Trends of Histopathology in Childhood Nephrotic Syndrom

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ABSTRACT:

BACKGROUND:

Nephrotic syndrome (N.S.) is clinical manifestation of different histopathological subtypes

OBJECTIVE:

This study was conducted to analyze the trend of histopathological subtypes in idiopathic nephrotic syndrome.

METHODS:

A prospective study was performed from January 2004 to May 2005, at Central child teaching hospital and Al-karama teaching hospital involving 113 patients aged up to 18 years with nephrotic syndrome. The following parameters were studied (age, gender, initial episode, relapse, predisposing factors, positive family history of nephrotic syndrome, clinical presentation and investigation, treatment and complication).

RESULT:

One hundred thirteen patients enrolled in this study, 71(63%) were males and 42(37%) were females, male to female ratio was 1.7/1. 23(20.3%) patients were with initial attack of nephrotic syndrome, while 90(79.6%) patients with relapse. Age at onset ranged between 0.7-14 (median 2.3) years. Family history of nephrotic syndrome was found in 8 (7%) patients. Biopsies was done in 74(65%) patients. 36(48.6%) patients showed focal segmental glomerulosclerosis. 17(22.9%) patients showed minimal change disease.10(13.5%) patients showed membranoproleferative glomerulonephritis. Other histopathological sub types were 6(8%) patients with mesangioproleferative glomerulonephritis, 3(4%) patients with global masengial sclerosis, and 2 (2.7%) patients with amyloidosis.

CONCLUSION:

This trend of histopathologic patterns has profound prognostic significance and has significant implications in the management of childhood nephrotic syndrome. There is shift toward an increasing incidence of focal segmental glomerulosclerosis and to lesser extent, the membranoproleferative glomerulonephritis in Iraqi children presenting with idiopathic nephrotic syndrome. Our finding is in agreement with the recommendation of performing renal biopsies on children with idiopathic nephrotic syndrome who are steroid dependant in addition to those who are steroid resistant particularly before starting cytotoxic medication.

KEY WORDS: nephrotic syndrome,histopathology.

INTRODUCTION:

Nephrotic syndrome (N.S.) is clinical manifestation of different histopathological subtypes.[1] Based on histopathological finding on renal biopsy, N.S. is classified into minimal change nephrotic syndrome (MCNS), focal segmental glomerulosclerosis FSGS), mesangioproliferative glomerulonephritis ((MesPGN),membranoproliferative glomerulonephritis (MPGN), membranous glomerulonephritis (MGN), and focal & global glomerulosclerosis.[2] The peak incidence of both MCNS and FSGS is preschool children, 80% are less than 6 years old at presentation, with median age at diagnosis being 2.5 years for MCNS and 6 years for FSGS. In young children, boys are more commonly affected than girls (ratio 3/2), but in teenagers and adults, the sex ratio is approximately equal. [1, 3, 4] Forms of primary nephrotic syndrome that may have familial occurrence include congenital diffuse mesangial sclerosis and focal segmental glomerulosclerosis.[5,6] The cause of idiopathic N.S. remains unknown, many clues strongly suggest

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involvment of the immune mediated process in this disorder. Secondary N.S. can complicate any disease that can perturb the podocyte and their slit diaphragm, and change the negative charge of the glomerular basement membrane. [7, 8, 9] MCNS Found in 85% of nephrotic children.[1, 10] Recent study showed that incidence of FSGS in children with INS has increased recently. [3, 11] MesPGN present in approximately 5% of INS. The remaining patients have rare types of glomerular lesion such as MPGN and MGN.[3,12] Edema is a cardinal feature of N.S. typical facial edema is noted first and usually increases gradually.[1,4,6] Hypertension occurs in 20-30% of patients with MCNS.[1,6,13] Gross hematuria is rare in INS. Microscopic hematuria in the presentation is observed in patients with FSGS, mesangial hypercellularity or hemoglobinopathies and renal vein thrombosis.[6,13] Growth may be severely affected in children with persistent nephrotic syndrome also in children with frequently relapsing course and glucocorticoid therapy.[1,9,14,15] Profuse , continuing proteinuria is a marker for more severe and more serious disease . Transit of protein across the glomerulous is damaging , proteinuria itself leads directly to production of chemotactic factors and damaging interstitial infiltrate which lead to acceleration of the original disease or secondary renal damage .[17] The aim of this study was to analyze the trend of histopathological subtypes in idiopathic nephrotic syndrome in children.

