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Occasional survey

Glomerular diseases in children

"The Iranian experience"

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Abstract. A total of 411 children, aged from 0.3 to 18 years, suffering from glomerular diseases, were studied by renal biopsy between 1976 and 1985. The clinical presentation included nephrotic syndrome (79% of cases), renal failure (43%), and arterial hypertension (38%). In all, 177 cases presented with primary nephrotic syndrome; all had complicated courses and most were either corticosteroid-dependent or -resistant. Only 26.6% had minimal change disease on renal biopsy; 56.5% had focal-segmental sclerosis; and immunofluorescent deposits were observed in half of the group. Acute poststreptococcal (36 cases), mesangiocapillary (80 cases), and lupus (34 cases) glomerulonephritis occurred frequently; IgA glomerulopathy (10 cases) and haemolytic uraemic syndrome (6 cases) were uncommon. Glomerular crescents were observed in 71 cases. These observations illustrate the types of glomerular diseases seen in Iranian children.

Key words: Glomerular diseases – Focal segmental sclerosis – Acute glomerulonephritis – Endo-extracapillary proliferation – Mesangiocapillary glomerulonephritis – Lupus erythematosus glomerulonephritis

Introduction

The introduction of renal biopsy has resulted in a more accurate classification of glomerular diseases and has contributed to our knowledge of the natural history as well as the aetiology and pathogenesis of these pathological states [1, 2]. Sequential renal biopsy can provide a means of assessing therapeutic efficacy.

Previous observations have suggested a relatively high frequency of severe glomerular diseases in Iranian children [3–6]. This report describes the light and immunofluorescent microscopic features of renal biopsies from 411 children with glomerular diseases.

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Patients and methods

Four hundred and eleven patients, aged from 0.3 to 18 years and suffering from glomerular diseases, were studied between 1976 and 1985. These represented about 25% of patients admitted with glomerular diseases and were those with the most severe manifestations of their diseases. Approximately equal numbers of cases were from metropolitan Teheran and rural Iran. All patients underwent detailed clinical and laboratory evaluations, which included quantitative protein excretion, urinary cellular count, serum protein electrophoresis, cholesterol, creatinine, electrolytes, CH50, C3, and C4 measurements. Microbiological and parasitological studies to detect pathogenic organisms, among them pyogenic bacteria, tuberculosis, hepatitis B (HBAg) or rarer diseases, and immunological tests such as immunoglobulin measurements and anti-DNA antibody titration were performed when indicated.

Renal failure was defined as the presence of more than two consecutive serum creatinine levels higher than the normal values for age [7] or repeated creatinine clearances (C_{cr}) below 75 ml/min per 1.73 m^2; patients with C_{cr} values below 40 ml/min per 1.73 m^2 were defined as having severe renal failure. Arterial hypertension was considered present when blood pressures were greater than the 97.5 percentile for height plus 30 mm Hg. Haematuria was defined as the excretion of more than 5,000 red blood cells/min in more than one urine specimen.

Indications for renal biopsy included: the need to define prognosis; proposed treatment with a cytotoxic agent; acute renal failure of unknown aetiology which did not resolve within a short period; progressive glomerular disorders; complicated nephrotic syndrome and persistent proteinuria with or without haematuria. Patients with chronic renal failure and a C_{cr} below 20 ml/min per 1.73 m^2 were excluded from the study.

