Case Report

Genetic predisposition to oxcarbazepine induced Stevens–Johnson syndrome

Pranay Wal, Ankita Wal[1], Umeshwar Pandey[2], Awani K. Rai[1], Anil Bhandari

Abstract

Stevens–Johnson syndrome (SJS) is a rare immunologic reaction that may involve skin or various mucosal surfaces. The etiology may range from multiple pharmacologic agents to viral infections. Associated findings can range from minimal skin and mucosal involvement to extensive dermal exfoliation, nephritis, lymphadenopathy, hepatitis, and multiple serologic abnormalities. We report a female patient of 38 years with a history of drug allergy who was administered oxcarbazepine for the management of right partial bronchial seizure due to left parasagittal mass lesion following which she developed papular rashes all over the body and diagnosed as SJS. Although carbamazepine (CBZ) is the most common cause of SJS, a new anticonvulsant, oxcarbazepine, which is structurally related to CBZ, has been shown to induce SJS.

Keywords: Hypersensitivity, oxcarbazepine, Stevens–Johnson syndrome

Access this article online

Website: www.ijccm.org

DOI: 10.4103/0972-5229.84904

Quick Response Code:

Introduction

Stevens–Johnson syndrome (SJS) is thought to be a hypersensitivity complex affecting the skin and the mucous membranes. A new anticonvulsant, oxcarbazepine, which is structurally related to carbamazepine (CBZ), was introduced for use in patients with epilepsy. Drug hypersensitivity reactions can occur with most drugs, although the frequency, severity, and clinical manifestations vary. Drug hypersensitivity can be defined as an inappropriate immune response leading to tissue damage from an otherwise nontoxic agent. Drug hypersensitivity reactions to benzodiazepines often fall into the category of type B (or bizarre) adverse drug reactions, according to the classification proposed by Rawlins and Thompson.[1]

The incidence of hypersensitivity varies according to the drug, the disease being treated, and the ethnicity of the patient.[2] Drug response (including drug hypersensitivity) is a multifactorial and multigenic process, dependent on a complex interaction between multiple genes and the environment [Figure 1]. Each gene contributes to the risk of developing the hypersensitivity reaction, but each individual gene is neither necessary nor sufficient by itself to cause the reaction.[3]

Case Report

A female patient of 38 years with a history of drug allergy was complaining of fever, sore throat, and fatigue, at the time of admission.

She was administered oxcarbazepine for the management of right partial bronchial seizure due to left parasagittal mass lesion following which she developed papular rashes all over the body and diagnosed as SJS.

In this case, during the first week, we used 600 mg/day oxcarbazepine for seizure control, and then increased the dose after 3 days to 900 mg/day. Both the initial and titration doses were slightly lower than the recommended doses.

After 10 days of treatment, ulcers and other lesions

From:
Jodhpur National University, Rajasthan, [1]Department of Pharmacy, Pranveer Singh Institute of Technology, [2]L.P.S. Institute of Cardiology, Kanpur, Uttar Pradesh. India

Correspondence:
Dr. Pranay Wal, Pranveer Singh Institute of Technology, Kanpur, Uttar Pradesh, India. E-mail: pranaywal@gmail.com

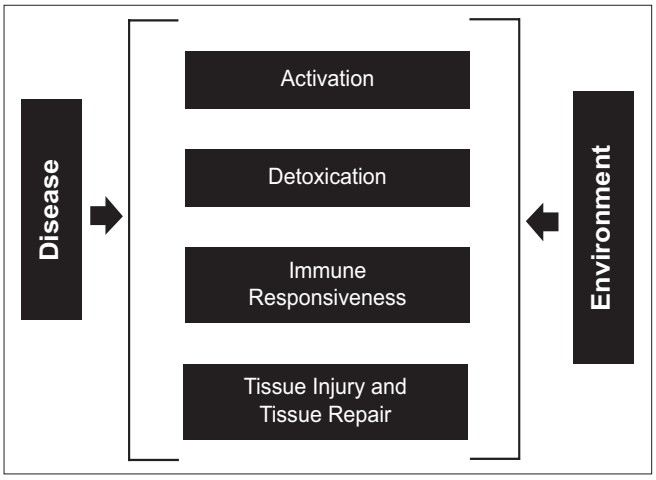

Figure 1: Drug hypersensitivity has a multifactorial and multigenic predisposition

begin to appear in the mouth and lips along with the genital and anal regions. Ulcers in the mouth are usually extremely painful and reduce the patient's ability to eat or drink. High fever and multiple maculopapular rashes were found over the patient's face and neck initially on the 12th day after taking oxcarbazepine. Two days later, some blisters were also observed on her thigh. Then, multiple oral ulcers and hyperemic conjunctivae were also noted.

She was brought to our emergency department and admitted under the presumed diagnosis of SJS. Laboratory investigations showed leukocytosis (WBC, 14660/µL; reference value, 4,000–10,000/µL), and elevated C-reactive protein (59.30 µg/mL; reference range, 0–5 µg/mL).

After obtaining informed consent, we carried out genotyping and took photos of the patient. HLA genotyping showed HLA-B*1518/B*4001. A skin biopsy was also performed. The stratum corneum appeared to be normal. There was marked liquefactive degeneration in the lower half of the epidermis with some dyskeratotic keratinocytes. The dermis showed predominant CD8+ lymphohistiocytic infiltration around the blood vessels and scanty eosinophils. The skin pathology finding was consistent with SJS. After corticosteroids (IV dexamethasone 1.0 mg/kg body weight) and antihistamine treatment for 10 days, the patient improved and was discharged from the hospital.

