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MORBIDITY AND MORTALITY OF TOXIC EPIDERMAL NECROLYSIS AND STEVEN JONSON SYNDROME TEN/SJS AMONG SUDANESE PATIENTS

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ABSTRACT

Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and their overlap are rare severe cutaneous adverse drug reactions with a fatal potentiality. They are characterized by epidermal necrosis which causes erosions of the mucous membranes, extensive detachment of the epidermis, and severe constitutional symptoms. Drugs are the major causes of SJS\TEN. The types of the drugs depend on the prevalent diseases in the country and the protocols of management in that country. This is a Retrospective hospital based study, was done to detect the morbidity and mortality of SJS / TEN and their overlap, among Sudanese patients admitted to Khartoum Dermatology and Venereology Hospital from April 2004 to April 2014. In our study 150 patients were enrolled, the main age distribution was between 21 - 40 years in (48.7%), 48% of the cases had SJS, 42.7% had TEN and only 9.3% had SJS\TEN overlap. Eighty percent of the patients had no past history of similar condition. The commonest drug reported to precede the development of the disease was antimalarial (artesunate) drug in 20.7% of the cases, followed by the antibiotics Septrin (Cotrimoxazole) in 20%, both contain sulpha group (40.7%) and (ciprofloxacin) in 20% of cases. Other culprit medications were anti-tuberculous, penicillin, carbamazepine, phenytoin, allopurinol and NSAIDS.Patients who dead throughout the last 10 years were 24/150 cases (16%), 14 % due to TEN, 1% with SJS, and 1% with Overlap SJS/TEN. The most implicated causes of deaths were septic shock in 86.5%, respiratory distress in 12.5%, and renal impairment in 1%.

KEYWARDS: TEN, SJS, Morbidity, Mortality.

INTRODUCTION

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), also collectively known as Lyell's syndrome, are rare life-threatening cutaneous drug reactions with a reported combined incidence of approximately 0.05–3 cases/million per year, although considerably higher in HIV-infected persons.[1], [2] In SJS there is <10% of epidermal detachment and in TEN there is >30%. SJS / TEN overlap lies between these two extremes.[3] The disease manifests clinically as epidermal stripping and baring of large areas of the dermis and mucosal membranes with resultant skin and mucosal failure. The skin failure is associated with loss of hemostatic function, fluid and electrolyte imbalance, metabolic abnormalities, impaired thermoregulation and loss barrier function allowing potential pathogens to gain access to the body predisposing to localized and bacterial systemic infection (BSI).[4]

The overall annual risk for SJS and TEN in the general population was found to be 1.1 and 0.9 per million for SJS and TEN, respectively in a German study.[5] Other authors like in United states of America, France, Italy, have estimated 0.4 to 1.2 per million for TEN and 1.2 to 6 per million for SJS.[7]

In SJS/TEN BSI is the leading cause of mortality, which can be up to 40% in tertiary centers and intensive care units with optimal care and facilities.[6],[7] Mucosal erosions, a hallmark of SJS/TEN, provide a further portal of entry for pathogens. A retrospective study in France by de Prost and colleagues showed that *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Enterobacteriaceae* were the most common organisms cultured in the blood of patients with SJS/TEN, implicating both the skin and the gastrointestinal tract as possible portals of entry by pathogens.[8] SJS and TEN have been described in all age groups including children, infants and even newborns[9-12], but the incidence rises with increasing age to the extent that in patients above 65 years the incidence was found to be 2.7 times higher than in younger patients.[13-14]

Aetiology

Usually it is very difficult to detect the cause of SJS \TEN. But, drugs were found to be the most common cause of the disease, accounting for 77 -97% of cases[5]

.More than 100 drugs have been identified as culprits.[15] Cotrimoxazole, sulfonamides, aminopenicillins, quinolones, cephalosporins, chlormezanone come on the top of drugs that used for short time. For drugs with long-term use, such as carbamazepine, phenobarbital, phenytoin, oxicam-non steroidal anti-inflammatory drugs (NSAIDs) and allopurinol, the crude relative risk was increased.[15] SJS\TEN were also reported following antimalarial medications like Fansidar (pyrimethamine and sulphadoxine)[16,17], mefloquine[18] and hydroxychloroquine.[19] Fansidarwas a recommended drug for use in travelers to Africa at risk of acquiring chloroquine-resistant Plasmodium falciparum[17] In Sudan Artesunate lately introduced to face the chloroquine – resistant malaria, but recent to our study there is no documented information about its adverse effects.

Prognosis

Seven independent risk factors (age, malignancy, tachycardia, body area, and serum level of urea, glucose and bicarbonate) leading to death constituted the toxic epidermal necrolysis-specific severity-of-illness score. Standardized treatment protocols were associated with lower mortality rate and children were thought to have a better prognosis and faster re-epithelization.[6]

Objectives

To identify the prevalence of SJS / TEN, morbidity and mortality rates and the most offending drugs among Sudanese patients admitted to Khartoum Dermatology and Venereology hospital.

