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HLA-DR TYPING AND DIFFERENT CLINICAL MANIFESTATIONS OF PAEDIATRIC SYSTEMIC LUPUS ERYTHEMATOSUS PATIENTS IN A TERTIARY HOSPITAL, BANGLADESH

Susmita Das, Manik Kumar Talukder*, Md Imnul Islam, Shahana A. Rahman, Md. Mahbubul Islam, Rumana Riaaz

Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh.

***Corresponding Author: Manik Kumar Talukder**

Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh.

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ABSTRACT

Introduction: Association of MHC (Major histocompatibility complex) with SLE is widely studied and it is evident that HLA class II genes are strongly associated with SLE. Among HLA-DR types, some alleles are considered as risk factors for certain clinical manifestations and some alleles may predict different organ involvement. **Objective**: To determine the association between HLA-DR typing with different clinical manifestations in paediatric SLE patients (pSLE). **Methodology:** It was a cross-sectional study. Thirty two newly diagnosed cases of pSLE were included in this study. Age and sex matched 10 apparently healthy children were selected as control. **Results:** Most common HLA-DR type among pSLE cases was DR15(63%) followed by DR07 (41%) and DR04 (31%). HLA-DR07 was positive in 80% of control group ($p<0.05$). In this study, pSLE patients presented with constitutional symptoms (93.8%) followed by skin rash (84%), renal features (75%), gastrointestinal (69%) and musculoskeletal (63%) manifestations. HLA-DR15, DR07 and DR04 were frequently positive in above mentioned manifestations, but HLA-DR13 was not present in patients with renal and haematological manifestations. HLA-DR11 and DR13 showed significant association with arthritis, and hematologic manifestation was associated with DR11.**Conclusions:** Among HLA-DR types, most frequently associated alleles were DR15 followed by DR07 and DR04.This study found significant association of HLA-DR typeswith different clinical manifestations in pSLE patients.

KEYWORDS: Major histocompatibility complex, HLA-DR.

INTRODUCTION

Systemic lupus erythematosus(SLE) is a chronic autoimmune disease characterized by multisystem inflammation and the presence of circulating autoantibodies directed against self antigens. Compared with adults, children and adolescent with SLE have more severe disease and more widespread organ involvement.[1] In a retrospective study done in tertiary hospital of Bangladesh, among patients having peadiartic rheumatic disease, showed prevalence of SLE was10%.[2] A Study from Eastern India found that. 3.9% of all children presenting to a paediatric rheumatology clinic had SLE.[3]

The precise etiology of SLE remains vague but genetic predisposition, environmental and hormonal factors are likely to play important role in its pathogenesis.[4] Genetic factors are important both in determining the overall susceptibility to SLE and influencing the remarkable clinical heterogeneity of disease presentation.[5] Association of MHC with SLE is widely studied and found that HLA class II genes are strongly associated with SLE.[6]

Among the HLA DR types, HLA-DR4, DR5, DR11 and DR14 are identified as protecting alleles against SLE and HLA-DR3, DR9 and DR15 as risk factors for SLE. In addition, DR4 and DR11 alleles might be protective and DR3 and DR15 are risk factors for lupus nephritis.[7]

HLA-DR01, HLA-DR04, HLA-DR11 and HLA-DR13 were detected as most frequently present alleles associated with SLE in Iranian children.[8] The presence of HLA-DR15 was regarded as a strong predispositional factor for lupus and lupus nephritis.[9] Wadi et al. showed that DR10 was associated with hematological manifestation in pSLE.[10]

The present study was designed to determine the association between HLA-DR typing with different clinical manifestations.

METHODOLOGY

It was a cross sectional study done in the department of paediatrics, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka during July 2016 to June 2018. Newly diagnosed 32 pSLE patients fulfilling the

ACR 1997 revised classification criteria were included as cases. Control group were selected from apparently healthy children after matching age and sex and without any family history of autoimmune disease. This study was conducted with prior approval of the institutional review board of BSMMU, Dhaka, Bangladesh. Baseline investigations to diagnose the disease were done by the treating rheumatologists. HLA-DR typing was done in the department of microbiology and Immunology of this institute.

The predesigned questionnaires were completed for each patient by interviewing them or their parents. The demographic and clinical characteristics including age, gender, diagnosis and duration of disease (month) were recorded in the questionnaire.

All data were recorded systematically in preformed data collection form. Statistical analysis were performed by using SPSS for windows version 22. Frequency was expressed as Mean (SD) and percentage. Association between variables and HLA-DR types was done by Fisher exact test and Chi square test.

RESULTS

In this study most of the patients were female (90.6%) and female: male ratio was 9.7:1. Mean age of the patients was 11.23 ± 3.03 years. Ten healthy children were included as control with mean age of 10.45±3.05 years (Table-I)**.** Most of the patients in this study presented with constitutional (93.8%) followed by skin manifestation (84%), renal, gastrointestinal, musculoskeletal, neurologic and hematologic manifestation (Table –II).

