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STEVENS - JOHNSON'S SYNDROME ASSOCIATED WITH LAMOTRIGINE – A CASE STUDY

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ABSTRACT

Introduction: Steven-Johnson's syndrome (SJS) is an immune complex mediated hypersensitivity reactions and has been linked as an adverse side effects to many drugs. Lamotrigine an FDA approved drug used as an anti-convulsive and also commonly used medication as mood stabilizer in bi-polar depression condition. **Case report:** we present a 62-year-old male a case of known epilepsy who developed SJS after 8 days of monotherapy with Lamotrigine. He was treated with steroids and supportive management. After one week he made eventful recovery. **Discussion:** Lamotrigine newer non-aromatic antiepileptic drug approved by FDA. Factors like monotherapy, post-partum, due to hormonal factors and strong association between HLA and antiepileptic drugs induces SJS/TEN. Here we are using SCORTEN (SCOR of Toxic Epidermal Necrosis) scale for knowing severity of illness for SJS/TEN. **Conclusion:** SJS and toxic epidermal necrolysis (TEN) are acute muco-cutaneous reactions characterized by generalized blistering, painful, lesions of bright erythema has high mortality and morbidity rate so requires careful attention as use of Lamotrigine in clinical practice.

KEYWORDS: Lamotrigine; SJS; Hypersensitivity reactions; Bi-polar depression, Toxic epidermal necrolysis.

INTRODUCTION

Stevens-Johnson syndrome (SJS) is an immune mediated type 4 hypersensitivity reaction involving skin and mucous membranes that was first described by Hebra in 1886 as erythema multiforme exudativium involving mucous membranes. It was named by Albert Mason Stevens and Grant Chambliss Johnson in 1922 in published case report from Bellevue Hospital, New York where two boys aged 7 and 8 with cutaneous eruptions but no known diagnosis.[1] SJS is a serious muco-cutaneous illness with systemic lesions, and epidermal detachment encompassing <10% of total body surface area. There are various factors which precipitate this condition, like viral infections, systemic illness and there are more than 200 drugs that have been associated like antibiotics, anti-epileptic drugs, NSAIDS are common agents responsible for SJS.[2,3]

Stevens-Johnsons Syndrome, with incidence of around 2.6 to 6.1 cases per million people per year with a mortality rate of around 5% was reported.[4] Although reported as a rare event Stevens-Johnson's Syndrome has been found more common in adults than in children. Women are affected more than men, i.e., (2:1).[5] SJS and TEN are two forms of life threating skin conditions in which cell death causes epidermis to separate from dermis. (TEN) is more severe form of SJS and associated with high morbidity and mortality. (TEN) has detachment of body surface more than 30%, whereas SJS has less than 10% of body surface area detachment.[6]

Clinical features of SJS include significant involvement of skin, oral, nasal, eye, vaginal, urethral, GI, and lower respiratory tract mucous membranes. Skin rash can begin as macules that develop into papules, vesicles, bullae, urticarial plaques or confluent erythema. Bullous lesion can rupture and may lead to further complications. Mucosal involvement includes erythema, edema, sloughing, blistering, ulceration and necrosis. GI and respiratory involvement may progress to necrosis. SJS is a serious systemic disorder with the potential for severe morbidity and even death. Whereas Toxic Epidermal Necrolysis has a higher mortality (30-35%).[7]

Presentation of a case

A 62-year old man who presented with fever up to 102.7.F, 90% rashes with redness and itching all over the body, conjunctivitis, fever with chills, puffiness of face, generalized weakness. The past history of the patient reveals that a known case of epilepsy for the past three years under sodium valproate 250 mg PO q 12hr. As per the patient, medication stopped since four months. However due to breakthrough seizures admitted in hospital and started on Tab.lamotrigine-100mg-OD. He continued showing improvement hence got discharged.

Above 8 days following hospital discharge he developed the above symptoms and admitted in ICU. On physical examination it was found that the lesions are erythematous macular lesions on neck, trunk and back side and also had oral mucosal involvement. History revealed that no such lesions occurred earlier. Family and personal history was not relevant. Lab reveals elevated WBC-14500ccm, with an elevated CRP (78.94). Serum Ig E was 80UI/ml during admission. Procalcitonin, liver function test and renal function test were normal.

His SCORTEN score was 3, during hospital admission, age greater than 40 years, tachycardia with greater than 120bpm, sodium bicarbonate less than 20mmol/L. The Naranjo algorithm scale was used to assess the casualty analysis the score was found to be 6, it was found "probable" with lamotrigine.

Outcome and follow up

The diagnosis of Stevens-Jhonson's syndrome associated with lamotrigine was confirmed. Offending drug was immediately stopped. He was started on Inj. Hydrocortisone injection 100mg; Inj. Pheniramine maleate injection 2 cc; Tab. Hydroxyzine- 25mg, TID; Refresh drops 2 drops each eye, TID; Choline Salicylate and Benzalkonium Chloride gel, BD; Nicotinamide gel, BD. Due to elevated CRP and fever for possible sepsis started on Inj.Cefriaxone+sulbactim-2gm –BD . The patient stabilized and got discharged with following medication Tab.Carbamazepine-200mg-OD.

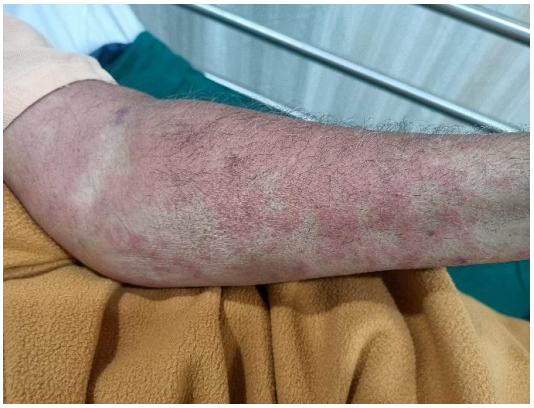

Figure 1: Maculopapular rash over left hand.

