International Journal Dental and Medical Sciences Research
Volume 5, Issue 6, Nov-Dec 2023 pp 427-434 www.ijdmsrjournal.com ISSN: 2582-6018

A Review on Steven-Johnson Syndrome

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Date of Submission: 20-12-2023 Date of Acceptance: 30-12-2023

ABSTRACT: Discussion: Stevens-Johnson syndrome (SJS) is a rare, potentially life-threatening, severe mucocutaneous and extends epidermal detachment characterized by adverse reactions; it's usually a reaction to medicine that starts with flu-like symptoms, followed by painful rash that spreads till blisters, then the top layer of affected skin sheds and begins to heal after several days. A more severe form of the condition is called toxic epidermal necrolysis (TEN). It involves more than 30% of the skin surface and extensive damage to the mucous membranes. SJS is estimated to affect two to seven per million people each year. It is much more likely to occur in people infected with the human immunodeficiency virus (HIV), with an estimated incidence of 1/1000.

Conclusion: SJS is a potentially fatal multi-organ disease with a strong etiologic link to some medications. As there is a widely used drug, physicians should be aware with this adverse reaction for early detection and intervention. Affected patient and their first-degree relatives should be instructed to avoid any identified drugs or chemicals that may be responsible.

Key Words - Stevens-Johnson Syndrome, Aceclofenac, Necrolysis, Skin, Blisters.

I. INTRODUCTION

Adverse drug reaction is defined as a noxious, unintended and undesirable effect which occurs due to drugs at doses used in humans for diagnosis, prophylaxis and treatment [1].

Stevens–Johnson syndrome (SJS) also known aserythema multiforme major is one of the most debilitating adverse drug reactions. There are four causative categories which include (a) infectious (b) drug-induced (c) malignancy-related and (d) idiopathic (4).Drugs that are implicated to cause SJS include as penicillin's and sulfa antibiotics, carbamazepine,valproic acid, lamotrigine, barbiturates, mirtazapine, infliximab, etanercept, adalimumabetc [2].

SJS is an immune-complex–mediated hypersensitivity complex that typically involves skin and mucous membrane. That includes an IgE mediated hyper sensitivity reaction characterized by erythematous maculae or fat, atypical targeted lesions with epidermal detachment of <10% body surface area, often complicated by ocular conjunctivitis or verities and symblepharon formation [3]. The SJS can also be called drug-induced Stevens-Johnson syndrome or mycoplasma-induced Stevens-Johnson syndrome if it's linked to a specific cause [4].

Each person's experience with the syndrome can be different. Skin can regrow in a matter of weeks, but recovery can take months if symptoms are severe. Some long-term reactions may develop. It may redevelop if one is exposed to the same medication known to have triggered the condition the first time. In such cases, second episode is usually more severe than the first episode [5].

Stevens-Johnson syndrome is, in most cases, triggered by medications, there's no way to know – before taking medications – that one might experience an adverse reaction to the drug. If a medication is identified that has triggered this condition, that drug can be avoided [5].

History

Two young boys had been admitted to Bellevue Hospital Center in New York City with skin eruptions of oval, dark red to purplish spots separated by normal tissue the appearance of each spot looked like a "bulls-eye." There was fever, conjunctivitis, inflamed mucus membranes, and one of the young boys had a total loss of vision. They had never seen this condition before and they had multiple consultants evaluate these patients. Their report was the first description of which later became Stevens-Johnson syndrome. The Lancet noted this article and described it as a new eruptive fever. When it became "Stevens-Johnson syndrome" is unclear [6, 7].

Epidemiology

More cases of SJS occur in female than male. Infections like pneumonia are the most likely cause of SJS in children, where as medications are the most likely cause of SJS in adults. Most patients with Stevens-Johnson syndrome are treated symptomatically [8]. In principle, the symptomatic treatment of patients with this disorder does not differ from the therapy applied to patients with extensive thermal or chemical burns [9].

International Journal Dental and Medical Sciences Research
Volume 5, Issue 6, Nov-Dec 2023 pp 427-434 www.ijdmsrjournal.com ISSN: 2582-6018

The disorder affects between 1 and 5 people/million. Incidence, severity, or both of these may be higher in bone marrow transplant recipients, in Pneumocystis,HIV patients, in patients with systemic lupus erythematous, and in patients with other chronic rheumatologic diseases [10].

Incidence range from 1.2 to 6 cases per million per year, the condition is fatal in 5% of treated cases and in 15% of untreated cases [11].

Due to the high risk of mortality, management of patients with SJS requires rapid diagnosis.Evaluation of the prognosis using SCORTEN Severity-of-Illness Score (SCORTEN is an illness severity score that has been developed to predict mortality in SJS cases). One point is scored for each of the seven criteria present at the time of admission. The SCORTEN criteria are: Age > 40 years, rapid identification and interruption of the culprit drug, specialized supportive care ideally in an intensive care unit, and the consideration of immune modulator agents such as high-dose intravenous immunoglobulin [12].

