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Association between Immunoglobulin M and Steroid Resistance in Children with Nephrotic Syndrome: A Retrospective Multicenter Study in Japan

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Abstract

Background The prognosis of steroid-resistant nephrotic syndrome (SRNS) in children is poorer than steroid-sensitive cases. Diagnosis of SRNS is made after observing the response to the initial 4-week corticosteroid therapy, which might be accompanied by side effects. However, predictive indicators at initial diagnosis remain unknown. We aimed to investigate whether selectivity index (SI) and other indicators at initial diagnosis—for example, serum IgM and total serum protein–albumin ratio (TA ratio, total serum protein level over albumin level)—can predict SRNS.

Methods A total of 80 children were enrolled from seven hospitals in Japan between January 2008 and December 2019 (mean age, 4.7 years; 65% male). Of the children enrolled, 13 (16%, M/F=5:8) had been diagnosed as steroid resistant after initial treatment with steroids. The association between serum IgM (tertile categories: low, 24–133; middle, 134–169; and high, 169.1–510 mg/dl), SI (<0.2 or ≥0.2), and TA ratio (tertile categories: low, 1.8–2.6; middle, 2.62–3.75; and high, 3.8–15.3) at initial diagnosis and steroid resistance was evaluated with logistic regression, adjusting for age and sex.

Results Low levels of serum IgM were significantly associated with steroid resistance (adjusted odds ratio, 6.94; 95% CI, 1.12 to 43.11). TA ratio and SI were not significantly associated with steroid resistance.

Conclusions Low levels of serum IgM at initial diagnosis might predict steroid resistance among Japanese children with idiopathic nephrotic syndrome.

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Key Points

- This multicenter retrospective study showed that an association between steroid-resistance and lower serum IgM children with nephrotic syndrome.
- Lower serum IgM might be a predictor of steroid-resistant nephrotic syndrome in children.

Introduction

There are two to seven cases of childhood idiopathic nephrotic syndrome per 100,000 children <16 years old (1). This syndrome is diagnosed by both severe proteinuria (>0.3 mg/dl per day) and hypoalbuminemia (albumin <2.5 g/dl) with systemic edema and no plausible secondary causes of nephrotic syndrome (2). The etiologic factors of idiopathic nephrotic syndrome remain unknown. Corticosteroids are an effective treatment, and an initial, 4-week prednisolone treatment (without performing a kidney biopsy) is recommended for children with nephrotic syndrome. However, the initial treatment can be ineffective, leading to a diagnosis of steroid-resistant nephrotic syndrome (SRNS) in about 15% of children with nephrotic syndrome.

According to the International Study of Kidney Disease in Children, SRNS is defined as a nonresponse to an 8-week exposure (at a minimum) of 60 mg/m^2 prednisone per day, or 2 mg/kg prednisone per day for 4 weeks followed by 40 mg/m^2 per day on alternate days for 4 weeks (3). Different diseases are observed

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between steroid-sensitive nephrotic syndrome (SSNS) and SRNS. Most children with SSNS have minimal change disease (MCD), whereas children with SRNS have FSGS, mesangial proliferative GN, or MCD (4). Observational studies of patients with FSGS have reported a 5-year kidney survival rate of 90% in patients with complete remission after any single or combination of tested therapies (5,6). Furthermore, half of the patients who did not achieve partial or complete remission suffered ESKD within 5 years (7).

Long-term prednisolone therapy in children with nephrotic syndrome increases the risk of adverse side effects, such as cataracts (8), hypertension, diabetes, fracture, and obesity (9). Thus, among patients with SRNS, early diagnosis of steroid resistance is important to reduce the risk of side effects from ineffective steroid treatment. However, few studies have revealed predictors of steroid resistance at diagnosis. The selectivity index (SI) is the clearance ratio of the high molecular weight IgG (150 kDa) to the middle molecular protein transferrin (76.5 kDa), which has been reported to predict steroid resistance to the initial therapy (10,11). The SI tends to depend on the underlying disorder that is responsible for SRNS. The fractional clearances of transferrin and IgG have been shown to be greater in patients with FSGS than in those with minimal change nephrotic syndrome (12). Thus, the lower selectivity of proteinuria indicates greater abnormality in the glomerular filtration barrier.

