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Epidemiology of primary nephrotic syndrome in Egyptian children

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Abstract

Background: **Primary nephrotic syndrome is a common renal problem in pediatrics, with great variation in patients' characteristics in different regions of the world. The aim of this study was to define these characteristics in Egyptian children with primary nephrotic syndrome.**
Methods: **Records of 100 primary nephrotic syndrome patients were retrospectively reviewed. Demographic, clinical, histopathological data and response to therapy were analyzed.**
Results: **The mean age of onset was 4.43 ± 2.7 years. Thirty-four percent of patients were steroid resistant, and 66% showed initial steroid response; 46 of the latter were steroid dependent. Forty patients underwent a renal biopsy with minimal change nephrotic syndrome occurring in 30%, mesangioproliferative glomerulonephritis in 37.5% and focal segmental glomerulosclerosis in 30%. Nine percent of cases developed chronic renal insufficiency. Response to cyclophosphamide and cyclosporine occurred in 37.5% and 33.3% of steroid-resistant nephrotic syndrome patients, respectively.**
Conclusions: **A greater percentage of steroid-resistant patients were found in our patients compared with those in other studies. Response to immunosuppressives was different from other studies, probably due to differences in the priority of selection for immunosuppressive therapy.**

Key words: *Immunosuppressive, Nephrotic, Renal, Steroid*

Introduction

Primary nephrotic syndrome (NS) is one of the commonest problems encountered in pediatric nephrology practice worldwide. There are differences in the patients' characteristics with regard to demography, clinical and histopathological data and response to therapy, in different regions (1-4).These changes may be due to the wide differences in genetic, cultural and environmental factors. Patients' characteristics have also changed remarkably over recent decades, with a greater frequency of the challenging condition focal segmental glomerulosclerosis (FSGS) (5).
In this study, we aimed to analyze the epidemiological, clinical and histopathological features in Egyptian children with idiopathic NS, and document their response to different therapies.

Subjects and methods

The records of 100 pediatric NS patients, chosen randomly from cases being followed in the nephrology clinic at Children's Hospital, Cairo University, were retrospectively reviewed. The patients' files numbers are arranged serially, files were randomly selected electronically using Microsoft office (Excel 2007). NS was defined as heavy proteinuria (urine protein excretion >40 mg/m^2 per hour), with associated edema and hypoalbuminemia. Only patients with age of onset >3 months (to exclude congenital NS) and <16 years with a duration of follow-up of at least 1 year were included. Any patient with inadequate data in the records, or who

dropped out during the follow-up period or had secondary NS (e.g., systemic lupus erythematosus) was excluded.
Data obtained from files included demographic data, clinical and laboratory data, clinical diagnosis based on definitions according to the International Study of Kidney Disease in Children (ISKDC) (4), biopsy results (biopsies are performed free of charge in our hospital for any steroid-resistant NS [SRNS] or steroid-dependent NS [SDNS] patients who relapse on high doses of steroids, unless parents refuse to give consent), therapeutic data and renal outcome. Unfortunately, no genetic study was performed in our patients because the insurance system in Egypt does not support it, so it is not routinely done, as in some other countries

Statistical analysis

All patient information was tabulated and processed using SPSS 14.0. For quantitative variables, means and medians (as a measure of central tendency), standard deviation, range and minimum and maximum (as measures of variability) were used. Frequency and percentage are presented for qualitative variables. Chi-square test and Fisher's exact test were used to estimate differences in qualitative variables.

Results

The study included 74 males and 26 females with a male to female ratio of 3:1. Their age ranged from 4 to 21 years with a mean of 9.84 ± 3.9 years. Age of onset ranged from 1 to 12 years with a mean of 4.43 ± 2.7 years, while duration of illness ranged from 2 to 13 years with a mean of 5.4 ± 2.5 years. Weight of patients at the time of study ranged from 14 to 80 kg with a mean of 34.12 ± 14.48 kg. Height ranged from 88 to 170 cm with a mean of 130.2 ± 19.6 cm. Body mass index (BMI) ranged from 11 to 33 with a mean of 19.6 ± 4.2. Of these patients, 10 were below the 5th percentile, and 2 were above the 95th percentile for weight, while 17 patients were below the 5th percentile for height.
All patients were given prednisone at a dosage of 2 mg/kg per day as an initial therapy. Sixty-six patients showed initial response to steroids, and of them, 46 had SDNS, 19 were infrequent relapsers and 1 was a frequent relapser, while 34 patients had SRNS (Fig. 1). In our center, patients who fail to achieve remission after 8 weeks of corticosteroid treatment are defined as SRNS (4).
Regarding biopsies, 40 patients had a renal biopsy, 30 of them for SRNS, 8 of them for SDNS and 2 for initial age of presentation >12 years. Figure 2 shows the results of these biopsies.

