British Journal of Medicine & Medical Research
4(34): 5415-5420, 2014

SCIENCEDOMAIN *international*
www.sciencedomain.org

Frequency of HLA-DRB1 in Iraqi Patients with Guillain-Barre Syndrome

Batool Mutar Mahdi[1*] and Zaki Noah Hasan[2]

[1]Department of Microbiology, Head of HLA typing research unit Al-Kindy Baghdad University, Baghdad, Iraq.
[2]Department of Medicine, Al-Kindy Baghdad University, Baghdad, Iraq.

Authors' contributions

This work was carried out in collaboration between all authors. Author BMM designed the study, performed in statistical analysis, wrote the protocol and wrote the first draft of manuscript, managed the analysis of the study and managed the literature search. Author ZNH send the patients for the study. All authors read and approved the final manuscript.

Original Research Article

Received 22nd March 2014
Accepted 4th June 2014
Published 29th July 2014

ABSTRACT

Background: Genetic backgrounds play an important role in susceptibility to and protection against Guillain Barré Syndrome. Certain human leukocyte antigens have been found to be associated with Guillain Barré Syndrome.
Aim of Study: This study aimed to study the relationship between the susceptibility of HLA Class II "DRBI" allele's frequencies in a sample of Iraqi's patients with Guillain Barré Syndrome compared with a healthy control group using PCR-SSOP method.
Patients and Methods: Thirty consecutive Iraqi Arab Muslim patients with Guillain-Barre syndrome admitted in the Neurological Department in neurosciences Hospital between September-2012 to June-2013 were assessed for HLA genotyping for HLADRB1. A control group consisted from thirty healthy volunteers among the staff of Al-Kindy College of Medicine that did not have any neurological disorders whether recent or previously and had negative family history for this diseases or other neurological disorders. HLA genotyping for HLADRB1 was performed for each patient and for the control persons using the PCR with sequence-specific oligoneucleotide primers. Allele frequencies were compared across groups.
Results: There was a significant higher rate of DRB1*03:01 frequencies in patients with GBS compared with healthy controls (p=0.007, Odds ratio=5.687, 95% CI: 1.59-20.33)

**Corresponding author: Email: batool1966@yahoo.com;*

Conclusions: HLA-DRB1*03:01 may have association with susceptibility to Guillain-Barre syndrome.

Keywords: Guillain-Barre syndrome; HLA; PCR.

1. INTRODUCTION

Guillain-Barré syndrome (GBS) is a group of autoimmune syndromes consisting of segmental demyelination and acute axonal degenerating forms Axonal GBS has been classified further into 2 groups: acute motor axonal neuropathy [AMAN] and acute motor and sensory axonal neuropathy [AMSAN] with albuminocytologic dissociation [1]. All GBS variants are rapidly evolving polyradiculoneuropathy preceded by a triggering event, most often an infection [2]. GBS generally manifests as progressive areflexic weakness with or without autonomic disturbances [1]. Its prevalence is between 0·6-4/100, 000 per year worldwide [3] an age range from 2 months to 95 years [4], most of the patients being between 15- 50 years [4-6].

GBS is characterized by an immune-mediated attack on peripheral nerve myelin sheath or Schwann cells of sensory and motor nerves, there is a considerable facts to support an autoimmune cause of this syndrome and the presence of autoantibody profile has been cooperative in confirming the clinical and electrophysiological relationship of the typical Guillain–Barré syndrome to certain other peripheral-nerve conditions [7]. Yu et al. [8] demonstrated that *Campylobacter jejuni* is the most frequent pathogen about 13% to 39% of cases then cytomegalovirus constituted 5% to 22%, Epstein-Barr virus 1% to 13% and *Mycoplasma pneumoniae* about 5% due to molecular mimecry between these pathogens and ganglioside.

Much of the researchers worked to find the cause of predisposition of small number of people with an infection to develop GBS; There is macrophage activation in GBS; circulating activated T lymphocytes evidenced by augmented expression of histocompatibility antigens (HLA-DR) suggest that there is an association between GBS and HLA alleles [9,10]. HLA typing in GBS was investigated in several studies worldwide suggesting various associations.

