# Patterns of idiopathic nephrotic syndrome in Upper Egyptian children

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## Abstract

**Background and aim of work:** Idiopathic nephrotic syndrome (INS) is a common and important chronic kidney disease in childhood. Steroid response pattern and the underlying histopathological spectrum of INS show variabilities in the different geographical regions. This work aimed to highlight the clinical profile, steroid response pattern and histopathological spectrum of INS in our locality in Sohag, Upper Egypt.

**Patients and Methods:** A prospective study included 77 children with INS aged from 1-15 years followed for at least one year, diagnosed and treated at our pediatric nephrology unit in the period from January 2010 to December 2014 was done. The patients' demographic features, clinical profile, steroid response pattern and the underlying histopathological spectrum were studied.

**Results:** Total included patients were 77 children. The mean age at disease onset was 4.87±2.94 (range 1.5-15) years. Male/female ratio was 1.6/1. Steroid was given to all patients, 79.2% of patients had steroid sensitive nephrotic syndrome (SSNS), while 20.8% had steroid resistant nephrotic syndrome (SRNS). Out of 61 steroid sensitive patients, about 54% developed either steroid dependent nephrotic syndrome (SDNS) or frequently relapsing nephrotic syndrome (FRNS). Biopsy was done in 33.8% of patients and revealed focal segmental glomerulosclerosis (FSGS) in 42%, minimal change disease (MCD) in 39% and mesangio-proliferative glomerulonephritis (MesPGN) in 19% of patients. End stage renal disease (ESRD) developed in 1 patient with SRNS and FSGS.

**Conclusion:** About eighty percent of our patients were steroid sensitive but more than half of them had SDNS or FRNS. The main histopathological pattern seen in renal biopsies was FSGS.

**Key words:** Idiopathic nephrotic syndrome, steroid response and focal segmental glomerulosclerosis.

## Introduction

Nephrotic syndrome (NS) is one of the most common chronic renal diseases in children.[1] It has an incidence of **2-16.9** per **100.00** children worldwide[2]**.** Idiopathic nephrotic syndrome is the most common form of NS in childhood representing about **90%** of all cases and it is composed of NS and primary glomerular disease without an identifiable causative disease or infection.[3] Up to **85%–90%** of children with INS are steroid sensitive, but follow a relapsing and remitting course in the majority of cases.[4] About half of those who relapse, show frequently relapsing or steroid dependent course.[5] The underlying histopathological characteristics of INS are of immense significance in determining steroid responsiveness and long-term prognosis.[6] The majority of children with INS have MCD which is generally responsive to steroid, so

renal biopsy is indicated in patients suspected to have histological types other than MCD.[7] Idiopathic nephrotic syndrome shows differences in its steroid response pattern and histopathological spectrum in the various geographical regions.[8-16] Therefore, this work was designed to study the clinical profile, steroid response pattern and the underlying histopathological spectrum in children with INS at our locality in Upper Egypt. Sohag City is about **500** Km South to Cairo city and Sohag University Hospital is a referral hospital serves patients from all Upper Egypt Governorates.

**Patients and methods**

This prospective study involved **77** patients with new onset INS aged **1-15** years diagnosed and followed in our paediatric nephrology unit, Sohag University Hospital in the period from Jan **2010** to Dec **2014.** Patients with less than one year follow up period or with incomplete data 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.[17,18] 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**.**[18,19]

The patients were divided into **3** age groups: preschool age (**1-6** years), school age **(6-12** years) and adolescence (**12-15).** Steroid (prednisone) was given to all patients in a dose of **2**mg/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.[17,20] 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). [17,20,21]

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 C**3**) and following therapy initiation for patients with initial or late SRNS and those with SDNS or FRNS before treatment with cyclosporine A (CsA).[17,19,22] Informed written consent was taken from the parents before the procedure and the specimens were examined by the same pathologist using light microscopy.

Statistical package for the social sciences (SPSS) version **16** was used

for data analysis. Quantitative variables were presented as mean ± standard deviation. Frequency and percentage were used for qualitative variables. For estimation of differences between qualitative variables, Chi-square and Fisher Exact Test were used. ***P*** values less than **0.05** were considered significant.

