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Original Article

Lamotrigine-Related Skin Side Effects Were Associated with some HLA-B Alleles in Iranian Epileptic Patients

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ABSTRACT

Background: Recent evidences revealed that some genetic factors strongly predict occurrence of lamotrigine (LTG)-related skin reactions. The present study aimed to assess the association between some human leukocyte antigen (HLA)-B alleles and risk of LTG-related skin reactions among a sample of epileptic patients.

Methods: Totally, 36 epileptic patients expressing LTG-related skin reactions and 70 sex- and age-matched healthy individuals were enrolled into this case-control study. Blood samples were collected from all participants and genomic DNA was extracted by salting-out method. HLA-B alleles were determined using standard sequence specific primer-PCR (SSP-PCR) technique.

Results: Of the 31 HLA alleles assessed in our survey, the frequencies of HLA-B*38 and HLA-B*40 were significantly higher in epileptic patients with LTG-related skin reactions when compared to the control group. In term of gender, the frequency of HLA-B*40 allele was significantly higher in the epileptic men with LTG-related skin reactions, whereas the frequency of HLA-B*38 allele was significantly higher in the epileptic women with LTG-related skin reactions than controls with the same gender. Moreover, the frequency of HLA-B*38 allele in patients with high grade of LTG-related skin side effects was significantly higher than patients with low grade of LTG-related skin side effects.

Conclusion: These results indicated possible association between HLA-B*40 and HLA-B*38 alleles and LTG-induced skin lesions in Iranian epileptic patients. HLA-B*40 and HLA-B*38 alleles might be differentially expressed in male and female epileptic patients with LTG-induced skin lesions.

Keywords: Epilepsy, Lamotrigine, HLA-B alleles, Skin reactions

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Introduction

Epilepsy is considered as the most prevalent neurological disorders and one of the most important health issues that that involves 0.5-1% of the population (1,2). The prevalence of active epilepsy is 7.87/1000 in Kerman city/ southeast of Iran (3). Lamotrigine (LTG) is one of the new anti-epileptic drugs with less cognitive impairment and overt sedation effects compared with other medications (4).

LTG acts as a weak dihydrofolate reductase inhibitor and was first introduced in the early 1980s and then approved by Food and Drug Administration in 1995 (4,5). Pharmacologically, LTG stabilizes presynaptic neuronal membranes by influencing the voltage-sensitive sodium channels as well as the releasing of some neurotransmitters, including aspartate and glutamate from presynaptic regions (6,7). The anti-epileptic action of LTG also take part through the suppression of N- and P-type calcium currents in cortical neurons, at the synaptic level (7). LTG is also administrated for the treatment of the different patterns of seizures (including focal, absence, and tonic-clonic seizures) and juvenile myoclonic epilepsy (8,9).

It should be noted that a number of adverse side effects have been attributed to LTG. Some non-serious side effects such as headache, nausea, vomiting, dizziness, ataxia, and tremor were considered as not life-threatening effects. However, some important and rare side effects with life-threatening consequences such as unexpected death in epilepsy, death in pregnancy period, aseptic meningitis, toxic epidermal necrolysis and Stevens-Johnson syndrome were associated with LTG medication (10,11). Skin rash is a common consequence for terminating the treatment with LTG, particularly when occurs simultaneously with systemic reactions including eosinophilia, lymphadenopathy, neutropenia, leukopenia and even dystonia (12-15).

Interestingly, recent evidences indicated that a number of genetic parameters strongly predict the occurrence of the LTG-related skin reactions. In this regard, the role of human leukocyte antigens (HLA), especially HLA-B genes, in predisposing of LTG-related skin reactions is now highlighted (16). It has been reported that specific HLA alleles increase the risk of drug-related hypersensitivity reactions (17). The HLA molecules present the antigenic peptides to helper T (Th) cells and cytotoxic T lymphocytes (CTL), and play a fundamental role in the regulation of the immune responses (18,19). Drugs may interact with HLA molecule and/or T cell receptor (TCR) and create neoantigens leading to HLA-TCR ligation and T cell activation (20). It has been reported that some anti-epileptic drugs, including carbamazepine, phenytoin, or lamotrigine bind to HLA molecules and then activate CD8+ T lymphocytes leading to the abnormal expansion of T cells (21). The association of the LTG-related skin reactions with HLA has been demonstrated in some investigations from different countries (22-24). However, there is no reports concerning the association of the LTG-related skin reactions with HLA in Iranian population. Therefore, this study conducted for the first time to assess the association of the LTG-related skin reactions with HLA-B alleles in a sample of epileptic patients from Kerman city placed in south-east of Iran.

