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Increase in Proteinuria and/or Microhematuria Following Upper Respiratory Tract Infections in Patients with IgA Nephropathy

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Exacerbation of urinary abnormalities after upper respiratory tract infections in patients with IgA nephropathy was examined. Twenty patients with IgA nephropathy and fourty patients with other glomerular diseases were evaluated in this study. The incidence of exacerbation in microhematuria after upper respiratory tract infections was significantly higher in patients with IgA nephropathy than those with other glomerular diseases. The improvement of microhematuria after upper respiratory tract infections was significantly delayed in some patients with IgA nephropathy.

It is indicated that upper respiratory tract infections might be a risk factor of exacerbation in patients with IgA nephropathy.

(Key Words: IgA nephropathy, Microhematuria, Proteinuria, Upper respiratory tract infections)

INTRODUCTION

IgA nephropathy is frequently preceded by episodes of upper respiratory and/or gastrointestinal tract infections which are presumed to have a viral etiology (4, 5, 6, 11). Recently, Tomino et al (7) suggested that an increase of IgA and total proteins in pharyngeal washings from patients with IgA nephropathy might be associated with local infections. Although an exacerbation of urinalysis after upper respiratory tract infections has been suggested in patients with IgA nephropathy (4), the relationship between the incidence and/or frequency of the upper respiratory tract infections and the exacerbation of urinalysis in such disease has not been examined thoroughly.

The purpose of this study was to elucidate the clinical association of abnormal urinalysis and upper respiratory tract infections in patients with IgA nephropathy.

PATIENTS AND METHODS

Patients: Twenty patients with IgA nephropathy and fourty patients with other glomerular diseases were examined. IgA nephropathy is characterized by a mesangial deposition of IgA in renal biopsy specimens by immunofluorescent staining (6). Patients with IgA nephropathy whose biopsy specimens were stained prominently for IgA in glomerular mesangial areas were included in this study after the exclusion of patients with systemic lupus erythematosus (SLE), Henoch-Schoenlein purpura nephritis (HSPN), liver cirrhosis or other systemic diseases. The histopathological changes of IgA nephropathy in our studies were classified as "minimal" (grade I), "slight" (grade II), "moderate" (grade III), and "advanced" (grade IV) stages as described previously (8). Among the fourty patients with glomerular diseases other than IgA nephropathy, there were 17 patients with membranoproliferative glomerulonephritis (MPGN), 15 patients with chronic proliferative glomerulonephritis (PGN) and eight patients with membranous nephropahty (MN). All these patients were diagnosed by light microscopic, electron microscopic and immunofluorescent analysis. Immunofluorescent staining was performed as

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described previously (10).

Disease Activities: Urinalysis for proteinuria and hematuria was performed one month before, during and one month after the upper respiratory tract infections such as tonsillitis and/or pharyngitis were diagnosed by the observation of the redness of pharynx, tonsillar enlargement, throat pain and/or tonsillar pus. Antibiotics such as cephalexin, ampicillin and josamycin were prescribed during such infections in patients with IgA nephropathy and other glomerular diseases. Proteinuria was determined by using a test-tape (Multistix® -III, No. 2820, Miles-Sankyo Co., Ltd, Japan). The degree of proteinuria was graded as none(−) (0mg/dℓ), trace(±) (about 10mg/dℓ), 1(+) (about 30 mg/dℓ), 2(+) (about 100mg/dℓ), 3(+) (about more than 300mg/dℓ)). The average of more than one red cell in a microscopic field with high power (x 400) magnification of urinary sediments was designed as microhematuria. The degree of microhematuria of more than two folds compared before upper respiratory tract infections was designed as the "exacerbation of microhematuria". The average of more than trace amount of protein in urine was designed as proteinuria. The degree of proteinuria of more than one rank, i.e. from (+) to (++) or from (++) to (+++), was designed as the "exacerbation of proteinuria". The levels of serum creatinine (s-Cr) and blood urea nitrogen (BUN) were examined before, and after the upper respiratory tract infections. The levels of serum immunoglobulins and complement components, i.e. IgG, IgA, IgM, C3, C4, and the titers of antistreptolysin-O (ASO) and antistreptokinase (ASK) were also examined before, and after the upper respiratory tract infections. the antibody titers for various types of viruses were also examined at those times. Circulating immune-complexes (IC) in sera examined before and after upper respiratory tract infections were also measured by a C1q-binding enzyme assay kit (Special Reference Laboratory, Tokyo, Japan). The normal value of C1q-binding IC was less than 3.0μg/mℓ. Immunofluorescent staining of circulating IC phagocytized by polymorphonuclear leukocytes (PMN) was performed as described previsously (8).

