Association between HLA and Guillain Barre' syndrome

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ABSTRACT

Background: Genetic factors play an important role in susceptibility to Guillain Barre' syndrome. Human leukocyte antigen (HLA) as part of immune system has a role in the disease process.

Aim of the study: to assess the relationship between HLA-A alleles with Guillain Barre' syndrome (GBS) compared with a healthy control group using PCR-SSOP method.

Type of the study: Cross-sectional study.

Patients and methods: Patient's group consisted of 30 Iraqi Arab Muslims patients with Guillain Barre' syndrome that consulted the Neurological department in Neurosciences Hospital between January-2013 to January- 2014 were genotyped for HLA-A alleles. A control group consisted of 30 healthy volunteers among the staff of AL-Kindi College of Medicine that did not have any neurological disorders.

Results: Present study found a decreased frequency of HLA-A:0101 allele (p=0.001) in GBS patients compared to healthy controls.

Conclusions: current results suggest that GBS is negatively associated with HLA-A:0101 allele.

Key words: Guillain Barre, HLA, PCR.

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Guillain - Barre' syndrome is a group of autoimmune syndromes consisting of demyelinating and acute axonal degenerating forms of the disease. Nerve conduction study helps to differentiate the heterogenous sub types of GBS (1). Patients exhibit a progressive paralysis that reaches a plateau phase. In most patients, resolution is complete or near complete (1). While most patients with GBS have an acute demyelinating neuropathy, some have axonal loss without demylination. (2) Mortality from GBS most often is associated with dysautonomia and GBS is usually associated with infection by one of several known pathogens. Cross-reactivity between the pathogen and the nerve tissue sets up the autoimmune response .(2) Cytomegalovirus is the most commonly associated virus, while Campylobacter jejune which causes gastroenteritis is the most Frequently associated bacterial infection.(3) GBS is considered an autoimmune disease ,with the immune system mistakenly attacking myelin or axons, the nerve conduits for signals to and from the brain. This mistaken immune attack may arise because the surface of Campylobacter- jejuni contain lipopolysaccharides that resemble glycoconjugates of the human nerve tissues. This resemblance has been termed (molecular mimicry) which is defined as the dual recognition, by a single B or T-cell receptor, of a microbes structure and an antigen of the host and is the mechanism by which infections trigger cross-reactive antibodies or T cells that can lead to autoimmune diseases.(3)

Whether vaccination increases the risk of GBS is unknown and there is no evidence of an increased risk of GBS after seasonal influenza vaccine (4). When GBS is preceded by a viral or bacterial infection, it is possible that the virus has changed the nature of cells in the nervous system so that the immune system treats them as foreign cells. It is also possible that the virus makes the immune system itself less discriminating about what cells it recognizes as its own ,allowing some of the immune cells such as certain kinds of lymphocytes and macrophages to attack the myelin. Sensitized T lymphocytes cooperate with B lymphocytes to produce antibodies against components of the myelin sheath and may contribute to destruction of the myelin. (5)

The human leukocyte antigens (HLA) system includes a complex array of genes located on chromosome 6 and their molecular products involved in immune regulation and cellular differentiation . Human leukocyte antigen (HLA) molecules are expressed on almost all nucleated cells, there are three classical loci at HLA Class I HLA-A , B and Cw and five loci at Class II: HLA-DR, DQ, DP, DM and DO. The system is highly polymorphic (6) .The contribution of the allelic diversity of Class I and II genes to immune recognition and alloreactivity can be analysed by serological methods and molecular methods at the DNA level by different methods like sequence specific primer (SSP) and oligotyping with locus and allele-specific oligonucleotide probes (SSOP) (7).MHC Class I proteins form a functional receptor on most nucleated cells of the body. There are three major and three minor MHC Class II proteins encoded by HLA. Major Class II HLA-DP encoded by HLA-DPA1 and HLA-DPB1, HLADQ encoded by HLA-DQA1 and HLA-DQB1 locus. HLA-DR encoded by HLA-DRB1, DRB3, DRB4 and DRB5 Loci, the other Class II proteins ,DM and DO are used in the internal processing of antigens, loading the antigenic peptides generated from pathogens onto the HLA molecules of antigen presenting cell (8)

So the aim of the study is to assess the association between HLA -A alleles and GBS in Iraqi patients.

