

A Study of Glomerular Minimal Lesion and Minimal Mesangial Proliferation with or without Nephrotic Syndrome; Pathologic, Immunopathologic and Clinical Correlations

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A total of 394 cases of minimal lesion were reviewed and reassessed clinically and by laboratory investigation, for 4 years from 1979 to 1982. Association with nephrotic syndrome is significantly higher in the cases with histologically normal-appearing mesangium than in the cases with mesangial proliferation. In 43% of the cases of minimal lesion, a minimal but prominent mesangial deposit of Immunoglobulin M with or without C3 deposit was found, and frequently accompanied with nephrotic syndrome, which is not sufficient to accept the condition as a specific disease entity such as "IgM Nephropathy" in our present study. Minimal lesion with a minimal but unmistakable deposit of IgA on the mesangium was noted less frequently and was accompanied or unaccompanied by nephrotic syndrome, a condition which call for an investigation to clarify the characteristics and the extent of IgA(Berger's) nephropathy. Response to steroids in minimal lesion nephrotic syndrome was better in children and in the cases without mesangial proliferation, but was unrelated to either hematuria or immunoglobulin deposit. However, the cases with mesangial proliferation are significantly lesser in therapeutic response. Transformation to another morphological type of original glomerular change during follow-up was not observed in 4 available cases of minimal lesion nephrotic syndrome. Henoch-Schönlein purpura was seen more commonly in children, and IgA(Berger's) nephropathy more commonly in adults.

Key Words: Minimal lesion, mesangial proliferation, minimal lesion nephrotic syndrome

Glomerular minimal lesion(ML) means normal or minimally altered glomeruli with no or minimal immune deposit(Churg *et al.* 1970), occurs more commonly in children(Seymour *et al.* 1971; Choi *et al.* 1980), and is frequently associated with steroid-responsive nephrotic syndrome(Barnett *et al.* 1978). This lesion might be not only difficult to differentiate

from the early stages of other kinds of glomerulonephritis morphologically, but it also might lead physicians and pediatricians to be confused when they plan treatment and attempt to give a prognosis.

This study is aimed to review the general features of minimal lesion, and to investigate the clinicopathological correlations of minimal lesion nephrotic syndrome(MLNS) with emphasis on the factors influencing therapeutic response to steroids.

MATERIALS AND METHODS

Three hundred ninety-four cases of ML from 1979 to 1982 were restudied with the focus on light microscopical and immunopathological findings. Percutaneously biopsied renal cores were divided into three portions, one for histologic, one for immunopathologic, and one for electron microscopic examinations.

For light microscopic examination, tissue was fix-

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ed in 10% neutral formalin, embedded in paraffin, serially cut in 3-4 micron thickness, and stained by hematoxylin-eosin, periodic acid-Schiff, and trichrome methods. A portion of unfixed frozen tissue was serially cut, exposed with FITC-antihuman-IgG, -IgA, -IgM, -C3, -C4, -Clq, and -fibrinogen(Meloy, Inc.), and examined with a Leitz dialouX immunofluorescent microscope. For electron microscopic examination fresh tissue was immediately fixed in 3% glutaraldehyde first and postfixed with 1% OsO₄, stained with uranyl acetate and lead citrate, and examined with a Hitachi H-500 transmission electron microscope.

Mesangial proliferation was defined as the presence of more than three mesangial cells in each of one or more mesangial areas.

The degree of therapeutic response of MLNS to steroids was assessed according to the classification

produced in the International Study of Kidney Disease in Children (ISKDC 1978), and cases rebiopsied were analyzed.

FINDINGS

Distribution among child and adult patients

Of the 394 cases of ML reviewed, 260 were children and 134 were adults (Table 1).

Clinical findings

Nephrotic Syndrome (NS) was found in 52.7% of the total number of cases of ML. Minimal mesangial proliferation was found accompanying NS in 22 of the 95 children and in 10 of the 59 adults found to have

Table 1. Age distribution of minimal lesion and mesangial proliferation

Year	Children(Under 15yrs)	Adults(Over 15yrs)	Total
1979 - 1980	101	17	118
1981	77	60	137
1982	82	57	139
Total	260	134	394

Table 2. Classifications of the cases with minimal lesion and mesangial proliferation

Diagnosis	Year	1979-1980		1981		1982		Total	
	Age	C	A	C	A	C	A	C	A
A. Nonfamilial form									
ML without deposit						8	1	8	1
ML with deposit		6	3	13	6	26	7	45	16
MLNS without deposit		10		4	6	3	3	17	9
MLNS with deposit		22	3	16	13	18	24	56	40
ML with mes prolif without deposit		3			1	1		4	1
ML with mes prolif with deposit		19	3	11	13	7	10	37	26
MLNS with mes prolif without deposit		1		1				2	
MLNS with mes prolif with deposit		9	3	9	6	2	1	20	10
B. Familial form									
Benign familial hematuria		3		2		2		6	
C. Henoch-Schönlein Purpura		24		19	1	11	3	54	4
D. IgA nephropathy		5	5	2	14	4	8	11	27
Total		101	17	77	60	82	57	260	134

C - children; A - adults; mes prolif - mesangial proliferation.

NS. This incidence was significantly low compared with the incidence found in cases having normal-appearing mesangium (Tables 2 and 3).

Hematuria was present in 38.5% of MLNS, 88.1% of which was microscopic in nature; it was frequently associated with mesangial immune deposit but not with mesangial proliferation (Table 4).