Discussion

Anticonvulsant hypersensitivity syndrome is a potentially fatal drug reaction with cutaneous and systemic reactions (incidence, 1 in 1000 to 1 in 10,000 exposures) to the arene oxide-producing anticonvulsants—Phenytoin, CBZ, and Phenobarbital sodium. CBZ and its derivatives are widely used anticonvulsants that can cause rashes in up to 10% of patients, and in occasional cases, this may be the precursor to the development of a hypersensitivity syndrome characterized by systemic manifestations such as fever and eosinophilia.[4]

The diagnosis of SJS is based on clinical manifestations with acute onset of rapidly expanding targetoid erythematous macules, necrosis and detachment of the epidermis along with erythema, erosions, and crusting of two or more mucosal surfaces.[5] Our patient had skin targetoid erythematous rashes and mucosa involvement 2 weeks after starting oxcarbazepine treatment. During these 2 weeks, she took no medicine except for oxcarbazepine. The skin pathology finding revealed lymphohistiocytic infiltration around the blood vessels and scanty eosinophils, which was consistent with SJS. The patients usually develop a hypersensitivity reaction between 2 and 12 weeks after starting medicine.[6] It has been postulated that metabolites and not the parent drug are the causal agents.

One of the first reports showed that HLA-B*1502 was present in 100% of CBZ-induced patients with SJS but in only 3% of patients tolerating CBZ and in 9% of the general population.[7]

Other studies have confirmed these results in Han Chinese and in the Thai population.[11]

In this case, we used a dose of 600 mg/day and then titrated it to 900 mg/day. It has been reported that higher daily doses of drugs are associated with an increased risk of SJS than lower doses, which is the case for allopurinol.[8] There is considerable debate about whether to treat SJS with systemic steroids. However, Lam *et al*. found that the early use of short-term systemic steroids for 3–5 days lacked any significant side effects and did not increase mortality or morbidity.[9]

Our patient was treated with intravenous dexamethasone and antihistaminics for 10 days. She improved and was discharged. No sequels were found during 3 months of follow-up.

Compared with other categories of drugs, such as antibiotics and NSAIDs, antiepileptic therapies are associated with a high incidence of SJS and toxic epidermal necrolysis (TEN).[10]

Case reports by Chen *et al*. suggest that identification

of such genetic factors[11] is important, not only to realize the prospect of developing preventive strategies but also to learn about the mechanisms of these reactions, which may ultimately lead to other preventive strategies through better drug design and to better treatment strategies for patients who develop the reactions.

References

1. Rawlins MD, Thompson JW. Mechanisms of adverse drug reactions. In: Davies DM, editor. Textbook of Adverse Drug Reactions. Oxford, UK: Oxford University Press; 1991. p. 18-45.
2. Demoly P, Gomes ER. Drug hypersensitivities: Definition, epidemiology and risk factors. Eur Ann Allergy Clin Immunol 2005;37:202-6.
3. Pirmohamed M, Park BK. Genetic susceptibility to adverse drug reactions. Trends Pharmacol Sci 2001;22:298-305.
4. Vittorio CC, Muglia JJ. Anticonvulsant hypersensitivity syndrome. Arch Intern Med 1995;155:2285-90
5. Frisch PO, Ruiz-Maldonado R. Erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrosis. In: Freedberg IM, Eisen AZ, Wolff K, editors. Fitzpatrick's Dermatology in General Medicine. 6th ed. New York: McGraw-Hill; 2003. p. 543-57.
6. Calligaris L, Stocco G, Lubicibus SD, Marino S, Decorti G, Barbi E, *et al*. Carbamazepine hypersensitivity syndrome triggered by a human herpes virus reactivation in a genetically predisposed patient. Int Arch Allergy Immunol 2009;149:173-7.
7. Chung WH, Hung SI, Hong HS, Hsih MS, Yang LC, Ho HC, *et al*. Medical genetics: A marker for Stevens-Johnson syndrome. Nature 2004;428:486.
8. Halevy S, Ghislain PD, Mockenhaupt M, Fagot JP, Bouwes-Bavinck JN, Sidoroff A, *et al*. Allopurinol is the most common cause of Stevens-Johnson syndrome and toxic epidermal necrolysis in Europe and Israel. J Am Acad Dermatol 2008;58:25-32
9. Lam NS, Yang YH, Wang LC, Lin YT, Chiang BL. Clinical characteristics of childhood erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis in Taiwanese children. J Microbiol Immunol Infect 2004;37:366-70.
10. Yang G, Deng YJ, Qin H, Zhu BF, Chen F, Shen CM, *et al*. HLA-B*15 subtypes distribution in Han population in Beijing, China, as compared with those of other populations. Int J Immunogenet 2010;37:205-12.
11. Chen YC, Chu CY, Hsiao CH. Oxcarbazepine-induced Stevens-Johnson syndrome in a patient with HLA-B*1502 genotype. J Eur Acad Dermatol Venereol 2009;23:702-3.

How to cite this article: Wal P, Wal A, Pandey U, Rai AK, Bhandari A. Genetic predisposition to oxcarbazepine induced Stevens-Johnson syndrome. Indian J Crit Care Med 2011;15:173-5.

Source of Support: Nil, **Conflict of Interest:** None declared.