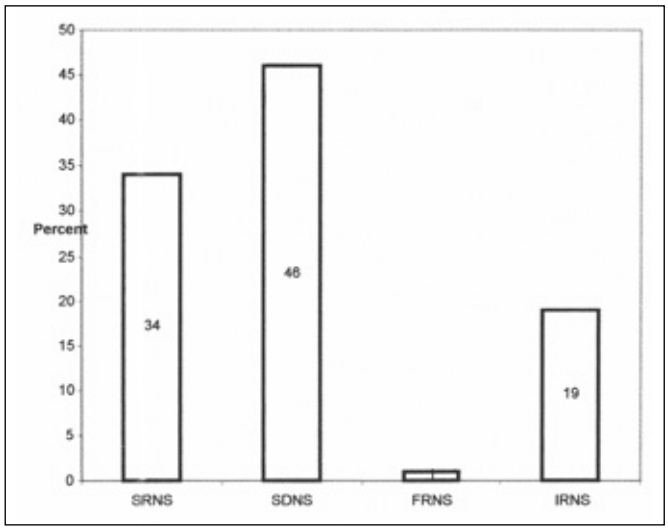

Fig. 1 - Clinical response after initial prednisone therapy. FRNS = frequently relapsing nephrotic syndrome; IRNS = infrequently relapsing nephrotic syndrome; SDNS = steroid-dependent nephrotic syndrome; SRNS = steroid-resistant nephrotic syndrome.

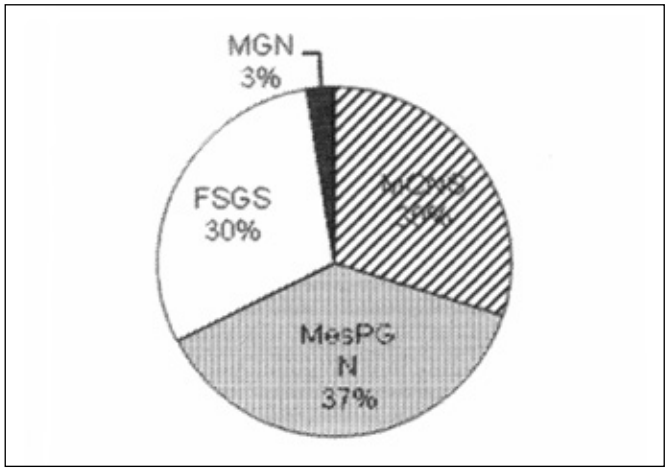

Fig. 2 - Results of renal biopsies. FSGS = focal segmental glomerulosclerosis; MCNS = minimal change nephrotic syndrome; MesPGN = mesangioproliferative glomerulonephritis; MGN = membranous glomerulonephropathy.

Of the SRNS patients who underwent a renal biopsy, 6 (20%) had minimal change NS (MCNS), while 24 (80%) had non-MCNS (12 with mesangioproliferative glomerulonephritis [MesPGN], 11 with FSGS and 1 with membranous glomerulonephropathy [MGN]).
Nine patients (9%) developed chronic renal insufficiency (CRI); all of them had SRNS. Of these, 6 patients reached end-stage renal disease (ESRD). All CRI patients had non-MCNS (4 MesPGN, 4 FSGS and 1 MGN) (p=0.013, for MCNS vs. non-MCNS) (Tab. I).

TABLE I
CHRONIC RENAL INSUFFICIENCY (CRI) BY PATHOLOGY

Pathology	CRI		No CRI		Total	
	No.	%	No.	%	No.	%
MCNS	0	0	12	38.7	12	30
Others	9	100	19	61.3	28	70
MesPGN	4	44.4	11	35.5	15	37.5
FSGS	4	44.4	8	25.8	12	30
MGN	1	11.1	0	0	1	2.5
Total	9	100	31	100	40	100

FSGS = focal segmental glomerulosclerosis; MCNS = minimal change nephrotic syndrome; MesPGN = mesangioproliferative glomerulonephritis; MGN = membranous glomerulonephropathy.
p=0.013, for MCNS vs. others; p=0.353, for MesPGN vs. FSGS.

