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Original Article

Retrospective analysis of severe cutaneous adverse drug reactions over a period of 6 years

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Abstract

Background severe cutaneous adverse reactions are a group of potentially lethal adverse drug reactions. Prompt diagnosis and management may reduce the morbidity and mortality. Early identification of the offending drug is necessary for early withdrawal and to prevent the recurrences of such a devastating illness.

Aims To study the demography, offending agents, clinical features and treatment, complications, morbidity and mortality of SJS/TEN in our hospital.

Materials and Methods In this retrospective study, we reviewed the medical records of SJS, TEN, SJS/TEN overlap of inpatients over a period of 6 years.

Results Among the 16 patients included, 7 (43,75%) were male with a mean age of 46.2 ± 15 years. Antimicrobials were the commonest group of drugs causing SCAR in 8/16 patients (50%). The most common morbidity noted in our study was due to sepsis leading to acute renal failure. The SCORTEN score for 5 TEN cases ranged from 0 to 5. Two of the SJS/TEN cases died giving a mortality rate of 12.50% (2/16).

Conclusion Antibiotics are the common offending agents of SJS/TEN in our study.

Key words
Severe cutaneous adverse reactions, Stevens-Johnson syndrome, toxic epidermal necrolysis, retrospective analysis.

Introduction

Toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS) are considered as two ends of the spectrum of a severe cutaneous adverse reactions (SCAR), which are mainly caused by drugs; and these are usually associated with high morbidity and mortality.[1,2] The incidence of SJS varies from 1.2 to 6/million patient-years and that of TEN being 0.4–1.2/million patient-years, with the mortality rate in TEN being three times higher than that of SJS.[3] A hospital-based retrospective study was done to study the demography, offending agents, clinical features and treatment, complications, morbidity and mortality in SJS/TEN in our hospital.

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Materials and Methods

Medical records of all inpatients, admitted with a diagnosis of SJS, TEN, and SJS/ TEN overlap over a period of 6 years from January 2012 to December 2017, in the Burns Unit, at our institute were reviewed. Of the total 18 medical records, 16 with complete data were selected. Bastugi's criteria[4] formed the basis for classifying these severe mucocutaneous reactions into SJS, TEN and SJS/TEN overlap. Parameters like age, sex, co-morbid conditions, etiology, clinical features, past history of drug reactions, period of hospital stay, investigations, treatment modalities, course and outcome of these 16 patients were recorded and analyzed.

Results

Of the 16 patients identified as having Stevens-Johnson syndrome/ toxic epidermal necrolysis during a 6-year period from January 2012 to December 2017.

Nine patients were classified as having Stevens-Johnson syndrome (56.25%), 5 had toxic epidermal necrolysis (31.25%) and the remaining 2 (12.5%) patients were classified as Stevens-Johnson syndrome/ toxic epidermal necrolysis overlap **(Table 1)**.

An offending medication was identified in 87.5 % of cases of Stevens-Johnson syndrome/ toxic epidermal necrolysis. In a total of 2 cases, patients were on multiple drugs with the potential to cause Stevens-Johnson syndrome/toxic epidermal necrolysis making it impossible to assign a single culprit drug with the average being 3.4 drugs. In 37.5% of cases where an offending medication was identified, the patient had a prior exposure to the identified trigger. Patients developed symptoms on average 27.3 days after initiation of the causative drug if there was no prior exposure to the medication. However if there was a previous exposure to the trigger, the time to development of symptoms was significantly shortened to 4.5 days after re-exposure **(Table 2)**.

Antibiotics, allopurinol and anticonvulsants, were the most commonly implicated triggers **(Table 3)**.

Antibiotics as a group made up the largest percentage of cases (50%), however allopurinol was the single most common offending medication, implicated in 18.75% of cases. Triggers were most commonly discontinued at the time of hospital admission, approximately 3 days after onset of symptoms or in hospital at the time of diagnosis, approximately 4 days after

Table 1 Characteristics of patients included in study analysis.

Total Number of Patients Admitted		16
Average Age		46.2 years (SD 15 years)
Sex male		43.75 % (N=7)
Disease Classification Based on Maximum body surface area Involvement	Stevens-Johnson syndrome	56.25% (N=9)
	Stevens-Johnson syndrome/ toxic epidermal necrolysis overlap	12.5% (N=2)
	Toxic epidermal necrolysis	31.25% (N=5)

Table 2 Timeframe of Stevens-Johnson syndrome/ toxic epidermal necrolysis development in patients with identified triggers correlated with medication exposure history.

Medication Exposure History	*Average Time to Development of Stevens Johnson syndrome/ toxic epidermal necrolysis*
Previous Exposure	4.5 days (SD 3.0 days)
No Previous Exposure	27.3 days (SD 42.1 days)
Unknown	14.1 days (SD 25.9 days)

Table 3. Triggers implicated in causing cases of Stevens Johnson syndrome/toxic epidermal necrolysis.

