JKAU: Med. Sci. **vol. 4**, pp. 25-34 (1414 A.H. / 1994 A.D.)

Clinicopathological Study of Primary Nephrotic Syndrome in the Western Area of Saudi Arabia

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ABSTRACT .The clinicopathological features of 142 cases of childhood nephrotic syndrome (N.S.) were studied in the King Abdulaziz University Hospital (K.A.U.H.) and the National Guard Hospital (N.G.H.) during the period 1983-1992. The clinical and laboratory findings were similar to those described in other parts of the world. Fifty two (36.62%) renal biopsies have been done. Minimal change nephrotic syndrome (M.C.N.S.) is the commonest, it constitutes 28.8% of those biopsied. It has the highest ratio of the total (73.9%) compared to Focal Segmental Glomerosclerosis (F.S.G.N.) (4.93%), mesangioproliferative (M.S.P.G.N.) (5.6%), membranous proliferative (M.P.G.N.) (4.93%), membranous (M.G.N.) (2.1%), and congenital nephrotic syndrome (C.N.S.) in (5.6%) Familial nephrotic syndrome (F.N.S.) was found in (2.8%). The relative frequency of pathological types of nephrotic syndrome in the western province of Saudi Arabia is similar to that reported in most other countries except that the congenital type is more prevalent in this study. However, the frequency of pathological types are different from those reported in the central part of Saudi Arabia.

KEY WORDS: Nephrotic syndrome, Glomerulonephritis, Saudi Children.

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Introduction

The clinical, pathological, and immunological features of childhood nephrotic syndrome in both temperate and tropical countries have been described by numerous authors[1-6]. It is believed that the most common type in the temperate region is the steroid responsive, minimal change type which has a good prognosis. This is in contrast to the type which was reported in Tropical Africa and South America which is characteristically steroid resistant, shows gross pathology on renal biopsy, and has poor prognosis[4]. There are few studies which describe the clinicopathological characteristics of nephrotic syndrome of childhood in Saudi Arabia[7]. Most of these studies were carried out on highly selected patients from the central part of the Kingdom of Saudi Arabia (K.S.A.) and reported a high frequency of (M.S.P.G.N.) and C.N.S.[1] The population in the central part of the K.S.A. have a single ethnic origin in contrast to that in the western part which have mixed ethnic origins. With this background, a retrospective study was initiated for children with nephrotic syndrome in the western part of the K.S.A. in order to determine the clinicopathological characteristics of the disease.

Patients and Methods

The authors studied all the records of children aged 1 month to 13 years who were admitted with the diagnosis of nephrotic syndrome in the K.A.U.H. and the N.G.H. in Jeddah, K.S.A. The study covers a 10 year period 1983-1992. The diagnosis of nephrotic syndrome was based on the presence of heavy proteinuria (> 40 mg/h per m2) in 24 hour urine associated with hypoalbuminaemia (serum albumin < 2.5 g/100 ml). Patients with secondary nephrotic syndrome were excluded from the study.

The following data were collected from the files: personal data (age, sex, nationality), presenting symptoms and signs; biochemical data (serum urea, creatinine, cholesterol, triglyceride); haematological data (Hb, packed cell volume, leukocyte count, platelet count, coagulation profile); sickling test, Hb electrophoresis if sickling is positive and serological data (serum C3, HbsAg). These tests were done using standard laboratory methods.

All patients, except those with congenital nephrotic syndrome or those with end stage renal disease, received treatment for their initial presentation and all the subsequent relapses in accordance with the standard therapeutic regimens outlined by the International Study of Kidney Diseases in Children[8].

A congenital nephrotic syndrome definition was considered in those less than 3 months of age. A disease remission was defined as 3 consecutive days of trace or negative proteinuria, while a relapse was characterized by 3 consecutive days of protein-positive urine 2 + of greater on dipstick[9,10]. Resistant nephrotic syndrome was defined as persistence of proteinuria and hypoalbuminemia after 4 weeks of a full dose of steroid. A patient was considered to be steroid dependent if there was recurrence either during tapering of the steroid or within two weeks after termination of treatment. A frequent relapser was defined as a child who suffered two or more relapses within 6 months of the initial presentation of four or more relapses within a twelve months period[10].

