IMMUNOGENETIC FEATURES OF STEROID-SENSITIVE NEPHROTIC SYNDROME AND FOCAL SEGMENTAL GLOMERU LOSCLEROSIS IN BRAZILIAN PATIENTS OF THE NORTHEAST REGION OF THE STATE OF SÃO PAULO

CARACTERÍSTICAS IMUNOGENÉTICAS DA SÍNDROME NEFRÓTICA CORTICOSSENSÍVEL E DA GLOMERULOSCLEROSE SEGMENTAR E FOCAL EM PACIENTES BRASILEIROS DA REGIÃO NORDESTE DO ESTADO DE SÃO PAULO

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ABSTRACT: Steroid-sensitive nephrotic syndrome (SSNS) and focal segmental glomerulosclerosis (FSGC) share immunologic and pathogenetic features. We studied 93 Brazilian patients (46 with SSNS and 47 with FSGC) and 104 control subjects with the objective of characterizing the immunogenetic profile of these varieties of idiopathic nephrotic syndrome. HLA-A, -B, and -DR antigens were typed using a complement-dependent microlymphocytotoxicity assay. No significanty association was observed with HLA-A or -B antigens in either group; however, HLA-B7 and -B12 antigens were increased in SSNS patients. HLA-DR7, -DR1 and the combination of HLA-DR1/DR7 antigens were significantly increased in the total group of patients with SSNS compared to controls or to FGSC patients. The study of only Caucasoid individuals revealed that HLA-DR7 antigen remained significantly increased in SSNS patients. The HLA-B7/DR7 haplotype was siginificantly increased in both SSNS and FSGC patients. Although the Brazilian population is highly miscigenated, the same antigen (HLA-DR7) which confers susceptibility to SSNS in other Caucasian population is still prevalent in this series.

UNITERMS: HLA Antigens. Nephrotic Syndrome. Glomerulosclerosis, Focal.

1. INTRODUCTION

The etiology and pathogenesis of idiopathic nephrotic syndrome remain obscure. Two major varieties are described: minimal change disease (MCD) and focal segmental glomerulosclerosis (FSGC)[(1)]. MCD, also designated steroid-sensitive nephrotic syndrome (SSNS), is more common in children, responds to glucocorticoid therapy[(2)]. Although FSGC can affect patients at any age, most cases are seen

between 25 and 35 years[3]. Since there is the possibility of transition from MCD to FSGC, it has been hypothesized that these diseases are two extremes of one spectrum and may represent different stages of a single disease[1,4]. It is also assumed that both conditions share immunopathogenetic mechanisms, i.e., association with diseases showing well-established immunologic features, response to glucocorticoids, alkylating agents and cyclosporine, increased incidence of atopic disorders in SSNS and recurrence of nephrotic syndrome after renal transplantation in FSGC[1,2,5] . In addition, the diseases associated with idiopathic nephrotic syndrome share several immunological alterations such as the presence of circulating factors which promote proteinuria and increased serum levels of autoreactive IgA antibodies and interleukins[5/10]. In family studies, the presence of multiplex cases of idiopathic nephrotic syndrome sharing HLA antigens has suggested the influence of immunogenetic markers[2,11]. Immunogenetic studies of unrelated patients conducted on distinct populations have shown associations with HLA class I (HLA-B8, –B12) and class II (HLA-DR7) antigens for idiopathic nephrotic syndrome patients irrespective of the variant FSGC[12/17]. In order to identify the immunogenetic profile in a Brazilian population from the Northeast region of the State of São Paulo presenting with SSNS or FSGC, and to address the question of whether SSNS and FSGC share immunogenetic markers, we typed HLA- (A,-B and -DR) antigens in 2 series of patients presenting with one of these two conditions. Considering that the Brazilian population is highly miscegenated, we further compared HLA frequency between Caucasoid patients (SSNS and FSGC) and controls.