We try in this study to find the association between this disease and HLA typing in our Iraqi patients.

2. PATIENTS AND METHODS

A cross-sectional case control comparative study included thirty Iraqi Arab Muslims patients who had demylinating ascending motor Guillain-Barre syndrome and admitted in the Neurological Department at Neurosciences Hospital between September-2012 to June - 2013. Age of patients group was ranged from 9-45 years and. Male to female ratio was 2:1 in the patients group. The inclusion criteria to select the patients were fulfillment of criteria described by Asbury and Cornblath 1990 [11]. This includes progressive weakness of more than two limbs, areflexia, and progression for no more than four weeks. Fortunately no case required assisted ventilation that was reported by their neurologic physicians. The exclusion criteria were patients with other possible causes of peripheral neuropathy like diabetes mellitus, nutritional diseases, connective tissue diseases, lead poisoning, vacuities, botulism,

and porphyria. The second control group consisted from thirty healthy volunteers among the staff of Al-Kindy College of Medicine that did not have any neurological disorders whether recent or previously and had negative family history for this diseases or other neurological disorders. The control group was ethnically similar to patients group; their ages were ranged from 10- 48 years. Male to female ratio in the control group was 2:1.

The Scientific and Ethical Committee of Al-kindy medical college and Medical City Hospital had approved the study. Informed consent was obtained from all patients and control group.

HLA genotyping: Peripheral venous blood samples from patients and control groups were collected in ethylenediaminetetraacetic acid-containing tubes and then stored at -20ºC until testing for class II- HLA-DRB1. Genomic DNA was extracted using Promega DNA extraction Kit-USA. DNA product was verified by electrophoresis in a 2% agarose gel containing ethidium bromide and was visualized under UV light. Locus- and allele-specific amplification of genomic DNA was performed for DRB1. Amplification and Hybridization was performed using a panel of sequence-specific oligonucleotide probes (SSOP) using HLA-DRB1 amplification and hybridization kits (SSO HLA type DRB1 plus and Mastermix for HLA type DRB1 Amp plus kits-Innogenetics-Belgium) using automated method by AutoLipa–48 Innogenetics-Belgum. The results were interpreted using LiRas version-5.0 software-Innogenetics-Belgium.

Statistical analysis was done using using Mini Tab version. 3.0 software. The distribution of HLA alleles in patients and control groups were compared using chi-square for continuous variable. Fisher's exact test was used when necessary. In each comparison, the Odds ratio (OR) along with the 95% confidence interval (95% CI) was used. P-value less than 0.05 were considered statistically significant.

3. RESULTS

Control and GBS patients groups were typed for identifying the DRB1* alleles using DNA-based methodology (PCR-SSOP). Allele's frequencies of HLA-DRB1for GBS patients and control group are shown in (Table 1). There was an increased frequency of HLA-DRB1*03:01 in patients with GBS compared with healthy controls (p=0.007, Odds ratio=5.687, 95% CI: 1.59-20.33). There is slightly increase in the HLA-DRB1* 07:01 and HLA-DRB1* 15:01 in patients with GBS compared with the control group, but the differences were not statistically significant. All the patients had demylenating type with no axonal type. Antiganglioside antibodies were not tested.

Table 1. Human leukocytes antigens (HLA-DRB1) allele's frequencies in patients with GBS and healthy control groups

HLA-DRB1* alleles	GBS patients group No.=30		Healthy control group No.=30		Odds ratio (95% confidence interval)	P-value
	No.	%	No.	%		
02:03	0	0	2	6.66	na	na
03:01	14	46.6	4	13.33	5.687(1.59-20.33)	0.007
03:17	0	0	4	13.33	na	na
03:21	2	6.66	0	0	na	na
04:02	2	6.66	0	0	na	na

