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A RARE CASE REPORT OF ASSOCIATION OF HLA-B*15:02 ALLELE IN CARBAMAZEPINE INDUCED TOXIC EPIDERMAL NECROLYSIS IN CENTRAL INDIA.

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ABSTRACT Carbamazepine is a well-tolerated drug, widely used for seizure and chronic pain disorders but can cause idiosyncratic cutaneous-adverse-drug reactions (cADR) in susceptible individuals. Toxic epidermal necrolysis (TEN) is one such reaction resulting in severe epidermal and mucosal loss with constitutional symptoms. Though morbidity and mortality are unpredictable, high level supportive care is required for these patients. Immune complex of HLA allele, offending drug and T-cell receptor are responsible for immunopathogenesis of these cADR in susceptible individuals. HLA-B*15:02 has the strongest association to cause carbamazepine induced TEN in South-Asian population. We report a case of TEN, caused by carbamazepine in an HLA-B*15:02 carrier from central India. He recovered uneventfully due to early diagnosis and high-quality multidisciplinary approach. HLA-B*15:02 allele screening must be mandatory before starting carbamazepine in populations with diverse gene-pool to prevent life threatening cADR.

KEYWORDS : Adverse drug reaction, Carbamazepine, HLA-B*15:02, Toxic epidermal necrolysis.

INTRODUCTION

Toxic epidermal necrolysis (TEN) is a severe autoimmune mucocutaneous reaction, most commonly caused by antiepileptics, anti-microbials, anti-retroviral, nonsteroidal anti- inflammatory drugs, etc. As a consequence of extensive keratinocyte death, there is separation of significant areas of skin at the dermo-epidermal junction, producing the classical scalded skin appearance. High-quality supportive treatment is the standard of care and can improve outcomes.

CASE REPORT

An eleven-year-old boy had presented with fever, sore throat and multiple lesions all over the body with peeling of skin over the trunk with pain and burning sensations. Detailed history revealed that the erythematous maculopapular rash appeared initially over the trunk then orderly progressed to involve neck, face and proximal parts of extremities. There were multiple oral, nasal, ocular erosions and ulcerations. After 2-3 days, lesions had extended to palms and soles sparing the distal parts of forearms and legs (Figure 1- A to D). By the fifth day, there was detachment of necrotic epidermis and bulla formation. Nikolsky's sign and Asboe-Hansen sign were present. Lesions had extended to distal portions of extremities and genital mucosa. The area of involvement increased from 50% to 82%. Intervention done with cyclosporine as immunosuppressant, antibiotic cover and supportive symptomatic treatment with multidisciplinary approach. By the seventh day, disease progression had stopped with fading out of red macular lesions and evidence of subsiding bullae and re-epithelization (Figure 1- E to H). Most of the lesions had re-epithelized by the fifteenth day (Figure 1 - I to L). Progression and features of lesions were suggestive of TEN and Tzanck's smear confirmed it. The patient was a known case of seizure disorder for which carbamazepine was prescribed to him. The patient had developed skin lesions after 10-12 days of starting carbamazepine. Carbamazepine was discontinued. The blood investigations were essentially normal except for leukocytosis and marginally raised liver enzymes.

The presence of the HLA-B*15:02 allele in this patient confirmed this occurrence of carbamazepine induced TEN. The primary treatment was done by discontinuing the drug carbamazepine and specific treatment with cyclosporine as immunosuppressant and antibiotic cover. Rest managed by supportive symptomatic treatment with multidisciplinary approach. The patient recovered uneventfully.

DISCUSSION

Childhood seizure disorder is a tiring affair for the parents to accept, adjust, manage and maintain compliance with the therapy protocols. Any adverse reaction to the drug adds up to morbidity and emotional turmoil. Aromatic anticonvulsants are safe and well-tolerated but can cause unpredictable and idiosyncratic type-B immunogenic reactions.[1] One such cutaneous adverse drug reaction (cADR) is the spectrum of TEN and Stevens-Johnson syndrome (SJS). Both have overlapping features ultimately resulting in a severe epidermal and mucosal loss. The associated constitutional symptoms are more troublesome as they are frequently underestimated and undertreated. The primary treatment is discontinuing the drug and supportive symptomatic treatment. Yet the morbidity and mortality in TEN/SJS are unpredictable.