PATIENTS AND METHODS:

A prospective study was performed between January 2004 and May 2005 at central child teaching hospital and Al-karama teaching hospital involving 113 patients aged up to 18 years with N.S. The data collected and recorded include the following information (age, gender, initial episode, relapse, predisposing factors, positive family history of N.S., clinical presentation and investigation, treatment and complication). Patients with congenital nephrotic syndrome (C.N.S.) or with systemic illness such as systemic lupus erythematous, henoch-schonlen purpura, sickle cell anemia, malignancies, metabolic disorders or hepatitis were excluded. Indications for renal biopsy were:

1. Steroid resistance.
2. Age older than 8 years.
3. Unusual presentation (such as significant elevation of serum creatinine or gross hematuria).
4. Prior cyclosporine therapy in frequent relapsers.
5. Steroid dependant nephritic and frequent relapser NS.

Renal biopsy was done under ultra sound guide with (18 G size) biopsy needle, two biopsy specimens were taken from each patient. The biopsy specimens were evaluated histopathologically by light microscopy. Histopathologic finding were interpreted by two pathologists. Adequacy of biopsy was defined as the presence of at least 5 glomeruli in the specimen on light microscopy.[18] Minimal change disease was characterized by the absence of any conspicuous abnormality on light microscopy. Mesangioproliferative glomerulonephritis was labeled in the presence of diffuse mesangial hypercellularity. Focal segmental glomerulosclerosis was characterized by the presence of at least one glomerulus showing asegmental area of sclerosis with or with out accompanying tubular atrophy and interstitial fibrosis. Membranoproliferative glomerulonephritis was labeled in the presence of intense cellular proliferation on light microscopy. In the absence of atypical presentation of childhood N.S., the practice is to treat patients with corticosteroid. The group of patients who readily responded to prednisolone (39 (35%)) was presumed to have MCNS; renal biopsy in such patients was not performed. All patients were treated initially with prednisolone at a dose of 60mg/m2/day (maximum 80mg/day) for 4 weeks. 14 patients were treated with cyclophosphamide . Cyclosporine A was used in 13 patients with FSGS, 8 steroids dependent and 6 steroid resistant. Definitions : [1, 4]

Nephrotic syndrome:
The association of heavy proteinuria and hypoalbumenemia. The response to therapy was classified according to the definition from the British Pediatric Nephrology Association:

Steroid sensitive:
complete resolution of proteinuria within 4 weeks of prednisolone therapy.

Steroid resistant:
failure to respond after 4 weeks of prednisolone 60mg/m/day.

Steroid dependence:
recurrence of nephrosis when the dose of prednisolone is reduced or within 2 weeks after discontinuation of therapy.

Frequent relapses:
2 or more episodes of nephrosis

within 6 months of the initial response or 4 or more within any 12 months period.

Congenital N.S.:

nephrotic syndrome presented at less than 3 months of age.

RESULTS:

