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Steven-Johnson Syndrome/Toxic Epidermal Necrolysis in Pediatric Patients: A Literature Review

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ABSTRACT

Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) is a clinical condition characterized by cutaneous and mucosal involvement. It is an emergency condition with an annual incidence ranging from 0.8 to 5.4 cases per one million children. Although cases of SJS/TEN are very rare, this condition has significant morbidity and mortality. SJS/TEN represents a significant health concern, particularly in pediatric populations. The rarity of the disease, the unclear etiology, the difficulty in making a diagnosis, and the numerous complications that arise in patients can have an unfavorable impact on the patient's prognosis. With a comprehensive discussion of SJS/TEN, it is expected that the future diagnosis and management of SJS/TEN can be more optimal and effective.

Keywords: Steven-Johnson syndrome; toxic epidermal necrolysis; pediatric.

INTRODUCTION

Steven-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) has been identified as an immunologically induced disease with a high incidence of morbidity and mortality [1,2]. SJS/TEN is an emergency condition characterized by manifestations on the skin, mucosa, and sometimes various organs [3,4]. The severity of SJS/TEN is categorized based on the affected body surface area (BSA), with SJS <10% BSA, SJS-TEN overlap 10-30% BSA, and TEN >30% BSA [5]. The etiology of SJS/TEN varies widely. In pediatric patients, drugs and infections are the culprits in the majority of cases. It is also possible for a single patient with SJS/TEN to have more than one suspected etiology simultaneously, which presents a challenge for healthcare professionals in determining the actual etiology [6].

The annual incidence of pediatric SJS/TEN ranges from 0.8 to 5.4 cases per million children [1]. Although cases of pediatric SJS/TEN are very rare, the morbidity and mortality associated with this condition are significant [7]. Flu-like syndrome and skin symptoms that resemble those seen in other illnesses are usually the first clinical signs of SJS/TEN. This renders it challenging for healthcare professionals to identify and diagnose SJS/TEN during the acute phase. A variety of systemic complications accompany the acute phase and may eventually lead to multi-organ failure. In addition to the high mortality rate observed during the acute period, patients who have recovered from SJS/TEN often experience significant long-term sequelae [8]. It is indubitable that this will have a considerable effect on pediatric patients who are still undergoing active growth and development.

SJS/TEN represents a significant health concern, particularly in pediatric populations. The rarity of the disease, the unclear etiology, the difficulty in making a diagnosis, and the numerous complications that arise in patients can have a negative impact on the patient's prognosis. In light of the aforementioned factors, the authors are interested in conducting a comprehensive discussion of Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis, with a primary focus on pediatric patients.

DEFINITION AND CLASSIFICATION

Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) refers to a severe mucocutaneous condition marked by epithelial blistering and sloughing [8].

The term 'Stevens-Johnson syndrome' first appeared in a medical report in 1922, following the identification of two cases of acute mucocutaneous syndrome in male pediatric patients. The condition manifested as macular purpura, severe stomatitis with disseminated mucosal necrosis, and acute purulent conjunctivitis. Following the discovery of the cases, in 1956, Alan Lyell documented four patients with eruptions that resembled skin burns. These cases eventually created a new medical term known as 'toxic epidermal necrolysis' [9]. At present, the two disease terms are regarded as a single spectrum of diseases, distinguished only by varying degrees of severity [10].

The first consensus on the classification of SJS/TEN was established in 1992. The consensus proposed a classification system for severe bullous skin reactions, comprising five categories. The first classification is bullous erythema multiforme, which involves less than 10% of the body surface area and presents with a typical target lesion or a localized protruding atypical target lesion. The second classification is Steven-Johnson syndrome, which affects less than 10% of the body surface area and may present with macules or widespread flat atypical targets. The subsequent classification is SJS-TEN overlap, which presents the same clinical hallmarks as SJS but affects the body surface area ranging from 10% to 30%. The last classification is TEN. This classification exhibits a similar clinical presentation to the one observed in SJS, but with a body surface area involved greater than 30% of the total surface area. Additionally, this classification can be further subdivided into two categories: those with and without spots [11].

ETIOLOGY

SJS/TEN is an immunologic reaction that manifests in a variety of ways in different individuals. This is why the etiology of SJS/TEN is highly variable from case to case. This discussion will divide the etiology of SJS/TEN into two categories: drug-related and non-drug-related. The potential influence of genetic factors on the onset of SJS/TEN will also be addressed.

