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Original Research Article

A descriptive retrospective study on children with newly diagnosed nephrotic syndrome presented to Tripoli Children Hospital during the period between Jan. to Dec. 2014

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Abstract

Abstract

Introduction: Nephrotic syndrome (NS) is a clinical picture characterized by severe proteinuria, hypoalbuminemia, edema and hypercholesterolemia. A retrospective study was carried out in order to describe disease pattern in newly diagnosed NS of children admitted to Tripoli children hospital during the year 2014.

Methods: The medical data of 56 patients aged between 1 year and 11 years diagnosed with idiopathic nephrotic syndrome were analysed using SPSS software. The data included gender differences, sensitivity to steroid therapy, relapses withen six months of follow up and the effect of variable factors such as family history, hypertension, hematuria, serum urea on the degree of relapse.

Results: Out of 56 patients with newly diagnosed NS, 60.7% were boys and 39.3% were girls, with a mean age 4.2±2.2 years. Age was related significantly to the response to steroid therapy, where 79.5% of patients aged between 2-8 years (group 1) had steroid sensitive NS (SSNS) compared with only 41.7% of patients aged less than 2 years or more than 8 years (group 2) (P<0.001). Although girls relapsed more than boys (70.5% versus 57.1%) during six months of therapy, this difference was not statistically significant. Similarly, no other factors

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measured such as family history of NS, hypertension, hematuria, serum complement and urea had any effect on the percentage of relapse in patients with newly diagnosed NS.

Conclusion: NS is one of the commonest reasons for admission to nephrology ward. It is more common in boys than girls. The age at presentation related significantly to the response to steroidal therapy. Regarding relapses, girls seems to relapse more frequent than boys and relapses was seen more in age group 1 than group 2, however, these differences were not significant. Other factors studied seems to have no effect on the relapse rate of children with newly diagnosed NS.

Key-words:

Idiopathic nephrotic syndrome, Steroid sensitive nephrotic syndrome, Steroid resistant nephrotic syndrome, Proteinuria.

1. INTRODUCTION

Idiopathic nephrotic syndrome (INS) is one of the commonest chronic glomerular diseases in children [1]. It is characterized by proteinuria, hypoalbuminaemia, generalized edema and hyperlipidemia [2]. It is a common reason for admission to paediatric nephrology unit and it accounts for mortality and considerable morbidity in young children [3]. According to the criteria of the International Study of Kidney Disease in Children (ISKDC), INS was defined as urinary protein excretion of ≥40 mg/m^2/h, hypoalbuminaemia of <25 gm/L and generalized edema [4]. Eighty percent of children with INS have a minimal change disease. Other pathology of INS includes focal segmental glomerulosclerosis, congenital NS and NS secondary to glomerulopathies. Number of published reports mentioned changing trends in the histopathology of NS toward the increasing incidence of FSGS, not only in adults, but also in children [5-8]. The incidence of INS in children is 2–7 cases per 100,000 per year whereas its prevalence is nearly 12-16 cases per 100,000 [1, 9-11]. Most Caucasian series report INS as a disease of pre-school aged children with peak age incidence of 2-3 years and affecting males more than females [12]. There is epidemiological evidence of a higher incidence of NS in children from south Asia [9]. The male: female ratio found to be 2:1 while the age at the onset is generally between 18 months and 6 years [13]. Along with the classical presentation of INS, there are a number of cases present with atypical presentation (age of onset ≤ 2 years or ≥ 8 years) which may include presence of hematuria, renal impairment and low serum complement [14, 15]. The prognosis and outcomes of treatment of these children are poor in comparison with classical NS [16]. The prognosis of INS in children correlates with the spectrum of responsiveness to steroid therapy, which ranges from steroid-sensitive NS (SSNS) to steroid-resistant NS (SRNS). SRNS is the most common acquired cause of end-stage renal disease (ESRD) in children [17]. However, there is an increase in incidence of initial steroid resistance in

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childhood NS [18]. Steroid therapy is the first line of treatment in children with INS. New guidelines from Kidney Disease: Improving Global Outcomes (KDIGO) were published in 2012 regarding the clinical practice guidelines on glomerulonephritis (GN) to assist practitioners caring for patients with GN which is different from ISKDC regimen [19, 20]. Relapse within the first year is a powerful independent predictor of subsequent relapse, and relapse within the first 6 months of presentation is highly predictive of subsequent course [21, 22]. This study was carried out to describe the status and relapses during the first 6 months of treatment of newly diagnosed NS patients admitted to Tripoli children hospital during 2014 and to explore the factors affecting the occurrence of relapses.

