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C3 Deposition in IgA Nephropathy in Children and Adolescents

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The aim of this study was to assess the significance of C3 deposition in IgA nephropathy in children and adolescents. One hundred and two patients aged 5-21 years (57 male and 45 female) were studied. The findings of C3 deposition were classified into 8 groups by immunofluorescent (IF) pattern and intensity as follows: group MC3+ (N=12): mesangiocapillary pattern and 3+ in intensity; group MC2+ (N=13): mesangiocapillary and 2+; group MC1+ (N=4): mesangiocapillary and 1+; group M3+ (N=11): mesangial and 3+; group M2+ (N=24): mesangial and 2+; group M1+ (N=18): mesangial 1+; group S (N=12): only segmentally positive; and group N (N=8): negative. Histological changes were scored semiquantitatively as an activity index (cellular proliferation, necrosis, interstitial cell infiltration, and cellular crescents) and a chronicity index (mesangial sclerosis, segmental and global glomerular sclerosis, fibrous crescents, adhesion and tubulo-interstitial change). IF findings were scored semiquantitatively and laboratory findings were also studied. The following results were obtained: 1) The scores of total activity index in MC groups were higher than in the M, S or N groups, and the greater the degree of C3 deposition, the higher the score; 2) Such result was not evident in the chronicity index; 3) High IF scores of IgG and IgM were found in the MC3+ and MC2+ groups; 4) Hematuria was more severe in MC3+ and MC2+ than in other groups, and proteinuria was more prominent in the MC than other groups. Thus the degree of C3 deposition was parallel with histological activity and urinary findings.

Key Words
C3 deposition, IgA nephropathy, Childhood

Introduction

IgA nephropathy, originally described by Berger in 1969 [1], is now widely accepted as a distinct clinicopathologic entity and is common in children [2]. Although the full pathogenesis is unknown, it is characterized by the diffuse deposition of IgA in the mesangium with the frequent association of C3. Immunologic

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studies of the mesangial depositis in IgA nephropathy reveal frequent C3 deposition and properdin in a pattern similar to that of IgA, and the classical complement pathway proteins Clq and C4 are usually absent. These findings suggest a pathologic role for the alternate complement pathway in this disease [3–5]. Complement is believed from many experimental and clinical studies [4, 6] to be important in glomerular inflammation. C3 is a key complement protein in both classical and alternative complement pathways [7]. Thus the question of how complement activation acts as a mediator in inflammation of the glomerulus is important in understanding IgA nephropathy.

In the present study we classified the patients with IgA nephropathy according to the pattern and degree of C3 deposition by immunofluorescence (IF), and performed a clinicopathological analysis.

Subjects and Methods

The diagnosis of IgA nephropathy was based on generally accepted criteria. One hundred and two patients with IgA nephropathy were studied. Their ages ranged from 5 to 21 years and there were 57 males and 45 females. The IF findings of C3 deposition were classified into 8 groups according to the pattern and intensity of deposition as follows: group MC3+ (N=12): mesangiocapillary pattern and 3+ in intensity; group MC2+ (N=13): mesangiocapillary and 2+; group MC1+ (N=4): mesangiocapillary and 1+; group M3+ (N=11): mesangial and 3+; group M2+ (N=24): mesangial and 2+; group M1+ (N=18): mesangial and 1+; group S (N=12): only segmentally positive; and group N (N=8): negative. All the clinical and histological findings were analysed by comparing these 8 groups.

