Clinicopathological Features of Primary Nephrotic Syndrome in Iraqi Children

Monir Hamid Naif* FIBMS**, Taghreed Fadhil Mohammed*** CABP

ABSTRACT

Background*:* Nephrotic syndrome is a clinical manifestation of different histopathological subtypes.

Objective: To study the histopathological lesions in idiopathic childhood nephrotic syndrome based on renal biopsy and to make clinicopathological correlation.

Methods: The data were collected retrospectively from records of the pediatric nephrology units at central child teaching hospital and Al-Kathemia Teaching Hospital during the period from January 2005 to May 2012, involving one hundred four patients aged up to 18 years with nephrotic syndrome whom renal biopsy had been done for them. The following data were collected from the files; personal data (age, sex), presenting symptoms and signs, biochemical data (serum urea, creatinine, cholesterol), C3 level if indicated. Initial episode, relapse, predisposing factors, familial history of nephrotic syndrome, treatment and complication.

Results: Percutaneous renal biopsies were done in one hundred four children. They were fifty-six (54%) males and forty-eight (46%) females, male to female ratio was 1.2:1. Age at onset ranged between 0.8-15 (median 3.6) years. Steroid sensitive patients were 58% and 41.3% of them were steroid resistance. Based on histological finding on renal biopsy, 39.4% were minimal change disease, 24.03% were focal segmental, 16.3% were membrano-proleferative glomerulonephritis. Other histological subtype were 10.6% mesangio-prolefrative glomerulonephritis, 6.7% were global mesangial sclerosis, 0.96% were membranous nephropathy.

Conclusion: This study gives a detailed information about the primary nephrotic syndrome in childhood. Minimal change disease was most common type followed by focal segmental glomerulosclerosis, but frequency of focal segmental glomerulosclerosis and to lesser extent the membranoproliferative glomerulonephritis had been increasing in Iraqi children with INS. Clinical feature, age, sex and respond to steroid are similar to most parts of world.

Keywords: Nephrotic syndrome, Histopathological lesion, Children.

Iraqi Medical Journal Vol. 65, No. 2, July 2019; p.155-160.

Idiopathic nephrotic syndrome (INS) is a common childhood renal disease characterized by a remitting and relapsing course associated with different histopathological subtypes. The estimated annual incidence of NS is 2-7/100,000 children, affecting mostly those under 6 years of age[1,2].

Histopathological examination of the renal biopsy helps in establishing the diagnosis, guides treatment and prognosis in children with INS[3].

Percutaneous renal biopsy has now been established as a safe and low risk procedure, to obtain tissue for histopathological analysis in children[4].

Advent of an automated biopsy device and real time ultrasound for percutaneous renal biopsies has enhanced the probability of obtaining adequate tissue for diagnosis and has reduced the complications associated with the procedure[5,6].

Minimal change disease (MCD) is the most common histopathological subtype in children with idiopathic NS. The incidence of focal segmental glomerulosclerosis (FSGS) has shown an increasing trend in patients with idiopathic NS[7,8].

The aim of this study is to document the histopathological spectrum of primary nephrotic syndrome based on the renal biopsy and to make clinicopathological correlation.

*Central Child Teaching Hospital, Baghdad, Iraq.

Methods

The data were collected retrospectively from medical records of the pediatric nephrology units at central child teaching hospital and Al-Kathemia teaching hospital during the period from January 2005 to May 2012, involving one hundred four patients with age (1-15 years), median age 3.5 years, with nephrotic syndrome whom renal biopsy had been done for them. The following data were collected from the files; personal data (age, sex), presenting symptoms and signs, biochemical data (serum urea, creatinine, cholesterol), complement level if indicated, initial episode, relapse, predisposing factors, familial history of nephrotic syndrome and the treatment and complications. The definitions used to describe patients with nephrotic syndrome in the study[1,3].

Nephrotic syndrome: proteinuria >40 mg/h/m^2 or > 50 mg/kg/day or protein/creatinine ratio > 0.2 g/mmol (> 2 g/g) and hypoalbuminemia < 25 g/l with or without edema.

Remission: proteinuria <4 mg/h/m^2 or 0-trace on Albustix for three consecutive days.

Steroid responsive: complete remission achieved with steroid therapy.

