

Study of Stevens - Johnson syndrome

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ABSTRACT

Stevens-Johnson Syndrome is uncommon and consequential disease which affects the specific organs like the skin, mucous membrane, genitals, and eyes. Stevens-Johnson syndrome and Toxic epidermal necrolysis both are compatible and correlate with erythema multiforme. It is mainly caused due to some drugs like antibiotics, anticonvulsants, some NSAIDS, anti-epileptic and anti-gout drugs. Of antibiotics, penicillins and sulfa drugs are eminent offenders.. Based on case registries and observational studies, 1-3 cases per million were reported per year. Diagnosis of this syndrome is carried out depending on the symptoms, physical examination, histological examination of the affected area for any specific bacterial infection, and patient's medical history. Patients must be treated with particular attention to respiratory and hemodynamic stability, electrolyte balance, burns and pain control. If there is any symptom of SJS the victim have to withdraw the drug and consult the doctor immediately for preventing further complications. Doctors should carefully prescribe the medication that includes antibiotics and high-risk drugs must be given in small doses.

Keywords: Stevens-Johnsons Syndrome, Toxic Epidermal Necrolysis, Erythemamultiforme, Haemodynamic Stability.

1. INTRODUCTION

Stevens-Johnson syndrome is a type IV hypersensitivity reaction [1]. It is uncommon and consequential disorder which affects the specific organs like the skin, mucous membrane, genitals and eyes [2]. It can be described by all-embracing erythematous macules and targetoid lesions with full-thickness epidermal necrosis, at least focally with the participation of the cutaneous surface at an greater extent. Generally, the mucous membrane is involved [3].

Stevens-Johnson syndrome and Toxic epidermal necrolysis are compatible and both correlate with erythema multiform [4, 5]. Erythema multiforme is identical to Stevens-Johnson syndrome, slightly close, skin reaction which is typically caused by infection, especially herpes viral infections, and bacteria called mycoplasma which causes chest infections [2].

Stevens-Johnson Syndrome is mainly caused due to some drugs. Patients with this disease undergo with severe inflammation of skin penetrating mucous membranes that covers the internal organs. As the disease progress, corresponding organs may also get affected and the condition gets severe which may lead to death [6].

1.1. Classification

The simplest classification have been reported and divided into three types depending upon the detachment of body surface area (BSA). They are as follows.

- Stevens-Johnson syndrome – detachment of 10% of body surface area.
- Overlapping Stevens-Johnson syndrome/toxic epidermal necrolysis-detachment of 10-30% of body surface area.

- Toxic epidermal necrolysis-detachment of more than 30% of the BSA [1].

2. ETIOLOGY

Various factors have been incriminated as causes of Steven Johnsons Syndrome. However, four main etiologica factors are characterized, which includes following three factors.

1. Infectious
2. Drug-induced
3. Genetic factors

2.1. Infectious sources

Some of the viral diseases that may cause Stevens-Johnson syndrome are listed below.

- ✓ Encaphalitis caused by Herpes simplex virus,
- ✓ HIV/AIDS,
- ✓ Infections caused by Coxsackie virus,
- ✓ Influenza,
- ✓ Hepatitis,
- ✓ Mumps

Some of the bacterial diseases are listed below.

- ✓ Diptheria
- ✓ Brucellosis
- ✓ Mycoplasma pneumonia [7,8]
- ✓ Rickettsia

Some of the fungal diseases are listed below.

- ✓ Coccidiomycosis
- ✓ Histoplasmosis
- ✓ Dermatophytosis

2.2. Drug-induced

Stevens-Johnson Syndrome is mostly caused by frequent usage of antibiotics followed by analgesics, NSAIDS, anti-epileptics and anti-gout drugs. Of antibiotics, penicillins and sulfsdrugs are eminent offenders [9].

Some of the drugs which cause Stevens-Johnson syndrome due to high usage are listed according to their categories.

These drugs are listed below.