This study was approved by the ethical committee of Sohag University

## Results

The total studied patients were **77 (47** males and **30** females) with male/female ratio **1.6/1.** Mean age of patients at disease onset was **4.87±2.94** (range **1.5-15**) years, with peak incidence at **1-6** years representing **71.4%** of total patients. The mean follow up duration was **2.30±1.15** (range **1-5)** years. Initial hematuria was detected in **20 (26%)** patients with gross hematuria in **2 (2.6%)** patients and microscopic hematuria in **18 (23.4%)** patients. Initial hypertension was found in **14 (18.2%)** patients. Initial renal impairment was present in **2 (2.6%)** patients which improved later on. Steroid therapy was given to all patients, of whom, **61 (79.2%)** achieved remission and **16 (20.8%)** were steroid resistant **(table 1).**

**Table (1): Steroid response pattern and its relation to age, sex, initial hematuria and initial hypertension in studied patients**

| | Steroid response | | | | | | |
|---|---|---|---|---|---|---|---|
| | Steroid sensitive | | Steroid resistant | | P-value | Total | |
| Variables | No | % | No | % | | No | % |
| Frequency | 61 | 79.2% | 16 | 20.8% | | 77 | 100% |
| Age groups | | | | | | | |
| 1-6 years | 41 | 74.5% | 14 | 25.5% | | 55 | 71.4% |
| 6-12 years | 19 | 100% | 0 | 0 | | 19 | 24.7% |
| 12-15 year | 1 | 33.3% | 2 | 66.7% | | 3 | 3.9% |
| Sex | | | | | 0.893 | | |
| Males | 37 | 78.7% | 10 | 21.3% | | 47 | 61% |
| Females | 24 | 80% | 6 | 20% | | 30 | 39% |
| Hematuria | 12 | 19.7% | 8 | 50% | 0.019 | 20 | 26% |
| Hypertension | 5 | 8.2% | 9 | 56.2% | 0.000 | 14 | 18.2% |

Out of **61** steroid sensitive patients, **5 (8.2%)** had no or only one relapse, **21 (34.4%)** had infrequently relapsing nephrotic syndrome (IRNS), **27 (44.3%)** developed SDNS, **6 (9.8%)** developed FRNS and **2 (3.3%)** developed late SRNS.

Renal biopsy was done in **26 (33.8%)** patients. The indications for biopsy were: initial SRNS in **14 (53.8%)** patients, SDNS and FRNS before CsA use in **4 (15.4%),** late SRNS in **2 (7.7%)** and initial atypical presentation in **6 (23.1%)** patients. The main histopathological type was FSGS (figure **1**). The relations of histopathology with the patients' clinical profile and steroid response are shown in table **(2).**

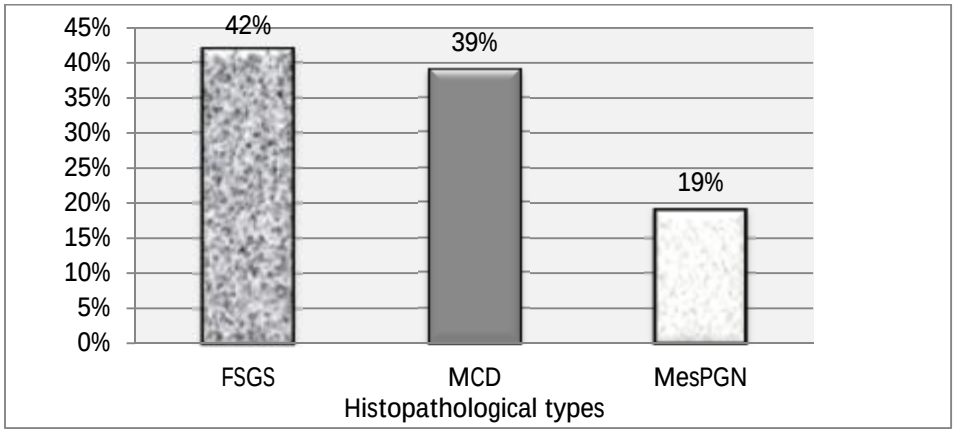


**Figure (1): Histopathological spectrum of biopsied patients (FSGS, focal segmental glomerulosclerosis; MCD, minimal change disease; MesPGN, mesangioproliferative glomerulonephritis)**

By the end of the study, persistent proteinuria (no or partial remission) was present in **10 (13%)** patients (**7** with FSGS and **3** with MCD). One **(1.3%)** patient with FSGS and multi-drug resistance developed ESRD. Death occurred in **2 (2.6%)** patients (one with MCD and the other with FSGS), both were difficult multi-drug resistant cases. The causes of death were sepsis and ESRD.

**Table (2): Histopathology in relation to clinical profile and steroid response**

| | Histopathology | | | | | | |
|---|---|---|---|---|---|---|---|
| | FSGS | | MCD | | MesPGN | | Total |
| Variables | No | % | No | % | No | % | |
| Frequency | 11 | 42% | 10 | 39% | 5 | 19% | 26 |
| Age groups | | | | | | | |
| 1-6 years | 8 | 45% | 6 | 33% | 4 | 22% | 18 |
| 6-12 years | 1 | 16% | 4 | 68% | 1 | 16% | 6 |
| 12-15 year | 2 | 100% | 0 | 0 | 0 | 0 | 2 |
| Sex | | | | | | | |
| Males | 5 | 33% | 7 | 47% | 3 | 20% | 15 |
| Females | 6 | 55% | 3 | 27% | 2 | 18% | 11 |
| Hematuria | 7 | 45% | 4 | 40% | 4 | 80% | 15 |
| Gross | 1 | 9% | 0 | 0 | 1 | 20% | 2 |
| Microscopic | 4 | 36% | 4 | 40% | 3 | 60% | 13 |
| Hypertension | 8 | 73% | 1 | 10% | 2 | 40% | 11 |
| Renal impairment | 2 | 18% | 0 | 0 | 0 | 0 | 2 |
| Steroid resistance | 9 | 82% | 4 | 40% | 3 | 60% | 16 |
| Persistent proteinuria | 7 | 64% | 3 | 30% | 0 | 0 | 10 |

