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MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS IN SIBS*

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Idiopathic membranoproliferative glomerulonephritis (MPGN) is a chronic renal disease with variable clinical expression and several distinct morphological subtypes. Two sibs, aged 10 and 13, presented with clinical and laboratory findings of MPGN at the time of admission. After an interval of one year, the diagnosis of MPGN was established by renal biopsies. The complement pathway was unremarkable. HLA typing in the unrelated parents and the two male sibs revealed common HLA A2,A11,Bw60, DR2,DQw1 antigens in the brothers. Of these antigens, A2 has been reported previously in cases of MPGN. The other antigens regarding this disease need to be evaluated from the standpoint of genetic importance. *Key words: membranoproliferative glomerulonephritis, sibling, renal failure, childhood, familial.*

Membranoproliferative glomerulonephritis (MPGN) was first recognized in the mid 1960's[1]. The disease occurs after two years of age, and it may be associated with hypertension and nephrotic syndrome in addition to urinary abnormalities[1]. Mild to moderate renal insufficiency may be observed, but the typical patient usually reveals no evidence of renal failure at diagnosis.

On the basis of morphological characteristics, Habib et al[2] divided the glomerular changes seen in patients with MPGN into two types. Type I was characterized by a double contour appearance of the capillary walls due to mesangial cell interposition with nonargyrophilic subendothelial deposits which were finally granular with electron microscopy (EM) and immunofluorescent microscopy. Type II was characterized by linear dense deposits within the basement membrane. Strife et al[3] described a third variety (Type III) which had some characteristics of Types I and II. Most cases are truly idiopathic. The evidence obtained up until now as for genetic factors predisposing to MPGN is an apparent association of Type I with inherited deficiency of complement components (C6,

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C3)[4-6], and the rarity of the disease in blacks[7]. Although the presence of MPGN in siblings has been reported previously, documentation is incomplete in most cases[5,8,9]. The aim of this report is to present biopsy-proven MPGN in sibs and to emphasize the familial aspect of the disease.

Case Reports

Case 1 (M.Y.)

A 10 year-old-boy was admitted in December 1990, for evaluation of hypertension, oliguria, proteinuria and hematuria. There was no relevant past history. Physical examination revealed peripheral edema and a blood pressure of 160/100 mmHg. The protein excretion rate was 76 mg/m^2/h, and there was microscopic hematuria. The blood chemistry revealed serum creatinine 10.6 mg/dl, BUN 96 mg/dl, serum total protein 5.4 g/dl, albumin 2.6 g/dl, and uric acid 11 mg/dl. The serum C3 and C4 levels were 10 mg/dl and 14 mg/dl, respectively (normal C3, 60-120 mg/dl; C4, 20-40 mg/dl). Serologic investigations including ASO titer, hepatitis B surface antigen (HBsAg) and antibody (HBsAb), and antinuclear antibody (ANA) were negative. Serum immunoglobulins were within normal limits for the age of the patient.

We were not able to perform a renal biopsy during the acute clinical stage of the disease. Drug therapy included corticosteroids and cyclophosphamide. The tentative diagnosis of rapidly progressive glomerulonephritis necessitated prompt dialysis. During the follow-up period, the patient was enrolled in a hemodialysis program. The clinical and laboratory status improved after six months of therapy and renal functions could be maintained without dialysis. One year after the onset of disease, a renal biopsy was performed following admission of the patient's brother to the hospital who had similar clinical manifestations and a diagnosis of biopsy-proven MPGN. At the time the biopsy was taken, laboratory investigations revealed creatinine clearance 17 ml/min/1.73 m^2, C3 64 mg/dl, C4 24 mg/dl and total hemolytic complement pathway CH50 33 U/ml (normal 15-55 U/ml):

Renal biopsy findings (light microscopy): The hematoxylin and eosin stained semiserial sections showed 10 glomeruli on the average. All glomeruli were smaller than normal. Five showed complete sclerosis, while the remaining glomeruli had occluded capillary lumens with variable mesangial cellularity. The tubuli showed atrophy, areas of thyroidization, and dilatation. Interstitial mononuclear inflammatory cell infiltration was present. The arteriole walls and small-sized arteries showed hyaline thickening. The PAS (periodic-acid Schiff) and trichrome stained sections revealed an additional number of sclerosed glomeruli. In one or two relatively less damaged glomeruli, a pattern suggestive of membranoproliferative glomerulonephritis was present. In addition to glomerular sclerosis, trichrome staining also showed red dots, suggestive of immune deposits. Silver

with or without counterstain demonstrated complete or nearly complete sclerosis of the many glomeruli. One or two glomeruli without sclerosis had a double-contour appearance.

Diagnosis: End-stage glomerulonephritis with a few preserved patterns of membranoproliferative glomerulonephritis (Fig. 1-3).

