Acta Med. Nagasaki 57: 19－24

The incidence and distribution of biopsy-proven renal diseases in children

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The precise distribution pattern of pediatric renal diseases has seldom been reported especially for young children. In order to clarify the incidence and distribution of renal diseases in children, 599 renal biopsy specimens obtained from 547 pediatric patients (≦15 years old) were analyzed by routine light, electron and immunofluorescence microscopy. Among the total biopsy cases, the most common renal disease identified in childhood was IgA glomerulonephritis (IgAGN; 37%). More than 80% of patients with IgAGN were discovered by urinary screening at the school, showing asymptomatic proteinuria and/or hematuria. The other major renal diseases were minor glomerular abnormality (12.2%), Henoch-Schönlein purpura nephritis (HSPN; 10.6%), and thin basement membrane disease (7.1%). One of the major causes of pediatric nephrotic syndrome were minimal change nephrotic syndrome (58%), whereas the other causes were IgAGN (11.6%), HSPN (8.9%), membranous glomerulonephritis (5.4%), membranoproliferative glomerulonephritis (3.6%). In conclusion, IgAGN was the most common renal disease also in children as in adolescence. From the age of seven years, the incidence of IgA-GN was highest among all the pediatric renal diseases during whole childhood period, and the incidence and number of the patients increased as they grow. On the other hand, there are also many cases with non-progressive clinical courses, such as minor glomerular abnormality and thin basement membrane disease in children. The renal biopsy following routine urinary screening at the school may be important for the therapeutic and prognostic guidelines of pediatric group of patients with renal diseases.

ACTA MEDICA NAGASAKIENSIA 57: 19－24, 2012

Keywords: renal disease, children, disease distribution, renal biopsy, IgA glomerulonephritis

Introduction

Although renal diseases are not uncommon in children, the precise incidence of renal diseases in each age group of childhood has seldom been reported[1, 2]. In Japan, there has been an established urinary screening system for school students. By this system, pediatric patients with renal diseases can be identified at early stage. In order to confirm the diagnosis of the renal diseases and to select the appropriate therapy, renal biopsy is often recommended. However, renal biopsy has not been always performed, because it may be difficult to rationalized renal biopsy in children without apparent symptoms. Moreover, routine electron microscopic observation has not always been done, even when biopsy was performed. In this study, we reevaluated out cohort of patients by analyzing their light, electron and immunofluorescence microscopic features, to clarify the precise incidence and distribution of renal diseases in pediatric group of patients.

Materials and methods

The study subjects include 599 renal biopsies obtained from 547 cases (315 males and 232 females) under the age

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Received December 7, 2011; Accepted December 21, 2011

of 16 years. The samples were gathered in Department of Pathology at the Nagasaki University graduate School of Biomedical Sciences, collected from July, 1990 to August, 2010. All the samples were examined by light- and electron- microscopy and immunofluorescence. Although all the renal diseases were examined in this study, the cases with transplantation kidneys and tumors were excluded. For light microscopy, the sections were stained by hematoxylin-eosin, periodic acid Schiff, methenamine silver and Masson trichrome. For immunofluorescence, the frozen samples were cut by cryostat, and the sections were stained for the presence of human IgG, IgA, IgM, C3, C1q, fibrinogen, kappa light chain and lambda light chain. For the electron microscopic examination, the samples were processed by routine established procedures. Briefly, the small parts of renal tissue were fixed by glutaraldehyde and postfixed by osmium acid, sectioned by ultramicrotome, and stained by lead citrate and uranium. This study was approved by the ethical committee of the Nagasaki University Hospital.

Results

1. Clinical profile

The age of the patients are under 16 years old (11.6±2.5) at the time of biopsy. Fig. 1 shows age distribution of the all biopsy cases. From the age of 12 years, the number was considerably increased. Sex ratio (males to females) for our studied cases was 1:0.74. The clinical diagnoses at the time of biopsy were as follows; acute glomerulonephritis (GN), chronic GN, rapidly progressive GN (RPGN), nephrotic syndrome (NS), Henoch-Schoenlein purpura nephritis (HSPN), lupus nephritis, hereditary nephritis, asymptomatic proteinuria/ hematuria (mostly detected by urinary screening at the school), interstitial nephritis and others.

