment documented here was for both acute stage disease and late presenting patients, majority (five of seven patients) of patients presented after substantial ocular damage has occurred, a phenomenon previously noted by Shay and colleagues because of prior attention to the more dramatic skin lesions.[25]

Episodic flare-up of acute bilateral red eye was observed in all patients in this series, agreeing with findings by De Rojas, Dart, and Saw.[26] Empirical treatment of these flare-ups and acute stages of the diseases with glucocorticoids/antibiotic combination eye drops, were found beneficial, although we acknowledge the controversy surrounding the use of steroids in this condition.[1,7,27,28,29]

The most common medications we found necessary - artificial tears, topical steroid and topical antibiotic - agree with previously documented reports.[10] One patient developed bilateral peripheral corneal melting within four days of using diclofenac drops, used eight-hourly as a substitute for corticosteroid eye drop. The cornea healed rapidly on withdrawal of the drug and eye patching. Tear substitute was found necessary in all seven patients (100%) at some point in their treatment or follow-up to relieve symptoms of dry eyes, and 5 (71.4%) needed to use it on a permanent basis.

The surgical procedures done were to relieve strictures that were either restricting ocular motility or were cosmetically unacceptable, or to remove pannus that was occluding vision. The procedures were all on the ocular surface and lid. One affected patient who presented one year after onset needed repeat division of re-occurring symblepharon at six-monthly intervals for the subsequent 24 months, and for 12 months after this period.

Figure 1. Facial lesions of a severely affected girl at 6months; note hypo- and hyper-pigmented lesions and patchy alopecia; both eyes have upper and lower lids 'welded' together, occluding the eyeball



Lid and conjunctival surgery was found necessary in four of the patients, see Figures 1,2 and 3; three of them presented months to years after the acute episode. One patient (Figure 3) who presented five years after the onset of SJS had extensive fibrotic membrane /pseudopterygium abuting on the papillary area peeled off the cornea, and hypromellose was used subsequently as artificial tears. Hypromellose was found inadequate to relieve his symptoms of grittiness or to maintain corneal surface glistening and corneal transparency two days after the procedure. There was no improvement in vision although the membrane did not reform after 12 months of follow-up.

Figure 2. Same patient (figure 1) one day after surgery separating eyelids; reformation of tissue bands is worse in left eye

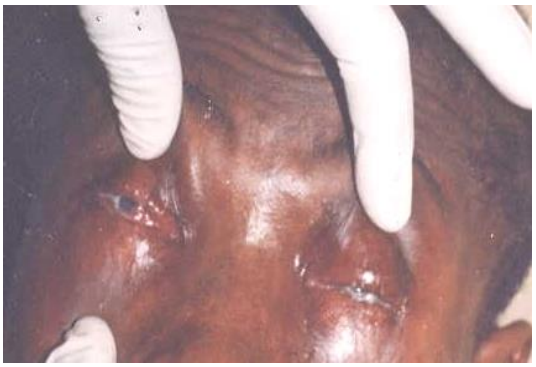
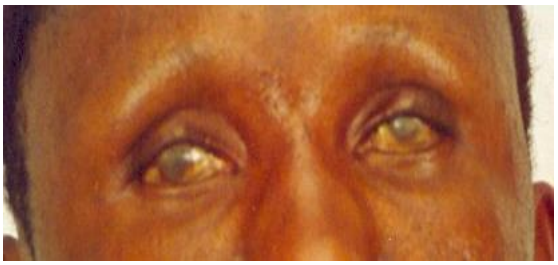


Figure 3. Severely affected SJS patient 4years after acute phase; note frontal alopecia, facial pigmentary changes, obliteration of lower fornix, and pannus from conjunctivae to corneas



Visual recovery was not achieved in three who presented with visual acuity of less than finger counting at three meters, in spite of successful lid and conjunctival anatomical reconstruction. This compares with report by Wright and Collins of good anatomical result from simple lid surgery to correct lid mal-position caused by SJS.[30] Timing of surgery appears critical as in severely affected

patients (Figures 1 and 2) in whom this surgery was done 12 months after the acute event. Reformation of fibrous bands was complete within three days of the surgery, completely fusing the upper and lower lids together. We find no guide for the timing of ocular surgery in late presenting SJS as compared to demonstrated good results by inserting amniotic membrane within 14 days of onset of the disease or the use of soft contact lens.[11,31,32] We do not, therefore, advocate surgical lid procedures in SJS of less than 12 months' duration.