A clinical association that has beenpreviously reported in very few cases in Indian population, Steven Johnson syndrome (SJS) is a life-threatening, bullouscutaneous disease considered as epidermal necrosis, erosion of mucous membrane and severe consideration symptoms [13].

Etiology

SJS can present as a nonspecific febrile illness (malaise, headache, cough, rhino rhea) with polymorphic lesions of skin and mucous membrane characterized by acute blisters and erosions. It is associated with a mortality rate of 1-5% which increases to 25-35% in case of TEN [14]. Among hospitalized patients approximately about 0.3 to 7% of deaths were reported to be caused by adverse drug reactions (ADRs). The spectrum of drug reactions can differ from mild to severe such as SJS which is an uncommon, but with a serious skin-mediated hypersensitivity reaction [15].

Antimicrobials have been commonly reported group of drugs followed by anticonvulsants, antipyretics, and NSAIDs to cause SJS. Sixteen patients (35.5%) had experienced SJS/TEN due to antimicrobials. The majority of cases (44%) were due to antimicrobials which was in concordance with the studies from (42%) West Germany & (44%) South India [16].

Mortality from SJS depends on the time of reaction onset, the extent of epidermal detachment, the patient's age, and underlying conditions. From the least to the most severe degree of skin involvement, mortality is almost 10% for patients with SJS, approximately 30% for patients with SJS/TEN overlap, and almost 50% for patients with TEN(Toxic Epidermal Necrosis). It should be noted that SJS and TEN are considered two clinical spectrum of the same disease [17].

Clinical Manifestation

The first symptoms of SJS often include fever and flu-like (such as general ill feeling, body ache, and cough). Within about 1 to 3 days, a red or purple rash forms, and then the skin begins to blister and peel, leading to "raw" areas of skin that are painful. This often starts on the face and then spreads to other parts of the body. The mucous membranes may also become involved during this time, which can lead to symptoms such as severe conjunctivitis (when the eyes are affected), trouble swallowing and breathing (when the mouth and airway are affected), and difficulty urinating and genital pain (when the genitals are affected) [18].

Involvement of mucous membrane is evident in approximately 90% of affected patients, and the absence of mucous membrane involvement should cast doubt on the diagnosis of SJS. Mucous membrane involvement can result in short- term dysfunction and morbidity, as well as long- term complications due to fibrosis and strictures [19] .The characteristic skin lesions seen in SJS are diffuse erythematous maculae with purpuric, necrotic centers and overlying blistering. These Cutaneous lesions often become confluent in some areas, and often demonstrate a positive Nikolsky sign, which is further detachment of the epidermis with slight lateral pressure. Targeted lesions are typically present and are caused by epidermal necrosis in the center of lesions [20].

Pathophyiology

SJS is not an inherited condition. However, the genetic changes that increase the risk of developing SJS can be passed from one generation to the next. The exact mechanism of Stevens-Johnson syndrome and toxic epidermal necrolysis is unknown; however, one theory holds that altered drug metabolism (e.g., failure to clear reactive metabolites) in some patients triggers a T-cell–mediated cytotoxic reaction to drug antigens in keratinocytes. CD8+ T cells have been identified as important mediators of blister formation [21].

Findings suggest that granulysin released from cytotoxic T cells and natural killer cells might play a role in keratinocytes death; granulysin concentration in blister fluid correlates with severity of disease. Interleukin-15 has also been found to be increased in patients with SJS/TEN and

has been found to increase granulysin production. Another theory is that interactions between Fas (a cell-surface receptor that induces apoptosis) and its ligand, particularly a soluble form of Fas ligand released from mononuclear cells, lead to cell death and blister formation. A genetic predisposition for SJS has been suggested [22].

Activation of the Fassignaling cascade leads to widespread keratinocyteapoptosis and subsequent epithelial necrosis. Early treatment of SJS via intravenous immunoglobulin (IVIG) blocks the activation of the Fas pathway, thus under scoring the potential effectiveness of IVIG entreating the disorder [23, 25].

Recent studies have also linked performing, a pore-making monomaniac granule released from natural killer T-lymphocyte since the development of SJS. Performing is believed to initiate the keratinolysis seen early in the development of SJS [(26).] Some evidence also exists linking IgE-mediated mechanisms and mast cell activation contributing to SJS [(27).]

Genetic polymorphism in the N-acetylation phenotype has important clinical relevance in terms of detoxifying carcinogenic substances and in drug metabolism. In particular, the increased frequency of bladder cancer induced by chronic arterial amine exposure (which requires N-acetylation for detoxification) is associated with a slow N-acetate phenotype. N-acetylation polymorphism also has clinical implications of drug metabolism, drug dose and drug side-effects, e.g., fast N-acetylators require higher doses of INH to maintain adequate drug serum levels than slow N-acetylators. Thus, slow N-acetylator phenotypes may be predisposed to adverse reactions of drugs requiring N acetylators [28.]

