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Spectrum of Renal Biopsy Finding in Idiopathic Nephrotic Syndrome in Children: A Five-Year Retrospective Analysis at A Nephrology Center in Kurdistan Region / Iraq

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Abstract

***Background**: The idiopathic nephrotic syndrome is a common renal disease in children. The renal biopsy is the standard diagnostic technique of nephrotic syndrome that provides valuable information for detection, assessment and monitoring of the disease.*
***Objective**: To understand and identify types of histopathological patterns of the renal biopsies in pediatric age group with Nephrotic syndrome in Kurdistan region.*
***Methodology**: This study was a retrospective observational study implemented in Kurdistan region/Iraq through reviewing data of renal biopsies collected from Dialysis center in Erbil city, Histopathology centers of Shorsh Teaching Hospital in Sulaimani city and Duhok General Teaching Hospital during the period of five years from 1st of January 2017, to 31st of December 2021 on convenient sample of 231 renal biopsies for children with idiopathic nephrotic syndrome. The idiopathic nephrotic syndrome diagnosis was done by Nephrologist and Pediatrician based on clinical and laboratory finding in addition to renal biopsy.*
***Results**: The histopathology examination of children with idiopathic nephrotic syndrome revealed that minimal change disease was the common histopathology finding (50.6%), followed by; focal segmental glomerulosclerosis (29.9%), membranous glomerulonephritis (3.9%), etc. A highly significant relationship was observed between younger age children with idiopathic nephrotic syndrome and focal segmental glomerulosclerosis histopathology findings (p<0.001). A highly significant relationship was observed between male gender of children with idiopathic nephrotic syndrome and focal segmental glomerulosclerosis histopathology findings (p<0.001).*
***Conclusions**: The minimal change disease is the common histopathology subtype of idiopathic nephrotic syndrome in children in Kurdistan region. However, there is increased in incidence of focal segmental glomerulosclerosis histopathology pattern in last years.*

***Keywords**: Idiopathic nephrotic syndrome, Renal biopsy, Histopathology.*

1. INTRODUCTION

The nephrotic syndrome (NS) is characterized by high proteinuria (>40 mg/m2 in one hour) leading to hypoalbuminemia (<30 g/L) that resulting in hyperlipidemia and edema (1). The abnormal glomerular permeability caused by damage of glomerular basement membrane is the main cause of NS. This abnormal permeability might be primary especially in children (idiopathic) or secondary mainly in adults that is related to infections, diabetes mellitus, neoplasia, systemic lupus erythematosus and some drugs (2–4).

The INS is a significant chronic pediatric disease with average annual incidence in healthy children of 2-7 new cases/100,000 children. The INS is predominant among male children than female children, but equal gender distribution is recorded at adolescence age. Higher incidence and aggressiveness of was shown in African American and Hispanic populations (5). The INS is commonly due to destructing the podocytes more than critical mass leading to irreversible glomerular damage. The mutations in podocyte proteins are recorded in families inheriting NS like mutation in plasma factor that changing glomerular permeability mainly in children with steroid-resistant nephrotic syndrome accompanied by changes in immune responses aggravating the T-cells changes that lead to abnormal permeability. The NS complications are attributed commonly to lipid metabolism dysregulation and abnormal lipid levels such as increased plasma levels of cholesterol, triglycerides and apolipoprotein B with decrease in endothelial lipoprotein lipase activity and decline in muscle and adipose tissues (6,7). The NS might be steroid-resistant, steroid-sensitive, steroid-dependent or frequently relapsing. The common clinical presentation of NS is edema which is located in face at earlier stages of the disease. In some cases, the moderate arterial hypertension is reported or and hypotension might be recorded due to hypovolemia. The microscopic hematuria is also reported by some cases, while macroscopic hematuria is rare and might be due to thrombosis of the renal veins. The renal failure is also recorded in rare cases (8).