Steroid resistant: failure to achieve remission following 4-week prednisone 60 mg/m^2, followed by three methylprednisolone pulses.

Relapse: proteinuria > 40 mg/h/m^2 or >50 mg/kg/day or Albustix +++ for three consecutive days after having been in remission.

Frequent relapses: Two or more relapses within 6 months of initial response or four or more relapses within a period of 1 year.

Steroid dependence: Two consecutive relapses during corticosteroid therapy or within 14 days after cessation of therapy.

Patient with congenital nephrotic syndrome or with systemic illness such as systemic lupus erythematosus, Henoch Schonlen purpura, malignancy were excluded.

Renal biopsies were performed percutaneously using ultrasound guidance with (18G, 16G size) biopsy needle in the following groups of patients; steroid resistance, age older than 8 years and less than 1 year. Unusual presentation such as long previous course of mild proteinuria, persistent haematuria, hypertension, low serum complement or persistent disturbance of renal function, steroid dependent or frequent relapses. The sample taken was preserved in formalin 20% and sent for histopathology study.

Results

During the period from January 2005 to May 2012, percutaneous renal biopsy was performed in 104 of 341 patients with primary nephrotic syndrome. With male to female ratio was 1.2: 1, (Table 1).

Table 2 shows the histological pattern seen in nephrotic syndrome making MCD as overall most common pattern in our population. Minimal change disease was found in forty-one (39.4%) patients followed by focal segmental glomerulosclerosis which seen in twenty-five (24.03%) patients. Membranoproliferative glomerulonephritis found in seventeen (16.3%) patients, mesangioproliferative glomerulonephritis was the fourth most common histopathological subtype found in (10.6%).

Associated features: overall, hypertension was present in 47.1% of biopsied children, renal failure in 16.3%, and haematuria in 25.9%. Hypertension occurred in 17.3% of patients with nephrotic syndrome were FSGS, 11.5% were MPGN and 8.6% were MCD. Renal failure was noted in FSGN (12.5%), also noted in two (1.9) children with MCD. Hypocomplementaemia was noted in 13.4% with MPGN, (Table 3).

In relation to histological subtypes with steroid responsiveness, steroid sensitive patients (SSNS), 22(36.06%) patients were MCD, 10(16.3%) patients were FSGN and

4(6.5%) patients were MPGN. While steroid dependent patients (SDNS) was 12(19.7%) in MCD, 3(4.9%) in MPGN and 2(3.2%) in FSGN. Steroid resistance patients (SRNS) in MCD, MPGN, FSGN were 7(16.2%), 4(9.3%) and 19(44.1%), respectively, (Table 4).

Table 1: Distribution of nephrotic patients according to gender.

Patients	No. of patients	%
Male	56	54
Female	48	46
Total	104	100

Table 2: Distribution of histopathological lesion.

Histopathological lesion	Male	Female	Total No.	All patients % (No. 104)
Minimal change disease MCD	23	18	41	39.4
Membranoproliferative glomerulonephritis MPGN	8	9	17	16.3
Focal segmental glomerulosclerosis FSGN	14	11	25	24.03
Mesangioproliferative glomerulonephritis MesPGN	7	4	11	10.6
Global glomerulosclerosis	4	3	7	6.7
Membranous nephropathy MN	0	1	1	0.96
Amyloid	0	2	2	1.9
Total	56	48	104	100

Table 3: Clinicopathological correlates in children with nephrotic syndrome.

Clinical and Lab. data	MCD	MPGN	FSGN	MesPGN	Global GS	MN	Amyloid
Hypertension	9 (8.6%)	12 (11.5%)	18 (17.3%)	5 (4.8%)	3 (2.8%)	1 (0.9%)	1 (0.9%)
Renal failure	2 (1.9%)	4 (3.8%)	13 (12.5%)	2 (1.9%)	4 (3.8%)	0	2 (1.9%)
Haematuria	3 (2.8%)	10 (9.6%)	6 (5.8%)	3 (2.8%)	3 (2.8%)	1 (0.9%)	1 (0.9%)
Low C3	0	14 (13%)	0	0	0	0	0

MCD Minimal change disease, **MPGN** Membranoproliferative glomerulonephritis, **FSGS** Focal segmental glomerulosclerosis, **MesPGN** Mesangioproliferative glomerulonephritis, **Global GS** Global glomerulosclerosis, **MN** Membranous nephropathy

Table 4: Distribution of histopathological lesion according to steroid responsiveness.

