

## CLINICAL REPORT

# Aetiology in Sixteen Cases of Toxic Epidermal Necrolysis and Stevens-Johnson Syndrome Admitted within Eight Months in a Teaching Hospital

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Toxic epidermal necrolysis and Stevens-Johnson syndrome are serious cutaneous reactions associated with significant mortality and morbidity. Eight patients with toxic epidermal necrolysis and eight patients with Stevens-Johnson syndrome were admitted consecutively to a single centre between August 2001 and March 2002. An aetiological study including viral serology and PCR was performed in view of the clustering of admissions related to these two conditions. The majority of cases were drug induced, the drug most commonly involved being allopurinol (toxic epidermal necrolysis, 50%; Stevens-Johnson syndrome, 13%). Two cases were related to drug abuse. Possible aetiological co-factors were cancers, radiotherapy and renal failure. No association with viral infection, including human herpesvirus-6 and parvovirus B19, was detected in the present series. Early diagnosis and prompt withdrawal of suspected drugs remain the most important measures in managing this condition. Further studies to identify the co-factors precipitating severe cutaneous drug reactions are warranted. **Key words:** *toxic aetiology; epidermal necrolysis; Stevens-Johnson syndrome; virus.*

(Accepted November 25, 2002.)

Acta Derm Venereol 2003; 83: 179–182.

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Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe cutaneous blistering reactions often related to drug therapies, with a mortality rate of between 16% and 30% for TEN and <5% for SJS (1, 2). The conditions often begin within 3 weeks of initiation of therapy or much earlier upon re-exposure (3) and is also associated with altered immune states as in human immunodeficiency virus (HIV) infection, mycoplasma pneumonia, immunization and systemic lupus erythematosus (4).

A retrospective analysis of all cases of TEN and SJS treated in our hospital was carried out between August 2001 and March 2002 (8-month period). A search for a virological role in the pathogenesis of this condition was prompted by the recent upsurge in the number of patients with TEN and SJS admitted to our unit. The

objective of this study was to determine the local aetiology, including the possible role of viral infection as a co-factor.

## PATIENTS AND METHODS

A search of all cases of TEN and SJS treated in a 1,350-bed teaching hospital between August 2001 and March 2002 was undertaken. All patients within this period were under the care of the same dermatologist in the unit. Queen Mary Hospital is the only adult hospital in the cluster with a burns unit. As many patients with TEN need burns unit care, the group of patient in the series accounted for most adult patients with the condition in this territory over this period.

The diagnosis of TEN was based on clinical features of an acute onset epidermal detachment or blistering covering greater than 30% of the total body surface area, including mucous membrane. The diagnosis of SJS was defined by features of atypical target lesions or confluent purpuric macules over the face and upper body with epidermal detachment of less than 10% of body surface area, associated with mucosal erosion. Skin biopsies were performed in all patients to confirm the diagnosis. The search for the drug responsible for TEN or SJS was performed based on commencement of each individual drug 1 to 3 weeks before the skin eruption and withdrawal of a drug less than 1 week before the onset with the exception of drugs with a very long half-life, such as phenobarbital.

A virological study was carried out for all patient diagnosed with TEN or SJS. Samples of patients' serum were tested for HHV-6 and HHV-7 viral DNA and IgG in the plasma (5), Epstein-Barr viral capsid antigen (EBV VCA) IgG and IgM and antibody to the EBV nuclear antigen (6), for cytomegalovirus (CMV) IgM (VIDAS, bioMerieux, Marcy l'Étoile, France) and parvovirus B19 IgM and IgG (Biotrin International Ltd., Dublin, Ireland).

## RESULTS

*Main characteristics of patients with TEN and SJS*

A total of 8 patients with TEN and 8 patients with SJS were admitted to our hospital between August 2001 and March 2002 (8 males and 8 females). All the patients were Chinese with the exception of one patient from Nepal. The average age was 60 years (range 23–73). Three patients with TEN and 4 patients with SJS were aged 65 years or above. The extent of skin loss in TEN ranged from 10% to almost 100% involvement of the total body surface area with a mean of 37%. Body surface area involvement was below 20% in 8 patients

(50%), between 20 and 50% in 4 patients (25%) and above 50% in 4 patients (25%). Seven of these patients were managed in the burns unit and 3 patients were referred to the intensive care unit because of respiratory failure secondary to bronchial epithelial involvement and septic shock. The mean duration of stay in the burns unit was 11 days (range 3–18 days). All potential aetiological drugs were discontinued immediately.