Renal biopsy and assessing histopathology of INS is essential in diagnosis and management of the disease that represented a great challenge to nephrologists. The common challenges are steroid resistant, steroid sensitivity, relapses and taking decisions regarding cytotoxic agents (9). The most common pathology of INS is the minimal change disease

that is usually idiopathic and represented the pathology of 77-85% of NS in children. The light microscopy in these cases revealed no change, while obliteration of foot processes is detected by electron microscopy. The second common pathology of INS is focal segmental glomerulosclerosis which present in 10-15% of cases with sclerosis of glomeruli and tubular atrophy shown by light microscopy. The other pathological presentation of nephrotic syndrome is the membranoproliferative glomerulonephritis which involves immune complex deposition with thickening of basement membrane by light microscopy. The membranous glomerulonephritis represented only 2-4% of INS cases in children, while highly incident in adults that is characterized by thickening of basement membrane and spike and dome appearance by light microscopy (10,11).

In Iraq, the nephrotic syndrome is the second common renal disease in Iraqi children following urinary tract infections (12). The peak age incidence of INS among Iraqi children is in range of 1-5 years. The most common clinical presentation of INS in Iraq is generalized edema and oliguria was the second common symptom (13). Steroid resistant nephrotic syndrome is the most common indication for renal biopsy in Iraq, while the minimal change disease and focal segmental glomerulosclerosis are the most common histopathological lesions in primary kidney diseases (14). The nephrotic syndrome represented the main indication of renal biopsy in Erbil city and the histopathology examination revealed that focal segmental glomerulosclerosis and minimal change disease were the most frequent findings in younger age patients, while the membranous glomerulonephritis was common in older age patients (15). The purpose of this study was to understand and identify types of histopathological patterns of the renal biopsies in pediatric age group with Nephrotic syndrome in Kurdistan region.

2. Methodology

The design of present study was a retrospective observational study implemented in Kurdistan region/Iraq through reviewing data of renal biopsies collected from Dialysis center in Erbil city, Histopathology centers of Shorsh Teaching Hospital in Sulaimani city and Duhok General Teaching Hospital during the period of five years from 1st of January 2017, to 31st of December 2021. The studied population was all renal biopsies for idiopathic nephrotic syndrome. Inclusion criteria were renal biopsies of children and

adolescents (age group 1 month-16 years) with idiopathic nephrotic syndrome and satisfactory specimen with at least 5 glomeruli and one arterial blood vessel. Exclusion criteria were renal biopsies of adults, insufficient specimens as renal medulla only (without cortex) or extra renal tissue (fatty or muscle tissue, children with small or single kidney, chronic kidney disorders, incomplete or missing data and lost to follow up. The study ethics were implemented in regard to Helsinki Declaration by documented approval of health authorities and confidentiality of data. A convenient sample of 231 renal biopsies for children with idiopathic nephrotic syndrome was enrolled in current study after eligibility to inclusion and exclusion criteria.

Information of children was collected retrospectively by researcher through a prepared questionnaire designed by the researcher himself according to previous literatures (9,14). The questionnaire included general characteristics of children with idiopathic nephrotic syndrome (age, gender and residence), clinical characteristics of children with idiopathic nephrotic syndrome (clinical presentation, steroids therapy, duration of disease, ultrasound examination, general urine examination and serology) and histopathology findings of children with idiopathic nephrotic syndrome. The idiopathic nephrotic syndrome diagnosis was done by Nephrologist and Pediatrician based on clinical and laboratory finding in addition to renal biopsy. In laboratory, the specimens were categorized based on adequate assessment of native renal biopsies with light microscopy (LM), and immunofluorescence microscopy (IF).

Data of children were entered and interpreted statistically by SPSS program-26. Suitable statistical tests (Fishers exact test) for data were implemented accordingly and p value of ≤0.05 was significant.

