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CHILDHOOD MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS: A HISTOPATHOLOGICAL AND IMMUNOFLUORESCENT STUDY OF 104 CASES*

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Membranoproliferative glomerulonephritis (MPGN) is a rather common, well defined and distinctive form of the primary glomerular disease originally described in 1965 by West et al[1], and Gotoff et al[2]. To date two types of this glomerulonephritis, based on their ultrastructural features, have been universally accepted[3-8]. Type I MGPN is characterized by the presence of subendothelial electron-dense deposits, mesangial cell proliferation and splitting of the glomerular basement membrane (GBM). Type II MPGN has been referred to by many authors as the dense deposit disease (DDD)[9-12]. The existence of other subtypes of MPGN is suggested by some investigators[9-11]. In terms of its clinicopathologic features, MPGN is also subdivided into primary MPGN and secondary MPGN.

The present study aims to review MPGN as in occurs it children, including its clinical, histopathologic and immunohistochemical features. The incidence of childhood MPGN among all of the biopsy-requiring glomerular diseases encountered at the Medical Center of the Hacettepe University Institute of Child Health is also evaluated.

Material and Methods

This study involved 104 patients. For 101 of them a single renal biopsy had been obtained, and for the other three two biopsies were available. All of the 107 specimens evaluated were percutaneous (needle) biopsies, including one from a transplanted kidney.

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For light microscopic studies the tissue was fixed in Duboscq-Brazil's solution, embedded in paraffin and sectioned at 2 to 4 microns. Sections were stained with hematoxylin-eosin (HE), periodic acid Schiff (PAS), Jones silver and trichrome stains.

Immunofluorescence studies were carried out on 96 specimens, of which 82 proved adequate, that is at least three glomeruli were present. Half of the biopsy material was frozen in a mixture of carbon dioxide ice and acetone, cut in cryostat at 2 microns and incubated with the following fluorescent antibodies in all cases: anti- C3, anti-IgG, anti-IgA and anti-IgM; in addition anti-fibrinogen was also used in 61 cases, anti-HBsAg in 55 cases and anti-IgE in 32 cases. Sections were immediately observed in an Ortho-Lux Leitz microscope with an epifluorescent lamp. Microphotographs were taken using Ektachrome high-speed film.

In the assessment of the histopathologic data the following criteria were used.

Lobulation :

Grade	Number of lobules	Glomeruli
–	3 ↓	
+	4 - 6	Some
++	6 - 8	Most
+++	9 and ↑	All

Glomerular polymorphonuclear leukocytes :

Grade	Number of leukocytes	Glomeruli
–	3 ↓	Some
+	3 - 10	Most
++	10 - 30	All

Mesangial matrix increment :

Grade	Percentage of involved glomerular area
±	10
+	11-25
++	26-50
+++	51 and ↑

Tubular, interstitial and vascular damage were evaluated on a subjective scale from (–) to (+++), on the basis of the percentage of the area involved with respect to the total area of the specimen. The presence of tubulo-interstitial foam

cells was also indicated on this basis. The degree of vascular damage was determined as a function of the luminal narrowing.

For evaluation of discrimination between type I and type II MPGN, both light and fluorescent microscopic findings were considered as shown in Tables I and II.

TABLE I

Light Microscopic Findings in Membranoproliferative Glomerulonephritis

	Type I MPGN	Type II MPGN
BMs*	GBM: – thickened (almost always) – silver stain: double-contour (more prominent than type II)	GBM: – intense staining with histochemical stains, almost all capillary walls (hallmark) – silver stain: irregular thickening of GBM that is homogeneous, ribbon-like and non-argyrophilic
	Bowman's capsule BM and TBM: no change	Bowman's capsule BM and TBM: changes similar to those in GBM
Cellular and matrix increment	Prominent (more than type II); major alteration	Mild (compared to type I) early biopsy: more severe mesangial alteration.
Masson's trichrome	Fuchsinophilic deposits – Occasional – Subendothelial	Round fuchsinophilic deposits – often – mesangium
Crescents	Less than 10%	More than 10%
Tubular and interstitial changes	Early in course: None or inconspicuous Later in course: – Interstitial fibrosis – Interstitial mononuclear cells – Interstitial foam cells – Tubular atrophy	
PMNs	Present in mesangium, in a small number of specimens.	Often present in capillary lumens; and with combination of interposition results in narrowing or loss of patency of capillaries.

* Abbreviations: GBM: Glomerular basement membrane
BM : Basement membrane
TBM: Tubular basement membrane
PMN: Polymorphonuclear leukocyte

TABLE II

Fluorescent Microscopic Findings in Membranoproliferative Glomerulonephritis

Immune reactants	Type I MPGN	Type II MPGN
C3	– Irregular and granular, outlining periphery of the lobule – Variable localization in the mesangium	– Discontinuous linear ("railroad track") pattern outlining the • GBM • Bowman's capsule BM • TBM • Occasionally arterioles – Large globular masses of C3 in mesangium ("mesangial rings") may be the sole complement component deposits.
C1q and C4	Less often than C3; usually in association with prominent Ig deposits.	Lesser intensity and a more sparse distribution
Properdin	Similar distribution in a lesser degree	More than in cases of C1q and C4
Factor B	Similar distribution, in a lesser degree	
IgA	Present in 33% of cases	Absent
IgG, IgM	– Absent in 1/2-1/3 of cases; – When present: • Inconsistent and segmental granular along the GBM • Less often in mesangium	IgG absent IgM present in 50% of cases

GBM: Glomerular basement membrane
TBM: Tubular basement membrane

For the tabulation of the clinical data the records were reviewed for the following: sex, age at the onset of the clinical disease, history of preceding infection (sore throat or others); clinical, physical and laboratory findings at the onset (hypertension, proteinuria, hematuria, hypercholesterolemia, low serum complement, hypoalbuminemia, increased serum creatinine, edema and anemia). The following definitions were used: *significant proteinuria*: urinary proteins above 40 mg/h/m^2 of body surface; *hypoalbuminemia*: serum concentration below 2.5 g/dl; *hypercholesterolemia*: serum concentration above 250 mg/dl; *normal serum complement level*: 60-120 mg/dl; *normal antistreptolysin-O (ASO) titer*: up to 500 U.

