Section: Pediatrics

Original Research Article

CLINICAL PROFILE OF IDIOPATHIC LATE ONSET NEPHROTIC SYNDROME - A SINGLE CENTER RETROSPECTIVE EXPERIENCE

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Abstract

Background: To study the clinical profile and outcome of Idiopathic late onset Nephrotic syndrome in children. **Materials and Methods:** A retrospective review of hospital records of 54 children who were diagnosed as Idiopathic late onset Nephrotic syndrome between January 2006 to December 2013 with minimum one year follow up was undertaken. Clinical features, treatment, and response were evaluated for those with atypical features requiring biopsy. **Result:** Of the 54 evaluated, mean age was 13 years. Mean duration of follow up was 24.5 months. Complete remission was observed in 53.7%, partial remission in 22.2% and no remission in 24.1%. Renal histology showed Minimal change nephrotic syndrome (MCD) in 38.9%; Mesangial Hypercellularity (MES HC) in 33.3%, FSGS (Focal segmental glomerulosclerosis) in 22.2% and DPGN (Diffuse proliferative glomerulonephritis) in 15.8%. Nephritic features of hypertension were noted in 14.8%, 51.9% had hematuria microscopically, and 7.2% had Renal failure (eGFR< 60 ml/min/1.73m2). ANA was positive in 3 children. After 6 weeks of adequate daily steroids, 48.1% were Steroid resistant (SRNS), 46.29% were Steroid sensitive and 3.7% were steroid dependent. **Conclusion:** Late onset NS has higher frequency of atypical features, steroid resistance, and histopathology showing lesions other than MCD. Early biopsy may be useful guide to management.

INTRODUCTION

Idiopathic nephrotic syndrome is defined by the combination of a nephrotic syndrome (proteinuria, hypoalbuminemia, hyperlipidemia, and edema) and non-specific histological abnormalities of the kidney.[1] The prevalence of NS is estimated at 2 to 7 per 100,000 children around the world.[2] Children between 2 to 7 years of age get affected by this condition more often, particularly boys.[3]

Proteinuria can result from glomerular alterations such as damage to the podocytes, the epithelial surface, or the glomerular basement membrane. In proteinuria, albumin is the main constituent, accounting for 85%.[4] Primary idiopathic nephrotic syndrome has three distinct histological variants: minimal-change nephrotic syndrome (MCNS), focal segmental glomerulosclerosis (FSGS), and membranous nephropathy.[5] Complications of nephrotic syndromes can include blood clots, higher blood cholesterol and triglycerides, poor nutrition, hypertension, acute and chronic kidney disease, and infections.[6]

Nephrotic syndrome can be caused by amyloidosis, minimal change disease (MCD), focal segmental glomerulosclerosis, diabetes-related nephropathy, lupus, and membranous nephropathy in adults.[7] The most noticeable symptom is swelling – especially around the eyes and face. Additional signs and symptoms include frothy urine, weight gain, fatigue, loss of appetite and infection due to loss of antibodies through urine.[8,9]

It can be diagnosed by urine tests, blood test to check for low levels of the protein albumin and often decreased levels of overall blood protein, kidney biopsy and ultrasound.[10,11]

In most cases, steroids can be used to treat nephrotic syndrome, then it is known as steroid-sensitive nephrotic syndrome (SSNS). A nephrotic syndrome that doesnot respond to corticosteroid treatment is known as steroid resistant nephrotic syndrome (SRNS).[12] When there is two consecutive relapses during corticosteroid therapy or within 14 days of stopping therapy, then it is known as steroid-dependent nephrotic syndrome (SDNS).[13] When a child is first diagnosed with nephrotic syndrome, they often need to take the steroid medication prednisolone for at least 6 weeks. After that, they

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usually take a lesser dose every other day for an additional 6 weeks. This prevents the child's kidneys from releasing protein into their urine.[14] Second-line steroid-sparing immunosuppression with a variety of medications, including as antiproliferatives, levamisole, calcineurin inhibitors, mycophenolate mofetil, and, more recently, rituximab, is recommended if the patient exhibits recurrent episodes or steroid-dependent illness.[15] Other medications like diuretics, anticoagulants and Cholesterol-reducing medications can also be used for the treatment of nephrotic syndrome. Some dietary modification may also help in nephrotic syndrome like cutting down the amount of salt, fat and cholesterol in diet while increasing the intake of lean sources of protein.[10,14]

Aim of our research article is to study the clinical profile and outcome of Idiopathic late onset Nephrotic syndrome in children. This research can help identify specific diagnostic and therapeutic strategies, ultimately improving management and diagnosis for affected children.

