Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis at the University Hospital of the West Indies, Jamaica

AD East-Innis, DS Thompson

ABSTRACT

Objective: *Stevens-Johnson syndrome and toxic epidermal necrolysis are uncommon acute dermatologic disorders. The purpose of this study was to examine the frequency, aetiology and outcome of cases of Stevens-Johnson syndrome and toxic epidermal necrolysis admitted to the dermatology ward at the University Hospital of the West Indies.*

Methods: *This was a retrospective study looking at all patients who were admitted with a diagnosis of Stevens-Johnson syndrome, Stevens-Johnson syndrome/toxic epidermal necrolysis overlap syndrome and toxic epidermal necrolysis over a nine-year period.*

Results: *The results showed almost equal numbers of males and females. The drugs most commonly implicated were phenytoin and cotrimoxazole. The most common complications were hepatic impairment and ophthalmic complications.*

Conclusion: *Stevens-Johnson syndrome and toxic epidermal necrolysis contribute significantly to morbidity and mortality of patients on the dermatology ward although mortality was low compared to other studies.*

Keywords: Acute dermatologic diseases, epidermal necrosis, dermatological admissions

El Síndrome de Stevens-Johnson y la Necrólisis Epidérmica Tóxica en el Hospital Universitario de West Indies, Jamaica

AD East-Innis, DS Thompson

RESUMEN

Objetivo: *El síndrome de Stevens-Johnson (SSJ) y la necrólisis epidérmica tóxica (NET) son trastornos dermatológicos agudos poco frecuentes. El propósito de este estudio fue examinar la frecuencia, la etiología y el resultado de casos de síndrome Stevens-Johnson y necrólisis epidérmica tóxica ingresados en la sala de dermatología del Hospital Universitario de West Indies.*

Métodos: *Se trata de un estudio retrospectivo con todos los pacientes que fueron ingresados con diagnóstico de síndrome de Stevens-Johnson, síndrome de solapamiento entre el síndrome de Stevens-Johnson y NET, y necrólisis epidérmica tóxica, por un período de nueve años.*

Resultados: *Los resultados mostraron casi igual número de varones y hembras. Los fármacos más comúnmente implicados fueron la fenitoína y el cotrimoxazol. Las complicaciones más frecuentes fueron deterioro hepático y complicaciones oftálmicas.*

Conclusión: *El síndrome Stevens-Johnson y la necrólisis epidérmica tóxica contribuyen significativamente a la morbilidad y mortalidad de los pacientes en la Sala de Dermatología, aunque la mortalidad fue baja en comparación con otros estudios.*

Palabras claves: Enfermedades dermatológicas agudas, ingresos dermatológicos, necrosis epidérmica

West Indian Med J 2013; 62 (7): 589

From: Section of Dermatology, Department of Medicine, The University of the West Indies, Kingston 7, Jamaica, West Indies.

Correspondence: Dr A East-Innis, Department of Medicine, Section of Dermatology, The University of the West Indies, Kingston 7, Jamaica, West Indies. E-mail: althea.eastinnis@uwimona.edu.jm

INTRODUCTION

Both Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are acute dermatologic diseases characterized by purpuric macules and targetoid lesions with full thickness epidermal necrosis histologically. However, in SJS, there is detachment of up to 10% of the cutaneous surface with mucous membrane involvement, whereas in TEN more than 30% of the cutaneous surface is involved, also with mucous membrane involvement. Similar clinical and histological features with 10 to 30% skin detachment are called Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) overlap syndrome (1). Medications are commonly implicated in the causation of SJS but infections such as mycoplasma and herpes simplex may also be culpable. In TEN, drugs are the commonest cause. When the area of denudation of the skin is less than 10% (SJS), the mortality rate is 1 to 5%. However when it is more than 30% (TEN), the mortality rate is between 25% and 35% and may approach 50% (2). In all these syndromes, there may be significant involvement of oral, nasal, eye, vaginal, urethral, gastrointestinal and lower respiratory tract mucosa.