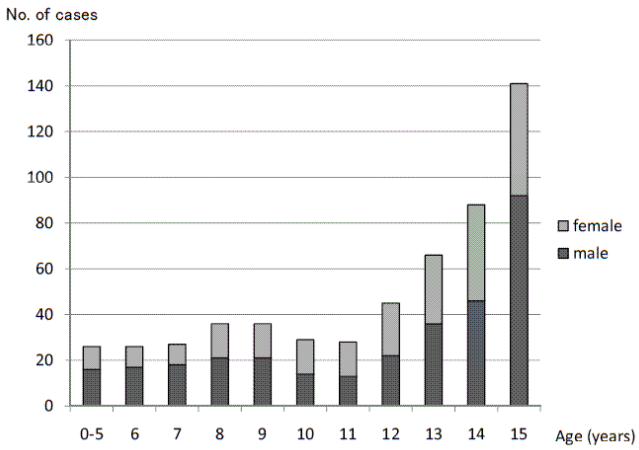

Fig.1. Age distribution of total cases.

2. General aspects of total cases

Table 1 shows incidences of renal diseases in all the cases. Most of the cases were classified in glomerular diseases, whereas only 8 cases (1.8%) were diagnosed as non-glomerular diseases. The most common disease was IgA glomerulonephritis (IgAGN) with the incidence of more than one third of all the studied cases (37%), and was significantly higher than the other diseases. The other common diseases were minor glomerular abnormality (MGA; 12.2%), Minimal change nephrotic syndrome (MCNS; 11.9%), Henoch-Schönlein purpura nephritis (HSPN; 11.2%), thin basement membrane disease (TMD; 7.1), mesangial proliferative glomerulonephritis of non-IgAGN type (Mes PGN; 5.3 %)

Table 1. The total number of renal diseases in all children cases

Pathological diagnosis	Number(%)
Glomerular disease	
IgAGN	203 (37.0%)
MGA	67 (12.2%)
MCNS	65 (11.9%)
HSPN	58 (10.6%)
TMD	39 (7.1%)
Mes PGN	29 (5.3%)
Lupus N	28 (5.1%)
MGN	16 (2.9%)
Acute GN	13 (2.4%)
MPGN	5 (0.9%)
Crescentic GN	5 (0.9%)
Infantile/congenital NS	5 (0.8%)
Hereditary nephritis	4 (0.7%)
FSGS	2 (0.3%)
Non-glomerular disease	
Tubulointerstitial nephritis	3 (0.5%)
Reflux renphropathy	2 (0.4%)
Nephronophthisis	2 (0.4%)
Renal dysplasia	1 (0.2%)
Total	547

IgAGN=IgA glomerulonephritis;
MGA=minor glomerular abnormality;
HSPN=Henoch-Schoenlein purpura nephritis;
MCNS=minimal change nephrotic syndrome;
TMD=thin basement membrane disease;
Lupus N=lupus nephritis;
Mes PGN=mesangial proliferative glomerulonephritis of non-IgAGN type;
MGN=membranous glomerulonephritis;
MPGN=membranoproliferative glomerulonephritis;
FSGS=focal segmental glomerulosclerosis

and lupus nephritis (Lupus N; 5.1%).

The incidences of the remaining renal diseases were under 5 %.Although acute GN was previously one of the most common renal diseases in children, its occurrence has been considerably decreased in last several decades. In this study, the incidence of acute GN was found to be 2.4 %.

3. Age distribution of each renal disease

Table 2 shows the number of renal diseases in each age in the cases between the age of 2 and 15.As the renal diseases of the cases under 2 years old were quite different from other age group, they are separately described. In the age group over 1 year, most common renal disease was IgAGN. (Fig.2). The cases of MGA are noted at the age 6, but mostly seen in older than 11 years and its number increased as the patients grow. HSPN distributed widely in all age group, and showed the peak incidence at the age of 8. MCNS also distributed widely, appearing as early as 1 year of age. TMD was mainly seen in the school going age, and the number increased in older students. Although membranous glomerulonephritis (MGN) was not frequent in children, it was widely distributed from 3 years old.

Eight cases under 2 years old consist of 3 cases with infantile NS, 2 cases with congenital NS, 2 cases with MCNS and one case with renal dysplasia.

Concerning with gender distribution, female was considerably predominant to male in lupus nephritis. However, male predominance was noted in IgAGN, MGA and MCNS. In the remaining disease, sex ratio was almost equal (Table 2).

