

Clinical Features and Long-Term outcomes of Patients with Late Steroid Resistant/Sensitive Nephrotic Syndrome: A Single Center Study

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Objective: To find out clinical features and long-term outcomes of idiopathic childhood nephrotic syndrome(NS) patients with late steroid resistance(LSR)/late steroid sensitiveness(LSS).

Patients and Methods: A retrospective chart review was performed on 480 patients diagnosed with idiopathic childhood NS at Asan Medical Center Children's Hospital from 1990 to 2013. Twenty-four patients whose responsiveness to steroids changed over a minimum 2 year follow-up period (2–17.5 years) were investigated. All patients had undergone a renal biopsy.

Results: Among 480 nephrotic children, 428 (89%) were sensitive to the first steroid course. Of those who initially responded, 11 (2.5%) developed resistance to steroid therapy after relapses. LSR mostly developed between 1 month and 1 year after the initial episode. Six patients showed a minimal change and five showed focal segmental glomerulosclerosis (FSGS). Nine (82%) responded to cyclosporine or methylprednisolone pulse therapy. Of these, two had no further relapse, whereas the other seven experienced several relapses that ranged in length from 1.1 to 13.9 years. Three of the nine who initially responded to immunosuppression went on to experience several changes in steroid responsiveness. Two (18%) with resistance to immunosuppressants, including steroids, eventually progressed to end stage renal disease. Among the 52 patients (11%) who were initially steroid resistant, 13 (23%) were converted to steroid sensitive at relapses. Among these, 9 showed minimal change and 4 showed FSGS. Two had no further relapse and the other 11 responded to steroids on subsequent relapses ranging in length from 1.3 to 9.4 years. All these patients have had no further changes in steroid responsiveness with normal renal function.

Conclusions: In this study, 2.5% of initial steroid responders and 25% of initial steroid non-responders changed their responsiveness to steroids at subsequent relapses. Eighteen percent of LSR patients developed end stage renal disease. All of the LSS patients showed preserved normal renal function. Responsiveness to immunosuppressants seemed to be the most important factor determining long-term outcomes in LSR/LSS patients.

Key words: Idiopathic nephrotic syndrome, Late steroid resistance, Late steroid sensitiveness, Long-term outcome

Introduction

The incidence of idiopathic nephrotic syndrome (NS) is estimated to be 2–7/100,000 in children below 16 years of age¹. Idiopathic NS in children is classified as steroid sensitive or steroid resistant. Steroid sensitivity is most often associated with minimal changes in histology and a more favorable prognosis with resolution of relapsing NS, whereas steroid resistance is frequently associated with a focal segmental glomerulosclerosis (FSGS) histology^{2,3}. Children with steroid resistance are prone to having a complicated clinical and therapeutic course, with end-stage renal failure in 30–40% of them progressing to end-stage renal disease (ESRD) during long-term follow-up⁴. Some initially steroid-sensitive patients later develop steroid resistance, while the opposite also occurs. However, data on the variability of steroid responsiveness in idiopathic childhood NS patients with respect to disease course and prognosis of LSR (late steroid resistance)/LSS (late steroid sensitiveness) patients are scarce². We hypothesized that these patients showed relatively different clinical course and long-term outcome compared to those with initial steroid sensitivity/resistance. The purpose of this study was to find out the variability in steroid responsiveness and long-term outcomes of LSR/LSS patients with idiopathic childhood NS.

Materials and methods

1. Patients

We retrospectively reviewed the medical records of 480 cases with idiopathic childhood NS who had been managed with standard steroid therapy at Asan Medical Center Children's Hospital from 1990 to 2013. Twenty four patients with changed responsiveness to steroids within a minimum 2 year period of follow-up (2–17.5 years) were investigated.

Demographic variables, blood pressure, and laboratory data including serum creatinine, serum albumin, urinalysis, and 24 hour urine protein were reported at the time of initial diagnosis of NS and during follow-up. Time to development of LSR after the diagnosis of NS and the frequency of relapses until development of LSR were reported. Each non-steroid immunosuppressive drug used and patient responsiveness to each drug were

reported. Changes in steroid responsiveness and the final clinical status were reported. All patients underwent a renal biopsy and further biopsies were performed in patients who presented unexpected clinical deterioration. The specimens were examined by light, immunofluorescence, and electron microscopy by the renal pathologist.

