Changes in Steroid Response pattern in Childhood Idiopathic Nephrotic Syndrome in Sohag

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Abstract

Background and aim of work: Nephrotic syndrome (NS) is a common chronic kidney disease in childhood and it is mostly idiopathic. Steroid response pattern remains the most important issue in prognosis of NS. Increase in steroid resistant nephrotic syndrome (SRNS) frequency over years was documented in some studies. This work aimed to demonstrate the change in steroid response pattern of idiopathic nephrotic syndrome (INS) over years in our locality at Sohag in Upper Egypt.

Patients and Methods: Combined retrospective and prospective studies were done; including **280** children with INS, aged from **1** to **15** years, diagnosed and followed in our pediatric renal unit in Sohag University Hospital, Egypt in the period from January **2000** to December **2014**. The patients' demographic features, steroid response pattern in both groups were studied.

Results: A total of **280** patients (**203** in the retrospective group and **77** in the prospective group) with INS were included with mean age at disease onset **4.60±2.58** (range **1-15**) years and male/female ratio **1.8/1.** Mean follow up duration was **4.44±3.24** (range **1-15**) years. Steroid was given to all patients. **94.1%** and **79.2%** of patients in the retrospective and the prospective groups respectively were steroid sensitive, and the rest of patients were steroid resistant. Renal biopsy was done in **36** and **26** patients in the retrospective and prospective studies respectively. Biopsy results revealed minimal change disease (MCD) in **55.6%** and **38.5%,** focal segmental glomerulosclerosis (FSGS) in **22.2%** and **42.3%,** mesangioproliferative glomerulonephritis (MesPGN) in **22.2%** and **19.2%** of biopsied patients in the retrospective and prospective groups respectively. End stage renal disease (ESRD) was developed in **4** patients all of them were steroid and other immunosuppressive therapies resistant and with FSGS histopathology. Death occurred in **5** patients.

Conclusion: Steroid sensitive NS is the most common form of INS in children but there is increase in the frequency of SRNS over years in our locality.

Key words: idiopathic nephrotic syndrome, steroid resistant, focal segmental glomerulosclerosis.

Introduction

Nephrotic syndrome is one of the most common chronic renal diseases in pediatrics (**Kaneko et al, 2015**). It has an incidence of **2-16.9** per **100.00** children worldwide (**Chanchlani et al, 2016**). Idiopathic nephrotic syndrome is the most common type in childhood, representing about **90%** of all cases and it is composed of nephrotic syndrome and primary glomerular disease without an identifiable causative disease or infection (**Pais et al, 2016**). Corticosteroid remains the mainstay of treatment of INS since **1950s** till now. Based on the response to corticosteroids, children with idiopathic nephrotic syndrome segregate into a steroid sensitive group (up to **80%**) that has a good long-term prognosis, but risk of relapses, and a steroid-resistant group with a higher risk of developing chronic kidney

disease **(Chanchlani et al, 2016).** Increase in SRNS frequency over years was documented in some studies **(Kim et al, 2005; Banazak et al, 2012).** The most common pathology in steroid-resistant nephrotic syndrome is FSGS **(Seif et al, 2013).** Rise in the frequency of FSGS was documented in several studies all over the world **(Srivastava et al, 1999; Felix et al, 1999; Gulati et al, 1999; Kari, 2002; Filler et al, 2003; Banazak et al, 2012; Bakr et al, 2014; Arif et al, 2016).** This work aims to demonstrate the changes in steroid response pattern of INS over years in our locality at Sohag in Upper Egypt.

Patients and methods

This study included total of **280** children with INS, aged from **1-15** years, diagnosed and followed in our pediatric nephrology unit in Sohag University Hospital in the period from Jan **2000** to Dec **2014**. This work is composed of two parts; retrospective and prospective parts. The retrospective part involved **203** patients with INS diagnosed in the period from Jan **2000** to Jan **2010** and completed their follow up till the end of the study; their previous data were collected from the medical records. The prospective part involved **77** new cases diagnosed and followed in the period from Jan **2010** till Dec **2014.** Patients with incomplete data or less than one year follow up duration were excluded.