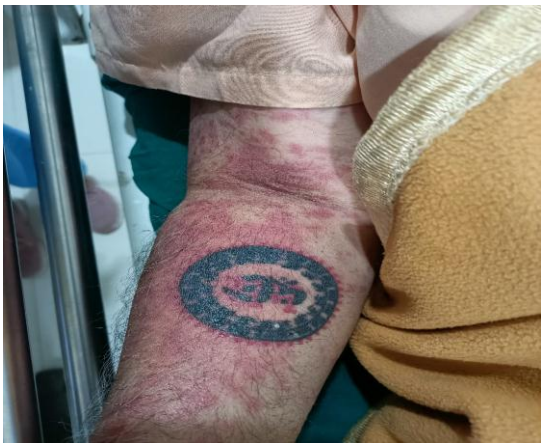

Figure 2: Maculopapular rash over right hand.

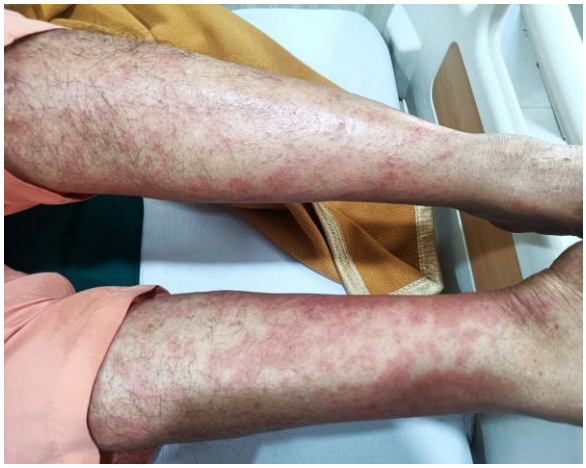

Figure 3: Maculopapular rash over both legs.

DISCUSSION

Lamotrigine is a new non-aromatic antiepileptic medication which is also used as a mood stabilizer. Side effects of generally include CNS symptoms like headache, fatigue, dizziness, sleep disturbance, tremor, movement disorder, agitation, confusion, hallucinations, Gastrointestinal symptoms like diarrhea, nausea/vomiting, hepatic dysfunction and skin & cutaneous side effects like rash. Stevens-Johnson's syndrome has also been mentioned as a rare hypersensitivity reaction/ side effect in the drug information of Lamotrigine specified by severe rash, fever, lymphadenopathy, hepatic dysfunction, blood disorder, and Disseminated Intravascular Coagulation with multi organ dysfunction.[8,-10]

Hypersensitivity reactions like SJS happen due to body's inability to metabolize and detoxify drugs and their metabolites, which is detected as antigens by the body. This results in cytotoxic T cells attacking keratinocytes and epithelial cells in the mucosa/epidermis, leading to cell death and followed by sloughing of the skin due to a release of perforin (glycoprotein responsible for pore formation on cell wall) and granzymes (a serine proteases), which are cytolytic proteins secreted by T-lymphocytes and natural killer cells . This perforin cytolytic proteins breakdown the epithelial cells and form pores allowing granzymes to induce apoptosis. Pro-inflammatory cytokines such as TNF-alpha and interferon gamma attract immune cells and cause a cascade of further damage.[11] Distinctive diagnoses for SJS/TEN include: hypersensitivity syndrome, drug rash with eosinophilia, and systemic symptoms (DRESS), dermatitis, angioimmunoblastic T- cell lymphoma, viral eruption, vasculitis, erythema multiforme major, staphylococcal scaled skin syndrome, and toxic shock syndrome.[9,10] There have been very few reports of SJS as a result of monotherapy Lamotrigine--0.03% to 0.08% incidence in adult populations. Reports with combined use of valproic acid and Lamotrigine, however, have more commonly been diagnosed. Since higher doses of Lamotrigine are associated with SJS, it is best to start on the lowest dose and titrate up.[11]

Also few evidences suggests this condition may also due to dermal sweat duct alterations and vaculopathy but no such evidences are not reported in this patient.[12] However these severe cutaneous lesions are connected to higher doses, due to concomitant use of Lamotrigine based upon inter individual parameters this might act as one of associated factor. Also recent studies have suggested a strong association between Human Leukocyte Allele-B 1502 and Antiepileptic drugs induced SJS/TEN in patients of Asian ethnicity. However the test for allele was not done. Also use of Lamotrigine was less in the past few years compared to present trends which might have also been a factor for reporting lesser number of cases.[13]

As per SCORTEN SCALE that is used to calculate severity of illness, he was found to be associated with (score-3) 35% risk for mortality.[14]

CONCLUSION

Severe exfoliative dermatitis like Stevens -Johnson's syndrome and Toxic Epidermal Necrolysis are less reported with newer antiepileptic drugs like Lamotrigine as monotherapy compared to aromatic anticonvulsants like Carbamazepine. Phenytoin, Phenobarbital. As Stevens-Johnson's Syndrome a life threatening condition with elevated morbidity and mortality requires immediate interventions and adequate management. In addition as Lamotrigine is FDA approved drug its usage was increased so we would like to alert that the use of Lamotrigine should be monitored. Therefore health care professionals need to educate public regarding drugs that cause hypersensitivity reactions like SJS and TEN.

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