**Clinical Science** 



# Carbamazepine induced Stevens Johnson Syndrome in a patient of Migraine- An Observational Study

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**ABSTRACT** Stevens-Johnson syndrome (SJS) is a rare but serious idiosyncratic drug reaction characterized by diffuse mucoepidermoid injury and high mortality. Keratinocytes in both skin and mucous membranes (including eyes, mouth and genitalia) are injured resulting in a diffuse maculopapular rash, blistering lesions and epithelial detachment with minimal force (Nikolsky's sign). An Indian woman, 46 years old with a past history of Migraine being treated with Carbamazepine (400mg Thrice Daily), admitted to a tertiary care hospital of Eastern India with difficulty to eat food, swelling of the lips and maculopapular rash. Presumptive diagnosis of carbamazepine -induced Stevens-Johnson syndrome was made after excluding other causes. Carbamazepine was withdrawn and other supportive care (Intravenous Fluid, Injection Dexamethasone 8mg Twice Daily, Injection Paracetamol 1000 mg Twice Daily, Triamcinolone oral paste local application Thrice Daily) was provided to the patient during her hospital stay. She recovered after 2 weeks. Thus, Carbamazepine can induce Stevens Johnson Syndrome and a strict vigilance of adverse drug reaction is required in patients being treated with Carbamazepine.

KEYWORDS: Carbamazepine, Stevens Johnson syndrome, Observational study

## INTRODUCTION

Stevens Johnson syndrome (SJS) is a reaction induced by medication characterized by widespread epidermal necrosis and mucous membrane involvement <sup>113</sup>. The cardinal manifestation of Stevens-Johnson syndrome is a febrile illness along with headache, cough, malaise, rhinorrhea occurring along with prodromal 'target' type skin lesions that develop later into a diffuse erythematous rash involving both skin and mucous membranes<sup>2</sup>.

Mucous membrane involvement is reported to occur in 90%–100% of cases and can involve virtually all areas of the body including the mouth, nose, genitalia, eyes and visceral organ <sup>34</sup>.

Carbamazepine, is widely used to treat seizure disorder, bipolar disorder, trigeminal neuralgia, and chronic pain. It is one of most common causes of drug hypersensitivity reactions<sup>5</sup>. This has resulted in increased incidence of nausea, vomiting, and serious hematological toxicities such as aplastic anemia, agranulocytosis, eosinophilia, lymphadenopathy, and splenomegaly<sup>12</sup>. The reported frequency of serious carbamazepine hypersensitivity reaction is between 1/1,000 and 1/10,000 new exposures to the drug<sup>6</sup>.

The pathogenesis of Stevens Johnson syndrome has not yet been established. It is characterized as a hypersensitivity syndrome because of the preexistence of pharmacogenetic and immunologic abnormalities to the administered drug. The death of keratinocytes due to apoptosis is currently thought to be the major mechanism<sup>7,11</sup>.

## PRESENTING CONCERN

A 46 year old Female with a past history of migraine being treated with Propranolol ( 40mg Once Daily ) and Carbamazepine (400 mg Thrice Daily ) presented with acute onset of painful skin lesions, fever  $>39^{\circ}C$  (102.2°F), sore throat, generalised erythema, difficulty to eat and swelling of the lips.

Further history revealed that Carbamazepine was started 5 days ago.

On the  $2^{nd}$  day of medication, a mild fever and generalised weakness had occurred. On the  $4^{th}$  day after starting Carbamazepine painful skin lesions, oral mucosal involvement and swelling of the lips were found.On the fifth day, the patient visited the emergency room and was admitted with a presumptive diagnosis of Stevens Johnson syndrome.



Swelling of the Lips (Figure 1)



 Swelling of oral mucosa(Figure 2)

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## Skin Lesions at abdomen(Figure 3)



#### Skin lesion involving hand(Figure 4)

On physical examination, the patient was febrile, hypotensive, stinging erythema and painfully crusted erosions on both the lips(Figure 1 and 2), had pruritic rash(Figure 3 and 4). Pharyngitis was present and she was unable to swallow food. Conjunctiva and genital mucosa were not involved. There were no enlarged lymph nodes.

