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Histopathological Characteristics of Pediatric Steroid-Resistant Nephrotic Syndrome in Sudan: A Single-Center Retrospective Study

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ABSTRACT

Background: Steroid-resistant nephrotic syndrome (SRNS) in childhood is a significant therapeutic challenge and represents a high-risk factor for advancing towards end-stage renal disease (ESRD). Renal biopsy is necessary to define the exact histopathological type, which would direct subsequent therapy. Therefore, this study aimed to investigate histological patterns and correlations between these patterns and clinical presentations and therapeutic outcomes in Sudanese children with SRNS. *Methods:* This is a retrospective study of 62 children with SRNS seen at the Pediatric Nephrology Unit of Soba University Hospital, Sudan, from July 2017 to September 2021. All patients have undergone ultrasound-guided percutaneous renal biopsy. Demographic data, clinical presentation, histological findings, treatment modalities, and therapeutic outcome were collected. *Results:* There was a male preponderance (69.4%), with a mean age of 10.96 ± 4.82 years. Generalized edema and hypertension were the most common presentations (95.2% and 69.4%, respectively). Among the different histopathological types noted, there were FSGS (43.5%) and MCD (28.5%) of the cases. Around 8% of the studied sample had a positive family history. The most common treatments used were angiotensin-converting enzyme inhibitors (ACEIs) and calcineurin inhibitors in 89% and 79% of the patients, respectively. Around 82% of the patients had sustained remission, and 14.5% developed ESRD. *Conclusion*: Among the SRNS-studied cases, various histopathological features were observed, with FSGS being the most common. Although most children were well-responsive to calcineurin inhibitors, the chance of progressing to ESRD remains high, which highlights the need for prompt renal biopsy and the significance of genetic testing in these cases.

Keywords: Steroid-Resistant Nephrotic Syndrome, Focal Segmental Glomerulosclerosis, Pediatric Nephrology, Renal Biopsy, Calcineurin Inhibitors, Sudan.

1. INTRODUCTION

Idiopathic nephrotic syndrome (NS) is among the commonest glomerulopathies in children that features massive proteinuria (greater than 40 mg/m²/hr),

hypoalbuminemia, edema, and hyperlipidemia (Noone et al., 2018). Even though the vast majority of idiopathic NS cases can be managed using corticosteroids, about 10-20% are resistant to such treatment and, therefore, considered as steroid-resistant nephrotic syndrome (SRNS), which entails lack of remission following four to eight weeks' treatment with 60 mg/m²/day of prednisolone (Trautmann et al., 2020; Roy et al., 2023). Patients suffering from SRNS exhibit a high tendency to develop end-stage renal disease (ESRD) that complicates their management process considerably (Nourbakhsh and Mak, 2017).

Histopathology appears to play an important role in the outcome and treatment responses (Kirpekar et al., 2002; Gulati et al., 2006). Common idiopathic NS histopathological types include MCD, FSGS, MPGN, and mesangial proliferative glomerulonephritis (Lombel et al., 2013). During recent years, FSGS has become the leading cause of SRNS in the world and exceeded MCD as the most common lesion in many populations (Mubarak et al., 2012). The treatment of patients with SRNS usually starts with corticosteroids and involves other immunosuppressive agents, including calcineurin inhibitors (cyclosporine and tacrolimus) and mycophenolate mofetil (Trautmann et al., 2020). ACE inhibitors represent the main add-on medication for blood pressure and proteinuria reduction (Trautmann et al., 2020; Kashif et al., 2022).

Very few epidemiological and histopathological data concerning SRNS in Sub-Saharan Africa, including Sudan, are available. This research aims to identify histopathological features of SRNS in a sample of Sudanese children, as well as assess the relationship between the former and clinical characteristics of the disease and management options.

2. METHODS

Study Design, Setting, and Population

The current study utilized an observational, retrospective study design and was conducted at the Pediatric Nephrology Unit of Soba University Hospital, which is located in Khartoum, Sudan. The population of this study was all SRNS children who underwent a percutaneous renal biopsy during the period (July 2017 - September 2021). SRNS was conceptually defined as “persistent proteinuria after a minimum of four weeks of daily prednisolone therapy at 60 mg/m²/day”.