Patients and Methods

A retrospective, hospital based, crossed-sectional study (April 2010 to April 2014), included all patients who had been admitted to Khartoum Dermatology and Venereology Hospital. All medical files of patients, whom were diagnosed with TEN, SJS, and TEN/SJS overlap, have been well researched to identify the possible culpable drug and the prognosis of the patient.

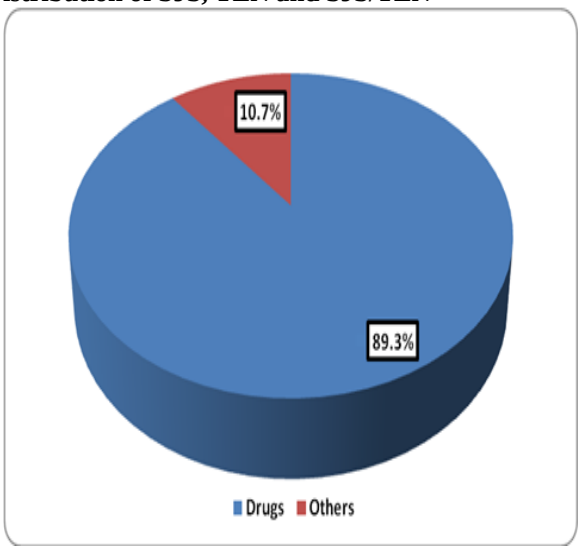
Ethical Issues

The research methods have been endorsed and approved by the Ethical Committee at Sudan Medical Specialization Board.

RESULTS

150 patients have been sorted, 64(42.7%) with TEN, 72(48%) with SJS, and 14 (9.3%) with TEN/SJS overlap. Females were double males. Around 50% of patients' age was between 21 and 40 years old. 134 (89.3%) of them had a confirmed drug intake prior to the illness. The remaining 16 patients denied any drug intake and failed to recognize any cause. The medical background of 98(65.3%) of the patients showed no history of chronic illness and the rest distributed as follow; 27(18%) had diabetes mellitus, 18 (12%) had hypertension, 8(5.3%) had Epilepsy and 4(2.7%) had gout. 80% developed the disease for the first time. The culprit drugs were Artesunate in 31(20.7%) of cases, Septrine in 30(20%), Ciprofloxacin in 28(18.7%), Anti-tuberculosis in 12(8%), Penicillin in 3(7%), Phenytoin 8(5.3), Carbamazepine in 4(2.7%), Allopurinol in 7(4.7%), NSAIDS in 6(4%) and only 2(2.7%) patient for other not known drug names. Sixteen percent of patients were dead, 14% with TEN (92% of all deaths), while SJS and TEN/SJS equally shred the 2% (4% of all deaths, for each). The direct causes of death were septicemia (Septic Shock) in 88.3%, respiratory distress in 12.5%, and renal impairments in 4.2% of deaths.

Distribution of SJS, TEN and SJS/TEN



Etiological Factors implicated to SJS, TEN, and SJS/TEN

Syndrome	No	%
Steven Johnson syndrome	72	48.%
Overlap SJS/TEN	14	9.3%
Toxic epidermal necrolysis	64	42.7%
Total	150	100.%

Suspected drugs to induce SJS, TEN, and SJS/TEN

Drug	No	%
Artesunate	31	20.7
Septrin	30	20.0
Ciprofloxacin	28	18.7
Carbamazepine	4	2.7
Phenytoin	8	5.3
Allopurinol	7	4.7
Anti-tuberculosis	12	8.0
NSAIDS	6	4.0
Penicillin	3	0.7
Other	2	2.7
Total	150	100.0

Number and causes of death in (SJS), (TEN) and their overlap

No. of deaths	**Syndrome**	**No**	**%**
	Steven Johnson syndrome	1	1
	Overlap SJS/TEN	1	1
	Toxic epidermal necrolysis	22	14
	Total	**24**	**16.**
Cause of death	**Complications**	**No**	**%**
	Sepsis	20	13
	Respiratory distress	3	2
	Renal impairment	1	1
	Total	**24**	**16**

DISCUSSION

In 150 cases, admitted to Khartoum Dermatology and Venerology Teaching Hospital and diagnosed as SJS, TEN and SJS/TEN overlap in 10 years ago, are analysis in our study and has shown that the cause of SJS\TEN in 89.3% of patients is probably drug, which goes well with the reported data in the international studies.[20] Drugs are thought to be the commonest cause of EN. In Sudan drug prescription practices are not well controlled and there is a lack of awareness amongst doctors of the risk of adverse drug reactions. The sex ratio, Female to male in our study is 2:1 which is in keeping with The female to male ratio in most series.[21,22]

