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Research Article

Study to assess the prevalence of human leukocyte antigen-A*3101 allele among Indian epileptic patients and its influence on safety and efficacy of antiepileptic therapy

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ABSTRACT

Background: The objective was to study the prevalence of human leukocyte antigen (HLA)-A*3101 allele among epileptic patients and to assess the safety and efficacy of antiepileptic therapy.
Methods: 295 subjects were selected and divided into two groups, Group I had 192 epileptic patients and Group II had 103 normal healthy controls. After written informed consent, 30 ml of mouthwash sample was collected from each subject and DNA was extracted by standard salting-out technique and used for HLA-A*3101 genotyping by two-step nested allele-specific polymerase chain reaction amplification and agarose gel electrophoresis.
Results: In Group I, 12 (6.25%) of the 192 patients were tested positive for HLA-A*3101 allele and all were taking carbamazepine (CBZ). Among them, 56 (30%) subjects had developed less severe adverse effects such as headache and giddiness, skin rashes and memory disturbances, and HLA-A*3101 was present in 8 of them while 136 had no adverse effects in which 4 of them were tested positive for the allele. In Group II, 3 (2.9%) of the 103 healthy controls were tested positive for the allele. No difference was found in response to antiepileptic therapy between allele positive and negative patients.
Conclusion: The present study had shown that HLA-A*3101 is prevalent in 6.25% of the Indian epileptic population under study. The presence of this allele has a significant association with the development of mild cutaneous reactions like skin rashes. However, no difference was observed in allele positive patients in response to antiepileptic therapy in comparison with allele negative patients.

Keywords: Human leukocyte antigen-A*3101, Carbamazepine, Rashes, Genotyping

INTRODUCTION

World Health Organization has defined an adverse drug reaction (ADR) as "any noxious, unintended, and undesired effect of a drug, which occurs at doses normally used in humans for prophylaxis, diagnosis or therapy of disease, or for the modification of physiological function."

United States Food and Drug Administration (USFDA) has defined an ADR as "any events relating to drugs or devices in

which the patient outcome is death, life-threatening (real risk of dying), hospitalization (initial or prolonged), disability (significant, persistent, or permanent), congenital anomaly, or required intervention to prevent permanent impairment or damage."

ADR is identified as the fifth leading cause of death among all diseases and responsible for 5-8% of all hospitalizations worldwide.[1] ADRs are classified into two types: Non immunological and immunological based on the etiology.[2]

Non immunological ADRs are more common and predictable because of the known mechanisms of actions of drugs and account for 75-80% of ADRs. Immunological ADRs, which account for 20-25%, are unpredictable and responsible for true hypersensitivity reactions. Skin is the most frequently involved target organ in immunological reactions.[3] Cutaneous ADRs (CADRs) constitute 30-45% of all ADRS and account for 2% of hospitalizations.[4] CADR is defined as "any undesirable change in the structure or function of the skin, its appendages or mucous membranes and it encompass all adverse events related to drug eruptions, regardless of the etiology."[5]

No drug is absolutely safe. The manifestations of CADRs ranges from mild erythematous maculopapular skin rashes to rare, more severe, potentially life-threatening CADRs with extensive mucosal, and epidermal involvement such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). Such severe CADRs (SCARS) account for 2-3% of all hospital admissions. Several drugs are at high risk of inducing SJS/TEN. These include antiepileptic drugs (carbamazepine [CBZ], phenytoin, phenobarbital, lamotrigine), antibiotics (sulfonamides, cotrimoxazole, penicillins, cephalosporins, quinolones), non-steroidal anti-inflammatory drugs (oxicams) and allopurinol. Among these drugs, SJS and TEN are more common with the drugs used for chronic therapy. SJS and TEN usually occur when the patients are exposed to cytochrome P450-inducing aromatic amine compounds like CBZ, phenytoin, phenobarbitone, and lamotrigine. The greatest risk of SJS/TEN are seen in the first 2 months of use.[6] Among the antiepileptic drugs, CBZ is the leading cause for SJS/TEN in India.[7-9]

