An Epidemiological Study of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis during 2010-2015 at Shahid Faghihi Hospital, Shiraz, Iran

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Abstract

The Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are two ends of the spectrum of severe immunobullous state characterized by keratinocyte apoptosis. The present study aimed to draw attention to various epidemiological features of SJS and TEN diseases such as causative drugs, underlying diseases, duration of hospitalization, and types of treatment. The records of all patients with the diagnosis of SJS, TEN, and SJS/TEN overlap during 2010-2015 were retrospectively reviewed. The records belonged to patients who were admitted to the Dermatology Tertiary Referral Center of Shahid Faghihi Hospital affiliated to the Shiraz University of Medical Sciences, Shiraz, Iran.

From a total of 97 patients with such skin disorders, we identified SJS in 89 (91.8 %), TEN in 5 (5.1%), and SJS/TEN overlap in 3 (3.1%) patients. The most commonly consumed drug was Lamotrigine (21.6%) and the most common drug category was anticonvulsants (46.4%). In line with many studies, especially in Iran, Lamotrigine and anticonvulsant drugs were the most common causative drug and epilepsy was the most common underlying disease. Patients with SJS/TEN overlap or TEN were treated with combination therapy, whereas SJS patients received systemic corticosteroids.

Keywords ● Stevens-Johnson syndrome ● Drug eruptions ● Epidemiology ● Iran

Introduction

The Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are two ends of the spectrum of severe immunobullous state, with long-term morbidity and high mortality, characterized by keratinocyte apoptosis.1 Multiple organs may be involved in these conditions. In TEN, epidermal loss influences more than 30% of the total body surface, while SJS involves less than 10% of the body surface area. SJS/TEN overlap is characterized by epidermal detachment and the detachable skin between 10%-30%.2 SJS and TEN are primarily diagnosed clinically and can also be confirmed by histopathology. SJS/TEN are rare diseases and their incidence rate in Europe and
the USA is approximately 2 to 3 per million population per year.\(^8\) The risk of mortality in SJS is generally below 5%, while in TEN it is estimated to be 30%-50% in the acute phase of the illness.\(^4\) While there are different causes for the skin disease, such as infections and malignancy, medication is the main cause.\(^5\) Although a substantial number of drugs can cause SJS and TEN, some of the most common drugs associated with these skin diseases are anticonvulsants, antibiotics (mainly sulfonamides), non-steroidal anti-inflammatory drugs (NSAIDs), and allopurinol.\(^6\) Management of SJS/TEN includes immediate recognition and withdrawal of the causative drug(s), initiation of supportive care, and administration of specific drugs such as systemic steroids and intravenous immunoglobulin (IVIG).\(^7\) A substantial amount of research has been published on different epidemiologic aspects of SJS and TEN. However, to the best of our knowledge, epidemiologic studies in Iran are scarce. Note that the number of cases in our study in comparison with others was relatively considerable.

The present study aimed to draw attention to various epidemiological features of SJS and TEN diseases such as causative drugs, underlying diseases, duration of hospitalization, and types of treatment.

### Patients and Methods

The records of all patients with the diagnosis of SJS, TEN, and SJS/TEN overlap during 2010-2015 were retrospectively reviewed. The records belonged to patients who were admitted to the Dermatology Tertiary Referral Center of Shahid Faghihi Hospital affiliated to the Shiraz University of Medical Sciences, Shiraz, Iran. The study was approved by the Ethics Committee of Shiraz University of Medical Sciences, Shiraz, Iran (code: ir.sums.med.rec.1395.s154).

A total of 97 SJS/TEN patients with hospital records were included in the study. The diagnosis of these patients was mainly based on clinical signs and symptoms, and in a few cases, a skin biopsy was done to rule out any other conditions. Detached and detachable skin >30% of the total body surface was labeled as TEN, <10% as SJS, and between 10% and 30% as SJS/TEN overlap. From the records, patients' admission and progress notes, charts, examination results, and treatments were retrospectively evaluated. The following details were recorded in our data gathering form: demographic data, duration of hospitalization, history of causative drug intake, time of drug consumption before the onset of symptoms, and type of treatment. The score for toxic epidermal necrosis (SCORTEN) was also recorded. The most probable causative drug(s) that had been prescribed within four weeks before the onset of symptoms was considered as causative drugs.

Descriptive statistics were reported as mean±SD or frequency (%) for quantitative and qualitative data, respectively. The association between the two categorical variables was assessed using the chi-square or the Fisher's exact test, where appropriate, and non-parametric Kruskal-Wallis test was used to test quantitative variables among the three types of disorders. Statistical analysis was performed using the SPSS software (version 18.0) and P<0.05 was considered statistically significant.

