Longterm Renal Outcome of Idiopathic Nephrotic Syndrome in Children

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ABSTRACT

Objective: To study longterm renal outcome of Thai children with idiopathic nephrotic syndrome (INS).
Methods: We retrospectively reviewed 75 followed-up in a tertiary care, university hospital. Male to female ratio was 2:1. Mean age at diagnosis was 6.2 years, and 56.0% were less than 5 years old. 57.3% previously received prednisolone from other hospitals and 32 patients (42.7%) were steroid resistant nephrotic syndrome (SRNS). Initial short stature was found in 1.3%. Hypertension and hematuria was found in 34.7% and 14.7%, respectively. Renal biopsy performed in 40 patients (53.3%) revealed minimal changes disease in 17 (42.5%), focal and segmental glomerulosclerosis (FSGS) in 12 (30.0%), mesangial proliferative glomerulonephritis in 5 (12.5%), IgM nephropathy in 4 (10%), and IgA nephropathy in 2 (5%) patients. Immunosuppressive medications included Cyclophosphamide in 64.5%, Tacrolimus in 14.7%, Cyclosporin in 8.0% and Mycophenolate mofetil in 4.0%. Enalapril was given in 48.0%.
Results: Mean follow-up time was 7.4 years. Complete remission was achieved in 77.3%. One patients (1.3%) had Chronic Kidney Disease stage 3 and 5 patients (6.7%) had End Stage Renal Disease (ESRD). One patient with ESRD died of severe respiratory tract infection. The factor associated with poor renal outcome was FSGS (p=0.032). Renal survival at 5,10, and 15 years were 95.3%, 85.7% and 57.2%, respectively. At last follow-up, short stature was found in 4.0% and hypertension in 20.0%. Other complications included cataract (29.3%), glaucoma (9.3%), diabetes mellitus (2.6%), septicemia (9.3%), other infections (10.6%).
Conclusion: We suggest that although renal outcome in Thai children may be better than in caucasian, longterm follow up is still needed, especially in children with FSGS.

Keywords: Idiopathic nephrotic syndrome; steroid sensitive nephrotic syndrome; steroid resistant nephrotic syndrome; focal segmental glomerulosclerosis; end-stage renal disease; chronic kidney disease

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INTRODUCTION

Idiopathic nephrotic syndrome (INS) or primary nephrotic syndrome (PNS) is characterized by massive proteinuria, hypoalbuminemia, hyperlipidemia, and edema without secondary causes such as systemic lupus erythematosus, infection or medications. Histological abnormalities of the glomeruli are mainly minimal changes disease (MCD), focal and segmental glomerulosclerosis (FSGS), and diffuse mesangial proliferation (DMP). Most INS patients, especially those with MCD, respond well to steroid therapy (steroid sensitive nephrotic syndrome; SSNS). However, some do not respond to steroid (steroid resistant nephrotic syndrome; SRNS) or have frequent relapses or are steroid-dependent and thus may require additional immunosuppressive drugs. Short and long-term compli-

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cations such as infections, hypovolemia, growth retardation and drug side effects are common. As high as 50% of SRNS patients were reported to develop end-stage renal disease (ESRD) after a follow-up of 10 years.[1] Progression to ESRD was reported to be more rapid in some races, for example 50% of African and Hispanic children were found to reach ESRD within 3 years and 95% after 6 years.[2] There are few reports on long-term renal outcome in Asian INS children.[3] This study aimed to study the complications and long term renal outcome of Thai children INS treated in a tertiary care university hospital.

MATERIALS AND METHODS

Patients less than 15 years old with a diagnosis of INS attending the renal clinic, Department of Pediatrics, Faculty of Medicine Siriraj Hospital, Mahidol University during 2004-2014 were reviewed. Those with an onset of disease during the first year of life or less than 2 years follow-up time were excluded.

Clinical, management and laboratory data at the time of presentation to the hospital and throughout the follow-up period were recorded. Renal pathological findings including light microscopy, immunofluorescence study, immunoperoxidase study and electron microscopy were noted. Estimated Glomerular Filtration Rate (eGFR) was calculated according to Schwartz equation.[4] Chronic kidney disease (CKD) and ESRD were classified according to the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative clinical practice guidelines for chronic kidney disease in children and adolescents.[5]

This study was approved by Siriraj Institutional Review Board (Si 274/2015).

Definitions

Complete remission: proteinuria less than 4 mg/m^2/hr or urine protein per creatinine ratio (UPCR) less than 0.2 mg/mg or urine albumin dipstick negative or trace.

Steroid sensitive nephrotic syndrome (SSNS): remission with steroid therapy alone in 4-8 weeks

Steroid resistant nephrotic syndrome(SRNS): no remission with steroid therapy for 8 weeks

Relapse: recurrence of proteinuria more than 40 mg/m^2/hr or urine protein per creatinine ratio (UPCR) more than 2 mg/mg or urine albumin dipstick not less than 3+.

