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ASSOCIATED CONDITIONS IN CHILDHOOD MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS DURING 15 YEARS OF EXPERIENCE AT THE HACETTEPE CHILDREN'S HOSPITAL*

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Membranoproliferative glomerulonephritis (MPGN) is a form of chronic glomerulonephritis seen with greater frequency in children than adults. Although West et al[1] called this entity "hypocomplementemic persistent (chronic) nephritis", it was Habib et al[2,3] who first applied the commonly used term "membranoproliferative glomerulonephritis". The more recent term "mesangiocapillary glomerulonephritis" has merit as a morphological description of the disease, although it has not gained universal acceptance.

MPGN may be a primary glomerular disease or secondary to a variety of infectious, hereditary or multisystem diseases[3,4]. The primary (idiopathic) forms are quite heterogeneous and have been further categorized on the basis of ultrastructural and immunofluorescent patterns. Even though large series of idiopathic forms of MPGN have been reported, there is no similar trend for the secondary form in the literature. The list of MPGN-associated diseases and/or conditions is enlarging slowly with single case reports and various small series. Accumulation of new reports, we believe, will add new concepts for obtaining a better understanding of the pathogenesis of MPGN. In this study childhood MPGN cases diagnosed in our center during the last 15 years are reevaluated, associated conditions are compiled and the results are compared and discussed in the light of the literature.

Material and Methods

This study involves 21 patients selected on the basis of a renal morphologic diagnosis of membranoproliferative glomerulonephritis from renal biopsy samples evaluated between 1966 and 1981. For light microscope studies, the tissue samples were

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fixed in Duboscq-Brazil's solution and sections of 2-4 microns were stained with hematoxylin-eosin, periodic acid-Schiff (PAS), silver methenamine, and Masson trichrome stains.

Immunofluorescent studies were carried out on 11 specimens, of which 9 proved adequate (i.e., presence of at least three glomeruli). The tissue was quick-frozen immediately after removal, 2 μ sections were cut in cryostat and incubated with the following fluorescein-conjugated antiserums: in all cases, anti-C3, anti-IgG, anti-IgM and anti-IgA were used; anti-fibrinogen and anti-HBsAg used in 7 cases each.

The diagnosis of MPGN was made histologically with the following alterations by light microscope examination: proliferation of endocapillary cells, increase in mesangial matrix, and the "double contour" or "tramline" appearance.

The clinical records of all patients in whom a histopathologic diagnosis of MPGN was made were reviewed in detail at the outset for clinical, physical and laboratory findings.

Results

Clinical Features

Clinical findings in 21 MPGN patients with the childhood secondary form are outlined in Table I. As can be seen there is no sex predilection; 11 of 21 cases (52.4%) are male and 10 (47.6%) are female. The age of the patients at onset varied from 6/12 to 16 years, with the arithmetic mean being 8.6 years and the median 10 years. The first biopsy was obtained at intervals varying between one week to three years after the onset of the disease, with an average of 7.7 months and a median of 3 months. History of parental kinship was obtained in 2 cases (9.5%), paternal renal disease in 1 (4.8%), sibling death (cause unknown) in 7 (33.3%) and jaundice in 4 (19.0%).

The main complaint of the patients differed according to the underlying disease. The initial physical examination revealed edema in 63.2% of the cases (generalized in 21.1% and localized in 42.1%). Blood pressure was recorded to be high in 21.4% of the patients. Goiter was present in 2 (9.5%) of the cases.

Urinalysis revealed hematuria in 57.9% of the patients (microscopic in 47.4% and macroscopic in 10.5%), and proteinuria was present in 85.7%, i.e. all but three cases with subclinical nephritis (cases 3, 4 and 9).

In addition to the underlying disease, diagnosis of glomerulonephritis was made in 12 (57.1%) and nephrotic syndrome in 4 (19.1%) of the cases. Five of the patients (23.8%) were asymptomatic.

Anemia was encountered in over half (52.9%) of the patients, and it was due to iron deficiency in three cases. Biochemical studies revealed elevated levels of BUN in

52.9%, decreased creatinine clearance in 3/7 (42.8%), elevated cholesterol level in 23.5% and increased serum creatinine in only two patients at the first examination.

β-hemolytic streptococci were cultured from the throat in 21.4%, high titer of ASO was obtained in 2/6 (33.3%), and C3 level was low in 8 out of 10 patients (80.0%).