Histopathological lesion	SSNS No. (%)	SDNS No. (%)	SRNS No. (%)
Minimal change nephrotic syndrome MCD	22 (36.06%)	12 (19.7%)	7 (16.2%)
Membranoproliferative glomerulonephritis MPGN	10 (16.3%)	3 (4.9%)	4 (9.3%)
Focal segmental glomerulosclerosis FSGS	4 (6.5%)	2 (3.2%)	19 (44.1%)
Mesangioproliferative glomerulonephritis MesPGN	2 (3.2%)	6 (9.8%)	3 (6.9%)
Global glomerulosclerosis	0	0	7 (16.2%)
Membranous nephropathy MN	0	0	1 (2.3%)
Amyloid	0	0	2 (4.6%)
Total	38(36.5)	23(22.1)	43(41.3)

Discussion

From the histopathology of the renal biopsy, disease pattern and change over time can be analyzed. The present study aimed to provide update epidemiological data of childhood nephrotic syndrome from renal biopsy. The new automated ultrasound guided percutaneous renal biopsy is safe in children. Success rate is high and failure to reach a diagnosis is rare, especially in experience hands. In the present study failure rate was (3.8%) as compared to (3.5%) in Lin WC, Yang Y, Wen YK, et al[9].

Although oedema is found in most of the patients, hypertension, gross hematuria and persistent microscopic hematuria was more common in patients with FSGS, a finding which is in consistent with that reported in other study[11].

In the present study minimal change disease (MCD) has been cited as the commonest histological pattern in idiopathic nephrotic syndrome found in 41 (39.4%) patients, followed by focal segmental glomerulosclerosis in 25(24.03%) patients, membranoproliferative glomerulonephritis in 17(16.3%) patients, mesangio-proliferative glomerulonephritis in 11(10.6%) patients. The histopathological patterns in some studies from other geographical locations are presented in table below[10-15].

Study	This study	Nammalwar et al[10]	Arif et al[11]	Absar et al[12]	Bakr et al[13]	Asinobi et al[14]	Mubarak et al[1]
Location	India	India	Pakistan	Pakistan	Egypt	Nigeria	Pakistan
Number of patients	N=22	N=250	N=75	N=41	N=741	N=41	N=538
Male/female	15/7	-	50/25	29/12	441/300	26/15	347/191
Mean age			11.2±3.7	7.6±3.3 years	7.4±3.6	2-13years 7.9years	9.79±4.59
Most common indication for renal biopsy	Atypical age of diagnosis of NS (45.5%)	Steroid resistant nephrotic syndrome (65.2%)	Steroid resistant nephrotic syndrome (48%)	Steroid resistant nephrotic syndrome (68%)	Steroid resistant nephrotic syndrome (44.4%)	Not mentioned	Not mentioned
Histopathology							
Minimal change disease	10%	52.1%	25.3%	37%	54.3%	9.8%	43.8%
Focal segmental glomerulosclerosis	-	-	46.8%	12%	-	4.9%	38.1%
Membranous glomerulonephritis	-	-	14.7%	7%	-	9.8%	7.9%
Membrano-proliferative glomerulo nephritis	10%	-	5.3%	10%	-	51.2%	3.1%
Mesangial proliferative glomerulo nephriti	40%	-	5.3%	-	-	-	4.8%

The incidence of focal segmental glomerulosclerosis (FSGS) is observed to be increasing over the years[11,12,15].

Geographical variation seems to be significant contributors for the different histopathological findings of nephrotic syndrome in children. While other studies reported from Iraq and Saudi Arabia showed that, the focal segmental glomerulosclerosis was the most common histopathological subtype[16,17].

While a study from Turkey showed that MespGN was the most common histopathological subtype, followed by MPGN[18].

In the present study among 43 patients who failed to respond to steroid, 16.2% had MCD, 44.1% had FSGS, while 9.3% of patients had MPGN, and 6.9% had MespGN. There is a report from international study of kidney disease in children showed that among 55 patients who failed to respond to steroid 45.5% had MCD, 47.5% had FSGS and 7% had MespGN[16].