Table 1. Clinical features of the patients studied

Diagnosis (number of cases)	M/F	Mean age (years) at presentation (range)	Hypertension	Presenting clinical features			
				Nephrotic syndrome	Acute nephritis	Renal failure	
						Moderate	Severe
Primary NS ($n = 177$)	128/49	5.0 (0.3–14.0)		177			
AGN ($n = 36$)	32/4	4.2 (4.0–14.0)	27	10		7	29
MPGN ($n = 80$)	21/59	8.7 (2.0–14.0)	45	74	50	28	40
MGN ($n = 24$)	22/2	7.6 (2.0–12.0)		9			
IgA neph. ($n = 10$)	5/5	6.4 (2.0–12.0)	6	5	7	5	
HSP ($n = 20$)	10/10	9.3 (1.0–13.0)	9	5	19	5	5
SLE ($n = 34$)	10/24	8.9 (1.5–17.0)	19	28	18	15	
Vasculitis ($n = 9$)	5/4	7.5 (5.0–13.0)	8	5	6	3	6
HUS ($n = 6$)	3/3	7.4 (1.5–18.0)	4				6
Alport's ($n = 7$)	5/2	6.6 (1.6–12.0)	3	3		2	3
MISC ($n = 8$)	6/2	4.3 (0.1–13.0)		8			

Primary NS = Primary nephrotic syndrome; AGN = acute glomerulonephritis; MPGN = membranoproliferative glomerulonephritis; MGN = membranous glomerulonephritis; HSP = nephritis of Henoch-Schönlein purpura; IgA neph = IgA nephropathy; HUS = Haemolytic uraemic syndrome; MISC = miscellaneous; M = male; F = female

Kidney tissue was obtained by open renal biopsy in 368 patients and by percutaneous needle biopsy in the remainder. All the biopsy specimens were studied by immunofluorescence microscopy using standard methods to prepare the tissue. In a few cases, diced renal tissue was also examined by electron microscopy using standard techniques. At least ten glomeruli were available for light microscopy and four for immunofluorescence in all biopsies.

The classifications used were those of the World Health Organization [8]. The intensity of immunofluorescent deposits was scored from 0 to 4+, but occurrence in a non-contributing site was considered as "non-significant".

Results

Data from the 411 patients have been classified according to the clinical presentation and histopathological characteristics (Table 1). The pattern of deposits encountered in immunofluorescence was granular in the whole group.

Primary nephrotic syndrome ($n = 177$)

The clinical picture was complicated by microscopic haematuria (65.0% of cases), transient hypertension (18.0%), and renal failure (11.3%). Most patients were corticosteroid-dependent or -resistant. The histology demonstrated minimal glomerular lesions in 47 cases, diffuse mesangial proliferation in 30, and focal segmental sclerosis in 100.

Immunofluorescent findings did not discriminate between these categories. Flecks of deposits, coarse granules, filament or Comma-like features with 1 to 2+ intensity were seen in more than 50% of the cases. They were mainly distributed focally or segmentally with mesangial and/or peripheral distribution. Peripheral deposits were more frequently encountered in focal-segmental sclerosis (FSS). IgM, C3 and fibrinogen were the most frequently seen proteins; IgG, Clq, C4 and IgA deposits occurred less often.

Acute post-infectious glomerulonephritis ($n = 36$)

All of the patients had a history of recent upper respiratory infection. A streptococcal origin was demonstrated in 30 cases. The histological pic-

ture, severe in almost all biopsies, showed intensive cell proliferation with inflammatory infiltration. Diffuse endocapillary changes were present in all biopsies, with additional extracapillary proliferation present in 12, two of which demonstrated widespread crescents. The diffuse discrete glomerular deposits stained with the greatest intensity for C3 (2+ to 4+), less so for IgG and fibrinogen, and rarely for IgM, Clq, IgA and C4. Fibrinogen was deposited in Bowman's space in extracapillary proliferative disease. In rare cases, C3 or other deposits extended to vessel or tubular basement membrane. In 2 cases, vascular changes were prominent; proliferation of the intima with multiple thromboses was seen in one patient.

Mesangiocapillary or membranoproliferative glomerulonephritis ($n = 80$)

A streptococcal infection was documented in 25 cases. Ten patients presented with chronic nephritis and 11 with only haematuria and proteinuria, 5 of the latter subsequently developing the nephrotic syndrome. Fifty-six of the patients had type I membranoproliferative glomerulonephritis (GN); 24 had these changes plus extracapillary proliferation; and 10 of these latter patients manifested diffuse glomerular crescents. Immunofluorescent microscopy revealed characteristic fine granular deposits (2+ to 4+ intensity) along the capillary walls and in the mesangium. C3 was invariably present, IgG and fibrinogen were frequent, while IgM, C4, Clq and IgA were seen less often. Two patients had dense deposit (type II) disease, and both had crescents.

