International Journal of Medical Science and Clinical Research Studies

ISSN(print): 2767-8326, ISSN(online): 2767-8342

Volume 03 Issue 01 January 2023

Page No: 31-34

DOI: https://doi.org/10.47191/ijmscrs/v3-i1-08, Impact Factor: 5.365

Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis: Epidemiology and Risk Factors

Alejandra Jeraldine González Barajas[1], Andrea Eyenith Magdaleno Torres[2]

[1,2]Universidad Autónoma de Guadalajara

ABSTRACT

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe mucocutaneous responses caused by drugs that are characterized by widespread necrosis and epidermal detachment. It is essential to know the risk factors and those agents involved in the development of this pathology in order to use them with caution in susceptible patients and to have a high index of suspicion.

ARTICLE DETAILS

Published On:
10 January 2023

Available on:
https://ijmscr.org/

INTRODUCTION

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe mucocutaneous responses caused by drugs that are characterized by widespread necrosis and epidermal detachment. More than 90% of patients have mucous membrane damage, frequently at two or more separate locations (ocular, oral, and genital).[1]

SJS and NET are considered continuous diseases and are defined largely by their severity, which is determined by the proportion of body surface area affected by blisters and erosions. [1]:

- SJS is the least severe condition, in which skin shedding is <10 percent of the body's surface.
- TEN involves the shedding of >30 percent of body surface area (BSA)
- The SJS/TEN overlap describes patients with skin shedding of 10 to 30 percent of the BSA.

The annual incidence of Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and SJS/TEN is estimated to be two to seven cases per million persons. According to data from a German national registry, the prevalence is likely one to two per million each year. SJS is more prevalent, outperforming TEN up to three to one in some circumstances. Between 2009 and 2012, the estimated occurrences of SJS, SJS/TEN, and TEN among children in the United States were 5.3, 0.8, and 0.4 cases per million children per year, respectively.[2]

The prevalence of SJS/TEN is substantially greater among HIV-infected adults and cancer patients than in the general population. [3]

SJS/TEN can affect people of any age. It affects women more than males, with a male-to-female ratio of roughly 1:2.[4]

The total mortality rate among patients with SJS/TEN is around 30%, ranging from roughly 10% for SJS to 50% for TEN. Up to a year after the disease's inception, mortality continues to rise. [5]

The total death rate in a large cohort of SJS/TEN patients was 23% at six weeks, 28% at three months, and 34% at one year, according to a survival study. When patients were classified according to severity, death rates at six weeks were 12% for SJS, 29% for SJS/NET overlap, and 46% for NET, rising to 24% for SJS, 43% for SJS/NET overlap, and 49% for SJS after one year. Mortality after three months of illness initiation was linked with advanced age (>70 years) and the prevalence of severe comorbidities, but not disease severity. [6]

ETIOLOGY

SJS/NET syndrome is primarily caused by medications. [7] SJS/NET appears to be rare during the first eight weeks of therapy. Medicines used for a longer period of time are unlikely to be the cause of SJS/TEN. The normal exposure duration from the initial continuous usage of the medicine to the beginning of the response is four days to four weeks. However, 25 to 33 percent of cases, and most likely an even larger proportion of pediatric cases, cannot be firmly assigned to a medicine. [8]

The following agents or sets of agents were most often implicated in a large global case-control research that included 379 SJS/TEN patients and 1505 controls[9]:

- allopurinol

- Aromatic anti-seizure medications and lamotrigine
- Antibacterial sulfonamides (including sulfasalazine)
- nevirapine
- Nonsteroidal anti-inflammatory drugs (NSAIDs) Oxicam

Sulfonamide antimicrobials, phenobarbital, carbamazepine, and lamotrigine are the medicines most commonly related with SJS/NET in children. A minor link with acetaminophen/paracetamol has also been documented, although this remains suspect because these medications are routinely used to treat prodromal or early signs of the disease (fever, headache, malaise, burning eyes, burning in the mouth). Furthermore, a history of previously tolerated usage of these medicines renders their link with SJS/TEN much less likely.[10]

Penicillins, notably amoxicillin and ampicillin, are less frequently linked to SJS/NET. Since these medicines are implicated, it is critical to re-examine the medical history to ensure that penicillin was not used to address symptoms that were likely indications of the SJS/NET prodrome, when the most likely causal drug was administered 4 to 4 days before the prodrome began.[10]

Several conventional and targeted anticancer medicines, including thalidomide, capecitabine, afatinib, vemurafenib, tamoxifen, and immune checkpoint inhibitors (ipilimumab, pembrolizumab, nivolumab), have been linked to SJS/TEN. However, some of these instances may show SJS/TEN-like responses that differ clinically and/or histopathologically from SJS/NETs.[11]

Infections, such as Mycoplasma pneumoniae infection, are the second most prevalent cause of SJS/TEN, especially in youngsters. According to a comprehensive examination of case series and single case reports, M. Pneumoniae patients are most typically characterized by moderate to severe involvement of two or more mucosal locations and little or no skin involvement. However, it cannot be ruled out that these instances of M. pneumoniae-associated mucositis (MIRM) with limited or no skin involvement represent a distinct entity or an unusual type of erythema multiforme major. [12]