2. Definitions

Our study applied the following definitions. NS was defined as proteinuria of ≥ 40 mg/hour/m² and hypoalbuminemia of ≤ 2.5 mg/dL. The definition of steroid resistance (SR), which was based on the International Study of Kidney Diseases in Children (ISKDC), was failure to respond during the first 8 weeks to prednisone therapy (60 mg/m²/day for 4 weeks, followed by 40 mg/m² three times a week for 4 weeks) during the first episode of NS⁵. Another definition used was (The French Pediatric Society of Nephrology) failure to go into remission after a treatment of 4 weeks with daily steroid therapy (60 mg/m²/day) followed by three pulses of methylprednisolone (1000 mg/1.73 m²) every other day⁶.

LSR was defined as initial complete remission (CR) of proteinuria in response to steroids and subsequent resistance to steroid therapy. LSS was defined as initial resistance to steroid and subsequent response to steroid therapy. Frequently-relapsing nephrotic syndrome (FRNS) was defined as NS with two or more relapses within 6 months, or four or more relapses within 12 months. A positive response to a drug was defined as protein-free urine (less than 4mg/hour/m² or negative dipstick) on at least three consecutive days.

3. Treatment

Children diagnosed as LSR were treated with the following regimens. Cyclosporine (CsA) was started at 5 mg/kg/24 h and then the dose was modified to achieve a trough level of 100–150 ng/mL. If patients responded to CsA, we had used this for average 1 year. If patients had not achieved CR with CsA for 3 months, we discontinued CsA and used the Mendoza protocol with methylprednisolone pulse and cyclophosphamide⁷.

Table 1. Characteristics of medical course in 11 children with LSR

Pt	Age at onset	Sex	Time to become LSR	Order of relapse	Immunosuppressants/Response	Pathology	Course of Steroid responsiveness	Final Serum Cr(mg/dL)	Final Status/ Medication	Duration of Follow up
1	1y3m	M	8m	1 st (IR)	CsA/CR	MCD	SR(1 st)>SS(3 rd)>SR(5 th)>SS(6 th)	0.6	IR/Steroid	10y6m
2	1y3m	M	3m	1 st (IR)	CsA/CR	MCD		0.2	No relapse	3y4m
3	2y5m	F	2y1m	2 nd (IR)	CsA/CR	FSGS		0.7	No relapse	13y
4	4y8m	M	12m	1 st (IR)	CsA/CR	FSGS	SR(1 st)>SS(2 nd)>SR(7 th)	0.8	IR/Steroid	7y10m
5	6y4m	M	4m	2 nd (FR)	mPD+CTX/CR	MCD	SR(2 nd)>SS(5 th)	0.4	FR/None	6y4m
6	6y6m	M	5m	1 st (IR)	CsA/NR mPD+CTX/NR	MCD>FSGS(32m)		17.6	ESRD(17y)	13y
7	7y6m	F	5m	2 nd (FR)	mPD+CTX/CR	FSGS	SR(2 nd)>SS(3 rd)	0.6	IR/CsA	16y5m
8	7y8m	M	3y4m	7 th (FR)	CsA/NR mPD+CTX/NR	MCD>FSGS(9y)		1.5	ESRD/KT(17y)	17y6m
9	12y10m	F	2m	1 st (IR)	CsA/CR	MCD	SR(1 st)>SS(2 nd)	0.7	FR/None	6y
10	14y3m	F	4m	1 st (IR)	CsA/CR	MCD	SR(1 st)>SS(4 th)	0.6	IR/None	5y10m
11	15y	F	6m	1 st (IR)	mPD+CTX/CR	MCD>FSGS(18m)	SR(1 st)>SS(2 nd)>SR(3 rd)>SS(4 th)>SR(5 th)>SS(6 th)	0.8	IR/Steroid	10y7m

LSR, late steroid resistance; IR, infrequent relapser; FR, frequent relapse; CsA, cyclosporine; mPD + CTX, methylprednisolone pulse+cyclophosphamide; CR, complete remission; MCD, minimal change disease; FSGS, focal segmental glomerulosclerosis; ESRD, end-stage renal disease; KT, kidney transplantation

Results

1. Incidence of changes in steroid responsiveness

Four hundred and eighty patients with idiopathic NS received the standard steroid therapy described above at the first episode of NS. Initial CR was achieved in 428 patients (89%). Fifty two patients (11%) were SR. In those patients who achieved CR with standard initial steroid therapy, 11 patients (2.5%) developed steroid resistance during subsequent relapses. Of the 52 initial SR patients, 13 patients (25%) later achieved CR with steroid therapy during subsequent relapses. Overall, 24 (5%) of patients with idiopathic childhood NS experienced a change in steroid responsiveness.