Epimembranous or membranous glomerulonephritis ($n = 24$)

The clinical presentation was less acute and less severe in this group. Proteinuria and haematuria were the sole manifestations in 14 patients; only 9 had nephrotic syndrome and 1 had chronic nephritis. Using a silver stain, the capillary wall changes were characteristic in all but 7 cases. The changes were more complex in 5 patients, all of whom had circulating HBAg. Two of these had associated mesangial cell proliferation. The immunofluorescence picture was typical. IgG was present in all cases; fibrinogen, IgM, C3, Clq, C4 and IgA were seen less frequently. A pseudolinear picture was observed in 2 cases. In those children who had hepatitis B antigenaemia associated with abnormal hepatic enzymes at some time during the survey, the kidney disease appeared clinically more active and the biopsy tissue demonstrated more confluent deposits on immunofluorescence.

Primary IgA glomerulonephritis ($n = 10$)

In only 3 cases was recurrent macroscopic haematuria the sole presenting feature. All other patients had additional presenting features (Table 1). Four patients had diffuse proliferative changes, 4 both endo- and extracapillary GN, and 2 focal-segmental disease. Deposits, with 1 to 3+ intensity, were mainly distributed in the mesangium. IgA was constant, IgG and C3 occurred less frequently, and C1q and C4 were still less common.

Henoch-Schönlein purpura with nephritis ($n = 20$)

One patient presented with only macroscopic haematuria. At the time of renal biopsy all patients had nephrotic syndrome. Diffuse proliferative GN was observed in 15 patients, capillary wall thickening and extracapillary proliferation in 10 cases, 8 of whom had wide spread crescents, and focal segmental GN in 5. IgA was seen consistently; IgG, fibrinogen, and C3 were less frequent; Clq and C4 were rarely present.

Lupus erythematosus glomerulonephritis ($n = 34$)

Trimethadione, phenytoin and penicillamine were incriminated as aetiological agents in 3 patients. In the remainder, the development of nephrotic syndrome, hypertension or renal failure frequently occurred after a period of months of no or minimal urinary abnormalities. Three patterns of histological changes were seen. Diffuse proliferative GN occurred in 26 cases, of whom 11 had both endo- and extracapillary changes. Five of these latter patients had diffuse crescents. Four patients had mesangiopathic changes and 4 membranous changes.

Patterns of immunofluorescence were typical for systemic lupuserythematosus – diffuse, irregularly distributed granular deposits of 2 to 4+ intensity in the capillary wall and mesangium. All biopsies were positive for IgG; Cl9, C3, C4, IgA, fibrinogen and IgM were present in most of the cases. Occasionally deposits extended to the tubular basement membranes and vessels.

Vasculitis ($n = 9$)

A preceding streptococcal infection was documented in 5 cases. Six patients presented with acute nephritis and 3 with chronic nephritis associated with severe hypertension. At the time of biopsy, however, all patients had developed renal failure, which was severe in 6; 8 were hypertensive and 5 nephrotic. Light microscopy revealed

diffuse endocapillary proliferation with extracapillary proliferation in 8 cases, 3 having diffuse crescents. The 9th patient had a diffuse proliferative GN. Typical lesions were observed in medium and small-sized arteries. Immunofluorescence demonstrated C3, fibrinogen and IgG to be most common. In 1 patient the deposits extended to the tubular basement membranes.

Haemolytic uraemic syndrome ($n = 6$)

Arteriolar lesions were predominant in 4 patients. Widespread deposits of fibrinogen with 2 to 3+ intensity were distributed in the vessel wall and in glomeruli in a focal-segmental fashion. Scattered deposits of C3, Clq, and IgG were also noted.

