

Significance of Mesangial IgA Deposition in Minimal Change Nephrotic Syndrome: A Study of 60 Cases

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We studied 60 cases of minimal change nephrotic syndrome (MCNS) with mesangial IgA deposits occurring over a 6 year period. There were 43 adults and 17 children. Hematuria occurred in 69.0% of the adults and 88.2% of the children. Two adults and six children had gross hematuria during the course of the disease. Mesangial IgA deposits were noted in 100% of the cases, and concomitant IgG or IgM deposits were found in 78.6% of adults and 73.7% of children. The fluorescent intensity of mesangial IgA deposits was trace (\pm) to 1+ in 86.1% and 70.6% of the adults and children respectively. Most of the patients showed electron microscopic findings consistent with minimal change nephrotic syndrome. We speculate that most of our cases are variants of minimal change nephrotic syndrome but are neither IgA nephropathy nor an overlapping syndrome, and that environmental or genetic factors may be related to the deposition of IgA in these MCNS patients.

Key Words: Mesangial IgA deposit - minimal change nephrotic syndrome

Minimal change nephrotic syndrome (MCNS) is characterized by minimal alteration of glomeruli with diffuse effacement of glomerular foot processes, and may or may not be associated with minimal immune deposits. Mesangial IgA deposition in MCNS is rarely encountered and has been reported in the 1980s, by the titles of MCNS (Saint-Andre *et al.* 1980; Sinnassamy and O'Regan 1985), IgA nephropathy (Mustonen *et al.* 1983; Wu *et al.* 1985; Rambausek *et al.* 1987; Ko *et al.* 1988) or an overlapping syndrome of the two (Lai *et al.* 1986). However, there has not yet been any consensus regarding nomenclature or pathogenesis of this condition.

IgA nephropathy (IgAN) associated with nephrotic syndrome tends to have more severe glomerular alterations and abnormal laboratory findings, but most cases of MCNS with mesangial IgA deposit have been misinterpreted and reported as IgA nephropathy.

We analyzed MCNS with IgA deposits from both the clinical and histopathological aspects in an attempt to clarify whether or not it represents a specific entity.

Materials and Methods

We selected 60 cases (43 adults and 17 children) of MCNS with mesangial IgA deposits among 363 cases of MCNS diagnosed from Jan. 1980 to Dec. 1986. Nephrotic syndrome was defined by generalized or periorbital edema and more than 3 gm excretion of urinary albumin. By light microscopy the glomeruli showed normal or minimal alteration without glomerular basement membrane thickening or diffuse mesangial hypercellularity. Mesangial proliferation was defined by more than 3 cells per peripheral glomerular area and cases belonging to this category were excluded from the study. During the same period, 205 cases of IgA nephropathy were diagnosed in our institution.

The patient's age, sex, and presence or absence of hematuria and of hepatitis B surface antigenemia were recorded. Hematuria of nonglomerular origin was excluded by intravenous pyelography and/or cystoscopy.

The renal biopsy specimen was divided into 3 pieces for light, immunofluorescent and electron

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microscopy. For the light microscopical examination, the specimen was fixed in 10% neutral formalin, embedded either in paraffin or plastic, serially cut at 4-5 μ or 1 μ thickness and stained with hematoxylin-eosin, periodic acid-Schiff, Masson's trichrome and periodic acid-Schiff-methenamine silver stains.

For the immunofluorescent microscopic examination a portion of the fresh renal tissue was frozen, and exposed to FITC-conjugated antihuman-IgG, -IgA, -IgM, -C3, -C4, -C1q and -fibrinogen (Meloy Inc) and examined with a Leitz Dialoux immunofluorescent microscope. The intensity of mesangial immune deposits was divided into four categories of trace (\pm), mild (+), moderate (++), and severe (+++).

For the electron microscopic examination, a small piece of renal tissue was fixed in 3% glutaraldehyde, postfixated with OsO₄, embedded in epon mixture, double stained with uranium acetate and lead citrate, and examined with a Hitachi H-500 transmission electron microscope.

