CAUSATIVE FACTORS AND CLINICAL OUTCOME IN STEVEN JOHNSON SYNDROME AND TOXIC EPIDERMAL NECROLYSIS

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ABSTRACT

Objective: To identify the main factors causing Steven Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) and their clinical outcome in the patients in our local setup.

Methodology: This case series was conducted at Lady Reading Hospital, Peshawar. A total of 54 consecutive patients who presented with Steven Johnson syndrome and toxic epidermal necrolysis over a two year period (2013-2015) were included in the study. Relevant information including bio-data, causative agents, duration of hospital stay and outcome in terms of improvement or mortality was collected. Analysis was done using SPSS version 20.

Results: The mean age of patients presenting with SJS/TEN was 25.9±17.4 years with a minimum age of 1 year and a maximum age of 65 years. Majority of patients were between 18-45 years of age. The causes identified for triggering SJS/TEN were anticonvulsants (38.9%), followed in equal frequency by antibiotics and NSAIDS (27.8%) while 5.5% of cases were secondary to herpes virus infection. Patients had a variable course with 83.3% of patients improving with no sequel on follow-up and 16.7% succumbing to the disease.

Conclusion: Anticonvulsants, antibiotics and NSAIDS were the most frequently responsible drugs for development of SJS & TEN. The Observed mortality rate was 16.7%.

Key Words: Steven Johnson syndrome, Toxic epidermal necrolysis, Anticonvulsants, Antibiotics, Clinical outcome

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INTRODUCTION

Steven Johnson syndrome and toxic epidermal necrolysis are immune-mediated reactions, due to various etiological factors like drugs, infections, malignancy and radiation therapy; however drugs are most commonly implicated in 95% of cases[1]. They are characterized by high fever, wide-spread blistering, exanthematous macules and targetoid lesions, accompanied by mucosal involvement[2]. Both are a spectrum of the same disease process with variation in body surface area (BSA) involvement. In SJS, detachment of the epidermis is less than 10% of the body surface area occurs; whereas in TEN it is more than 30%[2]. Patient may initially present with SJS, which subsequently evolves into TEN or SJS-TEN overlap. Diagnosis mainly relies on clinical signs and histopathology of skin lesions[3].

The annual incidence of SJS and TEN in the general population is known to be 1–6 and 0.4–1.2 per million people, respectively. In Pakistan, the exact incidence remains unknown. Incidence is higher in HIV positive patients than the general population[1]. The condition is common in all age groups and both genders[6].

Both SJS and TEN are considered T cell mediated disorders in which activation of CD8 T lymphocytes results in apoptosis and necrosis of keratinocytes[6]. The etiology is primarily attributed to drugs with antimicrobials, anticonvulsants, and antipyretics being the most common culprits[7]. The drugs commonly implicated as the cause of these drug reactions vary depending on host factors and the prescription pattern of drugs in that particular area[8]. Amongst the less common causes, *Mycoplasma pneumoniae* infections are widely documented to cause SJS and TEN without initial exposure to drugs. Furthermore, *Herpes simplex* virus was recognized in several cases of SJS, especially in children[9].

Complications include thermo-dys-regulation, infection, fluid and electrolyte imbalance, eye complications and multi organ involvement[6]. The mortality rate is higher in TEN (30%) as compared to SJS (1-5%)[4]. Pres-

ence of a major systemic disease before the onset of SJS/TEN is associated with a poor prognosis[8].

The mainstay of treatment in SJS and TEN is supportive care which includes fluid and electrolyte replacement, temperature control, control of infection (dermal coverage), nutrition, pain, topical skin care and use of several immunomodulative therapies particularly glucocorticoids and immunoglobulins[6,10].

The aim of the study was to identify the main factors causing SJS and TEN and the clinical outcome in the patients in our local setup and how it compares with the international/national data so as to provide an update to the scientific literature available on SJS/TEN.