Results

Clinical features. From the 713 pediatric renal biopsies evaluated at Hacettepe Children's Hospital between the years 1975 and 1981, 104 cases were diagnosed as MPGN. Thus the incidence of MPGN among pediatric nephrologic diseases in our center was found to be 14.6%. There were 39 females and 65 males, giving a male to female ratio of 1.6. The age of the patients (without distinguishing secondary MPGN from the idiopathic form) at the onset varied from three to 18 years, with the arithmetic mean, mode and median all being the same: 10 years (Figure 1). The first biopsy was obtained two weeks to eight years after the onset of the disease, with an arithmetic mean of 14.4 months, a mode of two months and a median of 4.5 months.

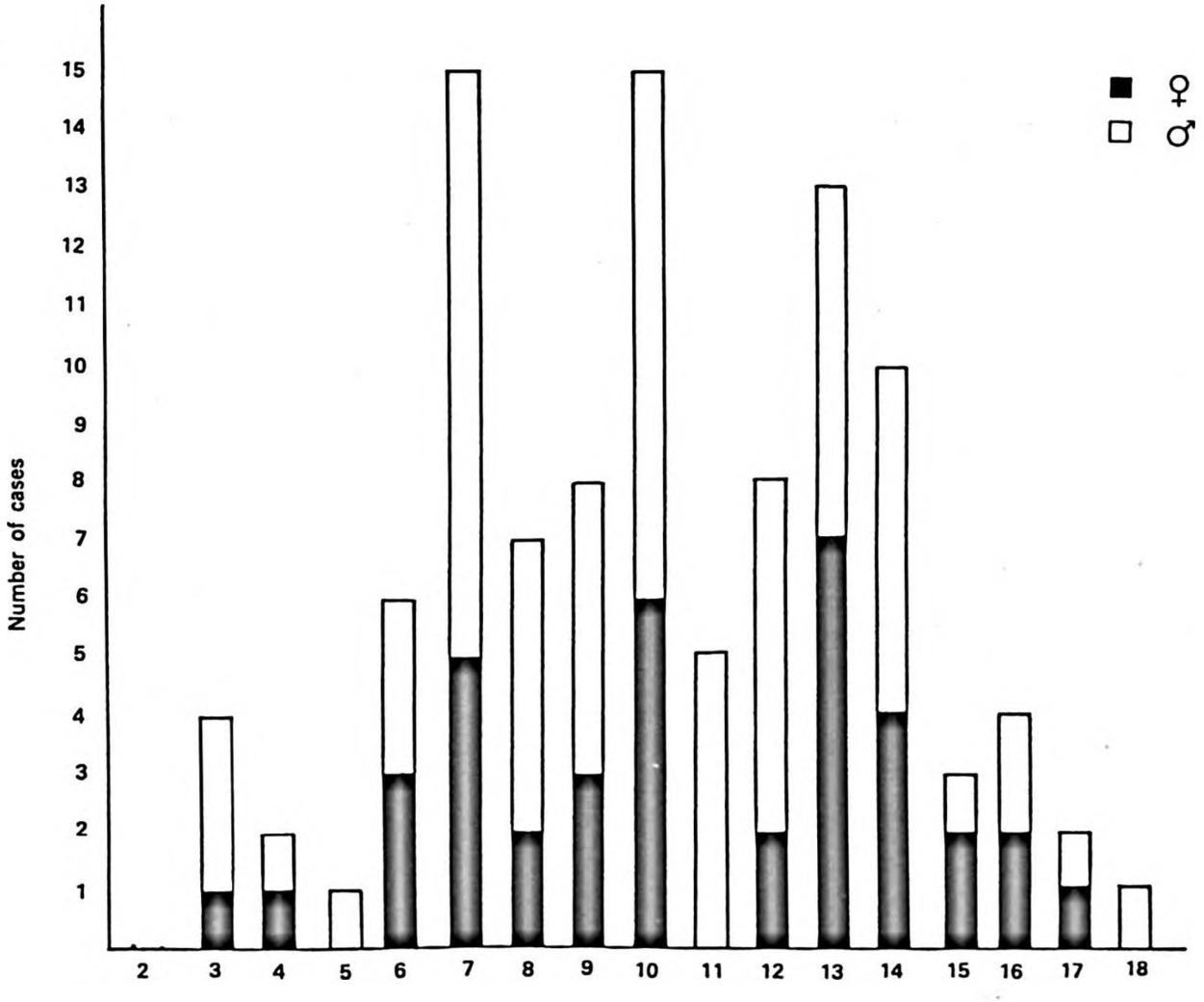

Figure 1

Sex and age at onset of the disease in 104 MPGN patients.

Renal symptoms were preceded by an upper respiratory tract infection in 34 cases (32.7%), and of these 14 had a raised ASO titer. In 9 of the 104 cases of MPGN (8.6%) an underlying primary disease was present. In two patients the underlying primary disease was systemic lupus erythematosis (SLE), and there was one case each of staphylococcic sepsis (due to osteomyelitis), Henoch-Schönlein purpura, thalassemia (splenectomized), rheumatismal valvular disease, postnecrotic cirrhosis and HBsAg (+) chronic active hepatitis. Finally, in one patient myocarditis, hepatitis and glomerulonephritis were all present, and presumed to be viral in origin (Table III).

