ORIGINAL ARTICLE

HISTOPATHOLOGICAL PATTERNS IN PAEDIATRIC IDIOPATHIC STEROID RESISTANT NEPHROTIC SYNDROME

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Background: Steroid-resistant nephrotic syndrome (SRNS) is a common problem but difficult to treat for pediatric nephrologists. Due to paucity of studies done in few centres in southern Pakistan regarding the histopathological aspects in paediatric patients with SRNS, this study was conducted to determine the histopathological spectrum in children with SRNS at our centre. **Methods:** This descriptive study has been conducted at the Nephrology department, The Children's Hospital Lahore from February 2014 to January 2015. Based upon history, physical examination and laboratory results, all patients diagnosed as idiopathic SRNS were included in the study and renal biopsy was done to determine the underlying pathology. Histopathology reports were retrieved and data analysis done using SPSS-20.0. **Results:** There were a total of 96 patients, 64 (66.7%) males and 32 (33.3%) females. The age range was from 0.80 to 15 years with mean age of presentation being 6.34+3.75 years. The most common histo-pathological pattern was mesangio-proliferative Glomerulonephritis found in 79 (82.3%) cases followed by Focal segmental glomerulosclerosis (FSGS) in 9 (9.4%) patients while Minimal change disease (MCD) was seen in 5 (5.2%) subjects. **Conclusion:** Mesangioproliferative glomerulonephritis is the most common histological pattern seen in children presenting with idiopathic SRNS at our centre followed by FSGS and MCD.

Keywords: Histopathology, Renal Biopsy, Mesangio-proliferative Glomerulonephritis, Focal Segmental Glomerulosclerosis, Minimal Change Disease.

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INTRODUCTION

Childhood nephrotic syndrome (NS) is defined as proteinuria of >40 mg/m^2/ hour along with oedema, hyperlipidaemia and hypoalbuminemia.[1] Albumin is the mainly excreted protein in urine of these patients. The prevalence of NS is children range from 12–16 per 100,000 population.[2] Focal segmental glomerulosclerosis (FSGS) and mesangioproliferative glomerulonephritis account for about 20% of NS and the rest is contributed by Minimal Change Disease (MCD).[3]

The International Study of Kidney Diseases in Children (ISKDC) defines Steroid resistant nephrotic syndrome (SRNS) as persistence of proteinuria after taking oral prednisone (60 mg/m^2/day) for four weeks followed by three pulses of methylprednisolone.[4] Though SRNS is disease without hope yet its management is an uphill task for the paediatric nephrologists. The histopathology directs the course of disease and its management[5] but the query remains if renal biopsy acts as a central pillar in management of SRNS.[6] In adults SRNS accounts for 40% of idiopathic NS while in paediatric population it accounts for only 10%.[7] Progressions to end stage renal disease occurs in about 50% of such cases.[8]

In addition to steroids treatment of SRNS includes calcineurin inhibitors (cyclosporine A, tacrolimus), angiotensin converting enzyme inhibitors (ACEIs) and alkylating agents (cyclophosphamide, chlorambucil).[9,10] Plasmapheresis[11] and mycophenolate mofetil[12] have also been used for treatment of SRNS. Rituximab,[13] a chimeric monoclonal anti-CD20 antibody, is the recent emerging choice for treatment in such patients. The rationale of this study is to determine the histopathological patterns of idiopathic steroid resistant nephrotic syndrome in Pakistani paediatric population as compared to other paediatric patients in other parts of the world and showing the prevalence of the most common underlying pathology for steroid resistance.

MATERIAL AND METHODS

This descriptive study was conducted in the Department of Paediatric Nephrology at The Children's Hospital and The Institute of Child Health Lahore over a period of one year from February 2014 to January 2015. The paediatric patients diagnosed as steroid resistant nephrotic syndrome who failed to show response to oral steroids after taking induction dose 60 mg/m^2/day for 4 weeks followed by three pulses of methylprednisolone were included in study. Other inclusion criteria were patients of either sex aged less than 16 years. Children who were excluded from the study were SRNS with congenital or syndromic

forms and patients with membranoproliferative Glomerulonephritis presenting as SRNS. Patients with bleeding diathesis, marked azotaemia, scarred kidneys detected by ultrasound at the time of renal biopsy and those for whom consent for the procedure was refused were also excluded. In hypertensive patients blood pressure was controlled before renal biopsy. Percutaneous renal biopsy was performed under ultrasound guidance from the lower pole of either kidney with automated biopsy gun. Two samples of renal biopsy were routinely obtained for full pathological evaluation and biopsy tissue was fixed in 10% buffered formalin. One renal biopsy core was sent to histopathology department and processed in automatic tissue processor for light microscopy (LM) and immune-stains while the other biopsy core was sent for immune-fluorescence (IF) study. All biopsies were examined by the experienced pathologists at our institute along with collaboration of paediatric nephrology department to arrive at the best possible correlative diagnosis. The SPSS 20.0 has been used for data analysis.

