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Treatment Strategy for Pediatric Patients with Nephrotic Syndrome with Microscopic Hematuria at the Onset: A Retrospective Study of the Need for Kidney Biopsy

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Summary

Nephrotic syndrome (NS) in children responds well to steroid therapy, therefore kidney biopsy before treatment is often avoided. However, the indications for kidney biopsy in children with NS with microscopic hematuria are controversial. In the present study, the indications for pretreatment kidney biopsy at the onset of pediatric patients with NS with microscopic hematuria were evaluated. Clinicopathologic correlations were retrospectively examined from patients enrolled in a database from January 2005 to December 2018. Fifty-nine pediatric patients with NS were enrolled. Among them, 6 with hypocomplementemia, gross hematuria, or onset at less than 1 year of age were excluded. Of the 53 enrolled patients, 38 without hematuria were assigned to Group A, and 15 patients with microscopic hematuria comprised Group B. There was a significant difference in the renal biopsy rate between Group A (n = 19, 50%) and Group B (n = 13, 87%) (P = 0.01). Two patients in Group B avoided biopsy. Pathology results for patients in Group B included 4 patients with minimal change disease, 2 with focal segmental glomerulosclerosis, 6 with mesangial proliferative glomerulonephritis (non-IgA), and 1 with membranous lupus nephritis (LN). The first three are commonly found in pediatric patients with NS, and all are treated with steroid therapy. LN could be diagnosed by kidney biopsy at the time of steroid resistance. LN presenting with nephrotic syndrome is also treated with steroids. Thus, the treatment strategy would not have changed even if the kidney biopsy had been performed before treatment. These results suggest that renal biopsy is not always mandatory during the initial stage for pediatric patients with NS with microscopic hematuria.

Key Words: Child, Hematuria, Kidney biopsy, Minimal change disease, Nephrotic syndrome

Introduction

The pathogenesis of nephrotic syndrome (NS) in adults is more variable than in children[1-4]. Therefore, in adults, kidney biopsies are performed early in the course of the disease to confirm the histologic diagnosis. Treatment with steroids and immunosuppressive agents is usually initiated after that[1]. In contrast, more

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than 90% of patients with childhood-onset NS are minimal change disease (MCD), and most patients with MCD respond to steroid therapy[5]. Kidney biopsies are invasive procedures with a risk of bleeding in pediatric patients. Therefore, steroids are often given as initial treatment to avoid kidney biopsies in children with NS[3].

Recently, clinicians have had differing opinions regarding the indications for kidney biopsies for childhood-onset NS. Ishikura *et al.*[3] recommend that kidney biopsies are performed before initial steroid treatment if a diagnosis other than MCD is suspected. For example, kidney biopsies should be considered when the child is less than 1 year old and has persistent hematuria, gross hematuria, hypertension, renal dysfunction, hypocomplementemia, and extrarenal symptoms such as purpura. The KDIGO guideline (2021)[6] recommends kidney biopsy for patients with gross hematuria but does not mention microscopic hematuria. Hama *et al.*[7] also argued that the indications for kidney biopsy before steroid treatment are controversial. They suggested using the maximum RBC range (30-49/HPF) as a criterion for kidney biopsy in patients with NS with hematuria may be reasonable in clinical practice.

The present study examined whether kidney biopsies can be avoided when initial steroid therapy is administered to children with NS with microscopic hematuria. Whether initial steroid therapy is acceptable in children with NS was also evaluated, including various other non-MCD histologic types.

Materials and Methods

Pediatric patients with NS seen in the Department of Pediatrics, Dokkyo Medical University Hospital (Mibu, Japan) were reviewed, when treatment was started at the onset of the disease. The observation period for this study was 14 years, between January 2005 and December 2018. In addition, enrolled patients were studied retrospectively using the electronic database at the hospital. To gain access to patient medical records for this investigation, application was made to the Research Ethics Committee of Dokkyo Medical University and approval obtained (Approval No. R-28-7 J).