1. Analgesics : Tramadol, cocaine[12,13,14]
2. Anti-epileptics: Phenytoin, Carbamazepine, Valproic acid, Lamotrigine, Mirtazapine, Phenobarbital.
3. Anti-gout : Allopurinol[10]
4. Anti-retroviral drugs :Niverapine, Indinavir[12,13,14].
5. NSAIDS: Meloxicam, Piroxicam, Tenoxicam, diclofenac, Indomethacin, Sulindac.
6. Antibiotics :
 - Cephalosporins :Cefaclor,cefapirin, cefixime, cefalexin, cefatrizine, cefpodoxime, ceftriaxone and cefuroxime.
 - Aminopenicillins : amoxicillin and bacampicillin.
 - Macrolide : azithromycin, clarithromycin, roxithromycin, erythromycin and spiramycin.
 - Tetracyclins :Minicycline, doxycycline, and metacycline.
 - Quinolones : ciprofloxacin, levofloxacin, norfloxacin, ofloxacin and grepafloxacin[2].

Mockenhaupt et al emphasized that the symptoms of this disease may appear within 60 days of use of anti-convulsants[10].

In 2014, the Food and Drug Administration (FDA) needed the acetaminophen manufacturers to include the Stevens-Johnson syndrome as a risk warning in the package [15].

2.3. Genetic factors

Due to genetic disposition in the following human leucocyte antigens, there is a maximum chances of occurrence of the disease.

- HLA-B*5801
- HLA-B*1502
- HLA-B*44
- HLA-A*0206
- HLA-A2
- HLA-A2
- HLA-B12
- HLA-DQB10601
- HLA-DR7

1. In these alleles there is a high contingency of evolving the disease when exposed to particular drugs. A screening was carried out in southeastern Asian ethnicity for HLA-B*1502 allele in patients prior to the treatment with carbamazepine under the recommendation of US Food and Drug Administration (FDA). HLA-B*5801 has a risk of causing reactions with allopurinol [16]. Pretreatment sieving of these alleles is not accessible till now [17].
2. White people with HLA-B*44 allele are seem to be much liable to spread Stevens-Johnson Syndrome. Apart from this the alleles, HLA-A29, HLA-B12, and HLA-DR7 are responsive to sulfonamides. On the other hand, HLA-A2 and HLA-B12 are stimulant to Non-steroidal anti-inflammatory drugs(NSAIDS).
3. Genetic dysfunction in the alleles such as HLA-A*0206 and HLA-DQB1*0601 causes ocular disease in Stevens-Johnson syndrome [18-19].
4. Despite anything to the contrary, either way the existence of these alleles make up a leaning to Stevens-Johnson syndrome or these alleles are in interdependence loss of equilibrium with adjacent genes is not known[20].

3. RISK FACTORS

The factors which may cause Stevens-Johnson syndrome are listed below.

- Viral infections – herpes, hepatitis and AIDS.
- Fragile immune system–because of some diseases like HIV or AIDS, autoimmune diseases such as lupus or some specific treatment methods like chemotherapy and organ transplants, the patient may become susceptible to Stevens-Johnson syndrome.
- Past history- if the disease has previously occurred due to the drugs and the patient is continuing the drugs even, then he has the chances of reoccurring of the disease.
- Family history of Stevens-Johnson syndrome- in a family, if there is any patient suffering with Stevens-Johnson syndrome then there is a higher chance of occurring this disease to their closed ones in their family.

4. EPIDEMIOLOGY

As Stevens-Johnson syndrome is a rare disease, 2.6-6.1 cases per million were reported per year. In United States, each year above 300 cases were diagnosed. Occurrence of this disease is most common in adults than children [21-22]. Depending upon the observational case studies, the cases reported were 1 to 3 per million in one year [23-25].

4.1. Demographical report of Race, Age and Sex-related:

Although Stevens-Johnson syndrome is common in white people but it may occur in any of the races. Fascinatingly this disease is not limited to humans; it may occur in animals too such as dogs, cats and monkeys. In a group of 315 patients, the huge chain of 39.9% of only females were reported with Stevens-Johnson Syndrome [26,17].

5. PATHOPHYSIOLOGY

5.1. Brief summary

Though the exact mechanism of Stevens-Johnson syndrome is unclear, there are some assumptions of appearance of the disease as a result of immune-mediated response to specific drugs. In various Asian populations, a genetic disposition for illness was uncovered which forced the FDA to recommend for pre-genetic screening. Further research has brought into focus on the phenomenon of vitamin derivatives on the disease process.

