Congenital and Infantile Nephrotic Syndrome Single Center Study

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ABSTRACT:

BACKGROUND:

congenital nephrotic syndrome occurring in the first 3 months of life and infantile presenting after 3 to12 months.It differs from the nephrotic syndrome in older children in terms of histopathological finding and carries a poor prognosis.

OBJECTIVE:

To study the diagnosis and treatment of nephrotic syndrome cases manifested in the first year of life and their outcome.

PATIENTS AND METHODS:

A single-center retrospective study was conducted in the nephrology unit in central child teaching hospital, Baghdad, Iraq. During the study period from the 1st of July to end of December 2017, the records of all patients who diagnosed as nephrotic syndrome below one year from January 2007 to December 2016 with minimal follow up of six months in the nephrology department reviewed and analyzed.

RESULTS:

Seventy cases were diagnosed with nephrotic syndrome below one year from a total number of nephrotic 620 cases (30 of them congenital and 40 were an infantile type), their mean age 5.242 months. Male was higher than female (67.1% versus 32.9%) with a male to female ratio 2.04:1. In this study, patient represented infantile nephrotic were the higher proportion (57.1%) than congenital type (42.9%)both types represented (11.29%)of all nephrotic cases .concerning family history was slightly higher than those with negative history (52. 9%).The higher proportion of parents without consanguinity (67.1%).

Study patient who suffered from sepsis were of the higher proportion (62. 9%).In regard to hypertension in this study (92.9%) had no hypertension with a significant association between hypertension and infantile type. The proportion of those with elevated serum creatinine was (11.4%), anemic patients (51.4%) in regard to thyroid function all patients with congenital nephrotic had hypothyroidism while only (6.2%)of 32 cases with infantile had hypothyroidism. According to biopsy finding in (60) patients, Finnish type representing (91.3%)of patient with congenital nephrotic while in infantile type focal segmental glomerulosclerosis represent the highest proportion (54. 1%). regarding the outcome of study cases (80%) of these cases were ended with no remission, while remission was noticed among only (20%) of cases.

CONCLUSION:

Nephrotic syndrome in the first year constitute a small percentage of nephrotic syndrome and it had a poor prognosis, Finnish type represent the highest proportion of biopsy in congenital nephrotic syndrome and focal segmental glomerulosclerosis highest proportion in infantile type.

KEYWORDS: congenital nephrosis, Finnish type, outcome

INTRODUCTION:

Nephrotic syndrome (massive proteinuria, hypoalbuminemia, edema and hypercholesterolemia) occurring in the first year is comprised of congenital nephrotic syndrome) which is occurring in the first 3 months of life and infantile nephrotic syndrome (INF presenting after 3 - 12 months.

It differs from the nephrotic in older children, in terms of the histopathological lesion and carries a very poor prognosis[(1)]. Congenital nephrotic syndrome may be classified as primary or as secondary [(2)].

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Number of structural and functional abnormalities of the glomerular filtration barrier causing congenital nephrotic syndrome have been elucidated. In the children with congenital nephrotic syndrome, 85% carried disease-causing mutations in 4 genes (*NPHS1*, *NPHS2*, *WT1*, and *LAMB2*),the first 3 of which encode components of the glomerular filtration barrier[3]. The Finnish type of congenital nephrotic syndrome is caused by mutations in the *NPHS1*or *NPHS2* gene, which encodes nephrin and podocin, critical components of the slit diaphragm[4]. Denys-Drash syndrome is caused by mutations in the *WT1* gene, which results in abnormal podocyte function [5].Mutations in the *LAMB2* gene, Pierson syndrome, lead to abnormalities of β2-laminin, a critical component of glomerular and ocular basement membranes [6].Secondary congenital nephrotic syndrome may be due to the infection (syphilis, HIV, CMV, congenital rubella and toxoplasmosis), Lupus erythematosus with nuclear antibodies and hypocomplementemia. It is important to remember that idiopathic NS which is by far the most common form of childhood NS, can sometimes present during the first year of life. It can resolve with treatment of the underlying cause[7, 8].The management of primary congenital nephrotic syndrome includes intensive supportive care with intravenous albumin and diuretics, regular administration of intravenous γ-globulin, and aggressive nutritional support (often parenteral), while attempting to pharmacologically decrease urinary protein loss with angiotensin-converting enzyme inhibitors, angiotensin II receptor inhibitors, and prostaglandin synthesis inhibitors, or even unilateral nephrectomy. If conservative management fails, bilateral nephrectomies and chronic dialysis are initiated. Renal transplantation is the definitive treatment of congenital nephrotic syndrome [9, 10].