The length of hospitalization ranged from 7 days to 38 days with a mean of 17 days. In this series of 16 cases, the mortality was 13%. One patient died of multi-organ failure and sepsis. The deceased patient was a 24-year-old Nepalese male who had suffered from TEN with nearly 100% involvement of the body surface area. The cause was probably related to the inhalation of an organic solvent for recreational purposes. Another patient died of underlying gastric cancer 10 days after diagnosis of SJS.

#### Drugs as aetiological agents

The aetiology in our series was mostly drug-related (Table I), with 4 patients taking only one drug. One case of TEN was thought to be related to inhalation of an organic solvent. The mean duration of drug exposure prior to the onset of symptoms was 14 days, with a range of 1–40 days. The short onset of eruption in one patient with SJS was explained by a history of previous SJS when the same drug was used. Only in one case of SJS, the likely responsible drug was not identified. An underlying neoplasia was present in 3 patients (19%). The most common drug was allopurinol (31%), followed by anticonvulsants (25%), antibiotics and NSAIDs. These drugs were prescribed for gouty

Table I. Suspected aetiology of toxic epidermal necrolysis (patients 1–8) and Stevens-Johnson syndrome (patients 9–16).

Patients No./Sex	Age (years)	Implicated drugs	Onset after exposure (days)
1/F	77	Allopurinol	28
2/M	24	“Organic solvent”	NM
3/M	54	Carbamazepine	20
4/M	18	Phenobarbital	NM
5/F	60	Phenytoin	10
6/F	76	Allopurinol	40
7/M	29	Allopurinol	14
8/M	82	Allopurinol	17
9/M	79	Diclofenac	2
10/M	84	Griseofulvin	8
11/F	49	Chinese herbs	–
12/F	80	Carbamazepine	14
13/F	53	Amoxicillin	1*
14/M	87	–	–
15/F	51	Allopurinol	20
16/F	55	Allopurinol	20

NM: not mentioned.

\*Re-exposure of drug with known allergy.

arthritis (31%), convulsion prophylaxis (13%) and neuralgia (13%). The drugs potentially responsible for TEN and SJS were largely the same. Two cases were probably attributable to drug abuse for recreational purposes, including inhalation of organic solvents and use of oral phenobarbital, although both cases denied use of any regular medication at the outset. One case of SJS was thought to be caused by “traditional Chinese herbs”

#### Factors other than drugs

In our series, serum and plasma specimens were collected from 6 patients with TEN and 6 patients with SJS at the time of diagnosis or within the first 11 weeks after diagnosis. Sera were also collected from 13 age- and sex-matched patients with other dermatological diagnoses admitted during the same period as controls for serological comparison. All the patients were negative for CMV and parvovirus B19 IgM. None of the 12 patients had HHV-6 or HHV-7 DNA detected in the plasma. There was no difference in seroprevalence between patients and controls for EBV VCA IgG, parvovirus IgG, HHV-6 IgG or HHV-7 IgG.

#### DISCUSSION

TEN and SJS are now considered to be variants within a continuous spectrum of different severity (7). The incidence of TEN has ranged from 0.5 cases/million/year in the USA, 1.2 cases/million/year in France and in Germany around 0.93, and 1.1 cases/million/year for SJS and TEN, respectively (8–10). The results of our analysis showed a female to male ratio of 1:1, in contrast to a slight female preponderance in other series (3). The mean age for males was 57 years, and for females was 63 years. In our series, we found that the most important prognostic factors were the percentage of skin detachment and malignancy.