5.2. Pathophysiology

Stevens-Johnson syndrome is noticeable by the broad eruption of macules and papules which further develop into severe necrosis of skin and shedding of skin. Up to now, the disease was thought to be occurred due to genetic disposition. However, researchers are trying to expose the exact cause of spreading of the disease. Genetic research established several combinations of Alleles and drugs when compounded, increases the risk of the disease. In an article which was published by Mawson, Eriator and Karre in 2015, these authors hypothesised that the disease occurs when any drug damages the liver, which is responsible for the storage of vitamin A which allows the free-retinoid molecules run into the blood circulation, causation of acute, systemic Vitamin A toxicity. It is observed that in Stevens-Johnson syndrome, a cytotoxic protein named Granulysin is commonly found in the blisters of the body. Granulysin is produced in large masses by CD8+ T-Lymphocytes and natural killer cells. It is expected that this granulysin acts as cytokine for the destruction of retinoid molecules, together combined are responsible for the keratinocyte apoptosis in Stevens-Johnson syndrome. Because of the apoptosis, the epidermis gets detached from the dermis and leads to tissue necrosis causing complete eruption of the skin. While the mechanism is still unclear, it is believed that CD8+ T-Lymphocytes get hyperactive when exposed to retinoic acid and produces granulysin in large quantity. Then Granulysin gets attracted to retinol which is cytotoxic in nature and induces keratinocyte apoptosis.

The specific class of drugs like analgesics, NSAIDS, anti-convulsants, anti-gout and antibiotics on their high usage cause Stevens-Johnson syndrome. The mechanism behind is, these medications increases the retinoid levels in the systemic circulation in two ways : one by damaging the hepatic cells which are the storage site for vitamin D and secondly by inhibiting the metabolism of retinoic acid. By any one of these ways, retinol level increases. A symptomatic of the onset of the disease can be seen in hepatic injury as the patient shows hazy illness for one week before the rashes appear on the skin.

5.3. Implications: Pathophysiology

On the basis of the pathophysiology, treating the patient and preventing the further spreading of the disease will be easygoing. It was established that retinol toxicity is responsible for the Stevens-Johnson syndrome. The levels of retinol in the systemic circulation may reduce with the help of plasmapheresis. According to the article published by Mawson in 2015, plasmapheresis has reduced the mortality in the patients with Stevens-Johnson syndrome.

In Asian patients, the FDA has recommended genetic screening of the patients before treating with carbamazepine as positivity of genetic predisposition has been reported in patients of Asian ancestry with HLA-B1502 Allele when exposed to carbamazepine. Stevens-Johnson syndrome is also reported in India especially in HIV patients. Phenytoin-induced risk is also identified in Japanese and Europeans who carries HLA-A301 allele [27-36].

6. SIGNS AND SYMPTOMS

Clinical features of Stevens-Johnson syndrome varies according to the severity of the disease. Depending upon its severity SJS is classified into two phases.

- Acute phase
- Late phase and Sequela

6.1. Acute phase:

Early signs/symptoms:

- Fever,
- Malaise,
- Fatigue And Mucosal Lesions,
- Headache
- Bleeding
- Dehydration

As the days progress, these symptoms precede cutaneous manifestations involving the

Trunk and face area, erythema of buccal cavity, ocular involvement followed by respiratory and gastrointestinal tracts, genitals, palms and soles are also involved[37,38].

Ocular symptoms are listed below.

- Conjunctivitis,
- Swollen eyelids,
- Erythema formation in the eyes,
- Catarrhal discharge,
- Corneal erosion,
- Adhesion of the conjunctiva [39-40].

6.2. Late phase and Sequelae

Magina et al in his article [42] mentioned following symptoms as the disease progress :

- Anomalous pigmentation of the skin,
- Dry eyes,
- Symblepharon,
- Loss of vision,
- Dischiasis,
- Entropion,
- Ankyloblephron,
- Corneal ulceration[41],
- Hypertrophic scars may be seen in some patients[43],
- Nail dystrophy

In 73% of the patients with Stevens-Johnson syndrome, mostly oral-oesophageal and ocular mucosa are involved. When the situation gets complicated, the symptoms extend to lungs and genitals [44].