2. PATIENTS AND METHODS

2.1. Subjects

Forty-six (29 males) steroid-sensitive nephrotic syndrome patients, age of onset 1-10 years (median = 3), 38 Caucasoids (83%), 5 Mulattoes (11%) and 3 Negroes (6%), seen at the Division of Pediatric Nephrology, School of Medicine of Ribeirão Preto, University of São Paulo, Brazil, from 1986 to 1995, were studied. A total of 26 children were diagnosed before the age of 4 and 20 after that age. The diagnosis of SSNS was performed on the basis of clinical and laboratory evidence of nephrotic syndrome, i.e, edema and proteinuria > 40 mg/hour/m^2/day, and serum albumin < 3.0 g/dl. Neither macroscopic hematuria nor elevation of arterial pressure was observed. All patients responded to treatment with 60 mg/m^2/day predisone for 4-6 weeks, presenting remission of clinical and laboratory features of nephrotic syndrome. After a follow-up period of 5 years, 148 relapses, ranging from 1 to 11 (median=3 relapses), occurred in 38 (83%) of these patients, and 19 patients were steroid-dependent. These patients who responded to the treatment with prednisone were included in the SSNS group.

Forty-seven (29 males) patients with idiopathic focal segmental glomerulosclerosis, aged 12-74 years (median = 31), 37 Caucasoids (79%), 5 Mulattoes (12%) and 4 Negroes (9%), seen at the Division of Nephrology, School of Medicine of Ribeirão Preto, University of São Paulo, Brazil, from 1986 to 1995, were also studied. The clinical/laboratory features of the patients can be summarized as follows: a) all patients presented nephrotic syndrome; b) 14 (30%) had normal blood pressure and creatinine clearance; c) 18 (38%) presented hypertension and low creatinine clearance; d) 15 (32%) exhibited only hypertension or only low creatinine clearance; e) relapses were observed in 16 patients (34%). All patients underwent renal biopsy (light plus immunofluorescence microscopy) which was characteristic of FSGS. Other underlying diseases were excluded. Treatment with prednisone 1.0 mg/kg body weight, or alkylating agents (cyclosphosphamide or chlorambucil) combined with low doses of prednisone was followed by complete remission (38%) or partial remission (17%) or absence of remission (29%). Five patients (10%) had end-stage renal disease and 2 (4%) were on enalapril treatment.

A total of 104 control individuals, 85 Caucasoids (82%), 14 Mulattoes (14%) and 4 Negroes (4%), from the same geographical area and presumably of similar ethnic background, were also typed for HLA antigens.

2.2. HLA antigens

Mononuclear peripheral blood cells were isolated using a Ficoll-Hypaque gradient at a density of 1.077 g/ml. B-lymphocytes were recovered by adherence to nylon wool (Robbins Scientific - USA). HLA typing was performed using a complement-dependent microlymphocytotoxicity assay[18]. The following antisera were used: HLA - A(A1, A2, A3, A9, A10, A11, A19, A23, A24, A25, A26, A28, A29, A30, A31, A32, A33, A34, A36); HLA-B(B5, B7, B8, B12, B13, B14, B15, B16, B17, B18, B21, B22, B27, B35, B37, B38, B39, B40, B41, B42, B44, B45, B47, B48, B49, B50, B51, B52, B54, B55, B56, B60, B61, B64, B65,

B70) and HLA - DR (DR1 - DR10), DR52, DR53, from France Transplant (France) and Biotest (Germany). Complement was obtained from a pool of normal rabbit sera.

2.3. Statistical analysis

Comparisons of HLA frequencies between patients and controls were estimated using the two-tailed exact Fisher test, with corrections of p value (pc) according to the number of HLA specificities tested and the number of comparisons. Differences were considered significant only when pc< 0.05. Relative risk (RR), which indicates how many times more often the disease occurs in individuals with the HLA marker compared to those without it was calculated. A relative risk greater than 1 is seen when the antigen is more frequent in patients than in controls and indicates an increased risk to develop the disease. When the RR is greater than 1 the etiologic fraction (EF) can be estimated and it is also called the attributable risk at the population level, i. e., the EF indicates how much the HLA marker under study contributes to the development of the disease at population level [19].