Idiopathic nephrotic syndrome was diagnosed depending on the presence of nephrotic range proteinuria >**40** mg/h/m^2 or protein/creatinine ratio (uPCR) >**2** g/g and hypoalbuminemia <**25** g/l with or without edema in the absence of systemic or extrarenal disorders **(Naudet et al, 2009; Pais et al, 2011).** In addition to full medical history and detailed physical examination, the following investigations were done for all

patients at presentation: urine analysis by dipsticks and microscopy, urine **24-**hours proteins or first morning uPCR, serum total protein and albumin, blood urea nitrogen, serum creatinine, total serum cholesterol and triglyceride, full blood count, serum electrolytes, Complement **3** (**C3**) and abdominal sonography. Antinuclear antibodies (ANA) test was done for patients more than **10** years old at disease onset **(Pais et al, 2011; Bagga, 2008).**

Steroid (prednisone) was given to all patients in a dose of 2mg/kg/day, for **4-6** weeks, followed by **1.5** mg/kg on alternate days for **4-6** weeks then gradually withdrawn over **2-5** months **(Niaudet et al, 2009; Bagga, 2008).** The following definitions were used to categorize the steroid response patterns: complete remission (proteinuria <**4** mg/h/m^2, 0-trace on Albustix or uPCR <**0.2** g/g); partial remission (proteinuria reduction of **50%** or greater from the presenting value and absolute uPCR between **0.2 −2** g/g); steroid response (remission with steroid therapy); relapse (nephrotic range proteinuria for **3** consecutive days after having been in remission); frequent relapses (≥**2** relapses within **6** months of initial response or ≥**4** relapses within a period of **12** months); steroid dependence (**2** consecutive relapses during steroid therapy or within **14** days after cessation of successful steroid therapy); steroid resistance (failure to achieve remission after **8** weeks of steroid therapy); initial steroid resistant (steroid resistance during the first episode); late steroid resistance (persistent proteinuria during ≥ **4** weeks of steroid following one or more remissions) **(Niaudet et al, 2009; KDIGO, 2012; Gispon et al, 2009).**

Renal biopsy was indicated at presentation for patients with atypical features (age >**10** years, persistent hypertension, gross hematuria, renal

impairment not attributable to hypovolemia or low **C3**) and following therapy initiation for patients with initial or late SRNS and those with steroid dependent NS (SDNS) or frequently relapsing NS (FRNS) before treatment with cyclosporine A (CsA) **(Niaudet et al, 2009; Bagga, 2008; Valentini et al, 2007).** Informed written consent was taken from the parents before the procedure and the specimens were examined by the same pathologist using light microscopy.

Steroid resistant patients were biopsied and treated with steroid in addition to one or more of the immunosuppressive medications including:

cyclophosphamide, cyclosporine and mycophenolate mofetil.

Statistical package for the social sciences (SPSS) version **16** was used for data analysis. Quantitative variables were presented as mean ± standard deviation and analysis of variance (ANOVA) was used for comparing means for statistical significance. Frequency and percentage were used for qualitative variables. For estimation of differences between qualitative variables, Chi-square was used. *P* values less than **0.05** were considered significant.

This study was approved by the ethical committee of Sohag University

Results

A total of **280** patients (**203** patients in the retrospective study and **77** patients in the prospective study) with INS, were included. The mean follow up duration was **4.44±3.24** years (range **1-15** years). Mean age of patients at initial presentation was **4.60±2.58** years (range **1-15** years). There were **180** males and **100** females with male/female ratio **1.8/1.**

Steroid therapy was given to all patients. Frequency of steroid resistance was significantly higher in the prospective study **(21%)** relative to the retrospective study **(6%)** with (P=**0.000**). Steroid response pattern in both retrospective and prospective studies is shown in Figure (1).