TABLE III

Some of the Clinical Features of Nine Cases of Secondary Membranoproliferative Glomerulonephritis

Age (years)	Sex	Primary disease	Renal findings
13	F	SLE	Hematuria, proteinuria
16	F	SLE	Hematuria, proteinuria
13	M	Osteomyelitis (Staphylococcus aureus sepsis)	Incidental proteinuria and hematuria IVP: renomegaly
10	M	Thalassemia (splenectomized)	Proteinuria IVP: renomegaly
11	M	Rheumatic carditis Infective endocarditis	Proteinuria, hematuria IVP: renomegaly C3 : ↓
7	M	Henoch-Schönlein	Hematuria, proteinuria IVP: normal C3 : normal
10	M	Chronic hepatitis HBsAg (+)	Proteinuria IVP: normal
10	F	Post-necrotic cirrhosis	Proteinuria, hematuria
4	M	Viral (?) myocarditis, hepatitis	Proteinuria

TABLE IV

Comparison of Some of the Findings of Idiopathic MPGN in the Literature With Those of the Hacettepe Series

	Habib et al[4] (n: 105)	Other literature[24,33]	Hacettepe* (n: 95)
Age (years)	2-17 Mean: 10	5-30	3-18 Mean: 10
Sex	57% girls	Girls slightly predominant	63% boys
Upper respiratory tract infection	45%	30-50%	36%
Nephrotic syndrome	67%	40-50%	60%
Nephritic syndrome	33%	20-33%	38%
Asymptomatic proteinuria	42%	25-30%	–
Edema	43%	–	97%
Hypertension	25%	33%	29%
Hematuria	88%	68-88%	66%
Proteinuria	**	50 massive 50 slight	100
ASO≥500 U	12%	40%	40% (12/30)
BUN 20 mg/dl	31%	33%	37%
GFR 80 cc/dk/1.73m^2	***	33%	52% (34/66)
C3 60 mg/dl	48% (14/29)	70%	25% (5/20)
Anemia	15%	50%	15%
Incidence	7% of renal biopsies	6-20% of renal biopsies	13% of renal biopsies

* Primary MPGN patients.

** Proteinuria (mg/kg/24hr) ≥ 250: 9 cases; 100-250: 33 cases; ≥ 250: 48 cases; Undetermined: 15 cases

*** Renal functions degraded in 33 of 105 cases

( ) Numbers in brackets show the number of patients giving positive findings out of the number of patients tested.

In 100 patients (96.2%), the initial manifestation was edema, in two patients painless gross hematuria, in one it was a Henoch-Schönlein type of rash and in the other it was oral ulcerations. (The latter patient was later shown to have SLE.)

The initial clinical diagnosis was nephrotic syndrome in 57.7% of the cases, nephritic syndrome in 37.5%, asymptomatic proteinuria and hematuria in 1.9% and chronic renal failure in 1.9%.

Hematuria was present in 61.5% of the cases, proteinuria in all, hyperazotemia in 37.5%, a decreased glomerular filtration rate in 55.5% (40/72), hypercholesterolemia in 68.3% and hypertension in 25%.

Clinical findings for idiopathic MPGN cases only (95), are given in Table IV for purposes of comparison with the literature.

Histopathologic findings. (Figures 2-7) For the evaluation of discrimination between type I and type II MPGN, both light microscopic and immunohistologic findings were taken into account and 69% (66/96) of the cases were determined to be type I MPGN and 31% (30/96) to be type II MPGN. In eight patients it was not possible to distinguish between the two.

Glomerular findings. All cases showed a thickening of the capillary wall. In 30 cases this thickening was diffuse (present in all capillaries of a given glomerulus) and generalized (involvement of all glomeruli present in the specimen) in distribution. This appearance was accentuated by strong chromophilic staining with HE, trichrome and PAS stains. Jones silver staining technique disclosed an irregular ribbon-like, homogeneous thickening of the GBM with a pale uniform central area bordered on either side by strongly argyrophilic lines. In most of the 30 cases classified as the dense deposit variety of type II, a similar appearance was encountered in the basement membrane of Bowman's capsule and in the tubules and more rarely in the arteriolar wall.

In the other 66 cases the GBM thickening was due to mesangial interposition and segmentation was not present. In contrast to type II, there was no similar thickening in the basement membranes (BMs) of Bowman's capsule and tubules. In the type I cases there was splitting of the GBM.

Mesangial matrix increment featured in all cases. It was minimal (±) in 10, mild (+) in 62, moderate (++) in 25 and severe (+++) in 7 of the 104 cases.

There was no lobulation in 74 of the cases, but it was mild (+) in 12, moderate (++) in 10 and severe (+++) in 8 of the 104 cases. This last group was diagnosed as having lobular glomerulonephritis (LGN).

The glomerular presence of polymorphonuclear leukocytes was noted in 31 of the 104 cases, absent in the other 73. It was mild (+) in 14 of the 104 cases and moderate (++) in 17.

Extracapillary epithelial cell proliferation (crescent) was present in 5.7% (6/104) of our cases.

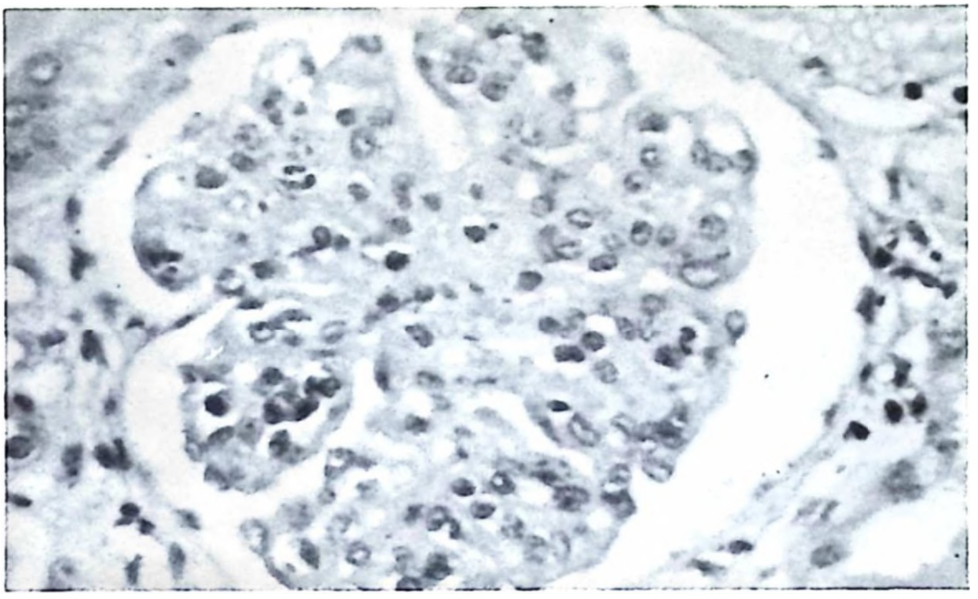

Figure 2

An enlarged glomerulus showing marked lobulation accompanied by early centrilobular sclerosis (HE X 350).