For histological examination the sections were stained with hematoxylin and eosin, periodic acid-Schiff and periodic acid-silver methenamine. Histological changes were scored semiquantitatively as an activity index and a chronicity index by the method of Andreoli et al [8] with some modifications. The activity index comprised 4 detailed changes: cellular proliferation, necrosis, interstitial cell infiltration and cellular crescent formation. The chronicity index comprised 6 different changes: mesangial sclerosis, segmental glomerular sclerosis, global glomerular sclerosis, adhesion, fibrous crescents and tubulo-interstitial change. The scoring of these 8 histological changes was as follows: in cellular proliferation and mesangial sclerosis: severe=3.0, moderate= 2.0, mild=1.0, minimal change=0, moderate to severe=2.5, mild to moderate=1.5, and minimal change to mild=0.5; in the other 7 changes, the percentages of positive glomeruli or area affected were calculated and scored as 51–100%=3.0, 36–50%=2.5, 21–35%=2.0, 11–20%=1.5, 0–10%=1.0 and 0%=0. For IF study, the usual technique was used by direct staining using fluorescein-conjugated commercial antisera to human IgG, IgA, IgM, C4 Clq, C3 (Behring-werke), fibrinogen and properdin (Kent). Classification of the IF findings was performed similarly to that of C3 deposition. The IF findings were scored semiquantitatively as follows: mesangiocapillary pattern and 3+ in intensity=4.0; mesangiocapillary and 2+=3.0; mesangiocapillary and 1+=2.0; mesangial and 3+=3.0; mesangial and 2+=2.0; mesangial and 1+=1.0; segmentally positive=0.5 and negative=0.

Statistical analysis was performed using the Student t-test for comparison of means. Results are given in the figures and tables as mean ±1 standard deviation.

Results

Clinical findings

One hundred and two patients were classified as shown in Table 1. The number of patients showing segmental or negative staining of C3 was 20, acounting for about 20% of the patients. Sex ratio, age at onset, ratio discovered by chance proteinuria and/or hematuria, age at renal biopsy and duration from onset to biopsy are shown in Table 1.

Table 1. Patients' profiles (1)

Group	No	Sex ratio M/F	Age at onset	Discovered by chnace P/H	Age at renal biopsy	Duration from onset to biopsy
MC3+	12	5/7	10y 2m (4–14y)	6 (50%)	11y 2m (5–15y)	12m
MC2+	13	7/6	9y 9m (5–13y)	7 (54%)	10y 2m (6–13y)	6m
MC1+	4	3/1	9y 6m (6–12y)	2 (50%)	11y 9m (10–13y)	21m
M3+	11	8/3	11y11m (8–17y)	9 (82%)	13y (9–21y)	15m
M2+	24	14/10	9y11m (2–18y)	14 (58%)	10y 7m (5–18y)	8m
M1+	18	9/9	9y 3m (5–13y)	10 (56%)	10y 2m (5–15y)	11m
S	12	7/5	8y 9m (5–10y)	9 (75%)	10y11m (6–14y)	27m
N	8	4/4	9y10m (6–13y)	5 (63%)	10y 7m (7–14y)	9m
Total	102	57/45	9y10m	62 (61%)	10y10m	12m

P/H: Proteinuria/Hematuria

Table 2. Patients' profiles (2)

Group	Treatment before Bx	Hematuria (>200/HPF)	Proteinuria (>2+ of Sulfo)	Gross hematuria	Nephrotic syndrome*	Hypertension**
MC3+ (N=12)	2 (17%)	6 (50%)	10 (83%)	8 (67%)	3 (25%)	3 (25%)
MC2+ (N=13)	0 (0%)	6 (46%)	10 (77%)	6 (46%)	2 (15%)	0 (0%)
MC1+ (N=4)	1 (25%)	1 (25%)	3 (75%)	3 (75%)	1 (25%)	0 (0%)
M3+ (N=11)	0 (0%)	0 (0%)	4 (36%)	5 (45%)	0 (0%)	0 (0%)
M2+ (N=24)	0 (0%)	6 (25%)	7 (29%)	7 (29%)	0 (0%)	0 (0%)
M1+ (N=18)	0 (0%)	6 (33%)	6 (33%)	7 (39%)	0 (0%)	0 (0%)
S (N=12)	4 (33%)	2 (17%)	4 (33%)	7 (58%)	0 (0%)	0 (0%)
N (N=8)	0 (0%)	1 (13%)	2 (25%)	2 (25%)	1 (13%)	0 (0%)
Total (N=102)	7 (7%)	28 (27%)	46 (45%)	45 (44%)	7 (7%)	3 (3%)