Erythema multiforme (EM) is a more benign condition with target and targetoid lesions usually in an acral distribution with involvement of less than 10% of the skin and commonly with oral involvement. Most cases are secondary to herpes simplex infection and recur with herpetic recurrences. Morbidity is low and there is no mortality. For a long time, SJS and TEN were thought to be part of a spectrum with EM but now some evidence suggests that EM may be a distinct entity (1, 3–5).

Stevens-Johnson syndrome and TEN are often drug-induced but the pathophysiologic mechanism is unknown. T cells, especially $CD8^+$ lymphocytes have been posited to play an important role (6). There also seems to be a genetic predisposition, especially in particular ethnic groups and for particular drugs. An association between the HLA-B*1502 allele and SJS/TEN due to carbamazepine, phenytoin and lamotrigine in Han Chinese in Hong Kong has been demonstrated (7). In Thailand, an association was found between HLA-B*5801 allele and allopurinol-induced SJS/TEN in both Asians and non-Asian populations (8).

In the United States of America (USA), the incidence of TEN was reported to be 0.5 per million population per year according to one study (9). In Germany, the incidence rates for SJS, SJS/TEN overlap and TEN are one to two cases per million population per year (10).

Sepsis and respiratory distress are the most common causes of death. To assess the prognosis of patients with SJS/TEN, the severity of illness score of TEN (SCORTEN) is used (2, 11). This scoring method takes into consideration important prognostic factors including age, the presence of underlying malignancy, heart rate, the percentage loss of body surface area, blood urea nitrogen, serum glucose level and bicarbonate level. Other negative prognostic factors are persistent neutropaenia, hypoalbuminaemia and persistent azotemia. After re-epithelialization, patients may have long term sequelae including corneal scarring, entropion of eyelashes, photophobia, watery or dry eyes, corneal and conjunctival neovascularization, all of which may lead to blindness. Lesions may heal with dyspigmentation, nails may grow abnormally and phimosis of the penis or vaginal synechiae may result.

Stevens-Johnson syndrome and TEN occur in all age groups, including children. However, both SJS and TEN occur more frequently in the older population. In one study, allopurinol was found to be the most common cause of SJS and TEN in Europe and Israel (12). In a study in India, the common offending agents were antimicrobials and non-steroidal anti-inflammatory drugs [NSAIDs] (13). Overall, the most commonly cited drugs as causes of SJS and TEN are the anticonvulsants, sulphonamide antibiotics, NSAIDs and allopurinol (14). In a study in the USA, aminopenicillins were frequently implicated in patients with SJS (15). Among persons with human immunodeficiency virus (HIV), the commonest causes were nevirapine, cotrimoxazole, stavudine and clarithromycin (16). The usual time between initiation of drug use and onset of SJS/TEN was two to eight weeks (17).

In this study, the aim was to examine the frequency, aetiology and outcome of SJS/TEN among patients admitted to the dermatology ward at the University Hospital of the West Indies (UHWI), Jamaica.

SUBJECTS AND METHODS

Ethical approval was obtained from the University Hospital of the West Indies/University of the West Indies/Faculty of Medical Sciences Ethics Committee. The study was conducted retrospectively. The dermatology admissions recorded for a nine-year period, from January 1997 to December 2005, were reviewed. All patients who were admitted with a diagnosis of SJS, TEN or SJS/TEN overlap syndrome were included in the study. All diagnoses had been confirmed by skin biopsy. A data collection sheet was designed for the purpose of organizing the abstraction of data from patient records. Data included patient demographics, date and duration of admission to hospital and a detailed drug history including any previous episodes of drug sensitivity. All drugs reportedly ingested by the patients up to three months prior to their cutaneous reaction were documented and the period of time between drug ingestion and the appearance of skin lesions was also noted. Medication started within eight weeks of the onset of lesions was deemed most likely to have caused the eruption. Additionally, clinical diagnoses, co-morbidities, histopathological diagnoses, final outcome and all ensuing complications were noted. The data retrieved were collated and analysed using SPSS 12.0.