3. RESULTS

The frequency of HLA-A, -B, and -DR antigens observed among patients (SSNS and FSGS) and controls is shown in Tables I-III. In addition, the frequency of HLA antigens, studying only Caucasoid patients and controls, is also shown in these tables.

No significant HLA-A or -B association with SSNS or FSGS was found (Tables I and II).

Compared to the respective control group, HLA-DR7 antigen was significantly increased in total group and Caucasoid patients presenting with SSNS (pc = 0.016 and 0.017, respectively), conferring RR of 4.31 and 4.29, respectively, and an EF of 0.4 for both groups. HLA-DR1 antigen was significantly increased only in the total group of SSNS patients (pc = 0.036), conferring an RR of 3.83 and a EF of 0.45 (Table III). Comparisons within subsets of SSNS (no relapses, infrequent relapses or frequent relapses, and age of onset < 4 years or >4 years) did not show significant differences. In the SSNS group as a whole, the combination of both HLA-DR1/DR7 antigens occurred in 15 of 46 patients and in only 3 of 104 controls (pc < 0.001, RR = 15.30, EF = 0.31).

Table I - Frequency (%) of HLA-A antigens in patients with steroid-sensitive nephrotic syndrome (SSNS), focal segmental glomerulosclerosis (FSGS), and control individuals, regarding all ethnic groups (total) and only the Caucasoid (Cauc) group

HLA-A	SSNS		FSGS		CONTROL	
	Total (n=46)	Cauc (n=38)	Total (n=47)	Cauc (n=37)	Total (n=104)	Cauc (n=85)
A1	39	42	32	38	24	22
A2	46	39	45	43	48	52
A3	24	26	17	13	12	12
A9	37	37	21	18	24	18
A10	2	3	4	5	17	16
A11	17	18	10	5	16	16
A23 (9)*	-	-	6	8	3	3
A25 (10)	-	-	2	-	4	3
A28	20	16	21	22	10	9
A29 (19)	2	3	4	5	10	8
A30 (19)	-	-	6	8	4	3
A31 (19)	-	-	-	-	4	3
A32 (19)	-	-	-	-	5	3
A33 (19)	-	-	6	8	2	1
A34 (10)	-	-	2	-	-	-
A36	-	-	4	5	-	-

* ( ) splits of HLA-A

Table II - Frequency (%) of HLA-B antigens in patients with steroid-sensitive nephrotic syndrome (SSNS), focal segmental glomerulosclerosis (FSGS), and control individuals, regarding all ethnic groups (total) and only the Caucasoid (Cauc) group

HLA-B	SSNS		FSGS		CONTROL	
	Total (n=46)	Cauc (n=38)	Total (n=47)	Cauc (n=37)	Total (n=104)	Cauc (n=85)
B5	28	21	28	32	13	13
B7	39	37	23	27	15	16
B8	6	8	27	24	15	15
B12	37	42	17	11	15	19
B13	4	5	10	11	11	11
B14	11	10	6	8	16	18
B15	2	3	-	-	7	6
B16	-	-	-	-	1	1
B17	-	-	8	8	4	5
B18	-	-	8	8	19	21
B21	19	24	4	3	16	19
B22	2	3	2	3	2	2
B27	2	-	2	3	2	2
B35	15	5	8	11	22	15
B37	-	-	2	3	1	1
B38 (16)*	-	-	-	-	1	1
B39 (16)	-	-	2	-	2	2
B40	-	-	4	-	2	-
B41	5	5	-	-	2	1
B44 (12)	-	-	10	13	7	6
B45 (12)	-	-	4	5	2	1
B65 (14)	-	-	2	3	-	-

* ( ) splits of HLA-B

The comparisons of HLA-DR antigen frequency between patients with FSGS (total group or only Caucasoid) and controls were all non-significant; however, the comparison of these frequencies between the total group of SSNS and FSGS patients showed an increased frequency of both HLA-DR1 and HLA-DR7 in SSNS patients (pc = 0.008 and 0.026, respectively). Estimation of RR and EF for these specificities were 5.75, 0.50 and 5.32, 0.42; respectively.