Materials and Methods

Subjects

From January 2015 to January 2017, 36 epileptic patients with LTG-induced cutaneous reactions (12 men and 24 women, age range: 25 to 50 years) referred to Shafa Hospital of Kerman (a city placed in southeast of Iran) were enrolled into this case-control study. The presence of epilepsy was confirmed by an expert neurologists. The epileptic patients were treated with LTG by a daily dose of 200 mg. In addition to the treatment with LTG, 13 epileptic patients were also treated with Valproate by a dose of 50 mg, daily. The LTG-related skin reactions were emerged within 6 weeks after the initiation of the medication and were disappeared following the discontinuation of treatment.

According to the severity of skin reactions, the patients were classified as patients with low grade of LTG-related skin reactions (n= 26) and high grade of LTG-related skin reactions (n= 10). In low grade patients, less than 10.0% of their body surface was affected while in the high grade patients, ≥10.0% of their body surface was involved.

All baseline information including demographics, dose of lamotrigine and other clinical characteristics were collected. Those who were treated with other drugs that had cross-reactivity with lamotrigine or those with skin disorders before prescribing lamotrigine were excluded from the investigation. A second sex- and age-matched group consisting 76 healthy individuals without a history of drug-related sensitization who were candidate for organ donation was also selected as the control. Control individuals were in good health without history of allergic disorders and without history of adverse drug reactions. Furthermore, the control group had no neurological disorders, cardiovascular disease, diabetes mellitus, renal failure, pulmonary diseases, neoplasia and any suspicious immunologic disorders. This study was evaluated and approved by the Ethical Committee of Kerman University of Medical Sciences (Ethical approval number: IR.KMU.REC.1396.2507, Grant number:940094). Moreover, patients were recruited if they agreed for blood sampling. Five milliliters of peripheral blood sample was taken from all participants for HLA genotyping.

HLA-B genotyping

DNA was extracted from peripheral blood leukocytes by salting out method as previously described by Miller *et al*. (25). The quantity and the purity of DNA samples were determined by measuring the optical density at 260 and 280 nm wavelengths using spectrophotometry (Ependorf, Germany). To determine HLA-B alleles, the blood samples were collected in an EDTA and then the genomic DNA was extracted by salting-out method. The HLA-B alleles were determined by standard sequence specific primer-PCR (SSP-PCR) technique using commercial OLERUP SSP-PCR kits (GenoVision Inc., West Chester, Pennsylvania, USA).

Statistical analyses

Chi-square test was used to assess the differences of the HLA-B allele frequencies between LTG-sensitive and control groups. P values of <0.05 were considered statistically significant. Data analysis was performed using SPSS software version 22.0 (SPSS, Chicago, IL, USA).

Results

The distribution of the HLA-B alleles in LTG-sensitive and control groups has been summarized in Table 1. The frequency of HLA-B*16 in LTG-sensitive patients was markedly higher than that in the control group but the difference was not statistically significant (P=0.06). The frequency of HLA-B*38 allele (a split of HLA-B16) in LTG-sensitive patients was significantly higher than that in the control individuals (P<0.01). The HLA-B*38 allele was associated with a higher risk of LTG-related skin reactions [OR: 5.85 (95% CI: 1.12–30.30)]. The frequency of HLA-B*40 allele in LTG-sensitive patients was also significantly higher in comparison to control individuals (P<0.05). The HLA-B*40 allele was associated with a higher risk of LTG-related skin reactions [OR: 52.59 (95% CI: 1.01– 8.06)].