METHODOLOGY

This descriptive case series study using a consecutive sampling technique was conducted over a two year period (2013-2015) in the Department of Dermatology, Lady Reading Hospital Peshawar. After taking an informed consent, 54 clinically diagnosed cases of SJS and TEN, of all ages and both genders were included in the study.

Diagnosis was established on the basis of clinical manifestations of sudden onset of constitutional symptoms, spread blistering, exanthema of macules and targetoid lesions and mucosal involvement. Patients in whom the clinical picture was vague a biopsy was taken for diagnosis.

Exclusion criteria was patients with pyrexia of unknown origin; eye, ear disease and any other major systemic illness like cardiovascular and respiratory disease (e.g. tuberculosis) and patients who were taking systemic steroids for some other co-morbid condition.

Relevant information including bio-data, causative agent, time interval between exposure to offending agent and adverse cutaneous drug reaction, hospital course and outcome in terms of improvement or development of complications and subsequent mortality were recorded for all patients. Laboratory investigations were carried out where necessary. All these patients were treated with standard doses of steroids with the exception of those in whom viral etiology was suspected. Prophylactic antibiotics were administered and supportive care which included fluid and electrolyte replacement, environmental temperature control, control of infection (dermal coverage), nutrition, strict intake output monitoring and topical skin care was provided to all patients. Analysis was done using SPSS version 20. The frequencies and percentages were calculated for all variables. For numerical values student t test was applied and for qualitaivetive data chi square was used. The age group was expressed in range. Ratio was determined for gender. The data was presented in tables.

RESULTS

The mean age of patients presenting with SJS/TEN was 25.9±17.4 years with a minimum age of 1 year and a maximum age of 65years. The majority of patients were between 18-45 years of age (table 1).

The male to female ratio was 1:1 with 50% males and 50%females. The mean hospital stay was 8.8±4 days.

Anticonvulsants were responsible for 38.9% of cases. Frequency of other agents for SJS/TEN is shown in table 2. Amongst the anticonvulsants, carbamazepine accounted for 29.6% of cases. From the antibiotic group cephalosporins were the primary culprits in 11.1% and ibuprofen was the top implicative NSAID (20.4%). (Table 3)

In our study 72.2% of patients did not experience any complication however 27.8% of patients did develop infection, primarily super added skin infection. The majority of the patients improved (83.3%) and were discharged with follow-up advice; remaining 16.7% succumbed to the disease and expired during hospital stay.

A statistically significant relationship was observed between the cause of SJS/TEN and age of the patient (p vale 0.027) (Table 4). The relationship between causes and gender (p 0.354); and causes and complications (p 0.16) was statistically not significant.

Table 1: Age wise distribution of sample

Age Groups of the sample	Frequency	Percent
Up to 18.00 years	19	35.2
18.01 to 45.00 years	27	50.0
45.01 years & above	8	14.8
Total	54	100

Table 2: Causes of SJS/TEN

Causes	Frequency	Percent
Antibiotics	15	27.8
NSAIDS	15	27.8
Anticonvulsants	21	38.9
Infection (herpes)	3	5.5
Total	54	100

Table 3: Drugs Causing SJS/TEN

Drugs	Frequency	Percent
ANTIBIOTICS (cephradine)	6	11.1
ANTIBIOTICS (ciprofloxacin)	2	3.7
ANTIBIOTICS (penicillin)	5	9.3
ANTIBIOTICS (sulphonamides)	2	3.7
ANTICONVULSANT (carbamazepine)	16	29.6
ANTICONVULSANT (lamotrigine)	5	9.3
Infection (herpes simplex)	3	5.6
NSADS (mefenamic acid)	1	1.9
NSAIDS (ibuprofen)	11	20.4
NSAIDS (diclofenac sodium)	1	1.9
NSAIDS (indomethacin)	2	3.7
Total	54	100