Alport's syndrome ($n = 7$)

A family history of renal disease was present in 5 cases, and sensorineural deafness was found in 3 patients. Proteinuria and long-standing haematuria were present in all cases. Focal glomerular sclerosis was ubiquitous on biopsy, while capillary wall thickening was noted in 5 patients. Tubulointerstitial changes, including foam cells, were observed consistently. Immunofluorescence was usually negative, although small deposits of fibrinogen, C3 and IgM were observed in some instances.

Miscellaneous group ($n = 8$)

In this group were 2 infants with congenital nephrotic syndrome who showed cystic formations on biopsy, and a 5-year-old boy with nephrotic syndrome and diffuse mesangial sclerosis. Immunofluorescence was negative except for the last patient, who had deposits of IgM.

Five patients aged 4–13 years presented with nephrotic syndrome. Four of the patients had a history of a preceding acute respiratory infection, and all had haematuria. Renal biopsy performed 3–12 months after the onset showed endocapillary GN in 4 cases, while immunofluorescence disclosed focal-segmental deposits of 1 to 2+ intensity with C3 and IgG. The light microscopy in the 5th patient revealed a mesangiocapillary GN but immunofluorescence was negative.

Discussion

A survey of admissions and mortality rates in The Children's Center, Teheran, during 1973 showed that patients with glomerular diseases comprised 6.8% of the total admissions and ranked highest after haematology and cardiology admissions. The overall mortality rate was 10.0% and that of renal origin 3.1%. The admission rate did not exceed 20.0% of the whole consulting population.

The clinical picture in the majority of the patients we studied was severe: nephrotic syndrome, acute nephritis syndrome, renal failure and hypertension occurred in 79%, 44%, 43%, and 38% of the patients, respectively. In primary nephrotic syndrome, FSS was found in 56.5% of our cases. This lesion was identified in only 10.9% of the patients in the ICSKDS survey [9], but 38%, 33% and 17% in surveys from France, Tunisia and Korea [10–12], although the methods used to select cases for study differed in the various series.

In primary GN, acute poststreptococcal GN and mesangiocapillary GN, type I, were most frequent. These entities are becoming rare in western countries [13, 14]. Cameron et al. [15] described 45 children with mesangiocapillary GN observed in England in a 14-year period, and Levy et al. [16] have mentioned an incidence of 7% in 1300 children studied in France over 16 years, while a Japanese survey has shown an incidence of 15% [17]. Extracapillary proliferation or crescents were observed frequently (71 cases or 36%) in both primary and systemic GN. While they may be considered as secondary lesions, their presence, especially when they are numerous and circumferential, is an ominous prognostic sign. Diffuse crescents were observed in 42% of our patients. Miller et al. [18] have reported 56 cases with extracapillary proliferation in 372 children from Canada during a 20-year observation, and Niaudet et al. [10] have studied 41 cases with diffuse extracapillary proliferation in France during a 12-year survey.

That lupus GN was observed in 34 cases, Henoch-Schönlein GN less commonly in 20, primary IgA GN in only 10 cases, and haemolytic uraemic syndrome in only 6 children seems noteworthy. The clinical and histological pictures were severe in most of them. These findings are in contrast with Indian paediatric experience [19], which mentions that haemolytic uraemic syndrome is very frequent, IgA GN less, and lupus GN even rarer.

During our survey, parasitic diseases such as malaria or schistosomiasis, as well as congenital syphilis, hepatitis B and tuberculosis, were rarely seen. While leishmaniasis is endemic in some areas, it does not present with renal signs. The sole aetiological factor that we encountered frequently was a preceding streptococcal infection. This occurred in patients with a wide variety of histological changes in the glomeruli. It is inter-

esting that, like the Indian experience, the frequency of poststreptococcal GN is decreasing in our patients. The admission record reveals a rate that decreased 55% between the periods 1969–1976 and 1977–1984. Nevertheless, reports from Argentina, the Cameroons, China, Mexico and Thailand have mentioned its high frequency [17].