Pharmacogenomic mediated by immune over the past decade, there have been many connections established between SJS-TEN and the HLA allele of Class I and II majorhisto compatibility complex (MHC). Several studies have been conducted to explain how small synthetic molecular compounds (drugs) arerecognized by T cells dependent on MHC,including the concept of hapten / prohaptenmodel, pharmacological interaction (pi)model, which is pharmacological interaction of drugs with immune receptor and the changed repertoire model. However, the findings cannot be confirmed in Europe.Thus, the risk of EN is associated with high-risk drug exposure and genetic predisposition. For safety purposes, pre-clinical drugs must be screened to evaluate the interactions between drugs and HLA [29, 30].

Histopathology typically shows wide spread keratinocyte apoptosis and full-thickness epidermal necrosis and detachment with a sparse dermal monotypic (predominantly T cell) infiltrate. Without immediate medical intervention, uncontrolled separation of the epidermis can lead to large denuded areas that cause extreme pain, massive loss of fluid and protein, bleeding, evaporative heat loss with subsequent hypothermia, and infection [31.]

As the drugs are too small to trigger an immunogenic response, three mechanistic models have been proposed to explain how small molecular synthetic compounds are recognized by T cells in an MHC dependent fashion. These include the hapten/prohapten model, the pei model, and the altered repertoire model [57.]

The hapten/prohapten concept: This conceptproposes that the drug or its metabolite reacts with aself-protein through covalent binding to produce a Renovo product, which then under goes processing by the antigen resulting in generation of a novel MHC ligand that is consequently loaded onto the MHC and trafficked to the cell surface. Here it activates the antigen-specific T lymphocytes [32, 33.]

Pharmacological interaction with immune receptors model: This model proposes that anon-covalent, labile interaction of the drug with the MHC receptor at the cell surface is involved in MHC-dependent T cell stimulation by various neither drugs [34] .Neither cellular metabolism nor antigen processing isrequired in such an interaction.

Altered repertoire model: This concept proposesthat drugs or drug metabolites can bind to specific MHC molecules, within the pocket of their peptidebinding grooves, with exquisite specificity, thus allowing a new repertoire of endogenous self-peptidesto be bound and presented [35.]

Current studies dealing with Pharmacogenomic have advanced our known edge on the genetic pre-dispositions to adverse drug reactions. With the identification of specific HLA alleles as the predisposing factor to the disease, it therefore becomes clear that the pathogenesis of drug-mediated SJS involves MHC-restricted activation of cytotoxic T Lymphocytes (CTL) response. This response mediated through cytotoxic T lymphocytes requires several downstream signaling or release of mediators, to eventually trigger extensive keratinocyte death [36.]

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Volume 5, Issue 6, Nov-Dec 2023 pp 427-434 www.ijdmsrjournal.com ISSN: 2582-6018

Treatment

Patients should be treated with special attention to airway and hemodynamic stability, fluid status, wound/burn care, and pain control. Therapy for Stevens-Johnson syndrome proceeds as follows:

- Withdrawal of any agent suspected of causing the condition is critically important
- Oral lesions are managed with mouthwashes; topical anesthetics are useful in reducing pain and allowing the patient to take in fluids
- Areas of denuded skin must be covered with compresses of saline or Burow solution (an aqueous solution of aluminum triacetate)
- Tetanus prophylaxis must be addressed

Extensive debridement of nonviable epidermis followed by immediate cover with biologic dressings is among the recommended treatments [37].

Intravenous immunoglobulin (IVIG) can inhibit the Fas-L bond with Fas [42.] A highdose is recommended, 0.75 g/kg/day for four consecutive days. [43, 44] A high IVIG dose administration will increase life expectancy [45] However, IVIG also cannot be standard of therapy because pathways other than Fas-Fas L pathway are involved in the occurrence of EN. [46] Stella et al reported their experience withtreating TEN both with and without IVIG. Intheir report, they treated eight TEN patientswith extensive epidermal debridement and coverage with artificial skin substitutes inthe pre-IVIG series (patients not treatedwith IVIG) and treated 23 patients with IVIG (0.7g/kg/day for 4 consecutive days) and conservative wound management in the IVIG series. The IVIG-treated group also received methylprednisolone at doses of 250mg every six hours for the first 48 hours of admission. Cessation of further epidermal detachment from the onset of IVIG therapy averaged five days and complete wound healing occurred after an average of 12.3 days. The average SCORTEN score was 3 in both groups with approximately 35 percent of patients expected to die. The observed mortality was 75 percent and 26 percent in the pre-IVIG and IVIG-treated groups, respectively.In four cases, the cause of death was septicshock and multiple organ failure. 36causes of death were respiratory failure and disseminated intravascular coagulopathy [44.]