PATIENTS AND METHODS

A descriptive retrospective study was conducted on children with newly diagnosed NS presented to Nephrology Unit at Tripoli Children Hospital during the period between Jan. 2014 and Dec. 2014. The follow up period was 6 months after diagnosis. Tripoli Children Hospital is a referral and teaching hospital covers most of paediatric service in west of Libya. In this study NS was diagnosed according to the criteria of the international study of kidney disease in children (ISKDC) [4]. Children with congenital and secondary NS were excluded from this study.

Case sheet used for data collection included: age at presentation (which was further divided into two age groups, children presented between 2-8 years of age as group 1 and children less than 2 years and above 8 years as age group 2), presence of hematuria either microscopic or macroscopic, presence of hypertension, presence of renal impairment, level of serum complement, family history of NS and response to steroid therapy (which was divided into three groups, steroid sensitive NS (SSNS), steroid dependent NS (SDNS) and steroid resistant NS (SRNS). The outcome of the patients divided into four groups: continue regular follow up on steroid therapy, off treatment with no relapse, missed follow up and children who passed away.

According to nephrology unit guidelines, all children with suspicious diagnosis of NS are admitted and subjected to the following investigations: renal function, complete blood count, ESR, serum albumin and total protein, serum cholesterol, serum complements, urine analysis for existence of RBC and proteins. Diagnosis of NS was confirmed if urinary protein to creatinine ratio (uPCR) is greater than 2mg/mg (nephrotic range proteinuria).

Since 2012 treatment of children with NS in our nephrology unit was according to Kidney Disease Improving Global Outcomes (KDIGO) guidelines 2012 [19,22].

Complete remission is defined as uPCR less than 2mg/mg or obtaining less than one plus (+) of protein on urine dipstick for 3 consecutive days. SDNS is defined as two consecutive relapses during steroids therapy or within two weeks of ceasing therapy. Infrequent relapse is defined as one relapse within 6 months of initial response or one to

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three relapses in any 12 months period. Frequent relapse is defined as 2-3 relapses within 6 months of initial response or four or more relapses in 12 months period. SRNS is defined as an inability to achieve complete remission with a minimum of 8 weeks treatment with corticosteroids therapy [19].

SPSS software version 16 was used for data analysis to obtain descriptive statistics including frequencies, percentage, mean and standard deviation. Chi square and Mann-Whitney test was used to compare between groups. *P* value <0.05 was considered statistically significant in all comparisons.

RESULTS

Table 1 shows that the total number of hospital admissions in Tripoli children hospital during 2014 was 5408 children. Three hundred and thirty nine (6.2%) children were admitted to nephrology unit of which 188 (55.45%) were boys and 151 (44.5%) were girls, 140 (41%) of them referred from outside Tripoli. One hundred and sixty five (48.6%) of the 339 children admitted to nephrology unit were having NS, 56 (34%) of them were newly diagnosed. Out of the 56 children newly diagnosed NS, 34 (60.7%) were boys and 22 (39.3%) of them were girls. Fourthy four (78.5%) of the newly diagnosed NS were in group 1 (2-8 years old), of these 25 (44.6%) were boys and 19 (33.9%) were girls. On the other hand, only 12 (21.5%) of the newly diagnosed NS were in group 2 (<2 &>8 years old), of these 9 (16%) were boys and 3 (5.3%) were females. The mean age for both genders at presentation was 4.2 ± 2.2 years (range from 1 - 11 years). Thirteen (23.2%) of the newly diagnosed NS children had positive family history of NS.

Table 1: Classification of patients admitted to the Tripoli Children Hospital during the years 2014.