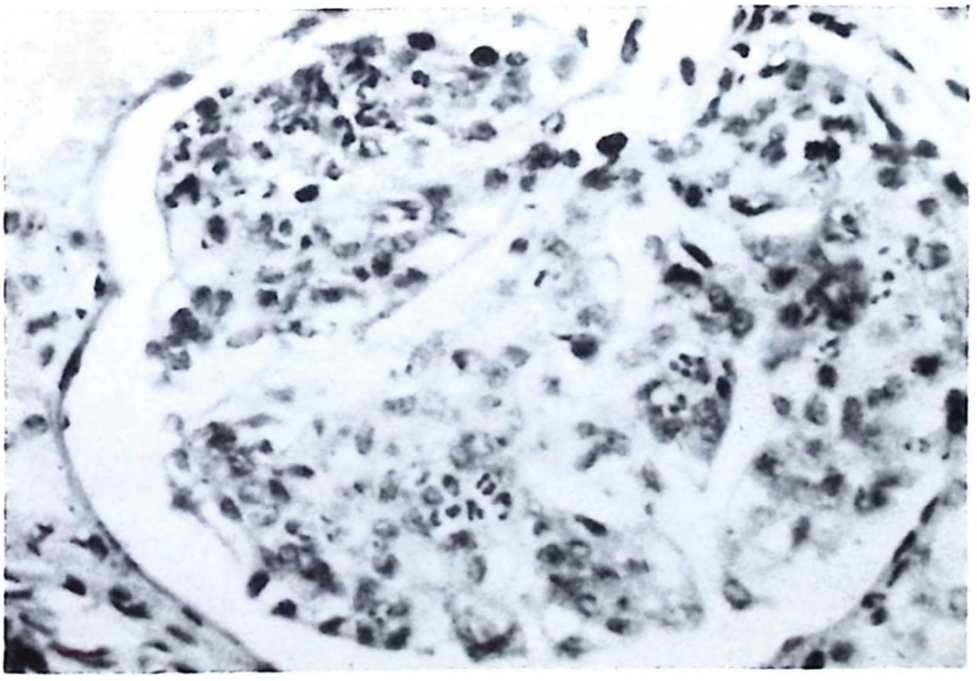

Figure 3

An enlarged glomerulus showing mainly endocapillary proliferation associated with leukocytic infiltration and a lesser degree of mesangial hyperplasia (HE X 450).

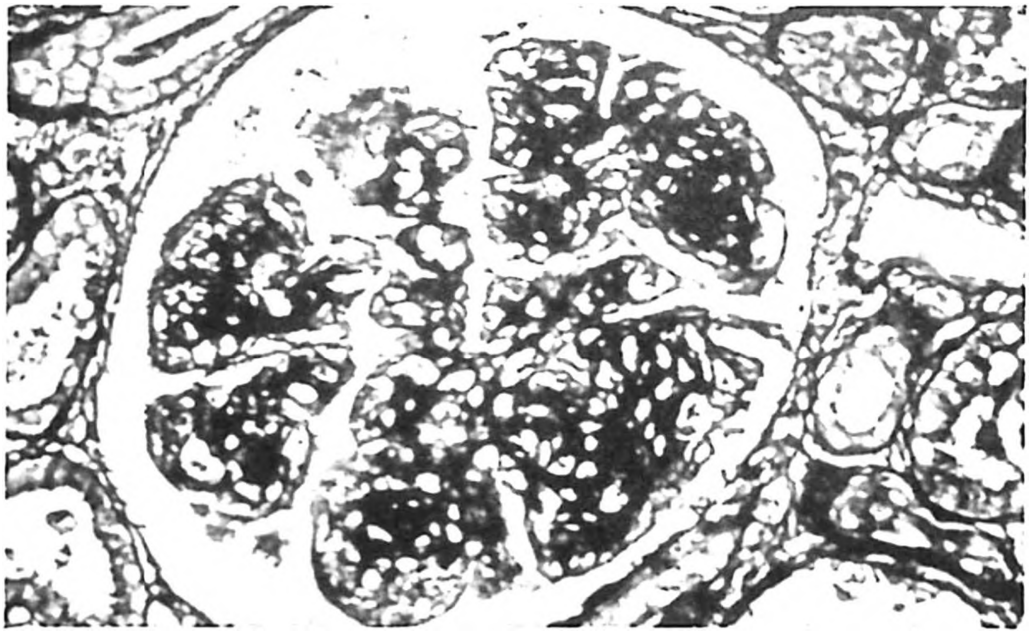

Figure 4

Mesangial hyperplasia, mesangial matrix increment and hyperlobulation of the glomerulus (J. silver stain X 350).