Renal biopsies were performed percutaneously using ultrasound guidance in the following groups of patients :

1. Infants with congenital nephrotic syndrome.
2. Steroid resistant, dependent of frequent relapsers.
3. Patients who presented with persistent haematuria, hypertension, low serum complement or persistent disturbance of renal function.

The core of renal tissue was relieved in normal saline on ice. The tissue was examined by light microscopy while fresh to determine if there was cortical tissue or not. It was then divided into three pieces. One for histopathology. Study, the second for immuno-histochemistry, and the third for electron microscopy.

1. Histopathology

The piece of rental tissue was fixed in 40% buffered formalin and then processed routinely for paraffin blocks. Three sections were stained with Hx-E, PAS and Trichrome and Silver stain.

2. Immuno-histochemistry

Fresh tissue was embedded in OCT Media and rapidly frozen. Cryostat sections were stained by fluorescent labelled human antibodies for immuno globulins G, M and A, complements C_3 and C_4 and Fibrinogen.

3. Electron Microscopy

A small piece of cortical tissue that contained at least one glomerulus was fixed in Trumps fixative (2% glutaraldehyde and 3% formaldehyde in 0.2 M phosphate buffer at Ph 7.2), subsequently post fixed in 2% Osmium tetroxide, then dehydrated in upgraded ethanol, processed through propylene oxide and embedded in EMBED 812 preparation. Ultra thin sections were obtained by an ultramicrotome, stained with uranyl acetate and lead citrate and examined by Phillips 400 transmission electron microscope. MESPGN was diagnosed by the presence of three or more mesangial cells in the stalk region of most glomeruli.

Results

During the 10 year period, 142 cases of childhood nehphrotic syndrome were studied in the K.A.U.H. and the N.G.H. They constitute: 0.52% of the total paediatric cases admitted during this period, and 12.65% of patients seen with renal diseases. The age ranges from 1 month to 13 years with a mean (S.D.) of 6.2 (3.7) years. There were 114 Saudis (80.3%) and 28 Non-Saudis (19.7%). Ninety-six (67.6%) were males and 46 (32.4%) were females, giving a ratio of 2:1. The commonest age of presentation was between 1 to 7 years, 80 cases (56.34%), 28 children were between 7 to 10 years (19.72%) and 26 children (18.32%) above 10 as shown in Table 1. Congenital nephrotic syndrome was diagnosed in 8 children (5.63%) and familial nephrotic syndrome in 4 families (2.8%). It was interesting to find that one of those children's mother had nephrotic syndrome when she was 6 years old. In two other families: there is history of 4 siblings and in the other family 2 siblings respectively had a nephrotic syndrome.

TABLE 1. Age distribution of 142 patients with nephrotic syndrome.

Age (Years)	Number	%
< 1 year	8	5.63
1-7 years	80	56.34
7-10 years	28	19.72
> 10 years	26	18.31
Total	142	100

Oedema was the most constant clinical feature in all cases. Transient microscopic haematuria was found in 44 (30.98%) children. Thirty five (24.6%) children had hypertension (BP > 95) centile for age and sex. The mean (S.D.) for serum albumin was 16.88 (4.52) and for cholesterol 11.99 (4.08).

None of the patients had sickle cell anaemia or was HBsAg positive. Nephrotic syndrome was associated with a single kidney in one child.

Steroids were used in 131 patients (92.25%) and an initial response was obtained in 117 children (89.31%). The rest were steroid resistant (10.69%) Table 2. Renal

TABLE 2. Clinical features and response to steroid of the biopsied patients with primary nephrotic syndrome.

Histopathological	Number %	Haematuria	Hypertension	Response to steroid
M.C.N.S.	15	-	3 (20%)	14 Dependent 1 resistant
F.S.G.S.	7	4 (57%)	3 (42.85%)	6 Dependent 1 resistant
Mesangio proliferative	8	4 (50%)	4 (50%)	6 Dependent 2 resistant
Membranoproliferative	7	7 (100%)	6 (75%)	1 Dependent 6 resistant
Membranous	3	3 (100%)	1 (30%)	2 Resistant
End stage renal disease	2	2 (100%)	2 (100%)	-
Congenital nephrotic syndrome	8	6 (75%)	8 (100%)	used in 1 resistant
Crescentic glomeno-nephritis	2	2 (100%)	2 (100%)	used in 1 resistant
Total	52			