Bx: Biopsy; *: Albumin, <2.5 g/dl; **: >140/90 mmHg

Table 3. Clinical data (1)

Group	Azotemia[1]	Decreased GFR[2]	s-IgA[3]	u-FDP[4]	u-β2MG[5]
MC3+ (N=12)	1/12 (8%)	2/10 (20%)	1/12 (8%)	7/8 (88%)	1/8 (13%)
MC2+ (N=13)	0/13 (0%)	0/12 (0%)	2/12 (17%)	3/12 (25%)	0/10 (0%)
MC1+ (N=4)	1/4 (25%)	0/4 (0%)	0/4 (0%)	2/3 (67%)	0/4 (0%)
M3+ (N=11)	0/11 (0%)	0/10 (0%)	1/10 (10%)	1/10 (10%)	0/7 (0%)
M2+ (N=24)	0/24 (0%)	0/24 (0%)	1/24 (4%)	11/23 (48%)	0/20 (0%)
M1+ (N=18)	0/18 (0%)	0/18 (0%)	0/18 (0%)	3/16 (19%)	0/16 (0%)
S (N=12)	0/12 (0%)	1/12 (8%)	0/12 (0%)	1/11 (9%)	0/10 (0%)
N (N=8)	0/8 (0%)	0/ 8 (0%)	0/8 (0%)	4/7 (57%)	1/5 (20%)
Total (N=102)	2/102 (2%)	3/100 (3%)	5/100 (5%)	32/90 (36%)	2/80 (3%)

[1] BUN, >30 mg/dl or Cr, >1.2 mg/dl; [2] Ccr, <60ml/min/1.73m^2; [3] >2 standard deviation;
[4] >0.25 ug/ml; [5] >1000 ug/l

Table 2 shows clinical profiles including treatment before biopsy, hematuria of more than 200 RBC/HPF, proteinuria of more than 2+ sulfo, gross hematuria, nephrotic syndrome and hypertension. Hematuria or proteinuria of this degree were often observed in groups MC3+, MC2+ and MC1+. Nephrotic syndrome and hypertension were also found in groups MC3+, MC2+, and MC1+ except in one patient. Tables 3 and 4 show laboratory values or incidence. Azotemia or decreased glomerular filtration rate (GFR) were found in the MC3+ and MC1+ groups, although there were no significant differences between the groups in other values.

Table 4. Clinical data (2)

Group	CIC (>5ug/ml)	C3 (mg/dl)	C4 (mg/dl)	CH50 (u/ml)
MC3+ (N=12)	4/7 (57%)	96.3 (56-127)	28.9 (9.6-42.0)	32.7 (25.0-52.0)
MC2+ (N=13)	2/6 (33%)	99.3 (60-138)	30.2 (18.0-52.0)	28.8 (24.1-47.0)
MC1+ (N=4)	1/3 (33%)	116.0 (77-153)	41.6 (33.0-46.0)	40.2 (22.7-47.0)
M3+ (N=11)	4/7 (57%)	76.2 (65-87)	22.6 (10.8-43.0)	33.0 (29.0-43.0)
M2+ (N=24)	3/15 (20%)	78.2 (55-118)	29.8 (11.9-49.0)	34.9 (22.0-45.0)
M1+ (N=18)	3/10 (30%)	83.6 (52-155)	23.3 (10.0-44.0)	35.4 (23.0-46.0)
S (N=12)	2/6 (33%)	77.9 (43-108)	26.3 (8.9-42.4)	34.0 (21.0-42.0)
N (N=8)	2/7 (29%)	88.9 (43-117)	27.6 (19.3-32.9)	32.1 (26.0-35.0)
Total (N=102)	21/61 (34%)	86.5	27.8	33.9