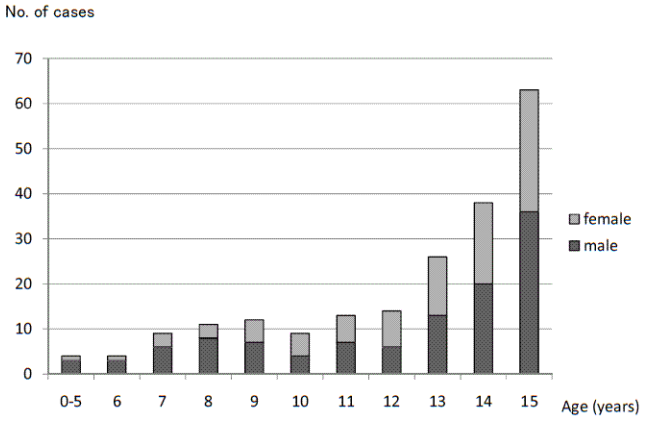

Fig.2. Age distribution of the cases with IgA glomerulonephritis

4. Incidences of renal diseases in each age group

The incidences of renal diseases are compared in four age groups (Table 3, Fig. 3). The diseases with higher incidences than 3 % are listed in Table 3. In group 1 (2 -5 years old), MCNS was the most common disease, followed by IgAGN and HSPN. In group 2 (6 - 9 years old), IgA-GN and HSPN showed almost similar incidence, and were the most common diseases in this group of patients. In group 3 (10 - 12 years old), the incidences of IgAGN (35.3%) and HSPN (12.7%) were quite different. In group 4 (13 - 15 years old), difference of incidences of IgAGN (43%) and HSPN (2.7%) became considerably wider.

Fig. 3 shows pattern of renal disease in different age groups. IgAGN was the most common disease in groups 2 to 4, and the incidence was increased as the patients grew.

Table 2. Diseases distribution at each age (2-15 years)

Age(year-old)	2	3	4	5	6	7	8	9	10	11	12	13	14	15	male	female	total
IgAGN		1		3	4	9	11	12	9	13	14	26	38	63	112	92	203
MGA					1	1		2	1	1	6	12	12	31	47	20	67
HSPN			2		7	9	11	8	4	5	4	1	5	2	33	25	58
MCNS	4		1	3	1	5	6	4	4	1	7	12	7	8	41	22	63
TMD					1		2	2	0	1	3	3	14	13	22	17	39
LupusN					1	1		1	3	3	6	2	4	7	6	22	28
MesPGN	1				2		1	3	1	2	2	5	2	10	16	13	29
MGN		1			4	1		1		1	1	1	2	4	8	8	16
Acute GN	1				1		2	1	2		1	2	1	2	10	3	13
Crescentic GN					2		1		2						2	3	5
MPGN								2			1	1	1		3	2	5
Hereditary N					1	1	2								2	2	4
FSGS					1				1						2	0	2
Others									2	1		1	2	1	6	1	7
Total	6	2	3	6	26	27	36	36	29	28	45	66	88	141	310	229	539

Others include non-glomerular renal diseases

Table 3. Incidences of renal diseases in each age group

Group 1		Group 2		Group 3		Group 4	
2 - 5 y-o (n=17)		6 - 9 y-o (n=125)		10 - 12 y-o (n=102)		13 - 15 y-o (n=295)	
	%		%		%		%
MCNS	47.1	IgAGN	28.8	IgAGN	35.3	IgAGN	43.0
IgAGN	23.5	HSPN	28.0	HSPN	12.7	MGA	18.6
HSPN	11.8	MCNS	12.8	MCNS	11.8	TMD	10.2
Mes PGN	5.9	Mes PGN	4.8	Lupus N	11.8	MCNS	9.2
MGN	5.9	MGN	4.8	MGA	7.8	Mes PGN	5.8
Acute GN	5.9	TMD	4.0	Mes PGN	4.9	Lupus N	4.4
		MGA	3.2	TMD	3.3	HSPN	2.7
		AGN	3.2	AGN	2.9	MGN	2.4
		Hereditary N	3.2	MGN	2.0	Acute GN	1.7
		Lupus N	2.4	Cres N	2.0	MPGN	0.7
		Crescentic. N	2.4	MPGN	1.0	Others	1.4
		MPGN	1.6	FSGS	1.0		
		FSGS	0.8	Others	2.9		

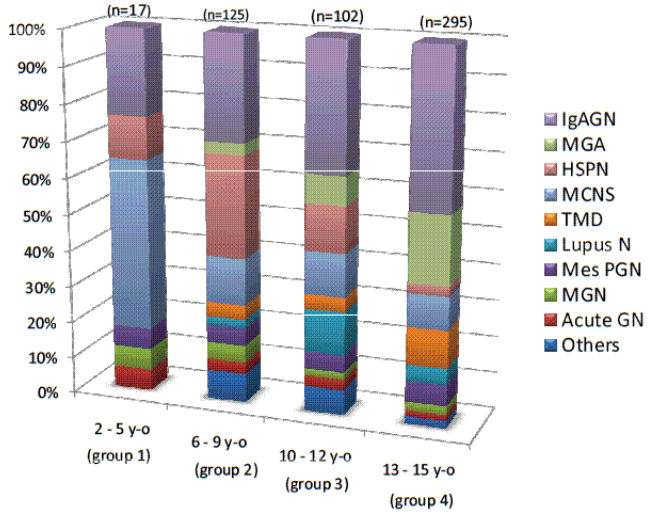

Fig.3. Incidences of renal diseases in each age group.