biopsy was done in 52 cases. The histopathological findings are summarized in Table 3. M.C.N.S. was found to be the commonest as it was found in 15 (28.84) out of 52 biopsies followed by F.S.G. (4.93), M.E.S.P.G.N. (5.63%), M.P.G.N. (4.93), and membranous (2.1%). Congenital N.S. was reported in 8 (5.63%); 6 were of congenital glomerulosclerosis, one was of M.P.G.N. and one was Finnish type. There were two biopsies with end stage renal disease and two with crescentic glomerulonephritis. Immuno-fluorescent microscopy was done in 37 cases and the results were either negative, as in M.C.N.S. or showed only small amounts of immunoglobulin, namely IgM or IgG, and deposition of complements 3 and 4, especially in M.S.P.G.N. and M.P.G.N.

TABLE 3. Distribution of histopathological types of 52 biopsied patients with primary nephrotic syndrome.

Histopathological types	Number of cases	% of those biopsied
M.C.N.S.	15	28.84
F.S.G.S.	7	13.46
M.S.P.G.N.	8	15.38
M.P.G.N.	7	13.46
M.G.N.	3	5.77
Cong. N.S.	8	15.38
Fin	1	1.92
Cong. glome	6	11.54
M.P.G.N.	1	1.92
Crescentic GN	2	3.84
End stage renal dis.	2	3.84
Total	52	100

The clinical features of the biopsied cases are shown in Table 4. Thirty three (63.46%) were males and 19 (36.54%) were females. Their age ranged from 1 month to 13 years. If we subtract the congenital nephrotic syndrome (8 cases), the mean (S.D.) of age of the remaining 14 patients was 8.2 (2.6) years. Haematuria and hypertension were found in 20% of the cases with M.C.N.S. and in patients of other

TABLE 4. Main clinical features of 142 children with nephrotic syndrome.

Clinical	Number of children*	%
Microscopic haematuria	44	30.98
Hypertension	35	24.64
Initial response to steroid	117	89.3
Corticosteroid resistance	14	10.69
Corticosteroid dependent	30	22.9

types. Fourteen of the M.C.N.S. were steroid dependent and one was resistant while in the other types, the resistance to steroid, ranges from 50% to 100%.

It is noticed also that serum urea nitrogen was high in one case of M.C.N.S., serum creatinine was normal in all, while they were raised in 100% of the congenital nephrotic syndrome and other chronic glomerulonephritis, Table 5.

TABLE 5. Renal biopsy and laboratory findings in patients with primary nephrotic syndrome.

Histopathological	Number %	BUN	Creatinine	C3
M.L.N.S.	15	High in one	All normal	Normal
F.S.G.	7	High in two	Normal	Normal
MeSPOGN	8	Normal	Normal	Normal
MPGN	7	High in four	High 2 cases	Low 2
Membranous	3	High in one	Normal	Low 1
Congenital nephrotic syndrome	8	High in all	High in all	Normal
Crescentic GN	2	High in two	High in two	Normal
2nd stage renal dis.	2	High in two	High in two	Normal
Total	52			

Discussion

In this study, primary nephrotic syndrome in children of the western part of Saudi Arabia accounts for 12.65% of total renal problems encountered. This is comparable to other reports from the central part of Saudi Arabia (13.5%)[11] but is less than that reported from other countries (19.2%)[12].

The admission rate of children with N.S. was 0.52% of the total patients seen during this period which is nearly similar to that reported in the central part of Saudi Arabia 0.44%[11]. However, it is intermediate between those reported in temperate countries (0.03-0.04%) and tropical countries with rates higher than 2%[8]. In the present study, M.C.N.S. was the commonest type accounting for 73.94% of the total, and this is comparable to previous studies[13], but it is higher than that reported in the central part of Saudi Arabia (48.7%)[11]. This could be explained by the fact that their patients are more selected and probably by genetic and racial factors. This difference in incidence of M.C.N.S. (52-78%) has been reported previously[14-16].

Our patients resemble children with nephrotic syndrome in the central part of the K.S.A. and in temperate countries in their age, sex and response to steroids. It was noticed that 80 children with M.C.N.S. presented between age 1-7 years which constitutes 76.2% of the total, and this is similar to that noted in a previous report (74.59%)[17]. This study shows initial response to steroids in 89.3% of the cases which is comparable to others in K.S.A. 84% and Kuwait[18] but is higher than that reported in Iran[19].