More than a third of SJS/NET cases have no known cause. Vaccines, systemic disorders, contrast medium, external chemical exposure, herbal drugs, and diets are all debatable and seldom documented causes of SJS/NET. It has not been determined if medications or drug metabolites found in food as additives or pollutants are involved in idiopathic cases.[10]

Cases of SJS/TEN following bone marrow transplantation have been documented as a sign of acute graft-versus-host disease rather than a drug-induced response. Radiation therapy, in conjunction with anticonvulsant drugs (e.g., phenobarbital, carbamazepine) or amifostine, may cause SJS/NET, with lesions mostly found at radiation therapy sites. [13]

RISK FACTORS

HIV infection, genetic factors, underlying immunologic illnesses or malignancies, and perhaps physical conditions are all risk factors for Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/NET) (such as ultraviolet light or radiation therapy).[14]

Patients with HIV have a 100-fold increased risk of adverse medication responses and a 100-fold increased risk of SJS/TEN compared to the general population. The causes of this sensitivity are unknown, although exposure to many medicines, immunological dysregulation, the existence of concurrent infections, and polymorphisms in genes implicated in drug metabolism may all play a role. In a genome-wide association analysis of 151 HIV-infected Malawian adults with nevirapine hypersensitivity and 182 tolerants, researchers discovered that human leukocyte antigen (HLA)-C*04:01 predisposes Sub-Saharan Africans to nevirapine-induced SJS/TEN but not to other hypersensitivity events. [15]

The risk of SJS/TEN from drugs has been linked to specific kinds of human leukocyte antigens (HLA)[16]

- HLA-B*15:02: Patients with the HLA-B*15:02 phenotype are more likely to develop SJS/TEN as a result of carbamazepine and other aromatic anticonvulsants (e.g., oxcarbazepine, phenytoin, phenobarbital). This allele is seen in a large proportion of Asian and South Asian patients, ranging from 7 to 10%.
- HLA-B*15:11: In Asian populations, a relationship between HLA-B*15:11 and carbamazepine-induced SJS/TEN has been documented.
- HLA-A*31:01 - Genome-wide studies have also discovered a link between the HLAA*31:01 allele and carbamazepine-induced severe cutaneous drug responses, such as SJS/TEN, in people of Japanese, Indian, and European ancestry. However, a subsequent multinational study and meta-analysis discovered that HLA-A*31:01 is strongly associated with carbamazepine-induced drug reaction with eosinophilia and systemic symptoms (DRESS) in European and Asian patients but has a much weaker association with SJS/TEN in European and Asian patients.
- HLA-A*24:02 - In a southern Chinese Han population, HLA-A*24:02 has been discovered as an additional possible risk factor for SJS/TEN produced by carbamazepine, lamotrigine, and phenytoin.
- HLA-B*13:01 - In Thai patients, HLA-B*13:01 was found to be related with dapsone-induced severe skin responses, mostly DRESS but also SJS/TEN.
- HLA-B*58:01 - In both Asian and non-Asian populations, a systematic review and meta-analysis discovered a substantial connection between HLA-B*58:01 and allopurinol-induced SJS/TEN. A later case-control research in a Thai population found a link between HLA-B*58:01 and allopurinol-induced DRESS or SJS/TEN.

If carbamazepine or oxcarbazepine is being considered, the US Food and Drug Administration recommends screening individuals of Asian and South Asian descent for HLA-B*15:02. Because the HLA-A*31:01 allele is ubiquitous in

most ethnic groups, one consensus panel has advocated screening all carbamazepine-naive patients for it prior to commencing therapy, regardless of race or ethnicity. [17]

In no community has the clinical value of testing for the HLA-B*58:01 allele prior to allopurinol therapy been proven. However, the Clinical Pharmacogenetics Implementation Consortium (CPIC) advises against prescribing allopurinol to individuals who are known HLA-B*58:01 bearers. [18]

Polymorphisms in the CYP2C19 gene, which codes for a cytochrome P450 isoform, may increase the risk of SJS/TEN after phenobarbital, phenytoin, or carbamazepine treatment. Other CYP2C variations known to be related with impaired phenytoin clearance, such as CYP2C9*3, may be associated with an increased risk of severe cutaneous adverse responses to phenytoin, such as SJS/TEN and DRESS. Polymorphisms in the interleukin (IL) 4 receptor gene, the prostaglandin E receptor 3 gene, and a collection of genes in the 6p21 region (BAT1, HCP5, MICC, and PSORS1C1) that are in linkage disequilibrium with HLA-B*58:01 are also likely related with SJS/TEN. Larger investigations are needed, however, to determine the significance of genetic variation in the pathophysiology of SJS/TEN.[19]

Other variables that may raise the risk of SJS/TEN are as follows:

Medication at high dosages. Systemic lupus erythematosus (SLE)

Patients with SLE tend to be at a greater risk of SJS/TEN.

In certain circumstances, physical stimuli such as UV light or radiation treatment may operate as cofactors.

CONCLUSION

It is essential to know the risk factors and those agents involved in the development of this pathology in order to use them with caution in susceptible patients and to have a high index of suspicion.

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