Steven Johnson syndrome: Retrospective study

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ABSTRACT

To evaluate the pricipal epidemiological and evolutive characteristics of Stevens Johnson Syndrome. A retrospective descriptive study was conducted of all cases of Steven Johnson Syndrome was notified to Moroccan Center Anti Poison and Pharmacovigilance by professionals health between the period January 2010 and December 2012. During this period, 23 cases of Steven Johnson Syndrome have been reported an average of 8 cases / year. Women are the most affected (sex ratio (F / M = 2.2). The most incriminated drugs were: Allopurinol (21%), Ethambutol, Isoniazid/Rifampicin, Pyrazinamide paracetamol, sulfamethoxazole / trimethoprim 5% each. The causality according to WHO method showed that 62% were probable and possible in 38% of cases. The outcome was favorable in 86% of cases, one case was fatal and 9% of cases, have not been not been specified.
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INTRODUCTION

Steven Johnson syndrome is a cutaneous drug reaction resulting suddenly occurring from a serious drug allergy, exceptional and unpredictable. This allergy leads to a more or less extensive destruction of the most superficial part of the skin called: toxic epidermal necrolysis. The mortality rate is estimated between1 5% [4]. Steven Johnson Syndrome has multiple etiologies, it may be idiopathic (5% of cases)[2], secondary to infectious diseases or drug induced more frequently (75%)[7].The most offending drugs are: Allopurinol, Anti-infective Sulfonamides, Nevirapine, Carbamazepine, lamotrigine, Phenobarbital, Phenytoin, Nonsteroidal Anti-inflammatory derivatives Oxican[3]. On the pathophysiological mechanism of Steven Johnson is unknown, it may be due to an abnormal mechanism of drug promoting excess production of reactive metabolites, and then develops an auto-immune reaction against these metabolites coupled to proteins in the epidermis[11]. The systemic involvement in the Steven Johnson Syndrome requires an early multidisciplinary management of patients to reduce the severity; it is a dermatological emergency whose prognosis is at present derogatory. Prevention of this disease requires knowledge of drugs involved for better management of risk factors.

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Indeed, in Morocco there no studies on this subject of this disease. The literature is limited to the description of clinical cases. This work aims to establish the epidemiological profile of Steven Johnson Syndrome through the cases collected by the Moroccan Center Anti Poison and Pharmacovigilance (CAPM)

MATERIALS AND METHODS

This work is a retrospective study on cases of Steven Johnson Syndrome related to drugs notified to CAPM for three years from January 2010 until December 2012, established from the declarations forms of adverse events from health professionals, and the pharmaceutical industry.

The CAPM is located in Rabat Morocco's capital, the first Arab countries and Africa who participated in international pharmacovigilance program. It was created in 1989 by the Ministerial Circular No. 2 DR/10 dating from 1992 that the adverse reaction reporting by health professionals and the pharmaceutical industry has become essential. The yellow plug is the reporting of information by health professionals for the collection of unwanted effects support on this record are noted the following parameters:

- The sociodemographic characteristics of the patient (sex, age, history...)
- The data on adverse events (date of appearance, time to onset of adverse effects, evolution...)
- The data on drug involved (name of specialty dosage corrective treatment...)

Subsequently reported cases are entered on Vigiflow which is a management system the adverse drug effects, developed and hosted by the Uppsala Monitoring Centre located in Sweden. Statistical methodology was based on the calculation of frequencies or averages of each variable studied. The descriptive analysis included age, sex, origin, nature of adverse effects, the most incriminated therapeutic classes, severity, time to onset of adverse effects, hospitalization, evolution...). To identify links between these variables, we used the chi-square test ($\chi 2$). Statistical analysis was performed by statistical software. On the other hand, to study and view existing correlations between variables, we used principal components analysis.

RESULTS

During this period, 23 cases of Stevens Johnson Syndrome (SSJ) were recorded, an average of 8 cases per year. SJS represents 2% of all reported cases of drug reactions and 9.5% of serious drug reactions. The region of grand Casablanca declared 39% of cases of SJS, followed by the Rabat region (35%) [TABLE I]. Mode spontaneous reporting represented 74% and 26% were collected in a active mode.

TABLE 1 : Epidemiological characteristics of the study population

Variables	Terms	n	n (%)	X^2 à 5%	P
Sex	Female	11	48	8,33	0,016
	Male	6	26		
	Unkown	6	26		
Age groups	Children	1	4	27,9	P <0,001
	Adult	19	83		
	Elderly	2	9		
	Unkown	1	4		
Serious	Hospitalized	22	95	23	P < 0,001
	Unkown	1	5		
Type of report	Spontaneous	17	74	19,2	P < 0,001
	Active	6	26		
Country	Casablanca	9	39		
	Rabat Salé Zammour Zaer	8	35		
	Fez-Boulmane	5	22		
	Gharb Chrarda Beni Hssen	1	4		

The average age of patients was 45.1 ± 15.3 years of. The sex ratio (F / M) was 2.2 with a significant difference (P<0.05). The age group most affected was that of adults (83%) females (χ_2 to (5%) = 34.8 P <0.001), followed by the elderly (9%) and children (4 %). According to results, 90.1% of patients are older than 15 years with extremities ranging from one year to 80 years. To compare the distribution of the age variable in the two modalities (male / female), we juxtaposed on the same graph the two boxplots are defined respectively for the male group and female group, using the same scale [Figure 1].