2. Clinical presentations and outcomes in children with LSR

A total of 11 patients developed LSR during the study period. The follow-up period of these patients ranged from 3 years to 17.5 years (10.0±4.6 years). Patient characteristics at initial diagnosis of NS, the responsiveness to the immunosuppressant regimen, and the clinical course over the study period are presented in Table 1. All 11 patients had documented CR after the initial course of standard steroid therapy. The patients comprised 6 males(54%) and

5 females(45%) with a mean age at diagnosis of NS of 7.1±4.3 years. The mean serum albumin concentration at presentation was 1.68± 0.47g/dL and the mean serum creatinine concentration was 0.42± 0.15 mg/dL. Median time from the diagnosis of NS to the development of LSR was 10.7 months (range: 2–40 months). In 9 of the 11 patients, the time to late resistance after onset of NS was shorter than 1 year. Seven patients developed LSR at the 1st relapse and three patients developed LSR at the 2nd relapse. Except for three patients, all LSR patients were infrequent relapsers until late resistance developed.

The 11 patients with LSR received initially immunosuppressant regimens with cyclosporine over the study period. Of these patients, six achieved CR. Three patients responded to a methylprednisolone pulse and cyclophosphamide after their disease could no longer be controlled by cyclosporine. Only two patients (18%) did not respond to these immunosuppressants (no. 5 and no. 8). Patients with resistance to therapy eventually developed ESRD. Two of nine patients who responded to therapy did not have relapse during follow-up period(no. 2 and no. 3). The other 7 (63%) subsequently relapsed for 1.2 to 10.6 years and 4 of them continued to respond to steroid. Three of 7 later experienced several changes in steroid responsiveness. One of 3 patients who developed subsequent steroid resistance

at the 5th relapse; one patient developed steroid resistance at the 7th relapse; and one patient developed steroid resistance at the 3th and 5th relapses (no. 1, no. 4, and no.11). All 3 patients finally became steroid sensitive and had normal renal function. At the last follow-up of 7 patients with frequent relapses, 3 patients were receiving low dose prednisolone on alternate days, while one patient was managed with CsA.

All the 11 patients with late steroid resistance who were initially SS underwent a renal biopsy. MCNS was observed in 5 patients and FSGS in 6. Of 6 FSGS patients, 3 had MCNS at the initial renal biopsy.

Responsiveness to immunosuppressants other than steroids was considered to be the most important determinant for the long-term prognosis of LSR patients.

3. Clinical presentations and outcomes in children with LSS

Initial steroid resistance was noted in 52 (11%) patients. Of 52 steroid non-responders, 24 responded to CsA or methylprednisolone pulse with cyclophosphamide. Following this treatment, 11 patients went into remission and showed no relapses until the end of the observation period. However, 13(25%) of 52 initial steroid non-responders developed further relapses that were steroid sensitive. We defined this phenomenon as late steroid sensitiveness.

All 13 patients with LSS relapsed after cessation or during reduction of CsA and showed changes in steroid responsiveness during this period. The follow-up period of these patients ranged from 2 years to 13.8 years (7.4±4.1 years). Patient characteristics at initial diagnosis of NS and the clinical courses are presented in Table 2. All 13 patients had documented CR in response to CsA. The patients comprised of 12 males (92 %) and one female (8 %) with a mean age at diagnosis of NS of 3.9±1.5 years. The mean serum albumin concentration at presentation was 1.36±0.44g/dL and the mean serum creatinine was 0.35±0.19 mg/dL. Median time from the diagnosis of NS to the change in steroid responsiveness was 10.01 months (range:4–33 months). Twelve patients changed to LSS at the 1st relapse and one patient changed to LSS at the 3rd relapse. The time to a change in steroid responsiveness in 10 of 13 patients was shorter than 1 year from initial diagnosis of NS (Table 2).