MATERIALS AND METHODS

The study was conducted retrospectively based on the hospital's medical records. All the subjects seeking care at the pediatric nephrology department of a teaching medical college between January 2006 to December 2013 were enrolled. All the subjects were followed for a minimum period of one year. The inclusion criteria include subjects of age eight years and above presenting with clinical presentation of renal failure evaluated clinically and histologically with a minimum one year of follow up with the department. Children with Chronic Kidney Disease (CKD), End Stage Renal Failure (ESRF) or on dialysis, and those who were not followed up for a minimum period of one year were excluded from the study.

A total of 179 children are diagnosed with idiopathic nephrotic syndrome within the above mentioned timelines. Of these, 54 children who were followed for one year were presented in the study. All the included children were treated with daily steroids for 6 weeks. Post treatment depending on the urine protein and urine creatinine ratio (UP/UC) children were diagnosed with complete remission (UP/UC less than 0.2g/g), partial remission (UP/UC 0.2 to 2g/g), and no remission (UP/UC more than 2g/g). Based on remission status and clinical presentation the children were categorized as steroid resistant nephrotic syndrome (SRNS) if UP/UC ratio is persistent despite steroid therapy for at least six weeks, steroid dependent nephrotic syndrome (SDNS) if recurrence of symptoms is observed within the 2 weeks after stopping treatment and steroid-sensitive nephrotic syndrome (SSNS) if no signs and symptoms were observed after steroid treatment. The steroid-sensitive nephrotic syndrome is further classified as Frequent nephrotic syndrome (FRNS) and Infrequent nephrotic syndrome (IFRNS). For all the children renal biopsy was conducted to understand the underlying pathology of the nephrotic syndrome. The privacy and confidentiality of participants were rigorously upheld, with their identities being anonymized to ensure confidentiality.

Statistical Analysis

The objective of the study was to describe various parameters observed in the children with idiopathic nephrotic syndrome. The data was collected in Microsoft excel sheet, cleaned and validated and analysis was done. The continuous data was presented as mean and standard deviation. The categorical data was presented as proportions and percentages.

RESULTS

The study included 54 children who were followed for a minimum duration of one year. The mean (±sd) age of the population was 13.3 (±1.4) years and the mean duration of follow up was 24.5(± 20.1) months. The gender distribution of the population was males accounting for 66.7% and females at 33.3%. Hypertension was observed in 8(14.8%). Haematuria in microscopy was found in 28 (51.9%) study participants. Anti-Nuclear Antibodies investigation was done for 50 children and only 3(5.6%) were found to be positive. The results were presented in [Table 1].

After the six weeks of steroidal therapy complete remission was found in 29 (53.7%) participants. No remission and partial remission were observed in 13 (24.1%) and 12 (22.2%) members of the study population respectively. Based on the response to steroidal therapy the participants were diagnostically classified as SRNS in 26 (48.1%) children followed SSNS in 25 (46.29%) children. The details are presented in [Table 2].

The observed nutritional status improved with pre-albumin levels rising from 2.1 to 3.7 g/dL post treatment. Creatinine levels slightly increased from 0.8 to 1.0 mg/dL. Cholesterol levels were high, averaging 335.5 mg/dL. Hemoglobin levels in the study population averaged at12.1 g/dL. Observed levels of urine creatinine were 3.3 mg/dl and urine protein was 8.0 mg/dl. [Table. 3]

The prevalence of various kidney conditions was diagnosed through biopsy. The most common conditions are MCNS 21(38.9%), MES HC 18(33.3%), and MESPGN 13(24.1%). Less common conditions include FSGS (22.2%), DPGN (15.8%), and MN (7.4%), with the least common being FSPGN, PROLIF GN IGG, MPGN IGG, C3, and FSPGN IF FH, each at 1.9%. [Table 4]

After 6 weeks of treatment, complete remission was seen in patients with diagnosis of MESPGN (61.5%), FSGS (58.3%), MN (25%), DPGN (12.5%), MES HC (77.8%), MCNS (58.6%) and PROLIF_GN_IGG (100%). Patients with FSPGN, MPGN_IGG_C3 and FSPGN_IF_FH was seen with partial remission.