Total admission of patients to TCH*	5408	
Total admission to nephrology unit	339 (6.2%)	
	Boys 188 (55.45%)	Girls 151 (44.55%)
Total admitted as NS*	165 (48.6%)	
Newly diagnosis NS	56 (34%)	
	Boys 34 (60.7%)$	Girls 22 (39.3%)$
Age group 1 (2-8 years)	44 (78.5%)$	
	Boys 25 (44.6%)$	Girls 19 (33.9%)$
Age group 2 (<2 & >8 years)	12 (21.5%)$	
	Boys 9 (16%)$	Girls 3 (5.3%)$
The mean age at presentation (years)	4.2 ±2.2 from (1-11)	
Family history of NS	Yes 13 (23.2%)	NO 43 (76.8%)

**** TCH: Tripoli Children Hospital, * NS: nephrotic syndrome. $ Percentage from the total number of newly diagnosed NS.***

Analysis of data showed that age at presentation related significantly to the response to steroidal therapy (Table 2). Thirty five (79.5%) of patients aged between

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2-8 years (group 1) were SSNS compared with only five (41.7%) of patients aged less than 2 years or more than 8 years (group 2). On the other hand, three patients (6.8%) of group 1 were SRNS compared with seven patients (58.3%) in group 2.

Table 2: Distribution of age at presentation to the clinical type of NS in newly diagnosed patients.

Age at presentation		clinical types			Total
		SSNS	SDNS	SRNS	
Group 1	44	35	6	3	44
	(78.5%)	79.5%	13.6%	6.8%	100.0%
Group 2	12	5	0	7	12
	(21.4%)	41.7%*	0.0%	58.3%*	100.0%
Total	56	40	6	10	56
	(100%)	71.4%	10.7%	17.9%	100.0%

**** Significantly different from the corresponding values in group 1 (P< 0.001).***

In the follow up period (Table 3), 45 (80.4% of all newly diagnosed NS) had documented note about occurrence of relapse, while 11 (19.6%) had no documented data regarding relapse. Of these documented cases, 28 (62.2%) patients had relapsed and 17 (37.8%) patients had no relapse of the disease within the first 6 months of therapy. Fourteen (25%) of the patients relapsed only once during the period of the follow up, while the other 14 patients had 2 or 3 attacks of relapse in the same period of illness (10.7% and 14.3% respectively).

Some important factors related to the occurrence of relapse regarding the 45 documented patients while they were on treatment is given in (Table 3). Although girls relapsed more than boys (70.5% from the total number of documented girl patients versus 57.1% from the total number of documented boys patients), this difference was not statistically significant (P<0.528). Similarly, relapses was insignificantly slightly higher in age group 1 at presentation more than in group 2 patients (63.2% versus 57.1%); where as 60% of patients with family history of NS relapsed compared with 64.7% of patients with no family history of the same disease. 61.1% of patients complicated with high blood pressure, suffer from disease relapse for one time or more versus 63% of patients with no hypertension. 66.7% of the relapsed patients had hematuria versus 63.4% of the relapsed patients had no hematuria.

Serum complement level was available for 22 patients only, 21 out of them had normal level (66.7% complicated with relapse) and one patient had low complement and did not relapse within the first 6 months after diagnosis. Urine protein-creatinine ratio and urea was slightly higher among non-relapsed patients. Platelets count and serum cholesterol both were slightly higher among relapsed patients (433±20.6 vs. 373±36.2 and 421±25 vs. 336±24 respectively), while serum albumin was low in both relapsed and non-relapsed groups (Table 3). At the end of

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6 months, 41 (73%) of children was still under follow up in nephrology clinic and on treatment, 7 (12.5%) of children missed follow up, 7 (12.5%) of children remain off therapy at the end of 6 months and only one child expired.

Table 3: Demographic and Laboratory Findings in Children with Idiopathic NS in relation to relapse in the first 6 months after presentation.

	Parameters	Relapse	Not relapse	*P* value
Sex	Boys	16 (57.1%)*	12 (42.9%)*	0.528$
	Girls	12 (70.6%)*	5 (29.4%)*	
Age group	Group 1	24 (63.2%)*	14 (36.8%)*	0.763$
	Group 2	4 (57.1%)*	3 (42.9%)*	
Family H/O	Yes	6 (60%)*	4 (40%)*	0.786$
	No	22 (64.7%)*	12 (35.3%)*	
Hypertension	Yes	11 (61.1%)*	7 (38.9%)*	0.900$
	No	17 (63%)*	10 (37%)*	
Hematuria	Yes	2 (66.7%)*	1 (33.3%)*	0.910$
	No	26 (63.4%)*	15 (36.6%)*	
Serum complement	Low	0 (0%)*	1 (100%)*	0.364$
	Normal	14 (66.7%)*	7 (33.3%)*	
Urea	(median±SE)	21±2.8	23.5±1.7	0.435
Platelets count	(median±SE)	433±20.6	373±36.2	0.546
Serum Albumin	(median±SE)	1.6±0.09	1.6±0.11	0.724
Serum Cholesterol	(median±SE)	421±25.3	336±24.5	0.176
Urine protein-creatinine ratio		8±1.9	12.2±4.5	0.136

$by chi – square test. * Percentages from total number of patients in the relapse and non-relapsed groups.

