Clinical Course of Idiopathic Nephrotic Syndrome in Children: predictors of steroid resistance

Nurdan Yildiz (nbilgenyildiz@gmail.com)
Marmara Universitesi Tip Fakultesi https://orcid.org/0000-0001-6805-5313
Neslihan Cicek
Marmara Universitesi Tip Fakultesi
Sercin Guven
Marmara Universitesi Tip Fakultesi
Ibrahim Gokce
Marmara Universitesi Tip Fakultesi
Harika Alpay
Marmara Universitesi Tip Fakultesi

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Abstract

Background: Nephrotic Syndrome (NS) is one of the most common renal diseases in children. Clinical response to corticosteroids is an important prognostic factor for long-term renal outcome. We aimed to evaluate the clinical parameters, histopathological findings and complications of NS patients and factors predicting steroid resistance in a single tertiary center.

Methods: A hundred and sixty two children (57 girls, 105 boys) with NS followed between 1998 and 2018 in Department of Pediatric Nephrology were analyzed in a retrospective cohort. Secondary causes and infantile NS cases were excluded.

Results: The median (IQR; range) age of the children at presentation and follow up time were 4.9(5.7; 0.1-16.8) and 5.5(5.4; 0.1-20.3) years, respectively. A hundred and thirty four (82.7%) patients were steroid-sensitive nephrotic syndrome (SSNS) and 28(17.3%) were steroid-resistant nephrotic syndrome (SRNS). Age at the first presentation was lower in SSNS group ($p=0.002$). Hypertension, macroscopic and microscopic hematuria were higher in SRNS group ($p<0.001$). Percutaneous kidney biopsy was performed in 56(34.6%) patients. The most common histopathological findings were focal segmental glomerulosclerosis (FSGS), minimal change disease (MCD) and membranoproliferative glomerulonephritis (MPGN) respectively. Four patients with FSGS were subsequently diagnosed as Alport syndrome due to electron microscopic findings and genetic analysis. Four patients with FSGS and one with MPGN reached to end stage kidney disease.

Conclusion: The late onset is still an important sign for SRNS. Microscopic and macroscopic hematuria and hypertension may also give a hint for potential steroid resistance. We emphasize that FSGS is a biopsy finding that may reveal to different diagnosis in SRNS.

What Is Known

- An increasing incidence of SRNS and FSGS in both adults and children is reported over the past 20 years.
- In children with INS, response to steroid therapy is the most important prognostic factor in the long-term follow up.
- There is no specific laboratory or clinical parameter to distinguish SRNS.

What is new:

- The incidence of SRNS or FSGS was not increased in the last decade.
- Microscopic hematuria and late onset are still important predictors of SRNS.
- Focal segmental glomerulosclerosis is not a disease but a histopathological diagnosis leading to different entities such as Alport syndrome.

Introduction

Nephrotic Syndrome (NS) is a common pediatric kidney disease in children and characterized by massive proteinuria, hypoalbuminemia, generalized edema, and hyperlipidemia. Approximately 90% of children with NS have a form of primary or idiopathic nephrotic syndrome (INS) [1, 2]. The incidence of INS in children has been reported as 1.15–16.9 per 100,000 children [3].

Minimal change disease (MCD) is the most common form of INS in children, with an incidence of 85% of total cases, and most frequently seen between 2–7 years of age with male predominance. Corticosteroids (CS) remain the first-line treatment of INS and more than 90% of children with MCD respond to CS monotherapy [1]. Other histopathological lesions, including focal segmental glomerulosclerosis (FSGS), were observed in less than 10% of biopsies. Some recent studies have shown an increasing incidence of FSGS in both adults and children over the past 20 years [4, 5]. Patients with FSGS are often resistant to CS therapy, progress more often to end stage renal disease (ESRD) and may recur soon after kidney transplantation [2, 6]. However, there are racial and regional differences in respect of histopathological features and steroid responsiveness in childhood INS, making these results not uniform. In last two decades, many studies reported a significant increase in both primary and secondary steroid resistance in childhood NS compared with ISKDC data [7]. Steroid sensitive and steroid resistant NS (SRNS) have similar clinical presentations and there is no specific laboratory or clinical parameters to distinguish these two clinical entities.