The peak incidence of drug associated SJS\TEN occurs at the age interval (18–40) years. This fact is contrary to the prevailing figures in the European literature[14,23], which reported a higher incidence among elderly people but fits well with the reported data from India,[24,25] However if this can be explained on ethnic or geographic basis, we should note that countries in Asia like Japan[26] reporting similar figures to the Europeans.[13,14]

Further, more in our study to categorize the relation between the condition and geographical areas in Sudan, we concluded the most cases came from west of Sudan region, we not known exactly why, but may be due to low infrastructure and community awareness about drug use. The overall annual risk for SJS and TEN in the general population was found to be 1.1 and 0.9 per million for SJS and TEN, respectively in a German study.[5] Other authors like in United states of America, France, Italy, have estimated 0.4 to 1.2 per million for TEN and 1.2 to 6 per million for SJS.[7,27-30] A lower incidence rate was reported in Singapore[31], indicating a geographic difference, being high in Europe as represented by Germany and lower in Asia as represented by Singapore. Unfortunately we could not find any figures for African countries including Sudan.

In regard to the medical background of the patients study, we find the most cases had no chronic illness, but the most co-morbidity with disease had diabetes mellitus, contribute 18% of percentage, this probably because it is one of the most common chronic illness disease in Sudan. The most cases had no past history of similar condition in 120(80%), making the possibility of sensitization less likely and postulate immune reactions process with different mechanism. The pathogenesis of SJS/TEN is not fully understood. But, it is believed to be an immune-mediated reaction due to abnormal metabolism of a certain drugs. This will lead to deposition of the drug in the epidermis and result in apoptosis and keratinocyte death.[15]

Antimalarial drug, Artesunate was found to be the commonest drug to cause SJS\TEN among our patients. This is because it is the first line of treatment of malaria in Sudan. However it is composed of Artesunate and Fansidar (Sufladoxine and Pyremethamine) which has created a problem in detecting which one of the components is the cause. Since Fansidar was reported to cause the disease[32,33] and Artesunate (Artemesinin group) was considered a relatively safe Antimalarial.[34,35] Fansidar was reported among patients who used it as prophylaxis against malaria.[34,35] Worth mentioning that Artesunate is a new Antimalrial drug, which has become the treatment of choice for severe malaria. It is an Artemesinin derivative, derived from the planet Artemisia Annua. It is not used as a monotherapy and needs to be combined to another Antimalarial. This is because there have been signs that malarial parasites are developing resistance to the drug. It has water soluble, lipid soluble forms and others.[36]

The recent study from Europe has shown that Allopurinol[37] is the commonest cause of EN replacing the old data which had shown that Septrin (Cotrimoxazole) and NSAIDs (Piroxicam) were the common in the non-developed countries.[38,39] Allopuranol was reported in one patient in our study, which can be explained by the less use of it according to the profile of diseases in our country. In Asia anticonvulsants were the offending drugs in most cases, namely Carabamezapine.[40] It is known that Antiretroviral drugs can cause SJS\TEN[38], but in our study we didn`t come across such a case. This might be explained by the fact that inspite of the high incidence of HIV there is very limited use of Antiretroviral medications, simply because they are not available in the right quantities in the public sector and almost completely absent in the private sector because of the unaffordable prize. Antituberclosis and antiretroviral drugs are the common causes of SJS\TEN in the developing countries.[27]

In categorization of patients, we find most of cases were SJS, but the most cases of death were TEN. All number of deaths, which admitted in Khartoum Dermatology and Venerology Teaching Hospital from (April 2004 –April 2014) were (24/150) patients, and represent (16%).The most of the Morbidity cases admitted to Khartoum Dermatology and venerology Teaching hospital in the period between (2008 – 2011) were 59(39%), Between (April 2004- 2007) in 49(32%) and (2008- April 2014) in 42(29%), this could be explained by the improvement in diseases awareness among our staff .Besides that, the most of the Mortality cases admitted to Khartoum Dermatology and venerology Teaching hospital in the period between (2008 – 2.011) is (10/24), which represent 7%, Between (April 2004- 2007) is (8/24), which represent 5% and (2008- April 2014) in (6/24), which represent 4% . Regarding mortality rate in our study is (16%), which is not matching with international records (30%), may be due to our study only in one major hospital in Sudan. In general it is mostly due to septic shock, which contribute 14% of death causes in Sudan, which may be explained by poor hygiene and herbal medication and possible to antiseptic measure.

CONCLUSIONS

Drugs were reported in most of the cases developed epidermal necrolysis in our study.

The antimalarial drug (Artesumine) was found to be the commonest drug involved in this disease in Sudan followed by the antibiotic Septrin (Cotrimoxazole).

Regarding the spectrum of EN, SJS and TEN occur almost equally while SJS\TEN overlap occurs less.

The most cases of death occur among TEN patients.

Sepsis (septic shock) is the most cause of death involved in this disease in Sudan.

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