Inclusion and Exclusion Criteria

The inclusion criteria for patients were having SRNS, having available information on renal biopsy, having full information related to both clinical and laboratory findings, and having been followed for at least six months. The exclusion criteria were if any patient had other diseases that cause nephrotic syndrome (lupus nephritis, hepatitis B/C-nephropathy), or immunosuppressive treatment before hospital admission. Based on these criteria, 62 children were included in the research.

Data Collection tool

A comprehensive, structured checklist was used to collect the data from the medical files of SRNS children. The researchers developed this checklist to meet the study’s objectives and then validated it before use, which contained sociodemographic data, clinical presentation, family history, treatment regimens, histological findings, and clinical outcomes.

Statistical Analysis

The collected data were coded and then analyzed using SPSS Statistics software version 25.0 (IBM Corp., Armonk, NY, USA). For categorical data analysis, descriptive statistics are reported using frequencies and percentages and are illustrated through tables and graphs.

Ethical Considerations

This research study was carried out in accordance with the principles of ethics described in the Declaration of Helsinki of 1975. The approval of the Institutional Review Boards of SMSB and the Ethics Committee of the Soba University Hospital was sought before starting the study. All subjects participated voluntarily, and informed consent was taken from the parents or guardians of all subjects participating in the study.

3. RESULTS

Demographic and Clinical Characteristics

Sixty-two children who were diagnosed with SRNS were evaluated. There was a higher proportion of males, accounting for 69.4% of the sample size, resulting in a sex ratio of 2:1. The average age was 10.96 ± 4.82 years. The age group 5-10 years accounted for 37.1% of the total population (Table 1).

Table 1. Demographic Characteristics of the Study Population (n=62)

Characteristic	Frequency (n)	Percentage (%)
Age Group (years)		
1 - 5	6	9.7
5 - 10	23	37.1
11 - 15	17	27.4
16 - 18	16	25.8
Gender		
Male	43	69.4
Female	19	30.6
Family History of Nephrotic Syndrome		
Yes	5	8.1
No	57	91.1

At the time of diagnosis, generalized edema was found the most common presentation in 95.2% of cases. Hypertension was considered as the second common symptom in 69.4% of patients. Other presenting symptoms included arthralgia, skin rash, and oliguria.

Histopathological Findings

From Figure 1, it can be deduced that the most common histopathological lesion was FSGS, occurring in 43.5% of patients (n = 27). The second most common lesion was MCD in 28.5% of patients (n = 18), while DMP was seen in 16.1% (n = 10) of patients and MPGN in 11.3% (n = 7) of the participants.

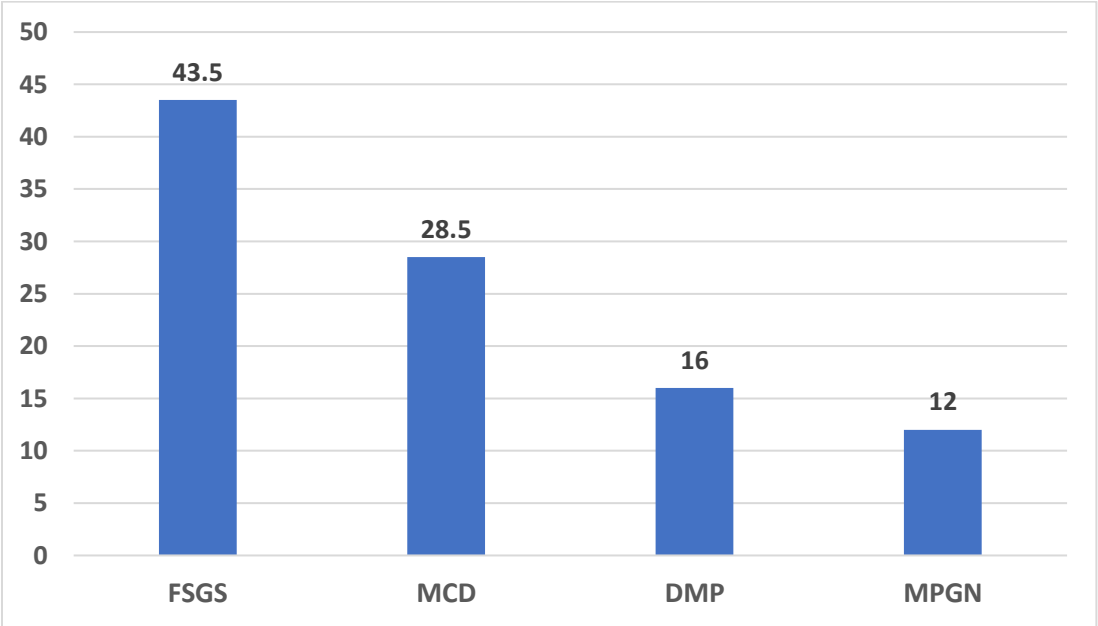

Figure 1. Distribution of NS pediatric patients according to histological subtypes (n= 62)