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Conditions like MN, DPGN, MES HC, and MCNS show significant associations with treatment responses (p-values < 0.05), indicating different remission outcomes. Other conditions do not show significant associations. [Table 5]

Patients with SDNS shown 100% complete remission, Patients with SRNS shown, 23.1% complete remission, 50% no remission, and 26.9% partial remission. Patients with SSNS shown, 84% complete remission and 16% partial remission. SRNS and SSNS have significant associations with remission outcomes (p-values < 0.001), indicating different remission statuses. Other conditions like FRNS, IFRNS, SDNS, and Lupus Nephritis do not show significant associations (p-values > 0.05). [Table 6]

Table 1: Descriptive analysis of background parameters in the study population (N=54).

Parameters	**n(%)**
Age in years (Mean ± SD)	13.3 ±1.4
Gender	
Male	36 (66.7%)
Female	18 (33.3%)
Mean duration of follow up in months (Mean ± SD)	24.5 ± 20.1
Hypertension	
Yes	8 (14.8%)
No	46 (85.2%)
Hematuria in Microscopy	
Yes	28 (51.9%)
No	26 (48.1%)
Antinuclear Antibodies	
Positive	3 (5.6%)
Negative	47 (87.0%)
Not Done	4 (7.4%)

Table 2: Remission status and Diagnosis observed in the study population (N=54)

Remission status (N=54)	
Response	**n(%)**
Complete Remission	29 (53.7%)
No Remission	13 (24.1%)
Partial Remission	12 (22.2%)
Diagnosis	
LUPUS NEPHRITIS	1 (1.9%)
SDNS	2 (3.7%)
SRNS	26 (48.1%)
SSNS	25 (46.29%)
SDNS: Steroid Dependent Nephrotic Syndrome, SRNS: Steroid Resistant Nephrotic Syndrome, SSNS: Steroid Sensitive Nephrotic Syndrome.	

Table 3: Renal function parameters pre and post steroidal therapy

Parameters	**Mean ± SD**	**Minimum**	**Maximum**
Pre -Albumin (g/dl)	2.1 ±0.9	1	4.6
Post_Albumin (g/dl)	3.7 ±1.0	1.2	5.1
Pre_Creatine (mg/dl)	0.8 ±0.8	0.25	6.18
Post_Creatine (mg/dl)	1.0 ±1.4	0.2	10.7
CHOLESTROL (mg/dl)	335.5 ±186.9	123	1100
Hemoglobin (g/dl)	12.1 ±1.5	8	14.7
Urine_Protein	8.0 ±8.3	0.03	54
Urine_Creatine	3.3 ±8.8	0.015	58

Table 4: Frequency Distribution of Biopsy findings in the study population

Biopsy findings	
Parameters	**n(%)**
MESPGN: Mesangial Proliferative Glomerulonephritis	13 (24.1%)
FSGS	12 (22.2%)
MN	4 (7.4%)
DPGN	8 (15.8%)
MES HC	18 (33.3%)
MCNS	21 (38.9%)
FSPGN	1 (1.9%)
PROLIF GN IGG	1 (1.9%)
MPGN IGG,C3	1 (1.9%)
MESPGN: Mesangial Proliferative Glomerulonephritis, FSGS: Focal Segmental Glomerulonephritis, MN: Membranous Nephropathy, DPGN: Diffuse Proliferative Glomerulonephritis, MES HC: Mesangial Hypercellularity, MCNS: Minimal Change Nephrotic Syndrome	

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Table 5: Comparison of Response and Biopsy background parameters

Parameters	Response				P.Value
	Complete Remission	No Remission	Partial Remission	Total	
MESPGN	8 (61.5%)	1 (7.7%)	4 (30.8%)	13	0.263
FSGS	7 (58.3%)	4 (33.3%)	1 (8.3%)	12	0.377
MN	1 (25%)	3 (75%)	0 (0%)	4	**0.043**
DPGN	1 (12.5%)	4 (50%)	3 (37.5%)	8	**0.037**
MES HC	14 (77.8%)	2 (11.1%)	2 (11.1%)	18	**0.043**
MCNS	17 (850%)	2 (100%)	2 (100%)	2	**0.006**
FSPGN	0 (0%)	0 (0%)	1 (100%)	1	0.168
PROLIF_GN_IGG	1 (100%)	0 (0%)	0 (0%)	1	0.645
MPGN_IGG_C3	0 (0%)	0 (0%)	1 (100%)	1	0.168
FSPGN_IF_FH	0 (0%)	0 (0%)	1 (100%)	1	0.168

MESPGN: Mesangial Proliferative Glomerulonephritis, FSGS: Focal Segmental Glomerulonephritis, MN: Membranous Nephropathy, DPGN: Diffuse Proliferative Glomerulonephritis, MES HC: Mesangial Hypercellularity, MCNS: Minimal Change Nephrotic Syndrome.