- **Drug**

A substantial proportion of SJS/TEN cases, up to 90.3%, have been identified as being caused by drug reactions. Previous studies have indicated that 93.7% of SJS cases, 97.4% of SJS-TEN overlap cases, and 83.7% of TEN cases were caused by adverse drug reactions. A total of 379 distinct medications have been documented as a cause of SJS/TEN [12]. In pediatric patients, the drug classes that have been identified as potential causes of SJS/TEN are antibiotics, antiepileptics, nonsteroidal anti-inflammatory drugs (NSAIDs), salicylates, benzodiazepines, acetaminophen, corticosteroids, antihistamines, mucolytics, vitamins, and vaccines. Of the aforementioned drug classes, it was determined that acetaminophen, valproic acid, and NSAIDs may potentially elevate the probability of adverse outcome in pediatric [13].

- **Non-Drug**

A previous study indicated that up to 12% of SJS/TEN cases have a non-drug-related etiology. The most common non-drug causes are infections, radiotherapy and chemical compounds. A study also found that infection is a more common trigger in children (31%) than in adults (10%-15%). Mycoplasma pneumonia infection has been reported in 22% of children and herpes simplex virus infection has been found in 9% of children [12,14].

- **Genetic Factors**

A number of Human Leukocyte Antigen (HLA) and Human Cytochrome P450 (CYP) alleles appear to be potential risk factors for the development of this disease in specific population groups. Genetic predisposition increases the likelihood of individuals experiencing adverse reactions when exposed to certain drugs. Furthermore, family members of patients diagnosed with this condition are also at risk of developing the same disease and should avoid all drugs that have been identified as potential culprits [15,16].

EPIDEMIOLOGY

SJS/TEN can affect individuals of any age, including infants and children. The disease is observed with a greater frequency in the female population than in the male population, with a ratio of approximately two to one [8]. A study conducted in the United States mentioned that the incidence per 100,000 children was 6.3 for SJS, 0.7 for SJS-TEN overlap, and 0.5 for TEN. The incidence increased with age, reaching a highest value of 38.4 cases per 100,000 children in the 11-15 years age group. Furthermore, the severity of SJS/TEN was found to be directly proportional to the mortality rate. The mortality rate was reported to be 0.35% for SJS, 3.33% for SJS-TEN overlap, and 4.17% for TEN. In addition to the significant mortality rate, patients with TEN also exhibited prolonged hospitalization and higher healthcare costs compared to those with other severity [17]. The specific epidemiology of drug-induced SJS/TEN remains poorly understood due to the limited scope of existing pediatric SJS/TEN studies. These studies have primarily comprised case series with small sample sizes and retrospective analyses [2]. More studies are needed to ascertain the prevalence of this disease in diverse populations. Furthermore, additional studies involving population genetics are required to identify potential triggers of SJS/TEN in specific populations.

PATHOPHYSIOLOGY

The molecular and cellular level mechanisms that contribute to SJS/TEN are still incompletely understood. It is currently believed that the pathophysiology of this condition involves both innate and adaptive immune-mediated reactions. The histopathology results revealed evidence of epidermal destruction, manifested as cell apoptosis and extensive epidermal necrosis. Additionally, mucosal biopsies also demonstrate keratinocyte necrosis. Histiocyte and lymphocyte infiltration is mostly seen in the dermis layer and forms a mild perivascular pattern.

The presence of eosinophils in the skin layer is only found in a few cases and usually occurs in small numbers. The detachment of the dermal-epidermal junction leads to the degeneration of basal cell vacuoles and the formation of vesicles or bullae at the subepidermal level, which are hallmarks of SJS/TEN patients [8,18].

Keratinocyte death is caused by natural killer (NK) cells and CD8+ cytotoxic T cells through interaction with the patient's HLA and drug antigens [18]. Additionally, pro-apoptotic substances such nitric oxide synthase, TNF-α, and interferon-γ may act as a mediator between keratinocyte damage and drug-induced immune responses [19].