Treatment and Response

According to Figure 2, the most common medication used was ACEIs (Lisinopril) for its antiproteinuric and antihypertensive properties, used in 89% of the total population. Among the immunosuppressants, calcineurin inhibitors (cyclosporine) were the most commonly administered drugs, used in 79% of patients. Mycophenolate mofetil was another common drug. Cyclosporine showed a favorable response in 82% of patients, either resulting in full or partial remission.

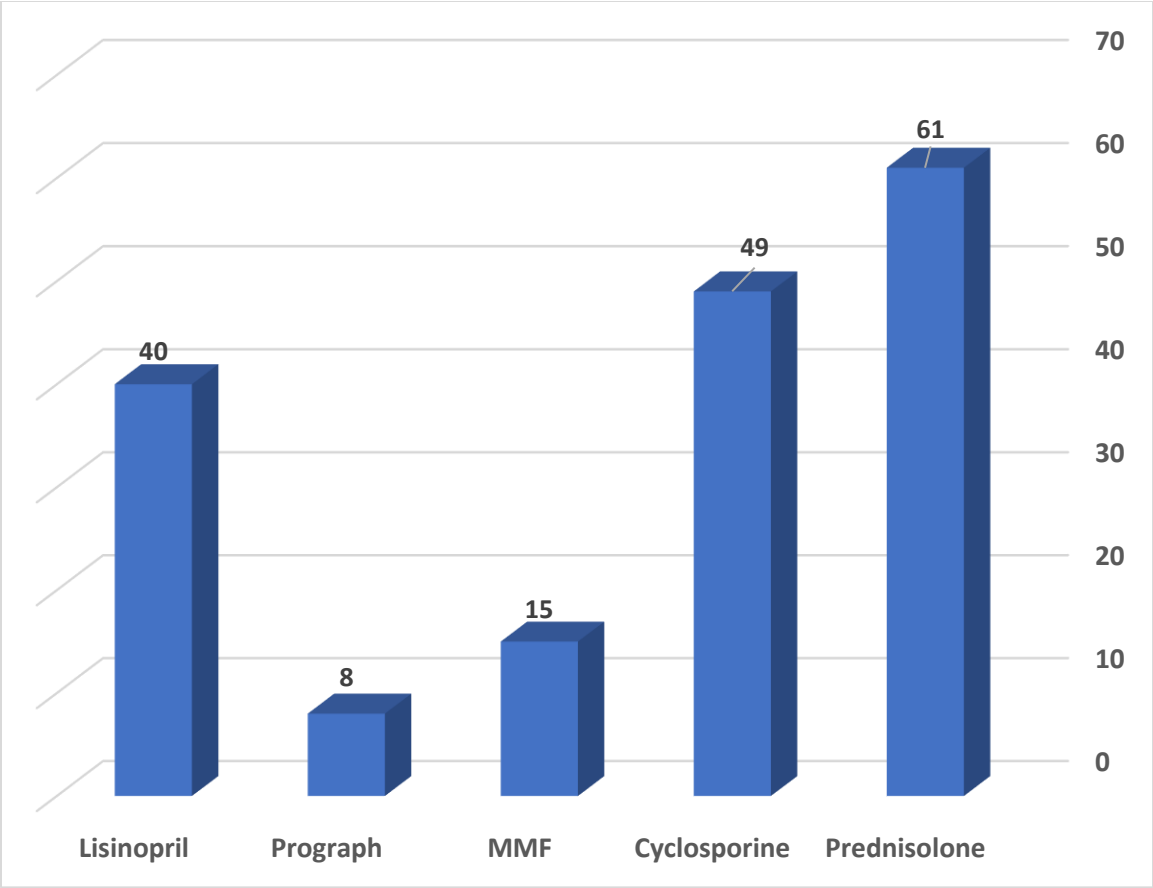

Figure 2. Treatment Patterns in Steroid-Resistant Nephrotic Syndrome (SRNS)

Prognosis and Outcomes

Out of the 62 children studied, there were 51 (82.2%) who showed a favorable outcome, which was sustained remission and no signs of ESRD progression. Nine patients developed ESRD, representing 14.5% of the total population, while two patients had undergone kidney transplants, representing 3.2%.

