

## ORIGINAL ARTICLE

## Description of Renal Biopsy in Frequently Relapsing and Corticosteroid Non Responsive Nephrotic Syndrome in Childhood

by

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### Abstract

A study of 71 children with nephrotic syndrome admitted to the Department of Child Health, Medical School, Sriwijaya University/Palembang General Hospital between November 1981 and November 1983 has been reported.

Of the 71 children, there were 50 (70.4%) boys and 21 (29.6%) girls, in which 31 were less than 6 years of age. During the first eight weeks complete remission was found in 66 patients. The other five were steroid resistant.

Among the 66 patients who responded to steroid, 61 had remission within the first 4 weeks. Further observation up to two years, 3 patients were still in remission, 36 had one relapse and 22 had frequent relapses.

The other 5 patients, who had remission on the second 4 weeks, one had one relapse, two had frequent relapses and the other two were not available for follow up.

Renal biopsy was performed in 31 patients. The representative results of the renal biopsy were found in only 20 patients :

- Eleven patients showed minimal change nephrotic syndrome (MCNS). Ten of these patients had frequent relapses, while one patient was steroid resistant. Two had renal insufficiency.
- Three patients had focal glomerulosclerosis (FGS); two of them were frequently relapsing patients and the other one had steroid resistant.
- Four patients had mesangial proliferative glomerulonephritis (Mes. PGN). All of them had frequent relapses.
- One patient with diffuse proliferative glomerulonephritis (DPGN) was steroid resistant.
- One patient with crescentic glomerulonephritis (CrGN) was also steroid resistant.

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### Introduction

Corticosteroid has been used for the treatment of nephrotic syndrome in children since more than 20 years ago (Arneil, et al., 1966). The response of treatment varied. Most children with idiopathic nephrotic syndrome (INS) responded to steroid within 8 weeks, but in the course of the disease they usually have subsequent relapse (White et al., 1970; Arneil, 1971; Schwartz et al., 1974).

Generally, children who responded to steroid within four weeks had minimal change nephrotic syndrome (MCNS) and 93.7% of them were less than six years of age (ISKDC, 1981).

Children who were steroid resistant or had frequent relapses, or had symptoms of nephritis such as hematuria, hypertension, renal insufficiency, particularly who were 6 years of age or older, were likely to have other glomerular features on renal biopsy examination. Some authors have reported the renal morphology of these patients (Churg et al., 1970; White et al., 1970; Habib et al., 1979).

The purpose of this paper is to report the description of renal biopsy in patients who have frequent relapse INS or are resistant to steroid in association with clinical and laboratory findings.

### Materials and Methods

Seventy one patients with INS were hospitalized at the Department of Child Health, Medical School, Sriwijaya University/Palembang General Hospital between November 1981 and November 1983.

The diagnosis of INS was based on the presence of classical and laboratory features of edema, hypercholesterolemia ( $>250$  mg%), hypoalbuminemia ( $<2.5$  g/dl) heavy proteinuria ( $>40$  mg/hour/M2 BSA), no evidence of underlying systemic disease or exposure to agents known to be associated with nephrotic syndrome.

The corticosteroid (prednisone) was given to the patients in accordance with the scheme of ISKDC (1981).

Initial prednisone treatment was 60 mg/24 hours/M2 (maximum dosage 80 mg/24 hours/M2) in divided doses for 4 weeks, followed by 40 mg/24 hours/M2 in divided doses 3 consecutive days out of seven for 4 weeks.

Furthermore the following criteria were defined :

- Remission: no edema and urine free of protein by qualitative testing for 3 consecutive days.
- Response: a reduction in rate of urinary excretion of protein to 4 mg/hour/m2 BSA for 3 consecutive days.
- Relapse: Reappearance of proteinuria 40 mg/hour/m2 BSA (sulfosalicylic acid test ++ or more) for 3 consecutive days.
- Frequent relapses two or more relapses within six months of the initial response.
- Steroid resistant: if no remission occurred within the period of 8 weeks after the initial period of treatment.
- Hematuria: if more than 3 RBC/HPF were found in the sediments of urine (Murphy et al., 1979).
- Hypertension: if a diastolic pressure exceeded 90 mmHg (Schwartz et al., 1974).
- Azotemia: if the serum urea level was more than 50 mg%.

Renal biopsy was performed in patients with INS based on the modification of criteria made by Solcedo and Parrish (1976).

- In all patients who were steroid resistant and or had frequent relapses.
  - In all patients over six years of age with nephritic manifestations i.e: hematuria, hypertension and renal insufficiency.
- Renal tissue was fixed in 10% formalin solutions and sent to the Department of Pathology, Medical School Sriwijaya Uni-

versity/Palembang General Hospital, as well as to the Department of Pathology, University of Indonesia/Cipto Mangunkusumo General Hospital, Jakarta. Renal specimens were only evaluated by light microscopy.