Considering the HLA-B/DR haplotypes more frequently associated with HLA-DR7 and DR1 in the Brazilian population, i.e., HLA-B7/DR7, B12/DR7, B12/DR1, B14/DR1, B5/DR1[20], haplotype HLA-B7/DR7 was significantly increased in SSNS patient (total group and only Caucasoids), and in FSGS (Table III). The susceptibility conferred by each of HLA-B7 or HLA-DR7 antigen was independent for SSNS patients (Table IV). The haplotypes HLA-B12/DR7 and HLA-B12/DR1 were also significantly increased in SSNS patients from the total group and from the Caucasoid group (Table III).

Table III - Frequency (%) of HLA-DR antigens and HLA-B/DR haplotypes in patients with steroid-sensitive nephrotic syndrome (SSNS), focal segmental glomerulosclerosis (FSGS), and control individuals, regarding all ethnic groups (total) and only the Caucasoid (Cauc) group. The corrected p value (pc), the relative risk (RR) and the etiologic fraction (EF) were estimated by comparing patients from each group with respective controls

HLA-DR	SSNS		FSGS		CONTROL	
	Total (n=46)	Cauc (n=38)	Total (n=47)	Cauc (n=37)	Total (n=104)	Cauc (n=85)
DR1	61*	60	21	24	29	28
DR2	52	53	40	40	38	40
DR3	6	5	21	19	27	32
DR4	17	13	17	22	22	20
DR5	8	10	36	30	21	21
DR6	-	-	14	16	6	7
DR7	52**	55***	17	19	20	22
DR8	-	-	6	8	2	2
DR9	-	-	2	-	1	1
DR10	2	3	2	3	1	1

* pc = 0.036; RR = 3.83; EF = 0.45
** pc = 0.016; RR = 4.31; EF = 0.40
*** pc = 0.017; RR = 4.29; EF = 0.40

Haplotypes HLA-B/DR (number of individuals)

B7/DR7	13 ◊	15 ◊	6 ◊	8	1	1
B12/DR7	17 ◊	21 ◊	4	3	2	2
B12/DR1	26 ◊	31 ◊	2	5	3	3

◊ $p \leq 0.004$

Table IV - Frequency of HLA-B7 and non-HLA-B7 antigens between HLA-DR7 positive and negative individuals, and frequency of HLA-DR7 and non-HLA-DR7 antigens between HLA-B7 positive and negative individuals. The number of individuals from the total group and from the Caucasoid group is indicated in square brackets. The calculation of the relative risk and of the p value among individuals with and those without the HLA marker is also shown. Numbers in parentheses refer to the estimation of the RR and p values for individuals in whom the HLA marker was absent

Populations	Number of individual in which HLA-B7 is:			
	Present	Absent	RR	P
HLA-B7$^+$ SSNS	7 [7]	11 [11]	9.5 (8.3)	0.04 (0.01)
HLA-B7$^+$ Control	1 [1]	15 [13]		
HLA-B7$^-$ SSNS	16 [13]	12 [7]	4.5 (5.5)	0.002 (0.001)
HLA-B7$^-$ Control	20 [18]	68 [53]		

	Number of individual in which HLA-B7 is:			
	Present	Absent	RR	p
HLA-DR7$^+$ SSNS	7 [6]	16 [14]	8.7 (7.7)	0.02 (0.09)
HLA-DR7$^+$ Control	1 [1]	20 [18]		
HLA-DR7$^-$ SSNS	11 [8]	12 [10]	4.1 (3.3)	0.005 (0.01)
HLA-DR7$^-$ Control	15 [13]	68 [53]		

SSNS - steroid-sensitive nephrotic syndrome

4. DISCUSSION

Since there is possibility of transition from MCD to FSGC, and since these two varieties of idiopathic nephrotic syndrome share immunological abnormalities, it is possible that the presentation of one variety or the other may depend upon immunogenetic markers. Most of the studies on HLA antigens have investigated the frequency of these antigens in these two conditions usually considered together. In this study, we have characterized serological HLA typing of patients presenting with SSNS or FSGC in a Brazilian population from the Northeast region of the State of São Paulo.