In our 15 years of experience, secondary MPGN constituted 92% of all MPGN cases.

Histopathologic Features

Twenty-four specimens from 21 patients were available; in each of two siblings with familial MPGN (cases 16 and 17) one more biopsy was obtained one year after the first one, and necropsy material was obtained after renal biopsy in case 18.

In all of the specimens, irregular but generally extensive thickening of the glomerular basement membranes (BMs) of the periphery of the capillary loops was present. Mesangial matrix increment and increased cellularity which resulted in accentuation of glomerular lobules also gave rise to a "double contoured" appearance with silver stains (Figure 1) due to extension and interposition. These alterations were both diffuse and generalized causing an increase in the expected size of the glomeruli and often lessening the patency of glomerular capillaries. In a small number of specimens leukocytes were encountered infiltrating the mesangium. Lobular accentuation was prominent especially in cases 1, 2 and 20 and in the second biopsy of case 16. Localized thickened areas of the Bowman's capsule and tubular BMs were seen in case 15, who had partial lipodystrophy (PLD). The main changes found in the repeat biopsies were an increase in lobularity and sclerosis in case 16 and endocapillary proliferation in case 17. No prominent change was noted in case 18 when compared with the first biopsy.

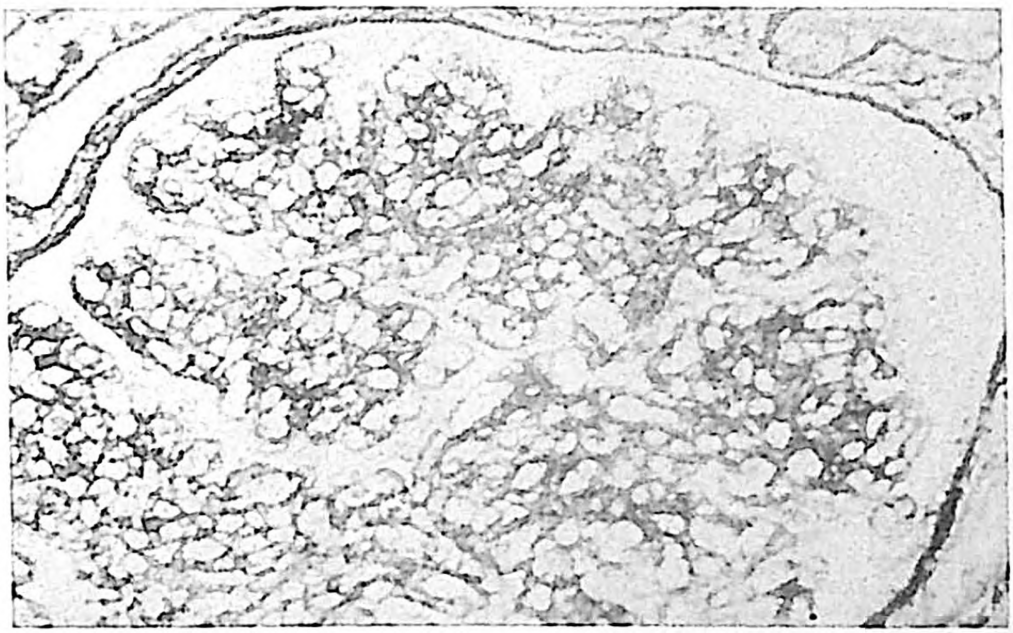

Figure 1

A glomerulus showing double contours (Silver methenamine stain).

TABLE I

Summary of the Clinical Findings of 21 Pediatric Patients with Secondary MPGN

Case No. Initials	Age Sex	Primary disease	Type of renal material	Renal findings	Miscellaneous	Clinical diagnosis
1 F.T.	10 years M (sib of 2)	Familial Hodgkin's disease (St. IV)	Biopsy during laparotomy	Proteinuria; IVP: renomegaly C3: low	Diagnosed as GN before Hodgkin's disease and C3 returned to normal during remission of tumor (in both sibs)	Glomerulo-nephritis
2 E.T.	7 years F (sib of 1)	Familial Hodgkin's Disease (St. IV)	Biopsy during laparotomy	Hematuria, Proteinuria IVP: renomegaly C3: low	Same	Glomerulo-nephritis
3 A.E.	11 years M	Hodgkin's disease (St. IIIA)	Biopsy during laparotomy	Urinalysis: N C3: N, IVP: N		Asymp-tomatic
4 A.K.	13 years M	Hodgkin's disease	Necropsy	IVP: N Urinalysis: N	Exitus	Asymp-tomatic
5 S.A.	13 years F	SLE	Needle biopsy	Hematuria Proteinuria	Euthyroidic goiter at onset	Glomerulo-nephritis
6 N.K.	16 years F	SLE	Needle biopsy	Hematuria Proteinuria	ANA: 1/360 (+) LBT: (+)	Glomerulo-nephritis
7 F.Ö.	15 years F	SLE	Necropsy	Hematuria Proteinuria	LBT: (+) Coombs: (+) Exitus	Glomerulo-nephritis

