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Stevens Johnson syndrome in Pakistan: a ten-year survey

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Stevens Johnson Syndrome in Pakistan: a Ten-Year Survey

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Abstract

Objective: A pre-tested questionnaire-based, retrospective study to highlight the causative factors, mode of presentation, complications and outcome of patients with Stevens Johnson syndrome.

Setting: Aga Khan University Hospital over a 10 year period.

Methods: All case records with a diagnosis of Steven Johnson Syndrome in the period 1990 to 2000 were retrospectively reviewed. Data was retrieved on a comprehensive questionnaire. The demographic variatbles and drugs taken within the previous 21 days were noted. Date analysis was done by Epi-Info Version 6.0.

Results: Of the 101 studied patient files, the most common offender was found to be the Penicillins as a group and Sulfadoxine-Pyrimethamine (Fansidar) when considering all drugs individually. Most common complications included electrolyte disturbances (13.9%) and congestive heart failure (6.9%). Mortality rate was high at 10.1%.

Conclusion: SJS was found to be a rare condition but having a mortality rate of 10.1%. As it can be induced by a large number of drugs, caution should be practiced while prescribing (JPMA 54:312;2004).

Introduction

Stevens Johnson Syndrome (SJS) is a generalized, multi-systemic hypersensitivity reaction usually to drug exposure in which skin and mucous membrane lesions are early manifestations. It was first fully described by Stevens and Johnson in 1922[1] and is a potentially life threatening illness considered to be part of the erythema multiform spectrum. Usually it is a self-limiting disease. No studies, pertaining to a large number of patients over a significant time period have been done in Pakistan that have investigated the eitiologies and course of Stevens Johnson Syndrome. Western reports represent their local experiences and drug prescribing. In addition to this, and probably most importantly, the mortality rate is not known in this part of the world.

Patients and Methods

Case Selection

A retrospective review of all the cases seen at the Aga Khan University Hospital, with a diagnosis of Stevens Johnson Syndrome (SJS) during 1990-2000 was carried out. Data was obtained from the patients' files. A total of 187 patients were identified with a discharge diagnosis of Stevens Johnson syndrome according to the International Classification of Diseases code ICD-9-CM 695.1. Since the ICD-9-CM code for erythema multiforme includes other illnesses in addition to Stevens Johnson syndrome and because these illnesses are occasionally misdiagnosed, the patients' primary medical records were sought to confirm whether a skin disease compatible with Stevens Johnson syndrome was present or not. Stevens Johnson syndrome was identified according to the following strict criteria of: (1) involvement of at least 2 different mucous membrane sites; (2) erosions covering >10% but <20% of the body surface area and (3) visible iris and target lesions. These criteria were assessed by reviewing patient charts, where these lesions had been professionally and precisely documented by a dermatologist.

Data Collection

To gather clinical information, comprehensive data collection was carried out, using a questionnaire that was designed after an extensive literature review using the University Library, Medline and the Internet. The questionnaire, amongst other things, included demographic variables, history of drug intake, signs and symptoms and ultimate outcome. A drug causally related to the condition was defined as every drug that had been taken close enough prior to the onset of any symptom (i.e., 21 days).

Final year medical students at The Aga Khan University undertook the task of data collection. The biostatistical program, Epi-Info (version 6.0) was used to analyze the gathered data. Frequencies and percentages of relevant variables were obtained and documented. The analysis is described below.

Results

Atotal of 101 patients were identified. The incidence of SJS in the population was found to be 1.89 cases per million per year. The mean age at presentation was 26.4 years with a standard deviation of 19.8 years. There were 62 females and 39 males. Amongst the female patients, 4 were pregnant at the time. Only 4 of the patients were from outside the city.