The comparison of the age distribution of patients with Stevens Johnson Syndrome-by sex (Figure 1) shows that the difference between the maximum age
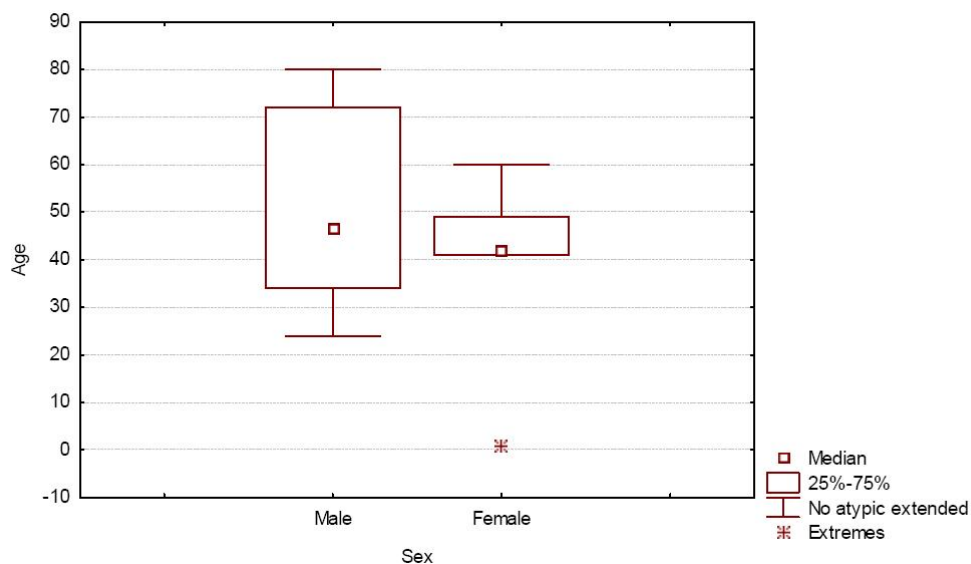
Figure 1: Comparison of the distribution of the variable age by sex

and the minimum age (Scope) is much higher in males (57 years) than in females (19 years). Thus the interquartile range (difference=third quartile - first quartile) is also important in males than females, this translates to a large dispersion of age in the category of male patients affected.

The main drugs involved were [Figure 1]: the hypouricaemic (Allopurinol 21%), the (association Sulfamethoxazol/Trimethoprim 5%), Antiinfective Sulfonamides, Analgesics (Paracetamol 3%), Antituber-culosis (Ethambutol 3% combination Rifampicin / Isoniazid 3% Pyrazinamide 3%) and Nosteroidal Anti-Inflammatory drugs (Piroxicam 3%).

In 39.1% of cases, it was polypharmacy and monotherapy in 60.9% of cases. The majority of drugs were administered per os (94%) and 6% intravenously. The median time to onset of Steven Johnson Syndrome after drug treatment was 18.4 days, with a three-day extremity up to 135 days. The hospitalization rate was 95% of cases. Causality according to WHO method
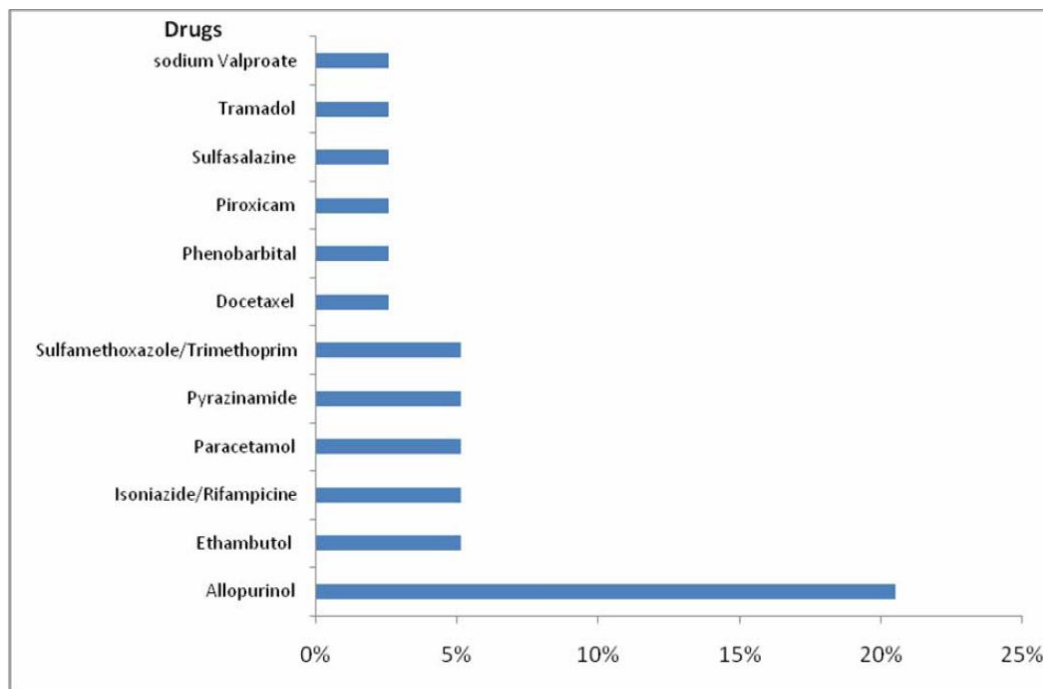