RESULTS

In this study there were a total of 96 patients of whom 64 (66.7%) were males and 32 (33.3%) were females (Table-1). The age range was from 0.80 to 15 years with mean age of presentation being 6.34 years and SD+3.75 (Table-2). The majority of patients were in age group of less than 12 years with peak age group presenting between 4–8 years (Graph-1).

Out of 96 patients the most common histopathological pattern of SRNS was Mesangioproliferative Glomerulonephritis which accounted for 79 (82.3%) cases, followed by Focal segmental glomerulosclerosis seen in 9 (9.4%) children. Minimal change disease was present in 5 (5.2%) while inconclusive biopsy was reported in 3 (3.1%) patients (Table-3). The gender split distribution showed Mesangioproliferative Glomerulonephritis in 54 male and 25 female patients, while Focal segmental glomerulosclerosis was present in 6 male and 3 female subjects. Minimal change disease was seen in 3 males and 2 females while inconclusive biopsy was reported in 1 male and 2 female patient (Table-4).

Table-1: Gender distribution

Gender	n	%
Male	64	66.7
Female	32	33.3
Total	96	100.0

Table-2: Age distribution

	n	Min (years)	Max (years)	Mean (years)	SD
Age (Years)	96	0.80	15.00	6.3416	±3.75446

Table-3: Histopathological diagnosis

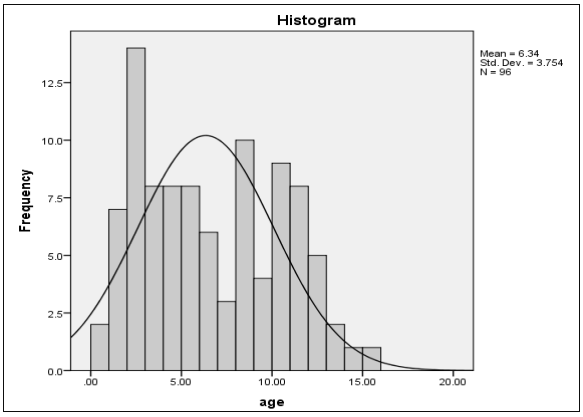
Diagnosis	n	%
Focal Segmental Glomerulosclerosis	9	9.4
Inconclusive	3	3.1
Minimal Change Disease	5	5.2
Mesangioproliferative Glomerulonephritis	79	82.3
Total	96	100.0

Table-4: Cross table gender and histopathological diagnosis

Diagnosis	Gender		Total
	Male	Female	
Focal Segmental Glomerulosclerosis	6	3	9
Inconclusive	1	2	3
Minimal Change Disease	3	2	5
Mesangioproliferative Glomerulonephritis	54	25	79
Total	64	32	96

Table-5: Comparison of histopathological patterns of our study with local and regional studies

Studies at different centres	Histo-pathological Patterns		
	Mesangio-proliferative Glomerulonephritis	Focal Segmental Glomerulosclerosis	Minimal Change Disease
Our Study	82.3%	9.4%	5.2%
Gulati S *et al*[6]	17.6%	58.8%	17.6%
Pradhan SK *et al*[14]	2.5%	30.0%	45.0%
Mubarak M *et al*[19]	10.2%	38.7%	23.1%
Azhar A *et al*[20]	8.8%	28.8%	13.3%
Moorani KN *et al*[21]	0.84%	29.66%	32.20%
Akhtar Ali A *et al*[22]	17.83%	18.30%	24.09%
Lanewala A *et al*[23]	4.1%	21.8%	29.4%
Seif EI *et al*[24]	1.9%	30.2%	24.5%



