Study of genetic association of HLA – B*1502 with oxcarbazepine induced Stevens-Johnson syndrome and Toxic Epidermal Necrosis in pediatric patients in a tertiary care teaching hospital of Western Rajasthan.

[1]Dr Manisha Gurjar, [2]Dr Manish Parakh, [3]Dr Rimple Jeet Kaur
[1]Associate Professor, Department of Biochemistry, Dr S. N. Medical College, Jodhpur, Rajasthan.

[2]Senior Professor, Department of Paediatrics, Dr S. N. Medical College, Jodhpur, Rajasthan.

[3] Assistant Professor, Department of Pharmacology, AIIMS, Jodhpur, Rajasthan.

Corresponding Author:
Dr Manish Parakh, Email:manparkh@hotmail.com Mobile No: 9414127335

ABSTRACT:

Background and Aims: Human Leukocyte Antigen (HLA)-B*1502is strongly associated with anti-epileptic drug (AED) induced Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis(TEN) in Asian populationsbut very few studies are available in Indian population. The present study was therefore conducted to find out genetic association of HLA-B*1502 allele with oxcarbamazepine induced SJS/ TEN in patients of age group 3 -15 years, receiving this antiepileptic drug.
Methods: This study was conducted in the Department of Pediatrics Medicine, of a tertiary care teaching hospital of Western Rajasthan. The study included two group ofpatients-
Control Group: Patients on oxcarbamazepine, for ≥ 6 months without any complains of adverse cutaneous event.
Test group: Patients with oxcarbazepine induced SJS/TEN.
HLA-B*1502 was detected from Genomic DNA usingcommercially available kit on RT-PCR.Frequency of HLA- B*1502 among controls and test group was determined.
Results: Total eight patients (Control:4 and Test: 4) were screenedfor HLA-B*1502 allele and none of the subject from test and control group tested positive. The frequency of HLA-B*1502 among control and test group was statistically insignificant.
Conclusion: Our study included a very small sample size as incidence of SJS/TEN is very low. Multi-centric screening studies including larger number of patients of pediatric age group must be conducted toconfirm the association of HLA-B*1502 withanti-epileptic drug induced SJS/TEN in Indian population.

INTRODUCTION

Stevens-Johnsons syndrome (SJS) and Toxic epidermal necrolysis (TEN) are rare life-threat ening disorder of skin and mucous membrane characterized by extensive necrosis and detachment of epidermis. Most of the cases of SJS and TEN occurs in response to drugs related to aromatic anti-epileptic drugs (AED) such as Carbamazepine (CBZ), carbazepine(OXC), antibiotics, anti-inflammatory drugs of the oxicam family and allopurinol. The incidence of SJS(one to six cases per million person-years) andTEN (0.4-1.2 cases per million person-years) is very low but morbidity and mortality associated with it is very high.[1]In a systematic review of drug-induced SJS and TEN in Indian population, the two most commonly implicated drugs reported were Carbamazepine (18.2%) and Phenytoin (13.4%).[2]

The Mechanism of SJS/TEN is not fully understood but pharmacogenetics studies had revealed that cytotoxic T-cell mediated-HLA-dependent hypersensitivity is mostly responsible for this adverse drug reaction. In many studies conducted on Asian population, Human Leukocyte Antigen (HLA)-

B*1502was found to be strongly associated with carbamazepine and oxcarbazepine induced SJS/TEN compared with other categories of drugs.[3]The US Food and Drug Administration (US-FDA) had recommended genetic screening of the HLA-B*1502 allele in the patients of Asian origin prior to CBZ therapy to prevent this adverse drug reaction.[4]As a derivative of carbamazepine, oxcarbazepinealso possess an aromatic ring and share a common risk allele to induce cutaneous adverse drug reactions (CADRs) related to HLA-B*1502.[5]

The present study was therefore conducted to find out genetic association of HLA-B*1502 and oxcarbamazepine induced SJS/ TEN in children on this antiepileptic drug.

METHODS

The study was conducted in the Department of Pediatrics Medicine, of a tertiary care teaching hospital of Western Rajasthan. It was a case-control observational study. Patients below 18 years of age attending the OPD for treatment of epilepsy receiving oxcarbazepine for ≥ 6 months were included in the study. The patientsreceivingmore than one antiepileptic or had allergy to any other AEDs were excluded from the study. The patients were divided into two groups:

Control Group: Patients on oxcarbamazepine, for ≥ 6 months without any complains of adverse cutaneous event.

Test Group: Patients with oxcarbazepine induced SJS/TEN.