TNF-α is not only involved in up regulation of Fas L in keratinocytes but also acts as a death receptor ligand by itself. Besides, TNFα was shown to enhance HLA class I expression on keratinocytes, rendering them more susceptible to T cell-mediated cytotoxicity [47.] The increased TNF-α level in SJS/TEN patients has led to the suggestions of using TNF-α inhibitors [48.] However, a well-known randomized controlled trial which used thalidomide for SJS/TEN treatment was terminated early due to excessive deaths in the treatment arm. Thalidomide is a potent inhibitor of TNF-α in vitro and in vivo, but paradoxical enhancement of TNF-α production was observed in the group treated with thalidomide [49.]

II. DISCUSSION

SJS-TEN is a severe life threatening mucocutaneous syndrome caused by hypersensitivity to drugs and is associated with significant morbidity and mortality [50.] It is important to suspect the culprit drug by the temporal relationship (2 days to 8 weeks) [51] but the extremely ‘rapid onset in this case. The exact anetiopathogenesis being imprecise is thought that some noxious metabolites, inflammatory mediators/modifiers, as well as cytotoxic T-lymphocytes, regulatory T cells and dermaldendrocytes could provoke apoptosis/necrosis of epithelial cells 8-10.

The human leukocyte antigen (HLA) system also plays an important role in the pathogenesis of TEN, since some drugs may bind directly to the HLA-complex and create self-reactivity due to the drug-modified HLA-peptide repertoire [52.] We must take in consideration that regional difference in drug prescription, the genetic background of patients (HLA, metabolizing enzymes) [53, 54,] can have an impact on the incidence so a detailed drug history is extremely significant when go-getting to recognize the offender drug in SJS-TEN.

Initial symptoms of SJS-TEN can be unspecific like fever, stinging eyes and discomfort upon swallowing which precede cutaneous manifestations by a few days [55.] Early sites of cutaneous involvement are the presternal region of the trunk, face, palms, and soles. Erythematic and erosions of the ducal, genital and/or ocular mucosa occurs in more than 90% of patients, with respiratory and gastrointestinal-tracts affected in few [56.]

SJS is thought to arise from a disorder of the immune system. The immune reaction can be triggered by drugs or infection. To date, more than 100 drugs have been associated with SJS 1 among which aromatic anticonvulsants, sulfonamide antibiotics; allopurinol, oxicamnon steroidal anti-inflammatory drugs, and nevirap, genetic factors are associated with a predisposition to SJS. Although SJS can be caused by viral infection and malignancies, the main cause in medication. The major causative drugs have been antimicrobials

{37.27%}, Antiepileptic {37.73%}, and NSAIDs {15.93%} [38, 39].

III. CONCLUSION

This review summarizes recent advances in the Pathophyiology, diagnosis, and treatment of SJS/TEN. SJS/TEN is a severe adverse drug reaction associated with a high mortality rate and its treatment algorithm has not been well established.

Accumulation of more data of these treatments is desirable. Finally, the pathogenesis of SJS/TEN has been elucidated in recent years and the breakthrough of these studies may help identify promising targets for the discovery of novel therapeutic agents.

Cutaneous adverse drug reactions can vary from mild reactions to severe, life-threatening, or even fatal reactions. Drug histories and family histories of drug reactions need to be enquired about in all patients before prescribing any medication. Thus, whenever a new drug is given to a patient, the physician needs to be cautious and monitor the patient vigilantly. And also, patients should be advised to avoid over-the-counter usage of medications and self-administration of drugs. If adverse drug reactions occur, it is advised to avoid re-administration of the culprit drugs. It is essential to prepare drug cards for the patient, mentioning both the culprit drug and cross-reacting drugs. Early identification of different morphological characteristics is crucial for identifying the culprit drug and stopping it right away to prevent iatrogenic morbidity and mortality.

There are gaps that need to be urgently addressed in SJS/TEN research. There is an urgent need for reproducible methods of measuring disease severity that are sensitive to changes induced by therapeutic interventions and that more accurately predict outcomes beyond the acute stage by including the systemic and internal organ effects of SJS/TEN. Potential solutions include consensus on definitions, advances in diagnostic imaging and biomarker assessment, and development of AI platforms for the detection and monitoring of disease.

Life-threatening SJS and TEN present a challenge in early detection and subsequent management. Evidence-based practice related to the care of patients with SJS is still evolving. Management includes early identification, withdrawal of the suspected drug, and early transfer to a specialized center. Further research and clinical evidence are needed to develop appropriate and cost-effective treatment guidelines for optimal care of these patients.

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