Most cases in our series were apparently drug-related. In a previous study by Roujeau et al. (11) where the responsibility of previously reported drugs was tested, allopurinol was considered to be of high risk during the first 2 months of therapy, but the risk was much lower beyond 2 months. This finding was consistent with our experience, as allopurinol was the most frequently responsible drug in our series. Five cases out of 16 cases in our series were related to the use of allopurinol for the treatment of gouty arthritis. The exposure duration ranged from 14 days to 40 days. The French series by Roujeau et al. reported a ratio of 1.3 TEN cases per 10<sup>8</sup> sales (7 cases out of 253 TEN patients) for allopurinol compared with 230 cases per 10<sup>8</sup> sales for sulphadiazine (1). The German series by Schopf et al. (9) reported 4 TEN cases per 10<sup>8</sup> sales for allopurinol (30 cases out of 259 TEN patients). Chan (12) reported 5 cases of TEN related to allopurinol out

of 20 patients in a 5-year series in Singapore. These Asian figures were comparable with those in our series but Chan did not observe any TEN cases linked to the use of anticonvulsants. The apparent increased number of cases of TEN and SJS related to allopurinol in Asians may be due to differences in genetic background, especially HLA types. Furthermore, the prescription rate for allopurinol may be higher in Hong Kong, owing to the lax practice of prescribing the drug for non-specific joint pain and inadequate general guidelines for using allopurinol.

Two patients with TEN, aged 18 and 24 years, were apparently involved in recreational drug use, but the medication history was not obvious on admission. A history of exposure to organic solvents by inhalation was obtained in one of the deceased TEN cases. We could not trace the exact nature of the solvent, as the patient was too ill to give a concise history before he died, within 4 days. A case of TEN related to the inhalation of trichloroethylene in an occupational setting has been reported (13). In the United Kingdom, 3.5 to 10% of young people have at least experimented with volatile substance abuse and mortality is more than 100 per annum (14). It is therefore important to pay attention to social history and clues concerning drug abuse especially in adolescents and young adults faced with severe drug eruptions.

One case of TEN and one case of SJS were related to the use of phenytoin as convulsion prophylaxis for brain metastasis after radiotherapy. Both cases occurred after tapering off systemic corticosteroids in the treatment of cerebral oedema. The occurrence of SJS and TEN in the setting of brain metastasis and phenytoin use is widely reported (15). The reduction of the dose of steroids may increase the risk of a hypersensitivity reaction. Caution should be exercised if patients receiving cranial radiotherapy develop scalp erythema after introduction of anticonvulsants and tapering of steroids. This may represent the very first sign of SJS and the drugs should be withheld immediately.

The observation of recent clustering of admissions related to TEN and SJS (16 cases within 8 months) led us to examine the possible role of recent viral infections in TEN and SJS patients. Given the relatively constant pattern of drug prescription and the idiosyncratic nature of drug reactions, factors other than drugs may play a role in the pathogenesis of TEN and SJS. In a previous study it was also reported that 6% of TEN patients had clinical and/or serological evidence of a recent viral infection (1). The best-known example of viral-induced drug eruption is morbilliform rash in nearly all patients with acute Epstein-Barr virus mononucleosis syndrome receiving ampicillin therapy (16). Moreover, cutaneous drug reactions are more common in patients with HIV infection and acquired immunodeficiency syndrome (AIDS) (17). The incidence of TEN

and SJS increased a thousand-fold in patients with AIDS (18, 19). Recent HHV-6 and CMV reactivation has been reported in patients with drug hypersensitivity syndrome characterized by skin rash, fever, liver dysfunction and lymphadenopathy (20–22). One patient developed TEN as part of the hypersensitivity syndrome (23). Whether this active multiplication of the virus has a pathogenic role or is simply a non-specific activation of a ubiquitous virus secondary to T-cell activation in response to reactive drug metabolites remains to be determined. All these findings suggest that underlying viral infections may trigger and activate the severe cutaneous reactions in susceptible individuals receiving drugs.

No evidence of recent HHV-6, HHV-7, CMV or parvovirus B19 infection was found in our series of patients with TEN and SJS despite the clustering of TEN and SJS. Prior studies of patients who developed adverse drug reactions, apart from drug hypersensitivity syndrome, also failed to show any increase in anti-HHV-6 antibodies (24).

In conclusion, early diagnosis, prompt withdrawal of suspected drugs and meticulous skin care in a burns unit remain the most important measures in managing this uncommon but potentially fatal disease. Further studies in identify co-factors precipitating TEN and SJS are warranted.

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