In conclusion; this study gives a detailed information about the primary nephrotic syndrome in childhood. MCD was on the top followed by FSGS, but frequency of FSGS and to a lesser extent the MPGN had been increasing in Iraqi children with INS. Clinical features, age, sex and respond to steroid are similar to most parts of the world.

Recommendation: Our finding is in agreement with the recommendation of performing renal biopsies for children with INS who are steroid dependent, steroid resistant, particularly before starting immunosuppressive therapy. Also, immunofluorescence and electron microscopy examination of the specimen must encourage. We must insist on proper documentation of information in the patients' medical records and the result of renal biopsy must involve in each record.

References

1. Burgstein JM. Nephrotic syndrome. In: Behrman RE, Kliegman RM, Jenson HB, (eds.). Nelson Textbook of Pediatrics. 18th ed. Philadelphia: Saunders WB. 2008. P.2430-42.
2. Viswanath D. Nephrotic syndrome in children. J Indian Acad Oral Med Radiol 2013;25:18 23.
3. Kumar J, Gulati S, Sharma AP, Sharma RK, Gupta RK. Histopathological spectrum of childhood nephrotic syndrome in Indian children. Pediatr Nephrol 2003;18:657-60.
4. Pio D, Figueiredo S, Silva P, Nunes S, Costa T, Carvalho E, et al. Renal biopsies in children. A twelve year review. Port J Nephrol Hypert 2010;24(3):215.

5. Tøndel C, Vikse BE, Bostad L, Svarstad E. Safety and complications of percutaneous kidney biopsies in 715 children and 8573 adults in Norway 19882010. Clinic J Am Soc Nephrol 2012;7(10):1591-7.
6. Muñoz AT, Valdez-Ortiz R, Gonzalez-Parra C, Espinoza-Dávila E, Morales-Buenrostro LE, Correa Rotter R. Percutaneous renal biopsy of native kidneys: efficiency, safety and risk factors associated with major complications. Arch Med Sci (AMS) 2011;7(5):823.
7. Churg J, Habib R, White RR. Pathology of the nephrotic syndrome in children: A report for the International study of kidney disease in children. Lancet 1970;295(7660):1299-302.
8. Bagga A, Mantan M. Nephrotic syndrome in children. Indian J Med Res 2005;122(1):13.
9. Lin WC, Yang Y, Wen YK, et al. Outpatient versus inpatient renal biopsy: A retrospective study. Clin Nephrol 2006;66:17-24.
10. Nammalwar BR, Vijayakumar M, Prahlad N. Experience of renal biopsy in children with nephrotic syndrome. Pediatr Nephrol 2006;21(2):286-8.
11. Arif MK, Arif M, Amjad N. A histopathological outlook on nephrotic syndrome: A pediatric perspective. Indian J Nephrol 2016;26(3):188.
12. Absar A, Diamond M, Sonia Y, Arshalooz R, Safia A, Waqar K, Shahid P. Ten-year experience of pediatric kidney biopsies from a single center in Pakistan. Indian J Nephrol 2010;20(4):190.
13. Bakr A, Eid R, Sarhan A, Hammad A, El-Refaey AM, El-Mougy A, et al. Pathological profile of biopsied Egyptian children with primary nephrotic syndrome: 15-year single center experience. J Nephrol 2014;27(4):419-23.
14. Asinobi AO, Gbadegesin RA, Adeyemo AA, Akang EE, Arowolo FA, Abiola OA, et al. The predominance of membranoproliferative glomerulonephritis in childhood nephrotic syndrome in Ibadan Nigeria. West Afr J Med 1999;18(3).
15. Mubarak M, Lanewala A, Kazi JI, Akhter F, Sher A, Fayyaz A, et al. Histopathological spectrum of childhood nephrotic syndrome in Pakistan. Clinic Experiment Nephrol 2009;13(6):589-93.
16. Nariman F Ahmed, Raghad Ibrahim et al. Childhood nephritic syndrome clinical and histopathological spectrum. Fac Med Baghdad 2007; 49 (3).
17. Kari JA. Changing trends of histopathology in childhood nephritic syndrome in Western Saudi Arabia. Saudi J 2002; 23(3):317-21.
18. Bircan Z Yavuz A, Katar S, Vitrinet A, Yildirim M. Childhood idiopathic nephritic syndrome in Turkey. Pediatrr Int 2002;44(6): 608-11.

IMJ 2019; 65(2): 155-160.