7. HISTOLOGICAL EXAMINATION

Histological examination of the skin is necessary to preclude the differential diagnoses for any autoimmune blistering diseases, bullous formation and skin erosion, infection causing bacteria in the skin should be examined. The biopsy of the skin can be carried out with the help of Direct Immunofluorescence analysis technique [42].

8. DIAGNOSIS

The diagnosis of Stevens-Johnson syndrome is carried out systematically based on the patient's :

- Symptoms
- Physical Examination
- Medical history if present [2].

In physical examination, the patient could be suffering with following illnesses :

- Fever
- Tachycardia
- Epistaxis
- Seizures
- Coma

Symptoms may be of:

- Skin lesions
- Nasal lesions
- Entropion
- Catarrhal discharge
- Mouth lesions

On slit lamp examination, following ocular symptoms can be testified. They are as listed below.

- Trichiasis
- Papillae
- Symblepharon
- Conjunctivitis
- Glaucoma
- Foreshortening of fornices
- Ankyloblephron
- Neovascularization [45-46].

9. TREATMENT

9.1. Terminate the condition:

If any adverse symptom is observed then immediately withdraw the drug which is prescribed and admit the patient in Intensive care unit for treatment [2].

9.2. Supportive therapy:

Maintaining body temperature

Maintaining body temperature at 30-32°C helps the patient from preventing loss of calories from the body through the skin. Heated air-body warmers could be useful to maintain warm temperature of the body.

Monitoring

- Frequent monitoring of vital signs is important for the management as they offer the first sign of a worsening systemic condition.
- Monitoring (both initially at baseline and subsequently at periodic intervals) includes parameters such as pulse rate, blood pressure, respiratory rate, fluid intake and urine output chart, blood glucose, serum electrolytes, serum creatinine and specific cultures.
- Complications such as septicemia and disseminated intravascular coagulation can be monitored by specialized tests such as coagulation assays, fibrin degradation products and D-dimer, by using specialized equipments.

Infection control

The following measures are to be considered to prevent infection:

- Patient should be handled carefully and maintain sterile conditions.
- Using hand washes before and after while handling the patient should be habitual by the health care providers and caretakers.
- Urinary catheters can be used if necessary, as constant insertion of catheters may cause infection.
- If urinary catheters, intravenous lines or central lines are used, they must be changed regularly.
- Monitor regularly for any development of sepsis on the skin.
- Environmental conditions should be maintained in standard conditions.
- Careful and sensible use of antibiotics.

Electrolyte balance

Fluids can be administered continuously for 96hrs without any replacement except when there is any indication of phlebitis or any infection at the site.

- The fluid requirements for the patient can be calculated by the Parkland formula
Fluid requirement = 4ml/kg body weight x percentage of body surface area involved.

- The fluid is titrated for maintaining urine output 1000-1500ml.
- Blood transfusion could be provided if situation demands.

Alimentation

- Oral liquid diet is preferred to the patient. Patient can be feed with nasogastric tubes. Total parenteral nutrition is also administered.
- Caloric intake is calculated as 30-35 kcal/kg/day. To inhibit negative nitrogen balance, proteins are given, calculated as 1.5 g/kg/day [48].
- If patient is getting oral feeding through oral-oesophageal tract then it will be difficult to swallow. So, to prevent pain during swallowing the food, oral anaesthetic mouthwashes are preferable for feasibility [2].

Topical management

- Dressing is must and should carried out to avoid infections and further spreading of the lesions, prevent heat loss and adhesion of skin to the clothes.
- Regular cleaning of wounds with normal saline and applying wound healing ointments. Cleaning of patient's bed and surroundings.
- For dressing the wound, gentian violet paint in dilution and silver nitrate (0.5%) can be used.
- Changing position of the patient, exposing to atmospheric air and use of air-fluid bed or water bed can help healing of lesions and prevent bed sores and patient be comfortable.