The human leukocyte antigen (HLA) which is one of the most polymorphic genes in the human genome plays a central role in the immune response to antigens, and it has been hypothesized that specific HLA molecules may present the drug to specific T-cells, which subsequently triggers an immune response. Two of such variants in the HLA gene namely HLA-B*1502 which was first reported in Han Chinese patients and HLA-A*3101, which has been reported in Japanese and European Caucasians are associated with high risk of getting CBZ induced SCADRs such as SJS and TEN. It is believed that CBZ form immune complexes with HLA proteins and thus activates T-cell mediated immune responses. The association between HLA-B*1502 and SJS, TEN have been well established whereas, the association of HLA-A*3101 allele with maculopapular rashes, SJS, TEN, HSS have not been well-established in Indian population. Hence, this study was carried out to find the prevalence of HLA-A*3101 allele, as well as the association with ADRs in epileptic subjects on treatment.

METHODS

The study was conducted after getting approval from Institutional Human Ethics Committee. Order No: IHEC/05/2013/Desp.No.264/Dt: 27.11.2013.

Patient recruitment and sample collection

A total of 295 subjects were recruited for the study and divided into two groups, Group I consisted of 192 epileptic patients who were attending the epilepsy clinic during the study period and Group II consisted of 103 normal healthy controls were the common public who were visiting the study site along with patients and they were not suffering from epilepsy. After getting written informed consent, 30 ml of mouthwash sample was collected from each subject and the DNA was extracted by standard salting-out method (Miller et al.).

*HLA-A*3101 genotyping*

HLA-A*3101 genotyping was done by two-step nested allele-specific Polymerase Chain Reaction (PCR) method. The primer set (forward: HLA-AF 5'-GAGGGTCG GGCRGGTCTCAGCCA-3' and reverse: HLA-AR 5'-GGGYGATATTCTAGTGTTG GTCCCAATTGT-3') for the first PCR was designed specifically to amplify the HLA-A locus. The first PCR was performed in a reaction mixture of 10 μL containing 20 ng of genomic DNA, 1.5 mM $MgCl_2$, 0.2 μM dNTPs, 0.3 μM of each primer. PCR conditions were 96°C for 1 mins, followed by 33 cycles of 98°C for 10 sec, 70°C for 30 sec, 72°C for 45 sec followed by extension at 72°C for 5 mins. PCR products were visualized by ethidium bromide under UV irradiation with 1.5% agarose gel electrophoresis.

The final PCR products of the first PCR were taken and then diluted 30 times with sterilized milliQ water and was used as a template for the second nested allele-specific PCR. The primer set (forward: A3101 F 5'-CCACTCCATGAGGTATTTCA-3' and reverse: A3101 R 5'-CTCGCTCTGGTTGTAGTAG-3') for the second PCR was designed specifically to amplify the HLA-A*3101. The second PCR was carried out in a reaction mixture of 10 μL containing 2 μL of diluted first PCR product, 1.5 mM $MgCl_2$, 0.2 μM dNTPs, 0.5 μM of each primer. The second PCR conditions were 94°C for 3 min, followed by 30 cycles of 95°C for 20 sec, 63°C for 20 sec, 72°C for 20 sec followed by extension at 72°C for 10 min. The PCR products were visualized by ethidium bromide under UV irradiation with 2% agarose gel electrophoresis.

RESULTS

There were 106 males and 86 females in Group I with a mean age of 36.06±13.86 years and 32.49±10.62 years respectively. In Group II, there were 81 males with a mean age of 36.58±10.66 years and 22 females with a mean age of 36.09±7.72 years.