Graph-1: Age and histopathology patterns distribution

DISCUSSION

About 10% paediatric patients with Idiopathic nephrotic syndrome (INS) show steroid resistance.[4] Late non-responders are patients who initially

respond to steroids and ultimately become SRNS and these patients account for 1–3% patients.[8] Renal biopsy is usually not performed in steroid sensitive patients as it is understood that in majority of these cases with idiopathic nephrotic syndrome histopathology will be minimal change disease.[4] The treatment of SRNS is an uphill task for paediatric nephrologists as it is quite a common problem encountered in children with INS.[14] The ultimate risk of most patients with SRNS is presentation with end stage renal failure due to progressive renal disease but nephrotoxicity is one of the side effects of immunosuppressant like calcineurin inhibitors. Also these patients are more prone to infections because of prolonged use of immunosuppressant therapy along with steroids.[15] Regarding the various treatment options and the role of renal biopsy in diagnosis and management of SRNS, there is no understanding among different centres as what drug regimen should be used and when[16] as different drugs are used for treatment of SRNS with variable response.[17] But the renal biopsy and histopathology do have central role in defining the prognosis of this glomerular disease as well as the response to treatment which matters the most.[6] This study reflects the histopathological pattern of SRNS in Pakistani paediatric population not only in Punjab but also the rest of northern part of Pakistan.

A study done by Pradhan SK *et al*[14] showed that Minimal Change Disease was the most common histopathological diagnosis seen in paediatric population as compared to our study in which mesangioproliferative Glomerulonephritis was the most common cause for SRNS. Like Pradhan SK *et al*[14] the second most common cause was focal segmental glomerulosclerosis in our study as well but MCD was down the list in our patients in this part of the world, though we share almost common back ground and population descent yet the difference in obvious. The literature[18] supports the fact that SRNS occurring secondary to MCD will show a favourable response to immunosuppressant therapy.

In another study done at one of the leading centres dealing with kidneys diseases in Pakistan by Mubarak M *et al*[19] it was concluded that the prevalence of FSGS accounted for 38.7% followed by MCD which was 23.1%, while mesangioproliferative Glomerulonephritis cases were only 10.2%. In contrast our study revealed that the most common variety of SRNS was mesangioproliferative Glomerulonephritis which was present in 82.3% patients followed by FSGS and MCD being 9.4% and 5.2% respectively. It is a significant difference in the prevalence of histopathological types in one part of the country as compared to the other which can be related geographically to the southern part of Pakistan in their study while our patients belonged to northern part of the country.

Another study by Azhar A *et al*[20] showed the prevalence of FSGS in 28.8% of paediatric population followed by MCD and Mesangioproliferative Glomerulonephritis in 13.3% and 8.8% respectively, while Gulati S *et al*[6] concluded that FSGS was seen in 58.8% patients along with equal prevalence of 17.6% both for MCD and mesangioproliferative Glomerulonephritis. MCD was found to be the most common underlying histopathological pattern (32.20%) by Moorani KN *et al*[21] with FSGS seen in 29.66% and mesangioproliferative Glomerulonephritis only in 0.84% patients as compared to our study. Akhtar Ali A *et al*[22] observed one study in Peshawar Pakistan showing the patterns of MCD, FSGS and mesangioproliferative Glomerulonephritis as 24.09%, 18.30% and 17.83% respectively. Lanewala A *et al*[23] also reported MCD as the leading histopathological pattern of idiopathic nephritic syndrome followed by FSGS while a study by Seif EI et al[24] conducted at a leading centre in Egypt showed the FSGS in 30.2%, patients followed by MCD in 24.5% patient. (Table-5) Still the MCD tops the list among histopathological patterns but in our study it ranks at the bottom.

Regarding sex incidence of SRNS, our study showed the male to female ratio of 2:1 which is comparable to the study by Banaszak B *et al*[18] conducted from 1996–2005 showing similar results while part of the study conducted in 1986–1995 showed the male to female ratio of 1.2:1. On the other hand Mubarak M *et al*[19] showed male-to-female ratio of 1.6:1.

The exact cause for difference in results of histopathological patterns is not known - it may be related to genetic, racial and environmental factors. Another factor which may contribute to the results is the observation and reporting of findings of renal biopsy as early changes in FSGS in comparison to MCD and Mesangioproliferative Glomerulonephritis can be missed.

CONCLUSION

This study has shown mesangioproliferative Glomerulonephritis to be the most common histopathological pattern in paediatric population in our part of the world who present with idiopathic SRNS in comparison to the west and also to studies conducted at the centre in Southern Pakistan. This is rather unusual that mesangioproliferative Glomerulonephritis is leading while FSGS and MCD were seen with decreasing frequency in our population.

AUTHOR'S CONTRIBUTION

SSHS: Article writing, Data collection, Data analysis. NA: Supervision, article review. FS: Renal biopsies, data collection. FUR: Data analysis

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