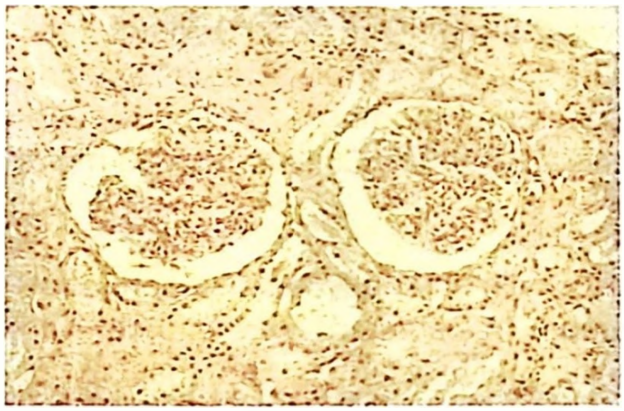

Fig. 1. Enlarged glomeruli showing mesangial expansion, increased cellularity and an accentuated lobular pattern. (Hematoxylin-eosin stain).

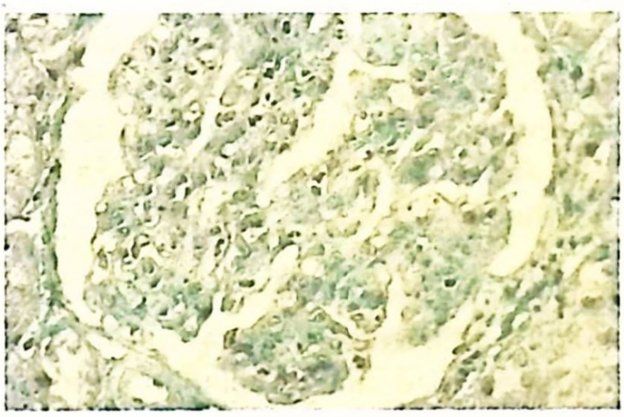

Fig. 2. The glomerulus under higher magnification shows an enlarged mesangial matrix with increased cellularity admixed with neutrophiles and a thickened basement membrane in places (Masson's trichrome stain).

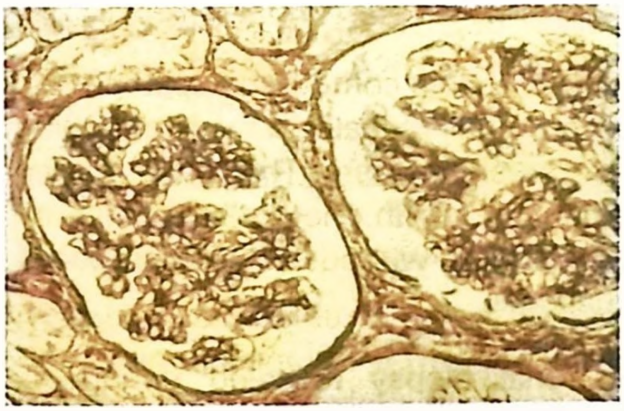

Fig. 3. The increased amount of mesangial matrix with thickening of the basement membrane and a double contour appearance at some points are seen. (Jones silver methenamine with HE).

Fig. 4. Irregular granular desposition of C3 is seen in the peripheral capillary basement membrane zone and some of the areas of the mesangium in the glomerulus (Direct Immunofluorescence microscopic study).

Direct immunofluorescence study of the renal biopsy revealed peripheral deposition of complement (C3) in the basement membrane zone, granular in pattern. The Igs were not demonstrated.

Note: In this patient, end-stage glomerulonephritis is not used as a clinical term, but pathologically, to indicate the late and non-specific nature of glomerular

sclerosis, which as in this patient, may have formed as a result of the progression of MPGN.

Case 2 (F.Y.)

The older brother of Case 1, who is 13-years-old was referred to our hospital for evaluation of edema, hypertension and proteinuria in December 1991. His blood pressure was 150/95 mmHg. Urine analysis revealed microscopic hematuria and proteinuria 48 mg/m^2/h. Serum creatinine was 2.3 mg/dl, uric acid 9 mg/dl, total protein 6.6 mg/dl, albumin 3.2 mg/dl, and BUN 60 mg/dl. Serologic investigations including ANA, anti-DNA, antiglomerular basement membrane antibody (anti-GBM Ab), HBsAg and HBsAb were all negative. The serum C3 level was 33 mg/dl and the C4 level 24 mg/dl.

Biopsy findings (light microscopy): The hematoxylin and eosin stained semiserial sections showed 20 glomeruli on the average. Involvement was diffuse with increased size and lobulation due to cellular proliferation. In the majority of glomerular tufts capillary lumens were obliterated. The proliferation of cells was mainly of the endomesangial type, but several polymorphonuclear leukocytes were also present. PAS staining showed an increase in the mesangial matrix with a thickened basement membrane. Even with this stain, reduplication in some areas could be seen when examined carefully. Trichrome stain showed red dots within the capillary walls, suggestive of immune deposits.