DISCUSSION

The total number of admissions in nephrology unit at Tripoli children hospital during 2014 was 339 patients, 165 (48.6%) of them were admitted as NS patients and only 56 (34%) of them were newly diagnosed NS. Our findings differ appreciably from those previously reported from Benghazi. They reported that children admitted with the diagnosis of NS accounted only for 18.9% of all admissions [23]. In our study, 60.7% were boys and 39.3% were girls, with male to female ratio 1.5:1. Other studies also disclosed a male preponderance among young children with this disease, at a male to female ratio of 2.1:1 [24, 25]. Although this

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gender disparity disappears by adolescence, making the incidence in adolescents and adults equal among males and females [8, 9, 24, and 26]. In this study, the mean age of these patients at the onset was 4.2 ± 2.2 years (range 1-11 years). Kumar et al. in India found that the mean age at onset of NS was 7.9 ± 5.1 years [15], which is older than the mean age of onset obtained in our study, while it was 4.3 ± 3.1 years in Saudi Arabia [27], which is close to ours. The extreme of age (<2yrs and >8yrs) at presentation of NS in our study was around 20%, not too far from that reported on a group of children from Saudi Arabia (16.9%) [28].

The age at presentation related significantly to the response of steroid therapy; it was found that 79.5% of patients aged between 2-8 years (group 1) were steroid sensitive compared with only 41.7% of patients aged less than 2 years or more than 8 years (group 2) (P<0.001). Similarly, 6.8% of group 1 were steroid resistant compared with 58.3% in group 2 (P<0.001). This atypical variety (group 2) had lesser steroid response compare to the typical (group 1) NS. Hematuria was found in 6.7% of our patients, which is much less than what was found by Thabet et al (63.6%) [29], Ibadin (60%) [30] and Begum et al (45%) [31]. The ISKDC stated that although gross hematuria is unusual in NS, microscopic hematuria might be seen in up to 23% of the patients with minimal change disease and in a higher percentage of patients with other histologic variants [32].

Hypertension was seen in 26.7% of our patients, which is nearly the same as what was reported in Thabet et al study (26.8%) [29]; while it was less compared to Begum et al (50%) [31] and Ibadin et al study (41.4%) [30]. Hypertension seems to have little effect on the rate of relapse where the percentage of relapse was 61.1% in hypertensive patients and 63% in non-hypertensive patients. In India, hypertension was seen in 2% of children with minimal lesions, in contrast, it presents in almost two thirds of children with other pathologies [33].

In this study, patients had normal renal function with no significant difference in blood urea between both relapsed and non-relapsed groups. Impaired renal function in accordance to the age and sex were observed in 26.7% in Thabet et al study [29] and 19% of patients in Begum et al. study [31].

Serum complement was performed only in twenty two patients, one of them had Hypocomplementemia (i.e. low C3 levels), who had no relapse within initial first six months. Our results are much lower than those reported by Begum et al study (15%) [31], Thabet et al study (23.2%) [29] and Geiger et al study (21%) [34].

Takeda et al [35] found that the mean serum albumin level in frequent relapse NS group was significantly lower than that of infrequent relapse NS group, which doesn't agree with our results where serum albumin was the same in relapsed and non-relapsed groups.

Family history of NS was present in 23.2 % of our patients. This high incidence of cases with family history in our population is most probably due to a very high rate of consanguineous marriages. Sixty percent of patients had positive family history of NS relapsed compared with 64.7% of patients with no family history of same disease, this difference is statistically insignificant.

CONCLUSIONS

In this study showed that idiopathic NS is one of the commonest reasons for admission to nephrology ward. It is more common in boys than girls. The age at presentation related significantly to the response to steroidal therapy. Regarding relapses, girls seems to relapse more frequent than boys and relapses was seen more in age group 1 (between 2-8 years) than group 2, however, these differences were not significant. Other factors studied (family history of NS, hypertension, hematuria, urea, platelet count, serum albumin) seems to have no effect on the relapse rate of children with newly diagnosed NS.