Case No. Initials	Age Sex	Primary disease	Type of renal material	Renal findings	Miscellaneous	Clinical diagnosis
8 A.A.	13/12 years F	Hydrocephalus (VA Shunt)	Necropsy	Hematuria Proteinuria C3: low	Exitus Staphylococcus albus cultured	Glomerulo-nephritis
9 A.Y.	6/12 years F	Hydrocephalus (VA Shunt)	Necropsy	Urinalysis: N C3: low	Exitus. Staphylococcus (+) cultured	Asymp-tomatic
10 C.K.	13 years M	Osteomyelitis, Staphylococcus aureus, sepsis	Needle biopsy	Chance proteinuria and hematuria IVP: renomegaly	Staphylococcus aureus cultured	Asymp-tomatic
11 M.K.	10 years M	Thalassemia (splenectomized)	Needle biopsy	Proteinuria IVP: renomegaly	Inadequate penicillin prophylaxis. Throat culture: β hemolytic streptococci. ASO: 1250 Todd U	Glomerulo-nephritis
12 B.D.	11 years M	Rheumatic fever; (MR+MS) endocarditis	Needle biopsy	Chance hematuria and proteinuria. IVP: renomegaly C3: low	Had ARF 1.5 yrs earlier. Inadequate penicillin prophylaxis. Urinalysis done first upon death of father, due to nephritis. Throat Culture: N ASO: 1250 Todd U CRP: +++	Asymp-tomatic
13 I.Ç.	7 years M	Henoch-Schönlein Purpura	Needle biopsy	Hematuria Proteinuria C3: N, IVP: normal		Nephrotic syndrome

TABLE 1 (continued)

Case No. Initials	Age Sex	Primary disease	Type of renal material	Renal findings	Miscellaneous	Clinical diagnosis
14 N.K.	6 years M	Polyarteritis nodosa	Necropsy	Hematuria Proteinuria	Exitus	Glomerulo-nephritis
15 M.T.	8 years F	Partial lipodystrophy	Needle biopsy	Hematuria Proteinuria C3: Low, IVP:N		Glomerulo-nephritis
16 H.G.	5 years F (sib. of 17)	Familial MPGN	Two biopsies, one year apart	Hematuria Proteinuria C3: low	Exitus (4 yrs after onset due to renal failure)	Nephrotic syndrome
17 A.G.	8 years M (sib. of 16)	Familial MPGN	Two biopsies, one year apart	Hematuria Proteinuria C3: low	Exitus (6 yrs after onset due to renal failure)	Nephrotic syndrome
18 K.S.	2.5 years M	Chronic active hepatitis	Biopsy and necropsy	Hematuria Proteinuria	Exitus. HBsAg (+) in serum and glomeruli. RVT diagnosed at necropsy	Nephrotic syndrome
19 F.B.	10 years M	Chronic active hepatitis (CAH)	Needle biopsy	Proteinuria IVP: normal	Daignosed as HBsAg (+). CAH two years earlier, treated with prednisolone and colchicine. At the time of biopsy, HBsAg was (−) in serum and renal tissue; goiter present.	Glomerulo-nephritis

Case No. Initials	Age Sex	Primary disease	Type of renal material	Renal findings	Miscellaneous	Clinical diagnosis
20 A.A.	10 years F	Postnecrotic cirrhosis	Needle biopsy	Proteinuria Hematuria	Jaundice of 2 months duration, 4 yrs earlier during an epidemic. N.S. developed after spleno-renal shunt to relieve portal hypertension and biopsy was done then (HBsAg (−) in serum)	Glomerulo-nephritis
21 O.Y.	4 years M	Viral (?) myocarditis and hepatitis	Needle biopsy	Proteinuria	Had jaundice 1,5 months earlier during an epidemic. Diagnosed as myocarditis 6 months earlier. HBsAg (−) in serum and renal tissue at the time of examination.	Glomerulo-nephritis