Most commonly found HLA-DR types among pSLE cases were DR15 (63%), DR07 (41%) and DR04 (31%). Other HLA-DR types were DR09, DR11, DR12 and DR13. Only HLA- DR 07 had higher rate of positivity in control group (Table-III). HLA- DR15, DR07 and DR04 were most frequently found among pSLE cases with common manifestations, but HLA-DR13 was absent in patients with renal and haematological manifestations. HLA-DR11 and DR13 showed strong association with arthritis and haematological manifestation (Table IV).

Table I: Demographic data of cases and controls (n=32 + 10).

Variable	Cases n(%)	Control n(%)
Female	29 (90.6)	9(90%)
Male	3 (9.4)	1(10%)
Disease duration(months) [mean±SD]	5.07 ± 6.09	
Age (year) [mean±SD]	11.23 ± 3.03	10.45±3.05
Age at disease onset (years)	10.70 ± 3.03	

Table II: Different clinical manifestations presenting among the paediatricSLE patients(n=32).

Clinical features	Numbers (n)	Percentage (%)
Constitutional	**30**	**93.8%**
Anorexia	30	93.8
Fatigue	28	87.5
Fever	25	78.1
Lymphadenopathy	13	40.6
Musculoskeletal	**20**	**62.5**
Arthritis /arthalgia	17	53.1
Myositis	2	6.3
Tendonitis	2	6.3
Neurologic	**8**	**25.0**
Headache	5	15.6
Seizure	4	12.5
Skin	**27**	**84.4**
Photosensitivity	22	68.8
Oral ulcer	21	65.6
Other rash	19	59.4
Malar rash	16	50.0
Alopecia	12	37.5
Discoid rash	3	9.4
Cutaneous vusculitis	2	6.3
Lividoreticularis	2	6.3
Periungual capillary abnormalities	1	3.1
Raynaud's phenomenon	2	6.3
Renal	**24**	**75.0**

Proteinuria	20	62.5
Oedema	13	40.6
Hypertension	11	34.4
Haematuria	10	31.3
Pulmonary	**1**	**3.1**
Gastrointestinal	**22**	**68.8**
Hepatosplenomegaly	22	68.8
Ascites	05	15.6
Hematologic	06	18.7

Table III: Frequency of HLA-DR in paediatric SLE patients and healthy control (n=42).

HLA-DR	Group		*p value	OR	95%CI
	Case (n=32) n (%)	Control (n=10) n (%)			
DR01	4 (12.5)	1 (10.0)	1.000	1.039	0.060-18.032
DR04	10 (31.3)	3 (30.0)	1.000	4.328	0.276-67.783
DR07	13 (40.6)	8 (80.0)	0.030	0.479	1.023-169.491
DR09	4 (12.5)	0 (0.0)	0.557		
DR11	2 (6.3)	0 (0.0)	1.000		
DR12	3 (9.4)	1 (10.0)	1.000	1.443	0.066-31.358
DR13	2 (6.3)	0 (0.0)	1.000		
DR14	0 (0.0)	1 (10.0)	0.238		
DR15	20 (62.5)	4 (40.0)	0.714	2.876	0.116-6.790

**Fisher Exact test*

Table IV: Association between HLA types and different clinical manifestations in Childhood SLE patients:(n = 32)

HLA types	Constitutional n (%)	Musculoskeletal n (%)	Skin n (%)	Neurological n (%)	Renal n (%)	Gastroenterological n (%)	Arthritis n (%)	Haematological n (%)
DR01	3 (75.0)	1 (25.0)	3 (75.0)	1 (25.0)	4 (100.0)	3 (75.0)	1(25.0)	1(25.0)
p value	***1.000***	***0.136***	***0.512***	***1.000***	***0.550***	***1.000***	***1.000***	***1.000***
DR04	9 (90.0)	4 (40.0)	8 (80.0)	3 (30.0)	8 (80.0)	8 (80.0)	2(20.0)	2(20.0)
p value	***0.387***	***0.119***	***0.637***	***0.681***	***100.0***	***0.440***	1.000	***1.000***
DR07	10 (76.9)	9 (69.2)	10(76.9)	3 (23.1)	9 (69.2)	10 (76.9)	1(7.7)	3(23.1)
p value	***1.000***	***0.713***	***0.374***	***1.000***	***0.684***	***0.467***	0.195	***1.000***
DR09	3 (75.0)	2 (50.0)	4(100.0)	0	2 (50.0)	3 (75.0)	2(50.0)	
p value	***1.000***	***0.620***	***1.000***	***0.550***	***0.254***	***1.000***	0.201	
DR11	2(100.0)	2(100.0)	2(100.0)	1 (50.0)	2(100.0)	2(100)	2(100.0)	2(100.0)
p value	***1.000***	***0.516***	***1.000***	***0.444***	***1.000***	***1.000***	0.042	***0.42***
DR12	3 (100.0)	3 (100.0)	3(100.0)	1 (33.3)	2 (66.7)	3 (100.0)	1(33.3)	
p value	***1.000***	***0.274***	***1.000***	***1.000***	***1.000***	***0.534***	0.536	
DR13	1 (50.0)	2 (100.0)	1 (50.0)	0	0	1 (50)	2(100)	
p value	***0.395***	***0.516***	***0.292***	***1.000***	***0.056***	***0.534***	0.042	
DR15	16 (80.0)	14(70.0)	18(90.0)	5 (25.0)	16 (80.0)	12 (60.0)	3(15.0)	5(25.0)
p value	*1.000*	*0.288*	*0.338*	*1.000*	*0.433*	*0.248*	0.397	***0.683***