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

## Discussion

Idiopathic nephrotic syndrome was most commonly seen in children **1-6** years old representing **71.4%** of patients, with male predominance in agreement with most previous studies as in Egypt[8], Iran[13] and New Zealand.[15] Steroid was given to all included patients, with **79.2%** achieved remission while **20.8%** were steroid resistant (SR). Kaddah et al. in Cairo, Egypt showed that **34%** of their patients had SRNS, which was explained by high consanguinity according to the authors' explanation.[8] In addition to this Kaddah et al. study revealed higher rate of MesPGN than ours. Lower steroid resistance was encountered in Yemen **(7.1%).**[12] Near results were encountered in Saudia Arabia **(21.4%),** Turkey **(18%)** and New Zealand (**19.6%).**[10,14,15] Higher results were detected in Iran **(24.8%),** Brazil **(29.9%)** and Japan **(36%).**[13,23,24] The underlying renal histology in addition to ethnicity and geographic location have important impact on the likelihood of steroid response in INS.[25] Variation in the definitions of SRNS and the involved age groups in the different centers also affect the results of various studies. About **54%** of the steroid sensitive patients developed either SDNS or FRNS in this study. Lower results were encountered in Iraq (**43.7%).**[11] Near results were reported in Denmark **(56%)** and New Zealand **(56.7%).**[26,15] Higher results were seen in Saudia Arabia **(62%)** and France **(68%).**[10,27]

Renal biopsy was indicated mainly for initial and late SRNS **(61.5%)** in this work. This was in agreement with Kaddah et al. in Cairo, Bakr et al. in Almansoura, Mortazavi et al. in Iran and Arif et al. in India as steroid resistance was the main indication for renal biopsy in their studies.[8,9,13,28] The main histopathological type in our biopsied patients was FSGS in **42%,** followed by MCD in **39%** and MesPGN in **19%** of patients. Differences between our study and other studies in distribution of histopathological types are shown in table **(3)**

**Table (3): Histopathological spectrum in the various studies**

| | Histopathological patterns | | | | | |
|---|---|---|---|---|---|---|
| **Studies** | **MCD** | **FSGS** | **MesPGN** | **MPGN** | **MN** | **Others** |
| **Our study (Upper Egypt)** | **39%** | **42%** | **19%** | **0** | **0** | **0** |
| **Kaddah et al, 2011[8] (Lower Egypt)** | **35%** | **30%** | **37%** | **0** | **3%** | **0** |
| **Bakr et al, 2014[9] (Lower Egypt)** | **54.3%** | **16.2%** | **23.7%** | **5.3%** | **0.5** | **0** |
| **Kari, 2002[29] (Saudia Arabia)** | **15%** | **35%** | **20%** | **30%** | **0** | **0** |
| **Asinobi et al, 2015[30] (Nigeria)** | **19%** | **47.6%** | **0** | **19%** | **0** | **14.4%** |
| **Mortazavi et al, 2011[13] (Iran)** | **40.8%** | **32.7%** | **26.5%** | **0** | **0** | **0** |
| **Mubarak et al, 2009[31] (Pakistan)** | **43.8%** | **38.1%** | **4.8%** | **3.1%** | **7.9%** | **1.5%** |
| **Arif et al, 2016 [28] (India)** | **25%** | **46.8%** | **5.3%** | **5.3%** | **14.7%** | **2.6%** |
| **Zhou et al, 2014[16] (China)** | **11.5%** | **16.5%** | **48.2%** | **4.6%** | **3.6%** | **15.6%** |

**MCD**, minimal change disease; **FSGS**, focal segmental glomerulosclerosis; **MesPGN**, mesangio-proliferative glomerulonephritis**;** **MPGN,** membranoproliferative glomerulo-nephritis; **MN,** membranous nephropathy

The noticed variations in the histopathological results among and the studies were not done in the same time periods.

In conclusion the demographic features of INS in our locality were comparable to those worldwide with its predominance in young age and male sex. Inspite of high response rate in INS more than half of steroid sensitive patients developed steroid dependent or frequently relapsing course. Steroid resistance was the main indication for renal biopsy and FSGS was the most prominent histopathological type in our biopsied patients.

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