Abbreviations:

St. : stage
SLE : systemic lupus erythematosus
IVP : intravenous pyelogram
LBT : lupus band test
CRP : C-reactive protein
VA : ventriculoatrial
N : normal
ANA : antinuclear antibody
ASO : antistreptolysin-O
MR : mitral regurgitation
MS : mitral stenosis
ARF : acute rheumatic fever
RVT : renal vein thrombosis

Renal infiltration of the tumor in 3 of the 4 Hodgkin's cases was noted. In addition to membranoproliferative alterations, characteristic histopathologic changes of diffuse proliferative lupus glomerulonephritis (wire-loop lesions, hyaline thrombi, fibrinoid necrosis and nuclear fragmentation) were present in all of the three SLE cases. In one of these three (case 5), some glomeruli with pure membranous changes were encountered among the many showing membranoproliferative changes (Figure 2). Diagnosis of polyarteritis nodosa was made by demonstrating the characteristic changes in a medium-sized artery in the liver at postmortem (case 14).

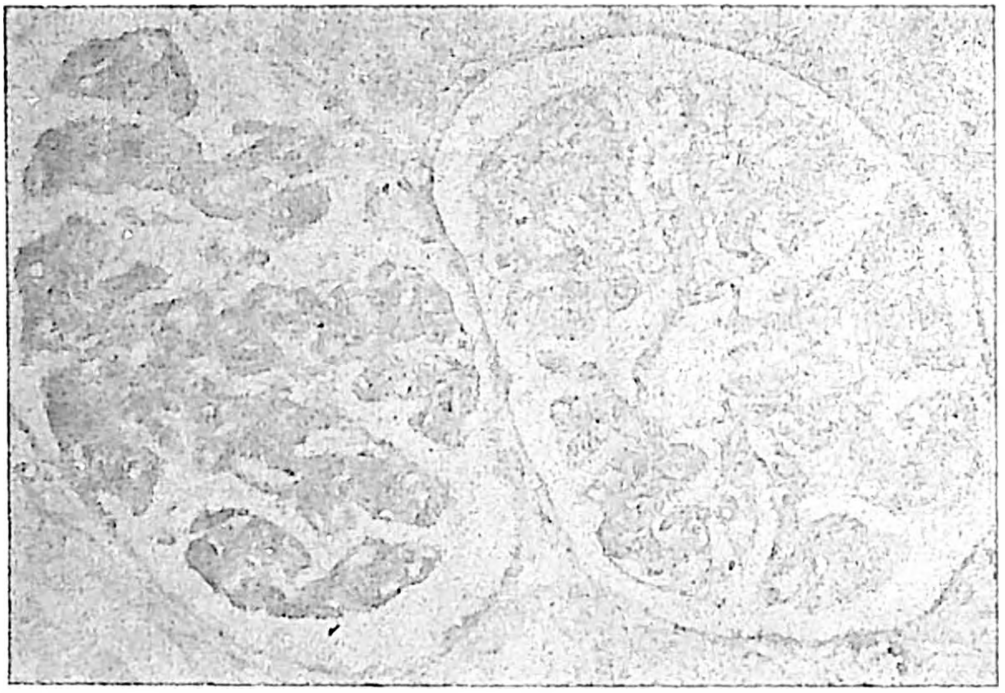

Figure 2

Microscopic appearance of renal biopsy from case 5; membranous changes of the left and membranoproliferative changes of the right glomerulus are noteworthy.

Immunofluorescent Features

Immunofluorescent studies were carried out on 11 specimens, 9 of which were adequate. C3 deposition was found in all of the biopsies in a granular capillary wall and mesangial pattern (Figure 3). IgG deposition was also found in all in the same manner. Fluorescence with anti-IgM was present in all, though four had minimal intensity. In some of the tubular BMs of the SLE cases, additional fluorescence with anti-IgG and anti IgM was present. Capillary wall deposition of IgA and fibrinogen was observed in 9/9 and 3/7 cases, respectively.