3. RESULTS

This study included 231 children with nephrotic syndrome (NS) presented with mean age of (8.5 years) ranged between 8 months -16 years; 32.4% of children were in age group ≤5 years, 28.6% of them were in age group 6-10 years and 39% of them were in age group of 11-16 years. Male NS children were more than females (55.8% vs. 44.2%). High prevalence of NS children were reported in Hawler city (44.2%); followed by Sulaimani city (29.9%), Duhok city (16.8%) and outside Kurdistan (9.1%). (**Table 1**).

The common clinical presentations of NS in studied children were frequent relapses (28.6%), history of nephrotic syndrome with increase in renal indices (26 %), generalized body swelling (22 %), hematuria (13%), etc. About one third of NS children were on steroids therapy. Mean duration of NS was (19.7 months); 39% of children had NS duration of more than 12 months. Abnormal ultrasound findings were detected in 15.6% of NS children, while albuminuria was the common general urine examination finding (88.3%) and the serology test was positive in three NS children only (**Table 2**).

The histopathology examination of children with NS revealed that minimal change disease was the common histopathology finding (50.6%), followed by; focal segmental glomerulosclerosis (29.9%), membranous glomerulonephritis (3.9%), IgA nephropathy with mesangium proliferation (3.9%), focal global gomerulosclerosis (3.9%), cresentric and sclerotic glomerulonephritis (2.6%), IgM nephropathy with mesangium proliferation (2.6%) and diffuse proliferative and cresentric glomerulonephritis (2.6%). (**Table 3**).

A highly significant relationship was observed between age groups of NS children and their histopathology findings ($p<0.001$), the minimal change somewhat equally disturbed throughout all age group , while focal global and focal segmental glomerulosclerosis were related to younger age of NS children. (**Table 4).** A highly significant relationship was observed between gender of NS children and their histopathology findings ($p<0.001$), 69.6% of focal segmental glomerulosclerosis were related to male NS children, while global and focal global glomerulosclerosis and diffuse proliferative and cresentric glomerulonephritis were related to female NS children. (**Table 5**).

Table 1. General characteristics of NS children (N=231).

Variable		No.	%
Age (year)	≤5	75	32.4
	6 - 10	66	28.6
	11 - 16	90	39.0
Mean age (SD)	8.5 (4.5)	-	-
Gender	Male	129	55.8
	Female	102	44.2
Residence	Hawler	102	44.2
	Sulaimani	69	29.9
	Duhok	39	16.8
	Outside KRG	21	9.1

SD: standard deviation of mean

Table 2. Clinical characteristics of NS children (N=231).

Variable		No.	%
Clinical presentation	Generalized body swelling	51	22.0
	Renal impairment	60	26.0
	Frequent relapses	66	28.6
	Weight loss	12	5.2
	Hematuria	30	13.0
	Hypertension	12	5.2
Steroids therapy	Yes	159	68.8
	No	72	31.2
Duration of disease (month)	≤12	141	61.0
	>12	90	39.0
Mean duration (SD)	19.7 (4.9)	-	-
Ultrasound examination	Normal	195	84.4
	Abnormal	36	15.6
General urine examination	Albumin	204	88.3
	Albumin, RBCs and crystals	15	6.5
	Hematuria	12	5.2
Serology	Positive	3	1.3
	Negative	228	98.7

SD: standard deviation of mean

Table 2. Histopathology findings of NS children (N=231).

Variable	No.	%
Cresentric and sclerotic glomerulonephritis	6	2.6
Minimal change disease	117	50.6
Focal segmental glomerulosclerosis	69	29.9
Membranous glomerulonephritis	9	3.9
IgA nephropathy with mesangium proliferation	9	3.9
IgM nephropathy with mesangium proliferation	6	2.6
Diffuse proliferative and cresentric glomerulonephritis	6	2.6
Focal global gomerulosclerosis	9	3.9

Table 4. Distribution of histopathology findings according to age groups of NS children