We considered whether the SI and the differences in clearance of high molecular protein between SSNS and SRNS may be involved in predicting steroid responses. Furthermore, we hypothesized that two other indicators, serum IgM and the total serum protein–albumin ratio (TA ratio; total serum protein level over albumin level) might predict SRNS. Serum IgM might relate to the severity of, or pathogenic factors in, idiopathic nephrotic syndrome. Low serum IgG and IgA and high serum IgM are observed in patients with MCD (13–15), which is also common among children with SSNS. Colucci *et al.* (16) demonstrated that atypical IgM on the surface of T cells predisposed patients to the onset of severe childhood idiopathic nephrotic syndrome. However, few studies have evaluated the difference in serum IgM between SSNS and SRNS. Conversely, the TA ratio would directly reflect protein excretion in the urine. Nakamura *et al.* (17) reported the clearance ratio of albumin to γfractions in serum and urine protein, and showed the SI protein fraction (SIPF) could be a useful predictor of steroid response in adult patients with nephrotic syndrome. Our hypothesis regarding the TA ratio (which was inspired by a previous report about the SIPF) was made on the basis that, clinically, the TA ratio is generated as a simplified SPIF. This study aimed to investigate the association between serum IgM and TA ratio at initial diagnosis and steroid resistance in children with idiopathic nephrotic syndrome.

Materials and Methods

Study Participants

We conducted a secondary analysis of the data from the Ochanomizu Children's Medical Network Registry (Ochanomizu PedNet Registry), which was constructed by seven hospitals from four prefectures (Tokyo, Chiba, Ibaraki, and Saitama) in Japan. The aim of this registry is to explore pathogenic- and convalescent-predictive factors of kidney disease in childhood. This registry included all inpatients in these hospitals who were diagnosed with nephrotic syndrome or nephritis at ≤20 years of age. In this study, we excluded those with congenital or infantile nephrotic syndrome. All participants were between 1 and 15 years old, had uncomplicated nephrotic syndrome at initial onset, and were treated at one of the hospital centers between January 2008 and December 2019. The registration period for the study occurred over 6 months between January and July 2020. Among the 106 patients registered as having nephrotic syndrome were 80 patients who did not show hereditary or secondary causes of nephrotic syndrome (mean age, 4.52 years; 65% male). The exclusion criteria for hereditary or secondary forms of nephrotic syndrome included absence of an elevated autoantibody titer (ANA, ANCA, anti-GBM), low complement components, known active chronic infection (hepatitis B virus, hepatitis C virus, HIV, and syphilis), and known active purpura. The study protocol was approved by the ethics committee at Tokyo Medical and Dental University (M2019-284).

Measurements

In Japan, steroid resistance is often diagnosed as a failure to induce complete remission after 4 weeks of standard steroid therapy with 60 mg/m^2 intravenous or oral prednisolone per day (18,19). In accordance with the guidelines of the International Study of Kidney Disease in Children, complete remission is defined as a reduction in proteinuria to <0.2 mg/mg protein-creatinine ratio in the first morning urine void, or negative dipstick test results for three consecutive days.

All of the biomarkers were measured only once upon patient admission to one of the seven participating hospitals. Specifically, SI, total serum protein, serum albumin, TA ratio, eGFR, total cholesterol, serum IgG, serum IgA, complement C3, total urinary protein, hematuria, and the urinary total protein–creatinine ratio were obtained. In addition, we obtained biopsy sample–proven histopathology findings. SI was calculated using the clearance ratio of IgG to transferrin (10,17). Serum IgG, IgM, IgA, and complement C3 were measured using a turbidimetric immunoassay. Serum albumin was measured using modified bromocresol green. Serum total protein was measured using the biuret method. Serum total cholesterol was measured using an enzyme assay. Standardization among the laboratories, which was based on guidelines from the Japan Committee on Clinical Laboratory Standardization, was achieved by a common measurement of the certified reference materials (20). After the laboratory data were measured clinically at each institution, they were collected in the Ochanomizu PedNet registry.