Although we did not find any significant association of HLA-A or -B antigens with SSNS or FSGC, some studies have reported association of HLA-B8 and HLA-B12 (including splits HLA-B44 and -B45), and HLA-B13 in English[21], South African[22], German and Irish children with SSNS[12,23,24]. In contrast, HLA-A28 and HLA-B12 have been associated with FSGC in North American Black or White children and in German children[12,15,25]. On the other hand, studies conducted on French or Japanese children with SSNS[13,14,26], and on White or Black North American patients with FSGC[27] have not shown any association with HLA-A or -B antigens.

HLA-DR7 specificity and the HLA-B7/DR7 haplotype were overrepresented in our series of patients with SSNS, both when considering the whole group or just the Caucasoid group. Since HLA-B7 is in linkage disequilibrium with HLA-DR7 in the Brazilian population[20], we next determined whether the susceptibility conferred by these antigens was dependent on this linkage disequilibrium. In order to detect the strongest association, we estimated the RR and EF for HLA-B7 (3.51 and 0.28, respectively) and for HLA-DR7 (4.31 and 0.40, respectively). In addition, we evaluated the presence of HLA-B7 antigen in patients and controls possessing or not the HLA-DR7 antigen, and the presence of HLA-DR7 in patients and controls possessing or not the HLA-B7 specificity (Table IV). Considering that, in all the combinations of HLA-B7/DR7 antigens studied, the RR and EF were high for both antigens, we concluded that these susceptibility markers were independent. There are several reports showing increased frequency of HLA-DR7 antigen in children with SSNS of distinct ethnic background, i. e., Australian[28], French[13,14,17], Spanish[29], German[15/17], English[30], North American[31] and Chinese children[32], whereas HLA-DR8 antigen is observed only in adult Japanese patients[33]. In addition, HLA-DQ2 antigen and the combination of HLA-DR3/DR7 antigens have also been positively associated with SSNS, whereas HLA-DR2, -DR6 and -DQ1 have been negatively associated with SSNS in children of French and German ancestry[17]. Besides serological HLA typing, restriction fragment length polymorphism typing of HLA*DRB and *DQB genes has also indicated increased frequency of HLA-DRB1*0701 and HLA-DQB1*0201 alleles in French, German and English patients with SSNS [16,17,30]. On the other hand, HLA-DR3 antigen and the HLA-DR3/DR7 or HLA-B8/DR3/DR7 combinations have been associated with steroid-resistant nephrotic syndrome in French and German children[14,15,17]. In addition to HLA-DR7 and HLA-DR1 antigen, the combination of HLA-DR1/DR7 antigens was also overrepresented in our series of SSNS patients as the whole group. Since HLA-DR1 has never been previously associated with SSNS, this specificity could be a characteristic marker for SSNS in this Brazilian population.

Although neither HLA-B7 nor HLA-DR7 antigens were increased in FSGC patients (total group or only Caucasoids), the frequency of haplotype HLA-B7/DR7 was significantly increased in relation to the control population. There are few studies evaluating HLA antigens exclusively in patients with FSGC. Family studies conducted on Hispanic[34] and Australian[35] siblings with FSGC have indicated the presence of HLA-DR8 and HLA-DR3/DR7 antigens, respectively. In unrelated patients, Glicklich et al. [25] reported an increased frequency of HLA-DR4 antigen in both White and Black North American patients with idiopathic FSGC. Freedman et al.[27], studying 605 renal transplant recipients with renal failure due to FSGC, detected no significant association with HLA-DR antigens in African Americans or Caucasian patients. Although these authors did not mention whether the patients had idiopathic or secondary FSGC, their results are similar to ours. In contrast, Gerbase-de-Lima[36] studying 19 Brazilian patients from the city of São Paulo presenting with FSGS (16 White and 3 of Japanese origin) found an association with HLA-DR4 antigen. The non-observation of significant association with HLA-DR antigens, as reported in this study, did not mean absence of association. Perhaps the study of HLA-DQ and DP specificities may disclose such an association. The comparative immunophenotyping of