Variable	Age (year)					
	≤5		6 - 10		11 - 16	
	No.	%	No.	%	No.	%
Minimal change disease	36	30.8	42	35.9	39	33.3
Focal segmental glomerulosclerosis	30	43.5	15	21.7	24	34.8
Membranous glomerulonephritis	0	-	0	-	9	100.0
IgA nephropathy	3	33.3	0	-	6	66.7
IgM nephropathy with mesangium proliferation	0	-	3	50.0	3	50.0
Diffuse proliferative and cresentric glomerulonephritis	0	-	0	-	6	100.0
Focal global gomerulosclerosis	6	66.7	3	33.3	0	-
Cresentric and sclerotic glomerulonephritis	0	-	3	50.0	3	50.0
P. value < 0.001 significant						

Table 5. Distribution of histopathology findings according to gender of NS children.

Variable	Gender			
	Male		Female	
	No.	%	No.	%
Minimal change disease	66	56.4	51	43.6
Focal segmental glomerulosclerosis	48	69.6	21	30.4
Membranous glomerulonephritis	6	66.7	3	33.3
IgA nephropathy with mesangium proliferation	6	66.7	3	33.3
IgM nephropathy with mesangium proliferation	0	-	6	100.0
Diffuse proliferative and cresentric glomerulonephritis	0	-	6	100.0
Focal global gomerulosclerosis	0	-	9	100.0
Cresentric and sclerotic glomerulonephritis	3	50.0	3	50.0
P. value < 0.001 significant				

4. DISCUSSION

The nephrotic syndrome (NS) is a pediatric renal disease manifested by various histopathological subtypes (16). Delayed diagnosis and starting treatment of NS affecting outcome of the disease. For that, histopathological evaluation of NS through biopsy is essential in diagnosis and planning of treatment in addition to improving prognosis fundamental not only in establishing the diagnosis, but also guides treatment and prognosis (17,18).

The present study showed that minimal change disease was the common histopathology finding (50.6%), followed by; focal segmental glomerulosclerosis (29.9%), membranous glomerulonephritis (3.9%), etc. These findings are consistent with results of Inamdar et al 9 retrospective observational study in India on 25 children with idiopathic nephrotic syndrome underwent renal biopsy which revealed that 52% of children had minimal change disease as common histopathology of INS followed by focal segmental glomerulosclerosis (24%). Our study findings are inconsistent with results of Özlü et al. (19)

retrospective study in Turkey which reported that focal segmental glomerulosclerosis was the common histopathology of children with INS (57%), followed minimal change disease (20.6%). This inconsistency might be attributed to differences in age groups of children between different studies in addition to variances in steroids sensitivity and resistance between studies with effect of different races and geographies. Previous study conducted in USA by Bonilla-Felix et al. (20) documented a significant changing in histopathology pattern of idiopathic nephrotic syndrome in children from minimal change disease to focal segmental glomerulosclerosisn with increasing incidence of focal segmental glomerulosclerosis for nephrotic syndrome among adults. This increase in incidence of focal segmental glomerulosclerosisn might due to racial differences (20). A prospective study on 77 children with idiopathic nephrotic syndrome carried out in Egypt by Abd-Elrehim et al. (21) also found that focal segmental glomerulosclerosis was the common histopathology (42%), followed minimal change disease (39%). This changing in histopathology pattern of INS was also detected by national literatures (14,15).

The current study revealed a highly significant relationship between age groups of NS children and their histopathology findings ($p<0.001$), children with focal segmental glomerulosclerosis were related to younger age of INS children. This finding is consistent with results of Mubarak et al. (22) observational study in Pakistan which reported higher incidence of focal segmental glomerulosclerosis histopathology finding in younger age children with idiopathic nephrotic syndrome. This trend of histopathology findings toward focal segmental glomerulosclerosis is indicative to changes of INS severity and steroids-resistances which acquired changes in diagnostic and management plans of INS (23). Our study showed a highly significant relationship between gender of NS children and their histopathology findings ($p<0.001$), 69.6% of focal segmental glomerulosclerosis were related to male NS children. This finding coincides with results of Shabaka et al. (24) review study in Spain which stated higher predominance of male gender in children with focal segmental glomerulosclerosis of INS. However, male predominance in INS with minimal changes disease in children was more obvious than INS with focal segmental glomerulosclerosis (9).

