

Steroid Resistant Nephrotic Syndrome in Pediatric Patients: Histopathological Patterns at King Hussein Medical Center

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ABSTRACT

Objective: To analyze the histopathological pattern of steroid resistant nephrotic syndrome in pediatric age group at King Hussein Medical Center.

Method: A retrospective study of record review was carried out at King Hussein Medical Center during the period from January 2007 to September 2014 for all pediatric patients with steroid resistant nephrotic syndrome who underwent percutaneous kidney biopsy. Medical records were reviewed for age, sex, symptoms treatment and histopathological diagnosis.

Results: One hundred children with the diagnosis of steroid resistant nephrotic syndrome were included in the study. 54% were males. The age ranges between 1-14 years. The most frequent symptom was puffiness of the eyes and lower limbs swelling. Focal segmental glomerulosclerosis was the most common histopathological pattern (54%), followed by minimal change disease (25%). Alport syndrome was found in (2%); however minimal change disease accounted only for (12%) after the age of 10 years.

Conclusion: Focal segmental glomerulosclerosis is the most common cause of steroid resistant nephrotic syndrome; which emphasize the importance of histopathological diagnosis in steroid resistant nephrotic syndrome for both treatment and prognosis.

Keywords: Focal Segmental Glomerulo Sclerosis (FSGS). Steroid Resistant Nephrotic Syndrome (SRNS), Nephrotic Syndrome (NS).

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Introduction

Nephrotic Syndrome (NS) is a kidney disease characterized by nephrotic range proteinuria leading to hypoalbuminemia, hyperlipidemia and edema.⁽¹⁻²⁾ It is one of the commonest glomerular disease during childhood, with an incidence of 2 -7 new cases per100, 000 children⁽³⁾ and a prevalence of 16 cases per 100 000 children.⁽⁴⁾ It can be classified according to the response to steroids into: steroid responsive and steroid

resistant. Children fail to achieve complete remission after 8 weeks of steroid therapy in a dose of 60mg/ m²/day, are labeled as SRNS.⁽⁵⁾ Approximately 10-20% of children with idiopathic nephrotic syndrome (INS) are steroid resistant (SRNS).⁽⁶⁾ The management of SRNS is believed to be a common challenge for nephrologists.⁽⁷⁾

Chronic kidney disease or end stage renal failure is a known complication of SRNS due to the fact that proteinuria can lead to

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progressive damage of the glomerular filtration barrier.⁽⁸⁾ The course of the disease usually affected by the histopathological finding of the kidney biopsy.⁽⁹⁾ Steroid-resistant nephrotic syndrome in children usually has a high risk of resistance to immunosuppressive treatment.⁽¹⁰⁾ In general Focal Segmental Glomerulosclerosis (FSGS) has been reported as a significant causes of SRNS worldwide.^(11,12) The International Study of Kidney Disease in Children showed that FSGS causes 70% of SRNS while Minimal Change Disease (MCD) to be the morphological lesions in 7% of SRNS.⁽¹³⁾ There is little information regarding the histopathologic finding in children presenting with SRNS in Jordan.⁽¹⁴⁾ This study was carried out to describe the histopathological spectrum of SRNS children in our region.

Methods

A retrospective study of record review was done at King Hussein Medical Center during the period extending from January 2007 to September 2014 including children between the age 1 and 14 years with steroid resistant nephrotic syndrome who underwent percutaneous kidney biopsy. The patients were divided into three groups: Group I; patients who are equal or below 2 years, group II; those who are more than 2 years but less than 10 years and Group III; those who are more than 10 years.

The diagnosis of SRNS was defined as inability to achieve remission after treatment with oral prednisolone in a dose of 60mg/m²/day for 8 weeks.⁽¹⁵⁾ Children with congenital nephrotic syndrome, nephrotic syndrome secondary to systemic lupus erythromatosis were excluded.

Medical records were reviewed for age, sex, treatment and histopathological diagnosis. Simple descriptive statistics (frequency, mean, and percentage) were used to describe the study variables. The histopathological data, including Light Microscopy (LM), Immuno Florescence (IF) staining and Electron Microscopy (EM) were studied by the same pathologist team.