One hundred thirteen patients enrolled in this study, 71(63%) were males and 42(37%) were females. Male to female ratio was 1.7/1. The median age at first presentation of N.S. was (2.3 years), (range 0.7-14 years). Four (3.5%) patients were aged <1year , 43 (38%) patients were aged 1-5 years, 37 (32.7%) patients were aged 6-10 years , 27 (24%) patients were aged 11-15 years and only 2 (1.7%) were aged 16-18 years . Table (1) Patients presented with nephrotic syndrome for the first time were 23 (20.3%), 65 (57.5%) patients were known cases of N.S. with frequent relapses, 25 (22.1%) patients were cases of infrequent relapses. Table (2). Renal biopsy was done for 74 (65%) patients. Table (1). FSGS was the most common histopathological subtype occurring in 36 (48.6%) patients, followed by MCD in 17 (22.9) patients, followed by MPGN in 10 (13.5%) patients. Other subtypes included MesPGN occurring in 6 (8%) patients, global GS in 3 (4%) patients and amyloidosis in 2 (2.7%) patients. Table (3). If we assumed that all patients that were not biopsied had minimal change disease (MCD) (presumptive MCD), the total incidence of MCNS (presumptive MCD + biopsy proven) was 50% which is lower than expected. Table (3), the prevalence of FSGS was significantly higher (48.6%). The increase fraction of patients with FSGS was significant, even if all patients including those who did not undergo biopsies was considered (48.6%) out of 74 patients versus (31.8%) out of 113 patients. P=0.02 There was a significant increase in the MPGN in biopsies patients (13.5%); however when we included patients who did not have renal biopsies as presumptive diagnosis of MCD the increase in MPGN was not significant (8.8%) P=0.21. Table (3). The mean age of MCD patients (presumptive and biopsy proven) was (3.7±2.4years). There was no difference between the presenting mean age of MPGN patients (2.5±3.2 years), and MCD patients, P=0.79. However, FSGS patients had an older mean age at presentation (7.11+4.12) P=0.04. Table (3). Regarding steroid responsiveness, 34 (30%) patients were steroid resistant , 5 patients never responded to steroid , 9 patients were initially steroid dependant and 20 patients were frequent relapsers and changed to steroid resistant after 6 months-1year from the time of first presentation. Thirty two (28.3%) patients were steroid dependant and 47 (41.5%) patients were steroid sensitive, 14 (29.7) patients were frequent relapsers and 33 (70.3%) patients were infrequent relapsers. Table (4). In relation to histopathological subtypes with steroid responsiveness, steroid sensitive patients: 8 (17%) patients were MCD, 4 (8.55) patients were FSGS and 5 (10.6%) patients were MPGN. Steroid dependant patients: 8 (25%) patients were MCD and 12 (37.5%) patients were FSGS. Steroid resistant patients: 1 (2.9%) patients were MCD and, 20 (58.8%) patients were FSGS and 4 (11.7%) patients were MPGN .Table (5).Chemotherapy used in 28 (24.5%) patients , 4 (3.5%) patients with MCD, 17 (15%) patients with FSGS patients , 2 (1.7%) patients with MesPGN , 4 (3.5%) patients with presumptive MCD and 1 (0.8%) patients with amyloidosis . Table (6) Cyclophosphamide was used in 14 patients, 6 patients with steroid resistant and 8 patients with steroid dependant. All patients with steroid resistant nephrotic syndrome had renal biopsy before the cyclophosphamide therapy and 6 of the steroid dependant nephrotic syndrome. All except one were found to have a non-minimal change histopathology. With cyclophosphamide therapy, 11 patients entered remission, however 3 patients did not have a sustained remission and require third line drug (cyclosporine therapy later), and no serious short term side effect complicated cyclophosphamide therapy. Cyclosporine was used in 13 patients, 4 patients with steroid resistant nephrotic syndrome, 7 patients with steroid dependant nephrotic syndrome and 2 patients with steroid responsive but with steroid toxicity. Eight (7%) patients with MCD had hypertension compared with 20 (17.6%) patients with FSGS. P= 0.40. Renal failure occurred in 1 (0.8%) patients with MCD, compared with 14 (12.3%) patients with FSGS .P=0.01. Table (7).Familial steroid resistant nephrotic syndrome was observed in 8 (7%) patients, 2 siblings with FSGS. Another patients with steroid resistant N.S. due to FSGS had a family history of 2 siblings who died from chronic renal failure that complicate steroid resistant N.S. Another female and male patients with FSGS who her sister and his brother died with N.S. Another male patients with MCD who his brother died with N.S. Lastly male and female patients with MesPGN who his brother and her sister died with N.S. Table (7) .