Statistical significance was evaluated by Mann-Whitney U-test (1).

RESULTS

(a) **IgA nephropathy:** Microhematuria was observed in 16 out of 20 patients (80.0%) with IgA nephropathy before upper respiratory tract infections. Proteinuria was observed in 13 out of 20 patients (65.0%) with IgA nephropathy before upper respiratory tract infections. The association of microhematuria and proteinuria was observed in 12 out of 20 patients (60.0%) with IgA nephropathy before such infections. Exacerbation of microhematuria after such infections was observed in 14 out of 20 patients (70.0%) with IgA nephropathy. Exacerbation of proteinuria after such infections was observed in ten out of 20 patients (50.0%) with IgA nephropathy. Exacerbation of macrohematuria after such infections was not observed in any patients with IgA nephropathy. Exacerbation of both microhematuria and proteinuria was observed in nine out of 20 patients (45.0%) with IgA nephropathy (Table 1). Although the improvement of upper respiratory tract infections was observed immediately after the treatment, that of aggravated microhematuria after those infections was significantly delayed in eight out of 14 patients (57.1%) with IgA nephropathy ($p < 0.05$). The improvement of aggravated proteinuria after those infections was observed immediately in all ten patients with IgA nephropathy (Fig. 1). There was no significant difference in the levels of s-Cr, BUN or circulating IC examined both before and after upper respiratory tract infections in patients with IgA nephropathy ($p > 0.1$). The levels of serum IgA examined after upper respiratory tract infections were slightly higher than those before such infections in some patients with IgA nephropathy, but the difference was not statistically significant ($p > 0.1$). There was no significant difference in the levels of serum IgG, IgM, C3 or C4 examined both before and after such infections in patients with IgA nephropathy. There was no significant difference in the titers of ASO, ASK or antiviral antibodies such as antibodies for influenza, parainfluenza, coxsackie, ECHO, adeno, and Epstein-Barr (EB) viruses as well as for mycoplasma examined both before and after such infections in patients with IgA nephropathy ($p > 0.1$). There was no significant correlation

between the degree of exacerbation of microhematuria and/or proteinuria and the histopathological gradings in patients with IgA nephropathy (Table 2).

(b) Other glomerular diseases: Exacerbation of microhematuria after upper respiratory tract infections was observed in four out of 17 patients (23.5%) with MPGN, in six out of 15 patients (40.0%) with PGN, and in two out of eight patients (40.0%) with MN. Exacerbation of proteinuria after such infections was observed in one out of 17 patients (5.9%) with MPGN, in nine out of 15 patients (60.0%) with PGN and in three out of eight patients (37.5%) with MN. Exacerbation of macrohematuria after upper respiratory tract infections was not observed in any patients with MPGN, PGN or MN. Exacerbation of both microhematuria and proteinuria after such infections was observed in one out of 17 patients (5.9%) with MPGN, in six out of 15 patients (40.0%) with PGN and in two out of eight patients (40.0%) with MN (Table 3). There was no significant difference in the levels of s-Cr, BUN, circulating IC, serum IgG, IgA, IgM, C3, C4 examined both before and after such infections in patients with MPGN, PGN and MN. There was no significant difference in the titers of ASO, ASK or antiviral antibodies examined both before and after such infections in those patients. There was no significant correlation between the degree of exacerbation of microhematuria and/or proteinuria and the histopathological gradings in patients with MPGN, PGN and MN.

DISCUSSION

Primary chronic glomerulonephritis is generally considered to be mediated by immune complexes although the antigens have not yet been identified (4, 5, 6, 7). Clarkson et al (2) reported that the onset of hematuria coincided with or commenced within hours of developing a sore throat (83%) or of gastrointestinal symptoms (17%). Recently, the authors (4) have reported that upper respiratory tract infections might be a risk factor for exacerbation in some patients with IgA nephropathy.