Patients and methods:

The study consisted of 30 Iraqi Arab Muslims patients who had Guillain Barre Syndrome that consulted Neurological department in Neurosciences hospital from January 2013 to January 2014 were assessed for HLA-A class I.

The study was carried out at the HLA typing research unit, AL-Kindi College of Medicine, Baghdad University. The second control group consisted of 30 healthy volunteers among the staff of AL-Kindi College of Medicine that did not have any neurological disorders and had negative family history for the disease. The control group was ethnically similar to the patient's group.

The age of the patient group ranged from 19-62 years , and the control group ages ranged from 22-61 years. The ethical committee of AL-Kindi College of Medicine, Baghdad university approved the study. All samples were obtained with informed consent in accordance with the AL-Kindi Teaching hospital declaration.

HLA-genotyping:. Peripheral venous blood samples from patients and control groups were collected in ethylene diamine tetra-acetic acid-containing tubes and then genomic DNA was extracted using promega DNA extraction Kit (promega corporation, Fitchburg, Wisconsin, USA). All DNA was stored at -20°c until used. HLA-A genotyping was done using PCR-SSOP (Innogenetics -Belgium) Kits. The results were interpreted by HLA fusion software version 2.0 (one lambda, canoga park, California, USA) .

Statistical analysis: The distribution of HLA alleles in the patient and control group was compared using chi-square for continuous variables using Mini Tab version 15 software in each comparison .The odds ratio (OR) along with the 95% confidence interval (95% CI) was also estimated. A P-value less than 0.05 was considered statistically significant.

Results: Alleles frequencies of HLA-A for GBS patients and control group is shown in Table 1 There was a decreased frequency of HLA-A:0101 in patients with GBS than control group (P-value=0.001, odd ratio= 0.030, 95% CI=0.003-0.251).

Discussion: Guillain Barre syndrome is a disorder in which the body's immune system attacks part of the peripheral nervous system. It is an autoimmune disorder , and one of the factors that may have an association with the disease occurance is HLA, which plays an important role in the body's immune responses and development of autoimmune diseases. (9)

This study found a decrease in frequency of HLA-A*0101 in GBS patients when compared to the control group and that can be considered as a protective factor in the disease occurrence. kaslow et al study showed a decrease in frequency of HLA-A11 in GBS patients when compared with control group (10) . Feeney et al study showed an increase in frequencies of HLA-A3 , B7 and a decrease in frequencies of HLA-44 and DR-7 (11). Hafez et al appeared a significant increase in frequencies of HLA-A3 and HLA-B8 (12). Another studies showed no association between HLA-A antigens and GBS for example Winer et al (13), Majj et al (14) and Van Doorn et al (15).

Although heterogeneity in the chemical structures of LPSs of various infectious agents contributes to the variability of bacterial virulence for GBS, the genetic susceptibility of patients to infectious agents may also contribute to differences in clinical outcomes of the patients. For example, several reports documented the involvement of host factors in certain patients that contributed to the failure to develop antiganglioside antibodies in pathogenesis of GBS (16) . Hartung and Toyka reported macrophage activation in GBS in which circulating activated T lymphocytes were found ,as evidenced by augmented expression of histocommpatibility antigens suggesting there is an association between GBS and HLA alleles. (17) Other studies have reported familial cases of GBS ,which postulate a genetic susceptibility making such cases worth reporting.(18)

Analysis of expression of these genes should be helpful in designing drugs useful in treating these conditions. Understanding the gene products may also help in designing suitable vaccines for their intervention. Future studies should be directed to these important challenges.The major contribution of the study of HLA and GBS has been done to show the genetic aspects of the disease, furthermore this study has contributed a great deal to a better insight in the pathogenesis of the disease. The differences in the association of HLA antigens in GBS in present study with other studies can be attributed to racial group variations, sample size and methods used in the study.

Conclusions:

GBS is negatively associated with HLA-Class I A*0101 which may has a role in the etiopathogenesis of the disease.