Statistical Analyses

First, we investigated univariate associations between SRNS and age, sex, serum IgM, SI, and TA ratio. We then performed multiple logistic regression between serum IgM (model 1), SI (model 2), and TA ratio (model 3) with SRNS, adjusting for age and sex. Serum IgM levels and TA ratios were divided into tertiles (serum IgM, low, 24–133; middle, 134–169; and high, 169.1–510 mg/dl; TA ratio, low, 1.8–2.6;

middle, 2.62–3.75, and high: 3.8–15.3), whereas SIs were divided into two groups (<0.2 or ≥0.2). We used 0.20 as a cutoff value for SI because several studies showed that low selectivity of proteinuria (SI >0.2) was associated with resistance to steroid treatment in patients with nephrotic syndrome (17,21,22). Because no previous study has used serum IgM to predict the response to steroid therapy in patients with nephrotic syndrome, we used the tertile categories of serum IgM to investigate the usefulness of these indicators in making such a prediction. All analyses were performed using Stata version 15 (Statacorp, College Station, TX). *P* values <0.05 were considered statistically significant.

Results

Among 80 patients with idiopathic nephrotic syndrome, 13 (male/female=5:8) were steroid resistant and 67 (male/female=47:20) were steroid sensitive (Tables 1 and 2). Although we could not evaluate the renal pathology in 18 patients, all of them were shown to have SSNS. All three patients with FSGS did not respond to the initial steroid therapy. Table 1 shows the characteristics of patients with SRNS, which were not significantly different from those of patients who were steroid sensitive, except for sex.

Table 3 describes the demographic characteristics of the study participants stratified by serum IgM level. The serum IgM level was significantly higher in females than in males ($P=0.03$). Age of onset and other biologic indicators were not significantly different when comparing the levels of serum IgM.

Table 4 shows the association between serum IgM, SI, and TA ratio and steroid resistance. In the crude model, no significant association was observed between steroid resistance and serum IgM (odds ratio [OR], 2.68; 95% CI, 0.61 to 11.78), SI (OR, 0.93; 95% CI, 0.18 to 4.77), or TA ratio (OR, 2.80; 95% CI, 0.64 to 12.29). After adjusting for age and sex, low serum IgM was significantly associated with steroid resistance (OR, 6.94; 95% CI, 1.12 to 43.11). Neither SI nor TA ratio were significantly associated with steroid resistance (SI, OR, 1.94; 95% CI, 0.18 to 20.87; low TA ratio, OR, 3.34; 95% CI, 0.70 to 15.98).

Discussion

This study showed that a low serum IgM level and female sex were significantly associated with SRNS. SI and TA ratio were not associated with SRNS (Table 4).

The association between low serum IgM and SRNS could be explained by the difference in selectivity of urinary protein between SSNS and SRNS. The prevalence of FSGS is higher in patients with SRNS than in those with SSNS (4,23,24); thus, the selectivity of urinary protein would be lower in patients with SRNS due to severe glomerular