In the present study, the incidence of exacerbation of microhematuria after upper respiratory tract infections in patients with IgA nephropathy was significantly higher than that in patients with other glomerular diseases. Moreover, the improvement of exacerbated microhematuria was delayed in some patients with IgA nephropathy. The incidence of exacerbation of proteinuria after upper respiratory tract infections in patients with IgA nephropathy or PGN was higher than that in patients with MN or MPGN. However, upper respiratory tract infections improved immediately after treatment in those patients. It was suggested that the administration of antibiotics prescribed at the time of upper respiratory tract infections might have a prophylactic effect against the exacerbation of primary chronic glomerulonephritis in the present study. It is postulated that upper respiratory tract infections might be lead to the exacerbation of histopathological injuries in glomeruli from patients with chronic glomerulonephritis although the mechanisms of exacerbation of urinalysis are still obscure. It was not determined whether the cause of upper respiratory tract infections in patients with chronic glomerulonephritis was due to bacterial or viral substances since no significant increases of ASO, ASK and antiviral antibodies were observed in such patients. However, Finlayson et al (3), Whitworth et al (12) and Tomino et al (7) have reported that the increase of IgA and total proteins in pharyngeal washings from patients with IgA nephropathy might be associated with local infections. Moreover, the authors (9) reported that IgA antibodies deposited in glomeruli specifically bind with nuclear regions of fibroblasts cocultured with freeze-thawed extracts of pharyngeal cells from patients with IgA nephropathy used by an autoradiographical analysis.

It is concluded that upper respiratory tract infections might be one of the risk factors in some patients with IgA nephropathy and other glomerular diseases. Further examinations are warranted to clarify the mechanisms of exacerbation of urinary findings after upper respiratory tract infections in patients with IgA nephropathy and other glomerular diseases.

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Table 1 Urinary findings and titers of ASO one month before, during and one month after upper respiratory tract infections in patients with IgA nephropathy.

Case	Age/Sex	Grading	Hematuria/HPF			Proteinuria			ASO	
			B*	D**	A***	B	D	A	B	A
1	27/M	III	10–50	>100	>100	+ +	+ + +	+	1:60	1:60
2	24/M	II	1–5	5–10	5–10	±	+ +	±	1:60	1:60
3	26/M	II	1–5	>100	>100	+ + +	+ + +	+ + +	1:40	1:40
4	41/M	III	1–5	1–5	1–5	±	±	±	1:160	1:160
5	38/M	III	<1	>100	50–100	±	+ +	–	1:60	1:60
6	26/M	IV	5–10	>100	50–100	–	+ + +	±	1:60	1:60
7	44/M	III	10–50	10–50	10–50	+ + +	+ + +	+ + +	1:80	1:80
8	20/M	I	10–50	10–50	10–50	–	+ + +	±	1:60	1:60
9	32/M	II	1–5	10–50	10–50	–	–	–	1:80	1:60
10	19/M	III	10–50	50–100	50–100	+ +	+ + +	+ +	1:60	1:60
11	38/M	II	1–5	1–5	1–5	+ +	+ +	+ +	1:240	n.d.
12	38/M	III	1–5	10–50	10–50	+ +	+ +	+ +	1:60	1:60
13	49/M	II	5–10	5–10	5–10	+ +	+ +	+ +	1:60	1:60
14	28/M	III	1–5	10–50	10–50	±	+ +	±	1:40	1:40
15	18/M	II	10–50	>100	>100	+ +	+ + +	+ +	1:80	1:80
16	32/M	II	10–50	10–50	10–50	+ +	+ +	+	1:80	1:80
17	38/M	II	<1	>100	>100	–	+ + +	–	1:80	1:160
18	28/M	II	<1	50–100	50–100	–	–	–	1:40	1:40
19	45/M	II	<1	10–50	10–50	–	+ + +	–	1:40	1:40
20	42/M	II	5–10	10–50	10–50	–	–	–	1:60	1:80

M; male, F; female, n.d.; not done.
B*: one month before, D**:during, and A***: one month after upper respiratory infections.