Table 4: Stratification of Causes with regard to age groups

Age Groups	Causes				P value
	Antibiotics	NSAIDS	Anticonvulsants	Infection (Herpes)	
Up to 18.00 years	6 (31.6%)	10 (52.6%)	3 (15.8%)	0 (0)%	0.027
18.01 to 45.00 years	6 (22.2%)	4 (14.8%)	14 (51.9%)	3 (11.1%)	
45.01 years & above	3 (37.5%)	1 (12.5%)	4 (50.0%)	0 (0%)	
Total	15 (27.8%)	15 (27.8%)	21 (38.9%)	3 (5.5%)	

DISCUSSION

Toxic epidermal necrolysis (TEN) and Steven Johnson syndrome (SJS) constitute severe life threatening conditions[1,8]. The outcome is variable with TEN having a higher mortality (30%) as compared to SJS (1-5%). In our study we observed that most cases of SJS/TEN were secondary to anticonvulsants (38.9%). Carbamazepine proved to be the most notorious (29.6%) followed by lamotrigine (9.3%). A similar trend was seen by Devi et al[8] with anticonvulsants being the commonest implicative drug group (53%) and carbamazepine the major culprit drug (81%). The majority of the patients were prescribed carbamazepine for neuropathic pain control particularly in the older age group and for children it was prescribed for seizures. A similar pattern was also highlighted by another Indian study which showed anti-epileptics to be the top cause (50%) and here too carbamazepine was the most often implicated drug (27%) followed by phenytoin (13.6%)[11].

We identified antibiotics and NSAIDS as the second commonest drug groups responsible in 27.8% of patients with cephalosporins being foremost constituting 11.1% followed in close order by penicillin group, quinolones and sulphonamides. Gomathay et al[11] also showed antibiotics as the leading drug cause of SJS and TEN (40.7%). In contrast, Barvaliya et al[1] implicated nevirapine and cotrimoxazole as the major culprits. The difference could probably be due to the primary disease and prescription patterns of different populations and also the prevalence of HIV in different parts of the world.

In our study NSAIDS were also responsible for 27.8% of cases; ibuprofen prescribed as analgesic and anti-inflammatory being the commonest. Less commonly associated were mefenamic acid and diclofenac sodium. This is probably because they are freely available as over the counter medicines and hence there is increased tendency to over-use/misuse (particularly by females who tend to use painkillers more). Similar statistics were reported by Jena et al[12] who enrolled 31 patients and observed NSAIDS to be the cause in 22.5% of cases; however in contrast to our findings, the majority of the cases were due to diclofenac sodium, followed by others.

In another study it was highlighted that SJS/TEN can rarely occur secondary to other causes most notably infections like *Mycoplasma pneumoniae* and *Herpes simplex* virus especially in children[11]. We diagnosed herpes simplex as the culprit virus in 5.5% of patients.

We observed a statistically significant relationship between the cause and age of the patient (p =0.027). However the relation between causes and gender (p =0.354); and causes and complications (p =0.16) was statistically not significant. Likewise we also couldn't observe a statistically significant difference between outcome and cause (p =0.819), outcome and gender (p 0.715) and outcome with regards to complications (p0.684).

Majority of the patients improved (83.3%) and was discharged with follow-up advice; remaining 16.7% succumbed to the disease and expired during hospital stay primarily due to multi-organ failure and sepsis. The mortality rate we encountered was comparatively less probably due to early hospitalization, effective treatment and good supportive care. The reported mortality rates for SJS and TEN vary from 5% to 70%[12].

CONCLUSION

Anticonvulsants, antibiotics and NSAIDS were the most frequently responsible drugs for development of SJS & TEN. The Observed mortality rate in our study was 16.7%.

RECOMMENDATIONS

We strongly recommend in light of our findings that awareness about drugs causing serious drug reactions like SJS/TEN will help doctors prevent such reactions by judicious use of drugs and manage them with minimum morbidity and mortality.

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CONTRIBUTORS

SMN conceived the idea, planned the study, and drafted the manuscript. MMP and HAK helped acquisition of data and did statistical analysis. All authors contributed significantly to the submitted manuscript.