Table 1. Demographic and clinical characteristics of study participants

Characteristics	Total	Steroid Sensitivity	Steroid Resistance	*P* Value[a]
Sex, *n* (%)	80 (100)	67.00 (84)	13.00 (16)	
Male	52 (100)	47 (90)	5 (10)	0.03
Female	28 (100)	20 (71)	8 (29)	
Age (yr), mean (SD)	4.72 (3.84)	4.88 (3.98)	3.87 (3.27)	0.39
Renal pathology, *n* (%)				
Minimal change	57 (100)	49 (86)	8 (14)	
FSGS	3 (100)	0 (0)	3 (100)	
Mesangial proliferative glomerular nephritis	2 (100)	0 (0)	2 (100)	
Unknown	18 (100)	18 (100)	0 (0)	
Selectivity index (*n*=73), mean (SD)	0.08 (0.11)	0.07 (0.11)	0.10 (0.10)	0.42
Serum total protein (g/dl, *n*=79), mean (SD)	4.22 (0.55)	4.2 (0.53)	4.31 (0.66)	0.47
Serum albumin (g/dl, *n*=80), mean (SD)	1.38 (0.54)	1.33 (0.52)	1.59 (0.61)	0.12
TP/Alb ratio (*n*=79), mean (SD)	3.64 (1.95)	3.76 (2.07)	3.04 (1.02)	0.22
eGFR (ml/m^2 per hour, *n*=72), mean (SD)	127.77 (56.41)	131.43 (57.5)	109.49 (48.64)	0.22
Total cholesterol (mg/dl, *n*=76), mean (SD)	402.28 (104.48)	396.34 (105.41)	437.36 (95.74)	0.23
Serum IgG (mg/dl, *n*=80), mean (SD)	330.39 (254.22)	322.44 (195.05)	371.35 (462.65)	0.53
Serum IgM (mg/dl, *n*=80), mean (SD)	167.00 (72.74)	171.33 (75.25)	144.65 (55.18)	0.23
Serum IgA (mg/dl, *n*=77), mean (SD)	121.39 (62.99)	124.06 (65.63)	108.29 (47.86)	0.41
Complement C3 (mg/dl, *n*=75), mean (SD)	133.72 (31.66)	132.77 (33.32)	138.25 (22.56)	0.57
Urinary total protein (mg/dl, *n*=79), mean (SD)	31.27 (10.03)	31.98 (10.62)	27.89 (5.6)	0.18
Urinary TP/Cre ratio (*n*=78), mean (SD)	15.66 (11.62)	15.56 (11.99)	16.16 (9.98)	0.87
Microscopic hematuria (*n*=69), *n* (%)				
Negative	38 (100)	32 (56)	6 (50)	0.92
Positive	31 (100)	25 (45)	6 (50)	

N=80. TP, total protein; Alb, albumin; Cre, creatinine.
[a]Chi-squared test.

Table 2. Demographic and clinical characteristics of study participants divided by sex

Characteristics	Male	Female	*P* Value[a]
Steroid sensitivity, *n* (%)	47 (90)	20 (71)	0.06
Steroid resistance, *n* (%)	5 (10)	8 (29)	0.29
Age (yr), mean (SD)	4.08 (3.34)	5.90 (4.46)	0.06
Selectivity index (*n*=73), mean (SD)	0.07 (0.13)	0.09 (0.75)	0.49
Serum total protein (g/dl, *n*=79), mean (SD)	4.28 (0.52)	4.28 (0.6)	0.49
Serum albumin (g/dl, *n*=80), mean (SD)	1.36 (0.5)	1.41 (0.63)	0.71
TP/Alb ratio (*n*=79), mean (SD)	3.56 (1.54)	3.8 (2.55)	0.61
eGFR (ml/m^2 per hour, *n*=72), mean (SD)	136.72 (58.21)	111.93 (50.62)	0.07
Total cholesterol (mg/dl, *n*=76), mean (SD)	399.76 (105.77)	407.11 (103.83)	0.77
Serum IgG (mg/dl, *n*=80), mean (SD)	297.99 (149.94)	390.55 (375.31)	0.12
Serum IgM(mg/dl, *n*=80), mean (SD)	151.45 (72.74)	195.86 (91.37)	0.008
Serum IgA (mg/dl, *n*=77), mean (SD)	119.34 (61.60)	125.2 (66.49)	0.70
Complement C3 (mg/dl, *n*=75), mean (SD)	138.8 (34.71)	124.68 (23.27)	0.06
Urinary total protein (mg/dl, *n*=79), mean (SD)	1631.6 (1724.59)	2058.43 (1660.47)	0.29
Urinary TP/Cre ratio (*n*=78), mean (SD)	15.13 (12.71)	16.66 (9.38)	0.58
Hematuria (*n*=69), *n* (%)	18 (58)	13 (42)	0.38

N=80. TP, total protein; Alb, albumin; Cre, creatinine.
[a]Chi-squared test.

injury. The low serum IgM level with its large molecular might reflect the lower selectivity of urinary protein and the severity of glomerular injury.