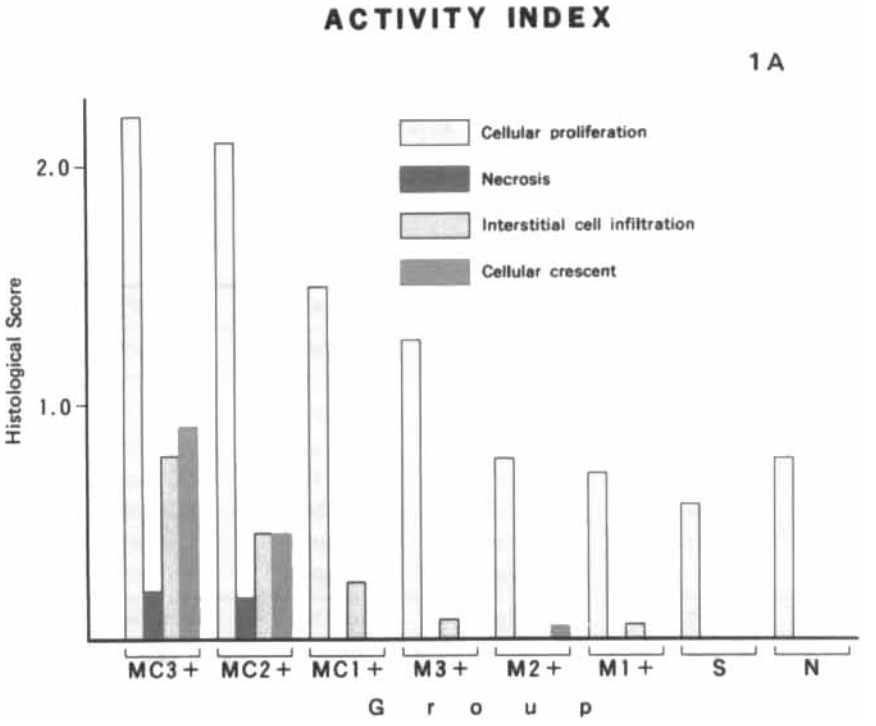
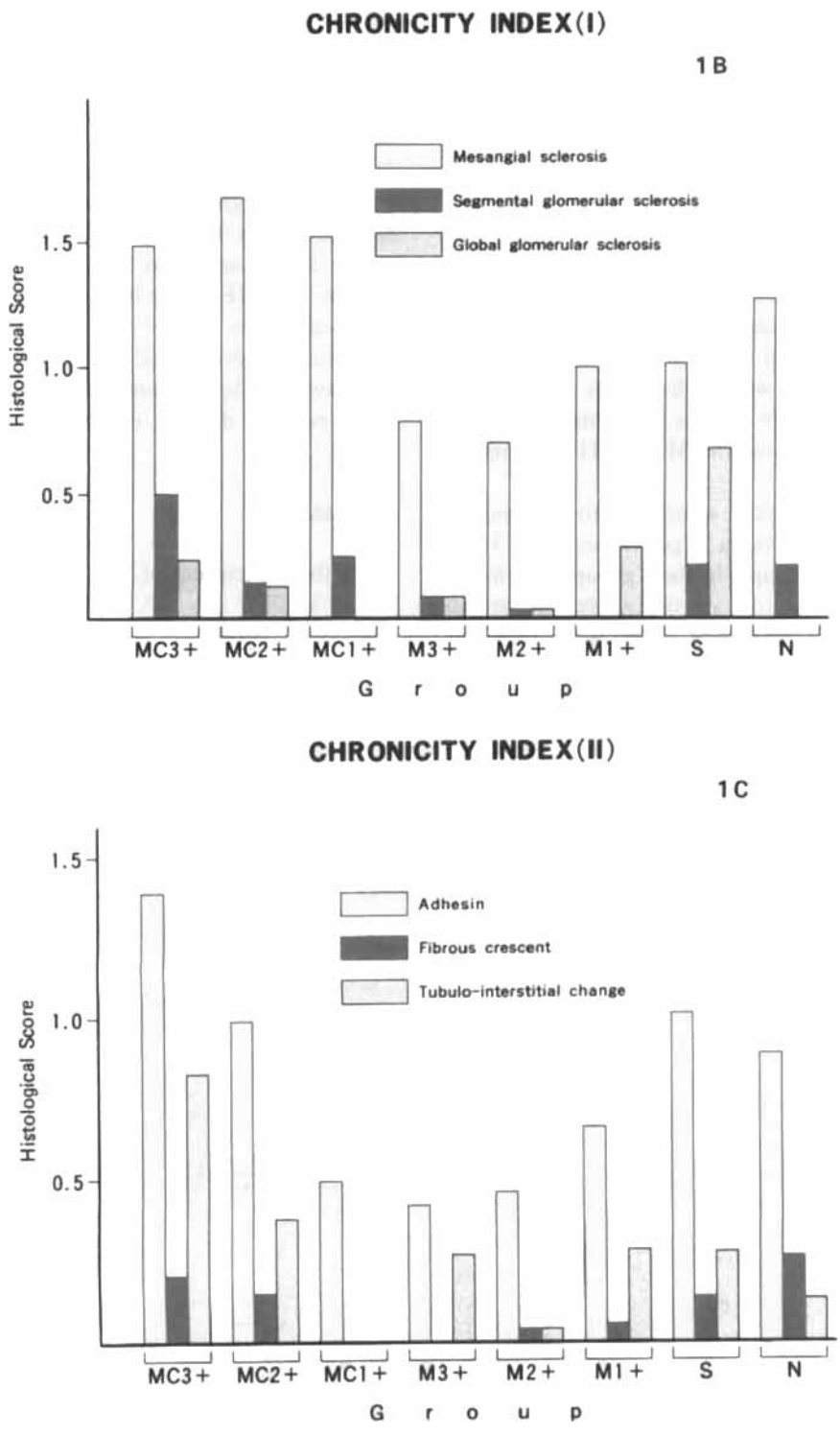