The relapse rate in childhood steroid sensitive NS (SSNS) is high and approximately half of them develop steroid dependency [8–10]. Many studies reported the long duration of the disease with relapses which may develop even in adulthood [11–13]. Early identification of patients who are likely to develop steroid-dependency or resistance is crucial for designing appropriate long-term treatment plans, reducing steroid side effects and morbidity.

In this study, we aimed to evaluate the demographic and clinical data, histopathological findings and complications of our patients presenting with NS and to determine the changes in the frequency of SRNS and factors predicting steroid resistance.

Methods

Patients

A hundred and sixty two children presenting with NS followed in pediatric nephrology outpatient clinic in a tertiary center between 1998 and 2018 were analyzed in this retrospective cohort study. Secondary causes and infantile NS cases were excluded. Demographic data, blood pressure, serum creatinine, albumin, cholesterol, complement 3 (C3) and complement 4 (C4) levels, hepatitis serology, urine analysis and urine albumin excretion, the number of relapses, histopathological findings, adverse effects and outcomes were recorded from the medical files of the patients. Steroid resistance was evaluated by comparing patients between 1998–2008 and 2009–2018.

Definitions

The patients with massive proteinuria (24-hour urinary protein excretion of more than 40 mg/m2/hour or urinary protein to creatinine ratio (Up/cr) more than 2 mg/mg), hypoalbuminemia (< 2.5 g/L) and generalized edema were defined to have NS. Remission was defined as a decrease of proteinuria to less than 4 mg/m2/hour or Up/cr less than 0.2 mg/mg or urine albumin dipstick of negative to trace for three consecutive days. Relapse was defined as recurrence of massive proteinuria to > 40 mg/m2/hour or Up/cr more than 2 mg/mg or urine albumin dipstick of 3 + to 4 + on three consecutive days, often with a recurrence of edema. Patients who were in complete remission within 4–8 weeks with response to CS therapy alone were referred to have SSNS. Patients who failed to achieve remission after the initial eight weeks of full dose CS therapy at a dose of 60 mg/m2/day were referred to have SRNS. Steroid dependent NS (SDNS) was defined by the occurrence of two consequent relapses during steroid tapering or within two weeks of steroid withdrawal. Non-relapsing NS (NRNS) was defined as no relapses for more than 2 years after the first episode [8].

Microscopic hematuria was described as the presence of five or more red blood cells per high-power field in centrifuged fresh urine sediment. Systolic or diastolic blood pressure > 95th percentile for age, gender and height on three occasions was considered hypertension [14].

Treatment protocol

As initial therapy, all patients except one patient with spontaneous remission received prednisolone 2 mg/kg/day (maximum 60 mg/day) in two divided doses for four weeks, and if the patient was steroid-responsive, prednisolone dose was switched to alternate day for another four weeks and tapered during the next 8 weeks. Relapsing patients were treated with same doses with a shorter duration.

Patients treated with CS therapy were evaluated regularly for side effects such as ocular complications, osteopenia (bone mineral density < -1), hypertension, cushing-like appearance, obesity, striae, hirsutism, myopathy and gastrointestinal side effects. Bone densitometry had been performed in all patients older than 5 years and using CS therapy for longer than six months.

Percutaneous ultrasound guided kidney biopsy was performed in patients with SRNS or SDNS and frequent relapsing nephrotic syndrome (FRNS) before introduction of second immunosuppressive drug and in presence of macroscopic hematuria, hypertension, low C3 levels or persistently high serum creatinine levels. Light microscopy, immune fluorescence and electron microscopic examinations were routinely performed in all biopsy specimens.

The study was approved by the local ethical committee (09.2016.241) and followed the guidelines of the Helsinki Declaration. Since the data was retrospectively analyzed using medical files, informed consent was not obtained for individual participants.