Only one of 13 patients who responded to steroids main-

tained remission for study period. The other 12 patients subsequently relapsed between 1.2 to 10.6 years after steroid response, and all of them were steroid sensitive throughout the study period. Five patients became infrequent relapsers and 7 became frequent relapsers. At last follow-up, 4 of 7 patients with frequent relapses continued to require immunosuppressive agents; of these 4 patients, 3 received CsA and one was managed with steroid. The mean final serum creatinine concentration was 0.47±0.16 mg/dL. Renal biopsies in 13 LSS patients demonstrated MCD in 9 and FSGS in 4. All patients with LSS tend to continue to be steroid sensitive and to have a good long-term prognosis.

Discussion

In this study, we characterized a subset of patients with childhood NS who developed a clinical course with late resistance to steroid treatment after initial responsiveness or late sensitivity to steroid treatment after initial resistance. LSS and LSR are rare phenomena, and their pathophysiologies are not well understood. Isolated larger studies of these patients have not been performed so far due to the rarity of this condition and the limited availability of data on the long-term outcomes of these children with childhood NS⁸.

Steroid resistance developed after initial remission in 3.3% of the ISKDC subjects⁵. According to the ISKDC, SR is defined as patients who fail to respond during the first 8 weeks to initial steroid treatment⁵. Kim et al. reported a higher incidence than that reported by the ISKDC. In this study, published in 2005, 115 (63%) out of 163 new-onset idiopathic NS patients were initially steroid sensitive, but 19 (17%) of these later became LSR [2]. In this study, SR was defined as no response after 4 weeks of daily steroid treatment. In the report of Zagury A. et al, LSR, defined as no response after 8 weeks of daily prednisone therapy, developed in 22 out of 639 (3.4%) children with SSNS¹⁰.

In our study, we defined SR as a lack of remission after 8 weeks of relapse treatment (60 mg/m²/d of corticosteroids for 4 weeks, then 40 mg/m²/day three times a week for 4 weeks, following the definition of ISKDC⁵). We also defined SR as a failure to go into remission after a treatment of 4 weeks with daily steroid therapy (60 mg per m²/day) followed

Table 2. Characteristics of medical course in 13 children with LSS

Pt	Age at onset	Sex	Time to become LSS	Order of relapse	Pathology	Final Serum Cr(mg/dL)	Final Status/Medication	Duration of Follow up(years)
1	1y6m	M	9m	1 st (IR)	MCD	0.5	No relapse	8y4m
2	1y10m	M	18m	1 st (IR)	FSGS	0.3	IR/None	8y10m
3	2y	M	8m	1 st (IR)	MCD	0.2	FR/None	8y3m
4	2y1m	M	6m	1 st (IR)	MCD	0.2	IR/None	2y
5	2y1m	M	4m	1 st (IR)	MCD	0.4	IR/Steroid	4y
6	3y3m	M	6m	1 st (IR)	FSGS	0.7	FR/None	8y4m
7	3y3m	M	9m	1 st (IR)	FSGS	0.3	FR/None	13y10m
8	4y3m	M	8m	1 st (IR)	MCD	0.1	FR/None	12y9m
9	4y6m	M	9m	1 st (IR)	MCD	0.3	FR/CsA	11y7m
10	4y9m	M	14m	1 st (IR)	MCD	0.8	FR/None	3y10m
11	5y5m	M	9m	1 st (IR)	MCD	0.2	FR/CsA	2y
12	6y8m	M	6m	1 st (IR)	MCD	0.4	IR/CsA	2y
13	8y10m	F	2y6m	3 rd (IR)	FSGS	0.1	IR/None	5y5m

LSS, late steroid sensitiveness; IR, infrequent relapser; FR, frequent relapse; MCD, minimal change disease; FSGS, focal segmental glomerulosclerosis; CsA, cyclosporine

by three pulses of methylprednisolone (1000 mg/1.73 m²) every other day, following the definition of the French Pediatric Society of Nephrology⁶. Applying this definition, the prevalence of LSR within our patients with initial SSNS amounted to approximately 2.5%. Kim et al. suggested that the epidemiology of steroid responsiveness in childhood NS patients is changing because prior reports done before 1990 showed that only 1% to 5% of children with NS develop LSR^{2,8,9}. However, our data were collected from patients diagnosed more recently than the data they collected. Thus, we believe that the high prevalence of LSR in Kim's report might be due to the shorter course of steroid.