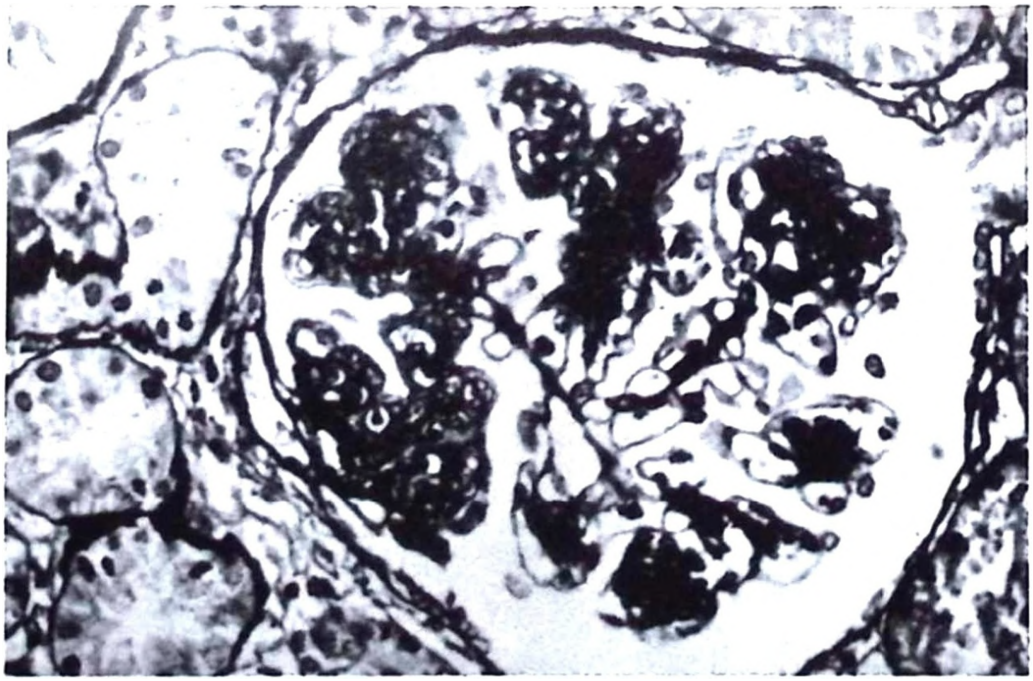

Figure 5

A glomerulus of type I MPGN. Mesangial matrix hyperplasia occluding the capillary lumens with double contour of the capillary wall on the right side (J. silver stain X 350).

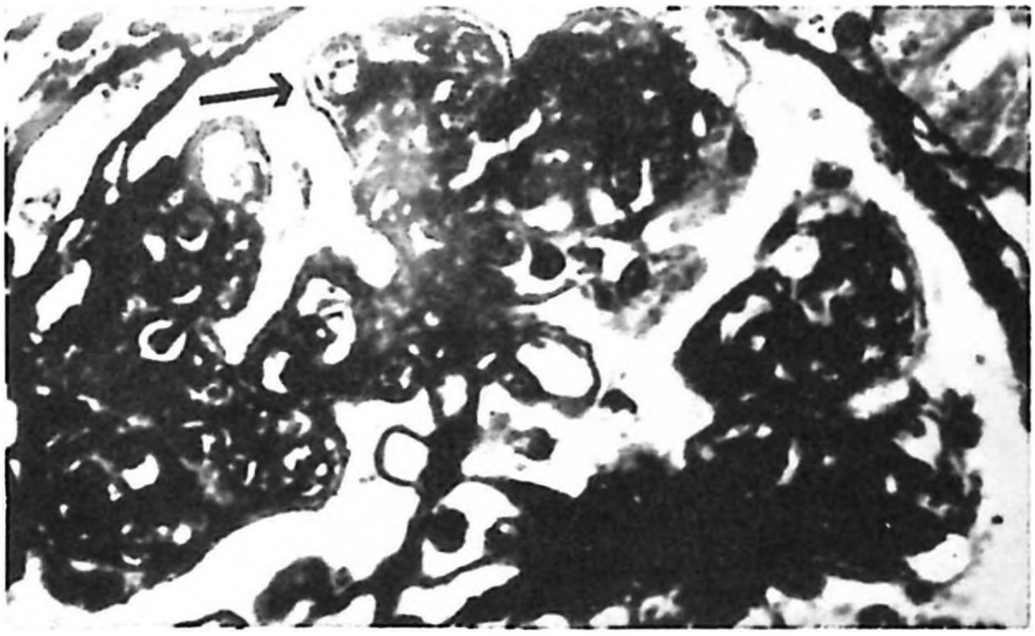

Figure 6

Same glomerulus as Figure 5. Demonstration of double contour (arrow) under higher magnification (J. silver stain X 500).

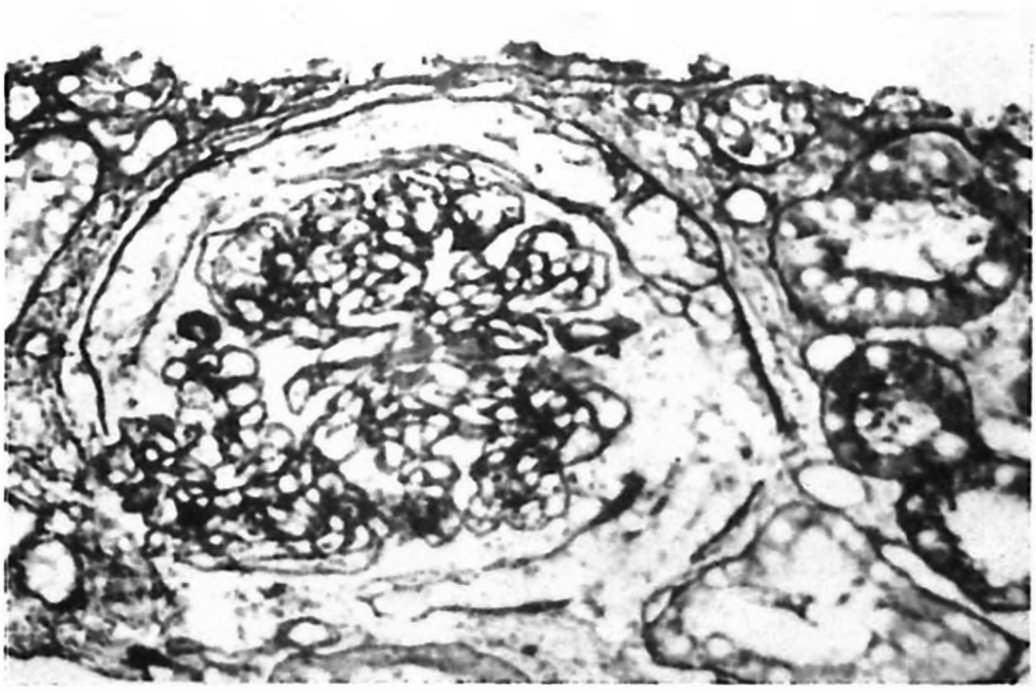

Figure 7

A glomerulus from type I MPGN with crescent formation: extra capillary proliferation (J. silver stain X 250).