Statistical Analysis

Statistical analyses were performed using the Statistical Packages for the Social Sciences SPSS Inc., Chicago, IL, USA) 23.0 package. A Shapiro-Wilk test was used to determine the normality of data. Normally distributed variables were presented as mean ± standard deviation (SD). The data not distributed normally are expressed as median interquartile range, IQR). Differences between the groups were analyzed using Student-t and Mann Whitney U tests when appropriate. Chi-square and Fisher's exact tests were used to analyze qualitative variables and to identify differences between 1998–2008 and 2009–2018. The association between variables was analyzed using the Spearman's correlation tests. Binary logistic regression was used to identify possible independent predictive factors for steroid resistance. A P-value of < 0.05 was considered statistically significant.

Results

A hundred and sixty two patients (57 girls, 105 boys) presenting with NS were included in the study. The median (IQR; range) age of the children at presentation and follow up time were 4.9 (5.7; 0.1-16.8) and 5.5(5.4; 0.1-20.3) years, respectively. Demographic and clinical features of the patients were presented in Table 1. The peak age at onset was about four years, and the male:female ratio was 1.8:1. At presentation, 21 (12%) patients were older than 12 years with a male:female ratio of 1.2:1.

Hypertension was present in 21 (13%) patients, oliguria in 25 (15.4%), microscopic hematuria in 39 (24.1%) and macroscopic hematuria in 5 (3.1%) at presentation (Table 1). All patients had varying degrees of edema ranging from mild periorbital and ankle edema to gross ascites, pleural effusion and genital edema. Genital edema was present in 16 (9.9 %) of the patients. Three of five patients with macroscopic hematuria were diagnosed as FSGS and two as membranoproliferative glomerulonephritis (MPGN).

A hundred and thirty four (82.7%) patients were SSNS and 28 (17.3%) were SRNS (Table 1). There was no significant difference in terms of SRNS between the decades of 1998-2008 and 2009-2018 (p=0.2). The proportion of FSGS and MCD patients was also not different in two consecutive decades (p= 0.195) (Figure 1). Among patients with SSNS, 15 (11.2%) were SDNS and 47 (35.1%) were NRNS (Table 1). Ten of the SDNS patients relapsed on low-dose steroid therapy, even before the steroid was withdrawn. Excluding SDNS patients, 275 relapses occurred in 72 (53.7%) patients. The median (IQR; range) number of relapses was 2 (4; 1-17) and the time to first relapse was 5 (6.3; 1-24) months. Number of relapses were significantly and negatively correlated with time to first relapse (r= -0.475, p<0.0001). The common trigger of relapses was mostly viral upper respiratory tract infections.

As shown in Table 1, there were no significant differences in means of gender, estimated glomerular filtration rate (eGFR), serum albumin and cholesterol values between SSNS and SRNS patients at presentation whereas the median age, hypertension and microscopic hematuria were higher in SRNS patients (p = 0.002, p=0.000 and p=0.000, respectively). Binary logistic regression analysis revealed that

age (OR: 0.89; 95% confidence interval (CI) 0.817-0.896; p= 0.019) and microscopic hematuria (OR: 0.263; 95% CI 0.112-0.618; p= 0.002) were significantly related to SRNS but hypertension (OR: 0.532; 95% CI 0.167-1.700; p= 0.287) was not an independent factor for steroid resistance (Table 2). Although not statistically different, eGFR was lower in SRNS patients (111 vs 183 ml/min/1.73 m^2, p=0.08).

Percutaneous kidney biopsy was performed for 56 (34.6%) patients. Indications for renal biopsy were steroid resistance in 27 (48.2%), steroid dependence in 9 (16%) and NS with accompanying late onset, serological abnormalities, macroscopic hematuria or kidney failure in 20 (35.7%) patients. The most common histopathological findings were FSGS in 23 (41.1%) patients, following MCD in 16 (28.6%) and MPGN in 10 (17.9%) patients (Figure 2). Four patients with FSGS were subsequently diagnosed as Alport syndrome according to electron microscopic findings and genetic analysis. Similarly, three of the patients previously diagnosed MPGN were re-diagnosed as C3 glomerulopathy.