In Group I, 12 (6.25%) of the 192 patients were tested positive for HLA-A*3101 allele and all of them were taking CBZ as monotherapy or in combination therapy. In the allele negative subjects (180 patients), the most commonly used drug was sodium valproate, which was prescribed to 104 (58%) subjects either as monotherapy or combination therapy. In Group II, 3 (2.9%) of the 103 healthy controls were tested positive for the HLA-A*3101 allele.

Safety profile of antiepileptic therapy

The safety of the antiepileptic therapy was determined from the adverse effects of the drugs. This information was obtained by "recollection method." Among the 192 subjects, 56 (30%) of them developed adverse effects such as headache and giddiness, skin rashes, and memory disturbances while 136 (70%) had no adverse effects. Among the 56 subjects who developed adverse effects, HLA-A*3101 allele was present in 8 subjects and in the remaining 136 subjects who had no adverse effects, 4 of them were tested positive for the HLA-A*3101 allele. The incidence of adverse effects in the HLA-A*3101 positive groups is significantly higher when compared with the HLA-A*3101 negative groups. They are summarized below in Table 1.

Among the 8 HLA-A*3101 allele positive subjects who developed adverse effects, 4 of them developed rashes and 3 headaches and giddiness and one memory disturbance. The number of patients with mild cutaneous adverse reactions (rashes) in HLA-A*3101 positive groups is significantly higher compared to HLA-A*3101 negative groups. The subgroup analysis of association of the HLA-A*3101 allele with the adverse effects are given below in Table 2.

Response to anti-seizure therapy

The response to the anti-seizure therapy showed that 46 (22%) of 192 subjects had seizure control for 1-year, and all of them were taking CBZ as monotherapy or in combination therapy. The overall response rate was 10%. The subgroup analysis of association of the HLA-A*3101 allele with the seizure frequency per month are given below in Table 3.

DISCUSSION

HLA-B*1502, a predictor of CBZ-induced hypersensitivity reactions in Asian population, seems to be specific in

Table 1: Comparison of incidence of adverse effects between HLA-A*3101 positive and negative patients.

Adverse effects	Number of patients positive for HLA-A*3101 allele (%)	Number of patients negative for HLA-A*3101 allele (%)	p-value
Present	8 (66.7)	48 (26.7)	0.0062**
Absent	4 (33.3)	132 (73.3)	

**Statistical analysis were done using Fisher's exact test and found that p value was significant. HLA: Human leukocyte antigen

Table 2: Frequency analysis of various adverse effects between HLA-A*3101 positive and negative patients.

Adverse effects	No of patients positive for HLA-A*3101 allele (%)	No of patients negative for HLA-A*3101 allele (%)	Total	p-value
Rashes	4 (50)	5 (10.4)	9	0.0173*
Headache and giddiness	3 (37.5)	28 (58.3)	31	0.4447
Memory problem	1 (12.5)	8 (16.7)	9	1
Others	0	7 (14.6)	7	

*Statistical analysis were done using Fisher's exact test and found that p value was significant. HLA: Human leukocyte antigen

Table 3: Frequency analysis of seizure attack per month between HLA-A*3101 positive and negative patients.

Seizure frequency per month	No of patients positive for HLA-A*3101 allele (%)	No of patients negative for HLA-A*3101 allele (%)	p-value
Controlled (past 1 year)	2 (16.7)	44 (24.4)	0.7607
0-1 per month	4 (33.3)	51 (28.3)	
1-3 per month	4 (33.3)	60 (33.3)	
3-5 per month	2 (16.7)	25 (14)	

Statistical analysis were done using Chi-square test for trend and found that there were no statistical difference observed. HLA: Human leukocyte antigen

predicting only the development of SCADRs such as SJS/TEN, but not for the development of mild reactions such as maculopapular eruptions. This finding led to the suggestion that these reactions have different etiology or genetic predictors.