CONCLUSION

For a chance at good ocular visual outcome in SJS early ophthalmic care is essential. Initial treatment with oral prednisolone combined with topical corticosteroid/antibiotics is useful. Amniotic membrane application may not be a possible option in less developed countries, because of cultural factors, and absence of medical systems and infrastructure associated with its deployment, as well as due to late presentation of patients. Surgery to correct late occurring anatomical distortions should only be contemplated after years of acute stage disease; we are unable to demonstrate any benefit in doing this earlier than two years, as adhesions reform rapidly. We found disappointing results as concerns visual improvement as an objective of surgery when severe ocular cicatrisation has occurred from SJS.

REFERENCES

1. Leaute-Labrezea C, Lamireaub T, Chawkib D, *et al*. Diagnosis, classification, and management of erythema multiforme and Stevens-Johnson syndrome. *Arch Dis Child* 2008; 83: 347-352.
2. Stevens M, Johnson FC. A new eruptive fever associated with stomatitis and ophthalmia; report of two cases in children. *Am J Dis Child* 1922; 24:526-533.
3. Guillaume JC, Roujeau JC, Revuz J, *et al*. The culprit drugs in 87 cases of toxic epidermal necrolysis (Lyell's syndrome). *Arch Dermatol* 1987; 123:1166–1170.
4. Roujeau JC, Stern RS. Severe adverse cutaneous reactions to drugs. *N Engl J Med* 1994; 331:1272–1285.
5. Griffith RD, Miller OF. Erythema multiforme following diphtheria and tetanus toxoid vaccination. *J Am Acad Dermatol* 1998; 19:758-759.
6. Duncan KO, Tigelaar RE, Bolognia JL. Stevens-Johnson Syndrome limited to multiple sites of radiation therapy in a patient receiving phenobarbital. *J Am Acad Dermatol* 1999; 40:493-496.
7. Patterson R, Dykewicz MS, Gonzales A, *et al.* Review Erythema multiforme and Stevens-Johnson syndrome. Descriptive and therapeutic controversy. *Chest* 1990; 98:331-336.
8. Hazin R, Ibrahimi OA, Hazin MI, *et al*. Stevens-Johnson Syndrome: pathogenesis, diagnosis, and management. *Ann Med* 2008; 40:129-138.
9. LeCleach L, Delaire S, Boumsell L, *et al.* Blister fluid T lymphocytes during toxic epidermal necrolysis are functional cytotoxic cells which express human natural killer (NK) inhibitory receptors. *Clin Exp Immunol* 2000; 119:225–230.
10. Chang YS, Huang FC, Tseng SC, *et al*. Erythema multiforme, Stevens–Johnson Syndrome, and toxic epidermal necrolysis: acute ocular manifestations, causes and management. *Cornea* 2007; 26:123–129.
11. Di Pascuale MA, Espana EM, Liu DT, *et al*. Correlation of corneal complications with eyelid cicatricial pathologies in patients with Stevens–Johnson Syndrome and toxic epidermal necrolysis syndrome. *Ophthalmology* 2005; 112:904–912.
12. Pereira FA, Mudgil AV, Rosmarin DM. Toxic epidermal necrolysis. *J Am Acad Derm* 2007; 56:181–200.
13. Knowles S, Shear, NH. Clinical risk management of Stevens–Johnson Syndrome/toxic epidermal necrolysis spectrum. *Dermatologic Therapy* 2009; 22: 441–451.
14. Alfirevic A, Jorgensen AL, Williamson PR, *et al.* HLA-B locus in Caucasian patients with carbamazepine hypersensitivity. *Pharmacogenomics* 2006; 7: 813–818.
15. Halevy S, Ghislain PD, Mockenhaupt M, *et al.* Allopurinol is the most common cause of Stevens–Johnson syndrome and toxic epidermal necrolysis in Europe and Israel. *J Am Acad Derm* 2008; 58:25–32.
16. Lee HY, Ariyasinghe JT, Thirumoorthy T. Allopurinol hypersensitivity syndrome: a preventable severe cutaneous adverse reaction. *Singapore Med J* 2008; 49:384–387.
17. Ghislain PD, Roujaeu JC. Treatment of severe of drug reactions: Stevens-Johnson Syndrome,