Table 1 continued……

04:01	6	20.00	0	0	na	na
0:76	2	6.66	0	0	na	na
07:01	10	33.33	7	23.33	1.642(0.52-5.11)	0.390
08:01	0	0	2	6.66	na	na
11:01	4	13.33	7	23.33	0.505(0.13-1.95)	0.322
11:02	2	6.66	2	6.66	1.00(0.13-7.60)	1.00
11:03	0	0	4	13.33	na	na
11:13	2	6.66	0	0	na	na
11:67	0	0	4	13.33	na	na
11:119	2	6.66	0	0	na	na
12:01	4	13.33	0	0	na	na
12:09	0	0	2	6.66	na	na
13:01	6	20.00	0	0	na	na
13:05	0	0	2	6.66	na	na
13;18	0	0	4	13.33	na	na
13:116	0	0	2	6.66	na	na
13:119	0	0	2	6.66	na	na
14:01	0	0	2	6.66	na	na
14:02	0	0	2	6.66	na	na
14;16	0	0	2	6.66	na	na
14:57	0	0	4	13.33	na	na
15:01	4	13.33	2	6.66	2.153(0..36-12.76)	0.398

na=not applicable

4. DISCUSSION

Guillain-Barré syndrome is an acute, sub acute immune-mediated paralytic disorder affecting the peripheral nervous system. The pathogenesis of this disease was due to molecular mimicry with cytomegalovirus, EBV and *C. jejuni* infection [12,13]. There is no any registry about the incidence of this disease in our country and some of them had a history of influenza vaccine before pilgrim period. HLA antigens play an important role in the body's immune responses and development autoimmune diseases especially Class II HLA-DR and DQ. GBS and its association with HLA typing being studied in different countries worldwide. In our study we found that there is a significant association between HLA-DRB1*03:01 and GBS in Iraqi Arab Muslims that is in agreement with Grodezky et al. [14] who reported an increase in HLA- DR3 in Mexican cases. Our patients did not have mechanical ventilation, so acquisition of this allele lead to mild form of GB. In our study HLADRB*01 was also tested and did not detected in GB patients. Other study demonstrated an increased HLA- DR2 in GBS patients with most profound muscle weakness [15] and the frequency of HLA-DRB1*01 was increased in patients who needed mechanical ventilation [16,17]. Our study showed an increase in HLA-DR*0301 while result of Monas et al. [15] who report a significant increase in HLA- DRB1*1301 in the GBS group. Many studies showed no correlation between HLA and GBS subgroups [18]. These differences with other studies may be due to race, patient's selection, religion also affect HLA typing between Arab Muslims and Arab Christians [19], method used, small sample size that influence the validity of the results and the incidence and prevalence of this diseases was not registered and other environmental factors that contribute to development of disease.

These results indicate an aberrant genetic make-up of the patients that makes them more susceptible to develop the syndrome after exposure to the environmental factor (s).

Although most GBS cases were sporadic; a lot of studies have reported familial cases of GBS which postulates a genetic susceptibility making such cases worth reporting [20]. Other study had assessed HLA typing in familial GBS [21].

It has been found that DRB1*03:01 (DR3) is associated with other autoimmune diseases and neurological diseases due to microglia or macrophages and astrocytes expressed HLA-DR on its surface were demonstrated in many neurological diseases like Alzheimer's, Parkinson's, Pick's, Huntington's diseases, parkinsonism-dementia of Guam, amyotrophic lateral sclerosis, Shy-Drager syndrome, multiple sclerosis and AIDS encephalopathy [22].

5. CONCLUSION

In conclusion, our study presents an additional confirmation on the role of HLA antigens in GBS in Iraqi sample. However, our finding differ from other studies because of significant variations in age, sex, ethnicity, racial background, diagnostic and clinical criteria, the number of cases and controls and the patient-selection methods employed in other studies. On the other hand, additional investigations, with larger and diverse populations are required to make clear association.

CONSENT

Not applicable.