Fig. 1A: Histological scores of activity index in 8 groups. Activity index is composed of 4 different histological changes.



Figs. 1B and 1C: Histological scores of chronicity index in 8 groups. Chronicity index is composed of 6 different changes: mesangial sclerosis, segmental glomerular sclerosis and global glomerular sclerosis (1B); adhesion, fibrous crescent and tubulo-interstitial change (1C)

Histological findings

1) Light microscopic examination

The scores of 4 histological changes in the activity index are shown in Fig. 1A. Necrosis or cellular crescents were found mainly in the MC3+ and MC2+ groups. Interstitial cell infiltration was also observed often in the MC groups, Total scores of activity index are shown in Fig. 2. The scores in MC groups were higher than in M, S or N groups and the greater the degree of C3 deposition, the higher the histological activity. The score of the M3+ group was higher than the M2+, M1+, S or N groups, and there was no differences among the M2+, M1+, S and N groups.

The histological scores in the chronicity index are shown in Figs. 1B and 1C. Total scores of 8 changes in the 8 groups are shown in Fig. 3. Although the score for group MC3+ was the highest, scores from the S and N groups were only slightly lower, and the tendency observed in the activity index was not absent. From these findings, the pattern and degree of C3 deposition are seen to be proportionate to the histological activity.

2) immunofluorescent examination

The IF scores of 6 components are summarized in Table 5. The IF score of IgA in the MC groups was higher than in other groups. High IF scores of IgG and IgM were observed in the MC3+ and MC2+ groups. Statistical analysis could not be performed in the case of Clq, C4 and properdin because some patients did not undergo IF examination.

Discussion

Since the description of IgA nephropathy by Berger in 1969 [1], IgA nephropathy is now the most common renal disease among primary glomerulonephropathies in children