kidney biopsies from normal versus FSGC individuals revealed a reduction of HLA class II antigens along with increased CD8-positive lymphocytes in sclerotic glomeruli, and an abnormal expression of HLA-DQ and -DP antigens in proximal tubular epithelial cells together with increased numbers of interstitial CD4-positive lymphocytes[37], suggesting the participation of HLA-DQ and -DP molecules in the pathogenesis of FSGC.

In conclusion, even though the genetic features of the Brazilian population are non-homogeneous, our series of patients with SSNS (total group or only Caucasoids) presented an immunogenetic marker (HLA-DR7) which is similar to that observed in more homogeneous Caucasoid populations reported in the literature. In addition, the haplotype HLA-B7/DR7, HLA-DR1 antigen and the combination of HLA-DR1/DR7 antigens may represent peculiar immunogenetic markers for SSNS Brazilian patients. In contrast, patients with FSGC presented no detectable HLA-A, -B or -DR antigen association; however, the HLA-B7/DR7 haplotype was also overrepresented in this series. Therefore, besides immunologic and pathogenic features, SSNS and FSGC also share increased frequency of the HLA-B7/DR7 haplotype. Although there are some diseases defined as idiopathic nephrotic syndrome, they may represent different stages of a single disease, depending on the immunogenetic background of the patient. Certainly, this subject deserves further investigation. The study of the major histocompatibility complex alleles at the molecular level may identify susceptibility/protective genes responsible for the association of HLA and idiopathic nephrotic syndrome.

DOMINGOS NAM; PAULA-SANTOS CM; FRANCO PB; KIMACHI T; VOLTARELLI JC & DONADI EA. Características imunogenéticas da síndrome nefrótica corticossensível e da glomerulosclerose segmentar e focal em pacientes brasileiros da região nordeste do estado de São Paulo. **Medicina, Ribeirão Preto, 33:** 47-54, jan./mar. 2000.

RESUMO: A síndrome nefrótica corticossensível (SNCS) e a glomerulonefrite esclerosante segmentar e focal (GESF) compartilham características imunológicas e patogênicas. Foram estudados 93 pacientes brasileiros (46 com SNCS e 47 com GESF) e 104 indivíduos-controle, para caracterizar os perfis imunogenéticos dessas variedades de síndromes nefróticas idiopáticas. Os antígenos HLA-A, -B e –DR foram tipificados, usando-se método sorológico. Embora nenhuma associação com os antígenos HLA-A ou –B fosse observada, as freqüências dos antígenos HLA-B7 e –B12 estavam significantemente elevadas nos pacientes com SNCS. Os antígenos HLA-DR7, HLA-DR1 e a combinação de antígenos HLA-DR1/DR7 estavam significantemente elevados nos pacientes com SNCS, em relação aos indivíduos-controle, ou em relação aos pacientes com GESF. A avaliação somente de pacientes caucasóides revelou que o antígeno HLA-DR7 continuava elevado nos pacientes com SNCS. O haplótipo HLA-B7/DR7 estava significantemente elevado nos pacientes com SNCS e GESF. Embora a população brasileira seja altamente miscigenada, a freqüência do antígeno HLA-DR7, que confere susceptibilidade a SNCS em outras populações, estava também elevada na série de pacientes caucasóides aqui estudada.

UNITERMOS: Antígenos HLA. Síndrome Nefrótica. Glomerulosclerose Focal.

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