

Changing Histopathological Trends in Idiopathic Steroid Resistant Nephrotic Syndrome in Pediatric Population

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Author's Contribution

¹Substantial contributions to the conception and design of the work.

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⁵Active participation in statistical interpretation and analysis.

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ABSTRACT

Objective: To determine the most prevalent histopathological subtypes of nephrotic syndrome in children and assess the response to corticosteroids therapy in different histological patterns.

Methodology: A cross-sectional analysis of 64 patients was conducted from February 2018 to June 2019 at the Pakistan Institute of Medical Sciences Hospital (PIMS), Islamabad. Patients were clinically assessed and investigated using criteria determined by the International Study of Kidney Disease in Children (ISKDC). Renal biopsies were performed where indicated and samples were examined with the help of light microscopy and immunofluorescence. IBM SPSS 24 and Excel 2010 were used for data interpretation and illustration.

Results: The study comprised of 64 patients including 32 (50%) females and 32 (50%) males, ranging from 2 to 12 years, with a mean age of 6.78 years. The results showed Minimal change disease (MCD) (28.13%) and Focal segmental Glomerulosclerosis (FSGS) (28.13%) as the most common pattern on histopathology, followed by Membranoproliferative glomerulonephritis (MPGN) (15.63%), Mesangioproliferative Glomerulonephritis (MesPGN) (9.38%), Membranous glomerulonephritis (MGN) (9.38%), Diffuse Proliferative glomerulonephritis (DGN) (3.13%), Lupus Nephritis (LN) (3.13%) and IgM nephropathy (IgMN) (3.13%). 87.5% of children were observed to be resistant to corticosteroid therapy while the remaining 12.5% of patients responded to corticosteroid treatment.

Conclusion: Resistance to corticosteroids has become more prevalent in all variants of nephrotic syndrome in children. FSGS and Minimal change disease are the most frequently seen histopathological patterns observed in the pediatric population of Pakistan, having Steroid resistant nephrotic syndrome (SRNS). Furthermore, an increase in the frequency of FSGS was observed in our population, in comparison to prior studies.

Keywords: Steroid-resistant nephrotic syndrome, focal segmental Glomerulosclerosis,

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Introduction

Renal diseases, according to the WHO bulletin, are one of the most ignored diseases worldwide and lead to an

estimated 5-10 million deaths each year.¹ Renal diseases affect all age groups, where the background etiology is variable but the outcome almost always has long term

and devastating consequences in the form of morbidity, mortality and disability.

Nephrotic syndrome is the most frequently encountered glomerular disease in children². Pediatric nephrotic syndrome is characterized by proteinuria of more than 40mg/m²/hour associated with edema, hyperlipidemia and hypoalbuminemia.³ Amongst children the incidence of idiopathic nephrotic syndrome is estimated to be around 1.15-16.9 per 100,000 children.⁴

According to a study conducted by the International Study of Kidney Disease in Children (ISKDC), the prevalence of minimal change (MCNS) was 77.1%, whereas focal segmental Glomerulosclerosis (FSGS) and membranoproliferative glomerulonephritis contributed 7.9% and 6.2% respectively.⁵ 80% cases of pediatric nephrotic syndrome respond to corticosteroid therapy and are hence classified as 'Steroid Sensitive', whereas the remaining are deemed to be 'Steroid Resistant'.⁶ Amongst the patients who have steroid sensitive nephrotic syndrome (SSNS), 60-70% usually have more than 1 relapse out of which more than 30% of patients suffer frequent relapses.⁷

Steroid resistant nephrotic syndrome (SRNS) is defined as proteinuria unresponsive to 4 weeks of therapy with prednisone 2mg/kg/day², followed by 3 doses of methylprednisolone⁸. The management of steroid resistant nephrotic syndrome has proven to be rather challenging, with around 50% cases leading to End stage renal disease (ESRD, within a decade).⁹ Apart from the use of corticosteroids, alternative treatments which are being employed, include the use cyclophosphamide, mycophenolic acid, calcineurin inhibitors and more recently monoclonal antibodies such as Rituximab.⁸

The present study purports to look into the histopathological trends of idiopathic nephrotic syndrome present in the pediatric population of Pakistan and focuses on assessing the role of corticosteroids as part of treatment therapy for idiopathic nephrotic syndrome. Furthermore, the study intends to compare the histopathological trends of idiopathic nephrotic syndrome and their prevalence within global pediatric population.

Methodology

This is a cross-sectional study, which was conducted from February 2018 to June 2019 at Pakistan Institute of Medical Sciences Hospital (PIMS), Islamabad. A total of 64 patients became a part of this study, ranging from 2 to

12 years of age, with a mean age of 6.78 years. These patients came from varying socioeconomic backgrounds and mostly arrived at the outpatient department from referral by primary health care settings. Patients were selected by Consecutive sampling with predetermined exclusion and inclusion criteria. Keeping in mind that Nephrotic syndrome is a rare condition, and based on our limitations of time and resources, we selected all possible consenting candidates who fulfilled our inclusion criteria hence a statistical sample size was not used in this regard. The study received approval from relevant institutional ethical review board, prior to being carried out.