Among various drugs implied to cause TEN/SJS, Carbamazepine is the frequent culprit. [2– 5] Besides seizure disorders, carbamazepine is also widely prescribed for chronic headaches and chronic pain syndromes. Devi et al. concluded that anticonvulsants-induced-SJS occurs in the first eight weeks of treatment, and the drug commonly responsible was carbamazepine.[2] Pharmacogenetic studies identify candidates genetically susceptible to life-threatening cutaneous adverse drug reactions. Among different alleles associated with carbamazepine induced cADR, HLA-B*15:02 has the strongest association in South-Asian population.

Susceptible carriers are frequently found among Han Chinese populations and less commonly among descendants of Vietnamese, Thai, Indian, and Malayan origins.[1,3,6,7]

The altered T-cell receptor (TCR) repertoire model has been proposed for drug-induced SJS/TEN. Activation of CD8 T-cell receptors by the immune complex of HLA allele, offending drug (e.g. carbamazepine) and the TCR causes the immunological reactions i.e. abnormal release of cytotoxins, multiplication of T cells in the skin and keratinocyte apoptosis.[1,6] The mechanism of SJS/TEN in non-carriers of HLA-B*15:02 is not fully understood.

The association of HLA-B*15:02 allele has been rarely reported among the Indian population. Mehta et al. had reported presence of this allele in six patients, native to western India who had carbamazepine-induced-cADR.[7] Aggarwal et al. had reported the allele in only two patients, native to northern India.[8] Devi had reported one case belonging to this allele from southern India.[6] To the best of our knowledge, this is the first case of HLA-B*15:02 allele from central India.

CONCLUSION

Awareness about such complications will result in judicious decision-making regarding drug selection and appropriate management of SJS/TEN. Ancestral history may not be possible in each case to raise suspicion. Immunogenetically diverse multi-ethnic genetic ancestry within the Indian population should warrant screening of every individual in whom carbamazepine therapy is indicated. Research into the role of other alleles in a mixed gene-pool population is also warranted as SJS/TEN has been documented in non-carriers of HLA-B*15:02

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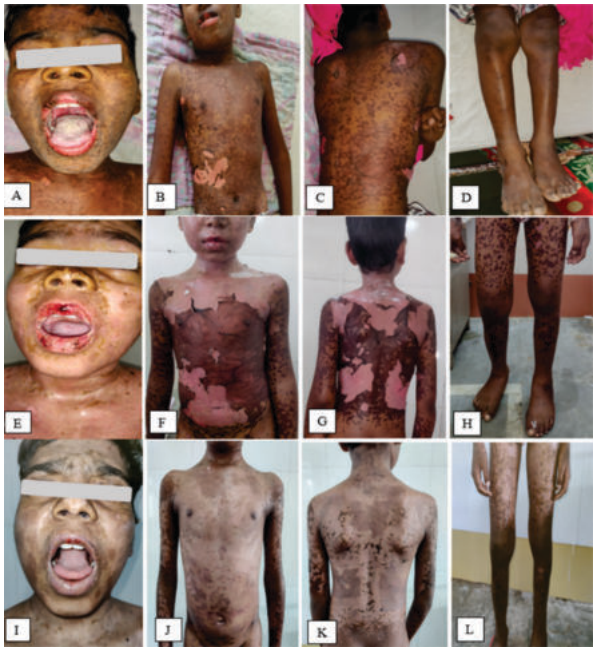

Figure 1

(A to D): Day 1 changes- Maculopapular rash with early bullae formation (A)- Face and neck with oral ulcerations, (B)- Trunk and UL, (C)- Back, (D)- Lower limbs with sparing of distal portions of legs

(E to H): Day 7 changes- Peeled off epidermis from lesions (E)- Face and neck with oral ulcerations, (F)- Trunk and UL, (G)- Back, (H)- Lower limbs.

(I to L): Day 15 changes- Re-epithelization of lesions and resolutions of cutaneous changes (I)- Face and neck with healed oral ulcerations, (J)- Trunk and UL, (K)- Back, (L)- Lower limbs

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