TABLE II
PATIENT DATA: STEROID-RESISTANT VERSUS STEROID-RESPONSIVE NEPHROTIC SYNDROME

Data	Steroid resistant (n=34)		Steroid responsive (n=66)		Total (n=100)	p Value
	No.	%	No.	%	No.	
Male	21	61.8	53	80.3	74	0.023
Female	13	38.2	13	19.7	26	
Family history	4	11.7	1	1.5	5	0.013
Hypertension	10	29.4	11	16.6	21	0.069
Gross hematuria	3	8.8	5	7.6	8	0.41
Low complement	2	5.9	4	6.06	6	0.486
Wt <5th percentile	7	20.6	3	4.5	10	0.006
Wt >95th percentile	0	0	2	3.03	2	0.153
Ht <5th percentile	9	26.5	8	12.1	17	0.035
CRI	9	26.4	0	0	9	<0.001
Age of CRI onset ≤6 years	24	70.6	57	86.4	81	0.05
Age of CRI onset >6 years	10	29.4	9	13.6	19	

CRI = chronic renal insufficiency; Ht = height; Wt = weight.

When comparing data for SRNS patients versus steroid-responsive patients, there was a significantly higher percentage of females in the SRNS patient group (38.2% females vs. 19.7% males, p=0.023). Positive family history was significantly higher in the SRNS patients (p=0.013). Hypertension was more common in SRNS patients but did not reach statistical significance. SRNS patients were significantly more often below the 5th percentiles for weight and height at the time of study (Tab. II).

Regarding treatment of SRNS patients, cyclophosphamide (CYC) was used as first-line therapy in 32 patients, 12 of them (37.5%) showed a good response, and 20 (62.4%) showed no (16 patients, 50%) or partial (4 patients, 12.4%) response. The percentage of those resistance to CYC varied markedly with pathology. In MCNS (6 patients), 66.7% responded to treatment, while in MesPGN (11 patients), 36.4% showed complete and 18.2% showed partial response (p=0.6), in FSGS (11 patients) only 9.1% showed complete and 18.2% showed partial response (p=0.11). Cyclosporine was used as second-line treatment in 18 patients, 6 of them (33.3%) responded. In MCNS (2 patients), 50% showed complete and 50% showed partial response, in MesPGN (7 patients), 28.6% showed complete and 14.3% showed partial response (p=0.15), while in FSGS (8 patients), 37.5% showed complete and 50% showed partial response (p=0.6). Mycophenolate mofetil (MMF) was used as third-line treatment in 4 patients, 2 of whom showed no response and 2 showed a partial response. MMF was used as second-line treatment after CYC in 2 patients, 1 of whom responded and the other did not respond except after the use of cyclosporine. Thus one sixth of patients who used MMF (16.7%) showed a good response to treatment, 2 (33.3%) showed a partial response and 3 (50%) showed no response.

On the other hand, SDNS patients who did not respond well to levamisole therapy or relapsed while on high steroid dose were given CYC, cyclosporine or azathioprine. Sixteen patients received CYC, 13 of them (81.3%) showed a good response with stopping (or marked reduction) of steroids and 3 (18.7%) showed no improvement.

Eight SDNS patients received cyclosporine, and all of them (100%) showed a good response to treatment. Only 1 SDNS patient was given MMF, showing a good response.

Seventeen patients used azathioprine for SDNS, 10 patients (58.8%) showed marked improvement with the ability to stop or reduce the steroid dose remarkably, 2 patients (11.8%) showed partial improvement with moderate reduction in the steroid dose, and 5 patients (29.4%) showed no improvement.

Discussion

As described in most studies (1-3, 6, 7), the childhood nephrotic syndrome has a male predominance (74% in our study). The mean age of disease onset was 4.43 ± 2.7 years, with patients having onset of ≤6 years constituting 81% of patients. In other studies, the mean age of onset ranged from 4.6 to 5.4 years (1-3, 6), while the percentage of patients ≤6 years ranged from 46% to 79% (1, 4, 7, 8).