Anticoagulation

- To prevent coagulation of blood, low molecular weight heparin can be used in some patients. Early shifting of the patient is also useful.

Inhalation care

There is chance of occurrence of pulmonary edema during fluid administration. So to prevent it pulmonary care should be given. Normal saline aerosols can be administered. Bronchial aspiration and postural drainage is performed by turning the patient in different positions. Salive and secretions should be cleared as they predispose during aspiration.

Antacids, analgesics, anxiolytics and antipyretics

- Administration of antacids reduces the prevalence of gastric bleeding.
- Opioids and analgesic may be useful for pain management only by the consideration of patient's clinical needs, possible route of administration.
- Anti-pyretics are not advisable as some of them may cause Stevens-Johnson syndrome [49, 50].

10. Medication summary

The main objective of the treatment is to reduce the disease condition, prevent adverse effects caused by drugs and provide better health care to the patient. By the way, there is no specific drug to treat with, but the patient can be treated symptomatically with a better supportive care.

10.1. Glucocorticosteroids

These are steroidal anti-inflammatory drugs that controls inflammation by controlling rate of protein synthesis, suppressing migration of polymorphonuclear leukocytes and fibroblasts, reversing capillary permeability and stabilizing lysosomes at cellular level. In larger doses, they decrease inflammation.

The drugs used for the treatment are Prednisone and Methylprednisolone.

- Prednisone: dose - 1-2 mg/kg/day
- Methylprednisolone: dose – 8-16 mg/day i.v. or i.m.

10.2. Immunosuppressants

These are the agents which minimize the occurrence of inappropriate immune responses.

The drugs which can be used to suppress the immune activity of the patient are :

- Cyclosporine and
- Cyclophosphamide

Cyclosporine

It is a calcineurin inhibitor. It suppresses cellular and humoral immunity mainly T-cells which is involved in the activation of Interleukins.

For children and adults, base dosing on ideal body weight.

Dose: 3-5 mg/kg/day for 14 days

Cyclophosphamide

Metabolites of cyclophosphamide interfere with malignant cell growth by cross-linking tumor cell DNA. It has a potent immunosuppressive activity.

10.3. Immune Globulins

These immune globulins are the different approach to the immunomodulation. They target the specific antigen and acts as an antibody and maintains normal immune activities in the patient.

Immune Globulin Intravenous (IGIV)

The pooled human immune globulins from donors used as replacement therapy for primary and secondary immunodeficiencies, may interfere with Fc receptors on the cells of the reticuloendothelial system for autoimmune disorders including cytopenias and ITP, may offer passive immunity by increasing antibody titer and antigen-antibody reaction potential.

Dose : > 3-6g/kg or <3-6g/kg.

10.4. Other therapies:

Other therapies that can be suggested are Plasmapheresis (an extracorporeal therapy-removal, treatment, and return of blood plasma and blood components), Pentoxifylline (a haemorheologic agent which improves blood flow by decreasing blood viscosity and increasing red blood cells flexibility), and N-acetyl cysteine(it lowers mucous viscosity of pulmonary secretions) had better impact on treating Stevens-Johnson syndrome. In patients with severe neutropenia, Granulocyte colony-stimulating factor which is a glycoprotein that stimulates the bone marrow to produce stem cells and granulocytes and release them to the blood stream was given as supportive therapy. Later it is suggested in patients without neutropenia[54,55,56].

11. Preventing Stevens-Johnson syndrome

To prevent the occurrence of Stevens-Johnson syndrome, the main step is to withdraw the suspected drug immediately and consult the doctor. In the family, if there is any person who suffered with Stevens-Johnson syndrome then there is chance of genetic inheritance [2].

12. CONCLUSION

Though Stevens-Johnson syndrome is a fatal disease, due to recent growth in the genetics, patient risk can be identified by genetic predisposition screening before the treatment to uncover patient susceptibility to the drug. Further studies should be carried out on the efficacy of plasmapheresis to treat this disease. Firstly, the doctors should monitor the medication twice before prescribing it to the patient, especially when high risk drugs are used. In case if any high risk drugs are prescribed then decrease the dose or use any safer alternatives.

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