Complications

One patient with FSGS had deep venous thrombosis in the lower extremity and was treated with low molecular weight heparin successfully. No serious infections, including spontaneous peritonitis, developed in any of the patients during CS therapy.

The most common side effects of CS therapy were Cushing-like appearance in 47 (29%) patients, obesity in 28 (17.3%), osteopenia in 28 (17.3%), hirsutism in 27 (16.7%), striae in 21 (13%) ocular complications in 18 (11.1%), hypertension in 10 (6.2%) who had normal blood pressure before CS therapy and myopathy in 2 (1.2%) patients (Table 3). One patient (0.6%) had gastrointestinal bleeding and was treated successfully with intravenous proton pump inhibitor. Eighteen (64.3%) of 28 patients with low bone mineral density had SSNS who used steroid therapy longer than six months.

Chronic kidney disease developed in five of 23 (21.7%) patients with FSGS and two of 10 (20%) with MPGN. Of these patients, four patients with FSGS and one with MPGN reached to ESRD. One of the FSGS patients is still on peritoneal dialysis for two years and one is on hemodialysis for three years. One patient had living-donor kidney transplantation and another patient died due to a complication of plasmapheresis before preemptive kidney transplantation. The patient on peritoneal dialysis with MPGN died due to sepsis.

Discussion

In this retrospective descriptive cohort study, we report the evaluation of INS in children from a single tertiary center. Nephrotic syndrome is one of the most common glomerular disease in children showing a higher incidence in boys with a male:female ratio of 2:1 [1, 15]. Similarly, the male:female ratio was 1.8:1 in our study. We also found the ratio of the affected boys to that of girls decreased to 1.2:1 as the age of onset increased above 12 years. Gender disparity disappears by adolescence, making the incidence in

adolescents and adults equal among males and females. This is also consistent with the lack of a significant effect of gender on steroid resistance, as seen in our results.

The most common age of INS at presentation is younger than 6 years in 70–80% of the children. There is an increasing trend in the incidence of SRNS with increasing age [16]. In our study, the peak incidence of INS was at four years of age, with SRNS patients showing a higher median age than the patients with SSNS. Logistic regression analysis showed that older age was significantly related to SRNS. The late onset still appears to be one of the most important factors predicting steroid resistance.

On the basis of the International Study of Kidney Diseases in Children ISKDC), almost 80% of children diagnosed with NS entered remission within initial 4–8 weeks of CS therapy. Approximately 10–20% of children with NS do not enter remission [1]. Similarly, 17.8% of our patients were SRNS. The characteristics of children with INS have changed over recent decades and it's reported that the incidence of FSGS is increased in NS patients [17]. However, we did not find any difference in terms of steroid resistance in patients with NS between decades of 1998–2008 and 2009–2018. The fact that there was no increase in SRNS patients in our study may be due to regional and ethnic differences or the fact that we are a tertiary care center that referral of SRNS patients are always high.

Hypertension and hematuria are not common findings in INS. Elevated systolic and diastolic blood pressures are initially present in 5–20% of the patients [18]. We found hypertension in 13% of the patients being significantly higher in SRNS. Therefore, we suggest keeping in mind that hypertension is a remarkable finding for SRNS. However, we could not demonstrated hypertension as an independent predictive factor in our study.

Macroscopic hematuria occurs in 2–3% and microscopic hematuria in 20% of children with NS [18, 19]. None of our patients with SSNS was presented with macroscopic hematuria. Despite the limited number of patients, we may predict that the NS patients initially presented with macroscopic hematuria mostly are SRNS. We also found microscopic hematuria more frequently in SRNS patients and logistic regression analysis showed that microscopic hematuria was significantly related to steroid resistance.

Steroid resistance is an important risk factor for ESRD and less than 5% of children with SSNS progress to ESRD, inversely [20]. None of our patients with SSNS had chronic kidney disease (CKD) but 25% of SRNS patients had CKD and also 71.4% of them reached ESRD drawing attention to this important issue.