Laboratory examination revealed mild leukocytosis, C-reactive protein, and ESR were mildly elevated. Malaria Dual Antigen and Dengue NS1 were negative. Blood Anaerobic Culture & Sensitivity: Showed No Growth (After 72 hours of incubation) Throat Swab Culture (Aerobic): Showed Growth of throat commensals (After 48 hours of incubation).

Carbamazepine was withdrawn and other supportive care (Intravenous Fluid, Injection Dexamethasone 8mg Twice Daily, Injection Paracetamol 1000 mg Twice Daily, Triamcinolone oral paste local application Thrice Daily, Hydroxyzine 50 mg Once Daily, Fexofenadine 180 mg Once Daily and Calamine lotion local application Twice Daily was provided to the patient during her hospital stay. Steroid treatment was given for 5 days and gradually withdrawn. On the eighth day the patient was discharged in good condition, with generalized desquamation and incomplete peeling of the skin on the trunk and forearm.

## DISCUSSION

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Stevens Johnson syndrome has multiple etiologies. it is commonly triggered by viral infections (herpes simplex virus is the infectious agent more commonly involved) and neoplasia(carcinoma and lymphomas). However, the most common cause is the use of medications. Among the drugs implicated more often are allopurinol, antibiotics, anticonvulsants, and non-steroidal anti-inflammatories<sup>2</sup>.

In a seven year study conducted by Devi et al in Thrissur, India concluded that anticonvulsants were the cause implicated most in Stevens Johnson syndrome especially in the first eight weeks of treatment, and the main drug responsible (more than 80%) was carbamazepine<sup>8</sup>.

At present, the mechanism by which Stevens Johnson syndrome develops is not well understood. Stevens Johnson syndrome usually

antigenic stimulation<sup>9</sup>.

Typically, the initial presentation is marked by symptoms of fever, myalgia, and generalised weakness for 1 to 3 days before the development of cutaneous lesions. The skin lesions are symmetrically distributed on the face and upper trunk areas. The rash spreads rapidly and is usually maximal within first four days, sometimes within hours. The initial skin lesions are usually poorly defined macules with darker purpuric centers that coalesce<sup>10</sup>.

occurs during the first course of drug ingestion (without prior sensitization). T-cells are already present in the body before drug exposure and elicit a robust immune reaction on carbamazepine

Diagnosis is clinical. However, skin biopsy helps to confirm the diagnosis, usually excluding bullous diseases not related to drug therapy. Immunofluorescence studies only help to exclude other bullous disease. Anemia and lymphopenia are frequent, eosinophilia is rare. Neutropenia suggests a poor prognosis<sup>10</sup>.

The main therapeutic action in Stevens Johnson syndrome is early recognition of the drug reaction and withdrawal of the drug, since any delay can be fatal. There is no universally accepted and specific treatment for acute Stevens Johnson syndrome other than supportive care. Glucocorticoids have not been proven useful in Stevens Johnson syndrome. They may be beneficial in the early stage of Stevens Johnson syndrome but may increase the risk of infection, prolong wound healing, or even increase mortality, if bullous eruption or mucosal erosion is fully developed. Although some retrospective studies have suggested that intravenous immunoglobulin may be effective in stopping the progression of Stevens Johnson syndrome, other studies showed limited benefit on the mortality rate or progression of the disease<sup>2</sup>.

### CONCLUSION

In conclusion, this is a case of Carbamazepine induced Stevens Johnson Syndrome in a patient of Migraine. This case serves to highlight the severe epidermal necrosis and mucosal membrane involvement that can occur following Carbamazepine therapy. Unfortunately, effective therapies for the treatment of Stevens Johnson Syndrome do not exist and supportive therapies with prompt discontinuation of the offending agent remain the standard treatment. Because of the possibility of cross-sensitivity among chemically related drugs, many physicians recommend avoidance of not only the medication that induced the reaction but also all drugs of the same pharmacological class.

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