PATIENTS AND METHODS:

A retrospective study, cohort review was performed on the mostpatients with nephrotic syndrome below one year, who were visit the outpatient nephrology clinic or admitted to nephrology ward, in central child teaching hospital, data were collected from medical record of the patient from 1st January 2007 to 31th December 2016. A total number of 70 patients had been included in this study period from July to December 2017. The patients included in the study ,whom met the criteria for the diagnosis of nephrotic syndrome and diagnosed as congenital and infantile nephrotic syndrome with a minimum follow up to 6 months from initial diagnosis. The questionnaire included the following data;

Demographic: (age at diagnosis, gender), The family history, History of consgaunity, Antenatal history, Birth history (asphyxia, IUGR= intrauterine growth retardation), prematurity and dysmorphic features, Signs and symptoms at presentation:(edema, oliguria, fever, hypertension, hematuria), Anthropometric measurement: weight in(kg), length in (cm) and OFC (occipitofrontal circumference), Lab finding at time of presentation and on follow up visit:B. Urea, Serum Creatinine, Complete blood count and differential, Total S. protein, S. albumin, and S. cholesterol, Thyroid function test, General urine examination for proteinuria (dipstick test used to evaluate proteinuria, patient regarded as a response when urine protein < 1+ on urine dipstick test for 3 consecutive days and no remission when 3+ or more on urine dipstick test) [11], Renal biopsies were done in 60 cases.

Treatment protocol: According to an international society of kidney diseases in children (ISKDC) recommendations[12].

Statistical analysis: The data analyzed using statistical package for social sciences (SPSS) version 23. The data presented as mean, standard deviation and ranges. Categorical data presented by frequencies and percentage. Chi-square test was used to test qualitative and frequency data and to find any association between certain outcomes with different risk factors with Fisher Exact test whenever applicable. A level of P- value less than 0.05 was considered significant.

RESULTS:

A seventy cases were diagnosed with nephrotic syndrome below one year from a total number of 620 nephrotic cases (30 of them were congenital and 40 were the infantile type of nephrotic syndrome).Study patient's age was ranging from 21 days to one year with a mean of 5.242 months and standard deviation (SD) of ± 3.269 months. In congenital NS, study patient's age was ranging from 21 days to three months with a mean of 2.12 months and standard deviation (SD) of ± 0.46 month. Regarding infantile type, study patient's age was ranging from three months to 12 months with a mean of 7.362 ± 1.29 months. Male was higher than female (67.1% versus 32.9%) with a male to female ratio of 2.04:1 and there was no significant association between nephrotic syndrome and gender of cases ($P \geq 0.05$). The higher percentage of Congenital NS was found among patients who had positive family history (56.8%) with significant association (P=0.012) between positive family history and increased prevalence of congenital NS.

Regarding the history of prematurity, consanguinity, and failure to thrive; the majority of cases had no prematurity history (94.3%). The higher proportion of parents of study patients was without consanguinity (67.1%). About two-thirds of cases were complained from failure to thrive (65.7%).there was no significant association between nephrotic syndrome and each of (history of prematurity, consanguinity, and failure to thrive) ($P \geq 0.05$). Table(1)

Regarding the clinical features at the time of presentation, Sepsis presented in the higher proportion (62.9%). the higher proportion of congenital NS was among patients who had sepsis (52.3%) with significant association (P=0.038) between sepsis and increased prevalence of congenital NS. Regarding birth asphyxia, the higher proportion of study patients had no birth asphyxia (94.3%), there was no significant association between nephrotic syndrome and birth asphyxia ($P \geq 0.05$). Majority of cases in this study had no hypertension and their proportion was (92.9%), the Significant association was found between INS (infantile) and hypertension (P=0.044), all hypertensive patients complained from INS (100%). The association between NS and each of (dysmorphic features, IUGR, and thromboembolic phenomena) was not significant ($P \geq 0.05$). Table (2)

Regarding the distribution of study patients according to laboratory results, the higher proportion of patients had no hematuria, (10%) had microscopic hematuria, and macroscopic hematuria was (5.7%). The proportion of those patients with elevated serum creatinine level was (11.4%). Anemic (51.4%). Regarding thyroid function, all patients with congenital NS had hypothyroidism (100%). While only (6.2%) of 32 cases with INS had hypothyroidism, there is significant association between congenital NS and hypothyroidism with P value 0.001. Table (3)

Regarding the patients with congenital NS, Finnish type represented the highest proportion of histological findings among those patients (91.3%). Concerning INS, the highest proportion of patients were diagnosed as FSGS (54.1%).