The incidence of MGA and TMD increased during the transition of group 3 to 4, while,. HSPN decreased during group 2 to 4. MCNS constantly has the similared incidence in group 1 to 3.

5. Histological analysis of nephrotic syndrome

Among 547 pediatric cases, 110 cases (20.1%) show NS (Table 4). The most common disease was MCNS, it occupies 59% of pediatric NS. The other diseases of NS were IgAGN (11.8%), HSPN (9.1%), MGN (5.5%), MPGN (2.7%), Lupus N (2.7%), Mes PGN (2.7%), and FSGS (0.9%). In the cases under 2 years old, congenital NS and infantile NS were the main causes of NS.

Table 4. Histological analysis of nephrotic syndrome

	No.	%
MCNS	66	60.0%
IgAGN	13	11.8%
HSPN	10	9.1%
MGN	6	5.5%
infantile/congenital NS	5	4.5%
MPGN	3	2.7%
LupusN	3	2.7%
Mes PGN	3	2.7%
FSGS	1	0.9%
total	110	

6. Disease distribution in the cases detected by urinary screening at the school

In this study, 295 cases were detected by urinary screening at the school. Disease distribution pattern of these groups of patients, in comparison to that of total biopsy cases are shown in Table 5. As the age of the school screened students were older than 5 years, the cases between aged 6 to 15 years were selected for the comparison. Although IgAGN was the most common disease in both groups, incidence of IgAGN in screening group (57.3%) was considerably higher than that in total case group (38.1%). That is, 169

Table 5. Comparison of incidences of renal diseases in cases detected by school screening and total cases (Age: 6-15 years old)

Total cases (n=522)		Screening cases (n=295)	
Diagnosis	%	Diagnosis	%
IgAGN	38.1	IgAGN	57.3
MGA	12.8	MGA	16.6
HSPN	10.7	TMD	10.2
MCNS	10.5	Mes PGN	8.1
TMD	7.5	MGN	4.7
Others	20.4	Others	3.1

cases (83.2%) with IgAGN were detected by urinary screening among total cases of IgAGN. The other main diseases in screening case group were was MGA (16.6%), TMD (10.2%), Mes PGN (8.1%) and MGN (4.7%).

7. Follow-up biopsy study

52 cases are examined by repeated biopsy, twice in 48 cases, three times in 2 cases and four times in one case. In these cases, repeated biopsy was performed for evaluation of treatment and histological behavior. In cases with MCNS, the reasons for repeated biopsy were exclusion of other related renal diseases, such as FSGS and for evaluation of nephrotoxicity of ciclosporine use in the cases with steroid-dependent or -resistant NS and frequent relapses.

Discussion

In this study, disease distribution of pediatric renal diseases in different age groups under 16 years old was analyzed. In all the examined children, the most common renal disease was IgAGN (37%), followed by MGA (12.2%), MCNS (11.9%), HSPN (10.6%) and TMD (7.1%). Rychlik et al. reported incidences of renal diseases in the Czech registry of renal diseases[1], and found that the most common diseases in the pediatric group were IgAGN (19.2%), MCNS (17.6%) and TMD (12.3%). These data are essentially similar to our observed data. In a separate report from Australia, the most common glomerulonephritis in children under the age of 5 years was found to be FSGS, followed by MCNS and IgAGN. In children of 5-14 years of age, the most common disease was lupus nephritis, followed by IgAGN and FSGS[2]. The difference of the incidence of renal diseases in children in this report and our cases may be caused by difference of indication of renal biopsy, though genetic difference could not be ruled out.

Yoshikawa et al reported that IgAGN accounted for between 18 and 40 % of all primary glomerular disease in children[3]. However, precise age distribution of IgAGN has not been reported. Our study represents that IgAGN is the most common renal disease, and counted 38 % of all performed renal biopsy in childhood. The youngest case of IgAGN was 3 years old. IgAGN become the most frequent renal disease at age of 7 years, and its number and incidence increased as they grew till the age of 15 years. The incidence of IgAGN was higher in the cases detected by urinary screening in the school than that of routine biopsy cases of the similar school age, between 6-15 years (57.3% vs 38.1%). Park et al.[4] reported that IgAGN was the most common disease in the cases detected by mass school urinary screening, but the incidence (38.9%) was considerably lower than our data. The difference of school screening system and indication of renal biopsy might reflect such difference of incidence. Among all the cases of IgAGN, 83.2 % were detected by school urinary screening in our study. On the prognostic aspect of IgAGN[5], mass screening for urinarysis appears to be an important system for early detection of the renal disease in the childhood even at asymptomatic stage.