With reference to Hama *et al.* (2015)[7], Diven *et al.* (2000)[8], Grossfeld *et al.* (2001)[9], and KDIGO 2012[10], the diagnostic criteria for pediatric NS and the criteria for hematuria used in this study were as follows: (1) The definition of pediatric NS was albumin < 2.5 mg/dl and urinary protein creatinine ratio ≥ 2.0 g/gCr; (2) hematuria was defined as an occult blood reaction of ≥ 2+ by the simple tape method/urine dipstick test or RBC ≥ 5/HPF on visual examination of sediment with a microscope lasting ≥ 2 days before treatment. The value of the most prominent finding was used for blood and hematuria data. When hematuria was evaluated using qualitative and sediment methods, data from the sediment method were used. The following patients were excluded as part of the findings for which kidney biopsy should be considered before treatment: infants less than 1 year of age and patients with gross hematuria, hypocomplementemia, or purpura. Patients over the age of 16-years were also excluded.

Patients with pediatric NS enrolled in the present study were classified into two groups: Group A included patients without hematuria, and Group B included patients with hematuria before initial treatment. Patients in Group A and Group B were further classified into two treatment groups: (1) patients with steroid-sensitive nephrotic syndrome (SSNS) and (2) patients with steroid-resistant nephrotic syndrome (SRNS). For each optimal situation, we studied the following parameters in detail: (1) gender and age at onset; (2) serum albumin and protein/creatinine ratio in urinalysis examination; (3) the percentage of patients with clinical edema, hypertension, estimated glomerular filtration rate from serum creatinine (Cr-eGFR) < 90 ml/min/1.73 m^2, and proteinuria selectivity index (SI) < 0.20; (4) the percentage of patients with SRNS; and (5) the percentage of patients who underwent kidney biopsy. The effectiveness of performing a kidney biopsy during the clinical follow-up of childhood-onset NS was investigated. Hypertension was defined as a mean systolic blood pressure ≥ 95th percentile (on the basis of age and gender)[11]. Cr-eGFR was calculated using the polynomial eGFR formula showing the relationship of body length and serum Cr level in Japanese children[12]. Those with Cr-eGFR < 90 ml/min/1.73 m^2 were considered as having renal impairment[13]. The selectivity index [clearance ratio of immunoglobulin (Ig)G to transferrin (Tf)] for proteinuria was calculated using

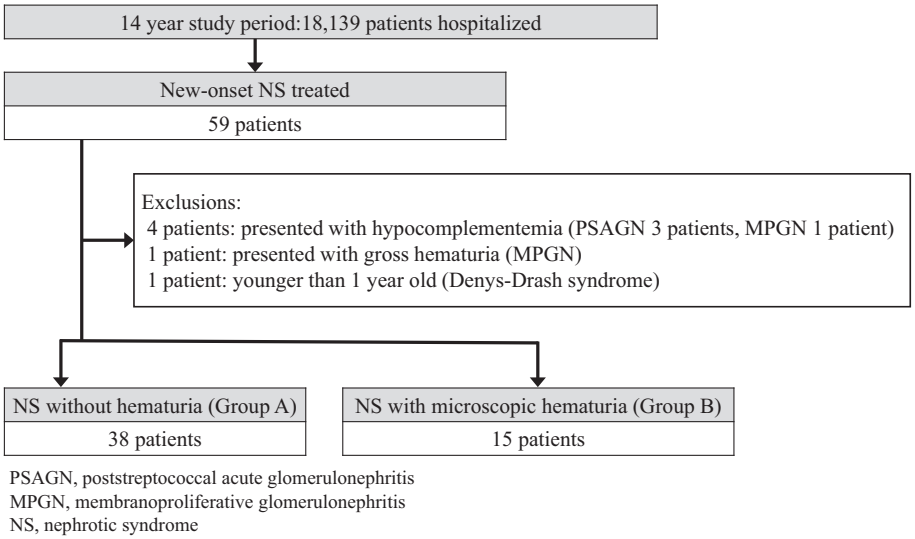


Figure 1 Flowchart of childhood-onset nephrotic syndrome (patients from the Department of Pediatrics, Dokkyo Medical University Hospital between 2005 and 2018)

the following formula; [SI = urine IgG/ serum IgG × serum Tf/urine Tf]. SI < 0.2 was defined as high selectivity[14].