Frequent relapse (FRNS): 2 relapses or more in 6 months or 4 relapses or more in 1 year Steroid dependent (SDNS): relapse during steroid therapy with tapering doses or within 2 weeks of steroid discontinuation.

Statistical analyses were performed using PASW 18.0. Baseline statistics were reported as mean±standard deviation. Chi-square test was used for comparing the categorical variables and p-values below 0.05 were considered significant.

RESULTS

Seventy-five patients were included in the study. Male to female ratio was 2:1, mean age at diagnosis was 6.2±3.6 years. 56.0% were less than 5 years old at diagnosis. 57.3% previously received prednisolone from other hospitals and 32 patients (42.7%) had SRNS. FRNS or SDNS were found in 19 patients (25.3%).

At Siriraj Hospital, initial height was at 3rd percentile or less in 1.3%. Most of the patients (82.7%) had height measurements between 25-90th percentile. Hypertension and hematuria was found in 34.7% and 14.7%, respectively. Serum albumin levels were 2.5 mg/dl or less in 78.1% (n=73). Mean serum cholesterol levels was 466.0±166.1 mg/dl (n=72) with 88% more than 250 mg/dl. Three patients (n=73) had transient eGFR levels less than 60 ml/min/1.73 m^2. (Table 1)

Renal biopsy performed in 40 patients (53.3% of 75 patients) revealed MCD in 17 (42.5%), FSGS in 12 (30.0%), DMP in 5 (12.5%), IgM nephropathy in 4 (10%), and IgA nephropathy in 2 (5%) patients. (Table 2) The indications for biopsy were mainly SRNS, FRNS, or SDNS.

Oral prednisolone 60 mg/kg/d was prescribed to complete at least an 8 weeks course. In patients with FRNS, SDNS, SRNS or those with serious steroid side effects, additional medications were prescribed. Cyclophosphamide was given orally in 49 patients (64.5%) including intrave-

TABLE 1. Initial clinical characteristic of 75 patients with Idiopathic nephrotic syndrome (INS).

Initial characteristic	Number (%)
Age ≥5 years at diagnosis	44.0
SRNS	42.7
Height ≤3rd percentile	1.3
Hypertension	34.7
Hematuria	14.7
Serum albumin ≤2.5 mg/dl (n=73)	78.1
Serum cholesterol ≥250 mg/dl (n=72)	88.0
eGFR ≤60 ml/min/1.73 m^2 (n=73)	4.1

Abbreviations: SRNS=Steroid Resistant Nephrotic Syndrome, eGFR=Estimated Glomerular Filtration Rate

nous cyclophosphamide in 1. Cyclosporin was prescribed in 6 SRNS patients (8.0%), Tacrolimus in 11 SRNS patients (14.7%), and Mycophenolate mofetil in 3 patients (4.0%). The decision for immunosuppressive agents were made by the attending physicians, the patients and their families. Cyclosporin and/or tacrolimus were prescribed mainly in SRNS. Enalapril was prescribed in 36 patients (48.0%) for proteinuria with or without hypertension. Other supportive treatments including antihypertensive agents, intravenous albumin, diuretics and antihyperlipidemia were given as indicated.

Mean follow-up time was 7.4±3.4 years. Complete remission was achieved in 58 patients (77.3%) and no remission in 11 patients(14.7%). One patient (1.3%) had CKD stage 3 (eGFR 47.8 ml/min/1.73 m^2) and another 5 patients (6.7%) reached ESRD including one patient who died from severe respiratory tract infection. Renal pathological findings in 6 cases with poor renal outcome revealed FSGS in 5 and MCD in 1. All received at least 6 weeks of oral cyclophosphamide, one patient also received cyclosporine, tacrolimus and mycophenolate mofetil, and another patient received tacrolimus alone. All 6 patients developed persistent proteinuria and several episodes of relapses during the follow-up period. On the other hand, 3 patients with initially decreased renal function recovered and none had CKD at last follow-up. No mortality was noted in the rest of the patients.

TABLE 2. Results of first renal biopsy in 40 patients.

Renal pathological diagnosis (n=40)	(%)
Minimal change disease	42.5
Mesangial proliferative glomerulonephritis	12.5
Focal and segmental glomerulosclerosis	30.0
IgM nephropathy	10.0
IgA nephropathy	5.0

Two patients with IgA nephropathy who presented with nephrotic syndrome were both female, aged 10.9 and 8.5 years at diagnosis. No hematuria or hypertension was detected. Prednisolone 2 mg/kg/d was tapered off after 4 weeks and Enalapril prescribed in both patients. One patient also received 12 weeks of cyclophosphamide. At last follow up, 10.9 years and 3 years, respectively, both patients were still in remission with normal blood pressure and eGFR.

