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IgA NEPHROPATHY OCCURRING IN TWO SIBLINGS OF THREE FAMILIES*

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There have been suggestions in the literature that IgA nephropathy may be familial. Genetic factors may influence the development of disease in an association between HLA antigens and IgA nephropathy. At the present time, no conclusion can be drawn. Here, two siblings with typical IgA nephropathy in three families are presented. A relation between HLA and IgA nephropathy was not detected in these family studies. The first family involved a 14-year-old girl and her brother, who at the age of 12 years were admitted to the hospital with macroscopic hematuria. All of the investigations, including serum IgA levels (104 mg/dl and 102 mg/dl respectively) showed normal kidneys with IgA deposition in the mesangium of the glomeruli. In the second family, a 15-year-old boy and his brother at nine years of age were admitted with macroscopic hematuria and gross hematuria, respectively. Laboratory investigations were normal. The serum IgA level (287 mg/dl) was normal in the first patient but the second was elevated at 485 mg/dl. IgA deposits were observed in the glomerular mesangium in these patients. The third family consisted of a 15-year-old boy and his nine-year-old sister who were both admitted with microscopic hematuria. Serum IgA levels (193 and 131 mg/dl, respectively) and laboratory investigations were normal. Renal biopsy specimens revealed C3 and IgA depositions in the glomerular mesangium of both siblings. In the first family the patients were HLA identical, while in the others the siblings were one-haplotype identical. Although IgA nephropathy and HLA antigens are strongly associated in the literature, we could not find this association. *Key words: IgA nephropathy, familial, HLA, lymphocyte subsets.*

Primary IgA nephropathy (pIgAN) is a clinical entity characterized by recurrent hematuria, asymptomatic microhematuria and/proteinuria in the absence of systemic disease, liver disease or lower urinary tract diseases. Inherited factors are known to be important in the pathogenesis of IgA nephropathy[1,2]. Recently, the occurrence of the disease in siblings, or one or more family members of patients, has been reported[3,4]. In this report, two siblings with typical IgAN in three families are presented. Routine biopsy of the siblings at the onset of disease revealed extensive IgA deposition in the mesangium; six patients, two parents and four healthy family members appear not to have a single identical HLA

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antigen, and have some immunological abnormalities. We speculated that these findings indicate that the pathogenesis of IgA nephropathy may be under genetic control in some patients.

Case Reports

Family 1

A 14-year-old girl and her 12-year-old brother were admitted to the hospital with macroscopic hematuria. Both were found to have normal blood pressure (100/70 mmHg and 110/80 mmHg). All of the laboratory investigations, including serum IgA levels (104 mg/dl and 102 mg/dl respectively) were normal (Table I).

Table I: Clinical and Laboratory Findings

	Family 1		Family 2		Family 3	
	Boy	Girl	Boy	Boy	Boy	Girl
Age at onset (years)	14	12	15	9	13	8
Follow-up period (years)	7	2	5	1.50	2	0.50
Blood pressure (mmHg)	100/70	110/80	120/80	95/70	120/80	95/70
Urine analysis						
Osmolarity (mOsm/kg)	915	825	625	886	545	950
Proteinuria (g/day)	0.21	0	1.05	0	0	0
Urine sediment (RBC/hpf)	100	50-100	100	100	100	50-100
Dysmorphism (%)	55	60	75	70	50	50
Ca/Creatinine ratio	0.01	0.05	0.08	0.07	0.11	0.13
Blood						
Na (mEq/L)	148	140	138	142	140	140
K (mEq/L)	5.00	4.00	4.50	3.90	4.20	4.60
Ca (mEq/L)	5.50	5.00	5.20	5.40	4.70	5.10
P (mg/dl)	4.60	4.60	3.80	4.00	4.40	4.80
ALP (KAU)	14.70	21.30	14	12.70	14	19
BUN (mg/dl)	10	10	10	10	14	8
Creatinine (mg/dl)	0.50	1.1	0.50	1.20	0.90	0.50
GFR (ml/min/1.73m^2)	183	146	175	71	100	184
Cryoglobulin (mg/dl)	(–)	(–)	(–)	(–)	(–)	(–)
C3 (mg/dl)	104	155	124	90	105	117
IgA (mg/dl)	104	102	287	485	193	101
Radiological investigations (US, IVI, VCU)	N	N	N	N	N	N

RBC/hpf: red blood cells per high-power field, ALP: alkaline phosphatase, BUN: blood urea nitrogen, GFR: glomerular filtration rate, US: renal ultrasound scan, IVU: intravenous urography, VCU: voiding cycto-urethrography.

Immunofluorescence studies of kidney biopsies showed deposition of IgA and C3 in the mesangium of the glomeruli in both siblings. Histological findings revealed mesangial, endothelial cell proliferation with crescent formation in four of 28 glomeruli in the sister (grade II according to the World Health Organization classification) (Fig. 1), and a mild increase in the mesangial matrix in the brother (grade I).