The findings were recorded from the original renal biopsy forms. Parents were counseled regarding the need for renal biopsy, and consent was obtained in every case before performing the kidney biopsy. Approval of our institution's ethical committee was obtained.

Results

A total of 100 children with the diagnosis of steroid resistance nephrotic syndrome who underwent percutaneous kidney biopsy were included in the study. Fifty-four percent were males and 46% were females. The age ranged between 1-14 years. The mean age was 6.13 ± 3.3 year. The most frequent symptom was puffiness of the eyes followed by lower limbs swelling. The most frequent diagnosis was focal FSGS (54%), followed by MCD (25%) as shown in Fig. 1.

In all age groups, FSGS was the most common histopathological finding, while MCD was the second most common cause below the age of 10 year (Table I and II). Whereas; Membrano-proliferative (MPGN) and membranous glomerulonephritis were more common than MCD after the age of 10 years (Table III). Alport syndrome was found in (2%) of patients who presented with SRNS.

Discussion

Nephrotic syndrome characterized by proteinuria ≥ 40 mg/m² body surface area /hour, hypoalbuminemia with a serum albumin <25 g/l, hypercholesterolaemia (according to age) and oedema.⁽¹⁶⁾ The prognosis of the disease can be predicted most of time by the clinical response to steroids.^(17,18) Kidney biopsy is indicated for some cases of idiopathic nephrotic syndrome.⁽¹⁹⁾ Steroid resistant nephrotic syndrome accounts for 10 - 20% of children with idiopathic nephrotic syndrome.⁽⁶⁾ In general MCD is found in 85% of idiopathic nephrotic syndrome; it has good response to treatment.^(20, 21)

Focal segmental glomerulosclerosis is characterized by higher rate of resistance to steroid therapy in comparison with MCD, with 50 %⁽²²⁾ recurrence in the transplanted

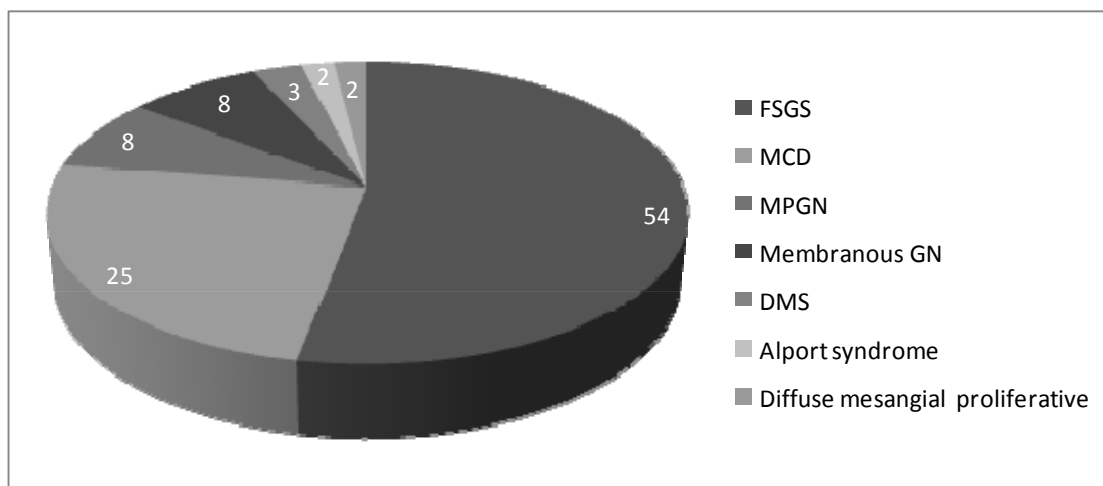


Fig. 1. Shows the different Histological Finding in SRNS.

Table I: Histopathological pattern of SRNS \leq 2 years.

Diagnosis	Number	Percentage %
FSGS	13	81.3
MCD	2	12.5
DMS	1	6.2

Table II: Histopathological pattern of SRNS between 2 and 10 years.