RESULTS

Two patients' records could not be located. Therefore, some data on these patients had to be obtained from other sources

such as histopathology request forms and ward admission records. During the nine-year period, there were a total of 959 dermatological admissions of which 101 were due to cutaneous drug reactions (CDRs). Twenty-one of these were SJS or TEN. Stevens-Johnson syndrome and TEN comprised 2.2% of all admissions and 21% of all CDRs admitted. There were 10 cases of SJS and 11 of TEN with no overlap syndrome. Two patients had a history of previous hypersensitivity to the drug implicated. Three of the TEN cases had died (27% of TEN cases) and unfortunately two of those medical records were the ones that could not be located. The cause of death in one case was renal failure.

The ages of patients with SJS and TEN ranged from 13 to 95 years with a mean age of 40.2 years. There were 10 females and 11 males with more males having TEN and more females having SJS (Fig. 1). In one case, two drugs were

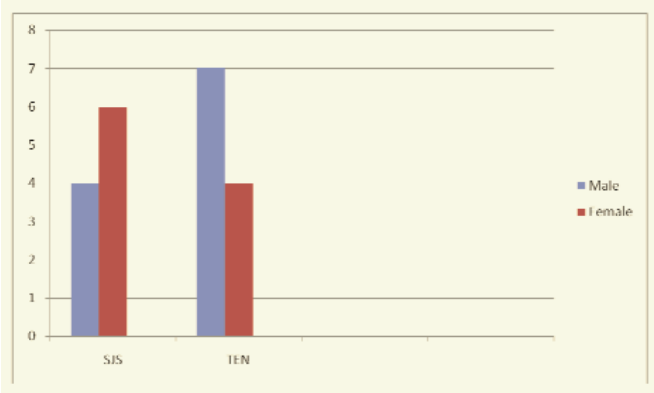

Fig. 1: Sex distribution of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN).

considered culpable as these were started during the same period. The drugs most commonly implicated were phenytoin in five cases, cotrimoxazole in four cases and amoxicillin/clavulanic acid in two cases (Table 1). When drugs were divided into classes (Table 2), the most common classes

Table 1: Drugs implicated in causation of Stevens-Johnson syndrome, toxic epidermal necrolysis and their frequencies

Drug implicated	Number of cases
Phenytoin	5
Cotrimoxazole	4
Amoxicillin + clavulanic acid	2
Amoxicillin	1
Benzathine benzylpenicillin	1
Ceftriaxone	1
Celecoxib	1
Diclofenac potassium	1
Diclofenac sodium	1
Erythromycin	1
Metamizole sodium	1
Metronidazole	1
Nevirapine	1
Roxithromycin	1

Table 2: Classes and frequencies of drugs implicated

Classes of drugs implicated	Number of cases
Hydantoin anticonvulsants	5 (22.7%)
Sulphonamides	4 (18.2%)
Penicillins	4 (18.2%)
NSAIDs	3 (13.6%)
Macrolides	2 (9.1%)
Others	4 (18.2%)

NSAIDs = non-steroidal anti-inflammatory drugs

implicated were hydantoin anticonvulsants (five cases), sulphonamide antibiotics (four cases), penicillins (four cases) and NSAIDS (three cases). When further divided into categories, antimicrobials were by far the most common cause with 13 cases (Fig. 2).