4. DISCUSSION

The findings of the current study significantly contributed to understanding the clinical and pathological presentations of SRNS in Sudanese pediatric patients. We found the prevalence of FSGS was 43.5%, which is in line with international data, whereby FSGS is the most prevalent histological association for SRNS, surpassing MCD (Mubarak et al., 2012; Kashif et al., 2022). Many factors may contribute to the high FSGS incidence, including genetic factors, environmental triggers, or delayed diagnosis because of inadequate and limited nephrology facilities in the region (Borham, 2021; Esezobor et al., 2021).

The male preponderance (69.4% of the sample) is higher than the ratio found in Indian, Egyptian, Sudanese, and Nigerian research, where ratios of males to females have usually been between 1.2:1 and 1.8:1 (Kashif et al., 2022; Borham, 2021; Naim et al., 2024; Ibeneme et al., 2021). The average age at diagnosis (10.96 years) and prevalence among the 5-10 year-old children agree with previous results obtained in other African populations, suggesting that SRNS predominantly occurs in late childhood in low- and middle-income countries (Trautmann et al., 2015; Niaudet and Boyer, 2016).

In the current study, there is a positive family history among 8% of patients, pointing to possible genetic causes of SRNS in this community. NPHS1, NPHS2, WT1, and PLCE1 are known mutations causing early-onset and familial SRNS (Trautmann et al., 2020; Saeed, 2020). The lack of any genetic analysis performed shows an evident limitation and suggests conducting genetic screening programs in Sudan to facilitate tailored treatment and avoid excessive immunosuppressive measures.

Furthermore, the response to treatment seen here can be associated with histopathology. The success rate of 82% with cyclosporine use is promising and correlates with the success rate of other studies conducted in India and Egypt at 80% (Kashif et al., 2022; Borham, 2021). These results confirm KDIGO guidelines advocating the use of calcineurin inhibitors as the first-line medication for SRNS after failure of steroids (Lombel et al., 2013).

There are several limitations to this study. First, its retrospective design and single-center involvement make the research findings non-generalizable and prone to selection biases. Secondly, since there was no genetic analysis, it was impossible to distinguish between primary and hereditary types of SRNS. Moreover, the study lacks information regarding socioeconomic status and its impact on access to healthcare services. Still, there are some strengths in this research: first, it was the first Sudanese study to evaluate histopathological pattern types of SRNS in children, secondly, all the cases were biopsy proven, and thirdly, this study utilized interdisciplinary approach with the input from nephrology and pathology specialists.

5. CONCLUSION

It was established that SRNS among Sudanese children showed varied histopathological presentations, with FSGS being the most common abnormality. While most of the subjects responded to the short remission therapy with calcineurin inhibitors, there was still a significant number who developed ESRD. This calls for an urgent kidney biopsy at diagnosis to determine the course of treatment and for further research into the genetics and immunology of SRNS.

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Authors' Contributions

Nahla Allam, Fatima Ali and Eltigani M. A. Ali: study concept or design, project administration, literature review, data collection, data analysis or interpretation, writing the paper. Yasir Mahgoup and Rasha Hussain: data collection and data analysis and interpretation, revision of the paper. Bashir A. Yousef: literature review, visualization, writing the paper. All authors were involved in manuscript drafting and revising and reviewed and approved the final version.

Informed consent

Written informed consent was obtained from all the guardians of participants before enrollment.

Ethical approval

The study was done in conformity with ethical guidelines. Participation was entirely voluntary, and all respondents provided informed consent. The participants' anonymity and confidentiality were ensured, and the data obtained were utilized purely for the study. The ethical guidelines for Human Subjects are followed in the study. Ethical approval was obtained from the Institutional Review Boards of the Sudan Medical Specialization Board (SMSB) and the Soba University Hospital Ethics Committee.

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Conflict of interest

The authors declare that they have no conflicts of interest, competing financial interests or personal relationships that could have influenced the work reported in this paper.

Data and materials availability

All data associated with this study will be available based on the reasonable request to corresponding author.

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