During the immune cell activation period, a number of cytotoxic signals, including granzyme B, perforin, and Fas/Fas Ligand, contribute to the destruction of skin and lead to the worsening of the disease. In addition, a variety of cytokines are in charge of T cell and other immune cell activation, proliferation, and inflammation. The levels of IL-6, IL-8, IL-15, granulysin, and TNF-α were elevated in few sites such as fluid in blisters, skin lesions, peripheral blood cells, and patient plasma [20]. A recent study revealed that granulysin and IL-5 are important molecules in the pathologic progression of disease. The production of substantial quantities of granulysin by fully activated natural killer (NK) cells and cytotoxic T lymphocytes (CTLs) results in uncontrolled cell death and damage to tissues, which manifests as a distinctive clinical presentation [20, 21].

CLINICAL MANIFESTATIONS

In cases of pediatric SJS/TEN, common clinical manifestations involve the skin and mucosa [22]. The initial manifestation of SJS/TEN is typically a flu-like syndrome, which emerges between four and 28 days following the administration of medication [23]. The most frequently observed symptoms in patients upon admission for treatment are as follows: skin blistering, rash, conjunctivitis, conjunctival hyperemia, acantholysis, fever, diarrhea, erythema, fatigue, nausea and vomiting, anorexia, dysphagia, pharyngitis, anemia, myalgia, and anxiety. Furthermore, patients may present with a variety of symptoms affecting multiple organs, including the eye, head and neck, respiratory organs, digestive organs, genitourinary organs, skin, hair, nails, nervous system, and others [24].

Blackish-red macules and flat atypical target lesions with blisters on the surface are characteristics of the primary lesion and typical features of SJS/TEN. The distribution of lesions is either isolated or clustered [8]. During the course of days 5 to 7, the quantity and size of the lesions will increase. The type of the skin lesions may vary, presenting as vesicles, bullae, or even skin necrosis, which may subsequently peel off the affected area. A positive Nikolsky sign indicates characteristics suggestive of SJS/TEN. Nikolsky sign is a displacement of the epidermis caused by tangential pressure on the skin. Applying pressure will cause the epidermis to shift above the dermis. Although not specific for SJS/TEN, this sign is a useful clinical indicator and may help in making a diagnosis [9].

The most common involvement of mucosal membranes is seen in the eyes, mouth, and urogenital region. The occurrence of eye involvement is more prevalent in patients who have undergone the loss of greater than 10% of their BSA [8,25]. The damage to the eye can range from a mild condition such as conjunctival hyperemia to a severe one, namely total ocular sloughing, which includes the tarsal conjunctiva and eyelid margins. In more severe cases, the eye may suffer from purulent conjunctivitis, uveitis, and corneal ulceration, which can eventually lead to blindness [16].

The clinical presentation of oral mucosal involvement in SJS/TEN is characterized by the presence of painful mucosal erythema, blistering, and ulceration. The lip margin will develop an adherent hemorrhagic crust with retention. In some instances, the disease may extend to the upper gastrointestinal and respiratory tracts, resulting in dysphagia [8].

It is also possible for pediatric patients to experience urogenital involvement. In a previous study comprising 31 pediatric patients, 74% exhibited genital involvement. The symptoms experienced by pediatric patients included dysuria, hematuria, urinary retention, scrotal/labial lesions, penile/vulvar lesions, meatus lesions, and acute kidney injury [27].

DIAGNOSIS

The diagnosis of SJS/TEN in more than 90% of cases is determined solely from clinical features. In the suspected case of SJS/TEN, the initial steps should be to conduct a comprehensive history taking and physical examination. In order to obtain an accurate historical record, it is essential that the healthcare professional obtain detailed information regarding the number and type of drugs consumed, dosage of drugs, mode of administration, and duration of drug administration. Subsequently, a series of examinations must be conducted to reinforce the diagnosis, rule out differential diagnoses, and identify any systemic complications [28].

For routine histopathologic analysis, a biopsy of the skin lesion closest to the blister may be performed. For direct immunofluorescence, a second biopsy can be obtained from the skin along the lesion's edge and should be sent in unfixed. A blood smear must be obtained from the affected skin and used for bacteriological examination. In order to determine whether pneumonia is causing SJS/TEN due to infection, a chest x-ray is necessary. Erythema and detached epidermis should be noted separately on the body map. The percentage of the patient's BSA involved should be estimated as a percentage. The following laboratory tests are advised: complete blood count, erythrocyte sedimentation rate, c-reactive protein, coagulation, mycoplasma serology, antinuclear antibodies, extractable nuclear antigen,

complement, immunofluorescence, urea, electrolytes, amylase, bicarbonate, glucose, and liver function tests [8].