HLA-B40 is composed of the HLA-B60 and HLA-B61 splits. The frequencies of HLA-B*60 and HLA-B*61 were respectively 2.80% and 19.70% in LTG-sensitive patients. None of the control subjects were positive for HLA-B*60 and HLA-B*61 alleles. The significant difference in the frequency of the HLA-B*40 allele between LTG-sensitive patients and control group may largely attributed to the HLA-B*61 distribution rather than HLA-B*60 (Table 1).

Table 1: Distribution of the HLA-B alleles in LTG-sensitive and control groups and according to their gender

HLA-B alleles	Total subjects (n=106)		P values	Men=50		P value	Women=56		P value
	LTG-sensitive group (n=36)	Control group (n=70)		LTG-sensitive men (n=12)	Control (n=38)		LTG-sensitive women (n=24)	Control (n=32)	
B5	13 (36.1%)	19 (27.1%)	0.34	5 (41.7%)	10 (26.3%)	0.31	8 (33.3%)	9 (28.1%)	0.67
B7	3 (8.3%)	6 (8.6%)	0.97	1 (8.3%)	2 (5.3%)	0.7	2 (8.3%)	4 (12.5%)	0.62
B8	5 (13.9%)	15 (21.4%)	0.35	1 (8.3%)	10 (26.3%)	0.19	4 (16.7%)	5 (15.6%)	0.92
B12	4 (11.1%)	3 (4.3%)	0.18	1 (8.3%)	1 (2.6%)	0.38	3 (12.5%)	2 (6.2%)	0.42
B13	1 (2.8%)	8 (11.4%)	0.13	0 (0.0%)	5 (13.2%)	NC	1 (4.2%)	3 (9.4%)	0.45
B14	0 (0.0%)	7 (10.0%)	0.09	0 (0.0%)	1 (2.6%)	NC	0 (0.0%)	6 (18.8%)	NC
B15	1 (2.8%)	5 (7.1%)	0.36	0 (0.0%)	3 (7.9%)	NC	1 (4.2%)	2 (6.2%)	0.73
B16	7 (19.4%)	5 (7.1%)	0.06	3 (25%)	3 (7.9%)	0.11	4 (16.7%)	2 (6.2%)	0.21
B17	4 (11.1%)	3 (4.3%)	0.18	0 (0.0%)	1 (2.6%)	NC	4 (16.7%)	2 (6.2%)	0.21
B18	4 (11.1%)	15 (21.4%)	0.19	2 (16.7%)	8 (21.1%)	0.74	2 (8.3%)	7 (21.9%)	0.17