The morphological classification is based on the classification adopted by Churg et al. (1970), which is correlated with the clinical and laboratory findings and response to treatment.

### Results

Of the 71 patients with INS there were 50 (70.4%) boys and 21 (29.6%) girls. The male/female ratio in this series was 2.4/1. More than half (56.3%) were under six years of age (table 1).

Table 1 : *Distribution of idiopathic nephrotic syndrome patients according to age and sex.*

AGE (YEARS)	SEX		No. of patients	%
	MALE	FEMALE		
1 - 3	6	4	10	14.1
3 - 6	17	4	21	29.6
6 - 9	15	3	18	25.3
9 - 12	12	9	21	29.6
12 - 15	-	1	1	1.4
TOTAL	50	21	71	100.0

Among the 71 INS patients, 66 (93%) showed remission within the first 8 weeks of treatment. The other five patients were resistant to steroid. Among the 66 patients who showed remission within the first 8 weeks, 61 occurred within first 4 weeks of therapy.

On further observation up to 2 years, 3

patients were still in remission and remained asymptomatic without medication, 36 had one relapse and 22 had frequent relapses. Of the five patients who showed remission in the second 4 weeks, one patient had only one relapse, two had frequent relapses and two were not available for follow up (table 2).

Table 2 : *Results after initial period of treatment with steroid*

Interval period of treatment	No. of patients	Remission	Relapse	Frequent relapses	Steroid resistant	Still in remission	No follow up
0 - 4 weeks	61	61	36	22	--	3	--
5 - 8 weeks	10	5	1	2	5	--	2
TOTAL	71	66	37	24	5	3	2

Renal biopsy was performed in 31 of the 71 patients: 22 specimens derived from patients with remission in the first 4 weeks, four from 5 patients with remission in the second 4 weeks and the other 5 from the steroid resistant group.

Twenty two patients who had remission

in the first 4 weeks showed frequent relapses. The representative results of the biopsy specimen were found in 15 patients consisted of :

- 9 with MCNS.
- 2 with FGS.
- 4 with Mes.PGN. (table 3).

Table 3 : *Correlation of steroid response with histopathological features in idiopathic nephrotic syndrome patients*

Response to steroid	Histopathological features				
	MCNS	FGS	DPGN	Mes.PGN	Cr.GN
within 4 weeks	9	2	-	4	-
within 8 weeks	1	-	-	-	-
steroid resistant	1	1	1	-	1
TOTAL	11	3	1	4	1

- MCNS : Minimal changes nephrotic syndrome.
- FGS : Focal glomerulosclerosis.
- DPGN : Diffuse proliferative glomerulonephritis.
- Mes. PGN : Mesangial proliferative glomerulonephritis.
- Cr. GN : Crescentic glomerulonephritis.

In four patients who had remission in the second 4 weeks, two had frequent relapses, one patient had only one relapse and the other one was not available for follow up. The representative result of biopsy was found in only one patient, who had frequent relapses in the form of MCNS.

Of the 5 specimens derived from patients with steroid resistant, the representative results of biopsy were found in 4 in the form of :

- one patient with MCNS.
- one with FGS.
- one with DPGN.
- one with Cr.GN. (table 3).

Hematuria was present at the time of the first examination in 30 (42.2%) patients. This symptom was found in :

- 23 patients who had remission within the period of 4 weeks in whom 3 patients were well and remained asymptomatic, 7 had one relapse and 13 had frequent relapses.
- 2 patients with remission in the second 4 weeks, later on became frequent relapser.
- 5 patients were resistant to steroid.

Of the 31 patients on whom biopsies were performed, 20 had hematuria, consisted of :

- 13 patients derived from the patients who had remission within the first 4 weeks. All of them had frequent relapses. The representative results of biopsy were only found in 8 patients, in which: 5 patients were MCNS, 1 was FGS and two were Mes.PGN.
- Two patients had remission in the second 4 weeks of treatment. All of these patients had frequent relapses. No re-

presentative results of biopsy were obtained from these patients.

- Five patients were steroid resistant. The representative results of biopsy were only obtained from four patients i.e: one with MCNS, 1 with FGS, 1 with DPGN, and one with Cr.GN.

Renal insufficiency was observed in 13 of the 71 patients, consisted of :

- 10 patients with remission in the period of the first 4 weeks. Six of them had only one relapse and the other 4 had frequent relapses.
- one patient with remission in the second 4 weeks period. In this patient relapse occurred only once.
- Two patients were resistant to steroid. Renal insufficiency were transient in 12 of the 13 cases, the other one developed end stage renal failure.