Children with idiopathic nephrotic syndrome are predominantly male (25,26). In the report from the International Study of Kidney Disease in Children, about 60%–70% of children with MCD or FSGS were male (27); however, in this study, female sex was significantly associated with SRNS (Table 4). Our results were consistent with previous studies, which demonstrated that females were slightly more prevalent among patients with SRNS (23,28–31). All of these studies described newly diagnosed cases and responsiveness for initial steroid treatments. For example, in a study of Australian children, Sureshkumar *et al.* (23) reported that the male/female ratio for SSNS was 1.5:1 compared with 0.5:1 for SRNS; additionally, in Yorkshire, United Kingdom, McKinney *et al.* (28) reported that the male/female ratio for SSNS was 1.7:1 compared with 1.2:1 for SRNS. Larger cohort studies are required to evaluate the association between sex and steroid resistance among children with nephrotic syndrome.

The nonsignificant association of SRNS with SI and the TA ratio could be explained in the following ways. Ramjee *et al.* (11) reported that SI predicted all patients with FSGS who were steroid resistant; however, they were able to predict only 42% of the patients with SRNS. In this study, the participants with SRNS included not only those with FSGS but also MCD, which might explain the nonsignificant association between SI and SRNS. Also, on the basis of a previous report, the clearance ratio of albumin to the γfraction was defined as SIPF, which was strongly correlated with SI (17). However, in our study, we used TA ratio instead of SIPF, which might explain the lack of a significant association between the TA ratio and SRNS.

This study has some limitations. First, the number of participants was small and all were of Japanese ethnicity; thus, our findings have limited generalizability. One of the reasons for the small number of participants was because the registration period was relatively short. Second, we were not able to consider genetic information, although >70 genes related to SRNS have been detected (32). However, we assumed that the participants of this study had no genetic link to SRNS because all patients with SRNS, except for one patient, achieved complete remission by additional therapy, such as cyclosporine A, methylprednisolone pulse, and rituximab. Only one patient had maternal heterozygosity for the WT1 mutation (data not shown). Büscher *et al.* (29) reported that 97% of patients with childhood SRNS who achieved complete remission were not genetically susceptible.

In conclusion, our study showed that lower serum IgM predicted steroid resistance to initial treatment in Japanese children with nephrotic syndrome. These findings might be useful in detecting SRNS in children with nephrotic syndrome at initial diagnosis.

Disclosures

All authors have nothing to disclose.

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Table 3. Demographic and clinical characteristics of study participants divided into tertiles on the basis of serum IgM