Only one of the patients was diagnosed as having focal segmental MPGN. The mesangium of the glomeruli not involved with segmental lesions was proliferative though this was mild compared to the severe proliferation of the segmental lesion. GBM thickening was only evident in the segmental lesions.

Capillary luminal obliteration in the glomerular tuft was encountered in 86 of the 104 cases, of which 18 were minimal (±), 40 mild (+), 22 moderate (++) and 6 severe (+++). It was absent in 18 cases.

Glomerular sclerosis was present in a total of 18 of the 104 cases, of which five were focal global, four focal segmental, seven focal and two segmental. Glomerular necrosis was present in 5 cases and was focal segmental in two, focal in two and segmental in one case.

Tubular interstitial findings. Tubular atrophy was found in 45 of the 104 cases; it was minimal (±) in 25, mild (+) in 13, moderate (++) in 4 and severe (+++) in 3. Usually tubular hyalin, granular casts and interstitial fibrosis accompanied the tubular atrophy. The severity of the interstitial fibrosis was seen to vary in accordance with the severity of the tubular atrophy.

Interstitial inflammatory infiltration was present in 13 of the 104 cases, 4 of which were minimal (±) and the other nine mild (+). Cells were usually lymphocytes.

Interstitial foam cells were absent in 92 of the 104 cases. They were minimal (±) in 3, mild (+) in 5 and moderate (++) in 4 cases.

Immunohistologic findings. Immunohistochemical reactions were tabulated in 82 cases (Table V). The most striking finding was the glomerular localization of C3

TABLE V

Renal Immunofluorescence: Distribution of the Deposits of the Immune Reactants in 82 Patients With MPGN

Immune reactants	No. of specimens stained	Positive staining No.	Positive staining %
C3	82	67	82
IgM	82	50	61
IgG	82	31	38
IgA	82	26	32
IgE	34	1	3
Fibrinogen	61	32	52
HBsAg	55	4	7

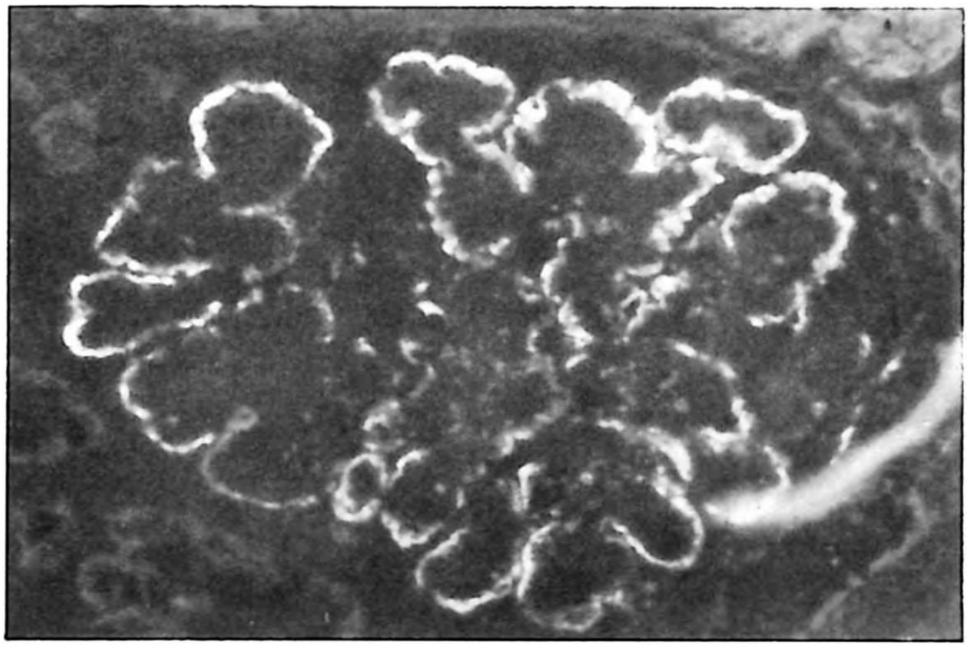

Figure 8

Immunofluorescent appearance of type I MPGN. C3 deposits in the peripheral capillaries showing an irregular, finely granular (pseudolinear) pattern.

(β1C) in 67 (82%) specimens; it was absent in 15 (18%). The pattern of deposition was of two types. In type I MPGN, it was perilobular, irregular and granular. In this pattern mesangial deposits were scanty or absent (Figure 8). In type II MPGN, it was characterized by the combination of mesangial and peripheral deposits. The distribution of C3 deposits was usually in accordance with BM abnormality, that is surrounding GBM, Bowman's capsule, tubules and occasionally arterioles, in a disrupted linear pattern. In addition to this feature, mesangial globular, coarse granular C3 masses were striking (Figures 9,10).

Staining with C1q and C4 gave a positive reaction in five of the six cases studied, being negative in only one.

Positive reactions for one or more of the immunoglobulins were observed in 59 of the 82 specimens (72%). In 56 instances one or several immunoglobulins coexisted with C3, the most common accompaniment being with IgM (73%) and the least with IgA (36%) (Table VI). In 10 out of 82 cases (12%) the only positive reaction was obtained with C3. The immunoglobulin most frequently encountered by immunofluorescence was IgM (61%).

Fibrinogen, IgE and HBsAg were observed in 32/62 (52%), 1/34 (3%) and 4/55 (7%) of the cases respectively. Immunofluorescent staining was absent in 12 cases (15%) out of a total of 82 patients.