### Results

From a total of 97 patients with such skin disorders, we identified SJS in 89 (91.8%), TEN in 5 (5.1%), and SJS/TEN overlap in 3 (3.1%) patients. The mean age of the patients was 38.7±17.9, 44.4±13.3, and 40.3±2.5 in patients with SJS, TEN, and SJS/TEN overlap, respectively. The number of female patients was 56 (90.3%) in the SJS, 3 (4.8%) in the TEN, and 3 (4.8%) in the SJS/TEN overlap categories. The number of male patients was 33 (94.3%) in the SJS and 2 (5.7%) in the TEN categories. Age (P=0.53) and sex (P=0.71) did not have a significant role in any category. The SCORTEN score for most (3 out of 5) of the TEN patients was 4 and for the other patients was 1 and 2. The mean age of the patients was 39±17.4 and they were mostly (63.9%) female.

The Fisher’s exact test showed that there was no association between sex and the type of disorder (P=0.71). The Kruskal-Wallis test indicated that the age of patients among the above-mentioned categories was not significantly different (P=0.53) (table 1). Also, there was no relationship between the period between drug consumption, and the onset of symptoms and type of skin disorder (P=0.51).

Duration of hospitalization in patients with TEN was 21.8±13.1 days, which was significantly higher than that of the patients with SJS or SJS/TEN overlap disorder (P<0.001). Dunn’s test confirmed that all the pairwise differences between the three types of diseases were statistically significant. Besides, regarding treatment allocation, the patients with SJS disorder were more likely to receive steroids as the main treatment. However, almost all patients with SJS/TEN overlap and TEN disorders received the combination therapy of systemic steroids and IVIG (table 1).
Lamotrigine (21.6%) was the most commonly consumed drug, and among the drug categories, anticonvulsants (46.4%) were the most common category. Also, 11 (11.3%) and 10 (10.3%) of the patients had a history of carbamazepine and ciprofloxacin, respectively. In the cephalosporin category, penicillin (9.3%) was ranked first, followed by amoxicillin (5.2%) and ceftriaxone (5.2%). In the anticonvulsant category, after lamotrigine, carbamazepine (10.3%), phenytoin (9.3%) and phenobarbital (4.1%) were ranked last. Ciprofloxacin (10.3%) was the most consumed drug in other antibiotics categories (table 2). Moreover, there was no association between the consumption of lamotrigine and the type of skin disorder (P=0.50).

Discussion

In the present study, lamotrigine was found to be the most commonly consumed drug, followed by carbamazepine and ciprofloxacin. Also, anticonvulsants were the most popular drug category followed by antibiotics. The latter is in line with previous studies carried out in Iran. In a study in Tehran (Iran), Rahmati-Roodsari and colleagues reported anticonvulsant drugs and antibiotics as the most common drugs. Another survey in Isfahan (Iran) supported our results and reported anticonvulsants and antibiotics as the common drug categories and lamotrigine and carbamazepine as the most common drugs that contributed to SJS and TEN, respectively. However, a few other studies have reported different results. Some studies reported sulfonamide as the most common drug. In a recent survey, Wang and Mei suggested antibiotics as the main causative drug category.

Our results indicated that NSAIDs were the third most frequent causative drug group. This is in line with many other studies that reported NSAIDs after antibiotics and anticonvulsants as one of the most common causative drug groups. Other new drugs could also be reported in the future. For instance, a recent study reported a pediatric case of SJS who had received Oxcarbazepine. We found that the most common underlying disease among patients was epilepsy followed by hypertension, hypersensitivity, DM, and brain tumor. However, some studies have stated other underlying diseases in SJS/TEN patients. In a nationwide retrospective study of 1,811 inpatient cases with SJS, the underlying diseases that led to a higher mortality were cirrhosis and metastatic cancer.

### Table 1: Patients’ clinical findings and kind of treatment

| Characteristic                      | SJS (n=89) | Overlap (n=3) | TEN (n=5) | P     |
|-------------------------------------|------------|--------------|-----------|-------|
| Duration of hospitalization         | 7.4 (4.8)  | 13.0 (6.1)   | 21.8 (13.1)| <0.001*|
| Time of drug consumption to onset of symptoms | 12.2 (10.7) | 15 (7.2)     | 11.4 (10.4) | 0.51* |
| Treatment                           |            |              |           |       |
| Steroid                             | 81 (91.0)  | 1 (33.3)     | 0 (0)     | <0.001††|
| Mix                                 | 8 (9.0)    | 2 (66.7)     | 5 (100)   |       |
*Kruskal-Wallis test; ††Chi-square test