In some areas, methenamine-silver stain showed double contoured "splitting" of the basement membrane. The epithelium of the tubuli revealed a hyaline droplet change, and a vacuolar appearance in some. Casts were rare. The brush border and the tubular basement membrane were intact. Only in one dot-sized area of the interstitium, a few inflammatory cellular infiltrates without eosinophils were present. The vessel walls appeared unremarkable.

Direct immunofluorescence study of the renal biopsy revealed peripheral depositons of C3 (++), C1q (+), and IgA (+) in the basement membrane zone and some in the mesangium (Fig. 4).

The patient was treated with one gm methylprednisolone intravenously for three consecutive days. This was followed by a six-month prednisolone regimen. Serum complements C3, C4, and CH50 levels were within the normal range three months following the onset of the illness. The patient's clinical and laboratory status improved, and he is at present in remission, and under no medication.

A summary of the initial clinical and laboratory findings are mentioned in Table I. The HLA typing of the members of the family is displayed in Table II.

Table I: Initial Clinical and Laboratory Findings of Patients

	Patient 1	Patient 2
Anemia	+	−
Edema	+	−
Hypertension	+	+
Hematuria	+	+
Proteinuria (*)	+	+
BUN	96 mg/dl	60 mg/dl
Serum creatinine	10.6 mg/dl	2.3 mg/dl
C3	10 mg/dl	33 mg/dl
C4	14 mg/dl	24 mg/dl
HBsAg	−	−
HBsAb	−	−

* Proteinuria > 40 mg/m^2/hr.

Table II: HLA Typing of the Patients and Parents

Case 1	: HLA A2, A11, B39, Bw60, DR2, DRw13, DQw1
Case 2	: HLA A2, A26, A11, Bw60, DR2, DQw1
Mother	: HLA A11, A31, B39, B35, DR2, DR7, DQw1, DQw2
Father	: HLA A2, A26, Bw60, DRw13, DQw1

Discussion

Membranoproliferative glomerulonephritis is an uncommon disease which rarely occurs in siblings[10,11]. The literature suggests that the incidence in siblings is variable, but that definite conclusions cannot be drawn regarding genetic predisposal to MPGN[8,9,11]. The sib pairs reported by Van Acker et al[8] were members of six separate families, while Berry et al[9] noted a familial incidence of about four percent.

Although predisposition to MPGN occurring in siblings may reflect a common environmental exposure, it is more likely that it indicates a genetic basis for the disease. The presented sib pairs were shown to have biopsy-proven MPGN, which could reflect exposure to a common environmental stimulus or alternatively a genetic predisposition manifest with or without an enviromental trigger.

Evidence to support the view that genetic factors predispose to MPGN has been limited to the rarity of the disease in blacks[7] and the reported association with

deficiency of complement components C3, C6, C7, C8[4-6]. The demonstration of circulating immune complexes in 50 percent of patients with MPGN and the presence of granular deposits of immunoglobulins and complement in the glomerular capillaries provide evidence of an immunological basis for the disease[12]. In our patients, there was suggestive evidence of classical pathway activation in the acute stage. In addition, the presence of C3, C1q and IgA depositions in immunofluorescence microscopy of the renal biopsies was another finding supporting the immunological origin of the disease. Complements C3, C4, and CH50 were at normal levels in the unrelated parents and also in the two brothers which exclude inherited complement deficiency conditions.

The role of genetic factors in the etiology of glomerulonephritis is unclear. Because of the importance of gene products of the major histocompatibility complex in both immune recognition and effector functions, the protein polymorphism in this region has been studied in most immune-related diseases including a number of types of glomerulonephritis[13]. Noel et al[13] reported an insignificant increase in the frequency of HLA-B7 in Type II MPGN, while Rashid et al[14] found insignificant increases in HLA-A2 and HLA-Bw44 in MPGN patients. Recently, Welch et al[15] reported an elevated frequency of HLA-B8, DR3 and C4A*Qo alleles. They also mentioned that the extended haplotype B8, DR3, SCO1, GLO2 is clearly not a necessary factor in the development of MPGN since most patients do not carry this haplotype, which may be also present in some healthy siblings and parents. The common HLA antigens of our patients were A2,Bw60,DR2 and DQw1, but only the presence of HLA-A2 is similar to reports in the literature[14]. There was no evidence of primary immunoglobulin deficiency in our patients and no repeated infections. Changes in the population of cytotoxic/suppressor T cells may theoretically lead to immune-related renal disease. We also examined the T cell subsets of the whole family and found that they were all in normal numbers.

The clinical manifestations of the disease were similar in both siblings which can be attributed to genes linked to common haplotypes. Although renal functions progressed to renal failure in the first case, in the second case, the symptoms disappeared after drug therapy. To explain these differences in outcome, it may be postulated that MPGN is of multigenic origin. Thus the response to a gene functionally predisposing to MPGN might be modified by other genes which control pertinent immune responses resulting in differences in the mode in which the disease is expressed.

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