RESULTS

Clinical findings

Mesangial IgA deposits were noted in 16.8% of the 363 cases of MCNS examined; in 43 adults and 17 children. The male to female ratio was 2.7:1 in adults and 3.3:1 in children. The mean age at the time of the biopsies was 29.8 and 9.3 yrs and the average duration of symptoms was 5.6 and 10.9 months in adults and children respectively. Hematuria was present in 69.0% of the adults and 88.2% of the children (Table 1). Six children and two adults showed one or more episodes of gross hematuria; in one child generalized edema was preceded by gross hematuria, but in the remainder gross hematuria developed almost simultaneously with or was slightly preceded by generalized edema (Table 2). Hepatitis B antigenemia was present in one adult and two children.

Table 1. Clinical data of MCNS with mesangial IgA deposit

	Adults	Children
Number of cases	43	17
Sex ratio (M:F)	2.7:1	3.3:1
Mean age at the time of Bx (yr)	29.8	9.3
Average duration of Sx before Dx (m)	5.6	10.9
Hematuria (%)	69.0	88.2

Bx; biopsy, Sx; symptom, Dx; diagnosis

Table 2. Clinical findings in patients with gross hematuria

Case No.	1	2	3	4	5	6	7	8
Age & Sex	39/F	29/M	13/M	8/M	9/M	9/M	6/F	8/F
Presenting Sx	Gen. edema	Gen. edema	Periorb. edema	Gen. edema	Gen. edema	Puffy face	Puffy face	Gen. edema
Duration of Sx before biopsy	2m	4m	20m	1/4m	Unknown	2m	1/2m	1m
Episodes of gross hematuria	Once	Several times	Three times		Once	Once	Once	Once
Blood pressure	120/80	110/70	130/80	100/70	110/70	110/60	120/90	
24hr U. prot(g)	1.26	12.2	2.1-7.5	9.2	ND	3.2	5.4	13.4
T. prot (g/dl)	6.5	3.5	4.8	3.3	3.6	5.5	4.4	3.7
Albumin (g/dl)	4.1	1.4	2.4	1.4	1.5	2.3	2.0	2.2
BUN (mg/dl)	10.8	13.0	9.3	11.0	14.0	8.0	12.5	32.6
Cr. (mg/dl)	0.8	0.7	0.7	0.5	0.8	0.7	0.5	0.7
HBs Ag	-	-	+	-	ND	-	-	-

Sx; symptom, prot; protein, Cr.; creatinine, ND; not done, Gen.; generalized, Periorb.; Periorbital

Table 3. Clinical findings in patients with HBs antigenemia

Case No.	1	2	3
Age & sex	47/F	6/M	13/M
Presenting Sx	Gen. edema	Gen. edema	Periorb. edema
Duration of Sx before Bx	2m	2wks	20m
Blood pressure	120/80	110/70	110/70
Hematuria	microscopic	microscopic	gross
Serology			
Albumin (g/dl)	1.3	2.1	2.4
BUN (mg/dl)	16.3	15.0	9.3
Creatinine (mg/dl)	0.9	0.5	0.7
SGOT (U/l)	15	35	24
SGPT (U/l)	64	20	32
HBs Ag	positive	positive	positive
Anti-HBs Ab	negative	negative	negative
Anti-HBc Ab	ND	ND	positive
HBe Ag	ND	ND	positive

Sx; symptom, Bx; biopsy, Gen; generalized, Periorb.; periorbital

All three had hematuria and one of the two children had episodes of gross hematuria (Table 3).

Light Microscopy

Minimal mesangial proliferation was noted in 14.0% of adults, and 5.8% of children.

Immunofluorescent Microscopy

The combinations of mesangial immunoglobulin deposits in adults and children are summarized in Table 4. Not only IgA but also IgM or IgG were deposited in 78.6% of the adults and 73.7% of the children. Mesangial IgA deposition is shown in figures 1 and 2 at trace and mild intensities respectively. The intensity of IgA deposition was trace (\pm) to 1+ in 86.1% and 70.6% of adults and children respectively, and none showed 3+ (Table 5).