Renal biopsy was done in **36** patients in the retrospective study and in **26** patients in the prospective study. Indications for renal biopsy in both studies are shown in table **(3).** Renal biopsy results in both retrospective and prospective studies are shown in table **(4).**

Table (3): Indications for renal biopsy in studied patients

Indications	Renal biopsy					
	Retrospective study		Prospective study		Total Patients	
	Count	%	Count	%	Count	%
Before steroid therapy	1	2.8%	6	23.1%	7	11.3%
		%	14	53.8%	24	38.7%
		%	2	7.7%	16	25.8%
		%	2	7.7%	10	16.1%
		%	2	7.7%	5	8.1%
		%	26	33.8%	62	22.1%
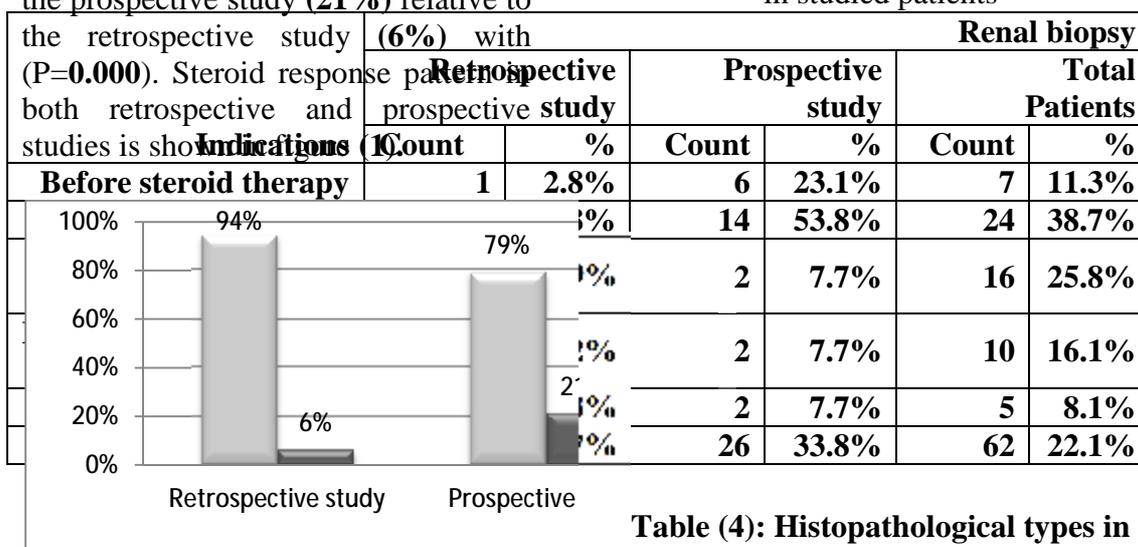
Figure (1): Steroid response in retrospective and prospective studies

Table (4): Histopathological types in biopsied patients

Histopathology	Renal biopsy		
	Retrosp	Prospe	Tota

	ective study (n=36)	ctive study (n=26)	l Patients (n=62)
MCD	20 (55.6%)	10 (38.5%)	30 (48.4%)
FSGS	8 (22.2%)	11 (42.3%)	19 (30.6%)
MesPGN	8 (22.2%)	5 (19.2%)	13 (21%)
P -value	0.227		

MCD, minimal change disease; **FSGS**, focal segmental glomerulosclerosis; **MesPGN**, mesangio-proliferative glomerulonephritis

Focal segmental glomerulosclerosis was the main histopathological pattern in steroid resistant nephrotic syndrome (SRNS) as shown in figure **(2).**
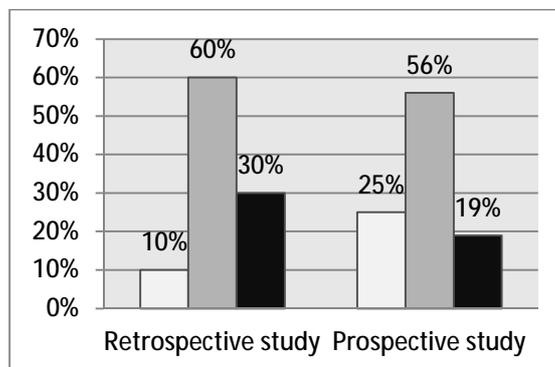
Figure (2): Histopathological spectrum in biopsied steroid resistant patients