Figure 2 : Drugs most implicated in the steven johnson syndrome

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was seen in 62% probable, possible in 38% of cases. The outcome was favorable in 86% of cases, not specified in 9% of cases and fatal in one case.

To determine and visualize correlations between gender, age groups and evolution, we used principal component analysis [Figure 3]. According to the first factor (58.35%), there was an association between infant, elderly and the favorable side (X +). While the adult, is closely linked with death (X-).

According the second axis which represents 22.23% of the variability there is a separation between the two sexes, the female side (Y) and the male side (Y +). These results confirm a strong correlation between the adult and the move towards the death on one hand, on the other hand, between the evolution toward healing and age groups of children aged and elderly.

DISCUSSION

Steven Johnson Syndrome is a severe bullous dermatosis caused by drugs. The term SSJ has been described for the first time in 1922 by Steven Johnson and as a febrile illness with stomatitis, purulent conjunctivitis and skin lesions[12]. It is a rare and severe drug hypersensitivity reaction that can be life-threatening for patients.

During the period 2010-2012, 23 cases of SJS were declared to the Anti Poison and Pharmacovigilance Centre with an annual average of 8 cases per year. As an indication the number of reported cases of SJS in France is about 120 cases per year[13] for a notification rate of 350 cases / million / year, while in Morocco at a rate of 100 cases of notifications / million / year, we received 23 cases of declarations, this is the one underreporting by health professionals do not have the culture of reporting adverse drug reactions is a discontinuous and irregular manner which allows not assess the real impact of this disease despite the presence of Anti Poison Centre and Pharmacovigilance.

In the literature, the SSJ is observed advantage in adulthood[2]. It occurs at any age but the risk increases beyond midlife women[9], in our series, the most affected group was that of adults. The predominance of the female sex is also described in other publications, with a sex ratio (F / M) of 2.1 [6], this result is similar to our study, the sex ratio (F / M) was 2.2.
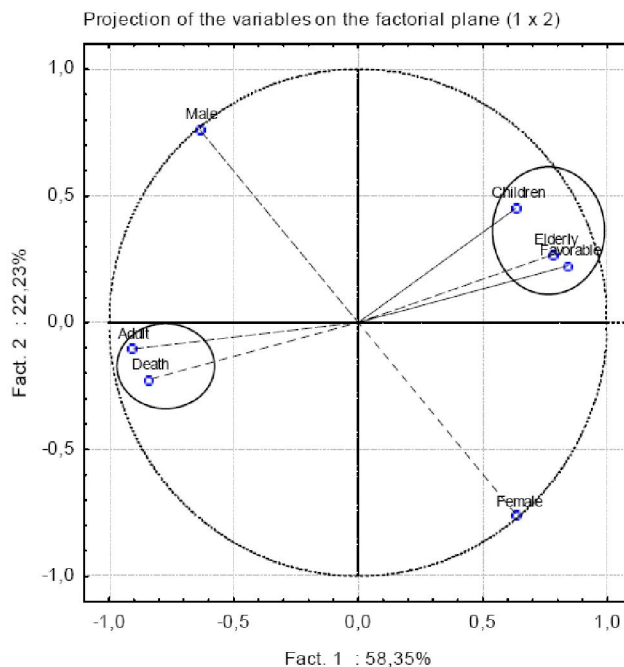

Figure 3 : The influence of age and sex groups on the evolution of patients

As indicated in the literature and in several studies, the main cause is overwhelmingly drug toxiderma[8,9], although some bacteria and viruses can be the cause. In the publication of Kalb RE[5], a case of SJS has been described in which infection with Mycoplasma pneumoniae was the causative agent in a man of 45 years. Drugs identified risks are: anti-infective sulfonamides (sulfamethoxazole / trimethoprim), tuberculosis (rifampin-isoniazid Association, anti-inflammatory drugs (Piroxicam), Antiepileptics (Phénolbarbital, Sodium valproate), hypo-uréciminits (Allopurinol), the Antiepileptic (Phenobarbital)[8-10]. This is consistent with our study. The drug withdrawal in question as soon as possible may improve the prognosis. The outcome was favorable (86%) deaths occurred in one case. In literature the death rate varies from 5 to 10%[10].

CONCLUSION

The SJS is a serious drug life threatening reaction that requires early diagnosis for the identification and removal of the causative agent. An immediate treatment is necessary, a public awareness before any dermatological symptoms will further reduce the incidence and improve the prognosis of this condition.

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