The predominant mode of presentation was primary Stevens Johnson Syndrome while only 5 patients developed
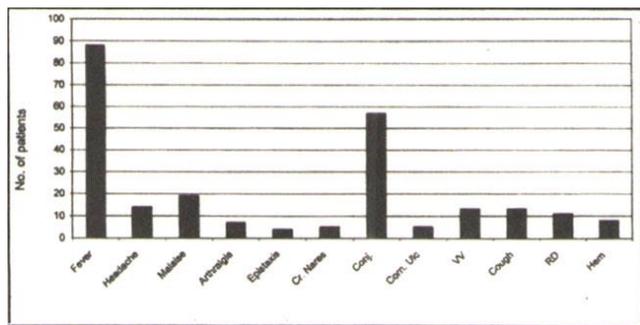
Figure 1. Signs and symptoms.
Key: Cr. Nares=Crusted nares, Conj.=Conjunctivitis, Corn. Ulc.=Corneal Ulcers, VV=Vulvovaginitis, RD=Respiratory distress, Hem=Hematuria.
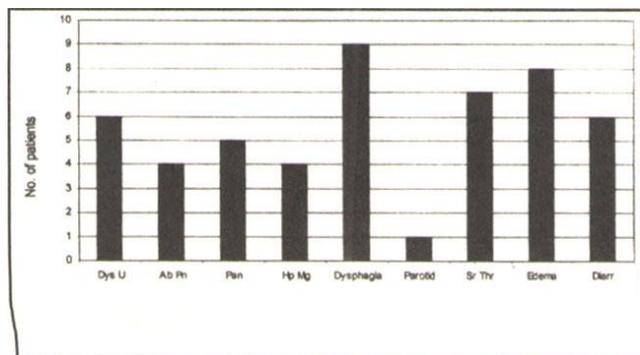
Figure 2. Signs and symptoms (cont'd.)
Key: DysU=Dysuria, Ab Pn=Abdominal Pain, Pan=Pancytopenia, HpMg=Hepatomegaly, Parotid=Parotid gland enlargement, Sr Thr=Sore Throat, Diarr=Diarrhea.
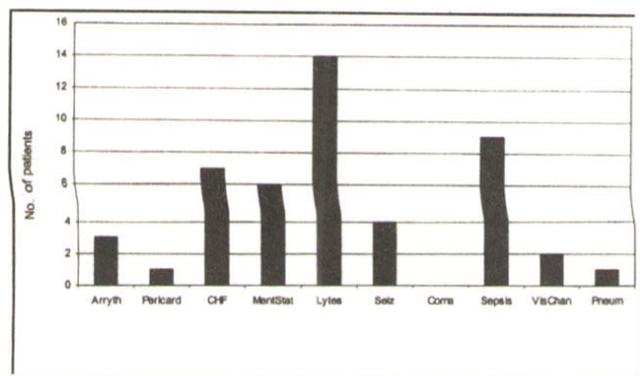
Figure 3. Complications.
Key: Arryth=Arrythmias, Pericard=Pericarditis, CHF=Congestive Heart failure, Ment Stat=Mental status changes, Lytes=Electrolyte disturbances, Seiz=Seizures, VisChan=Visual changes, Pneum=Pneumonia.

SJS secondary to treatment for another illness. Previous history of SJS was positive in a total of 9 patients. The duration of hospital stay was 10.2 days with a standard deviation of 8.9 days.

Of the 101 patients included in this study, 93 gave a positive history of drug intake prior to developing the signs and symptoms of Stevens Johnson Syndrome. Seven
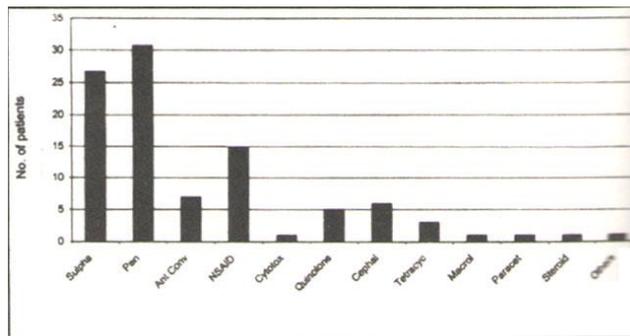
Figure 4. Offending drugs.
Key: Sulpha=Sulphonamides, Pen=Penicillins, Ant Conv=Anti-convulsants, Cytox=Cytotoxic drugs, Cephal=Cephalosporins, Tetracyc=Tetracyclines, Macrol=Macrolides, Paracet=Paracetamol

patients could not provide information regarding the most likely offender. Only one patient gave a history of meningitis vaccination. No other vaccination history was given. The exact dose of the administered drug was known in 48 cases, mode of administration was oral in 95 patients and parenteral in 6. Twelve patients gave a history of previous exposure to the offending agent. Signs and symptoms (Figures 1and 2), complications (Figure 3) and identity of offending drugs (Figure 4) are given in their respective figures. Ninety patients were discharged from the hospital after treatment while one patient was shifted to another hospital. Ten patients died giving a mortality rate of 10.1%. Mortality was not affected by the type of drug responsible.

Discussion

Stevens Johnson Syndrome (SJS) is an infrequently encountered condition and we were able to review 101 individual cases in a 10-year period at The Aga Khan University Hospital. The study was consistent with other literature regarding age, that it affected mainly the pediatric age group and young adults. However, one particular study we came across did not achieve this result.[2]

Our study revealed a male to female ratio of about 2:3. Studies vary in this matter. Some quote male sex as a well-known risk factor for the condition[3] whereas some document that being female carries a higher risk for these types of adverse drug reactions.[4-6]

Astudy of a primary presentation versus a secondary one was undertaken to see if other illnesses predispose to SJS. However, 96 of the patients presented with primary SJS and no significant conclusion could be determined.