An interesting finding in our study was that LSR during subsequent relapses, mostly occurred between 1 month and 1 year after the initial episode. We also found that 7 of 11(63%) LSR subsequently developed late resistance at the 1st relapse. In a study of Tarshish P et al., only 2 of 15 late non responders (13%) were frequent relapsers⁵. Kim et al. also reported that early relapse after initial remission and the occurrence of the first relapse while receiving the initial course of steroids were predictive factors of LSR². All these data including our study showed that an early relapse after initial remission and infrequent relapses were related to the occurrence of LSR.

Patients with late resistance seem to have a better outcome than those with initial resistance⁹. In the study of Jagury A et al., 2 (9%) of 22 children with late resistance and 55

(48.2%) of 114 with initial resistance progressed to ESRD¹⁰. Otukeshet al. found a better kidney survival rate in LSR: 83%of patients with LSR still had normal kidney function at 15 year after disease onset versus 34% of initial non responders at 15 years after disease onset¹¹. Straatmann C. et al. showed that 3 (10%) of 29 patients diagnosed as LSR developed ESRD and Schwadereret al. demonstrated no case of decreased renal function in 14 patients with LSR¹²⁻¹⁴. According to our study, of 52 initial steroid non-responders, 28 (54%) did not respond to immunosuppressants and 14 (27%) developed renal insufficiency, while only two (18%) of eleven LSR patients remained resistant to all treatments and progressed to ESRD. Therefore, LSR had better prognosis than initial SR as shown in other studies.

Of the 11 LSR patients in this study, MCD was observed in 8 patients and FSGS in 3 patients on initial histology. Diagnosis based on histologic findings did not seem to correlate with final outcome. Srivastava RN reported that of 11 LSR patients, 4 with resistance to cyclophosphamide eventually developed renal insufficiency⁹. Even though 7 of our LSR patients continued to have relapses and experience ongoing changes in steroid responsiveness, they maintained normal kidney function. Importantly, our findings showed that renal pathology or ongoing changes in steroid responsiveness did not influence the long-term prognosis of LSR patients and responsiveness to immunosuppressants was the most important prognostic factor¹⁵.

The concept of LSS in children with nephrotic syndrome who were initially steroid resistant is not yet established, and the epidemiology and long-term outcomes of children who experience LSS have not been studied. Our findings showed that a surprisingly large number of patients (13 patients, or 25%) changed their responsiveness to steroids at subsequent relapses, despite being initially steroid resistant. Interestingly, in contrast to LSR patients, patients with LSS experienced no further changes in steroid responsiveness and showed good long-term prognosis. It appears that the current prevalence of LSS and the clinical course of NS patients with LSS have not been reported. We also found that among 13 patients with LSS, 9 showed MCD and 4 showed FSGS on renal biopsies. Our observations suggest that patients with LSS are a heterogeneous group and that an FSGS histology is not invariably associated with a poor prognosis. This study represents an important step toward designing future studies on the unique phenomenon of LSS in pediatric NS patients.

This study has several limitations. First, this study is retrospective in nature. A retrospective study may be inadequate with respect to the enrollment of relevant patients and complete follow-up data. A complete follow-up period might have revealed less favorable outcomes in some patients. Second, all data were collected from a single center. Thus, simplicity of the geographic locations, impossibility to compare results between centers, and no variations in the management of childhood NS decrease the ability to extend the results of this study to other patients.

The strength of this study is that it is the first single center study to describe the long-term disease course and long-term outcome of LSR/LSS patients and it is the first observational study composed of a single ethnic group, Korean. While our data will increase our understanding of LSR/LSS, further study will be needed to develop evidence-based practice guidelines. A large prospective study is required to study the epidemiology, treatments, and outcomes of patients with LSR/LSS.

In summary, our data show that 2.5% of initial steroid responders and 25% of initial steroid non-responders changed their responsiveness to steroid. Our study showed that most patients with LSR/LSS have a relatively good long-term outcome when they are treated with immunosuppressive medications. Responsiveness of immunosup-

pressants seems to be the most important factor to take into consideration when making long-term prognoses for LSR/LSS patients.

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