Thirdly, the following were evaluated: (1) the histopathological findings in all patients who underwent kidney biopsy in childhood; (2) the relationship between the degree of hematuria and responsiveness to steroid therapy; and (3) the relationship between the degree of hematuria and histopathological findings at kidney biopsy.

Results

1. Clinical flowchart of pediatric patients with NS, with or without hematuria, and exclusion criteria

The overall flow of the present study is shown in Fig. 1. Enrolled patients were extracted from 18,139 hospitalizations during the 14 year study period. All patients with first-episode NS during this period were managed as inpatients. During the study period, 59 pediatric patients with NS were included. Among them are four patients with hypocomplementemia, including three with poststreptococcal acute glomerulonephritis, one with membranoproliferative glomerulonephritis, and another with membranoproliferative glomerulonephritis with gross hematuria, who were excluded according to the predefined exclusion criteria. In addition, one patient with macrohematuria with membranoproliferative glomerulonephritis and one with Denys-Drash syndrome onset at less than 1 year of age were also excluded. Of the 53 enrolled patients in the final cohort, 38/53 (72%) without hematuria were assigned to Group A, and 15/53 (28%) with hematuria were assigned to Group B. The age range of the enrolled patients with pediatric NS was 1 to 16 years.

2. Clinical features of Groups A and B with pediatric NS

The clinical characteristics of enrolled pediatric patients with a NS without hematuria (Group A) and with hematuria (Group B) are summarized in Table 1. For each patient, the following parameters were evaluated in detail: (1) gender and age at onset; (2) serum albumin level and urine protein/creatinine ratio; (3) complaints including edema, hypertension, Cr-eGFR < 90 ml/min/1.73 m^2, and SI < 0.20; (4) the percentage of patients with SRNS; and (5) the percentage of children who underwent kidney biopsy.

1) Gender and age at onset of patients with pediatric NS

In Group A, 26/38 (68%) patients were males. The mean age at onset of NS was 5.5 years (1.0-14.1 years). In Group B, 9/15 patients (60%) were males, with the mean age at onset of pediatric NS of 6.4 years (1.4 to 15.1 years). There were no statistically significant differences between groups A and B with respect to gender or age at onset of NS.

2) Serum albumin levels and urine protein/creatinine ratio

Mean serum albumin levels were 1.3 g/dl (0.8-2.4) and 1.1 g/dl (0.8-1.6) in Groups A and B, respectively.

Table 1 Clinical Features of Group A and Group B Pediatric Patients with Nephrotic Syndrome

	Group A (n = 38)	Group B (n = 15)	*P*
Male (%)	26 (68%)	9 (60%)	0.39
Age at onset of NS (years)	5.5 (1.0-14.1)	6.4 (1.4-15.1)	0.43
Serum albumin (g/dl)	1.3 (0.8-2.4)	1.1 (0.8-1.6)	0.08
UP/Cr (g/gCr)	11.6 (4.0-86.5)	17.7 (4.0-46.9)	0.94
Edema (%)	34 (89%)	15 (100%)	0.25
Hypertension (%)	11 (29%)	8 (53%)	0.09
Cr-eGFR < 90 (ml/min/1.73 m^2)	5 (13%)	5 (33%)	0.09
Selectivity Index < 0.20 (%)	37 (97%)	11 (73%)	0.007
SRNS (%)	4 (10%)	7 (47%)	0.004
Kidney biopsy (%)	19 (50%)	13 (87%)	0.01

NS, nephrotic syndrome; UP/Cr, urine protein to creatinine ratio; eGFR, estimated glomerular filtration rate; SRNS, steroid-resistance nephrotic syndrome; median (min-max).

In comparisons between the two groups, Groups A and B showed no statistically significant differences. The values of the ratio of protein to creatinine in urine were 11.6 g/gCr (4.0-86.5) and 17.17 g/gCr (4.0-46.9) in Groups A and B, respectively. Comparison between Groups A and B, showed no statistically significant difference ($P = 0.94$).