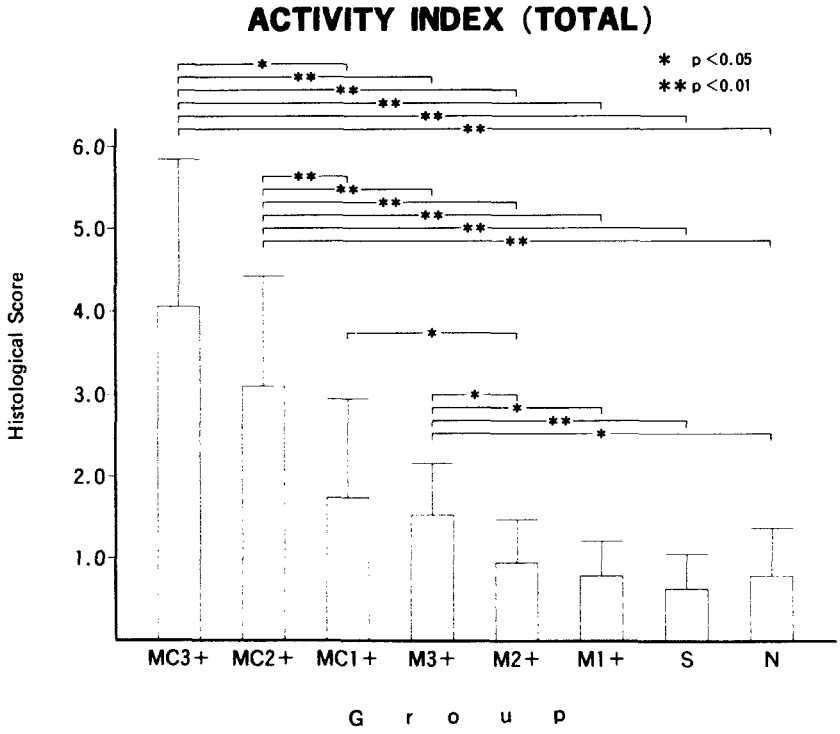


Fig. 2: Total histological scores of activity index in 8 groups.

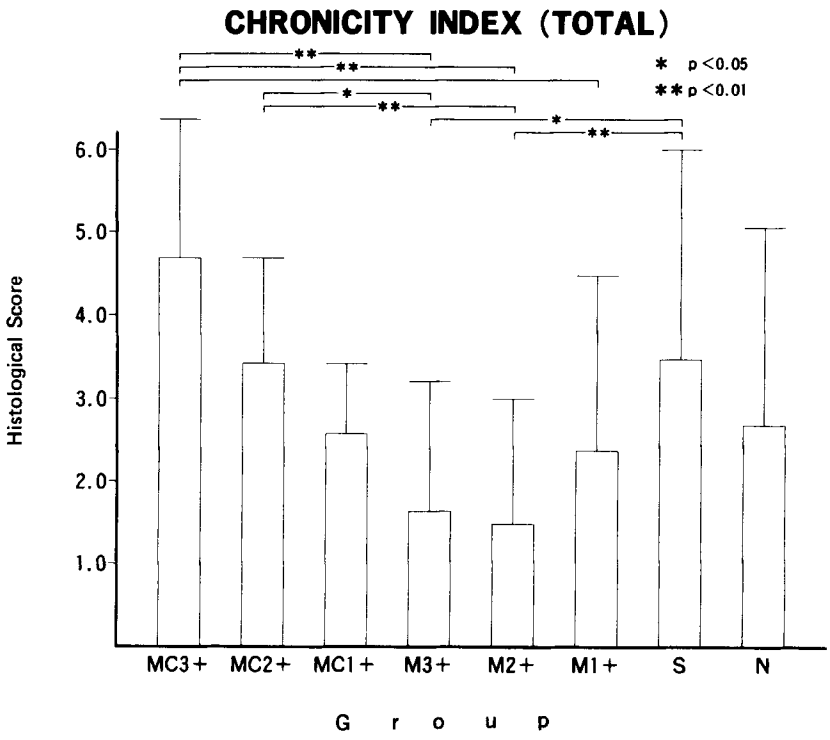


Fig. 3: Total histological scores of chronicity index in 8 groups.