The study of renal biopsy by combined light and immunofluorescence microscopy, new to Iran during this period, has allowed a quick, accurate diagnosis and a better understanding of glomerular disease in our children.

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References

1. Heptinstall RH (1983) Glomerular diseases. In: Heptinstall RH (ed) Pathology of the kidney, (3rd edn.) Little Brown, Boston pp 387–907
2. Brenner B, Rector FC Jr (1986) The kidney, (3rd edn.) Saunders. Philadelphia, 929–1113, 1114–1184
3. Bodaghi E, Parsa B, Bahrami M, Shamsa AMZ (1971) Glomerulonephrites prolongées idiopathiques de l'enfant. Second International Symposium of Pediatric Nephrology, Sandoz Publications, Paris, p 163
4. Mojtabai A, Abtahi J (1975) Statistical review of admission during 1973. Proc Children's Med Center (Ahari Hospital) 5: 7–11
5. Abtahi M (1976) Acute glomerular nephritis syndrome in children. Thesis, Teheran University
6. Bodaghi E, Shamsa AMZ (1978) Syndrome nephrotique primitif de l'enfant en Iran. Ann Pédiatr (Paris) 54: 61–70
7. Schwartz GJ, Haycock GB, Spitzer A (1976) Plasma creatinine and urea concentration in children: normal values for age and sex. J Pediatr 88: 828–831
8. Churg J, Sobin LH (1982) Renal diseáse – classification and atlas of glomerular diseases. Igaku-Shoin, Tokyo, pp 3–18
9. Churg J, Habib R, White RHR (1970) Pathology of the nephrotic syndrome in children. Lancet I: 610–619
10. Royer P, Habib R, Mathieu M, Broyer M (1983) Néphrologie pédiatrique. Flammarion, Paris, pp 223–401, 501–516
11. Ben Maiz H, Koukie F, Kheder MA, El Matri A, Ben Ayad H (1983) Aspects anatomocliniques du syndrome néphrotique en Tunisie: etude de 539 cas. Néphrologie 4: 36
12. Ka KW, Isha L, Kin DF, Cheong HI, Choi Y, Kim YI, Lee HS (1987) Childhood renal diseases in Korea. Pediatr Nephrol 1: 664–669
13. Di Belgio Poso GB, Baroni M, Pogbari B, Lavagni MF, Porri MT, Banfi G, Colasta G, Congalonieri R (1985) Is membranoproliferative glomerulonephritis reach decreasing? Nephron 40: 380–381
14. Junger P, Forcet D, Hannedouchet T, Noel LH, Droz D, Grunfeld JP (1987) Decreasing incidence of membranoproliferative glomerulonephritis (MPGN) and acute glomerulonephritis (AGN) in the past decade in France. X International Congress of Nephrology, London, 384
15. Cameron JS, Turner DR, Heaton J, Williams DG, Ogg CS, Chantler C, Haycock GB, Hicks J (1983) Idiopathic mesangiocapillary glomerulonephritis: comparison of type I and II in children and adults and long-term prognosis. Am J Med 74: 175–192
16. Levy M, Beziau A, Israel J (1983) Etude en immunofluorescence des néphropathies glomerulaires: rétrospective 1966–82. Semin Néphrol Pédiatr Hôpital des Enfants Malades, pp 18–25
17. Holliday MA, Barrat TM, Vernier RL (1987) Nephrology around the World. In: Halliday MA, Barrat TM, Vernier RL (eds) Pediatric nephrology. Williams and Wilkins, Baltimore, pp 346–365
18. Miller MN, Baumal R, Poucell S, Steele BT (1984) Incidence and prognosis importance of glomerular crescents in renal diseases of childhood. Am J Nephrol 4: 244–247
19. Srivastava RN (1987) Pediatric renal problems in India. Pediatr Nephrol 9: 238–244

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