Although all patients were within normal weight and height percentiles at onset of disease, there were 17 patients below the 5th percentile for height at the time of the study, 11 of them had SRNS and 6 SDNS, probably resulting from prolonged steroid therapy and the chronic nature of the disease. Two of the SDNS patients had extreme obesity with weight in the >95th percentile. A study by Mattoo et al (3) showed similar effects of steroid therapy.

Steroid resistance in our patients after the initial prednisone therapy occurred in 34% of cases, and was thus higher than that in most other studies, in which steroid resistance ranged from 9.4% to 22% (3, 6, 7, 9). Although we are a referral tertiary care hospital, this alone can not explain this high incidence, as most of the patients were referred to the hospital before initiation of any therapy. Whether the high percentage of positive consanguinity (18% in our study) is the cause or not, needs to be investigated.

Positive family history (another sibling with NS) was present in 5 patients, of these 1 was an infrequent relapser and 4 had SRNS, 3 of them developed CRI and all had positively consanguineous parents. The incidence of positive family history was higher than in other studies (2% in Gulati et al (10), and it might have been even higher if we had included patients who had other relatives with NS. This high correlation with positive family history is also reported by Mattoo et al (3) in a study done in Saudi Arabia, who reported a 6% positive family history. This is probably due to the same cultural background in Egypt and Saudi Arabia.

There was a great variation in the histopathological results among different studies; this may be due to the difference in the indications for biopsy in different centers. In our study, MesPGN was the most common pathology, occurring in 37.5% of biopsies. MCNS and FSGS each occurred in 30% of biopsies, and only 2.5% (1 patient) had MGN. No biopsies showed membranoproliferative glomerulonephritis (MPGN). Ozkaya et al (1) found a high incidence of MPGN in their biopsies (34%); with FSGS in 23%; MCNS and MesPGN in only 19% and 17%, respectively; and 7% other pathologies. Also, studies from Nigeria (11) and New Zealand (2) reported a high incidence of MPGN in their patients. Similar to our

results, the study from Saudi Arabia (3) showed no MPGN in their patients and only 2% with MGN. These differences may be related to environmental or ethnic factors.

In our study, female sex carried a significantly higher risk for the development of steroid resistance. This was similar to the results of Kari and Halawani, who found that 23 females and only 8 males were steroid resistant (12).

CYC had been the first-line treatment of SRNS and SDNS in our unit due to the higher cost of cyclosporine and the need for longer duration of therapy (though this trend has changed in recent years with more common use of cyclosporine in SDNS, especially with cyclosporine therapy now supported by the health insurance system, which covers all school and preschool children).

CYC achieved complete remission in 37.5% of SRNS patients and partial remission in 12.4%. Other studies (12-14) reported complete response in 25%-50% of cases when it was used as first-line therapy after steroids. Regarding cyclosporine, there was a 33.3% rate of complete responses, which is lower than in other studies (12, 13, 15), in which the response ranged from 53% to 75%. The percentage in our study may have been higher if cyclosporine had been used as first-line treatment in SRNS patients and not only as a second drug after failure of CYC therapy.

FSGS patients showed a much better response with cyclosporine, in comparison with CYC (87.5% partial and complete response with cyclosporine vs. 27.3% with CYC; p=0.009). In MCNS and MesPGN, both drugs showed similar results. The response of MesPGN in our study was lower than in other studies (13, 15), while that of MCNS and FSGS showed similar results. Regarding MMF, it was only used in patients resistant to other immunosuppressives, and there was a low percentage of responsiveness in this study. This is in concordance with Gargah and Lakhoua (16) who reported that out of 6 patients with SRNS who were treated with MMF, only 1 patient achieved complete remission, and 1 patient partial remission. In a study by Kari and Halawani (12), MMF was also used as a last option, but it obtained remission in 40% of cases. Two studies performed in China (17, 18) reported a high total remission rate in the MMF group, of 66.6% and 62.5%, respectively, but both studies used MMF as first-line treatment.

Nine patients developed CRI (26% of those with SRNS). In the study by Kari and Halawani (12), only 10% of SRNS patients developed ESRD; however, they had a shorter follow-up duration, and they counted only patients who started regular hemodialysis. Four of our CRI patients had FSGS, meaning that 25% of FSGS patients developed CRI. Other studies (19-21) showed an incidence of 15.3%-32.4% of CRI in FSGS patients.

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