Kidney histology provides an important contribution to the management of SRNS patients. The most common histopathological finding in SRNS is FSGS [19]. Ibrahim-Seif and Pilania reported FSGS and MCD as the most common histopathological findings, respectively [21, 22]. Conversely, the most common histopathological finding was MPGN in a retrospective study including 392 Turkish children with NS and it was stated that it might be due to unidentified causes such as infectious agents or environmental factors that can trigger MPGN [23]. In our study, the most common histopathological findings were FSGS, followed by MCD and MPGN respectively. Contrary to the observations published in recent years showing an increased incidence of FSGS in NS, we did not find an increase in the number of FSGS patients and

SRNS patients between two decades in a homogeneous population of Caucasian children. Most of the studies reporting high FSGS frequency include patients of different ethnic origins which may effect the results [4, 5, 17]. However, increased incidence of FSGS was also reported in Caucasian children with INS [24]. Further studies with larger numbers of children are still necessary to reach more accurate results about the change of the frequency of several histopathological subtypes by time.

Focal segmental glomerulosclerosis is not a disease but only a histopathological diagnosis. Patients with FSGS on biopsy may have mutations in COL4A3–5 genes and suggested to be classified and treated as Alport syndrome [25, 26]. Four of our patients with FSGS by light microscopy on biopsy diagnosed as Alport syndrome with electron microscopic findings and confirmed by genetic tests later. Our limited number of cases suggest that genetic–pathologic correlation improves diagnostic accuracy in FSGS. Besides, three of the patients who had a diagnosis of MPGN previously were re-diagnosed as C3 glomerulopathy by new insides to MPGN.

Children with NS may develop a number of life-threatening complications during their disease course, including venous thromboembolic disease. This complication arises in approximately 3% of childhood NS cases [27]. Despite our center is a tertiary care center, we observed only one venous thromboembolic complication in our NS patients which is less then general. The incidence of deep vein thrombosis and pulmonary embolisms has been reported much lower in Asians, and this has been attributed to ethnic diversity and genetic background. [28, 29].

The most frequent and important adverse effects of CS therapy are Cushing-like appearance, obesity, hypertension, growth retardation, ophthalmologic disorders including posterior subcapsular cataracts and raised intraocular pressure, behavioral changes and osteoporosis [19]. In our patients the most common side effects were Cushing-like appearance, osteopenia, obesity, and hypertension. In particular, bone mineral density may not be evaluated regularly in SSNS patients even those who had used long-term CS therapy. In our study, 18 of the 28 patients with low bone mineral density were SSNS patients who used CS longer than six months. We may suggest the evaluation of bone mineral density in patients who have received CS therapy longer than the standard protocol.

Our study has some limitations. The number of patients with SRNS and FSGS per 10-years periods between 1998 and 2018 was relatively small. We do not know whether there will be a difference in FSGS patients between the decades with a larger number of patients. Since our study includes a homogeneous population of Caucasian children, we do not know the trends of SRNS and FSGS in other ethnic groups. Because of the retrospective design of the study, some minor complications may not have been recorded in the medical files of the patients and triggers of the relapses been assessed. However, our study is important in terms of determining the factors that predict steroid resistance and stating that the frequency of SRNS and FSGS in 10-years periods is not different in a single tertiary center.

As a conclusion, the late onset is still an important marker for steroid resistance. The fact that microscopic hematuria was significantly related to steroid resistance and macroscopic hematuria was observed completely in SRNS patients gives a hint for potential steroid resistance at the beginning of the

disease. In addition, hypertension should also be considered as an important finding in terms of steroid resistance. Focal segmental glomerulosclerosis is not a disease but a histopathological diagnosis leading to different entities. Alport syndrome should also be kept in mind in patients with FSGS to avoid potentially toxic effects of immunosuppressive treatment.