Table 6: Comparison of Response and Diagnosis background parameters

Parameters	Response				P.Value
	Complete Remission	No Remission	Partial Remission	Total	
SRNS	6 (23.1%)	13 (50%)	7 (26.9%)	26	**<0.001**
SSNS	21 (84.0%)	0 (0%)	4 (16%)	25	**<0.001**
SDNS	2 (100%)	0 (0%)	0 (0%)	2	0.409
Lupus Nephritis	0 (0%)	0 (0%)	1 (100%)	1	0.168

SRNS: Steroid Resistant Nephrotic Syndrome, SSNS: Steroid Sensitive Nephrotic Syndrome, SDNS: Steroid Dependent Nephrotic Syndrome.

DISCUSSION

In this retrospective study we have assessed the clinical profile and outcome of Idiopathic late onset Nephrotic syndrome in children. All the children included were followed for a period of one year.

For this study we have taken the 54 children, of age group 10-16 years of age. Most of the patients were diagnosed with SRNS and SSNS, few were diagnosed with SDNS and lupus nephritis. All the patients have undergone biopsy after the treatment, in which most of the patients were diagnosed with MCNS, MES HC, DPGN, FSGS and MESPGN. During the study we have observed high level of cholesterol and low level of urine creatinine in patients. During the study we have seen the improvement in albumin level after the treatment of 6 weeks. Most of the patients in our study were not having hypertension and were having negative antinuclear antibodies. Most of the patients have shown the complete remission during the follow up of 1 year.

As per the International Study of Kidney Disease in Children (ISKDC), most of the studies are going for outcomes which are classified on the basis of patient's response to corticosteroids or other therapy and by NS relapse. Few or no relapses are linked to the least severe SSNS course. Individuals with SSNS who experience relapses frequently or who become dependent on steroids are more complex. Few patients with initial steroid response develop SRNS (late non-responders) and others present with SRNS. At last, the most severe NS instances are resistant to corticosteroids as well as other treatments. Childhood NS can result in long-term renal problems, such as adult NS relapse, hypertension, chronic kidney disease (CKD), and end-stage renal disease (ESRD).[16]

Hala Wannous et al, have reported the main indication of kidney biopsy was steroid-resistant nephrotic syndrome (SRNS) and the main histopathological patterns were minimal change disease (MCD) and focal segmental glomerulosclerosis (FSGS). FSGS was the most common histopathological pattern in idiopathic SRNS and had the worst prognosis. Calcineurin inhibitors could be an effective therapy to induce complete remission in SRNS.[17] In our study main indication of biopsy was SRNS and SSNS and the main histopathological patterns were MES HC, MCNS, MESPGN and FSGS.

In study by Mbanefo, et. al., they have assessed the pattern of steroid sensitivity and steroid resistance in childhood idiopathic nephrotic syndrome. In this study, SRNS was the main reason for renal biopsy and FSGS was the most common histopathological pattern.[18] In article by C. Straatmann et.al., they have assessed the renal outcome of patients with late steroid resistance, along with the risks and benefits of additional immunosuppressant therapy. In this according to the result, sustained complete or partial remission was achieved in 69 % of patients and it suggests that immunosuppressive treatment is a viable option in NS patients who develop LSR.[19]

The strength of this study is we attempted to comprehensively describe the clinical profile and outcome of Idiopathic late onset Nephrotic syndrome with its histopathological findings, more over the median duration of follow up was 15 months. As very few studies exist in describing the syndrome with a good follow up period, our study is emphasized to fill the gaps and provide more detailed understanding of the Idiopathic late onset Nephrotic.

Limitations of the study are that we have enrolled very small number of participants into study. The other limitation is that, this is unicentric study. So,

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more research is required for better understanding of the disease. Due to infrequent occurence of the disease a multicenter study with appropriate sample size is needed.

CONCLUSION

In our study most of the patients were diagnosed with SRNS and SSNS, and most common histological findings were MCNS, MES HC, FSGS and MESPGN. Majority of patients had shown complete remission at the end of follow up.

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