Table (1) :Distribution of nephrotic patients according to age

Age	Male	Female	Total	%
< 1 year	1	3	4	3.5%
1-5 years	27	16	43	38%
6-10 years	24	13	37	32.7%
11-15 years	18	9	27	24%
16-18 years	2	0	2	1.7%
Total	72 (63%)	41(37%)	113	100

Table (2) :Distribution of nephrotic patients according to presentation

Patients	Male	Female	Total	%
Initial attack	13	10	23	20.3%
Frequent relapser	42	23	65	57.5%
Infrequent relapsers	16	9	25	22.2%
Total	71	42	113	100%

Table (3) :Distribution of histopathological lesion

Histopathological lesion	< 1 year N (%)	1-5 year	6-10 year	11-15 year	16-18 year	Total (%)	Biopsy specimen % (No= 74)
MCD	1 (5.8%)	5 (29.4%)	10 (58.8%)	1 (5.8%)	0	17(15%)	22.9%
FSGS	1(2.7%)	13(36%)	5(13.8%)	16 (44.4%)	1 (2.7%)	36(31.8%)	48.6%
MPGN	1(10%)	2(20%)	5(50%)	2(20%)	0	10(8.8%)	13.5%
MesPGN	0	1(16.6%)	1(16.6%)	4(66.6%)	0	6(5.3%)	8%
GlobalGS	0	2(66.6%)	1(33.3%)	0	0	3(2.6%)	4%
Amyloid	0	0	1(50%)	1(50%)	0	2(1.7%)	2.7%
MCD-Pres.	1(2.5%)	19(48%)	15(38%)	4(10%)	1(2.5%)	39(35%)	0

Table (4): Distribution of nephrotic patients according to steroid responsiveness

Patients	No.	%
SSNS	47	41.5%
Frequent relapsers	14(29.7%)	
Infrequent relapsers	33(70.3%)	
SDNS	32	28.3%
SRNS	34	30.2%

Table (5) :Distribution of histopathological lesion according to steroid responsiveness

Histopathological lesion	SSNS (47) No. (%)	SDNS(32) No. (%)	SRNS(34) No. (%)
MCD (17)	8(17%)	8(25%)	1(2.9%)
FSGS (36)	4(8.5%)	12(37.5%)	20(58.8%)
MPGN (10)	5(10.6%)	1(3.2%)	4(11.7%)
MesPGN (6)	2(4.2%)	3(9.3%)	1(2.9%)
GlobalGS (3)	0	0	3(8.8%)
Amyloid (2)	0	0	2(5.8%)
MCD-Pres. (39)	28(59. %)	8(25%)	3(8.8%)

Table (6): Distribution of histopathological lesion according to cytotoxic agent used immunosuppressive drugs.

Histological lesion	N0. of patients	Cyclo sporine	Cyclo phosphamide	Leukran	%
MCD	4	3	1		3.5%
FSGS	17	6	11		15%
MPGN	0				
MesPGN	2	1	1		1.7%
GlobalGS	0				
Amyloid	1			1	0.8%
MCD-Pres.	4	3	1		3.5%
Total	28	13	14	1	24.5%

Note: of the 13 patients used cyclosporine, 4 patients steroid resistant NS.
The 14 patients used cyclophosphamide, 6patients steroid resistant NS and 8 patients steroid dependent NS.

Table(7): Histopathological lesion in relation to hypertension, renal failure. Family history of nephrotic syndrome.

Histopathological lesion	hypertension		Renal failure		Family history	
	Number	Percent	Number	Percent	Number	Percent
MCD	8	7%	1	0.8%	1	0.8%
FSGS	20	17.6%	14	12.3%	5	4.4%
MPGN	8	7%	2	1.7%		
MesPGN	3	2.6%	0	0		
GlobalGS	3	2.6%	2	1.7%	2	1.7%
Amyliod	0	0	2	1.7%		
MCD-Pres.	3	2.6%	3	2.6%		
Total	45	39.4%	24	21%	8	7%

DISCUSSION:

We have found an increase incidence of FSGS in children presented with I.N.S. in recent years, our results showed that FSGS was the most common histopathological-subtype in our patients who underwent renal biopsy during the study period.The International Study Of Kidney Disease in children (ISKDC) reported in the 1970s that MCNS was the most common histopathological lesion in renal biopsies from children with I.N.S.[19,20] A similar study was carried out by white et al in the United