Abbreviations

CKD: chronic kidney disease, CS: Corticosteroids, eGFR: estimated glomerular filtration rate, ESRD: end stage renal disease, FRNS: frequent relapsing nephrotic syndrome, FSGS: focal segmental glomerulosclerosis, INS: idiopathic nephrotic syndrome MCD: minimal change disease, MPGN: membranoproliferative glomerulonephritis, NS: Nephrotic syndrome, NRNS: Non-relapsing nephrotic syndrome, SDNS: steroid-dependent nephrotic syndrome SSNS: steroid-sensitive nephrotic syndrome, SRNS: steroid-resistant nephrotic syndrome

Declarations

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Conflict of/Competing Interest:

The authors declare no conflicts of interest

Availability of data and material:

Not applicable

Code availability:

Not applicable

Author Contributions

N Çiçek, N Yildiz and H Alpay participated in study design. N Çiçek and N Yildiz analyzed and interpreted the data. N Çiçek, S Güven and İ Gökçe collected clinical and laboratory data. N Çiçek and N Yildiz drafted the manuscript, and N Çiçek, N Yildiz and H Alpay reviewed the manuscript. Each author contributed important intellectual content during manuscript drafting or revision and approved the final version.

Ethics approval:

Ethics statement is approved by the local Marmara University School of Medicine committee of ethics (09.2016.241).

Consent to participate:

Not applicable, because only medical records were used retrospectively.

Consent to publish:

None to declare.

Tables

Table 1

Demographic and clinical characteristics of the patients

Characteristics of the patients	**SSNS n:134 (82.7%)**	**SRNS n:28 (17.3%)**	**P**
Age (years) (medianIQR))	4.51 (4.48)	9.05 (IR:7.95)	**0.002**
Follow-up time (years) (median(IQR))	5.56 5.12)	6.85 (IR:4.12)	0.26
Gender (F/M)	46/88	11/17	0.61
Oliguria	22	3	0.44
Hypertension	9 (6.7%)	12 (42.9%)	**0.000**
Microscopic hematuria	23 (17.2%)	16 (57.1%)	**0.000**
eGFR ml/min/1.73m^2 (median)IQR))	183 (136.7)	111 (176.7)	0.08
Kolesterol (mg/dl) (median(IQR))	363 (174.5)	351 (195)	0.53
Albumin (g/dl) (median(IQR))	1.7 (0.67)	2.1 (0.6)	0.12
Proteinuria (g/dl) (median(IQR))	116 (117.3)	81 (62.5)	**0.038**

eGFR: Estimated glomerular filtration rate, IQR: Interquartil range, NRNS: Non-relapser nephrotic syndrome, SDNS: Steroid-dependent nephrotic syndrome, SRNS:Steroid-resistant nephrotic syndrome, SSNS:Steroid-sensitive nephrotic syndrome

Table 2

Predictors of steroid resistant nephrotic syndrome in logistic regression analysis

Variable	B	SE	95% CI	Odds Ratio	p
Age	-0.110	0.047	0.817-0.982	0.896	**0.019**
Microscopic hematuria	-1.335	0.435	0.112-0.618	0.263	**0.002**
Hypertension	-0.630	0.592	0.167-1.700	0.532	0.287

Table 3

Side effects of corticosteroid therapy

Side effects of CS therapy	Patients n %)
Cushingoid features	47 (29)
Osteopenia	28 (17.3)
Obesity	28 (17.3)
Hypertension	10 (6.2)
Striae	21 (13)
Hirsutism	27 (16.7)
Ocular complications	18 (11.1)
Myopathy	2 (1.2)
GIS side effect	1 (0.1)