***P* value reached from Fisher Exact test**

DISCUSSION

SLE a systemic autoimmune disease in which organs and cells undergo damage is mediated by tissue binding autoantibodies and immune complexes. Studies on associations between HLA allele frequencies and susceptibility to systemic lupus erythematosus (SLE) found that there were protective as well as predispositional alleles of different HLA-DR types.[11]

Among the 32 pSLE cases in the present study 29 were females (M:F= 1: 9.7) with age range 11.23 ± 3.03 years and mean disease duration was 5.07± 6.09 months. Female preponderance is a known fact which could be due to the importance of hormonal factors in the clinical expression of the diseaser. Shirin et al. found 4 boys and 27 girls with age range 6 to 16 years in their study which was consistent with the present study. Majority of pSLE patients in this study were in the 5-14 years of age group.[8]

Rahman et al. found different clinical manifestations of pSLE patients which were very much similar to the

present study.[12] In this study most of pSLE cases presented with constitutional symptomps followed by skin manifestations, renal, gastrointestinal, musculoskeletal and hematological manifestations.

In the current study among the 32 pSLE cases, the HLA-DR15 was detected most frequently followed by DR07, DR04, DR09, DR11, DR12 and DR13. This finding was almost similar to a Brazilian study where they showed that HLA-DR15 was detected most frequently followed by HLA-DR07 and HLA-DR13 in their study.[16]One Iranian study observed that HLA-DR01, HLA-DR04, HLA-DR11 and HLA-DR13 were commonly found alleles in SLE.[8]

Though statistically not significant this study showed that DR04, DR 09, DR12 and DR15 might be identified as risk factors and DR07 might be a protective factor for pSLE.

Niu et al. reported that HLA-DR4, DR11 and DR 14 alleles might be protective factors and HLA-DR3, DR9, DR15 were potent risk factors.[7] Hussain et al. also found that HLA-DR04, DR07, and DR08 had protective roles against SLE.[14] These findings were more or less similar to the present study. Some dissimilarities are present which could be due to our small sample size.

In this study among HLA-DR types: DR15, DR07 and DR 04 were predominant in pSLE cases with above mentioned clinical manifestations. This findings are consistent with a Brazilian study where HLA-DR15 allele was predominant in patients with constitutional, renal, musculoskeletal, cutaneous and neuropsychiatric involvement.[13]

In the present study HLA DR15, DR07, DR11, DR04 and DR01 were frequent among pSLE patients with renal invlovement. Holanda et al. showed the presence of HLA-DR15 as a strong predispositional factor for lupus nephritis.[9] Though HLA DR15 was frequently found HLA type in our study but the association was not significant.

Negative association was found between HLA-DR13 and renal manifestations in this study which was significant ($p<0.05$). Sherbiniet al. found no relation between HLA-DR15 and renal involvement.[15] This finding was not consistent with the present study, may be due to different sample size and different ethnicity.

DR04, DR07, DR11, DR12 and DR15 were most frequently found alleles associated with neuropsychiatric involvement in this study. In a Brazilian study, HLA-DR3 and HLA-DR9 were most frequent alleles in SLE patients with neuropsychiatric involvement.[16] Vasconcelos et al. found that HLA-DR08 allele was present with increased frequency among SLE patients with neurological involvement;[17] a result that is different from the present study. This might be due to ethnic, geographic and sample size difference.

This study found significant association ($p<0.05$) of DR11 and DR13 with arthritis. DR15, DR11, DR07 and DR04 were frequent in hematologic manifestation of pSLE but only DR11 showed significant association ($p<0.05$). Wadi et al. showed association of DR10 with hematological manifestation in pSLE in their study.[10]

CONCLUSION

Among the HLA-DR types more frequently found alleles were DR15, DR07, DR04 and these were associated with different clinical manifestations of pSLE patients. This study found statistically significant association of HLA-DR11 and DR13 with arthritis and DR11 with hematologic manifestation among pSLE cases.

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