Diagnosis	Number	Percentage
FSGS	29	49.1%
MCD	20	33.9%
MPGN	3	5.1%
Membranous GN	3	5.1%
DMS	2	3.4%
Alport Syndrome	2	3.4%

Table III: Histopathological pattern of SRNS \geq 10.

Diagnosis	Number	Percentage
FSGS	12	48%
MPGN	5	20%
Membranous GN	3	12%
MCD	3	12%
Diffuse Mesangial Proliferation	2	8%

kidney and high rate of progression to end-stage renal disease.^(23- 26)

Therefore it is essential to detect its presence on biopsy especially in cases of SRNS, after which we can discuss the prognosis and the outcome with the family. In this study we tried to describe the histopathological pattern of SRNS in a tertiary center in Jordan over the last eight years.

Focal segmental glomerulosclerosis is increasing worldwide in both children and adult as shown in recent studies of renal biopsy specimen archives from several institutions in the United States which suggest

that the incidence of FSGS has increased over the past 20 years⁽⁹⁾ as well as epidemiologic data from the United States Renal Data Systems (USRDS) which showed the incidence of ESRF secondary to FSGS has increases as well.

Since King Hussein Medical center is a biggest referral center where kidney biopsy can be performed and our laboratory till recently was the only center in the country that is equipped with electron microscopy we believe that our results reflect the actual histopathological pattern of SRNS in Jordan.

The study results showed that FSGS is the most predominant histopathological finding in children with SRNS (54%) in Jordan. This result correlates generally with previous results shown from Metropolitan city of Karachi in Pakistan⁽⁷⁾ and India⁽²⁷⁾ where they observed a higher prevalence of FSGS as a histopathology lesion seen in children with SRNS with a rate of 38.7% , 59% respectively as well as from France⁽⁸⁾ and Japan.⁽¹⁸⁾

In the Arab countries; few studies exist describing the histopathological lesion of SRNS in children. A study from Saudi Arabia⁽¹¹⁾ reported that FSGS was the main histopathology lesion (39%) in SRNS in children which correlates with our results as well as results from Tunisia⁽²⁸⁾ and Qatar.⁽²⁹⁾ However, in contrast to our results, a study from Kuwait done by El Reshaid *et al*,⁽³⁰⁾ reported MCD as the commonest lesion found in children with SRNS (65%) followed by FSGS (15%), in our study MCD contributed only to 25 % of SRNS.

Membrano-proliferative glomerulonephritis found to be the most common cause of steroid resistant nephrotic syndrome after the age of 10 years as being described as it is typically a disease of older children and young adults.^(30,31) In comparison to data from Nigeria which reported MPGN as the most predominant histopathology finding with a rate of 43.5%, FSGS in 39.1% and while MCD accounted for 4.35% of the cases.⁽³²⁾ However, a study from Saudi Arabia concluded that, MPGN tends to present at an earlier age in the Arab countries.⁽³³⁾

Inheritable genetics forms of FSGS have been recently described.^(34- 35) Many cases of familial FSGS have been reported in Jordan especially in certain families in the north area due to high rate of consanguineous marriage in our country.^(36,37) This familial occurrence of FSGS supports the concept that genetically determined factors may be implicated in the pathogenesis of the disease and may be explaining the high rate of FSGS (81.3%) observed in children below the age of two years in our study. Alport syndrome was found in two patients (2%). Although the most common presentation is hematuria; nephrotic range proteinuria is a rare initial

presentation of Alport syndrome. These findings correlate with results from Iran.^(38, 39) Proteinuria is usually absent in childhood but eventually develops in patients with Alport syndrome and usually progresses with age and can occur in the nephrotic range in as many as 30% of patients.⁽⁴⁰⁾

Conclusion

Our results showed that FSGS is the predominant lesion among Jordanian children with SRNS, followed by MCD. This study defines the true spectrum of histopathological lesions underlying SRNS in children in Jordan. Which emphasize the importance is to determine the histopathological diagnosis of steroid resistance nephrotic syndrome for both treatment and prognosis.

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