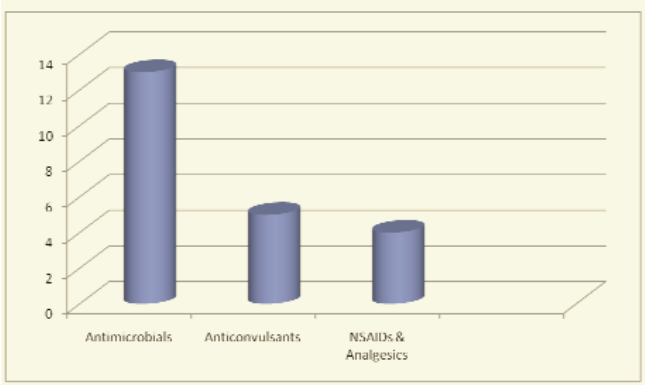

Fig. 2: Frequencies of different categories of drugs implicated. NSAIDs = non-steroidal anti-inflammatory drugs

The period of hospitalization for survivors ranged from six to 71 days. The mean period of hospital admission was 21 days (three weeks). The most common complication was hepatic impairment in seven cases followed by renal impairment in four cases and conjunctivitis in three patients (Table 3). However, it should be noted that there were six

Table 3: Complications and frequencies

Complications	Number of cases
Hepatic impairment	7
Renal impairment	4
Conjunctivitis	3
Anaemia	2
Symblepharon	2
Corneal abrasion	1
Dyschromia	1
Eosinophilia	1
Haematuria	1
Hyponatremia	1
Increased CPK	1
Labial (vulval) fusion	1
Pancytopenia	1
Stitch abscess	1

CPK = creatine phospokinase

patients with ophthalmic complications. By far, the most common referral to other specialties was made to ophthalmology (Table 4).

Table 4: Consultation requests to other specialties

Consultation requests to other specialties	Number of cases
Ophthalmology	7
General surgery	2
Haematology	2
Nephrology	2
Gynaecology	1
Internal medicine	1
Microbiology	1
Neurology	1
Nutritionist	1
Otolaryngology	1
Psychiatry	1
Pulmonology	1

DISCUSSION

The findings in our study were consistent with those in previous studies in several respects. At the UHWI, the distribution of males and females was almost equal in SJS and TEN as in other surveys (10). The list of most common causative agents identified were hydantoin anticonvulsants (22.7%), sulphonamide antibiotics (18.2%), penicillins (18.2%) and NSAIDS (13.6%). Although the drugs were similar, the frequencies differed from that found in a study in Togo which showed antibacterial sulphonamides (50.6%), nevirapine (23.6%), NSAIDs (5.6%) and anti-epileptic medications (3.4%) as the most commonly implicated drugs (18). This may reflect the different prescribing practices of local medical practitioners in these two studies.

The range and number of complications and referrals highlight the need for a team approach to management and the requirement for early intervention especially by the ophthalmology service. It also underscores how much resources are utilized on these patients. The mortality rate in our study on TEN patients was 27% which is at the lower end of the range of mortality rates found in other studies (2). The mortality rate in SJS cases was zero. These low mortality rates were not expected as our patients were not nursed in an intensive care unit or burns unit as is usually recommended due to lack of available beds. Instead, they were housed in the dermatology ward in an isolated area or room. However, day-to-day management was done by medical personnel trained in dermatological care with input from other specialties as appropriate.

The strength of this study is that it is the first to report data on Afro-Caribbean patients. The main limitation of this study was that it included only patients admitted to the dermatology ward and no data were collected on those who might have developed these reactions while on other wards including paediatrics. Prospective collaborative studies would be helpful in capturing this additional information.

In summary, SJS and TEN, though uncommon, use significant hospital resources for each patient and contribute significantly to morbidity and mortality on the dermatology ward.