Of the 31 patients on whom biopsies were performed, six had renal insufficiency, consisted of :

- 4 specimens derived from patients who had remission in the period of 4 weeks. All of these patients had frequent relapses. The representative results of biopsy were only found in two patients in the form of MCNS.
- two specimens derived from patients who were steroid resistant. The results of renal biopsy showed DPGN and Cr. GN respectively.

Hypertension was initially presented in two cases. At the time of the last examination it was still present in one case and was associated with the end stage renal failure. Those two patients were resistant to steroid therapy. Result of renal biopsy in each patient showed DPGN and Cr.GN.

Table 4 : *Correlation of clinical symptoms with histopathological features in idiopathic nephrotic syndrome patients*

Glomerular change	Number of patients	Clinical symptoms		
		Hematuria	Hypertension	Renal insufficiency
MCNS	11	6	-	2
FGS	3	2	-	-
DPGN	1	1	1	1
Mes.PGN	4	2	-	-
Cr.GN	1	1	1	1
<b>Total</b>	<b>20</b>	<b>12</b>	<b>2</b>	<b>4</b>

- MCNS : Minimal changes nephrotic syndrome.  
 FGS : Focal glomerulosclerosis.  
 DPGN : Diffuse proliferative glomerulonephritis.  
 Mes. PGN : Mesangial proliferative glomerulonephritis.  
 Cr. GN : Crescentic glomerulonephritis.

The results of histopathological examination and correlation with clinical finding were presented in table 4.

#### 1. MCNS (11 cases).

Ten patients had frequent relapses and the other one was steroid resistant. Hematuria was found in six and renal insufficiency in two patients.

#### 2. FGS (3 cases).

Two had frequent relapses and the other one was steroid resistant. Two patients showed hematuria.

#### 3. PGN (6 cases).

- DPGN in one patient was resistant to steroid and was accompanied by hematuria, hypertension and renal insufficiency.
- Mes.PGN (4 cases). All showed frequent relapses, two of them had hematuria.
- Cr.GN (1 case). This patient was resistant to steroid and had hematuria, hypertension and renal insufficiency.

### Discussion

The distribution of INS patients in our observation showed that the number of affected boys were more than girls, the male/female ratio being 2.4 : 1. White et al. (1970) reported a ratio of 1.6 : 1. We also

found that more than half of our cases were over six years of age. This finding differs from the results reported by some authors (White et al., 1970; Rance et al., 1976; Habib et al., 1979).

The majority of children with INS responded to steroid therapy and most of them had MCNS. Arneil and Lam (1966) reported 93% of childhood nephrosis responded to steroid and White et al. (1970) showed that 97% of the cases who responded to steroid had MCNS on biopsy.

Most children with MCNS will relapse but approximately 25% had frequent relapses (ISKDC, 1974).

In our study of 71 cases with INS, there were 66 (93%) cases who responded to steroid within the first 8 weeks of initial treatment, but in the course of the disease we found that 37 (56%) patients had one relapse, 24 (36.4%) had frequent relapses, 3 (4.5%) were in persistent remission and 2 were not available for follow up. The other 5 were patients who were resistant to steroid therapy.

Results of renal biopsy in 16 cases who had frequent relapses INS showed only 10 patients with MCNS. The other six consisted of : - 4 with Mes PGN.

- 2 with FGS.

The results indicated that it was not possible to identify the renal lesion precisely from patients response to steroid.

It seems that the other form of glomerular pathology in our cases may be related to age and clinical symptoms of the patients at the time of hospitalization.

The results of biopsy in INS patients with hematuria showed that 6 (50%) cases had MCNS (table 4), and the other six consisted of: two patients with FGS, two with Mes.PGN, one with DPGN and one with Cr.GN.

White et al. (1970) and Habib et al. (1979) stated that hematuria was rarely found in INS patients with MCNS and more often found in FGS and PGN. White et al. (1970) only found hematuria in 13% cases of INS with MCNS.

The difference between their finding and ours may be caused by the fact that materials in our study were small.

Steroid resistant patients generally showed other form of glomerular pathology i.e: FGS and DPGN (Habib et al., 1979).

Of the 4 steroid resistant patients the renal biopsies revealed: one with MCNS, one with FGS, one with DPGN and one with Cr.PGN. All of them showed hematuria, hypertension, and renal insufficiency.

The prognosis is bad in most of patients who do not respond to therapy (Mc Enery and Strife 1982). Death may occur because of renal failure (early or late) or because of intercurrent complications (infectious and thrombotic) most of which are related to therapy.

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