Characteristics	Serum IgM			*P* Value
	Low (range, 24–133 mg/dl)	Middle (range, 134–169 mg/dl)	High (range, 169.1–510 mg/dl)	
Sex, *n* (%)				
Male	22 (82)	18 (67)	12 (46)	0.03[a]
Female	5 (19)	9 (33)	14 (54)	
Age (yr), mean (SD)	4.52 (4.26)	4.52 (3.51)	5.12 (3.84)	0.81[b]
Selectivity index (*n*=73), mean (SD)	0.12 (0.17)	0.07 (0.07)	0.05 (0.05)	0.08[b]
Serum total protein (g/dl, *n*=79), mean (SD)	4.29 (0.67)	4.10 (0.38)	4.32 (0.66)	0.38[b]
Serum albumin (g/dl, *n*=80), mean (SD)	1.43 (0.60)	1.34 (0.52)	1.35 (0.52)	0.80[b]
TP/Alb ratio (*n*=79), mean (SD)	3.47 (1.42)	3.86 (2.82)	3.60 (1.21)	0.77[b]
eGFR (ml/m^2 per h, *n*=72), mean (SD)	140.50 (61.31)	116.38 (48.19)	126.24 (58.81)	0.32[b]
Total cholesterol (mg/dl, *n*=76), mean (SD)	388.07 (95.66)	416.96 (126.23)	403.52 (92.11)	0.62[b]
Serum IgG (mg/dl, *n*=80), mean (SD)	279.80 (143.29)	290.90 (166.24)	423.92 (374.94)	0.07[b]
Serum IgA (mg/dl, *n*=77), mean (SD)	105.27 (60.71)	117.80 (53.01)	142.91 (71.65)	0.10[b]
Complement C3 (mg/dl, *n*=75), mean (SD)	144.51 (25.36)	128.37 (38.37)	128.27 (22.56)	0.11[b]
Urinary total protein (mg/dl, *n*=79), mean (SD)	1563.66 (1265.38)	1887.19 (1795.20)	1906.98 (2031.51)	0.72[b]
Urinary TP/Cre ratio (*n*=78), mean (SD)	14.00 (10.10)	15.86 (14.32)	17.25 (10.17)	0.61[b]
Hematuria (*n*=69), *n* (%)	14.00 (42)	10.00 (57)	14.00 (36)	0.38[b]

N=80. TP, total protein; Alb, albumin; Cre, creatinine.
[a]Chi-squared test
[b]ANOVA.

Table 4. The association between candidate predictors and steroid-resistant nephrotic syndrome

Predictor	OR (95% CI)			
	Crude[a]	Model 1 (n=80)[b]	Model 2 (n=80)[b]	Model 3 (n=79)[b]
Age	0.92 (0.77 to 1.10)	0.89 (0.74 to 1.06)	0.85 (0.69 to 1.04)	0.86 (0.71 to 1.05)
Sex				
Male	Ref	Ref	Ref	Ref
Female	3.76 (1.09 to 12.91)	9.35 (1.92 to 45.59)	6.29 (1.51 to 26.21)	4.99 (1.31 to 18.97)
Serum IgM				
Low	2.68 (0.61 to 11.78)	6.94 (1.12 to 43.11)		
Middle	0.96 (0.18 to 5.24)	1.37 (0.22 to 8.42)		
High	Ref	Ref		
Selectivity index				
<0.2	Ref		Ref	
≥0.2	0.93 (0.18 to 4.77)		1.94 (0.18 to 20.87)	
TA ratio				
Low	2.80 (0.64 to 12.29)			3.34 (0.70 to 15.98)
Middle	1.09 (0.10 to 5.98)			1.20 (0.20 to 7.10)
High	Ref			Ref

OR, odds ratio; ref, reference; TA ratio, total protein-albumin ratio.
[a]Univariate association between each predictor and steroid-resistant nephrotic syndrome.
[b]Listed variables were simultaneously included in the model.

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Author Contributions

T. Fujiwara, K.K. Imai, Y. Matsuyama, and T. Morio provided supervision; A. Endo, T. Fujiwara, Y. Matsuyama, and T. Udagawa were responsible for methodology; T. Fujiwara, Y. Matsuyama, and T. Udagawa were responsible for validation, and reviewed and edited the manuscript; T. Fujiwara and T. Udagawa conceptualized the study and were responsible for software; T. Kanamori, E. Kikuchi, Y. Motoyoshi, M. Okada, M. Okutsu, T. Omori, M. Shimoda, N. Tada, M. Takahashi, and T. Udagawa were responsible for data curation; T. Kanamori, E. Kikuchi, Y. Motoyoshi, T. Omori, N. Tada, and T. Udagawa were responsible for project administration; Y. Matsuyama and T. Udagawa were responsible for formal analysis; and T. Udagawa wrote the original draft and was responsible for funding acquisition, resources, and visualization.

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