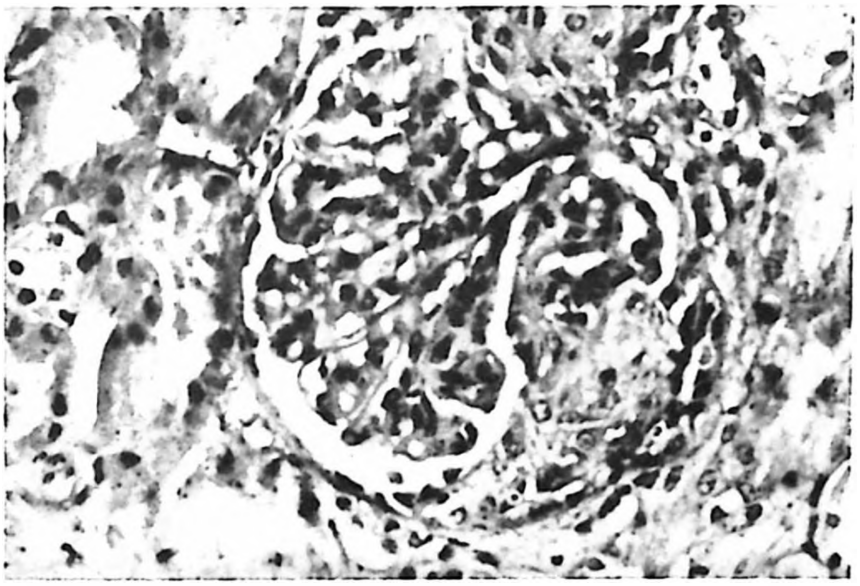

Fig. 1: One of four glomeruli with crescent formation showing a global mesangial increase in the renal biopsy from the female patient with IgA nephropathy in the first family. (H.E. x 40).

Family 2

A 15-year-old boy and his nine-year-old brother were admitted with macroscopic hematuria and gross hematuria, respectively. Blood pressures were normal (120/80 mmHg and 95/70 mm/Hg). The serum IgA levels were normal in the first patient (287 mg/dl) and elevated in the second (485 mg/dl). The other laboratory investigations were normal (Table I). On immunofluorescence studies of renal biopsy specimens, C3 and IgA depositions were observed in the glomerular mesangium in both patients. Light microscopy showed a segmental increase in matrix with cell proliferation in the first boy (grade II, Fig. 2) and segmental cell proliferation in his younger brother (grade I).

Family 3

A 15-year-old boy and his nine-year-old sister were admitted with microscopic hematuria. Blood pressures were normal (120/70 mmHg and 90/70 mmHg). Serum IgA levels (193 mg/dl and 131 mg/dl, respectively) were normal, as were

Fig. 2: Glomerulus in the renal biopsy from the first male child of the second family shows segmental minimal mesangial cell proliferation (arrows) and increased matrix (arrowhead). (H.E. x 40).

the other laboratory investigations (Table I). Immunofluorescence studies of renal biopsy specimens revealed C3 and IgA depositions in the glomerular mesangium in both siblings. On light microscopy studies an increase in matrix with segmental and global cell proliferation in the brother and a mild increase in matrix at some sites in the sister were observed (grade II).

HLA Characteristics

HLA typing was performed in all six patients, and in the fathers and two healthy siblings in the first and second families. In the first family the mother had died; the mother in the second family and the parents and healthy siblings in the third family were unwilling to participate in the investigation. Although there were no HLA-identical siblings in the second family, we observed identity/similarity in HLA antigens [HLA A2-A3-B52(5)-B35-DR11-DR13-DQ6-DQ7] in the first family and [HLA A68(28)-B27-DR4-DQ7] in the third family (Table II).

The pedigrees for the families are shown in Figure 3.

Immunological Findings

The lymphocyte subsets of peripheral blood were examined in the patients by flow cytometry. No significant change in T cell, CD4 or CD8 levels or in the CD4/CD8 ratio were observed in flow cytometry. Increased expression of IL-2 receptors and HLA-DR (+) T cell on T lymphocytes were observed during the

Table II: HLA Characteristics of the Patients and their Relatives

Family 1	HLA A	HLA-B	HLA-DR	HLA-DQ
Male patient	A2, A3	B35, B52	DR11, DR13	DQ6, DQ7
Female patient	A2, A3	B35, B52	DR11, DR13,	DQ6, DQ7
Sister	A1, A10	B16, B50	DR4, DR7	DQ2, –
Father	A1, A3	B50, B52	DR11, DR7	DQ2, DQ7
Mother	Exitus			
Family 2				
Elder male patient	A2, –	B5, –	DR4, DR13,	DQ2, DQ7
Young male patient	A2, –	B44, B35	DR4, DR11	DQ2, DQ7
Brother	A2, A33	B44, B22	DR11	DQ7
Daughter	A2, A24	B5, B44	DR4, DR11	
Father	A2, A24	B5, B22	–	–
Family 3				
Male patient	A68, A29	B8, B27	DR17, DR4	DQ2, DQ7
Female patient	A24, A68	B27, B35	DR4, DR11	DQ4, DQ7