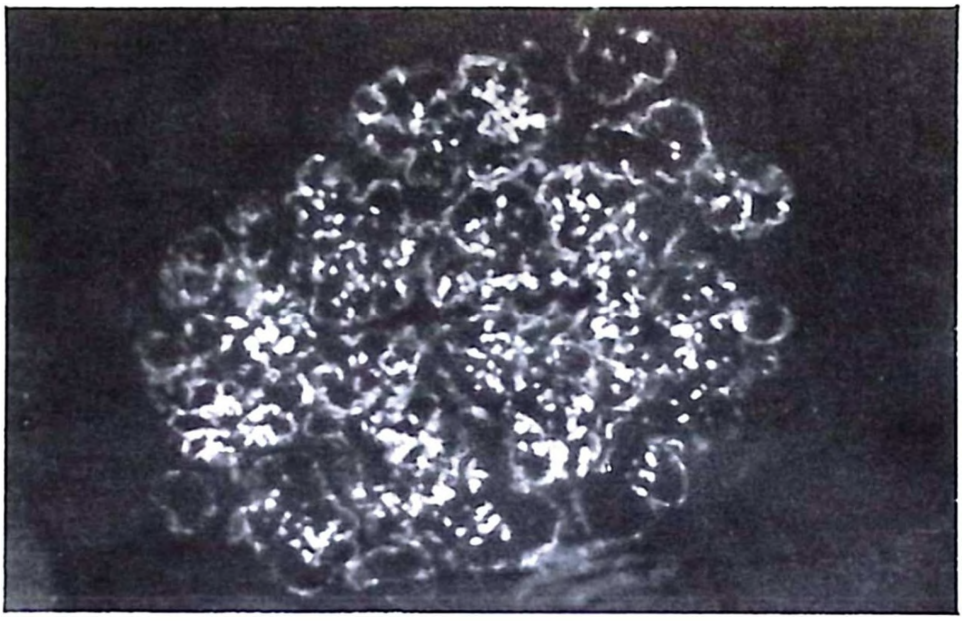

Figure 9

Dense deposits type: Deposits of C3: mixed pattern, peripheral irregular capillary coexisting with coarsely granular mesangial deposits (fluorescent microscopy X 350).

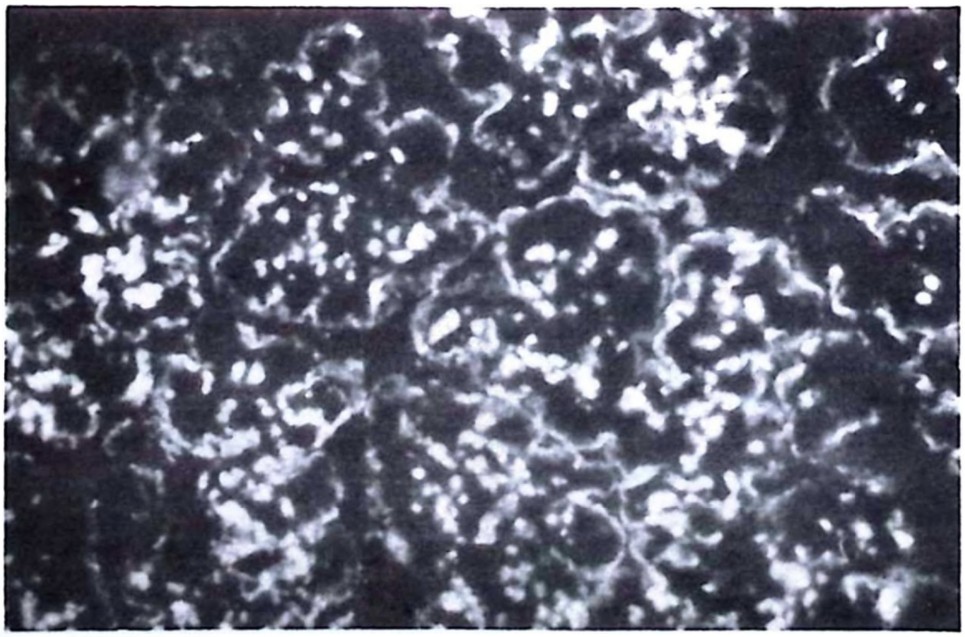

Figure 10

Same glomerulus as Figure 9 under higher magnification. This mixed pattern is typical of type II MPGN dense deposit variety (fluorescent microscopy X 600).

TABLE VI

Coexistence of C3 Deposition with Immunoglobulins

Immunoglobulins	Total no. of cases	Positive staining No.	Positive staining %
IgM	66	48	73
IgG	66	30	45
IgA	66	24	36

Discussion

Although the accurate recognition of membranoproliferative glomerulonephritis can be made only on morphologic grounds and by means of special methods (immunofluorescence and/or electron microscopy), the clinical picture can be highly suggestive of the diagnosis. A combination of nephritic and nephrotic features, the age of the patient between 7 to 12 years at onset, the persistence of the proteinuria and hypocomplementemia and the evolution to chronic renal failure represent strong suggestions for diagnosis.

Histopathologically, the glomerular lesions are quite characteristic in the majority of cases and consist of a combination of the following:

— enlarged glomeruli,
— enhancement of the lobular pattern,
— marked obliteration of the capillary lumen,
— capillary wall thickening,
— proliferation of mesangial cells, and
— increment of mesangial matrix.

Mesangial matrix extends to the periphery resulting in the interposition of the mesangium on the capillary basement membrane, resulting in the production of one of the most striking features of this disease, the "double contours". Double contours constitute the hallmark of the best known and the more common variety of the disease, classical, subendothelial or type I MPGN.

Another mechanism for the capillary wall thickening consists of dense deposits in the basement membrane the appearance for which the name "dense deposit disease" (DDD) is more commonly used in lieu of type II MPGN. Habib et al[3] suggest that this type has a poorer outlook in comparison with the classical type; this may be related to the more frequent presence of crescents in type II MPGN.

Because there are considerable differences in the various complement components in these two types of MPGN (that is C3 being low and C1q and C4 being normal in DDD and just the contrary being true in type I), different immune mechanisms are thought to be responsible for the lesions in each type. The classic type is now considered to be related to the formation of immune complexes, whereas DDD is related to the alternate activation of the complement cascade, probably secondary to the activity of a peculiar factor, named the C3 nephritic factor (C3NeF). C3NeF, though more constantly present in patients with type II MPGN, may be present in both types. Neither the C3 concentrations, nor the presence, quantity or absence of C3NeF bears any relation to clinical evolution in the majority of patients[16,17].