as well as in adults [2, 9]. Although immune mechanisms are thought to be involved in the pathogenesis, the exact mechanisms are still unknown. Generally, inflammation in the glomerulus is evoked by various cellular mediators, such as polymophnuclear leucocytes, macrophages, lymphocytes or platelets, or by complement activation, coagulation and fibrinolysis systems and others [6]. These mediators appear to interact in a complex fashion. Complement activation is the most important inflammatory mediator and it seems to be involved in IgA nephropathy, since C3 deposition is frequently observed by immunofluorescent study. Considerable evidence supports the existence of an alternative pathway in the pathogenesis of IgA nephropathy [3-5]. C3 is a key complement protein for both the alternative and classical pathways and the deposition of C3 is frequent in this nephropathy. However, the significance of this deposition has not been well studied, particularly in the pediatric field. The present study was performed with these points in mind and it was demonstrated that the pattern and degree of C3 deposition is proportionate to the histological activity and is reflected in urinalysis.

Doi et al [10] examined the relation between immune deposits and electron-dense deposits using immunoelectron microscopy. The findings suggested that C3 deposits dissociate from the immune deposits, and the locations of the immune deposits correlate with the severity of mesangial proliferation. They speculated that if the dissociation of C3 deposits occurs in proportion to the length of time since immune deposition, the presence of much C3 deposit suggests that the IgA nephropathy is in the active phase. Our study supports their speculation, since mesangial proliferation takes a great part of the activity index. C3 deposition in IgA nephropathy varied in degree from MC3+ to N in our

Table 5. Score of immunofluorescence examination

Group	N	IgA	IgG	IgM	Clq#	C4#	Properdin#
MC3+[1]	12	3.8±0.4	2.2±1.4	1.8±1.5	0.9 (0-2) (N=11)	0.7 (0-2) (N=7)	1.9 (0-3) (N=8)
MC2+[2]	13	4.0±0.0	2.5±1.7	1.2±0.9	0.3 (0-2) (N=12)	0.4 (0-2) (N=5)	2.1 (0-4) (N=9)
MC1+[3]	4	3.8±0.5	0.8±0.5	0.0±0.0	0.5 (0-2) (N=4)	0.3 (0-1) (N=4)	0.4 (0-1) (N=4)
M3+[4]	11	3.0±0.0	0.8±0.9	0.4±0.5	0.0 (N=11)	0.0 (N=6)	0.8 (0-2) (N=7)
M2+[5]	24	3.0±0.4	1.0±0.9	0.5±0.7	0.3 (0-2) (N=24)	0.0 (N=20)	1.0 (0-3) (N=17)
M1+[6]	18	2.8±0.7	0.7±0.7	0.6±0.7	0.2 (0-1) (N=17)	0.0 (N=14)	0.8 (0-2) (N=14)
S[7]	12	2.5±0.5	1.2±1.0	0.2±0.4	0.2 (0-2) (N=11)	0.0 (N=7)	0.6 (0-2) (N=6)
N[8]	8	3.1±0.4	0.1±0.4	0.6±0.9	0.3 (0-1) (N=8)	0.0 (N=4)	1.6 (0-3) (N=5)

Statistic	IgA	IgG	IgM
**: $p<0.01$	1 vs 4**	1 vs 4*	1 vs 3**
*: $p<0.05$	1 5**	1 5*	1 4**
	1 6**	1 6*	1 5*
	1 7**	1 8**	1 6*
	1 8**	2 4**	1 7*
	2 4**	2 5*	2 3**
	2 5**	2 6**	2 4*
	2 6**	2 7*	2 5*
	2 7**	2 8**	2 7**
	2 8**	3 8*	3 4*
	3 5**	4 8*	3 5**
	3 6*	5 8*	3 6**
	3 7**	6 8*	
	3 8*	7 8**	
	4 7**		
	5 7**		

#: Mean (range)

study. On the other hand, the degree of IgA deposition was not so variable, although the IF scores in the MC groups were higher than in other groups, as shown in Table 5. Thus it is suggested that C3 deposition can give guidance for treatment, and assessment of disease activity and progress.

Immunohistologic studies are usual in examining the role of complement activation in IgA nephropathy. Some investigators have examined serum complement proteins, and the concentrations of C3, C4 and other complement proteins were normal or elevated [11, 12]. In the present study no tendency was observed among the 8 groups. Wyatt et al [13] measured C3 activation using a sensitive new assay that detects a neoantigen of C3, and the results showed that complement activation could frequently be detected despite normal or elevated plasma levels of individual complement proteins in IgA nephropathy. However, the significance of this complement activation remains to be determined.