Amongst our 101 patients, 92 had no previous history of SJS. A previous attack is a known risk factor for the development of SJS.[3] The general risk of recurrence of SJS is said to be about 37%, but our figures suggest a much lower percentage of about 8.9%.

Of the 101 cases reviewed, drugs were clearly one of

Of the 101 cases reviewed, drugs were clearly one of the major offenders, contributing to about 93.9% of all cases, as compared to 43% in a study in the United States[7] and 54.5% in Malaysia.[8] This high incidence could be attributed to irrational, unnecessary and easy 'over the counter' use of medicines in this part of the world. Drugs are followed by infections (5.9%), vaccines (0.1%) and the unknown category also being 0.1%.

Amongst drugs (Figure 4), antibiotics were the cause of SJS in 67 cases (66.3%) making it the most common category of drug. This tallies with some previously published studies.[5,9-11] Amongst them the Penicillins had the highest incidence (30 cases) and the Sulphonamides had the second highest incidence (26 cases) of causing SJS. The remaining drugs comprised of Cepahalosporins, Macrolides, Tetracyclics and Quinolones.

When the drugs were analyzed on an individual basis (i.e. taken out of their groups), Sulfadoxine-Pyrimethamine (Fansidar) had the highest association with SJS; seen in 19 cases. This is probably due to the high incidence of malaria endemic in these parts of the world necessitating the use of cheaper anti-malarials. This statement can be supported by the high incidence of SJS in the inhabitants of Beira, Mozambique who were given Fansidar for mass prophylaxis against cholera[12] and in a study of Swiss travelers using the same drug, they reported severe cutaneous adverse reactions one thirtieth as large.[13]

NSAIDS accounted for 14 cases of SJS, which is comparatively lower than other studies[10,14,15], where NSAIDS were responsible for about 50-74% of SJS cases. This could be due to their relatively higher price in this country and cheaper alternatives. Other drugs that caused single cases of SJS consisted of Metronidazole, Diltiazem, Mebendazole and even one reported case due to the ingestion of Smarties®. A study in Thailand concluded that antituberculous drugs ranked third in overall incidence when causing SJS but no case was reported involving an antituberculous drug in our study even though Pakistan is considered to be an endemic region for the disease. This is in sharp contrast to a study in neighboring India.[16]

A cause for the high incidence of drug related SJS could be due to the fact that the indication of antibiotic use in some cases may have been for the treatment of early signs and symptoms of SJS due to other drugs. In one case, symptoms deteriorated following Amoxicillin use and the general practitioner involved increased the dose of the offending drug for a further 7 days.

Concerning signs and symptoms (Figures 1 and 2), fever was seen in 88 cases whereas ocular involvement occurred in 57 patients, making them the commonest nondermatological manifestations of SJS in our study group.

This coincides with some studies done abroad.[8] However, patients with SJS in this study also presented with some symptoms not found in standard literature or text. These included dysuria (9 cases), edema (8 cases), dysphagia (6 cases) and diarrhea (6 cases). The significance of these previously undocumented outcomes following SJS requires further investigations.

As regards to the complications during hospitalization (Figure 3), the most commonly found ones were electrolyte disturbances (14 cases) and congestive heart failure leading to pulmonary edema (7 cases). Some complications, not previously documented in standard medical literature, included hematochezia (5 cases), hyperglycemia (3 cases) and depression (1 case). Our complication rate was 59.4%. The study had a relatively low occurrence of permanent visual changes in patients following SJS. The rate of occurrence of permanent visual change was 1.9%, whereas studies have reported the rate as high as to 20%.[2] Regular referrals and follow-ups by the ophthalmologists were vital for this outcome.

The mortality in this group of patients was 10.1%, which roughly coincides with studies done in the West where it is 4.5-15% of the patients. Acute hepatic failure was responsible for 2 deaths and sepsis was the cause of 1 mortality. No association was found between the length of stay in the hospital and eventual outcome. An interesting fact which came up in the analysis was that one third of the patients that died had taken Amoxicillin as the initial offender for SJS.

Conclusion

One hundred and one cases in ten years indicates that SJS is a relatively rare condition. It is perhaps a first step for further studies in the future, comparing results with other countries in the region or even with that of toxic epidermal necrolysis (TEN), its deadly counterpart. With a 10.1% mortality rate, which correlates with the West, this syndrome should not be underestimated or overlooked SJS is a hypersensitive reaction to a varied range of etiologic factors and a large number of drugs may induce it. As such, knowledge about this condition should modify a physician's perception of the risk benefit balance of virtually any drug. To investigate this further, a larger study would be needed.

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