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THE CORRELATION BETWEEN THE CLINICAL, LABORATORY AND HISTOPATHOLOGICAL FEATURES OF CHILDHOOD MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS AND RESPONSE TO TREATMENT*

*Fatoş Yalçınkaya MD***, Erdal İnce MD****
*Necmiye Tümer MD*****, Mesiha Ekim MD******

SUMMARY: Yalçınkaya F, İnce E, Tümer N, Ekim M. (Department of Pediatric Nephrology, Ankara University Faculty of Medicine, Ankara, Turkey). The correlation between the clinical, laboratory and histopathological features of childhood membranoproliferative glomerulonephritis and response to treatment. Turk J Pediatr 34: 135-144, 1992.

In this study, the clinical, laboratory and histopathological features of 50 children with membranoproliferative glomerulonephritis are reviewed. Age distribution varied from 5 to 15 years. The clinical presentation in the patients was nephrotic syndrome (24%), acute nephritic syndrome (20%) and nephritic/nephrotic syndrome (56%). Hypertension, macroscopic hematuria and hypocomplementemia were present in 40 percent, 58 percent and 34 percent of the patients, respectively. Light microscopic findings were as follows: glomerular lobulation (36%), mesangial sclerosis (20%), tubulointerstitial findings (36%), and crescents (26%). C_3 (93%) was the most common immunofluorescence and IgM (86%), the most frequently encountered immunoglobulin. Response to treatment could not be anticipated by the initial clinical and laboratory features. Patients who did not have tubulointerstitial changes tended to have a greater response to therapy. *Key words: childhood, membranoglomerulonephritis, response to treatment.*

Membranoproliferative glomerulonephritis (MPGN) is a chronic nephritis which occurs most commonly in late childhood and early adulthood. The disease was first defined by West and co-workers[1] in 1965. Its etiology is unknown and the pathogenesis is unclear[2-4]. Although the clinical and laboratory features vary in individual patients, the disease has a generally progressive course.

Membranoproliferative glomerulonephritis has been demonstrated in only 5 to 14 percent of renal biopsy series[4-6]. However, the disease is responsible for more than 25 percent of the cases of terminal renal failure caused by glomerulonephritis[4]. It has been reported that 7 percent of patients have total remissions after the first treatment, but most patients have relapses[7]. No

* From the Department of Pediatric Nephrology, Ankara University Faculty of Medicine, Ankara.
** Resident in Pediatric Nephrology, Ankara University Faculty of Medicine.
*** Resident in Pediatrics, Ankara University Faculty of Medicine.
**** Professor of Pediatrics, Ankara University Faculty of Medicine.
***** Associate Professor of Pediatric Nephrology, Ankara University Faculty of Medicine.

treatment exists which can prevent progressive nephron loss, and end-stage renal disease occurs within ten years in approximately 50 percent of patients[8-12].

The aim of this study was to review the clinical, laboratory and pathological features of MPGN in children and to determine if a correlation exists between these features and early and late responses to treatment.

Material and Methods

Patients were selected for this study on the basis of clinical and laboratory features and a renal biopsy diagnostic for MPGN. The study involved 50 patients whose follow-ups were available. At the time of the first examination, the patients' ages were between one to 15 years (mean 9.8 ± 3.6 years) (Fig. 1). There were 28 males and 22 females.