The diagnostic criteria were based on clinical morphology of SJS/TEN: (Roujeau)[6]

SJS: Skin detachment of <10% of body surface area

SJS-TEN: Overlap 10-30% involvement of body surface area

TEN: >30% involvement of body surface area

Genomic DNA was extracted from 2 to 3 ml of peripheral venous blood using commercially available kit. The presence or absence of the HLA-B*1502 allele was determined with the use of the PG1502 DNA detection kit (Pharmigene), according to the manufacturer's instructions. The kit was based on real-time polymerase-chain-reaction assay, with sequence-specific primers for HLAB*1502.The results were expressed as positive or negative for HLA-B*1502 allele.Statistical analysis of the frequency of HLA- B*1502 among patients of test group and control groupwas performed using suitable test.

Parents were informed about the purpose of the study and written informed consent was obtained. Approval from the Institutional Ethics committee was taken before conducting the study.

RESULT

Total eight patients receiving oxcarbazepine for more than six months were screened for the presence of HLA–B*1502 allele by genotyping. Out of eight patients four patients had no ADR belongs to control group and four patients hadoxcarbazepine induced SJS/TEN belongs to test group. None of the patient of test group tested positive for HLA-B*1502 allele.Similarly, no patient in control group tested positive for HLA-B*1502 allele. The HLA-B*1502 frequency between the control group and test group was statistically insignificant.

Table No. 1: HLA-B*1502 in patients with oxcarbazepine induced SJS/TEN

Patient ID	Sex	Age (years)	Race	HLA-B*1502 allele
1.	Female	5 years	Indian	Negative
2.	Male	14 years	Indian	Negative
3.	Female	15 years	Indian	Negative
4.	Male	3 years	Indian	Negative

DISCUSSION

Adverse drug reactions are the unwanted outcomes associated with various drugs. Pharmacogenetic studies had reported that HLA genotype is the most common genetic factorwhich influences drug metabolism and the immune response. HLA genotype also increases the risk of drug induced hypersensitivitycausing SJS/TEN. [7]Chung et al and Tassaneeyakulet al reported strong association between HLA-B*1502 and CBZ

in the Han-Chinese, Thai, and Malaysian populations.[8, 9]They suggested to use it as a genetic marker. The studies performed in Indian populationalso showed HLA-B*1502 as a significant risk predictor of carbamazepine related SJS/TEN,2.5% of the North Indian population under study was reported to be the carrier of HLA-B*1502 allele.[10,11]Out of eight patients studied for the genotype, six patients were found to have the HLA-B*1502 allele in Indian population. [12]

Study conducted on Han Chinese population demonstrated an association between HLA-B*1502 allele and oxcarbazepine-inducedMaculo-papular-exanthema (MPE) also apart from CBZ. The risk ofOXC-induced MPE was significantly higher in the patients with theHLA-B*1502 allele, with an OR of 8.8 (95% CI: 1.853–41.790,P = 0.011). Furthermore, they also observed a higher frequency ofHLA-B*1502 allele in patients with OXC-induced MPE compared toOXC-tolerant controls.[5]Hung et alstudied HLA-B*1502 susceptibility to three different antiepileptic drugs, phenytoin (PHT), lamotrigine (LTG) and oxcarbazepine (OXC), which have structure similarity to CBZ.They found that HLA-B*1502 was present in eight out of 26 (30.8%) Phenytoin induced-SJS/TEN (OR: 5.1; 95% CI: 1.8-15.1; p = 0.0041), two out of six (33%) Lamotrigine induced -SJS (odds ratio [OR]: 5.1; 95% CI: 0.8-33.8; p = 0.1266) and three out of three (100%) OXC induced -SJS (OR: 80.7; 95% CI: 3.8-1714.4; p = 8.4 x 10(-4)) patients. They suggested that these drugs share structural similarity with CBZ and share a common risk allele for causing SJS/TEN.[3]

Results from several studies had indicatedHLA-B*1502 allele to be strongly associated with increased risk of developing SJS and TEN in patients receivingAEDs especiallyAsians.Thus,facilities should be developed for screening of HLA-B*1502 in the high-risk genetically susceptible individual, before prescribing these drugs.

CONCLUSION

Our study included a very small sample size as incidence of SJS/TEN is very low. Multi-centric screening studies including large number of patients of this age groupmust be conducted to confirm the association of HLA-B*1502 and AED induced SJS/TEN in Indian population.This will help in policy making for preventing life-threateningdisease such as SJS/TEN and for understanding the potential of using genetic markers as a screening tool before prescribing thearomatic AED to a patient, which might make them susceptible of developing SJS/TEN.

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CONFLICT OF INTEREST: None

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