REFERENCES

1. Bastuji-Garin S, Rzany B, Stern RS, Shear NH, Naldi L, Roujeau JC. Clinical classification of cases of toxic epidermal necrolysis, Stevens-Johnson syndrome and erythema multiforme. Arch Dermatol 1993; **129:** 92–6.
2. Bastuji-Garin S, Fouchard N, Bertocchi M, Roujeau JC, Revuz J. SCORTEN: a severity-of illness score for toxic epidermal necrolysis. J Invest Dermatol 2000; **115:** 149–53.
3. Roujeau JC. Stevens-Johnson syndrome and toxic epidermal necrolysis are severity variants of the same disease which differs from erythema multiforme. J Dermatol 1997; **24:** 726–9.
4. Roujeau JC. The spectrum of Stevens-Johnson syndrome and toxic epidermal necrolysis: a clinical classification. J Invest Dermatol 1994; **102:** 28S–30S.
5. Auquier-Dunant A, Mockenhaupt M, Naldi L, Correia O, Schröder W, Roujeau JC. Correlations between clinical patterns and causes of erythema multiforme majus, Stevens-Johnson syndrome, and toxic epidermal necrolysis. Arch Dermatol 2002; **138:** 1019–24.
6. Miyauchi H, Hosokawa H, Akaeda T, Iba H, Asada Y. T-cell subsets in drug-induced toxic epidermal necrolysis. Arch Dermatol 1991; **127:** 851–85.
7. Man CB, Kwan P, Baum L, Yu E, Lau KM, Cheng AS. Association between HLA-B*1502 allele and antiepileptic drug-induced cutaneous reactions in Han Chinese. Epilepsia 2007; **48:** 1015–18.
8. Somkrua R, Eickman EE, Saokaew S, Lohitnavy M, Chaiyakunapruk N. Association of HLA-B*5801 allele and allopurinol-induced Stevens Johnson syndrome and toxic epidermal necrolysis: a systematic review and meta-analysis. BMC Med Genet 2011; **12:** 118.
9. Chan HL, Stern RS, Arndt KA, Langlois J, Jick SS et al. The incidence of erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis. A population based study with particular reference to reactions caused by drugs among outpatients. Arch Dermatol 1990; **126:** 43–7.
10. Rzany B, Mockenhaupt M, Baur S, Schröder W, Stocker U, Mueller J et al. Epidemiology of erythema exsudativum multiforme majus (EEMM), Steven-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) in Germany (1990–1992). Structure and results of a population-based registry. J Clin Epidemiol 1996; **49:** 769–73.
11. Guégan S, Bastuji-Garin S, Poszepczynska-Guigné E, Roujeau JC, Revuz J. Performance of the SCORTEN during the first five days of hospitalization to predict the prognosis of epidermal necrolysis. J Invest Dermatol 2006; **126:** 272–6.
12. Halevy S, Ghislain PD, Mockenhaupt M, Fagot JP, Bouwes Bavinck JN, Sidoroff A. Allopurinol is the most common cause of Stevens-Johnson syndrome and toxic epidermal necrolysis in Europe and Israel. J Am Acad Dermatol 2008; **58:** 25–32.
13. Sanmarkan AD, Sori T, Thappa DM, Jaisankar TJ. Retrospective analysis of Stevens-Johnson syndrome and toxic epidermal necrolysis over a period of 10 years. Indian J Dermatol 2011; **56:** 25–9.
14. Wolf R, Orion E, Marcos B, Matz H. Life-threatening acute adverse cutaneous drug reactions. Clin Dermatol 2005; **23:** 171–81.
15. Strom BL, Carson JL, Halpern AC, Schinnar R, Snyder ES, Shaw M et al. A population-based study of Stevens-Johnson syndrome. Incidence and antecedent drug exposures. Arch Dermatol 1991; **127:** 831–8.
16. Mittmann N, Knowles SR, Koo M, Shear NH, Rachlis A, Rourke SB. Incidence of toxic epidermal necrolysis and Stevens-Johnson syndrome in an HIV cohort; an observational, retrospective case series study. Am J Clin Dermatol 2012; **13:** 49–54.
17. Knowles SR, Shear NH. Recognition and management of severe cutaneous drug reactions. Dermatol Clin 2007; **25:** 245–53.
18. Saka B, Kombaté K, Mouhari-Toure A, Akapso S, Tchangaï-Walla K, Pitché P. Stevens-Johnson syndrome and toxic epidermal necrolysis in a teaching hospital in Lomé, Togo: retrospective study of 89 cases. Med Trop (Mars) 2010; **70:** 255–8.