Trigger	drugs	Number of Patients	Percentage of Total
Antibiotics	céfaclor	1	6.25
	amoxicillin	4	25
	Trimethoprim/Sulfamethoxazole	1	6.25
	Ceftriaxone	1	6.25
	Ciprofloxacin	1	6.25
Allopurinol		3	18.75
Ibuprofen		1	6.25
Anticonvulsants	Phenytoin	1	6.25
	Carbamazepine	2	12.5
	Lamotrigine	1	6.25

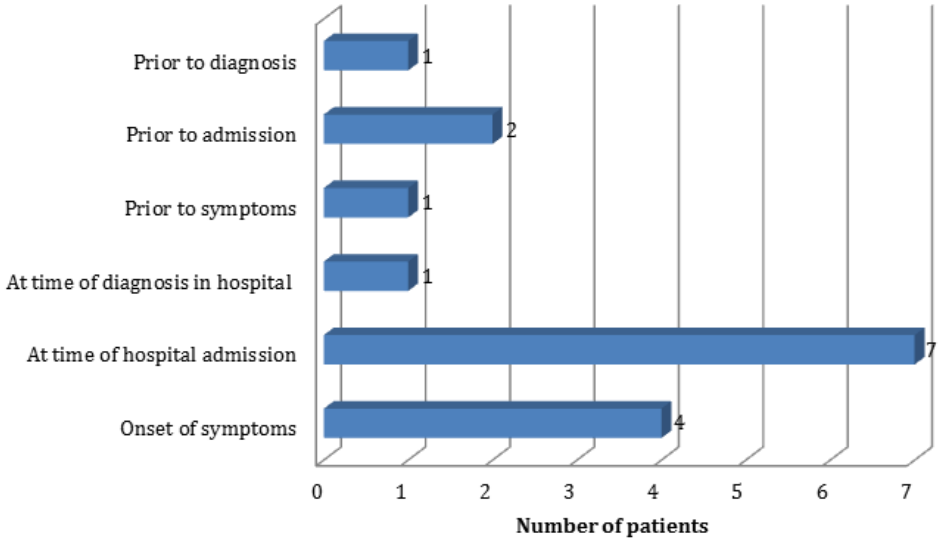

Figure 1 Timeframe of Removal pf SJS/ TEN Trigger.

onset of symptoms. In only 25% of cases was the offending medication removed at the time of onset of symptoms **(Figure 1)**. A total of 5 patients (31.25%) died in hospital due to complications arising from Stevens Johnson syndrome/toxic epidermal necrolysis.

All patients received definitive therapy in the form of dexamethasone,[12] methyl prednisolone pulse,[1] dexamethasone pulse.[3] Pulse therapy was given along with intravenous broad spectrum antibiotics. Overall, healing was noticed at 2-20 days after the onset of treatment. For dexamethasone pulse therapy, the onset of healing was on the third day of pulse, and for methylprednisolone pulse therapy, it was on the second day of pulse. The period of hospitalization ranged from 7 to 30 days.

The SCORTEN score for 5 TEN cases ranged from 0 to 5. Two of the SJS/ TEN cases died giving a mortality rate of 12.50% (2/16). The cause for death in all our patients was sepsis leading to acute renal failure.

Discussion

Toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS) are severe cutaneous drug reactions of unknown mechanism.[5]

High-risk drugs for the development of SJS-TEN include phenobarbital, phenytoin, carbamazepine, lamotrigine, nevirapine, nonsteroidal anti-inflammatory drugs, allopurinol, cotrimoxazole, homeopathic medicines, and fluconazole.[2,6-10]

Toxic epidermal necrolysis (TEN) is a potentially fatal disorder. Patients with TEN are often referred to burn centers for expert wound management and comprehensive care.[11]

It is a rare emergency, which has been observed worldwide without any particular ethnic predilection. This syndrome is observed at all ages but with an incidence in the elderly subject twice that in the young and a slight predominance of women.[12]

The mean age of patients was 46.2±15 years. This is similar to other studies done in Japan where Yamane *et al*.[13] noticed a mean age of 45.7 years and Roujeau *et al*.[14] from France observed a mean age of 46.8 years. However, in studies conducted in France and the United States, the mean age was higher (59.7 and 65.5 years, respectively).[15,16] In studie from India, the mean age of patients with SCAR was lower than that observed in our study (22.3 years).[6]

As all the studies had different demographic profiles, the differences in mean age may reflect the diversity of the populations studied. There was no significant predominance of gender, which was similar to that reported by other authors.[6,13,17]

In our study, antimicrobials were the most common group of drugs causing SCAR. This is also in concordance with the study done in China which showed antibiotics in 64.8% of SCAR cases.[18] Antibiotics, mainly beta-lactams, were the most common cause of SJS/TEN in Li Wang *et al*. study,[19] though a study from Brazil showed anticonvulsants as the most common implicated group.[20] These differences in the drugs involved could be justified by the different genetic susceptibilities of the populations studied.

The mean reaction time in our study was 4.5 days. Majority of them had manifested within 6 days of drug intake which is similar to other studies.[6,13,14,21]

The treatment was based on the withdrawal of the drug in all patients, and in systemic corticosteroid was prescribed. In this study, the mortality rate was 12.5%. The most common causes of admission was infection/sepsis, reflecting the severity of clinical conditions associated with SCAR and thus justifying the 12.5% mortality.

Conclusion

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe cutaneous adverse reactions, which are mainly caused by drugs; Early withdrawal of the offending agent and definitive treatment of SCAR and multispecialty care may reduce the morbidity, mortality rates, and thereby, duration of hospital stay.

What is known about this topic Stevens-Johnson syndrome and toxic epidermal necrolysis are severe cutaneous adverse reactions, usually associated with high mortality and morbidity.

What this study adds This study gives an idea about the demography, offending agents, clinical and treatment, complications, morbidity and mortality of SJS/ TEN in the region of Africa and especially in Morocco.

Competing interests The authors declare no competing interests.

Authors' contributions Youssef Moutaouakkil: conception, design, acquisition, analysis and interpretation of data and drafting the manuscript. , Rachid el Jaoudi: conception, design, analysis and interpretation of data.

Samira Serragui, Yahia Cherrah and Jamal Lamsaouri: conception, design, data collection, and reviewing of several drafts of the manuscript for important intellectual content. Samir Siah and Yassir Bousliman: conception, design, reviewing of several drafts of the manuscript for important intellectual content. All authors read and approved the final manuscript.

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