At last follow-up of the 75 children, height measurements were at 3rd percentile or less in 4.0% and hypertension was found in 20.0%. Other complications included cataract (29.3%), glaucoma (9.3%), diabetes mellitus type II (2.6%), septicemia (9.3%), and other infections such as urinary tract infection, peritonitis, pulmonary tuberculosis and cellulitis (10.6%).

Using Chi-square test (Fisher's Exact test if expected count was less than 5) to compare between patients 5 years old or more with those less than 5 years old, no differences were found in the percentages of hematuria and/or hypertension at diagnosis. Percentages of patients with FSGS and initial steroid responsiveness was also similar.

Comparing between female and male patients, no differences were found in the percentages of hematuria and/or hypertension at diagnosis. Although FSGS was more common in female (p=0.008), initial steroid responsiveness was not different.

The percentages of FSGS and non-FSGS in SRNS patients also revealed no difference (75.0 vs. 64.3%, p=0.716).

Comparing 58 patients with complete remission with 11 patients with no remission plus 6 with poor renal outcome revealed no difference in percentage of age ≥ 5 years at diagnosis (p=0.79) or sex (p=0.845). FSGS was found less common in those with complete remission (41.7% vs. 82.1%, p=0.01).

TABLE 3. Risk factors for poor renal outcome (eGFR ≤60 ml/min/1.73 m^2 at last follow-up).

Risk factors	HR (95% CI)	P
Onset age ≥5 years old	5.03 (0.56-45.01)	0.149
Sex male	0.71 (0.14-3.61)	0.681
Initial hypertension	0.56 (0.01-3.19	0.512
Initial hematuria	1.16 (0.13-10.42)	0.895
Not response to steroid	3.68 (0.42-32.64)	0.242
FSGS in first biopsy	10.54 (1.23-90.28)	0.032

Abbreviations: FSGS=Focal and Segmental Glomerulosclerosis, eGFR=Estimated Glomerular Filtration Rate

Renal survival analysis using Kaplan-Meier method was shown in Fig 1. Renal survival at 5,10, and 15 years were 95.3%, 85.7% and 57.2%, respectively. Risk factors for poor renal outcome (eGFR less than 60 ml/min/1.73 m^2 at last follow-up) using cox regression analysis with Hazard ratio was shown in Table 3. FSGS was the only factor found to be associated with poor renal outcome (p=0.032).

DISCUSSION

Some demographic data of the patients in this study at first presentation was similar to other studies i.e. male preponderance and more than half of the patients were younger than 5 years. Percentage of children with initial hypertension was higher (34.7% vs.6-20%), but hematuria was similar to other reports (14.7% vs.13-36%).[1,6-8] The increased incidence of hypertension in this study may be due to high percentage of FSGS

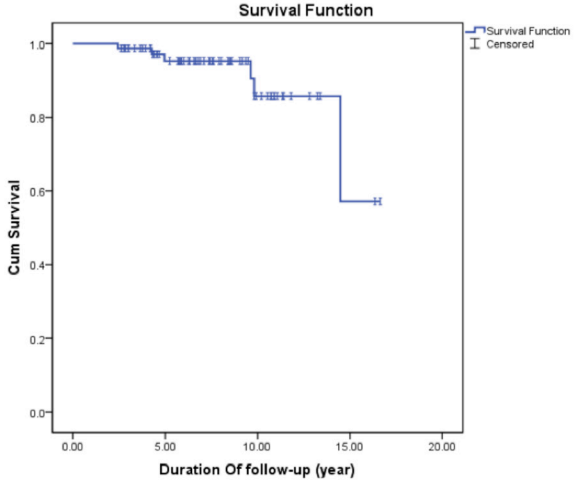

Fig 1. Renal survival at last follow up.

(30.0%) and the effect of previous treatment with prednisolone in more than half of the patients. Percentage of initial transient decreased renal function was also similar to other reports (4.1% vs. 0.8-19%).[1,6-8]

