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Association of Hla-B*1502 Alleles with Carbamazepine-Induced Stevens-Johnson Syndrome / Fixed Drug Eruption in South Indian Population of Tamil Nadu

C. Justin[1], Maheshkumar Poomarimuthu[2], Ramajayam Govindan[3]

[1]Professor, Department of Neurology, Madurai Medical College, India.

[2]Scientist – B, Multidisciplinary Research Unit, Madurai Medical College, Madurai, Tamil Nadu, India.

[3]Scientist – C, Multidisciplinary Research Unit, Madurai Medical College, Madurai, Tamil Nadu, India.

Corresponding Author: Dr. C Justin, Professor, Department of Neurology, Madurai Medical College Madurai 625020, India.

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KEYWORDS

Adverse Reactions; anticonvulsants; carbamazepine; skin diseases

ABSTRACT:

Background: Carbamazepine-induced Stevens-Johnson Syndrome (SJS) and Fixed Drug Eruption (FDE) represent severe cutaneous adverse reactions with a potential genetic predisposition. This study investigated the association between the HLA-B*1502 allele and carbamazepine-induced SJS/FDE in the South Indian Tamil population.

Methods: Our study employed a rigorous prospective case-control design conducted from January 2022 to December 2023 at a tertiary care hospital in Tamil Nadu. The study included 100 patients: 50 cases with carbamazepine-induced SJS/FDE and 50 controls without adverse reactions. HLA-B*1502 genotyping, a key component of our methodology, was performed on all participants. Our statistical analysis, which included the Haldane-Anscombe correction for odds ratio calculation and Fisher's exact test for significance, further ensured the robustness of our findings.

Results: The study population had a mean age of 37.4 ± 16.9 years, with 52 females and 48 males. HLA-B*1502 was positive in 7 patients (14%) from the case group, while none in the control group carried the allele. This association was statistically significant (p=0.012). The odds ratio analysis using Haldane-Anscombe correction showed that HLA-B*1502 positive individuals had 17.41 times higher odds of developing SJS/FDE (95% CI: 0.97-313.73).

Conclusions: Our study has revealed a significant association between HLA-B 1502 and carbamazepine-induced SJS/FDE in the South Indian Tamil population. These findings strongly advocate for the implementation of HLA-B 1502 screening before carbamazepine therapy, particularly in females and patients aged 21-40. The study also brings to light the underreported association between carbamazepine and FDE, emphasizing the potential impact of our recommendations on clinical practice.

INTRODUCTION

Carbamazepine (CBZ), an anticonvulsant medication widely used in the management of epilepsy and neuropathic pain, is known to cause severe cutaneous adverse reactions (SCARs), including Stevens-Johnson Syndrome (SJS) and Fixed Drug Eruption (FDE)[(1)]. The SJS is a life-threatening condition characterized by extensive skin detachment. At the same time, FDE presents as localized skin lesions that reappear at the same site upon re-exposure to the offending drug. The incidence of SJS is one to six cases per million person-years[(1)]. The incidence of these reactions is particularly concerning in populations with specific genetic predispositions. A significant association between the human leukocyte antigen HLA-B*1502 allele and CBZ-induced SJS has been established, especially among Asian populations. Studies in populations from

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Malaysia, Thailand, and Hong Kong have also reported an association between HLA-B*1502 and SJS induced by CBZ [2–4]. In India, where CBZ is given extensively, understanding the genetic factors contributing to these adverse reactions is crucial. Researchers have extensively studied SJS, and they increasingly recognize FDE as a significant adverse reaction to CBZ. FDE typically presents as well-defined erythematous plaques that can evolve into vesicles or bullae and recur upon re-exposure to the drug(5). T cells mediate the immune response involved in the pathophysiology of FDE, which genetic factors such as HLA alleles may also influence[5]. For the morbidity and mortality associated with these conditions, developing screening facilities for HLA-B*1502 before prescribing CBZ to patients with seizures or neuropathic pain is essential. The present study aims to investigate the association between the HLA-B*1502 allele and CBZ-induced SJS/FDE in the South Indian population of Tamil Nadu, with the broader goal of understanding the relationship between HLA-B allelic variations and carbamazepine-induced cutaneous adverse drug reactions (CBZ-CADRs) in this specific ethnic group.

MATERIALS AND METHOD

Study population

A prospective case-control study was conducted from January 2022 to December 2023 at the outpatient departments of Neurology and Dermatology, Venerology, and Leprosy in a tertiary care hospital in Tamil Nadu. The study included patients diagnosed with SJS or FDE, confirmed by a dermatologist based on clinical morphology. The CBZ was identified as the causal drug for SJS/FDE if cutaneous symptoms emerged within the first three months of exposure and resolved upon withdrawal. We recruited patients who had taken CBZ for at least three months without experiencing cutaneous reactions as controls from the same hospital. We excluded patients who experienced adverse drug reactions (ADRs) related to CBZ, SJS/FDE from other drugs or had pre-existing skin conditions such as psoriasis or contact dermatitis. One hundred patients were included in the study, comprising 50 in the case group and 50 in the control group. The Institutional Ethics Committee approved the study performed by the Helsinki Declaration.