Albumin, Antiproteinuric medication, and dialysis were representing the highest proportion of treatment that received by study patients (88.6%, 82.9%, and 61.4%) respectively, with significant P –value with the use of albumin, antiproteinuric medication, thyroxin, prednisolone, methyl prednisolone and cyclosporine (P –value < 0.05), The information about the treatment of study patients is shown in the table(4).

About the outcome of study cases, (80%) of these cases were ended with no remission, while remission was noticed among only (20%) of cases. The highest proportion of patients who ended with no remission were of congenital NS (53.6%) with significant association (P=0.0002) between no remission and increased prevalence of nephrotic syndrome. Table (5).

Concerning the patients who ended with no remission, about (57.1%) of those patients died, 26.8% had renal impairement and 16.1% with loss to follow up.

Table 1: Association between nephrotic syndrome below one year and general characteristic.

Variable	Nephrotic syndrome		Total (%) n=70	P- value
	Congenital NS (%) n= 30	INS (%) n= 40		
Gender				
Male	22 (46.8)	25 (53.2)	47 (67.1)	**0.339**
Female	8 (34.8)	15 (65.2)	23 (32.9)	
Family history				
Positive	19 (56.8)	18 (43.2)	37 (52.9)	**0.0128**
Negative	11 (27.3)	22 (72.7)	33 (47.1)	
History of prematurity				
Positive	3 (75.0)	1 (25.0)	4 (5.7)	**0.180**
Negative	27 (40.9)	39 (59.1)	66 (94.3)	
Consanguinity				
Yes	11 (47.8)	12 (52.2)	23 (32.9)	**0.556**
No	19 (40.4)	28 (59.6)	47 (67.1)	
Failure to thrive				
Yes	18 (39.1)	28 (60.9)	46 (65.7)	**0.383**
No	12 (50.0)	12 (50.0)	24 (34.3)	

Table 2: Association between congenital and infantile nephrotic syndrome and clinical features at the time of presentation

Variable	Nephrotic syndrome		Total (%) n=70	P- value
	Congenital NS (%) n= 30	INS (%) n= 40		
Sepsis				
Yes	23 (52.3)	21 (47.7)	44 (62.9)	**0.0383**
No	7 (26.9)	19 (73.1)	26 (37.1)	
Birth Asphyxia				
Yes	1 (25.0)	3 (75.0)	4 (5.7)	**0.180**
No	39 (59.1)	27 (40.9)	66 (94.3)	
Hypertension				
Yes	0	5 (100.0)	5 (7.1)	**0.0444**
No	30 (46.2)	35 (53.8)	65 (92.9)	
Dysmorphic features				
Yes	2 (66.7)	1 (33.3)	3 (4.3)	**0.394**
No	28 (40.9)	39 (59.1)	67 (95.7)	
IUGR				
Yes	1 (100.0)	0	1 (1.4)	**0.244**
No	29 (42.0)	40 (58.0)	69 (98.6)	
Thromboembolic phenomena				
Yes	1 (33.3)	2 (66.7)	3 (4.3)	**0.733**
No	29 (43.3)	38 (56.7)	67 (95.7)	

Table 3: Distribution of study patients according to laboratory results

Variable	Nephrotic syndrome		Total (%) n=70	P- Value
	CONGENITAL NS (%) n= 30	INS (%) n= 40		
Hematuria				
No hematuria	26 (40.1)	33 (55.9)	59 (84.3)	0.757
Microscopic	3 (42.9)	4 (57.1)	7 (10.0)	
Macroscopic	1(25.0)	3 (75.0)	4 (5.7)	
Hemoglobin level				
Anemic	14 (38.9)	22 (61.1)	36 (51.4)	0.489
Normal	16 (47.1)	18 (52.9)	34 (48.6)	
Serum creatinine				
> 0.8 mg/dl	2 (25.0)	6 (75.0)	8 (11.4)	0.278
< 0.8 mg/dl	28 (45.2)	34 (54.8)	62 (88.6)	
Thyroid function	n=30	n=32	n=62	
Hypothyroidism	30 (100)	2 (6.2)	32 (51.6)	0.001
Normal	0	30 (93.8)	30 (48.4)	