Although histological features of HSPN are essentially homogenous to those of IgAGN, active lesions, including crescents and electron dense deposits in glomerular capillary walls, are more frequently seen in HSPN than IgAGN[6,7]. In our analysis, the peak age were 8 years for histological diagnosis of HSPN, in contrast to 15 years in IgAGN in children. Mir et al. described that long-term morbidity of HSPN was predominantly associated with initial presentation and renal involvement[7]. They emphasize importance of renal biopsy at early stage of HSPN.

In the cases with MGA, no histopathlogical features were encountered by the methods of light microscopy, immunofluorescence or electron microscopy. The causes of urinary abnormality in cases of MGA may be different from glomerular diseases, such as exercise or orthostatic stress and Nut-cracker syndrome. The cases of MGA were increased in number in boys in junior-high schools, suspicious of urinary abnormality by exerciseor orthostatic stress. It is important to give the diagnosis of MGA for adequate advice for school life. In the previous report, the incidence of MGA ranges 2 to 14 % in mass screening cases[1,4,8].

Most patients with TMD present only with hematuria, with out additional symptoms or progression to renal impairment[9]. Electron microscopic observation is necessary to confirm the diagnosis of the condition. The age at diagnosis varied widely from the young children to the elderly. In our study, the

youngest patient is 6 years, and the patient number is increased in cases aged 14 and 15 years. As microscopic hematuria is noted in IgAGN and hereditary nephritis, confirmation of diagnosis of TMD is important in children for prediction of prognosis[10].

It is well known that MCNS is the most common cause in pediatric patients with NS. The incidence of MCNS among pediatric NS was 59% in our study and 50.5% in Czech biopsy registry[1]. However practical incidence of MCNS might be higher than the biopsy-proven data, as a certain number of patients with NS might not be examined by renal biopsy, especially for young children, when MCNS was clinically suspected. Therefore, the number of MCNS is very few in the age under 5 years in our study, though the clinical peak age of MCNS is between 2 to 4 rears[11]. The main purpose of renal biopsy in MCNS might before selection of treatment, confirmation of diagnosis and search for cyclosporine nephrotoxicity in the patients with steroid dependent NS or frequent relapses. IgAGN was the second cause of NS, accounted 11.6% among all the cases of NS and 6.9% of all IgAGN. Barratt et al. describes that NS occured in 5% of all patients of IgAGN, and more common in children. They also mentioned that patients might develop nephrotic-range proteinuria at different stage at of the disease, both when there was mild glomerular injury and when there was advanced glomerulosclerosis[12]. It is speculated that some of IgAGN patients with NS and mild glomerular injury might be superimposed by MCNS on IgAGN.

Heavy proteinuria and nephrotic syndrome are characteristic symptoms in adult cases with MGN. In our study, 14 pediatric patients (87.5%) of MGN are detected by school screening, 4 of them developing to NS. NS occurs in 6 patients (37.5%) among the all patients of MN. Tsukahara et al. reported that 8 patients (66.7%) of 12 Japanese children with MGN were detected by mass screening, and NS occurredin 3 patients (25%)[13]. In contrast to Japanese MGN, the incidence of NS in Korean patients with MGN was higher (61%)[14]. Among 113 Korean patients detected by school screening, only one case was diagnosed as MGN[4].

The number of patients with MPGN has been decreased in Japan and other countries, and the disease has been frequently identified by school screening in this decade. Kawasaki et al. reported that 35 patients (67.3%) with MPGN type 1 were detected by school urinary screening[15]. In our study, 2 patients (40%) are detected by school screening. Early identification by school urinary screening may enable early management and so improve prognosis of MPGN.

In summary, we have analyzed the incidence of biopsy-proven renal diseases in children, focusing on IgAGN and school urinary screening. IgAGN was the most common renal diseases also in childhood as in adolescence. From the age of seven years, the incidence of IgA-GN was highest among all the pediatric renal diseases during whole childhood period, and the number of patients increased as they grew. On the other hand, there were also many cases with non-progressive clinical courses, such as MGA and TMD among total biopsy cases. It is concluded that renal biopsy following school urinary screening may be important for the therapeutic and prognostic guideleines of pediatric group of patients with renal diseases.

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