Data collection

All patients provided written informed consent. We interviewed participants about the ethnic background of their biological parents and grandparents. We collected patient data, including baseline demographics, past medication history, and any prior ADRs. Blood samples were collected from the study population. We performed molecular analyses at the Multidisciplinary Research Unit, Madurai Medical College, Madurai.

HLA-B*15:02 Genotyping

3ml of blood samples were collected in an EDTA tube from cases and controls and subjected to DNA extraction using a DNA isolation kit (Qiagen, Germany). Genotyping of HLA-B*15:02 was performed by QuantStudio 5 Real-Time PCR System (Applied Biosystems, USA) using HELINI HLA B15:02 Real-time PCR Kit (HELINI Biomolecules, India) according to the manufacturer's instructions.

Statistical analysis

Statistical analysis were conducted utilizing R software (version 4.3.3; Vienna, Austria, 2024). Continuous variables are reported as mean ± standard deviation, while categorical variables are represented as numbers and percentages. The Haldane-Anscombe correction was applied to calculate odds ratios (OR), and Fisher's exact test determined 95% confidence intervals (CI). All statistical analyses were two-sided, and $P < 0.05$ was considered statistically significant.

RESULTS

The study population included 100 patients with a mean age of 37.4 ± 16.9 years. The gender distribution was nearly equal, with 52 females and 48 males. HLA-B*1502 genetic testing revealed that seven patients were positive for the allele, while 93 patients were negative. Among the population, 50 patients developed CBZ-CADR in the form of SJS/FDE, while the remaining 50 patients showed no adverse reactions.

Table 1: Demographic and clinical characteristics of patients on carbamazepine therapy

Variables	N=100 patients
Age, years	37.4 ± 16.9
Female	52

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Male	48
HLA-B*15:02	
Positive	7
Negative	93
Type of CBZ-CADR	
SJS/FDE	50
NIL	50

The data are represented as n.

CBZ-CADR: Carbamazepine-Induced Cutaneous Adverse Drug Reactions; FDE: Fixed Drug Eruption; SJS: Stevens-Johnson Syndrome

Table 1 describes the demographic and clinical characteristics of patients on CBZ therapy. We found a significant association between HLA-B*1502 and CBZ-CADR among the 100 South Indian Tamil Nadu patients prescribed CBZ in **Table 2**.

Table 2: Association between HLA-B*15:02 and CBZ-induced SJS/FDE

HLA-B*15:02	Case n=50 patients	Control n=50 patients	P-value
Positive	7 (14.0)	0 (00.0)	0.012
Negative	43 (86.0)	50 (100)	

The data are represented as n (%). P value <0.05 was considered statistically significant.

CBZ-CADR: Carbamazepine; FDE: Fixed Drug Eruption; SJS: Stevens-Johnson Syndrome

In the case group of 50 patients who developed SJS/FDE, seven patients (14.0%) were positive for HLA-B*1502, while none of the 50 tolerant controls carried this allele. The remaining 43 patients (86.0%) in the case group and all 50 patients (100%) in the control group were negative for HLA-B*1502. This association was statistically significant (p=0.012), suggesting that HLA-B*1502 may be a potential genetic marker for CBZ-CADR in the South Indian Tamil population.

Table 3: Association between HLA-B*15:02 and CBZ-induced SJS/FDE using the Haldane-Anscombe correction

HLA-B*15:02	Case n=50 patients	Control n=50 patients
Positive	7.5	0.5
Negative	43.5	50.5

OR=17.41 (95% CI: 0.97-313.73)

The data are represented as n.

CBZ-CADR: Carbamazepine; FDE: Fixed Drug Eruption; SJS: Stevens-Johnson Syndrome

The contingency **Table 3** was adjusted using the Haldane-Anscombe correction to address the presence of zero cells and ensure reliable statistical analysis. After applying this correction, seven of the 50 patients who developed SJS/FED were HLA-B*1502 positive, and 43 were negative. In the control group of 50 patients who tolerated CBZ, none were HLA-B*1502 positive, and all 50 were negative. The odds ratio analysis revealed that individuals who were HLA-B*1502 positive had 17.41 times higher odds of developing SJS/FED compared to those who were HLA-B*1502 negative (OR = 17.41, 95% CI: 0.97 – 313.73). However, the wide confidence interval, which includes 1, indicates that this association did not reach statistical significance at the 95% confidence level, likely due to the limited sample size in our study population.

