HLA PHENOTYPES AND IDIOPATHIC NEPHROTIC SYNDROME IN CHILDREN

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Summary

Ninety-four children with idiopathic nephrotic syndrome (17 steroid-resistant with a histological diagnosis of a focal segmental glomerulosclerosis) were typed for HLA-A, B and DR antigens. The patients showed a significant increase of DR7 (58% vs 18%, $p < 0.0001$) and of B8-DR3 (27% vs 5%, $p < 0.05$). Combination of both markers (DR7 and B8-DR3) was observed in 14 per cent of patients but in none of the controls (relative risk 15.2). Patients with B8-DR3 and DR7 had a more severe course of INS.

Introduction

In 1976 Thomson et al [1] described an association between HLA-B12 and steroid-responsive idiopathic nephrotic syndrome (INS) in children. Other

TABLE I. HLA-antigens and idiopathic nephrotic syndrome

Year	Author	Number of patients studied	Antigen	Patients	Controls	
1976	Thomson	71	B8	42%	25%	
1980	Lenhard	146	B8	27%	18%	
1980	O'Regan	54	B8	64%	34%	$p < 0.01$
1981	Noss	45	B8	72%	38%	$p < 0.03$
1976	Thomson	71	B12	54%	24%	$p < 0.02$
1980	Trompeter	45	B12	44%	25%	
1981	Noss	45	B13	20%	4%	$p < 0.0002$
1980	Alfiler	45	DR7	71%	30%	$p < 0.005$
1980	Mouzon-Cambon	54	DR7	67%	31%	$p < 0.001$
1982	Nunez	50	DR7	72%	38%	$p < 0.001$

investigators [2–6] found different INS associated HLA-A, B antigens, namely B8, B12 or B13. Alfiler [7] first reported a significant increase of HLA-DR7. This finding was confirmed by Mouzon-Cambon et al [8] and Nunez-Roldan et al [9]. Table I summarises these previous findings.

This study re-evaluates the associations between HLA and INS in a large group of paediatric patients. In addition, clinically and/or histologically well-defined INS subsets were analysed separately.

Materials and methods

Ninety-four patients with INS subdivided in the following clinical subgroups according to the international classification [10–12]:

1. Fourteen steroid-sensitive patients with no or only infrequent relapses (NR/IR). Eight had histologically confirmed minimal change lesions.
2. Forty steroid-sensitive patients with frequent relapses (FR), which were usually corticoid-dependent (CD). Thirty-three had histologically confirmed minimal change lesions.
3. Seventeen steroid-resistant patients. All showed focal segmental glomerulosclerosis on biopsy (FSGS).

In 23 cases no clear-cut subclassification could be made. Patients were usually treated according to the protocols of the International Study of Kidney disease [11] and the Arbeitsgemeinschaft für Pädiatrische Nephrologie [12].

A patient was defined as atopic if he had a history of allergy, a positive skin prick tests, and/or specific IgE antibodies to allergens as measured by radio-allergo-absorbent test (RAST). Nine patients were characterised as atopic and 20 non-atopic.

HLA typing was performed using the microlymphocytotoxicity test, 37 HLA-specifities (HLA-A:12, B:18, DR:7) were tested by a panel of 240 well defined antisera. One hundred healthy blood donors served as controls. Relative risks (RR), χ^2 and p values were calculated by Woolf's and Woolf Haldane's method. All p values in this study are corrected for the number of antigens tested (p = p corrected). In 14 patients HLA haplotypes were verified by family studies.

Results

No HLA-A or B antigen frequency in INS patients significantly differed from the controls, whereas the frequency of HLA DR7 was highly significantly increased: 53% vs 18%, $p < 0.0001$, relative risk (RR) 6.8. For the combination of B8 and DR3 a significantly increased frequency was also detected: 27% vs 5%, $p < 0.05$, RR = 7.0. Table II summarises these results. The increase of B8 and DR3 is only due to the combined occurrence as computed in Table IIIa. Haplotypes were determined in 14 B8 and DR3 phenotypic INS patients: without exception they also had the B8-DR3 haplotype (Table IIIb). Remarkably, the simultaneous presence of B8-DR3 and DR7 was found in 14 per cent of patients but in none of the controls (RR = 15.2).

TABLE II. Antigen frequencies in 94 INS patients and 100 controls

Antigen	Patients	Controls	Significancy	
A1	37%	25%	NS	
A2	46%	51%	NS	
A3	17%	25%	NS	
A9	22%	28%	NS	
A10	14%	8%	NS	
A11	15%	12%	NS	
A28	1%	8%	NS	
A29	12%	8%	NS	
Aw30	5%	5%	NS	
Aw31	0%	4%	NS	
Aw32	11%	5%	NS	
Aw33	2%	2%	NS	
B5	10%	13%	NS	
B7	12%	16%	NS	
B8	26%	13%	NS	Relative risk 2.5
B12	38%	24%	NS	
B13	12%	4%	NS	
B14	1%	7%	NS	
B15	16%	15%	NS	
B16	9%	9%	NS	
B17	12%	7%	NS	
B18	8%	10%	NS	
Bw21	10%	9%	NS	
Bw22	8%	7%	NS	
B27	7%	15%	NS	
Bw35	14%	19%	NS	
B37	3%	3%	NS	
B40	12%	14%	NS	
Bw41	3%	3%	NS	
Bw53	0%	1%	NS	
DR1	12%	18%	NS	
DR2	13%	27%	NS	
DR3	31%	14%	NS	Relative risk 2.7
DR4	23%	29%	NS	
DR5	32%	34%	NS	
DRw6	14%	13%	NS	
DR7	53%	18%	$p < 0.0001$	Relative risk 6.8
B8-DR3	27%	5%	$p < 0.05$	Relative risk 7.0
B8-DR3,DR7	14%	0%		Relative risk 15.2*