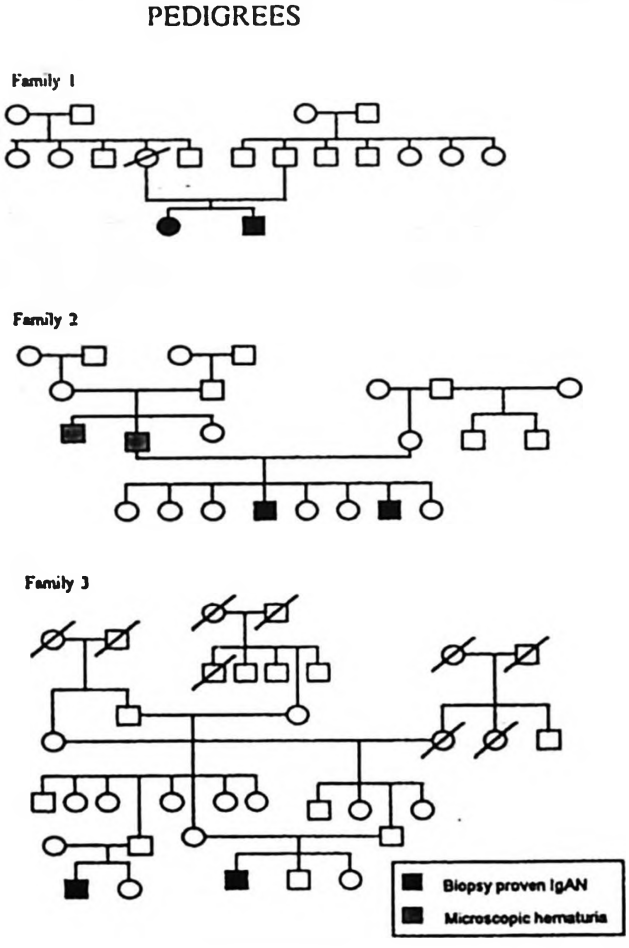

Fig. 3: Pedigrees of three families.

acute phase. High serum IgA levels and an increased number of IgA-bearing B lymphocytes were observed in the patient with IgAN. Immunological findings are shown in Table III.

Table III: The Findings of Cell-mediated Immunity in the Patients with IgAN

	Family 1		Family 2		Family 3		Controls
	Boy	Girl	Boy	Boy	Boy	Girl	n=16
CD3+T cell (%)	73	81	54	68	54	71	69.39
CD19+B cell (%)	11	9	11	8	5	8	7.36
CD4+T cell (%)	44	48	26	38	27	49	42.31
CD8+T cell (%)	36	38	33	31	39	32	31.44
CD4/CD8	1.40	1.30	0.80	1.20	0.70	1.50	1.42
HLA-DR(+) T cell (%)	5	9	10	4	3	12	4.72
IL-2R (%)	11	5	4	6	3	11	3.52
IgA binding B cell (%)	49	64	63	59	56	67	9
IgG binding B cell (%)	14	17	11	13	16	39	13.81
IgM binding B cell (%)	8	6	7	4	5	9	6.50

Discussion

Although intensive efforts have been made toward elucidating the pathogenesis of pIgAN, it remains unclear[4,5]. However, observing the occurrence of the disease in siblings and in renal allografts of patients with pIgAN, many investigators have reported the presence of familial pIgAN[3]. On the other hand, since no serologic marker has been found, diagnosis of the disease depends on an invasive procedure such as renal biopsy, even in family members or in patients with minimal urinary findings[6]. In the absence of any environmental factor, the pathogenesis of pIgAN has been suggested to include a genetic mechanism[1,7]; however, the mode of inheritance cannot be defined[1,2]. An association between pIgAN and DR4, B35 has been postulated in some countries since 1976[8] although more recent report have not confirmed a definite correlation between HLA and pIgAN[9,10]. In this study HLA A2-B35-B5-DR4-D11 and DR13 were found to be the most frequent HLA antigens. However, HLA A2-B35-B5 and A24 are the most common HLA class I antigens, but neither class II antigen is common in western Turkey[11]. Therefore, we could not accept the presence of these antigens as an association with pIgAN.

In conclusion, the existence of two siblings with IgA nephropathy in three families may support the hypothesis that genetic factors are important in the pathogenesis

of pIgAN in some patients. Some immunological abnormalities, such as high serum levels of IgA, an increased number of IgA-bearing B lymphocytes, increased expression of IL-2 receptors and HLA-DR (+) T cells, indicate that at least some determinants of pIgA may be under genetic control. Furthermore, some environmental factors may have effects on this familial tendency.

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