B21	2 (5.6%)	6 (8.6%)	0.58	0 (0.0%)	3 (7.9%)	NC	2 (8.3%)	3 (9.4%)	0.89
B22	3 (8.3%)	12 (17.1%)	0.22	2 (16.7%)	6 (15.8%)	0.94	1 (4.2%)	6 (18.8%)	0.10
B27	0 (0.0%)	1 (1.4%)	NC	0 (0.0%)	1 (2.6%)	NC	0 (0.0%)	0 (0.0%)	NC
B35	9 (25%)	15 (21.4%)	0.68	1 (8.3%)	9 (23.7%)	0.25	8 (33.3%)	6 (18.8%)	0.21
B37	1 (2.8%)	1 (1.4%)	0.63	1 (8.3%)	1 (2.6%)	0.38	0 (0.0%)	0 (0.0%)	NC
B38 (B16)	6 (16.7%)	2 (2.9%)	0.01	2 (16.7%)	2 (5.3%)	0.2	4 (16.7%)	0 (0.0%)	0.042
B39 (B16)	2 (5.6%)	3 (4.3%)	0.77	1 (8.3%)	1 (2.6%)	0.38	1 (4.2%)	2 (6.2%)	0.73
B40	8 (22.2%)	6 (8.6%)	0.05	6 (50%)	4 (10.5%)	0.003	2 (8.3%)	2 (6.2%)	0.76
B41	0 (0.0%)	4 (5.7%)	NC	0 (0.0%)	2 (5.3%)	NC	0 (0.0%)	2 (6.2%)	NC
B44 (B12)	4 (11.1%)	3 (4.3%)	0.18	1 (8.3%)	1 (2.6%)	0.38	3 (12.5%)	2 (6.2%)	0.42
B49 (B21)	1 (2.8%)	6 (8.6%)	0.26	0 (0.0%)	4 (10.5%)	NC	1 (4.2%)	2 (6.2%)	0.73
B50 (B21)	1 (2.8%)	1 (1.4%)	0.63	0 (0.0%)	0 (0.0%)	NC	1 (4.2%)	1 (3.1%)	0.84
B51 (B5)	12 (33.3%)	16 (22.9%)	0.25	5 (41.7%)	8 (21.1%)	0.16	7 (29.2%)	8 (25%)	0.73
B52 (B5)	2 (5.6%)	3 (4.3%)	0.77	0 (0.0%)	2 (5.3%)	NC	2 (8.3%)	1 (3.1%)	0.39
B53	1 (2.8%)	4 (5.7%)	0.5	1 (8.3%)	4 (10.5%)	0.83	0 (0.0%)	0 (0.0%)	NC
B55 (B22)	3 (8.3%)	12 (17.1%)	0.22	2 (16.7%)	6 (15.8%)	0.94	1 (4.2%)	6 (18.8%)	0.1
B58 (B17)	4 (11.1%)	3 (4.3%)	0.18	0 (0.0%)	1 (2.6%)	NC	4 (16.7%)	2 (6.2%)	0.21
B59	0 (0.0%)	1 (1.4%)	NC	0 (0.0%)	0 (0.0%)	NC	0 (0.0%)	1 (3.1%)	NC
B60 (B40)	1 (2.8%)	0 (0.0%)	NC	1 (8.3%)	0 (0.0%)	NC	0 (0.0%)	0 (0.0%)	NC
B61 (B40)	7 (19.4%)	0 (0.0%)	NC	5 (41.7%)	0 (0.0%)	NC	2 (8.3%)	0 (0.0%)	NC