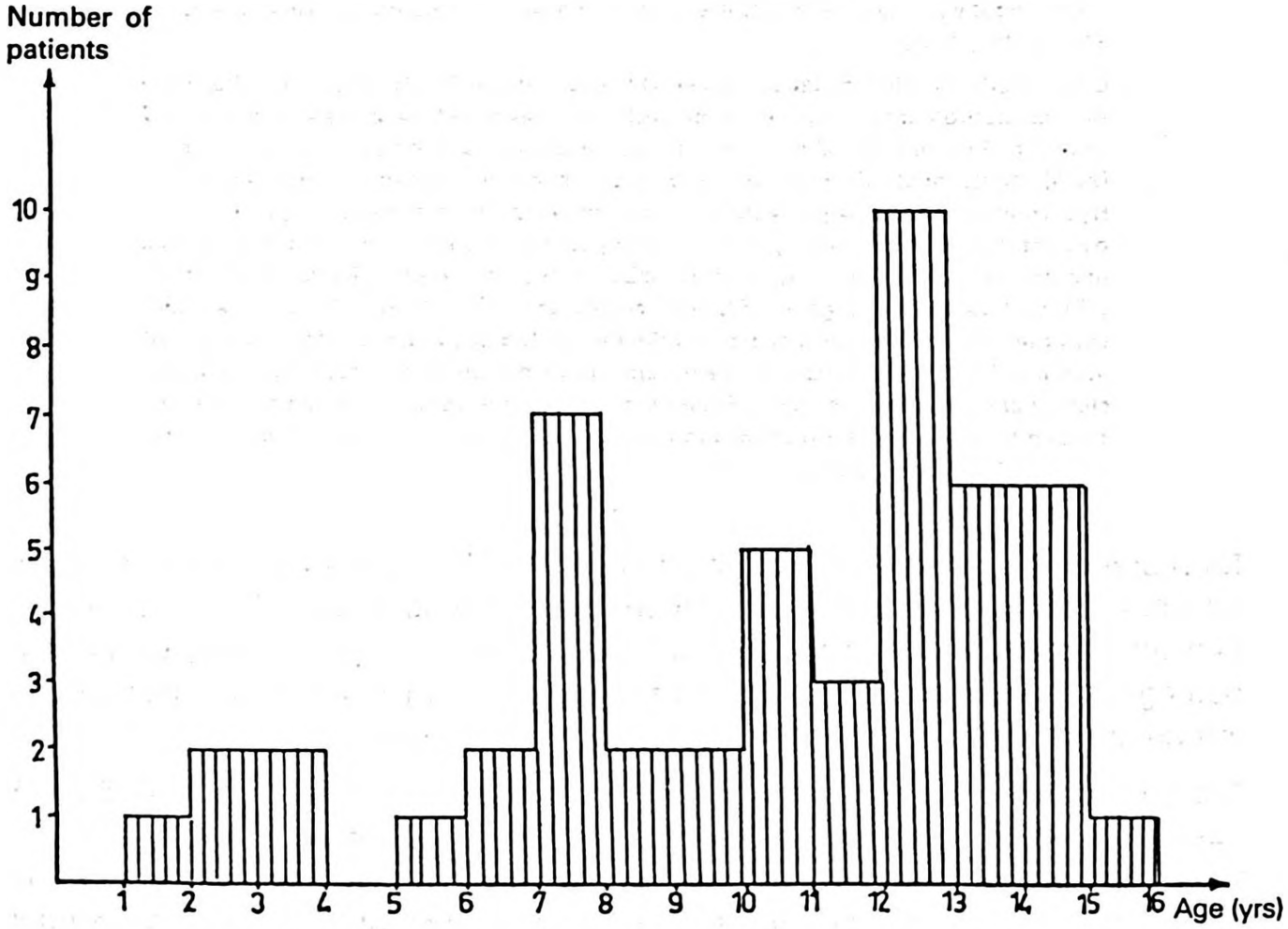

Fig. 1: Age at onset of disease.

Hypertension was defined as a systolic and a diastolic blood pressure ≧95 percent for age based on the Pediatric Task Force recommendations[13]. Proteinuria was evaluated by dipstick estimation and by a 24-hour quantitative measurement. Hematuria was defined as positive if the microscopic examination of the urinary sediment showed ≧5 RBC/hpf and gross if visible with the naked

eye. Renal insufficiency was defined as an elevation of the serum creatinine level above 1.2 mg/dl. Routine urinalyses and tests for urea, albumin and C_3 were performed by standard techniques.
Nephrotic syndrome was defined as massive proteinuria if exceeding 2 g/m^2/day and hypoalbuminemia if less than 3 g/dl, with or without edema. Patients were described as having acute nephritic syndrome when they displayed hematuria, edema, hypertension and/or renal insufficiency.