LIMITATION OF THE STUDY AND FUTURE RECOMMENDATION

The number of patients included in this study is small which doesn't permit confirmation of the results reported by other international studies about factors affecting the occurrence of relapse in children with newly diagnosed NS. A larger cohort and a longer duration study are required for a better understanding of these factors in Libyan patients.

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ملخص باللغة العربية

دراسة استعادية وصفية على الأطفال الذين يعانون من المتلازمة الكلوية تم تشخيصها لأول مرة بمستشفى طرابلس الأطفال خلال الفترة ما بين يناير إلى ديسمبر 2014

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الملخص

مقدمة: المتلازمة الكلوية هي الصورة السريرية التي تتميز ببروتينية شديدة، نقص ألبومين الدم، وذمة، وارتفاع الكولسترول. أجريت هذه الدراسة بتاريخ رجعي لوصف نمط المرض للمتلازمة الكلوية التى تم تشخيصها لأول مرة لأطفال أدخلوا إلى مستشفى طرابلس للأطفال خلال العام 2014.

الطرق: تم جمع البيانات الطبية من ملفات 56 مريضا تتراوح أعمارهم ما بين سنة واحدة وأحدي عشرة سنة ثم تشخيصهم لأول مرة خلال سنة 2014م بكونهم مصابون بالمتلازمة الكلوية مجهولة السبب باستخدام برنامج SPSS. وتضمنت البيانات الفروق بين الجنسين، والحساسية للعلاج بالستيرويد، الانتكاسات بعد ستة أشهر من المتابعة وتأثير العوامل المتغيرة مثل التاريخ العائلي، وارتفاع ضغط الدم، بيلة دموية، اليوريا في الدم على درجة الانتكاس.

النتائج: من بين الستة والخمسون مريضاً الذين تم تشخيصهم لأول مرة بأنهم يعانون من المتلازمة الكلوية، كان 60.7٪ ذكوراً و39.3٪ إناثاً، مع متوسط عمر 4.2±2.2 سنة. كما وجد أن هناك ارتباط وثيق بين العمر والاستجابة للعلاج بالأدوية الستيرويدية، حيث وجد أن 79.5٪ من المرضى الذين تتراوح أعمارهم بين السنتان والثماني سنوات (مجموعة 1) كانوا يتبعون مجموعة المتلازمة الكلوية الحساسة للأدوية الستيرويدية، مقارنة مع 41.7% فقط من المرضى غير النمطيين والذين تقل أعمارهم عن سنتان أو تزيد عن ثماني سنوات (المجموعة 2)، والذين يتبعون مجموعة المتلازمة الكلوية غير الحساسة للأدوية الستيرويدية. على الرغم من أن انتكاس الإناث كان أكثر من انتكاس الذكور (70.5٪ مقابل 57.1٪) بعد ستة أشهر من العلاج، فإن هذا الفرق لا يعتد به إحصائيا. وبالمثل، فإنه وجد أن العديد من العوامل الأخرى مثل التاريخ العائلي للمرض، ارتفاع ضغط الدم، البيلة الدموية، تكملة مصل الدم، واليوريا ليس لها أي تأثير إحصائي على درجة الانتكاس للمرضي الذين تم تشخيصهم لأول مرة بأنهم يعانون من المتلازمة الكلوية.

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الخلاصة: المتلازمة الكلوية هي أحدي الأمراض الأكثر شيوعاً بوحدة أمراض الكلى بمستشفى طرابلس للأطفال. كما أن هذه المتلازمة أكثر شيوعا في الأولاد من الإناث. وللسن تأثير كبير للاستجابة بالعلاج بواسطة الأدوية الستيرويدية. وفيما يتعلق بالانتكاسات، فإن الإناث أكثر عرضة للانتكاس من الأولاد، كما وجد هذا الانتكاس بنسبة أعلي بالمجموعة العمرية رقم 1، غير أن هذه الفروق لا يعتد بها إحصائياً. كما يبدوا أن العديد من العوامل الأخرى التي درست لم يكن لها أي تأثير على معدل الانتكاس في الأطفال الذين يعانون من المتلازمة الكلوية المشخصة لأول مرة.

الكلمات المفتاحية:

متلازمة الكلوية مجهولة السبب، المتلازمة الكلوية الحساسة للستيرويد، المتلازمة الكلوية المقاومة للستيرويد، الزلال البولي.