ETHICAL APPROVAL

Not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Arcila-Londono X, Lewis RA. Guillain-Barré syndrome. Semin Neurol. 2012;32:179-86.
2. Soysal A, et al. Clinico-electrophysiological findings and prognosis of Guillain-Barre syndrome—10 years' experience. Acta Neurologica Scandinavica. 2011;123:181.
3. Hughes RA, Cornblath DR. Guillain-Barré syndrome. Lancet. 2005;366(9497):1653-66. Review.
4. Walling AD, Dickson G. Guillain-Barré syndrome. Am Fam Physician. 2013;87:191-7.
5. Nachamkin I, Allos BM, Ho T. Campylobacter species and Guillain-Barre´ syndrome. Clin Micro Rev. 1998;11:555-567.
6. Pithadia AB, Kakadia N. Guillain-Barré syndrome (GBS). Pharmacol Rep. 2010;62:220-32.
7. Yuki N, Hartung H. Guillain-Barré syndrome. N Engl J Med. 2012;366:2294-304.
8. Yu RK, Usuki S, and Ariga T. Ganglioside molecular mimicry and its pathological roles in Guillain-Barré syndrome and related diseases. Infect Immun. 2006;74:6517–6527.
9. Sasazuki T, McDevitt HO. The association between genes in the major histocompatibility complex and disease susceptibility. Annu Rev Med. 1977;28:425-452.

10. Adams D, Gibson JD, Thomas PK, et al. HLA antigens in Guillain-Barre syndrome. Lancet. 1977;2:504-505.
11. Asbury AK, Cornblath DR. Assessment of current diagnostic criteria for Guillain-Barre´ syndrome. Ann. Neurol. 1990;27(Suppl.):21.
12. Nachamkin I, Allos BM, Ho T. Campylobacter species and Guillain-Barre syndrome. Clin Micro Review. 2013;11:555-567.
13. Blázquez M, López- Alburquerque T, Ciudad Bautista J, Fermoso García J. The Guillain Barre Syndrome due to cytomegalovirus in two siblings. Peak-flow meter as the mechanism of transmission. Med Clin. 2002;119:317-8.
14. Gorodezky C, Varela B, Castro- Escobar LE, Chavez-Negrete A, Escobar-Gutierrez A, Martinez-Mata J. HLA-DR antigens in Mexican patients with Guillain-Barre syndrom. J Neuroimmunol. 1983;4:1-7.
15. Winer JB, Briggs D, Welsh K, Hughes RAC. HLA antigens in Guillain-Barre syndrome. J Neuroimmunol. 1988;18:13-6.
16. Monas DS, Papaioakim M, Ho TW, Li CY, McKhann GM. Differential distribution of HLA alleles in two forms of Guillain- Barre syndrome. J Infect Dis. 1997;176:180-2.
17. Geleijns K, Schreuder GMT, Jacobs BC, Sintnicolaas K, et al. HLA class II alleles are not a general susceptibility factor in Guillain–Barré syndrome. Neurology. 2005;64:44-49.
18. Hillert J, Osterman PO, Olerup O. No association with HLA-DR, DQ, or DP alleles in Guillian Barre Syndrome. J Neuroimmunol. 1999;31:67-72.
19. Benedek G, Paperna T, Avidan N, Lejbkowicz I, Oksenberg JR, Wang J, Brautbar C, Israel S, Miller A. Opposing effects of the HLA-DRB1*0301-DQB1*0201 haplotype on the risk for multiple sclerosis in diverse Arab populations in Israel. Genes and Immunity. 2010;11:423-431.
20. Bar Joseph G, Etziani A, Hemli J, Gerhuni baruch R. Guillain Barre syndrome in three siblings less than 2years old. Arch Dis Childhood. 1991;66:1078- 9.
21. barzegar M, Rouhi AHJ, Farhoudi M, Sardashti S. A report of a probable case of familial Guillain Barre syndrome.Ann Ind Acad Neurol. 2012;15:299-302.
22. McGeer PL, Itagaki S, McGeer EG. Expression of the histocompatibility glycoprotein HLA-DR in neurological disease. Acta Neuropathol. 1988;76:550-7.

Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sciencedomain.org/review-history.php?iid=612&id=12&aid=5535