Renal biopsy was obtained three weeks to 12 months (average three months) after the onset of disease and before the initiation of treatment. Biopsies were performed using Franklin modified Vim-Silvermann needles. The number of glomeruli studied in each biopsy ranged from 8-24 (mean 16). Immunofluorescence studies were carried out on 30 available specimens. Fluoresceinated antisera specific for IgG, IgM, IgA and C_3 were employed in all cases. Discrimination of the types of MPGN was not available.
Patients received steroid therapy with or without cytotoxic agents for variable periods of time (3 to 18 months). Early response was recorded at the end of the first month of therapy and late response after completing the therapy.

Patients were divided into three groups for subsequent analyses according to clinical and laboratory findings: Group 1. Complete response: patients in whom clinical and urinary abnormalities resolved i.e., disappearance of edema, hypertension, hypoalbuminemia, hematuria and proteinuria. Group 2. Partial response: patients in whom a partial clinical and laboratory response had occurred i.e. disappearance of hypoalbuminemia and/or hematuria with or without hypertension. Group 3. No response: patients in whom no change was noted.

The average follow-up for all patients was 36.5 months, with a range of 12 to 112 months.
The chi-square and Fisher exact tests were used for statistical analyses because of the small sample size.

Results

Clinical features at onset of the disease are shown in Table I. The main complaints were edema (92%), gross hematuria (64%) and oliguria (20%). The initial physical examination revealed edema in 86 percent of the patients and hypertension in 40 percent of the patients.

Laboratory data are described in Table II. Urinalyses revealed that hematuria was present in 82 percent of patients (macroscopic 58%). All the patients had proteinuria and 88 percent had urinary protein exceeding 2 g/m^2/day. Elevated serum creatinine levels (>1.2 mg/dl) were detected in 42 percent of patients at presentation and hypocomplementemia in 34 percent of patients. HBs Ag was positive in the serum of 24 percent of the patients.

TABLE I: Clinical Features at Onset of Illness

Main Complaints	n (50)
Edema	46 (92%)
Gross hematuria	32 (64%)
Oliguria	10 (20%)
Initial Physical Examination	
Edema	43 (86%)
Hypertension	20 (40%)
Hepatosplenomegaly	15 (30%)
Ascites	14 (28%)
Growth retardation	5 (10%)
Goitre	4 (8%)

n: Number of patients.

TABLE II: Laboratory Data Prior to Renal Biopsy

		n (50)
Hematuria	Macroscopic	29 (58%)
	Microscopic	41 (82%)
Proteinuria	Mild	50 (100%)
	Massive	44 (88%)
Elevated Serum Creatinine (>1.2 mg/dl)		21 (42%)
Reduction of Serum C_3 (<50 mg/dl)		17 (34%)
Anemia		24 (48%)
Positive HBs Ag		12 (24%)

The mode of presentation of disease was nephrotic syndrome in 24 percent of the patients, acute nephritic syndrome in 20 percent and nephritic/nephrotic syndrome in 56 percent of the patients (Fig. 2). Six patients (12%) had secondary MPGN (five Henoch Schönlein purpura and one partial lipodystrophy).