Discussion

Membranoproliferative glomerulonephritis has been delineated and separated from other forms of glomerulonephritis only in recent years, but is now recognized as a

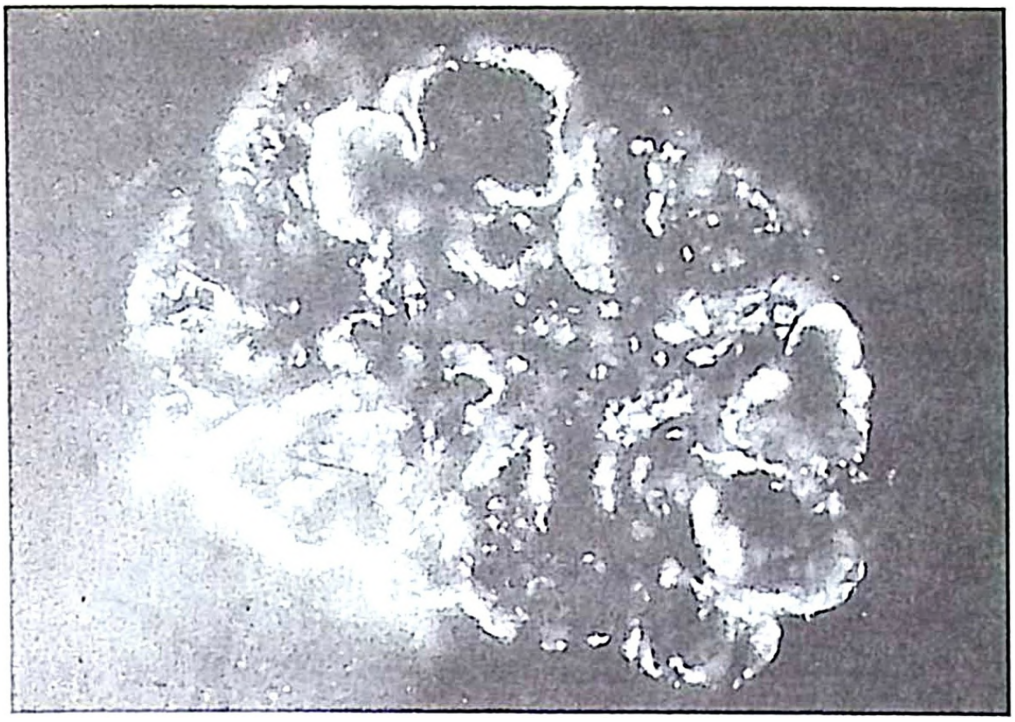

Figure 3

Immunofluorescent study of a glomerulus with anti-C3 shows pseudolinear appearance in a lobular pattern.

fairly distinctive clinicopathological entity and as one of the most important and serious forms of glomerular disease in late childhood and adolescence. In addition to its being a primary glomerular disease, it is also observed to be secondary to a variety of infectious, hereditary or multisystem diseases. Table II gives a long list of the different causes in the secondary forms[4,5].

As pointed out in Table I, the following were found as the underlying diseases in our series: Hodgkin's disease in 4, SLE in 3, infected ventriculo-atrial shunt in 2, staphylococcic septicemia in 1, streptococcic infection in 2, familial appearance in one sibship, and one case each of partial lipodystrophy, polyarteritis nodosa, Henoch-Schönlein purpura and chronic hepatitis with persistent antigenemia. In the last three cases presented in Table I, the relationship between MPGN and their primary diseases is presumptive, since HBsAg or another viral agent could not be demonstrated. Thus at least 10 different underlying diseases resulting in the secondary form of MPGN have been encountered at the Hacettepe Children's Hospital.

Nephrotic syndrome has been reported to occur in patients with malignant lymphomas such as Hodgkin's disease even in the absence of amyloidosis, tumor infiltration or renal thrombosis[5]. Symptomatic and asymptomatic glomerulonephritis associated with malignant lymphomas of children has been reported from the Hacettepe Children's Hospital[7-9]. The presence of immune complex deposits in the glomeruli and the disappearance of clinical and laboratory signs of glomerular involvement during remission of the malignancy suggest that immune reaction in the

TABLE II

Classification of MPGN*

A) IDIOPATHIC

1. Type I MPGN, with predominantly subendothelial deposits
2. Type II MPGN, with intramembranous dense deposits
3. Other structural variants, with subepithelial, subendothelial, and/or intramembranous deposits with GBM alterations (Types III, IV etc.)