Table (4) Distribution of study patients according to treatment

Treatment	Nephrotic syndrome		Total (%) n=70	P- Value
	CONGENITAL NS (%) n= 30	INS (%) n= 40		
Albumin				0.009
Yes	30 (48.4)	32 (51.6)	62 (88.6)	
No	0	8 (100.0)	8 (11.4)	
Antiproteinuric medication				<0.001
Yes	30 (51.7)	28 (48.3)	58 (82.9)	
No	0	12 (100.0)	12 (17.1)	
Thyroxin				<0.001
Yes	30 (93.8)	2 (6.2)	32 (45.7)	
No	0	38 (100.0)	38 (54.3)	
Prednisolone				<0.001
Yes	0	40 (100.0)	40 (57.1)	
No	30 (100.0)	0	30 (42.9)	
Methylprednisolone				0.008
Yes	0	9 (100.0)	9 (12.9)	
No	30 (49.2)	31 (50.8)	61 (87.1)	
Cyclosporine				0.033
Yes	0	6(100.0)	6(8.6)	
No	30 (46.9)	34 (53.1)	64 (91.4)	
Rituximab				0.254
Yes	0	3 (100.0)	3 (4.3)	
No	30 (44.8)	37 (55.2)	67 (95.7)	
Cyclophosphamide				0.999
Yes	0	1 (100.0)	1 (1.4)	
No	30 (43.5)	39 (56.5)	69 (98.6)	
Anti-coagulants				0.999
Yes	1 (33.3)	2 (66.7)	3 (4.3)	
No	29 (43.3)	38 (56.7)	67 (95.7)	
Dialysis				0.999
Yes	18 (41.9)	25 (58.1)	43 (61.4)	
No	12 (44.4)	15 (55.6)	27 (38.6)	
Fisher's exact test				

Table (5) Association between congenital and infantile nephrotic syndrome and outcome

Outcome	Nephrotic syndrome		Total (%) n=70	P- value
	CONGENITAL NS (%)n= 30	INS (%) n= 40		
Remission	0	14 (100.0)	14 (20.0)	0.0002
No Remission	30 (53.6)	26 (46.4)	56(80.0)	

DISCUSSION:

A nephrotic syndrome which appears early in life provides a diagnostic and management challenge to pediatric nephrologists. It is caused by heterogeneous glomerular diseases, and the diagnosis is based on clinical, laboratory and histological criteria[13].In the current study, the total number of patients was 70, all of them were diagnosed withnephrotic syndrome (30 of them were congenital and 40 were the infantile type of nephrotic syndrome). The mean age of presentation of study patient was 5.24 months which is approximately different from Mattoo et al [14](2 months) and different from Sahay et al[1] study (8.6 months) and Kari et al[15] study (1.6 months). In regardto gender, the male proportion was higher than female (67.1% versus 32.9%) with male to female ratio of 2.04:1 similar result observed in study done by Sahay et al[1]in which male (65.6%)and females (34.4%) with male to female ratio 1.9:1, different result observed in different study conducted by Kari et al [15] that observed in their study on forty-nine cases that female proportion was higher than male (25 females and 24 males) with male: female ratio of 1:1.04 this may be due to ethnic differences which were close to result obtained by Vachvanichsanong et al [16]in which NS found in 10 infants with equal incidence in both gender which explained by their small sample size in comparison to our study. Patient with positive family history of nephrotic syndrome was slightly higher than that those with negative family history (52.9% positive), The highest prevalence of congenital NS was found among patients who had positive family history (56.8%) with significant association, approximately similar result was obtained in Sibley et al[17] in which (35%) had appositive family history of nephrotic syndrome, Lower result observed in Sahay et al[1]that observed the family history of a patient with NS were only in two patient (6.6%)and in Kari et al[15] (10%) this is could be that five twinswere included in our study.