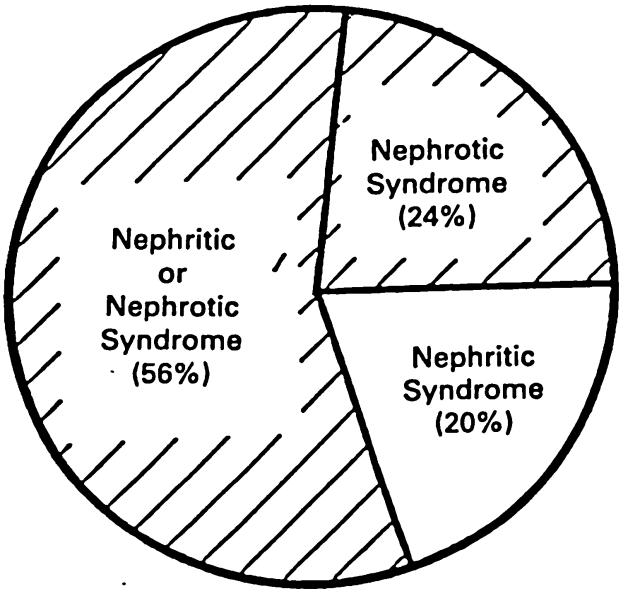

Fig. 2: Mode of presentation of disease.

Table III represents the light microscopic findings of the patients. All cases showed a thickening of the glomerular basement membrane (GBM) and proliferation of mesangial cells and/or matrices. Glomerular lobulation was present in 12 percent and mesangial sclerosis in 20 percent of the patients. Tubulo-interstitial findings (tubular atrophy and/or interstitial fibrosis) were found in 18 of the 50 patients. Epithelial crescents were present in 26 percent of the patients. The results of immunofluorescence studies of 30 specimens and a comparison with the literature are shown in Table IV. C_3 (93%) was the most

TABLE III: Light Microscopic Findings in MPGN

	n (50)
Thickened GBM	50 (100%)
Proliferation of Mesangial Cells and Matrices	50 (100%)
Glomerular Lobulation	6 (12%)
Mesangial Sclerosis	10 (20%)
Tubular Atrophy and/or Interstitial Fibrosis	18 (36%)
Crescents	13 (26%)

TABLE IV: Renal Immunofluorescence in MPGN (Comparison with the literature)

	Our Study 1990	Tınaztepe et al[6] 1986	Cameron et al[11] 1983		Mayo Clinic[14] 1979	
			Type I	Type II	Type I	Type II
	%	%	%	%	%	%
C_3	93	82	93	72	100	100
IgM	86	61	52	28	60	20
IgA	63	38	59	0	50	20
IgG	56	32	35	0	33	20
Negative	7	15	7	39		

common immunofluorescence while IgM (86%) was the most frequently encountered immunoglobulin. Immunofluorescent staining was absent in two cases (7%).

The patients received steroid therapy with or without cytotoxic agents for a period of three months to 1.5 years. After the first month of therapy, three patients (6%) experienced complete remission. Twelve patients were lost to study before completion of the treatment. Of the remaining 38 patients, 16 had a complete response, 16 had a partial response and six had no response at all (Table V).

TABLE V: Late Response to Treatment (n: 38)

Complete Response	Partial Response	Resistance
n	n	n
6 (42%)	16 (42%)	6 (16%)

No correlation could be found between the presence of nephrotic syndrome, hypertension, gross hematuria, elevated serum creatinine levels or hypocomplementemia at onset or during response to treatment. Of the 18 patients with tubulointerstitial findings, three were excluded from the study. Of the remaining 15 patients, five did not respond to treatment, nine had a partial response, and one patient had a complete response to treatment (Table VI).

TABLE VI: Tubulointerstitial Findings and Response to Treatment

Tubular Atrophy and/or Interstitial Fibrosis	Complete Response	Partial Response	Resistance
Positive n: 15	1	9	5
Negative n: 23	15	7	1
TOTAL n: 38	16	16	6

Discussion

In this study, comprising 50 patients with MPGN, we found the results to be only slightly different from reports in the literature[3,4,6,11,14-17] (Table VII). In general, the age at onset of MPGN is between five to 30 years,and a diagnosis before the age of six is uncommon[3,6]. Twelve percent of our patients were under six years of age (Fig. 1).