B) SECONDARY TO AN UNDERLYING DISEASE

1. Chronic or possible antigenemia-related states

I. Chronic infections
- Shunt nephritis
- Chronic active hepatitis
- Mycoplasma
- Malaria
- Candida
- Bacteremia with visceral abscesses
- Infective endocarditis
- Schistosomiasis
- Toxic epidermal necrolysis
- Allograft glomerulopathy (with vesicoureteral reflux)

II. Other chronic antigenic states
- Leukemia or lymphoma
- Heroin addiction

2. Soluble immune complex diseases

I. SLE
II. Mixed cryoglobulinemia
III. Sickle-cell disease
IV. Henoch-Schönlein purpura (rare)

3. Congenital complement component deficiencies

(C1r, C2, C3 and C1 esterase inhibitor deficiencies)

4. Others

I. Partial lipodystrophy
II. Polyarteritis nodosa
III. Alpha-1 antitrypsin deficiency and cirrhosis
IV. Hemolytic uremic syndrome
V. Berger's disease (rare)
VI. As a familial disorder

* Adapted from references 4 and 5.

kidney might be related to a tumor-specific antigen. Of our four cases with Hodgkin's disease, two are siblings who were hypocomplementemic and diagnosed as having glomerulonephritis before recognition of Hodgkin's disease; the C3 level returned to normal during remission of the tumor in both patients. The other two Hodgkin's cases did not show any signs of clinical renal involvement.

The three SLE cases presented in this series showed changes which were reminiscent of membranoproliferative glomerulonephritis; more interestingly, pure membranous alterations were found in some glomeruli of a specimen from case 5, making us wonder whether there is a transformation from membranous to membranoproliferative glomerulonephritis or vice versa in SLE cases.

Even though infection of ventriculo-atrial shunts is rather frequent and reported to be present in 3.5% to 11% of the shunts, glomerulonephritis secondary to the bacteremia caused by infected shunts is rare. Demonstration of C3 and immunoglobulins by immunofluorescence[10,11], and electron-dense material by electronmicroscopy[10] suggest that shunt nephritis occurs as an immune complex nephritis. In our cases (8 and 9), Staphylococcus albus was cultured from blood in the first and Staphylococcus coagulase (+) was cultured from the shunt of the second. Even though C3 was low in both, only the first had an abnormal urinalysis. An immunofluorescent study was performed in case 8, and granular deposition of C3 and IgG was observed. These findings strongly suggest that an immunologic mechanism played a role in the development of MPGN due to an infected ventriculo-atrial shunt in our cases. It is known that after removal of an infected shunt, recovery from nephritis occurs[10].

Staphylococcus aureus was cultured from many sites in case 10, who had osteomyelitis and later devoloped sepsis. Upon development of abnormal urine findings, a renal biopsy was performed and MPGN was diagnosed. So it can be concluded that staphylococci have certain properties that may induce MPGN-type changes as long as they produce persistent antigenemia[12].

Streptococci seemed to cause MPGN in cases 11 and 12, both of whom had a predisposition to streptococcal infections and elevated titers of ASO; β-hemolytic streptococci were cultured from the throat of only one of these two patients. Here again possibly chronic antigenemia, though caused by a different microorganism, induced immune complex nephritis, as shown by the presence of C3, IgG and IgM deposits in the glomerular basement membrane zone and the mesangium.

Henoch-Schönlein purpura is a rare underlying entity of MPGN[3], and we encountered only one case. Polyarteritis nodosa (PAN) has been reported associated with MPGN in an adult[13], and case 14 seems to be the first child reported to have MPGN and PAN together. The coexistence of these two entities supports the idea that some cases of MPGN are produced by circulating immune complexes.

Partial lipodystrophy (PLD), a disease well known in association with MPGN, was also encountered (case 15)[14,15]. Studies reported show that:

1. Complement abnormalities formerly regarded as characteristc of MPGN are indeed found in PLD, whether or not renal disease is present[15];
2. When glomerulonephritis complicates PLD, it is MPGN;
3. The onset of PLD antedates the renal disease, sometimes by long periods; and
4. Some patients suffered recurrent infection, but others were apparently in good health apart from PLD.

Our patient had PLD for two and a half years before producing glomerulonephritic symptomatology, and C3 was noted to be low; however C3 nephritic factor was not available. She benefited from prednisolone treatment.

Reports of sibling cases of MPGN are few[16,17]. In our study, of one sibship (Cases 16 and 17) both had hypocomplementemia, proteinuria, hematuria and a well-developed nephrotic state. Both developed renal failure and expired four and six years after onset, respectively. The familial nature of the disease added to the earlier observation of its predilection for the white race strengthens the concept that genetic factors are involved in its origin.