3) Number and percentage of patients with clinical signs of edema, hypertension, Cr-eGFR < 90 ml/min/1.73 m^2, and SI < 0.20

Clinical signs of edema were present in 34/38 patients (89%) in Group A and all 15 patients (100%) in Group B. The four patients in Group A who did not have edema were referred after proteinuria was diagnosed during a school medical check-up with urinalysis. Clinical features of patients with edema included: the most common body sites were bilateral eyelids, lower extremities, ankles, and instep. Scrotal edema was also observed in males. There were also patients with pediatric NS with ascites.

Hypertension was present in 11/38 patients (29%) in Group A and 8/15 patients (53%) in Group B. Cr-eGFR < 90 was found in five patients (13%) in Group A and five patients (33%) in Group B. The proportion was higher in Group B, although the difference was not statistically significant ($P = 0.09$). SI < 0.20 was found in 37 patients (97%) in Group A and 11 patients (73%) in Group B, showing a significant difference ($P = 0.007$).

4) Number and percentage of patients with SRNS

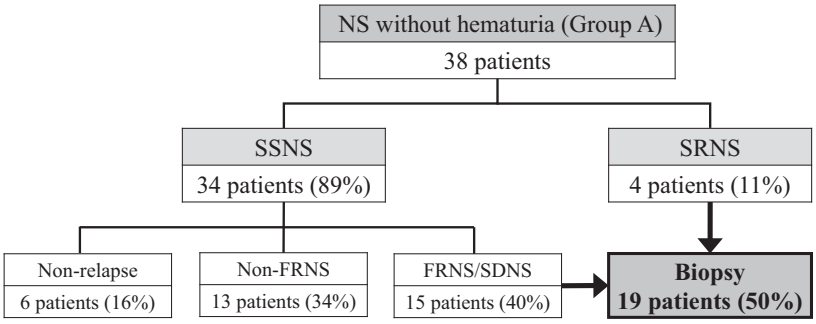
Clinically, SRNS was diagnosed in 4/38 patients (10%) in Group A and 7/15 patients (47%) in Group B with hematuria. Statistical analysis of the two groups showed a statistically significant difference, $P = 0.004$.

5) Number and percentage of patients who underwent kidney biopsy

In the present study, kidney biopsies were performed according to the criteria for JSKDC03 and JSRDC07[15,16]. Kidney biopsies were performed in patients refractory to initial steroid therapy and patients with frequent recurrences before and after calcineurin inhibitor therapy. Kidney biopsies were performed using ultrasound guidance and a special needle. During the procedure, patients were monitored for heart rate, respiratory rate, and SpO_2. Sedation was achieved by administering ≤ 0.3 mg/kg intravenous midazolam and ≤ 3 mg/kg intravenous ketamine hydrochloride. The specimens obtained from the kidney biopsies were evaluated using light microscopy, immunostaining, and electron microscopy. Two or more specialized pathologists evaluated all specimens.

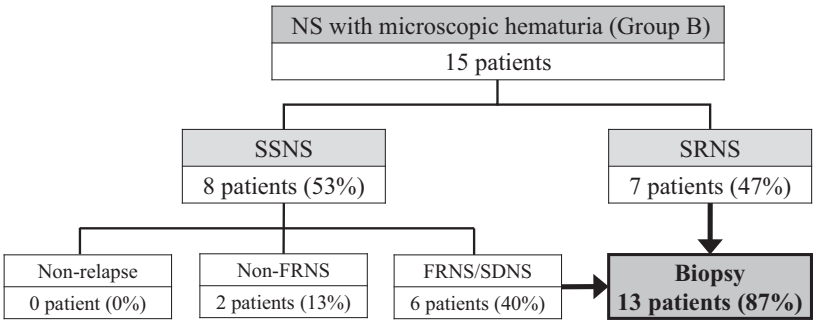
Kidney biopsies were performed after obtaining informed consent from the parents. Nineteen of 38 (50%) pediatric patients with NS without hematuria in Group A underwent kidney biopsy. In contrast, 13/15 (87%) patients with microscopic hematuria in Group B underwent kidney biopsy. Statistical analysis revealed significant differences ($P = 0.01$) between the groups.