A - Clinical findings

MPGN is a relatively common form of nephritis. In the International Study of Kidney Disease in Children 7.8% of the new nephrotics were observed to have MPGN. This disease constitutes 6-20% of the biopsy-requiring nephrologic diseases[4,16]. In this study of 713 biopsy-requiring childhood nephrologic diseases 104 patients, that is 14%, got the diagnosis of MPGN. Since in nine of these cases there was another underlying disease, these secondary MPGN cases constitute 9% (9/104) of all MPGN patients and approximately 1% (9/713) of all renal diseases[18-25].

In general, patients are between five and 30 years of age and there is a slight female predilection[24,25]. Our youngest patient was three years old; it was most commonly encountered between the ages of 7-12 years (56%) and most of these were 10 years old. In contrast to the usual slight preponderance of females, in our study males were more commonly (62%) encountered.

The clinical presentation is variable. MPGN of either type may present with nephritic syndrome[26,27]. In contrast to the expected early clinical recovery seen in acute poststreptococcal glomerulonephritis (APSGN), profuse proteinuria, hematuria and (if measured) a persistently low serum complement C3 are noted in nephritic syndrome of MPGN. A low serum C3 at eight weeks plus signs of clinical activity is a firm indicator that a biopsy is needed. In this study 37% of the patients presented with the characteristics of nephritic syndrome.

A full nephrotic syndrome is the most common mode of presentation for both types of MPGN, and accounts for half of the patients[16,27]. The coexistence of hematuria with proteinuria and the older age of the patients are clues to the clinician to consider a disease other than the minimal change nephrotic syndrome (MCNS). The prognosis of nephrotic patients is much worse than for those without a nephrotic syndrome, especially if it persists for years[16,24,27]. The most common clinical presentation in this series was also the nephrotic syndrome (58%).

Asymptomatic proteinuria and/or hematuria is seen in 25-30% of patients[26,27]. The low proportion seen in our series (2%) most probably reflects the inadequacy of the routine urinalysis.

A comparison of our findings with those of the literature is shown in Table IV.

B - Histopathologic findings

Glomerular findings. Many subgroups of MPGN are suggested, but type I and type II especially are universally accepted. It was West et al[1] who defined type I first and Berger and Galle[12] who defined type II. In most of the large series, type I is reported to constitute 65-75%, type II 20-30% and other variants the remainder of the cases. In our series the figures were within this range, 69% of the patients having type I MPGN and 31% type II MPGN. Mesangial matrix increment, being a prerequisite for inclusion in this study, was seen in all cases. It is this feature which is responsible for the capillary luminal obliteration which was observed in 86 patients (83%) but was minimal in 80 (77%). A similar trend was noticed in a study by Madrigal et al[28].

Glomerular lobulation, glomerular infiltration with polymorphonuclear leukocytes, tubular atrophy, interstitial infiltration and foam cells were less severe in our series than reported in the literature. Similarly, crescents were observed in only 6% of our patients.

Habib[29] first noticed focal segmental MPGN, and it has been reappraised in recent years[30]. In this variant, light microscopic evaluation reveals generalized mesangial proliferation in addition to segmental membranoproliferative lesions. Mesangial fluorescence with antiserum to C3 is present in all glomeruli while focal lesions are characterized by segmental granular fluorescence with antiserum to IgG. Focal segmental MPGN is thought to be an early manifestation of type I, or, rarely, of type III and the patients have an excellent prognosis. In this series there was one case diagnosed as focal segmental MPGN from a renal biopsy with the above-mentioned light microscopic features. Unfortunately no immunofluorescent study was available for this patient.

C - Immunohistologic findings

Even though it is possible to differentiate type I from type II via some characteristic immunofluorescent staining features, cases without any staining are also reported[24,32]. In our series 15% of the cases did not show any immunofluorescent staining and this is in accordance with the 17.5% stated in Cameron's study[24].

The most common immunofluorescence was seen to be with C3 (82%) and it is likewise reported to be 82% and 88% in Cameron's[24] and Madrigal et al's[28]

studies, respectively. Immunoglobulins are in second place: positive reactions for one or several immunoglobulins were observed in 59/82 (72%) cases. Existence of C3 with one or several immunoglobulins was found in 56/82 (68%) of the cases. These last two values are in accordance with the ones reported in the study of Madrigal et al[28], that is 74% and 66% respectively.

Positive reaction for only C3 (without any immunoglobulins) was noted in 10/82 (12%) of our cases. In the same manner the presence of only C3 and the absence of immunoglobulins is mentioned in the literature both for type I and type II MPGN[32].

Summary

In this study 104 cases of membranoproliferative glomerulonephritis (MGPN) diagnosed during the last seven years are reevaluated in regard to the clinical and pathological features and associated conditions. MPGN constitutes 14% (104/713) of the renal diseases in children requiring biopsy. 91% (95/104) of all the MPGN cases were idiopathic, whereas 9% (9/104) of the MPGN and 1% (9/713) of the tissue diagnostic approach requiring cases were secondary to an underlying disease: SLE, staphylococcic sepsis, Henoch-Schönlein purpura, splenectomized thalassemia, rheumatic carditis, post-necrotic cirrhosis, HBsAg (+) chronic hepatitis and viral myocarditis.

Age distribution varied from three to 18 years, with an arithmetic mean, mode and median of 10 years. Clinical presentations were as follows: nephrotic syndrome (58%), nephritic syndrome (38%), asymptomatic proteinuria and hematuria (2%) and chronic renal failure (2%).

Typing, based on light and fluorescent microscopic studies, revealed type I and II to be 69% and 31% respectively. Classical, lobular, crescentic and focal forms of MPGN were observed with the respective percentages of 85, 8, 6 and one. Immunofluorescent staining was absent in 15% and was most frequent with C3, which was usually accompanied by IgM.

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