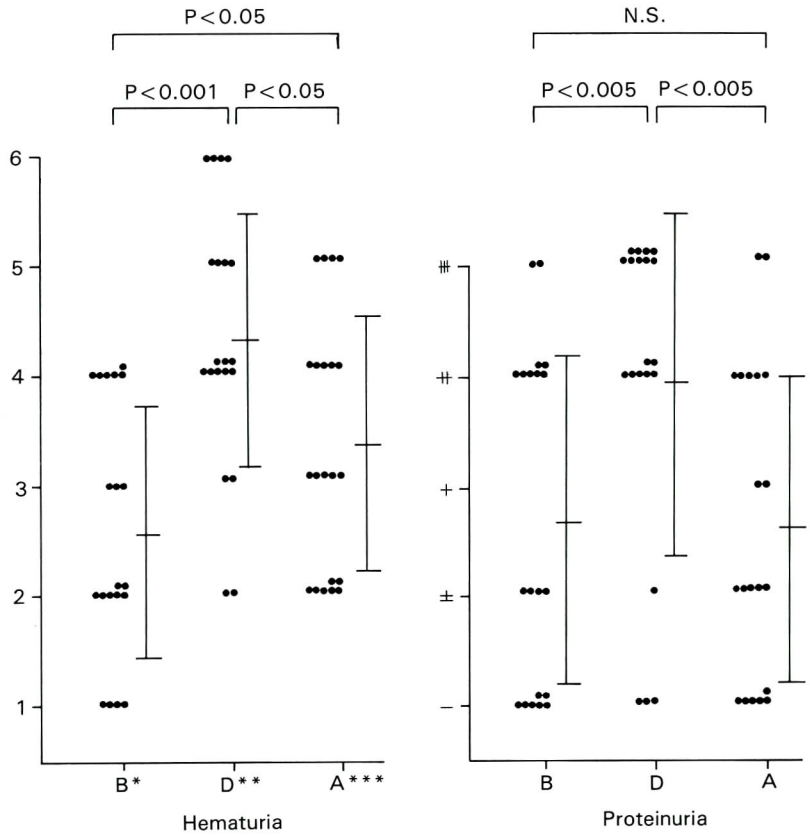
Table 2 Serological findings one month before and after upper respiratory tract infections in patients with IgA nephropathy.

Case	s-Cr (mg/dl)		s-IgA (mg/dl)		C1q-IC (μg/ml)	
	B*	A**	B	A	B	A
1	1.1	1.2	395	389	1.5	1.5
2	1.1	1.2	644	541	1.5	1.5
3	1.1	1.1	242	253	1.5	1.5
4	1.2	1.2	537	498	1.5	1.5
5	1.1	1.1	465	428	1.5	1.5
6	1.1	1.2	243	276	1.5	1.5
7	1.2	1.2	287	283	7.4	8.3
8	1.1	0.8	253	211	1.5	1.5
9	0.9	1.0	298	230	3.3	7.3
10	0.9	1.0	355	342	1.5	7.1
11	0.7	0.7	399	429	1.5	1.5
12	1.0	1.2	201	n.d.	1.5	1.5
13	1.1	1.1	244	270	1.5	1.5
14	0.8	0.9	356	444	1.5	3.2
15	1.0	1.0	253	274	1.5	1.5
16	1.0	0.7	477	451	1.5	1.5
17	1.1	1.1	165	189	2.2	3.4
18	1.0	1.0	199	270	24.0	n.d.
19	1.1	1.2	188	233	1.5	1.5
20	1.1	1.1	453	442	1.5	1.5

B*: one month before, A**: one month after upper respiratory infections.
n.d.: not done.

Table 3 Frequencies of exacerbation of proteinuria and microhematuria after upper respiratory tract infections in patients with IgAN, MPGN, PGN and MN.

Disease	Number of Cases	Exacerbation of Proteinuria		Exacerbation of Microhematuria	
IgAN	20	10/20	(50%)	14/20	(70%)
MPGN	17	1/17	(5.9%)	4/17	(23.5%)
PGN	15	9/15	(60%)	6/15	(40%)
MN	8	3/8	(37.5%)	2/8	(25%)



B*: one month before, D**: during, and A***: one month after upper respiratory infections.
1:less than one red cell, 2:1-5 red cells, 3:5-10 red cells, 4:10-50 red cells, 5:50-100 red cells and 6: more than 100 red cells per high power field in urinary sediments.

Fig. 1 Urinary findings one month before, during and one month after upper respiratory tract infections in patients with IgA nephropathy.