* Antigen frequency in controls was calculated as 1 instead of 0

TABLE III. Analysis of the antigen combination B8-DR3

A *Combination of B8 and DR3 in patients versus controls:*		B *B8-DR3 phenotype and B8-DR3 haplotype*	
B8+,DR3+:B8+,DR3−	RR = 11* p = 0.01	Number of B8-DR3 phenotype:	25
B8+,DR3+:B8−,DR3+	RR = 5* p = 0.02	Verification of patient's haplotypes:	14
B8−,DR3+:B8−,DR3−	RR = 0.7 NS	B8-DR3 haplotype:	14**
B8+,DR3−:B8−,DR3−	RR = 0.3 NS		

* Only the relative risk (RR) of patients with combined B8-DR3 is increased
** B8,DR3 phenotype in tested patients is always identical with B8-DR3 haplotype

In the different clinical groups, no differences could be detected in frequency of DR7 or B8-DR3: DR7 was found in 57 per cent in the NR/IR, 58 per cent in the FR/CD ($p < 0.005$), and 40 per cent in the FSGS patients; B8-DR3 in 21 per cent in NR/IR, in 27 per cent FR/CD ($p < 0.05$), and in 24 per cent in FSGS. Surprisingly, there were striking differences in the simultaneous occurrence of B8-DR3, DR7: 7 per cent (1 out of 14, RR 7.6) in NR/IR, 20 per cent (8 out of 40, RR 20.0) in FR/CD and 18 per cent (3 out of 17, RR 16.7) in FSGS. In Figure 1, relative risks for different subsets are shown.

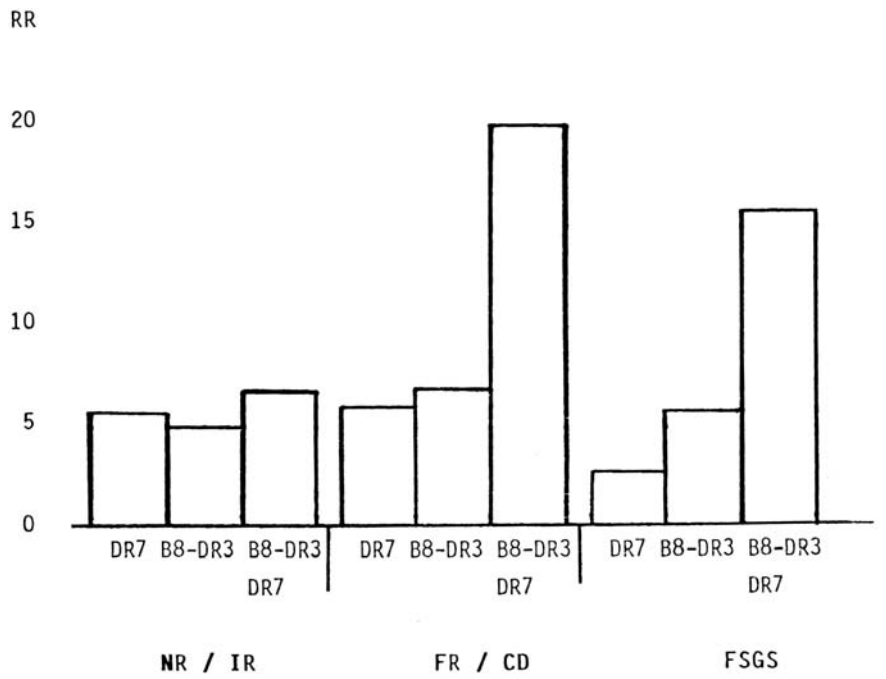

Figure 1. Relative risks for INS in different clinical groups. Relative risk (RR) for different subgroups is constant for DR7 or B8-DR3, but combined occurrence of both HLA markers coincides with a severe course of disease

No differences were found in the small group of well defined atopic and non-atopic patients.

Discussion

Apart from the Finnish type, the aetiology and pathogenesis of INS is completely unknown. Familial incidence is about 3–7 per cent and siblings are usually involved [13, 14]. Atopic features are more common in INS-patients [1]. Impaired T cell function and other immunogenetic factors have been proposed [15–17]. In addition, an increased frequency of DR7 has been reported by several groups [7–9]. Furthermore, we observed not only increased frequency of DR7 but also of B8-DR3. Interestingly, the simultaneous presence of both markers coincides with a severe course of disease. This may be explained by at least two different HLA-linked genes predisposing to INS. This hypothesis will have to be confirmed by further family studies. In any case, our data indicate that immunogenetic factors play a major role in the pathogenesis of INS.

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Open Discussion

UNIDENTIFIED SPEAKER Have you seen any influence of the HLA system on iron metabolism?

RUDER We have not investigated this.