CS: Corticosteroid

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Figures

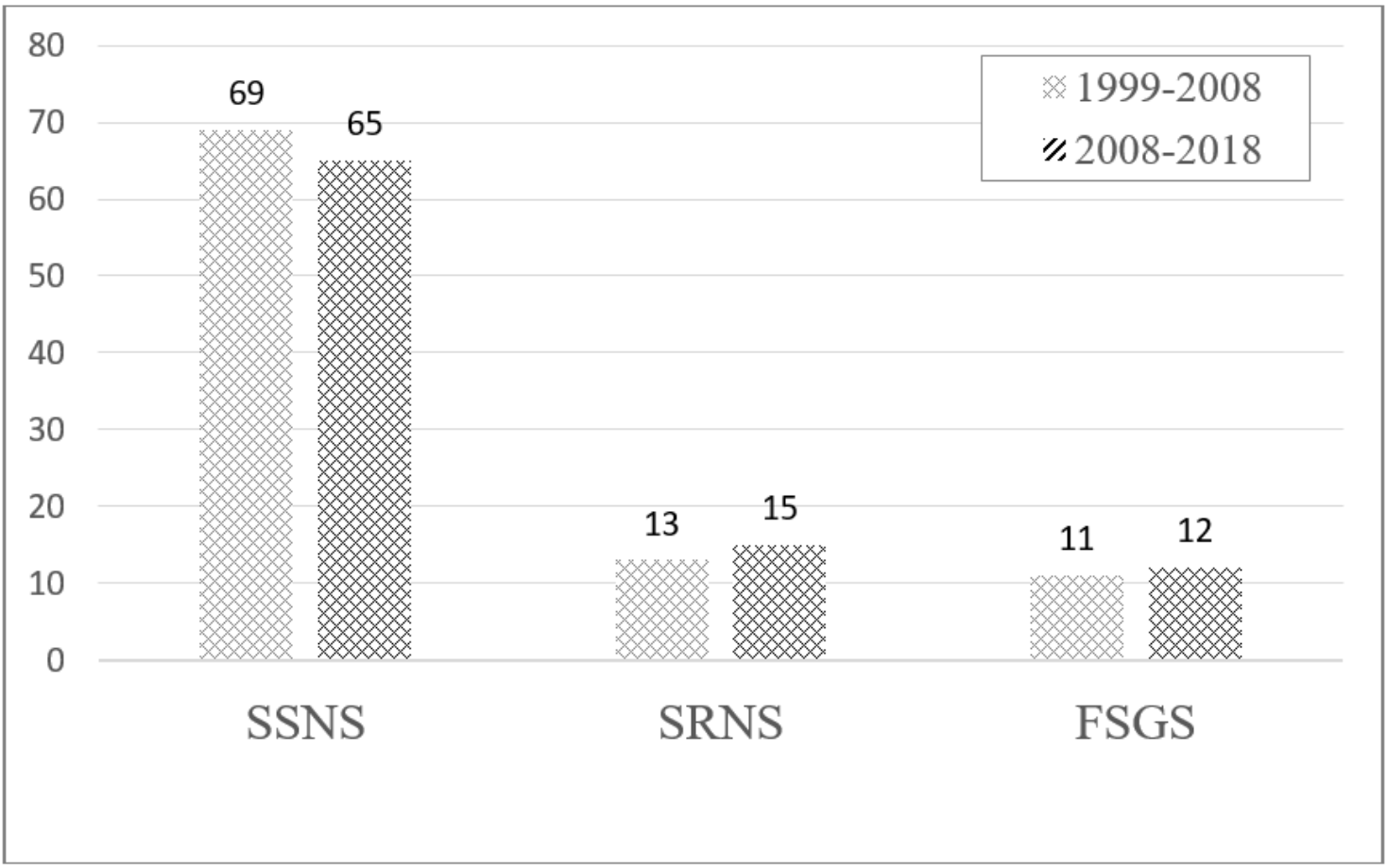

Figure 1

SSNS, SRNS and FSGS patients in the periods of 1999-2008 and 2008-2018

SSNS: Steroid sensitive nephrotic syndrome, SRNS: Steroid resistant nephrotic syndrome, FSGS: Focal Segmental Glomerulosclerosis