Association of chronic active hepatitis with persistent hepatitis B surface antigenemia and MPGN is known[18]. Our case 18 is an example. In this particular case, demonstration of HBsAg in the glomeruli[18] shows that immune complexes containing HBsAg are involved in the pathogenesis of the glomerular disease. We had three more cases (19,20,21); however HBsAg was negative in the serum at the time of biopsy, and since demonstration of HBsAg in renal tissue was not available, definite support for this particular relation is lacking.

Even though our series of secondary MPGN cases constitutes a heterogeneous group of primary diseases, since the type of glomerulonephritis was the same as in idiopathic MPGN, we tried to compare the clinical parameters in both (Table III) and noticed mainly these differences:

1. Whereas primary MPGN is not usually seen under the age of two, we found two cases under two years of age who had MPGN, and this was due to the presence of their predisposing primary disease, congenital hydrocephalus with an infected ventriculo-atrial shunt.
2. In the idiopathic form, the clinical presentation is generally nephrotic syndrome in 40-50%, nephritic syndrome in 20-33% and asymptomatic proteinuria in 25-30% of the patients. On the other hand, in the secondary form of MPGN nephritic syndrome was seen in 57.1%, nephrotic syndrome in 19.1% and the asymptom-

TABLE III

Comparison of Some Features of Idiopathic MPGN (from the literature) and Secondary MPGN (Hacettepe Series)

	IDIOPATHIC MPGN		SECONDARY MPGN
	Habib[19] (n: 105)	General literature[4, 20, 21]	Hacettepe (n: 21)
Age	All over 2 years 83% over 8 years	5 - 30 years	All over 6 months 83% over 5 years
Sex	57% F	F, slight	52% M
Upper respiratory tract infection	45%	1/3 - 1/2	Unavailable
Nephritic syndrome (%)	67	40 - 50	19
Nephritic syndrome (%)	33	20 - 33	57
Asymptomatic proteinuria (%)	42	25 - 50	24
Edema (%)	43	—	63
Hypertension	25%	1/3	21%
Hematuria (%)	88	68 - 88	58
Proteinuria (%)	•	50 massive 50 mild	86
ASO (%)	12	40	33 (2/6)
BUN	31%	1/3	53% (9/17)
Glomerular filtration rate	••	1/3	43% (3/7)
C3 (%)	48 (14/29)	70	80 (8/10)
Anemia (%)	15	50	53
Incidence	13% of renal biopsies	6 - 20% of renal biopsies	9% of all MPGN

Numbers in parentheses indicate the number of cases included in the particular study.

• Proteinuria (mg/kg/24hr):
- ≥ 250 : 9 cases
- $100 < 250$: 33 cases
- ≤ 100 : 48 cases
- Not determined : 15 cases

•• Renal function was lowered in 33/105 cases

atic situation in 23.8%. The higher incidence of a nephritic condition in the secondary form may be a feature of this type of MPGN*.

In summary, there are many diverse factors contributing to the development of childhood cases of a secondary form of MPGN, such as persistent antigenemia of various infectious agents (e.g. staphylococcus, streptococcus, hepatitis B virus) and of malignant lymphomas (e.g. Hodgkin's disease), soluble immune complex diseases (e.g. SLE and Henoch-Schönlein purpura), and genetic coding. Awareness of these many and different factors, we believe, will help in arriving at a diagnosis and developing a better understanding of the pathogenesis of this fascinating but brutal disease and will contribute to the efforts of the physicians in helping those affected.

Summary

During the last 15 years, 21 cases of the secondary from of MPGN were diagnosed, which constituted 9.2% of all the MPGN cases. The clinical parameters, compared with those of the idiopathic form, were found to be mainly the same except for those related to the underlying disease. The following were recognized as the underlying diseases in the Hacettepe series: Hodgkin's disease, systemic lupus erythematosus, infected ventriculo-atrial shunt, staphylococcic septicemia, streptococcic infection, familial predisposition, partial lipodystrophy, polyarteritis nodosa, Henoch-Schönlein purpura and chronic hepatitis. It is concluded that immune complex diseases, genetic coding and persistent antigenemia are the main predisposing conditions in the development of the secondary form of MPGN.

* It is also worth noting that proteinuria was not encountered in three of our cases (3,4,9). Since there were no clinical findings of renal involvement, recent urinalyses in these three cases were not available; therefore proteinuria was found in 86% of our patients. These three cases are thought to represent a subclinical type of nephritis.

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