In considering a patient's diagnosis, healthcare professionals also need to keep in mind the differential diagnoses that need to be considered as SJS/TEN has similar clinical features to several other diseases. The differential diagnoses are pemphigus vulgaris, bullous pemphigoid, mucous membrane pemphigoid, paraneoplastic pemphigus, generalized fixed drug eruption, erythema multiforme major, bullous lupus erythematosus, staphylococcal scalded skin syndrome, acute bullous graft-versus-host disease, linear IgA bullous dermatosis, phototoxic eruption, acute or subacute cutaneous lupus phototoxic eruption with epidermal necrosis (Rowell syndrome), and acute generalized exanthematous pustulosis [8,29].

TREATMENT AND MANAGEMENT

The treatment and management of pediatric patients is largely similar to that of adult patients. The most crucial elements of SJS/TEN management are prompt diagnosis, cessation of the suspected drugs, adequate supportive care, and a multidisciplinary approach. However, standardization of SJS/TEN management in pediatric patients is lacking [8,18].

- **Initial Management**

The first thing to do for the patients is the prompt recognition and discontinuation of all drugs and related substances. Discontinuation of drugs and substances that are suspected or proven to be causative agents of adverse reactions is an important intervention that should be carried out immediately. Such action may prove effective in reducing the risk of mortality [8,30]. The ALDEN (Algorithm of Drug Causality for Epidermal Necrolysis) has been developed with the objective of assisting in the identification of the causative drug in patients [31].

- **Supportive Therapy**

All patients presenting with suspected SJS/TEN should receive supportive therapy as the primary intervention. Some supportive cares that can be given are maintaining ambient temperature; monitoring vital signs; preventing sepsis; maintaining fluid and electrolyte balance; giving parenteral nutrition or through a nasogastric tube; giving topical antiseptics and bandaging the affected skin area; local therapy for the eyes, mouth, respiratory system, and urogenital system; giving antacids, analgesics, antipyretics, and anticoagulants if there are indications for administration; and providing psychological support to patients and their families [8,30].

- **Specific Therapy**

Once the patient's condition has been stabilized, disease-modifying therapy should be administered as soon as feasible with the objective of stopping the immunologic process that results in keratinocyte death. Numerous immunomodulating medications have been used as disease-modifying therapies, including systemic corticosteroids, cyclosporine, intravenous immunoglobulin (IVIg), and other modalities such as plasmapheresis, TNF-α inhibitors, N-acetylcysteine, and granulocyte colony-stimulating factor. The dosage of disease-modifying therapy is tailored to the specific needs of the individual patient. In the case of a patient presenting at a stage when disease activity has ceased, no further disease-modifying treatment is required. It is recommended for such patients to be managed with supportive care only [8,30].

If symptoms appear at a primary or secondary health facility, the first course of treatment should be started. Afterward, the patient can be referred to a tertiary health facility for specialist care [30]. The treatment may be provided in an isolation room with sterile field maintenance or in an intensive care unit, depending on the resources available. For critical care management and specialized care, patients who have more than 10% of their body surface area affected should be admitted to the pediatric intensive care unit (PICU). Given its similarity to a large superficial burn, patients who have more than 30% of their body surface area affected may be transferred to a burn unit, where intensive supportive management and direct therapy to the skin can be provided [8,30].

- **Monitoring and Complication Management**

Treatment of pediatric SJS/TEN patients and their complications with the assistance of specialists should be prioritized. Prior research has indicated that pediatric patients diagnosed with SJS/TEN require additional follow-up consultations with ophthalmologists, dermatologists, internists, ear, nose, and throat (ENT) specialists, neurologists, plastic surgeons, anesthesiologists, and rehabilitation specialists, as well as medical rehabilitation specialists [22]. And the most important thing to prevent future occurrences of SJS/TEN is to avoid culprit drugs or substances completely after the patient has recovered [30].

PROGNOSIS

Once the disease has stopped expanding, re-epithelialization should begin immediately. Re-epithelialization takes 2-3 weeks to restore the damaged mucocutaneous area. Delayed healing of SJS/TEN can lead to sepsis and systemic complications, worsening the patient's prognosis [8].