There were changes in the steroid response pattern within the same histopathological types in the prospective study relative to the retrospective study as shown in table **(5)**

The mean age at disease onset of INS was **4.60 ± 2.58** years in the present

Table (5): Histopathology in relation to steroid response

	Histopathology								
	Retrospective study			Prospective Study			Total Patients		
Steroid response	MCD n=20	FSGS n=8	MesPGN n=8	MCD n=10	FSGS n=11	MesPGN n=5	MCD n=30	FSGS n=19	MesPGN n=13
Steroid sensitive	19 95%	2 25%	5 62%	6 60%	2 18%	2 40%	25 83%	4 21%	7 54%
Steroid resistant	1 5%	6 75%	3 38%	4 40%	9 82%	3 60%	5 17%	15 79%	6 46%
P -value							0.000		

MCD, minimal change disease; **FSGS**, focal segmental glomerulosclerosis; **MesPGN**, mesangio-proliferative glomerulonephritis

By the end of the study, out of total studied children, four **(1.4%)** patients developed ESRD all of them were FSGS and multidrug resistant. Five deaths **(1.8%)** were present; **3** of them with FSGS and ESRD and **2** of them with MCD and massive sepsis, all of them were steroid and other immunosuppressive therapies resistant.

Discussion

study. This was in accordance to previous other studies **(Zaki et al,**

1989; Madani et al, 2010; Kaddah et al, 2012; Hacıhamdioğlu et al, 2015). A male preponderance was detected in our study, in agreement with others **(Felix et al, 1999; Wong, 2007; Kaddah et al, 2012).** Male preponderance in children, with a male to female ratio of up to **3.8:1**, is frequently reported in INS **(Niaudet et al, 2016).**

Statistically significant increase in the frequency of SRNS in our prospective study **(21%)** relative to the retrospective study **(6%)** was detected with (P=**0.000**). This rise in SRNS mostly is related to change in the frequency of the underlying histopathological types with increase in the rate of FSGS and decline in the rate of MCD. Also changes in the pattern of steroid response in patients with MCD have also occurred with increase in SRNS within them.

The rise in the rate of steroid resistance over years has also reported in other studies, as in Kim et al study, which was carried out over the period **(1994 to 2003)** in Korea, and demonstrated a tendency towards increasing rates of initial steroid resistance in childhood NS, compared with the results of International Study of Kidney Diseases in Childhood (ISKDC) report; **71%** in Kim et al. report versus **86%** in ISKDC report **(Kim et al, 2005).** Banaszak et al in Boland revealed increase in the frequency of steroid resistance in his Caucasian patients over years as it increased from 11.8% in the period (**1986-1995**) to **31.4%** in the period (**1996-2005**) associated with increased FSGS and MesPGN rates in the recent years **(Banaszak et al, 2012).**

In contrast to this, Nickavar et al, in Iran found a slight decrease in the rate of SRNS from **37.8%** in years (**1991-2002**) to **28.6%** in year (**2005-2012**). These findings were present inspite of insignificant increase in FSGS and

decline in MCD and MesPGN in recent years. This can be explained by significant impact of race and geographical distribution on clinical behaviour of INS **(Nickavar et al, 2014).**

Steroid resistance as an indication for renal biopsy increased from **27.8%** of biopsied cases in the retrospective study to **53.8%** of biopsied cases in the prospective study. This finding supported the concept of the significant increase in the steroid resistance in the prospective study.

In the present study, changes in the frequency of the various histopathological types over years were evident. There was increase in the frequency of FSGS and decrease in the frequency of MCD. Inspite of these changes no statistically significant differences between retrospective and prospective studies in the distribution of the various histopathological types was present **(P=0.227).** Many studies also documented the increasing frequency of focal segmental glomerulosclerosis in INS over years **(Felix et al, 1999, in USA; Kari, 2002 in Saudia Arabia; Bakr et al, 2014 in Lower Egypt).**

In conclusion the demographic features of INS in our locality were comparable to those worldwide with its predominance in young age and male sex. There was significant increase in the rate of steroid resistance within patients with INS associated with increase in the frequency of FSGS and increase in steroid resistance within those with MCD.

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