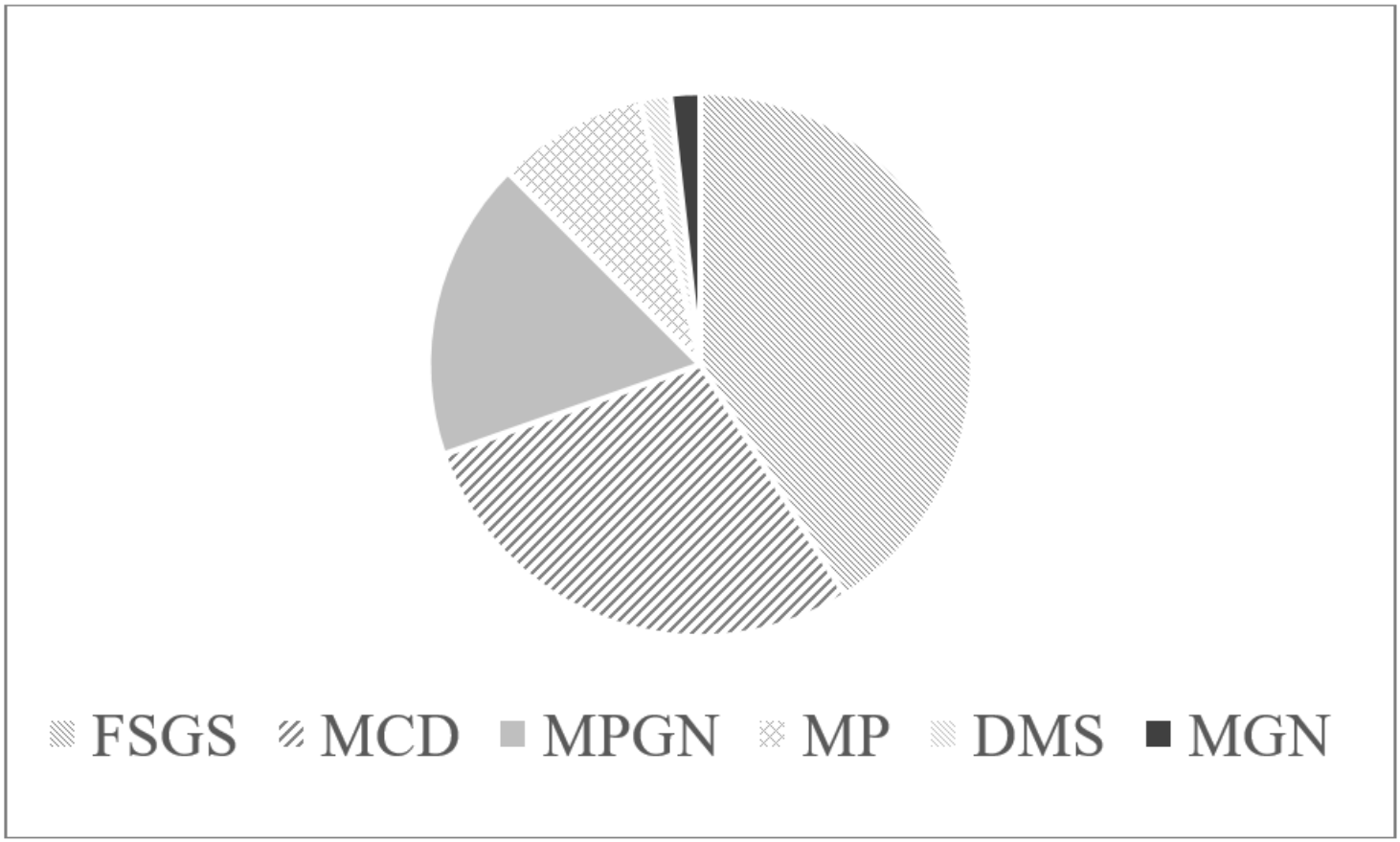

Figure 2

Histopathological findings in renal biopsies

FSGS:Focal segmental glomerulosclerosis, MCD:Minimal change disease, MPGN: Membranoproliferative glomerulonephritis, MP: Mesengial proliferatif glomerulonephritis, MGN: Membranous glomerulonephritis, DMS: Diffuse mezengial skleroz