The study excluded patients with underlying congenital causes for nephrotic syndrome, as well as those patients who were seropositive for hepatitis B surface antigen (HBsAg), Anti-HCV and HIV. Patients exceeding the age of 16 were also excluded from the study.

Patients were initially evaluated as per specified criteria before being included in the study. Their demographic, clinical and investigation data was collected. Criteria established by the International Study of Kidney Disease in Children (ISKDC) was used for determining diagnosis of nephrotic syndrome. Only cases which satisfied the said criteria, were included. Steroid resistance was labeled when the patient was unresponsive to 4 weeks of therapy with prednisone 2mg/kg/day, followed by 3 doses of methylprednisolone.

Renal Biopsy was performed where indicated, with an automated biopsy gun with real-time ultrasound guidance. The Biopsies were performed and examined by qualified and experienced pathologists. Informed consent was taken prior to performing the biopsy. Two specimens were obtained from renal biopsy for histopathological evaluation. One core was processed in 10% buffered formalin and sent for light microscopy (LM), whereas the other core was received in Michel's medium and sent for immunofluorescence (IF).

The sample for LM was stained with haematoxylin and eosin to observe the presence of cortical tissue. The sample was considered adequate if a minimum of 7 Glomeruli were present. The mean number of glomeruli per biopsy observed in our study was 9. The specimen for IF was stained by fluorescein isothiocyanate (FITC) conjugated antisera specific for IgM, IgA, IgG, C1q and C3.

Clinical, laboratory and histopathological findings were correlated, after which a definitive diagnosis was

established. IBM SPSS 24 and Excel 2010 were used for data interpretation and illustration. Because this is a descriptive study, having very simple objectives, the data analysis only involved descriptive statistics, which included percentages, proportions and frequencies.

Results

The present study comprised of a total of 64 patients, including 32 (50%) females and 32 (50%) males, ranging from 2 to 12 years of age (Figure 1). The mean age was 6.78 years with a standard deviation of ± 3.27 . Table 1 depicts the demographic characteristics of the pediatric population along with the histopathological subtypes.

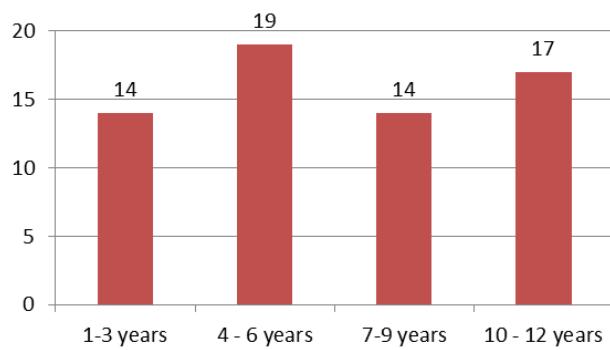


Figure 1: Frequency of Different Age Groups.

Our study indicated that Minimal change disease (MCD) and Focal segmental Glomerulosclerosis (FSGS) were the most frequently observed histopathological subtypes, each presenting in 18 out of 64 (28.13%) patients. Membranoproliferative glomerulonephritis (MPGN) is the third most frequently occurring subtype present in 10 out of 64 children (15.63%) followed by Mesangioproliferative glomerulonephritis (MesPGN) and Membranous glomerulonephritis (MGN), each appearing in 6 out of 64 (9.38%) cases. Diffuse Proliferative glomerulonephritis (DPGN), Lupus Nephritis (LN), IgM nephropathy (IgMN) had the least number of cases, with each representing 2 out of 64 (3.13%) cases of the total population sample. Male to female ratio for each histopathological trend can be seen in Table I.

Amongst the 64 children involved in the study, 56 (87.5%) were observed to be resistant to corticosteroid therapy, whereas, the rest of the 8 (12.5%) patients responded to corticosteroid treatment. Of these steroid sensitive children, 4 (6.25%) pertained to the FSGS

subtype, whereas, the other 4 (6.25%) belonged to the Minimal change disease pattern of nephrotic syndrome. Figure 2 depicts response to steroid treatment along with histopathological patterns and gender distribution.

Table 1: Male to female ratio, with respect to Histopathological Subtypes.