Chung and his colleagues were the first to identify the association between HLA-B*1502 and SJS/TEN in Han Chinese Taiwan population in the year 2004.[10] Several studies from Han Chinese populations have also confirmed the association of HLA-B*1502 with SJS/TEN.[11-16] This finding eventually led the USFDA to recommend genetic screening for HLA-B*1502 in most patients of Asian ancestry before starting on CBZ therapy. This association of HLA-B*1502 and SJS/TEN was also confirmed in other Asian populations such as Thai,[17-19] Malaysian[20,21] and Indian[22,23] population. However, such association has not been found in Japanese[24,25] or Korean[26,27] population. It is noteworthy to mention that HLA-B*1502 is a risk factor only for SJS/TEN, but not for other types of CADRS and it is also ethnic specific restricted only to patients of Asian origin.

HLA-A*3101 was first identified as a possible risk genotype for CBZ induced maculopapular eruptions in Han Chinese patients in the year 2006. Subsequently, the association of HLA-A*3101 with the development of SJS/TEN as well as maculopapular eruptions has been documented in Japan,[28,29] Europe,[30] Korea[31] and Canada[32] population. However, there are limited evidences to support the recommendation of screening for HLA-A*3101 allele before starting on CBZ therapy. Studies also reveal that HLA A*3101 appears to be a specific marker only for CBZ-induced hypersensitivity reactions and not for phenytoin or lamotrigine induced hypersensitivity reactions.[33]

This study has shown that most of the patients had mild cutaneous hypersensitivity reaction like rashes. More serious, life-threatening cutaneous reactions like SJS/TEN were not seen in any of the study population. The prevalence rate of HLA-A*3101 allele was found to be 6.25% (12/192) among the epileptics whereas it is about 2.9% (3/103) in general population which is much lower compared to the prevalence of this allele in Japanese population (Kaniwa et al. 2011 – 16.8%, Kashiwagi et al. 2008 – 14.3%).

Among the 192 epileptic subjects, 81 patients (42.2%) were taking CBZ either as monotherapy or in combination with other antiepileptic drugs. Among these 81 patients, 29 had adverse effects (CBZ-intolerant), and 52 patients had no adverse effects (CBZ-tolerant). The HLA-A*3101 allele was present in 8 (27.6%) out of 29 patients who were intolerant to CBZ whereas, this allele is present only in 4 (7.7%) out of the 52 patients who were CBZ-tolerant. When compared with the prevalence rate of this allele in Han Chinese (Hung et al. 2006), European Caucasians (Mccormack et al. 2011) Japan (Ozeki et al. 2011, Niihara et al. 2012), Korea (Kim et al. 2011) and Canada (Amstutz et al. 2013) population, the rate is high among both the CBZ intolerant and CBZ tolerant groups.

The overall prevalence rate of HLA-A*3101 in the total study population (295 subjects) is 5.08% (15/295) whereas a frequency of 18.9% was observed in normal population in Tamil Nadu Nadar caste (as mentioned in the allele frequency database). This high prevalence rate of HLA-A*3101 allele among the Nadar caste in Tamil Nadu[34-36] and other castes from different states in India[37] indicates that ethnicity or racial differences could play a major role to the prevalence of HLA-A*3101 allele.

CONCLUSION

The present study has shown that HLA-A*3101 is prevalent in 6.25% of the Indian epileptic subjects. The prevalence rate of the HLA-A*3101 allele in patients who were CBZ intolerant is 27.6%, whereas in CBZ tolerant patients it is found to be 7.7%. The presence of this allele is found to have a significant association with the development of mild cutaneous reactions like skin rashes. However, the more serious, life-threatening cutaneous reactions like SJS/TEN are not observed in our study population. Since there is a strong correlation between HLA-A*3101 allele with CADRs, estimation of HLA-A*3101 before starting on antiepileptic drugs may forewarn the treating physicians and the patients about the CADRs and the need for early treatment. This could prevent the complications that might occur due to CADRs as well as reduce the drug-related anxiety among the subjects. However, further studies in larger population are needed to ascertain the causal relationship between the prevalence of HLA-A*3101 and the occurrence of CADRs.

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