NC: not calculated

The distribution of the HLA-B alleles in LTG-sensitive and control groups according to their gender has also been summarized in Table 1. The frequency of HLA-B*40 allele in LTG-sensitive men was significantly higher compared to control men (50.0% versus 10.5%, P<0.003, odds ratio of 4.74 (95 CI: 1.15–16.61). No significant difference was observed between LTG-sensitive women and control women regarding the distribution of the HLA-B*40. Furthermore, no significant difference was observed between LTG-sensitive men and

LTG-sensitive women regarding the distribution of all investigated HLA-B alleles.

The distribution of the HLA-B alleles in LTG-sensitive patients according to the severity of skin side effects has been summarized in Table 2. As it is seen, the frequency of HLA-B*38 allele was significantly higher in LTG-sensitive patients with high grade of cutaneous side effects than in patients with low grade of the lesions (40.0% versus 7.70% versus, P<0.02, odds ratio of 5.20 (95% CI: 1.82 – 32.98).

Table 2: Distribution of the HLA-B alleles in LTG-sensitive group according to the severity of their reactions

B alleles	LTG-sensitive group (n=36)		P values
	Mild reactions (n=26)	Severe reactions (n=10)	
B5	8 (30.8%)	5 (50)%	0.28
B7	3 (11.5%)	0 (0.0%)	NC
B8	3 (11.5%)	2 (20%)	0.51
B12	4 (15.4%)	0 (0.0%)	NC
B13	1 (3.8%)	0 (0.0%)	NC
B15	1 (3.8%)	0 (0.0%)	NC
B16	3 (11.5%)	4 (40%)	0.05
B17	3 (11.5%)	1 (10%)	0.9
B18	3 (11.5%)	1 (10%)	0.9
B21	1 (3.8%)	1 (10%)	0.47
B22	2 (7.7%)	1 (10%)	0.82
B27	0 (0.0%)	0 (0.0%)	NC
B35	8 (30.8%)	1 (10%)	0.2
B37	1 (3.8%)	0 (0.0%)	NC
B38 (B16)	2 (7.7%)	4 (40%)	0.02
B39 (B16)	1 (3.8%)	1 (10%)	0.47
B40	7 (26.9%)	1 (10%)	0.27
B41	0 (0.0%)	0 (0.0%)	NC
B44 (B12)	4 (15.4%)	0 (0.0%)	NC
B49 (B21)	0 (0.0%)	1 (10%)	NC
B50 (B21)	1 (3.8%)	0 (0.0%)	NC
B51 (B5)	8 (30.8%)	4 (40%)	0.6
B52 (B5)	1 (3.8%)	1 (10%)	0.47
B53	1 (3.8%)	0 (0.0%)	NC
B55 (B22)	2 (7.7%)	1 (10%)	0.82
B58 (B17)	3 (11.5%)	1 (10%)	0.89
B60 (B40)	0 (0.0%)	1 (10%)	NC
B61 (B40)	7 (26.9%)	0 (0.0%)	NC

NC: not calculated

Discussion

Cutaneous adverse reactions is one of the most frequent limitations of the treatment with LTG (26), but the underlying pathophysiological mechanisms for this phenomenon remains to be cleared. In the present study, the HLA-B*38 and HLA-B*40 alleles were associated with a higher risk of LTG-related skin reactions in epileptic patients. Interestingly, HLA-B*38 and HLA-B*40 alleles may differently increase the risk of LTG-related skin reactions in men and women. So that, the HLA-B*38 and HLA-B*40 were associated with the expression of the LTG-related skin reactions in epileptic men and women, respectively. In agreement with our data, an association has also been reported between HLA-B*38 and LTG-related skin reactions in European epileptic patients (27). The relationship between HLA-B*38 allele and some skin disorders such as psoriatic arthritis and pemphigus vulgaris has been previously revealed (28,29). Concomitant use of lamotrigine with other drugs may be associated with more side effects (15).

In accordance with our findings, the association of HLA-B*40 with oxcarbazepine-induced maculopapular eruption has been reported in epileptic patients (30). However, a negative association has been reported between B*40 allele and carbamazepine-related Stevens-Johnson syndrome (31,32). The association of HLA-B*40 and drug-induced thyroid dysfunctions and antibiotics-related skin diseases has also been indicated (33,34). The data presented here also indicate that the distribution of the HLA-B*38 allele was significantly higher in LTG-sensitive patients with high grade of cutaneous side effects when compared with patients with low grade of the lesions. These findings represent that HLA-B*38 allele may be a risk factor for the expression of the severe cutaneous reaction related to LTG. An association has been also indicated between LTG-related skin reactions and HLA alleles A*6801, B*5801 and Cw*0718 in a sample of European patients with epilepsy (35). Moreover, a significant association was also found between the risk for LTG-induced SCAR in Korean patients and HLA-A*31:01, HLA-A*2402, HLA-Cw*0102, and HLA-Cw*0702 alleles, whereas the presence of the HLA-A*3303 allele was found as a protective allele (22,36). Our study had some limitations. First, we **e**valuated only HLA B for the patients. It is suggested to evaluate other HLA types in further studies. Second, we did the present study in Kerman, while it should be done in other part of Iran.

In conclusion, the results of this study indicated that HLA-B*38 and HLA-B*40 alleles may be considered as useful predictive markers for the prediction of the occurrence of LTG-related skin reactions in the Iranian population. HLA-B*38 was associated with LTG-related skin reactions in men and also with severe cutaneous reactions, whereas HLA-B*40 were associated with LTG-related skin reactions in epileptic women.

Conclusion

These results indicated possible association between HLA-B*40 and HLA-B*38 alleles and LTG-induced skin lesions in Iranian epileptic patients. HLA-B*40 and HLA-B*38 alleles might be differentially expressed in male and female epileptic patients with LTG-induced skin lesions.

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Conflict of interest

The authors have no conflict of interests.

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