Kingdom at the same time reporting an incidence of 76.5% and 8.3% of MCNS and FSGS respectively.[21] Another study was carried out by EL-Sheikh S in the western area of Saudi Arabia between 1983-1992 which reported MCNS in 79.5% and showed like others , that FSGS was a rare cause of nephrosis in children , observed in only 5.3% .[22]
More recent studies in adult and children showed changing trends of histopathology in adulthood [23, 24] and childhood [25, 26] N.S.with increasing incidence of FSGS during the last decade, accompanied by significant decline in the incidence of MCNS. We report the trend in the histopathological lesion in I.N.S. in Iraqi children; this observation is similar to previous reports from different parts of the world. Bonilla-Felix et al reported an increased incidence of FSGS in American children (23% before 1990 versus 47% after 1990).[25] Similarly , Srivastava et al found a higher incidence of FSGS in American children with reciprocal decline in the incidence of MCD in recent years .[27] Gulati et al reported an increased incidence of FSGS in Northern and Eastern Indian population from 20% between 1990 and 1992 to 47% between 1992-1996.[28] Similar to the authors in the above series , we were careful to exclude any known secondary etiology of FSGS and believe that there is a true universal increase in the incidence .
The increased incidence of FSGS in our study is in agreement with that reported in adult and pediatric population from other countries [23, 27] there is no similar reported study in pediatric population from Iraq. In the 1980s, Abdurrahman et al reported MesPGN as a frequent cause of non-minimal change N.S. in children from the central area of Saudi Arabia and they reported FSGS as a rare cause [29, 30] .In 1990 Matto et al reported the same observation on the same population. [31] However, they reported high prevalence of FSGS 39% in biopsies in children with I.N.S. The mean age of presentation over the recent years was smaller , while FSGS patients had an older age at presentation .[25,26] our finding support the nation that there is a global trend of increasing FSGS incidence in childhood N.S.[25,26] Unfortunately , as the etiology of FSGS is unkown , it is difficult to postulate a potential mechanism for this increasing incidence . Previous studies suggested that it could be secondary to environmental factors including infectious factors related to viruses , chemical exposure or many factors together .[25,26] Genetic background could play a role ,as familial FSGS was noticed in 2 families . Familial FSGS has been reported previously and genetic cause is the most likely predisposing factor in those families. [32] We have found also an increasing incidence of MPGN in recent years. MPGN is a rare cause of childhood I.N.S. [20,21,33] We have found that 13.5% of performed biopsies were MPGN , this is in contrast to the paucity of MPGN as a cause of I.N.S. in international studies.[25,28] MPGN was reported as the predominant histological lesion seen in childhood nephrotic syndrome in Ibadan ,Nigeria , were MCD remain a rare cause of N.S. [34] The observed increase in MPGN in recent years could be explained by environmental factors such as antigen-driven mechanism: infective antigen as well as food or other allergens .
We conclude that there is a shift toward an increasing incidence of FSGS and to lesser extent, the MPGN in Iraqi children presenting with I.N.S. This changing trend of histopathological patterns has profound prognostic significance and has significant implications in the management of childhood nephrotic syndrome. Our finding is in agreement with the recommendation of performing renal biopsies on children with I.N.S. who are steroid dependant in addition to those who are steroid resistant particularly before starting cytotoxic medication. This approach will be beneficial in the management of those patients and it will help to solve the mysteries of the disease process involved. We should insist on proper documentation of information in the patient's record & improve the laboratory work; renal biopsy needle must be available in hospitals.

CONCLUSION:

*There is ashift toward an increasing incidence of FSGS and to lesser extent , the MPGN in Iraqi children presenting with I.N.S.
*This changing trend of histopathologic patterns has profound prognostic significance and have significant implications in the mangment of childhood nephrotic syndrome .
*Our finding is in agreement with the recommendation of performing renal biopsies on children with I.N.S. who are steroid dependant in addition to those who are steroid resistant particularly before starting cytotoxic medication .
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