SJS/TEN has significant morbidity and mortality rates. The mortality rate of SJS/TEN among pediatric patients can reach 16% [1]. Therefore, the SCORTEN (Score of Toxic Epidermal Necrolysis) was introduced to predict the prognosis and mortality risk of SJS/TEN patients. Each prognostic indicator is considered one point in the SCORTEN calculation, and a higher SCORTEN score is associated with a higher mortality risk. Recently, modifications have been made to the SCORTEN formula to better suit the needs of pediatric patients. The pediatric version of SCORTEN assesses patients with abnormal laboratory values who have not received a stem cell transplant (SCORTEN A) and those who have received a stem cell transplant (SCORTEN B) [29,32].

COMPLICATION

- **Acute Complication**

In cases of SJS/TEN with extensive epidermal involvement, there is a significant risk of severe impairment of thermoregulatory control, which can lead to hypothermia. Additionally, the occurrence of skin damage results in a considerable loss of transcutaneous fluid, which is further exacerbated by a reduction in fluid intake because of the oral manifestation. A detachment of the epidermis exceeding 50% BSA will result in the loss of approximately two to three liters of water per day from the body, due to exudation and evaporation. Fluid depletion can result in end-organ hypoperfusion. This may subsequently result in the progression to acute renal failure [8].

Hematological complications are a common occurrence during the acute phase, with anemia and leukopenia being the most frequently observed conditions. Liver function abnormalities are a common finding in the early stages of the disease, though they rarely result in liver failure. Hypoalbuminemia is typically observed in cases of TEN. It is possible that hyperglycemia may manifest as a stress response in patients with acute SJS/TEN. The large shedding of the epidermis will consequently result in an increase in metabolic demands [8]. Bronchial erosion and airway obstruction due to detached epithelium can result after epithelial necrolysis in the bronchi. This affects 25% of patients and results in hypoxemia, hemoptysis, dyspnea, and increased bronchial secretions [33].

The most lethal acute complication is sepsis. In SJS/TEN, the sloughed dermis becomes a site of microbial colonization. The initial cause is usually Staphylococcus aureus, with gram-negative rods from the gastrointestinal flora, such as Pseudomonas aeruginosa, becoming the predominant cause at a later stage. Sepsis can rapidly develop subsequent to a skin infection, resulting in multi-organ failure [34].

- **Chronic Complication**

Patients who have recovered from the acute symptoms of SJS/TEN may experience long-term sequelae. Studies on the chronic complications of SJS/TEN have mostly centered on mucocutaneous and ocular complications. However, other organs may also be affected. Based on previous studies, the skin, eyes, mouth, gastrointestinal tract, genitourinary tract, lungs, and immune system may all be affected. Patients with SJS/TEN also frequently experience psychological consequences, including anxiety and depression [8,35,36].

CONCLUSIONS

Steven-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) has been identified as an immunologically induced disease with a high incidence of morbidity and mortality. SJS/TEN is an emergency condition characterized by manifestations on the skin, mucosa, and sometimes various organs. The severity of SJS/TEN is categorized based on the affected body surface area (BSA), with SJS <10% BSA, SJS-TEN overlap 10-30% BSA, and TEN >30% BSA. The etiology of SJS/TEN is highly variable between individuals. It can be classified into two categories: drug-related and non-drug-related. Additionally, A number of HLA and Human CYPs alleles appear to be potential risk factors for the development of this disease in specific population groups. The pathophysiology of SJS/TEN posits that it involves both innate and adaptive immune-mediated reaction. A recent study revealed that granulysin and IL-5 are important molecules in the pathologic progression of disease. The most commonly observed clinical manifestations of SJS/TEN involve the skin and mucosal membranes. The most common involvement of mucosal membranes is seen in the eyes, mouth, and urogenital region. The diagnosis of SJS/TEN in more than 90% of cases is determined solely from clinical features. The most crucial elements of SJS/TEN management are prompt diagnosis, cessation of the suspected drugs, adequate supportive care, and a multidisciplinary approach. SJS/TEN has significant morbidity and mortality rates. Delayed healing of SJS/TEN can lead to sepsis and systemic complications, worsening the prognosis of SJS/TEN. SJS/TEN can cause complications in various organs, both acute and chronic complications.

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