Electron microscopy

The electron microscopy revealed diffuse effacement of epithelial foot processes with microvillous transformation in 100% of the cases. In addition, four adults and six children showed basement membrane alteration, especially focal widening and rarefaction of the lamina rara interna; and 3 children showed long segment splitting. Mild mesangial proliferation was noted in 2 cases, and a mild increase of the mesangial matrix in 3 cases.

Table 4. Distribution of cases according to combination of immunoglobulin deposits in MCNS

Site & type of deposits	Adults	Children
Mesangium IgA only	9	6
with C3	4	4
without C3	5	2
IgA + IgM	16	7
with C3	9	3
without C3	7	4
IgA + IgG	4	0
with C3	3	0
without C3	1	0
IgA + IgM + IgG	14	4
with C3	11	3
without C3	3	1
Vessel C3 only	23	7
C3 + IgA	1	0

Table 5. Degree of mesangial IgA deposits in MCNS

Degree	Adults	Children	Total
\pm	14 (32.6)	6 (35.3)	20 (33.3)
+	23 (53.5)	6 (35.3)	29 (48.3)
<++	6 (14.0)	5 (29.4)	11 (18.3)
Total	43 (100.1)	17 (100.0)	60 (99.9)

The degrees of immune deposits are divided into \pm to +++ according to the brightness and extent.

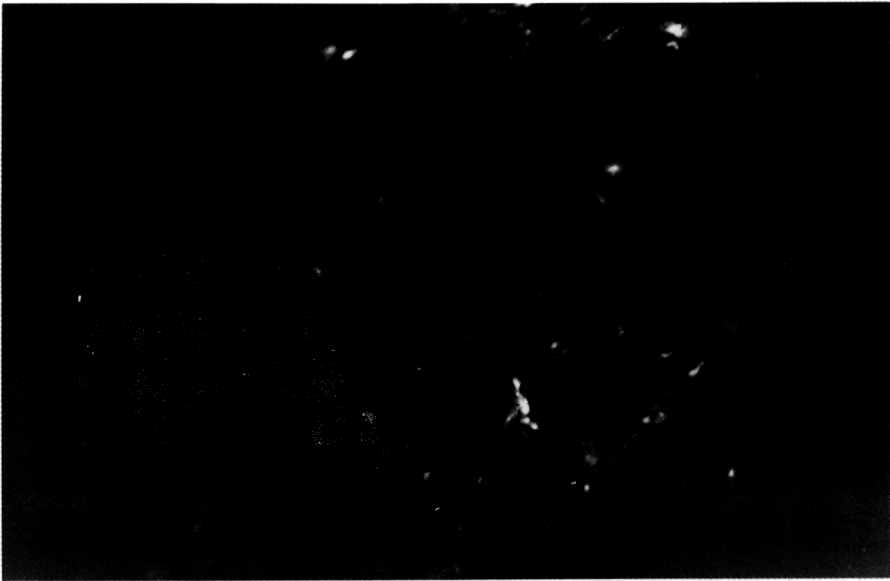


Fig. 1. A trace (\pm) intensity of IgA is deposited in the glomerular mesangium. immunofluorescent microscopy, $\times 200$.



Fig. 2. A mild (+) intensity of mesangial IgA deposition is found in a granular distribution. Immunofluorescent microscopy, $\times 200$.

DISCUSSION

Mesangial deposition of IgA can be found in many diseases, of which IgAN is the prototype. Recently,

mesangial IgA deposits have been reported in some patients with MCNS, especially in Orientals (Lai *et al.* 1986; Ko *et al.* 1988), which has been mostly reported as IgA nephropathy. However, this condition is similar to MCNS in that the patients responded well to steroid therapy, and the deposited IgA was minimal in inten-

sity compared to other immunoglobulins deposited in MCNS. Moreover, the concept of an overlapping syndrome was also proposed by Lai *et al.* (1986).