In this study history of prematurity (5.7%) which is approximately similar to Sibley et al[17] study (19%) ,higher result obtained in Sahay et al[1] study(23.3%).Regarding consgaunity in our study (32.9%) similar result to Sahay et al[1] (40%) and similar to Kari et al (31%)[15] while in Mattoo et al [14](59%) history of consgaunity this might be high prevalence of relative marriage in Saudi Arabia in comparison to our country. Failure to thrive in our study (65.7%) similar to Sahay et al [1](60%) while in Vachvanichsanong et al [16] all patient complain from failure to thrive due to poor nutritional state at Thai area (South East Asia). In our study INS had the highest proportion (57.1%) while congenital NS was (42.9 %) similar to Sahay et al [1]INS (80%) of nephrotic with (20%) being of congenital variety, in contrary congenital NS had the highest proportion (63%) in Kari et al [15]. Sepsis represented the higher proportion (62.9%) with a significant association between sepsis and congenital NS, similar result obtained in Sibley et al[1] (75%) of patients had features of sepsis. Birth asphyxia (5.7%) in our study while in Sahay et al[1] (13.3%). Hypertension in our study was reported in (7.1%) of patient they are mainly INS which is similar to Senguttuvan et al[18] in which hypertension present in (15%) of cases while in comparison to Sahay et al[1] (26.6%) were hypertensive. In our study, 3 cases reported had dysmorphic features as a percentage of (4.3%), no dysmorphic features observed in cases of Sahay et al[1] and Kari et al [15].

IUGR was (1.4%) in our study no comparable study found. Regarding thromboembolic event (4.3%) of cases diagnosed by clinical examination and confirmed by investigation, this goes with Mattoo et al [14] (11.7%) of cases diagnosed with thromboembolic complication. Distribution of study patient according to laboratory result, Anemic patient represented about half of the patient (51.4%) similar to Sahay et al[1](60%).Hematuria was reported in (15.7%) (5.7% macroscopic and 10% microscopic) while in Sahay et al[1] (13%) presented with hematuria which is mainly microscopic. In our study (11.4%) of the patient presented with increase serum creatinine at presentation which is different from Sahay et al[1] (60%) of the patient had increased serum creatinine at the time of diagnosis this could be due to delay presentation of the patient at the time of diagnosis at Sahay et al[1] study. In the current study (51.6%) of the patient had hypothyroidism at the time of diagnosis in comparison Vachvanichsanong et al[16] hypothyroidism found in (100%) while all patient were assessed in Senguttuvan et al[18] and had no hypothyroidism this is due to their small sample size. According to histopathology finding in our study Finnish type represented the highest proportion of patient's biopsy finding (40%) followed by FSGS (33%)and MCNS (18.3),in Sibley et al[17]study Finnish type (54.1%) and followed by MPGN (22.9%) and FSGS (18.7%), while in Sahay et al[1] Finnish type represented (26.6%) of cases followed by DMS and MCNS in percentage of (20%) for each of them; different study Kari et al [15] the highest prevalence of MPGN in (26.5%)followed by FSGS (24.4%) the difference in study result of histopathology might be due to difference in geographical area.

Our study shows astrong association between positive family history of nephrotic syndrome and histopathological finding of congenital Finnish and FSGS while in Sibley et al[17] there is no statistical difference in the frequency of any histological diagnosis with a family history of nephrotic syndrome. Regarding the treatment Albumin, Antiproteinuric medication and dialysis representing the highest proportion of treatment received by study patient (88.6%,82.9%,61.4%) respectively, in comparison to Kari et al [15]Study dialysis, antiproteinuric medication and steroid constitute percentage of (41%,34.6%,14.2%) respectively. The outcome of our study (80%) of cases were ended with no remission while remission constitute (20%) of cases and there is significant association (P=0.002) between no remission and increase prevalence of congenital nephrotic syndrome this association is similar in study of Sibley et al[17](P=0.0001),remission was achieved in (20%) of cases similar to Sibley et al[17](17%) and Kari et al[15] (16%) while no remission was achieved in Vachvanichsanong et al[16]due poor prognosis of nephrotic in Thai infant. As a final outcome at the end of study number of dead patient was 32 from total 70 in percentage of (45.7%) is similar to Sibley et al [17] (48%) and different from Kari et al [15] (24%) percentage of death this is might be due to better outcome in developed countries and or in Kari et al [15]study nephrectomy and renal transplantation one of the modalities of treatment. Loss of follow up in our study 9 from (70) as a percentage of (12.8%) similar to Kari et al [15] (10%).

CONCLUSIONS:

Nephrotic syndrome in the first year constitutes a small percentage of nephrotic syndrome and it had a poor prognosis, Finnish type represent the highest proportion of biopsy in congenital nephrotic syndrome and focal segmental glomerulosclerosis highest proportion in infantile type.

RECOMMENDATIONS:

Further studies are needed that adopt genetic analysis for all patients with nephrotic syndrome below one year to determine the strategy of treatment and predict prognosis. Intensive supportive care permits growth and the potential for survival via renal transplantation and/or dialysis.

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