Details of the patients for whom kidney biopsy was performed in Groups A and B are shown. In Group A, all four patients with SRNS of the 38 patients with NS



NS, nephrotic syndrome; SSNS, steroid-sensitive nephrotic syndrome; SRNS, steroid-resistance nephrotic syndrome; FRNS, frequently relapsing nephrotic syndrome; SDNS, steroid-dependent nephrotic syndrome

Figure 2A Classifying pediatric nephrosis without hematuria (Group A) and the rate of kidney biopsy



NS, nephrotic syndrome; SSNS, steroid-sensitive nephrotic syndrome; SRNS, steroid-resistance nephrotic syndrome; FRNS, frequently relapsing nephrotic syndrome; SDNS, steroid-dependent nephrotic syndrome

Figure 2B Classifying pediatric nephrosis with hematuria (Group B) and the rate of kidney biopsy

with no hematuria at the onset underwent kidney biopsy. In contrast, in Group B, 34 patients with SSNS, kidney biopsy was performed in 15 patients with frequent relapsing NS (FRNS) or steroid-dependent NS (SDNS) evaluation prior to calcineurin inhibitors (CNI) (Fig. 2A).

In Group B of 15 patients with NS with hematuria at the onset, all seven patients with SRNS underwent kidney biopsy. In the other eight patients with SSNS who responded to steroid therapy, six of the patients with FRNS/SDNS ultimately underwent subsequent kidney biopsy for evaluation prior to CNI, while kidney biopsy was avoided in the remaining two patients (Fig. 2B).

3. Pathological evaluation of kidney biopsies

Histopathology results of kidney biopsies performed on patients with NS are presented in Table 2. In Group A, 15 patients with SSNS and four with SRNS underwent kidney biopsies. In Group B, kidney biopsies were performed in six patients with SSNS and seven with SRNS.

In Group A, patients with NS without hematuria at initial presentation, the histological diagnosis of kidney biopsy results of SSNS in all patients was MCD. The four patients with SRNS in Group A included one patient with MCD, two with focal segmental glomerulosclerosis (FSGS), and one with non-immunoglobulin A (non-IgA) diffuse mesangial sclerosis (DMS), without SRNS-related genetic mutations.

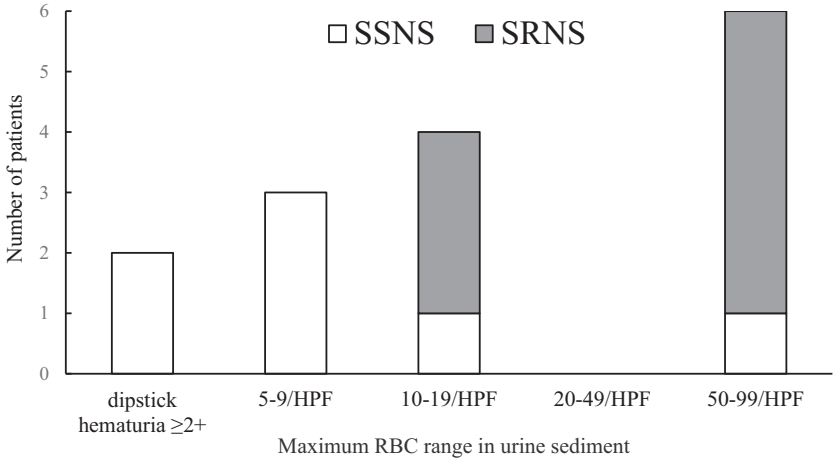
In Group B, of patients with NS with hematuria at the onset, all six patients with SSNS were diagnosed with idiopathic NS, four with MCD, one with FSGS, and one with mesangial proliferative nephritis (non-IgA). Of the seven patients with SRNS in Group B, only one had lupus nephritis (LN) class V, and the remainder had idiopathic NS. One patient had FSGS, and five had mesangial proliferative nephritis (non-IgA). All patients with SSNS underwent kidney biopsy for evaluation prior to CNI therapy.