In our study, there was a slight male predominance and more significant association of hematuria, both gross and microscopic, in the cases of MCNS with IgA deposits as compared with a previous report dealing with 394 cases of minimal lesion with or without nephrotic syndrome regardless of mesangial immunoglobulin depositions during a 4 year period (Choi *et al.* 1986). Gross hematuria was more frequently found in children than in adults. The occurrence of hematuria was coincidental with edema in most of the cases. Hematuria of nonglomerular origin was eliminated by clinical study. The alteration of the glomerular basement membrane, such as widening of the lamina rara interna may partially explain hematuria.

There is no difference in light microscopy between MCNS with and without IgA deposits. It is critical to determine whether IgA deposition plays a major pathogenic role, is a coincidental finding, or is a mere trapping. Generally, there is no immune deposition in cases of MCNS. However, a small amount, mainly IgG or IgM, can be deposited without significant consequences, and seems to be a trapping. Meanwhile, mesangial IgA deposits may be caused by derangement of mucosal immunity.

There are no convincing criteria for the intensity of deposited IgA necessary for a diagnosis of IgAN to be made. Recently, Jennette (1988) divided the scale of deposited IgA into 0-4 grades and reported that the diagnosis of IgAN can be made with more than a 2+ intensity of mesangial IgA in 98% of cases. The degree of IgA deposition in other conditions, excluding Henoch-Schönlein purpura and systemic lupus erythematosus, was reported to be more than 2+ in only 2%, with respect to the minor deposits of IgA in 86.0% and 70.6% of the adults and children of our study. For the above reasons, these deposits might not be significant enough to be diagnosed as IgAN, particularly in the case of MCNS.

Therefore, we suspect that the majority of cases of glomerular minimal change with mesangial IgA deposition associated with nephrotic syndrome are probably a variants of MCNS. Then, how and why is IgA deposited in these cases? This condition is exclusively reported in Orientals, which may suggest genetic or environmental factors. Among the environmental factors, HBs antigenemia was noted in 3 cases, and one of them presented with gross hematuria during the course of the disease. We believe that a variety of microbes or foods can evoke clonal proliferation

of IgA-producing plasma cells residing in the submucosa of the respiratory or gastro-intestinal tracts (Emancipator *et al.* 1983; Choi and Choi, 1987; Jin and Choi, 1990) in the course of MCNS. Thus, with a transient but appropriate stimulus, IgA-containing immune complexes may be formed, and a minimal amount of IgA may thus be deposited in the glomerular mesangium. Sinniah (1983) reported mesangial IgA as the predominant immunoglobulin in 8 cases of a control autopsy population of 200, which reflect a common environmental antigen. They interpreted this as the clearance of circulating non-nephritogenic immune complexes.

However, as several cases in our study showed prominent mesangial IgA deposition in MCNS, with alteration of glomerular basement membranes which was usually not seen in MCNS, a few of them could be considered as an overlapping syndrome. It is of interest that case 7 with gross hematuria had a second biopsy performed 7 months later when proteinuria had disappeared, and the laboratory findings had returned to normal except for microscopic hematuria. However, light microscopy at that time demonstrated a slight increase in mesangial cellularity and Ig deposition as well as basement membrane changes of splitting of the lamina densa, incorporation of small electron dense granules and widening of the lamina rara interna. Alterations of the glomerular basement membrane stated above were reported in IgAN (Sakaguchi 1978), Henoch-Schönlein purpura and other hematuria syndromes. A report from the Southwest Pediatric Nephrology Group demonstrated two cases of IgAN diagnosed 2 to 12 years after the onset of nephrotic syndrome, which suggests subsequent development of IgAN in patients with MCNS. Furthermore, we evaluated a case of MCNS with C3 deposits in the first biopsy, in which mesangial IgA deposition was found as well as C3 2 years later.

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