DISCUSSION

This study investigates the association between the HLA-B*1502 allele and CBZ-induced SJS/ FDE in a South Indian population.

Demographic analysis of the present study population revealed a predominance of female patients, with a mean age of 37.4 years. This finding aligns with the broader literature, where studies have documented a wide age distribution for SJS cases ranging from 3 to 78 years. Notably, most reported cases fall within the 21–40-year age bracket, a pattern consistently observed across multiple countries[6]. The female preponderance observed in the present study is also consistent with international data, suggesting a potentially gender-influenced susceptibility to these adverse reactions[6,7].

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This demographic consistency across geographical boundaries provides valuable context for understanding the typical patient profile for SJS cases.

With the present study findings, it is important to note the significant history and prevalence of CBZ-induced SJS in India. The first documented case of HLA-B*1502 allele-associated adverse reaction to CBZ in India was reported in 2009(8), followed by a notable case series from Gujarat where HLA-B*1502 was present in 75% (6 out of 8) of patients who developed CBZ-induced SJS(1). Reports from other Asian countries, particularly Taiwan and Japan, also identify CBZ as a primary antiepileptic drug associated with SJS, aligning with this pattern[9].

The role of HLA-B*1502 as a genetic marker for CBZ-induced SJS has been well-documented across multiple studies. In the Indian population, the HLA-B*1502 allele frequency averages 2.5%, with some variation (as low as 0.6%) across different communities. This prevalence rate is particularly relevant compared to Chinese populations, where the association has been extensively studied[1]. Our current investigation revealed a statistically significant association (p=0.012) between HLA-B*1502 and CBZ-induced SJS/FDE in the South Indian Tamil population. These findings are corroborated by similar results from Thailand, where a case-control study demonstrated a strong correlation between HLA-B*1502 and CBZ-induced SJS in patients treated for neuropathic pain[10]. The present study uses the Haldane-Anscombe correction to show an odds ratio (OR) of 17.41 (95% CI: 0.97-313.73) for the association between HLA-B*1502 and CBZ-induced SJS/FDE. This suggests a potentially increased risk of SJS/FDE in individuals with the HLA-B*1502 allele when taking CBZ. Similarly study done by Tassaneeyakul *et al.* [11] observed CBZ-induced SJS/TEN was significantly higher in the patients with HLA-B*1502, with an odds ratio (OR) of 54.76 [95% confidence interval (CI) 14.62-205] study by Amstutz *et al.* [12]reported an odds ratio OR of 38.6for the risk of CBZ-induced SJS/TEN in patients with HLA-B*1502**.**

The FDEs induced by CBZ are not extensively discussed in the literature[13]. Many reviews on FDEs do not prominently feature CBZ, and there are relatively few reported cases of CBZ-induced FDE[13]. This contrasts with the present study, demonstrating a clear association between CBZ and FDE in the studied population. The existing literature often highlights analgesics and antibiotics as common culprits in FDE. In contrast, this study and other case reports emphasize that CBZ can cause FDEs through distinct immunological mechanisms[13]. The study's findings, along with supportive case reports[13,14)(5], underscore the importance of considering CBZ as a potential cause of FDE despite its underrepresentation in broader reviews of drug-induced skin reactions.

Based on the present study, we recommend beginning with a low starting dose of CBZ and implementing a gradual dose escalation protocol to minimize the risk of adverse reactions. Provide detailed patient education about potential symptoms of SJS/FDE and create clear documentation of informed consent. Schedule frequent initial follow-up appointments during the first few weeks of therapy to monitor for any early signs of adverse reaction. Given their higher risk profile, exercise additional caution when prescribing to females and patients in the 21-40 age group. Consider alternative medications for patients who test positive for HLA-B*1502 or have a history of adverse drug reactions.

LIMITATIONS

The study had several limitations. The small sample size may have affected the statistical power, as evidenced by the wide confidence interval in the odds ratio analysis. The single-center nature of the study might limit the generalizability of findings to the broader South Indian population. While significant, the absence of HLA-B*1502-positive individuals in the control group suggests the need for more extensive population studies to validate these findings. The study's two years might not have captured long-term adverse reactions or seasonal variations in drug response.

CONCLUSION

In conclusion, there is a significant association between the HLA-B*1502 allele and CBZ-induced SJS/FDE in the South Indian Tamil population. The findings support the potential value of HLA-B*1502 screening before initiating CBZ therapy, particularly in female patients and those aged 21-40. The study also highlights the previously underreported association between CBZ and FDE, contributing new insights to the existing literature. The odds ratio suggests a substantially increased risk for adverse reactions in HLA-B*1502-positive individuals.

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