There were 15 patients with NS with hematuria at

Table 2 Histopathologic diagnoses

Histopathologic category	Group A without hematuria		Group B with hematuria	
	SSNS (n = 15)	SRNS (n = 4)	SSNS (n = 6)	SRNS (n = 7)
Minimal change disease	15	1	4	0
Focal segmental glomerulosclerosis	0	2	1	1
Mesangial proliferative glomerulonephritis (non-IgA)	0	0	1	5
Diffuse mesangial sclerosis	0	1	0	0
Membranous lupus nephritis	0	0	0	1

SSNS, steroid-sensitive nephrotic syndrome; SRNS, steroid-resistance nephrotic syndrome.



SSNS, steroid-sensitive nephrotic syndrome; SRNS, steroid resistance nephrotic syndrome

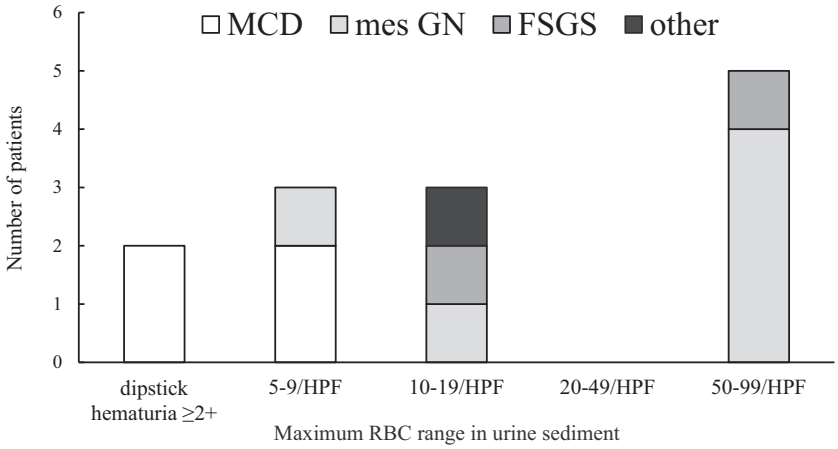
Figure 3 Degree of hematuria and steroid sensitivity

the onset. Of these, two patients (13%) had occult blood ≥ 2+, three (20%) had sediment 5-9/HPF, four (27%) had sediment 10-19/HPF, and six (40%) had sediment 50-99/HPF. Steroid resistance was observed more commonly in patients with a higher degree of hematuria except for one patient with 10-19/HPF and one with 50-99/HPF found to be steroid-sensitive (Fig. 3).

The relationship between the degree of hematuria and histopathology was investigated in 13/15 patients with NS with hematuria at the onset, excluding two patients who did not achieve SRNS or FRNS/SDNS. Patients with severe hematuria tended to be non-MCD (Fig. 4). Among them was a patient with 10-19/HPF with membranous LN (LN International Study of Kidney Disease in Children class V). The patient had C3 103 mg/dL, C4 14 mg/dL, and CH50 36 U/mL on admission with no apparent hypocomplementemia. Systemic lupus erythematosus was difficult to diagnose at initial presentation, except for antinuclear antibody, 160 times greater than the normal level, and renal impairment. This patient later developed SRNS, and a kidney biopsy revealed LN.

Discussion

The most common form of NS in children is MCD. Therefore, steroid therapy is often initiated without a kidney biopsy. In children with NS with hematuria, FSGS, and mesangial proliferative nephritis, histological types other than MCD are common[4,5,7]. Less frequently, there are patients with membranous nephropathy and IgA nephropathy in the pediatric population[4,5,7]. If a kidney biopsy reveals histology other than MCD, the policy for the initial treatment of NS in children with steroid therapy is the same[6,10]. Therefore, there may be no need to perform a kidney biopsy in the presence of edema prior to steroid therapy. The



MCD, minimal change disease; mes GN, mesangial proliferative glomerulonephritis; FSGS, focal segmental glomerulosclerosis

Figure 4 Degree of hematuria and histopathologic diagnosis

results of the present study support the concept that kidney biopsies are unnecessary in pediatric patients with NS.