In the present study, the common clinical presentation of INS in studied children was frequent relapses and edema (28.6%). This finding is similar to results of Al-Juboori study in Iraq (13). Our study showed that about two third of INS children were on steroids therapy. This finding is consistent with results of Mortazavi et al. (25) single center study in Iran on 165 children with INS which found that 75.2% of them were on steroids therapy. This inconsistency might be due to racial variation and differences in histopathology findings between two studies. The present study found that mean duration of INS was (19.7 months) and 39% of children had INS duration of more than 12 months. This finding is close to reports of Dumas De La Roque et al. (26) study in France which documented that INS mean disease duration of two years. Our study revealed that common diagnostic technique detected abnormality was the general urine examination. This finding is parallel to results of Sultana et al. (27) study in Bangladesh which reported the importance of general urine examination in diagnosis of idiopathic nephrotic syndrome among children.

5. CONCLUSIONS

The minimal change disease is the common histopathology subtype of idiopathic nephrotic syndrome in children in Kurdistan region. However, there is increased in incidence of focal segmental glomerulosclerosis histopathology pattern in last year's. This study recommended the mandatory renal biopsy of children with idiopathic nephrotic syndrome in order to acquire better diagnosis and management. Further national researches on epidemiology and histopathology of idiopathic nephrotic syndrome should be supported

6. BIBLIOGRAPHY

1. *Boyer O, Baudouin V, Bérard E,Dossier C, Audard V, Guigonis V, Vrillon I. [Idiopathic nephrotic syndrome]. Arch Pediatr 2017; 24(12): 1338-1343.*
2. *Hill AJ, Stone DE, Elliott JP, Gerkin RD, Ingersoll M, Cook CR. Management of Nephrotic Syndrome in the Pregnant Patient. J Reprod Med 2016; 61(11-12):557-561.*
3. *Raina R, Krishnappa V. An update on LDL apheresis for nephrotic syndrome. Pediatr Nephrol 2019; 34(10):1655-1669.*
4. *Dumas De La Roque C, Prezelin-Reydit M, Vermorel A, Lepreux S, Deminière C, Combe C, et al. Idiopathic Nephrotic Syndrome: Characteristics and Identification of Prognostic Factors. J Clin Med 2018; 7(9):265.*

5. McCloskey O, Maxwell AP. Diagnosis and management of nephrotic syndrome. Practitioner 2017 Feb; 261(1801):11-15.

6. Vukojevic K, Raguz F, Saraga M, Filipovic N, Bocina I, Kero D, et al. Glomeruli from patients with nephrin mutations show increased number of ciliated and poorly differentiated podocytes. Acta Histochem 2018; 120(8):748-756.

7. Esprit DH, Amin MS, Koratala A. Uncommon things to note about a common cause of nephrotic syndrome. Clin Case Rep 2018; 6(8):1645-1646.

8. Noone DG, Iijima K, Parekh R. Idiopathic nephrotic syndrome in children. Lancet 2018; 392(10141):61-74.

9. Inamdar PR, Patil MV, Majeeb A. Spectrum of renal biopsy finding in idiopathic nephrotic syndrome in children: An 18-month retrospective analysis at a tertiary care pediatric nephrology center in North Karnataka, India. J Sci Soc 2017; 44:80-82.

10. Joshi TA, Joshi AK. Renal biopsy in children with nephrotic syndrome: a study of histopathological pattern. Int J Contemp Pediatr 2019; 6:1243-1246.