The results of renal biopsy in this study showed that M.C.N.S. was the commonest lesion being responsible for 28.84% of those biopsied and 10.94% of the total. FSG was reported in 4.93%, and M.S.P.G.N. in 5.63%. Their frequencies are comparable to others[20-25]. If F.S.G. and M.E.S.P.G.N. are added to those presumed to have M.C.N.S. from their response to steroid, they constitute 84.5% of all primary causes of nephrotic syndrome in childhood, and this is comparable to previous studies[26-28]. The frequency of M.E.S.P.G.N. is markedly lower than has been reported in the central part of the K.S.A.[7] (17.6%), but comparable to other others[19-21,24]. In our study, the frequency of M.P.G.N. is 4.92%, M.G.N. is 2.1%, and their clinical features are similar to previous studies[29,30].

It is interesting to report a higher frequency 5.63% of congenital nephrotic syndrome in our study than previously reported by Habib and Kelinknecht[30] but remarkably lower than that found in the central part of the K.S.A.[7]This could be due to a higher rate of consanguinous marriages in the central part of Saudi Arabia. The incidence of familial N.S. in this study was 2.8% which is similar to previous studies[24,25,32], and all of them were presumed to be of M.C.N.S. because of their clinical features and a good response to steroids[11] although variations in response to steroids have been reported[33].

Conclusion

This study gives a detailed information about the primary Nephrotic Syndrome in childhood in western region of K.S.A. Its clinical and laboratory findings are similar to reports from central part of K.S.A. and other countries. The frequency of histopathological types in this study is different from those of the central part of K.S.A. but comparable to other countries. M.C.N.S. is the commonest type of N.S. in this study, a high frequency of congenital N.S. was observed, but less than that reported in the central part of K.S.A.

Clinical features, age, sex and response to steroids are similar to the central part of K.S.A. and most other parts of the world.

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دراسة سريرية باثولوجية لمرض الكلى لدى الأطفال في المنطقة الغربية بالمملكة العربية السعودية

سعاد الشيخ[1]، و عبد العزيز انديجاني[2]، و حسين السقاف[1]، و جميلة قاري[1]، و سعد الشهيب[3]، و أسامة ناصف[4]، و سوسن جلالة[4]

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المستخلص . أجريت دراسة سريرية باثولوجية لمائة واثنين وأربعين حالة مرض كلائي في الأطفال ، تمت دراستها في مستشفى جامعة الملك عبد العزيز ومستشفى الملك خالد للحرس الوطني ، وكلاهما في جدة - في المدة من ١٩٨٣م وحتى ١٩٩٢م .

وتبين لنا أن المظاهر السريرية والنتائج المخبرية للمرضى في هذه الدراسة مماثلة لما وصف في أماكن أخرى من العالم . أخذت خزعات من إحدى الكليتين من اثنين وخمسين مريضًا . أي بنسبة ٣٦,٦٢٠٪ من مجموع المرضى . وقد كانت نتائج التحليل النسيجي لهذه العينات كالآتي :

المرض الكلائي ذو التغيرات القليلة هو أكثرها شيوعًا ، حيث وجد في ٢٨,٨٪ من العينات ، وهذا يعادل ٧٣,٩٪ من المجموع الكلي للمرضى ، ووجد أن التليف الكبيبي البؤري القطعي يحتل نسبة ٤,٩٣٪ ، في حين يُكون الالتهاب المسراقي الكبيبي التكاثري نسبة ٥,٦٪ ، أما الغشائي التكاثري فهو بنسبة ٤,٩٣٪ ، والغشائي بنسبة ٢,١٪ ، والوراثي الكلائي بنسبة ٥,٦٪ ، والكلائيب العائلي ٢,٨٪ . تثبت هذه الدراسة التكرار النسبي للأنواع المختلفة من باثولوجيا المرض الكلائي في المنطقة الغربية من المملكة العربية السعودية ، الذي يماثل ما نشر في البلاد الأخرى من العالم ، عدا المرض الكلائي الوراثي ، حيث زادت نسبته في هذه الدراسة عن الآخرين . وهناك اختلاف في نتائج هذه الدراسة عن مثيلتها في المنطقة الوسطى من المملكة العربية السعودية .