In the present study, when steroid therapy was initiated without kidney biopsy in children with their first episode of NS with microscopic hematuria, kidney biopsy was avoided in 2/15 patients (13%). Routine kidney biopsies were performed before and after CNI administration during the study period[15,16]. Recent reports indicate that a kidney biopsy prior to CNI administration is unnecessary[15,17], and that CNI-induced nephrotoxicity is often minimal if blood levels are controlled[15,16,18,19]. Therefore, kidney biopsy could have been avoided in up to 8/15 (53%) patients, including 6 patients with SSNS with hematuria.

We describe the final histological diagnosis of 13 patients in the present study in which kidney biopsies were performed in patients with NS with hematuria. Five of the seven patients with SRNS included glomerulonephritis (GN). There was a patient with FSGS and a patient with LN among the remaining two patients. Four of the six patients with SSNS were classified as MCD. The remaining two included a patient with GN and one with FSGS. For these patients, it was determined that having a histological classification prior to initiating steroid therapy would not have significantly changed the course of treatment, including subsequent steroid therapy. In addition, one patient with LN could have been diagnosed after prior treatment without affecting the histologic classification. Although the proportion that responds is small, some patients with FSGS are effectively treated with steroids[5]. In the present study, there was a patient with FSGS in the SSNS group. In patients with steroid-sensitive FSGS, kidney biopsies may be avoided.

Evaluation of data reported by Hama et al. suggests that 16/29 (55%) kidney biopsies could have been avoided in patients with SSNS with hematuria. In addition, IgA nephropathy and membranoproliferative glomerulonephritis were steroid-resistant in all patients. Therefore, we infer that there were no clinical issues due to prior steroid therapy[7].

The clinical importance and associated risks of kidney biopsies in children must be considered[20]. Kidney biopsies may be avoided with prior steroid therapy in pediatric patients with NS with microscopic hematuria at the onset.

Clinical Limitations of the Present Study

The conclusions of the present study are not based on the results of kidney biopsies performed on all children with NS who had hematuria at the onset.

In addition, urine sediment was the gold standard for evaluating hematuria; however, dipstick hematuria was included in a few cases. Therefore, it is possible that the exact degree of hematuria could not be assessed. The group without hematuria was not included because an inclusion criterion of 2+ or higher for dipstick hematuria was used instead of 1+ or higher.

Another limitation is that a small number of patients

with IgA nephropathy and membranous nephropathy, which are causes of pediatric NS other than idiopathic NS, were included in the present study. During the study period, 22 first episode patients, 20 patients with IgA nephropathy, and two patients with membranous nephropathy presented. However, in the available clinical data, none of these children had nephrotic symptoms at the first episode. Japan has a school urine screening system for children, and many pediatric patients are often detected before they become nephrotic. In IgA nephropathy, patients with NS from the onset are rare[21]. In addition, it is also rare for pediatric nephrosis to be diagnosed as membranous nephropathy by kidney biopsy[4,22,23]. In general, about half of pediatric patients with NS due to membranous nephropathy are complicated by hematuria, and these patients are often steroid-resistant[22]. Therefore, a definitive diagnosis can be made during the evaluation of SRNS. Furthermore, even if membranous nephropathy is diagnosed at pretreatment with a kidney biopsy, the subsequent treatment strategy is the same as administering steroid therapy without a kidney biopsy[1].

The present study was a single-center study, and further investigation based on a more significant number of centers and patients is needed to determine the indications for kidney biopsy in children.

Conclusion

The results of the present study suggest that pretreatment kidney biopsies may not be necessary for first episode pediatric patients with NS presenting with microscopic hematuria. In this situation, prior steroid therapy may eliminate the need for kidney biopsies, an invasive procedure in children.

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(Yuji Kano and Yuhi Takagi are both listed equally as first authors)

Contributors

YK and YT were involved in study design, data collection, analysis, and interpretation. GI and SY were involved in data interpretation and assisted with preparing the manuscript. All authors critically revised the manuscript, approved the manuscript for publication, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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