Glomerular IgA deposition is sometimes associated with secondary disease, such as neoplasia, infection or liver disease. In primary IgA nephropathy C3 deposition is very frequent, whereas it is not found in most asymptomatic patients, such as in cirrhosis, at autopsy [14, 15]. This supports the view that complement deposition in the kidney is important in the pathogenesis of the clinical features, although the exact mechanism of the production of clinical signs, such as hematuria,

proteinuria, azotemia and hypertension, remains enigmatic. Indeed, proteinuria of more than 2+ sulfo or hematuria of more than 200 RBC/HPF were associated with the MC groups in our study.

Renal biopsies from patients with IgA nephropathy show variable amounts of IgG and/or IgM in addition to the predominant IgA deposits. In the present study IF scores of IgG and/or IgM depositions were high in the MC3+ and MC2+ groups, compared with other groups, which means that co-deposition of IgG and IgM are associated with histological activity and abnormal urinalysis. Syre [16] presented data which relate the degree of proteinuria in human IgA nephropathy to deposits in the peripheral capillary wall, and particularly to those of IgG and/or IgM. These observations and the relatively weaker functions of IgA antibodies suggest that co-deposits of IgG, IgM and/or complement may be responsible for glomerular injury in IgA nephropathy. Emancipator et al [17], using active and passive murine models of IgA nephropathy, demonstrated that co-deposition of IgG, IgM and glomerular complement, observed in most cases of human IgA nephropathy, might be important for inducing hematuria. More than 200 RBC/HPF were often observed in the MC3+ and MC2+ groups in our study, and these groups were associated with co-deposition of IgG and IgM. These results agree with their observation. However, the mechanism by which co-deposition of IgG, IgM and complement leads to hematuria remains unknown.

The pattern and degree of C3 deposition was parallel with histological activity. As shown in Fig. 1A the score of the activity index is mainly composed of cellular proliferation. Yoshikawa et al [18] reported that predominant mesangial hypercellularity is characteristic of early lesions of childhood IgA nephropathy, and progression of the disease leads to a gradual decrease of mesangial cellularity and an increase of the matrix with sclerosis. Although there was no obvious relation in our study between the time from the onset of disease to renal biopsy and C3 deposition, their observation seems to be supported by our study. In a follow-up biopsy study of IgA nephropathy (data not shown), proliferative change decreased in the second biopsy, which also agrees with this observation.

As mentioned above, the activity index is mainly composed of cellular proliferation. The proliferating cells are usually mesangial cells in IgA nephropathy. Mesangial cells, which are found in the center of the glomerular capillary tuft, are considered potentially important in the genesis of glomerulonephritis. Recently, several biologic properties of mesangial cells have been identified and associated with immunologic stimuli. Local mediators, such as reactive oxygen species [19] or interleukin 1 [20] or 6 [21] might influence mesangial function, including proliferation. Although complement activation might be important as a mediator for proliferation, further studies of the interaction of complement with glomerular cells, particularly mesangial cells, are necessary.

Deposition of the membrane attack complex (MAC) of complement has recently been demonstrated in IgA nephropathy, and a pathogenic role has been suggested [22, 23]. IgA and MAC are localized in corresponding glomerular sites. This is consistent with complete local activation of complement by glomerular IgA deposits through the alternative complement pathway. Because nucleated glomerular cells resist attack by MAC, a mechanism other than cell lysis may be involved in IgA nephropathy. Several mediators from injured cells are thought to act as a growth factor for mesangial cells and may stimulate the proliferation of mesangial cells [19, 20, 24]. To elucidate this, further studies are necessary.

Finally, the present study demonstrates that the deposition of C3 is proportionate to histological activity and reflected in urinalysis. Although the reason for this association is not clear, the finding may be useful clinically, since understanding the histological activity may lead to advances in treatment.

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