11. Mubarak M, Kazi JI, Shakeel S, Lanewala A, Hashmi S. The spectrum of histopathological lesions in children presenting with steroid-resistant nephrotic syndrome at a single center in Pakistan. Scientific World Journal 2012; 2012:681802.

12. Ali SH, Hussien FS, Abd Al-Amer H. Profile of renal diseases in Iraqi children: A single-center report. Saudi J Kidney Dis Transpl 2015; 26(3):613-618.

13. Al-Juboori KK. Nephrotic syndrome as initial episode and relapse in Iraqi children. International Journal of Advanced Research 2019; 7 (10): 65-71.

14. Fadhil MS. Clinicopathological Spectrum of Renal Biopsies in Children a Multicenter Study in Baghdad-Iraq. Kerbala Journal of Medicine 2017; 10 (1): 2641-2649.

15. Ali MA, Al-Mukhtar SE. The spectrum of biopsy-proved kidney disease: A retrospective single center study in Erbil-Iraq. Asian Journal of Medical Sciences 2019; 10 (2): 46-51.

16. Viswanath D. Nephrotic syndrome in children. J Indian Acad Oral Med Radiol 2013; 25:18–23.

17. Kumar J, Gulati S, Sharma AP, Sharma RK, Gupta RK. Histopathological spectrum of childhood nephrotic syndrome in Indian children. Pediatr Nephrol 2003; 18:657–660.

18. Pio D, Figueiredo S, Silva P, Nunes S, Costa T, Carvalho ES, et al. Renal biopsies in children. A twelve year review. Port J Nephrol Hypertens 2010; 24:215–221.

19. Özlü SG, Demircin G, Tökmeci N, Yılmaz AÇ, Aydoğ Ö, Bülbül M, et al. Long-term prognosis of idiopathic nephrotic syndrome in children. Ren Fail 2015; 37(4):672-677.

20. Bonilla-Felix M, Parra C, Dajani T, Ferris M, Swinford RD, Portman RJ, et al. Changing patterns in the histopathology of idiopathic nephrotic syndrome in children. Kidney Int 1999; 55(5):1885-1890.

21. Abd-Elrehim GAB, Ahmed AAE, Fadda SAA, Ali SH, Ahmed NF. Patterns of idiopathic nephrotic syndrome in Upper Egyptian children. Sohag Medical Journal 2017; 21 (1): 153-160.

22. Mubarak M, Kazi JI, Shakeel S, Lanewala A, Hashmi S. The spectrum of histopathological lesions in children presenting with steroid-resistant nephrotic syndrome at a single center in Pakistan. Scientific World Journal 2012; 2012:681802.

23. Downie ML, Gallibois C, Parekh RS, Noone DG. Nephrotic syndrome in infants and children: pathophysiology and management. Paediatrics and International Child Health Paediatr Int Child Health 2017; 37(4):248-258.

24. Shabaka A, Ribera AT, Fernández-Juárez G. Focal Segmental Glomerulosclerosis: State-of-the-Art and Clinical Perspective. Nephron 2020; 144:413–427.

25. Mortazavi F, Khiavi YS. Steroid response pattern and outcome of pediatric idiopathic nephrotic syndrome: a single-center experience in northwest Iran. Ther Clin Risk Manag 2011; 7:167-171.

26. Dumas De La Roque C, Prezelin-Reydit M, Vermorel A. Idiopathic Nephrotic Syndrome: Characteristics and Identification of Prognostic Factors. J Clin Med 2018; 7(9):265.

27. Sultana MN, Majumder B, Rahman MJ, Moniruzzaman AM, Suja AM, Ali ME, et al. Dipstick Method versus Spot Urinary Protein Creatinine Ratio for Evaluation of Massive Proteinuria in Childhood Nephrotic Syndrome. Mymensingh Med J 2018; 27(2):369-374.

Ethical Clearance:

All ethical issues were approved by the authors. Data collection was in accordance with Declaration of Helsinki of the World Medical Association, 2013, the ethical principles of research involving human subjects.

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