toxic epidermal necrolysis and hypersensitivity syndromes. *Dermatology Online J* 2002; 8: 5.
18. Ward K E, Archambault R, Mersfelder T L. Severe adverse skin reactions to non-steroidal anti-inflammatory drugs: a review of literature. *Am J of Health System Pharmacy* 2010; 67:206-213.
19. Okosa MC. Public Health Ophthalmology. Etukokwu Press Onitsha, Nigeria 2006; 10-12.
20. Haber J, Hopman W, Gomez M, Cartotto R. Late outcomes in adult survivors of toxic epidermal necrolysis after treatment in a burn center. *J Burn Care Rehabil* 2005; 26:33–41.
21. Pitche P, Padonou CS, Kombate K *et al*. Stevens-Johnson Syndrome and toxic epidermal necrolysis in Lome (Togo). Evolutional and etiological profiles of 40 cases. *Ann Dermatol Venereol* 2005; 132:531-534.
22. Salami TA, Asalu AF, Samuel SO. Prevalence of cutaneous drug eruptions in adult Nigerians with HIV/AIDS. *Niger Postgrad Med J* 2010; 17:160-163.
23. Enu CC, Elegbeleye OO, Femi-Pearse. Stevens-Johnson Syndrome in Africans. *Trop Geogr Med* 1980; 32:224-226.
24. Namayanja GK, Nankya JM, Byamugisha JK, *et al*. Stevens-Johnson Syndrome due to nevirapine. *African Health Sciences* 2005; 5:338-340.
25. Shay E, Keirkhah A, Liang L, *et al*. Amniotic Membrane Transplantation as a New Therapy for the Acute Ocular Manifestations of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis. *Surv Ophthalmol* 2009; 54:686-696.
26. De Rojas MV, Dart JK, Saw VP. The natural history of Stevens–Johnson Syndrome: patterns of chronic ocular disease and the role of systemic immunosuppressive therapy. *Br J Ophthalmol* 2007; 91:1048–1053.
27. Kakourou T, Klontza D, Soteropoulou F, *et a*l. Corticosteroid treatment of erythema multiforme major (Stevens-Johnson Syndrome) in children. *Eur J Pediatr* 1997; 156: 90–93.
28. Cheriyan S, Patterson R, Greenberger PA, *et al*. The outcome of Stevens-Johnson Syndrome treated with corticosteroids. *Allergy Proc*. 1995; 16:151-155.
29. Marvin JA, Heinback DM, Egrav LH, *et al*. Improved treatment of Stevens-Johnson syndrome. *Arch Surg* 1984; 119:601-605.
30. Wright P, Collin JRO. The Ocular Complications of Erythema Multiforme [Stevens Johnson Syndrome] and their management. Trans ophthalmol Soc UK 1983; 103:333-341.
31. Kheirkhah A, Johnson DA, Paranjpe DR, *et al* Temporary sutureless amniotic membrane patch for acute alkaline burns. *Arch Ophthalmol* 2008; 126:1059–1066.
32. Romero RT, Stavrou P, Cotter J, *et al*. Gas Permeable Scleral Contact Lens Therapy in Ocular Surface Disease. *Am J Ophthalmol* 2000; 130:25-32.

DISCLOSURES
Conflict of Interest - NONE
Financial Support - NONE