Final Diagnosis	Male	Female	Ratio	%
FSGS	12	6	2:1	28.13
Minimal Change disease	10	8	5:4	28.13
MPGN	6	4	3:2	15.63
Mesangioproliferative GN	0	6	0:1	9.38
Membranous GN	0	6	0:1	9.38
Diffuse proliferative GN	2	0	1:0	3.13
Lupus Nephritis	0	2	0:1	3.13
IgM Nephropathy	2	0	1:0	3.13
Total	32	32	1:1	

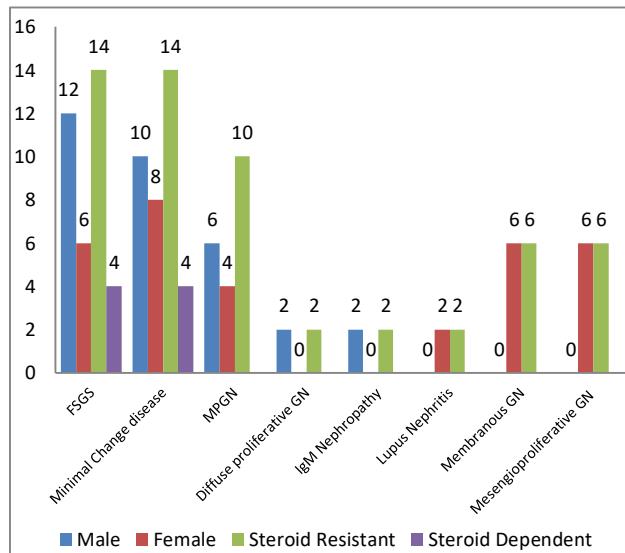


Figure 2: Types of Nephrotic Syndrome with Respect to Gender and Steroid Resistance

Discussion

Histopathological patterns of nephrotic syndrome are of substantial importance when it comes to determining the role of corticosteroids as part of treatment regimen and the prognosis of the disease in the long run.¹⁰ Earlier research indicates an increase in Steroid resistance in pediatric population with nephrotic syndrome.¹¹ The treatment of Steroid resistant nephrotic syndrome (SRNS)

is a challenging feat, considering the alternatives to Corticosteroids including alkylating agents (cyclophosphamide) and calcineurin inhibitors (cyclosporine A), carry the risk of nephrotoxicity.^{12 13} Patients with SRNS have 34-64% chance of developing End stage renal disease (ESRD), within a decade.^{9 14 15}

We studied and analyzed the data of 64 children; the results of our work are more or less consistent with what has been previously observed in the literature. Our study concluded that Steroid resistance was present in 87.5% cases reported to our center. Minimal change disease (28.13%) and FSGS (28.13%) were the most predominant histopathological subtypes on renal biopsy. This corroborates the study by KN Moorani¹⁶ (MCD 32.20%, FSGS 29.66%) and Lanewala A¹⁷ (MCD 29.4%, FSGS 21.8%) which concluded that Minimal change disease and FSGS were the most frequently observed histopathological trends, however, unlike our study, which shows an equal incidence of both subtypes, their study indicates a greater incidence for minimal change disease, as compared to FSGS. The same has been observed by Seif EI¹⁸ (MCD 24.5%, FSGS 30.2%) and Mubarak M¹⁹ (MCD 23.1%, FSGS 38.7%), their study also determined Minimal change disease and FSGS, as the most common patterns, however, they showed a greater incidence for FSGS than minimal change disease. MPGN (15.63%) is observed as the third most common diagnosis in our research, followed by Mesangiproliferative Glomerulonephritis (9.38%) which is consistent with the findings of Kumar J²⁰, which show MPGN (15%) and MesPGN (11%), as the most prevalent diagnosis on the histopathology spectrum after FSGS and Minimal change disease. However, in contrast to our work, Shah SS²¹, in their study described MesPGN (82.3%) as the most recurring pattern observed on histopathology, followed by FSGS and Minimal change disease respectively.

Studies conducted in Sri Lanka²², India^{18 23}, Saudi Arabia²⁴ and Tunisia²⁵ showed a higher frequency of FSGS, as opposed to studies which took place in France⁹ and Japan²⁶, which reported a greater number of cases pertaining to Minimal change disease.

Gender distribution for our data showed an equal ratio for males and females, however in FSGS and Minimal change disease, which are the most frequent patterns, male to female ratio is 2:1 (18.75% vs 9.38%) and 5:4 (15.62% vs 12.5%) respectively. Hence it is evident that FSGS and minimal change disease patterns of

nephrotic syndrome are more prevalent in males as compared to females. These results concur with the study carried out by Kumar J¹⁸.

The rationale behind the high variance amongst different studies, is not very well understood, but maybe linked to ethnical, environmental and hereditary variations. Another reason could be lack of appropriate investigative tools relevant to the study such as electron microscopy at several study centers, leading to less accurate diagnosis. Moreover, early FSGS, in contrast, to Minimal change disease and MPGN is more likely to go undetected, unless multiple sections are examined very thoroughly¹⁷ and since the skill set and experience of the individuals carrying out these studies differ, hence, it is more likely to produce variable outcomes.

Conclusion

We conclude that resistance to corticosteroids has become more prevalent in all variants of nephrotic syndrome in children. FSGS and minimal change disease are the most frequently seen histopathological patterns observed in the pediatric population of Pakistan, having Steroid resistant nephrotic syndrome (SRNS). Furthermore, an increase in the frequency of FSGS was observed in our population, in comparison to prior studies.

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