### Table 2: Causative drug of SJS/TEN at Shiraz Shahid Faghihi Hospital

| Category       | Drug          | Frequency (%) | Category       | Drug          | Frequency (%) |
|----------------|---------------|---------------|----------------|---------------|---------------|
| NSAID          | Penicillin    | 9 (9.3)       | Herbal         | Doxycycline   | 3 (3.1)       |
|                | Amoxicillin   | 5 (5.2)       | Other antibiotics | Cotrimoxazole | 2 (2.1)       |
|                | Coamoxiclave  | 1 (1.0)       |                | Sulfasalazine | 5 (5.2)       |
|                | Cephalexin    | 2 (2.1)       |                | Metronidazole | 2 (2.1)       |
|                | Ceftriaxone   | 5 (5.2)       |                | Ciprofloxacin | 10 (10.3)     |
|                | Cefazolin     | 0 (0)         |                | Ofloxacin     | 1 (1.0)       |
|                | Cefixime      | 3 (3.1)       |                | Gentamycin    | 2 (2.1)       |
| Total          |               | 25 (25.8)     | Total          |               | 25 (25.8)     |
| Anticonvulsant | Carbamazepin  | 11 (1.3)      | Other drugs    | Finasteride   | 1 (1.0)       |
|                | Depakine      | 3 (3.1)       |                | Allopurinol   | 3 (3.1)       |
|                | Acetazolamide | 1 (1.0)       |                | Alprazolam    | 1 (1.0)       |
|                | Phenytoin     | 9 (9.3)       |                | Flunonazol    | 2 (2.1)       |
|                | Phenobarbital | 4 (4.1)       |                | Vincristine   | 1 (1.0)       |
|                | Lamotrigine   | 21 (21.6)     |                | Unknown       | 1 (1.0)       |
| Total          |               | 49 (50.5)     | Total          |               | 9 (9.3)       |
*Stevens-Johnson syndrome; †Toxic epidermal necrolysis
diseases. In a large longitudinal observational study, Frey and colleagues found that there was comorbidity between SJS/TEN and some other diseases such as pre-existing depression, lupus erythematosus, chronic kidney disease, recent pneumonia, and active cancer. However, they considered the confounding factors like drug use.

The mean age of the patients in our study was 39±17.4 years and most (63.9%) of them were female. The mean age was slightly higher or slightly lower than some other studies. However, most investigations have reported that these skin diseases are more common in women. Also, there was no association between sex and the type of these skin disorders, which is in line with a previous survey in Iran.

The duration of hospitalization in TEN patients was significantly higher than that of the patients with SJS or SJS/TEN overlap. This seems to be logical and can be justified by the fact that TEN patients had a more severe clinical presentation and a larger total body surface involvement than others. As a direct result, these patients required a longer period of hospitalization. Besides, we found that patients with SJS were treated with steroids, but almost all of those with SJS/TEN overlap or TEN received combination therapy (corticosteroids and IVIG together). Among different treatments for SJS/TEN, the most universally accepted intervention for SJS/TEN is supportive care. Other common adjuvant therapies are systemic corticosteroids, IVIG, tumor necrosis factor (TNF) inhibitors (e.g. Etanercept, Infliximab, and Thalidomide), Cyclosporine A, and combination therapy (IVIG, corticosteroids, and plasmapheresis). However, at our center, we treated the patients mainly with systemic corticosteroids or combination therapies of IVIG and systemic corticosteroids. IVIG has an influential role in the management of these diseases. A meta-analysis with meta-regression of observational studies revealed that IVIG at dosages of ≥2 g/kg significantly decreased the mortality rate in SJS or TEN. On the other hand, a recent review article revealed that the supporting data of combination therapies of corticosteroids and IVIG are equivocal and require further investigation. Additionally, a few recent research studies indicated new therapeutic methods. For instance, Ma and colleagues proposed a novel technique for amniotic membrane transplantation in acute SJS. Therefore, further studies may develop novel treatment methods.

The main limitation of the present study was due to the quality of the hospital records. Some physicians’ notes were illegible or incomplete. We might also have missed out certain data or did not record the underlying diseases. Further studies with larger sample sizes are recommended.

**Conclusion**

There are some differences between the epidemiological features of SJS and TEN diseases. In line with many studies, particularly in Iran, lamotrigine and anticonvulsants were the most common causative drugs, and epilepsy was the most common underlying disease. In addition, patients with SJS/TEN overlap or TEN were treated with combination therapy, whereas SJS patients received systemic corticosteroids.

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**Conflict of Interest:** None declared.

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