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HLA-A	Patients No=30		Controls No=30		OR	CI	P value
	No	%	no	%			
A*0101	1	3.33	16	53.33	0.030	0.003-0.251	0.001
A*0201	13	43.33	10	33.33	1.529	0.536-4.360	0.426
A*0301	13	43.33	-	-	Na	Na	Na
A*0302	3	10	-	-	Na	Na	Na
A*2310	-	-	5	16.66	Na	Na	Na
A*2402	8	26.66	14	46.66	0.415	0.14 09-1.22 54	0.11 15
A*2501	4	13.33	3	10	1.384	0.28 21-6.79 59	0.68 85
A*2612	-	-	5	16.66	Na	Na	Na
A*2901	4	13.33	-	-	Na	Na	Na
A*3011	-	-	3	10	Na	Na	Na
A*3301	5	16.66	-	-	Na	Na	Na
A*6801	4	13.33	3	10	1.384	0.28 21-6.79 59	0.68 85

Na :not applicable

Table 1.Human leukocytes antigens (HLA-A) alleles frequencies in patients with GBS and healthy control groups.

References:

1) Asbury A. New concepts of Guillain Barre Syndrome; Journal of child neurology. 2000; 15: 183-191.
2)Hauser SL, Amato AA. Guillain Barre syndrome and other immune-mediated neuropathies: In: Longo DL ,Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J, editors. Harrisons Principles of Internal Medicine. 18th ed. NewYork(NY): McGraw-Hill Medical; 2012.p. 3473-3479.
3)Huizinqa R, Vandenberg B, Vanrijs W et al. Innate immunity to campylobacter jejuni in Guillain Barre Syndrome; Ann Neurol. 2015;78:343-54.
4)Stowe J, Andrews N, wise L and miller E. Investigation of the temporal association of Guillain-Barre syndrome with influenza vaccine and influenza like illness using the united kingdom General practice; American journal of Epidemiology.2009; 169: 382-388.
5)Robert K.YU , Usuki S and Ariga T. Ganglioside Molecular Mimicry And Its Pathological Roles In Guillain Barre Syndrome and Related Diseases ; Infection and Immunity.2006; 74: 6517-6527.
6) Erlich HA, Opelz G , Hansen J. HLA DNA typing and transplantation; Immunity.2001; 14: 347-356.
7)Mutar B. A glow of HLA typing in organ transplantation; Clinical and Transplantational Medicine. 2013; 2:6.
8)Mack SJ, Cano P, Hollenbach JA et al . Common and well-documented HLA alleles; Tissue Antigens. 2013; 81: 194-203.
9)Hassan N, Siddiqui AR, Abbas Z, Hassan SM , Soomro GB, Mubarak M, et al. Clinical Profile and HLA Typing of Autoimmune Hepatitis From Pakistan; Hepat Mon. 2013; 13: e13598.
10)Kaslow RA, Sullivan-Bolyai JZ, Hafkin B, et al. HLA antigens in Guillain-Barre Syndrome; Neurology. 1984; 34: 240.
11) Feeney DJ, Pollard JD, Mcleod JG, Stewart GJ, Doran TJ. HLA antigens in chronic inflammatory demylinating polyneuropathy; J Neurol neurosurg psychiatry. 1990; 53: 170-172.
12)Hafez M , Nagaty M , Al-Tonbary Y. ,El-Shennawy F.A, El-Mongui A, El-Sallab S and Attia S .HLA- antigens in Guillain Barre syndrome; Journal of Neurogenetics. 1985; 2: 285-290.
13)Winer J.B , Briggs D, Welsh K, and Hughes R.A.C. HLA antigens in Guillain-Barre syndrome; Journal of Neuroimmunology. 1988; 18: 13-16.
14) Majj, Nishimura M, Mines H, Kuroki S, Nukina M et al. HLA and T-cell receptor gene polymorphisms in Guillain – Barre syndrome ; neurology. 1998; 51: 379 - 384.
15) Van Doorn PA, Schreuder GMT, Vermeulen M, Amaro J.D and Brand A. HLA antigens in patients with chronic inflammatory demyelinating polyneuropathy; Journal of Neuroimmunology. 1991; 32: 133 – 139.
16) Sheikh K.A, Nachamkin I, Ho T.W, Willison H.J, Veitch J, Ung H, Nicholson M, et al. Campylobacter jejuni lipopolysacchrides in Guillain Barre syndrome. molecular mimicry and host susceptibility; Neurology. 1998; 51: 371-378.
17) Hartung H.P and Toyka K.V. T- cell and macrophage activation in experimental autoimmune neuritis and Guillain Barre syndrome; Ann Neurol. 1990; 27: 557-563.
18)Aquil N, Khan IA Soomro B. Guillain Barre syndrome in a family: a case report of four siblings; J Coll Physicians Surg Pak. 2011; 21: 179-181.