TABLE VII: A Comparison of MPGN Features Reported in the Literature With those Observed in Our Patients

		Our Study 1990 n: 50	Tinaztepe et al[6] 1986 n: 95	Cameron et al[11] 1983 n: 23	Habib et al[15] 1973 n: 105	Other Reports in the Literature[3,4,14,16,17]
Age (years) Mean		1-15 9.8	3-18 10	<15	2-17 10	5-30
Sex (males %)		56	63	40	63	no sex predominancy
Edema	%	86	97		43	40-63
Hypertension	%	40	29	22	25	20-30
Hematuria	%	82	66	96	86	86-100
Macroscopic	%	58		35		15-30
Proteinuria	%	100	100			
Renal Insufficiency	%	42	52	39		40
Hypocomplementemia	%	34	25	57	48	44-75
Underlying Primary Disease	%	12	9			16
Nephrotic Syndrome	%	80	60	31	67	31-60
Pure Nephritic Syndrome	%	20	38	30	33	15-41

The clinical features of this disease vary. We found the main symptom to be edema (86%), and more than half of the patients we studied had macroscopic hematuria. Cameron et al[11] reported that children presented more frequently with macroscopic hematuria at onset than hypertension. However, both hypertension (40%) and macroscopic hematuria (58%) were found to be more common in our series than in series reported in the literature[3-6,8,11,16].

Activation of the complement system is a hallmark of MPGN. Hypocomplementemia and reduced renal function were present in 34 and 42 percent of the patients, respectively. These results are similar to the data in reported series[4,6,11,14,16,17]. HBs Ag was positive in 24 percent of our patients. Since HBs Ag was not demonstrated in the glomeruli, we could not confirm that chronic viremia was the cause of MPGN in these patients. We can only speculate as to its being the cause; perhaps it is only a coincidence.

Nephrotic syndrome is the most common mode of presentation of MPGN in both children and adults[4,7,18]. If we evaluate the nephrotic syndrome group (including the patients with nephritic/nephrotic syndrome), 80 percent of our patients had nephrotic syndrome as the most common clinical presentation (Fig. 2).

A thickening of the glomerular basement membrane and an increment in the mesangial matrix were reason for inclusion in the study group. Crescents were observed in 26 percent of our patients, however, a lower incidence (6%) was reported in the Tınaztepe et al[6] series. We did not find a correlation between the presence of crescents and response to treatment. Our immunofluorescence microscopic findings were similar to the results of other studies[3,4,6,11,14] (Table IV). Immunofluorescence staining was negative in 7 percent of our patients, which is less than that reported by Tınaztepe et al[6] (15%) and Cameron et al[11] (23%).

There are many studies on the factors used to predict the prognosis of MPGN, but the results are controversial. The clinical features that appeared to be indicators of a poor outcome included the presence of macroscopic hematuria, hypertension, nephrotic syndrome, hypocomplementemia, and an elevation in the serum creatinine concentration[3-5,10,12,14,16]. Although, some authors have noted that clinical features are not useful indicators for the progression of the disease, they state that a number of pathological findings appear to be useful. Mesangial sclerosis, increased glomerular lobulation and the presence of crescents were reported as the features which may indicate a poor prognosis[16,19-21].

In our series, no correlation was noted between the presence of the clinical and pathological findings mentioned above and response to treatment. But of the 15 patients who had tubulointerstitial findings and whose follow-ups were sufficient, only one patient had a complete response to treatment. Five of the remaining patients did not respond to treatment and nine had only a partial response. On the

other hand, 16 of the 23 patients who did not have tubulointerstitial findings had a complete response to treatment (Table VI). These results are in agreement with Schmitt et al[22] and Taguchi et al[23], who showed a correlation between the tubulointerstitial changes and the unfavorable course of the disease.

We also noted that the patients who did not have tubulointerstitial changes tended to respond to therapy more than the others. Our study demonstrated the importance of tubulointerstitial findings and early renal biopsy to predict the response to treatment in childhood MPGN.

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