Renal pathological findings were repoted to vary according to race and environment.[8] The indications for biopsy may also vary in different centers. The International Study of Kidney Disease in Children studied histopathology in 521 INS children and reported 76.4% MCD, 6.9% FSGS, 7.5% Membranoproliferative GN, and 1.5% Membranous GN.[7] On the other hand, Gulati's study in 222 Indian INS children showed lesser percentages of MCD (34.2%), higher percentages of FSGS (39.1%), 16.2% Membranoproliferative GN, and 1.8% Membranous GN.[9] A study in 546 South African children showed a difference in the frequency of histopathology found in African and Indian INS children i.e. 13.5% and 46.8% MCD in African and Indian children, respectively. They also reported varied course of the disease among the groups, e.g. SSNS with MCD found in 37.5% of African versus 96.2% of Indian children.[10] Kirdpon S, et al in 1989 reported renal patholo-gical findings in 91 PNS children from Northea-stern part of Thailand revealed 16.5% MCD, 12.0% FSGS, 33.0% Mesangial proliferative GN, 30.8% Membranoproliferative GN, and 7.7% Membranous GN. The authors proposed that the causes of high incidence of Mesangial proliferative GN and Membranoproliferative GN may be chronic infection and malnutrition.[11] Another study by Chulamokha Y and Vanapruks V in 97 cases of Thai PNS aged 1-16 years also revealed high percentage of Mesangial proliferative GN and less MCD i.e. 49.5% Mesangial proliferative GN, 22.7% MCD, and 11.4% FSGS.[12] Kashem-sant C, et al studied 174 biopsy specimen in PNS children and found Mesangial proliferative GN to be the most common pathological findings (62.6%) whereas MCD was found in 10.9% and FSGS in 10.9%.[13] More than 20 years later, renal pathological findings in this study revealed 42.5% MCD, 30.0% FSGS, 12.5% DMP, 10% IgM nephropathy, and 5% IgA nephropathy. Overall, MCD was found to be less common and Mesan-gial proliferative GN more common in Thai chil-dren than in Cau-

casian and probably reflected the Asian population. Notably, IgA nephropathy was found in 5% of those who had renal biopsy in this study. This is similar to a study in 538 INS children in Pakistan where 1.1% of the histological lesions were IgA nephropathy. Comparing renal pathological findings between the adolescents and young children, FSGS and MCD were found in 36.4% and 28.9% in their adolescents patients and 39.2% and 51.2%, respectively in young children.[14] Recently, Shima Y, et al studied 426 children with IgA nephropathy, 7% of which presented with nephrotic syndrome (NS-IgAN) and found that renal survival was good (92.4% at 10 years), although significantly lower than non-NS-IgAN.[15] Both children with NS-IgAN in this study also had good long-term renal outcome.

However, as renal biopsy was performed mostly in those with FRNS, SDNS, or SRNS in this study and several others, pathological information in children with SSNS and infrequent relapse were probably not included.

Most children with INS responded to steroids and about 20% were SRNS.[16] Renal pathological findings in most children with SSNS were MCD. The new KDIGO guideline for SSNS recommend that corticosteroid therapy should be given for at least 12 weeks to reduce the risk of relapse. They also recommend that alkylating agents, cyclophosphamide or chlorambucil; Mycophenolate mofetil; Levamisole and calcineurin inhibitors be given for FRNS and SDNS.[17]

The incidence of SRNS was found to vary according to ethnic pattern and South Asian children had a lower risk.[18] The high incidence of SRNS in this study (42.7%) may reflect a selection bias as more than half of the patients were referred from other hospitals because of treatment difficulties. The KDIGO guideline for SRNS recommended a calcineurin inhibitor with low-dose corticosteroid as initial therapy. Angiotensin-converting enzyme inhibitors (ACEI), angiotensin II receptor blockers (ARB), Mycophenolate mofetil and high-dose corticosteroids may also be beneficial.[16]

Resistance to steroids and renal pathological findings of FSGS were reported to be important risk factors of CKD in INS. The progression to ESRD may be as high as 50% within 5 years. [16,19,20] A study in 181 French children with SRNS showed renal biopsy results to be MCD in 34.3% and FSGS in 65.7%. Renal survival rates were 65%,50%, and 34% at 5 ,10, and 15 years, respectively.[1] Another study in 372 Turkish children with INS revealed SRNS in 19.6% and 15.2% of the patients who were SRNS developed CKD and ESRD compared with 0% of SSNS. Renal pathology results were FSGS in 57% and SRNS was also higher in this group.[6] The Southwest Pediatric Nephrology Study group studied 75 children with FSGS and reported ESRD in 21% and CKD in another 23%.[21] On the other hand, a study in 92 FSGS children with SRNS from South Korea reported renal survival rates of 84%,64%, and 53% at 5,10,15 years respectively. ESRD was found in 21.7% and CKD in 9.8%.[22] Long-term outcome of 69 Japanese children with SRNS also revealed ESRD in 13%. Risk factors for ESRD were age not less than 11 years at diagnosis, FSGS as the first renal biopsy findings and cyclophosphamide as the first immunosuppressive agent.[3] In this study, renal survival was slightly better than Caucasian children and similar to Korean patients. We also found that FSGS was the only factor to be associated with poor renal outcome ($p=0.032$).

In conclusion, this study showed that long-term renal outcome of INS may be better in Asian children including Thai children. Apart from complications mainly due to medications, CKD and ESRD are still a threat in INS. Renal biopsy may be helpful in predicting those with poor renal outcome as we found that FSGS was the only factor to be associated with poor renal outcome.

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