Light microscopic findings

ML without mesangial proliferation comprised about two-thirds of total ML, and there was no positive correlation between mesangial proliferation and age.

Immunofluorescent microscopic findings

The amount of immunoglobulin or complement deposit found in the glomerular mesangium was minimal; it was present in 83.6% of the children and in 89.3% of the adults. Most frequently found was C3, but IgM was major in the amounts deposited: NS was

more frequently associated with IgM deposits than other immunoglobulin or complement.

In thirty-one of the children and 11 of the adults ML was found with no immune deposits; in 19 of the 31 children and 9 of the adults ML was accompanied by NS (Table 5).

Therapeutic response to steroids

A total of 109 cases were available for periods ranging from 2 months to 4 years for follow-up study.

Most (91.7%) of the cases of MLNS responded to treatment with steroids, the rate of therapeutic response being higher in children, particularly in the cases where there was no mesangial proliferation; it even appeared to be higher in the cases in which there was hematuria and also in the cases in which there were immunoglobulin deposits, regardless of the type of immunoglobulin deposits (Table 6). However, the percentage of therapeutic response in the presence of mesangial proliferation was significantly less.

Table 3. Frequency of nephrotic syndrome in minimal lesion and mesangial proliferation

	Nephrotic Syndrome		Total Number of Cases of ML	X ² -Value
	With	Without		
1. Children				
ML with Mes. Prolif.	22	41	63	8.7325*
ML without Mes. Prolif.	73	53	126	
Subtotal (%)	95 (50.2)	94 (49.8)	189 (100.0)	
2. Adult				
ML with Mes. Prolif.	10	27	37	23.5752*
ML without Mes. Prolif.	49	17	66	
Subtotal (%)	59 (57.2)	44 (42.8)	103 (100.0)	
Total (%)	154 (52.7)	138 (47.3)	292 (100.0)	

ML — Minimal lesion; Mes. Prolif. — Mesangial proliferation

* Statistically Significant ($P < .05$)

Table 4. Hematuria in minimal lesion and mesangial proliferation

	Hematuria			X ² -Value
	With (%)	Without (%)	Total (%)	
1. Mes. Prolif.				
Present	4 (18.2)	18 (91.8)	22 (100.0)	4.966**
Absent	39 (44.8)	48 (55.2)	87 (100.0)	
2. Mes. Immune Dep.				
Present	34 (38.6)	54 (61.4)	88 (100.0)	0.1439**
Absent	9 (42.9)	12 (57.1)	21 (100.0)	

Mes. Prolif. — Mesangial proliferation; Mes. Immune Dep. — Mesangial immune deposit

** Statistically not significant ($P > .05$)

Table 5. Immunopathologic findings of minimal lesion and mesangial proliferation

Findings	Year	1979-1980		1981		1982		Total	
	Age	C	A	C	A	C	A	C	A
Nonfamilial form									
I-F negative with NS	11				6	3	3	19	9
I-F negative without NS	3				1	9	1	12	2
Pred IgM deposit with NS	16		5	16	9	16	13	48	27
Pred IgM deposit without NS	14		4	7	5	18	3	39	12
Pred IgA deposit with NS	3		1	2	3	3	8	8	12
Pred IgA deposit without NS	5		2	2	4	8	12	15	18
Pred IgG deposit with NS	3			1	1	1	3	5	4
Pred IgG deposit without NS	2			1	2	1		4	2
Pred C3 deposit with NS	8			5	6		1	13	7
Pred C3 deposit without NS	5			15	8	6	2	26	10
Total		70	12	54	45	65	46	189	103

✓ Pred – predominant; NS – nephrotic syndrome
C – children
A – adults

Table 6. Predictability of response to steroid treatment

	Initial Response to Steroid Therapy			X ² -Value
	Present (%)	Absent (%)	Total (%)	
1. Age				
Children	70 (93.3)	5 (6.7)	75 (100.0)	2.25775**
Adult	30 (88.2)	4 (11.8)	34 (100.0)	
2. Mesangial Proliferation				
Present	18 (81.8)	4 (18.2)	22 (100.0)	10.6473*
Absent	82 (94.3)	5 (5.7)	87 (100.0)	
3. Hematuria				
Present	41 (95.3)	2 (4.7)	43 (100.0)	1.2526**
Absent	59 (89.4)	7 (10.6)	66 (100.0)	
4. Ig or C deposit				
Present	82 (93.2)	6 (6.8)	88 (100.0)	4.2455**
Absent	18 (85.7)	3 (14.3)	21 (100.0)	
Total	100 (91.7)	9 (9.2)	109 (100.0)	

* Statistically Significant (P<.05)

** Statistically not Significant (P>.05)

Of the cases that responded relapses occurred only infrequently in 54% and no relapses occurred in 34% (Table 7).

Follow-up biopsy

A follow-up biopsy was done in 9 of the cases, but 4 of them were excluded to study because either a prior biopsy had been performed improperly or the diagnosis had shifted from ML to focal segmental glomerulosclerosis (FSGS) due to insufficient original biopsy.

Of the remaining 4 children, in 3 the major deposit was IgM, and transformation of original glomerular morphology to other histological types was not observed during 2, 9, and 11 months of follow-up on them. In one case in which initially there was ML with mesangial proliferation with prominent C3 deposit, IgA deposits were found superimposed on a second biopsy done 2 years after the first biopsy (Table 8).

Others

Fifty-eight cases of Henoch-Schönlein purpura and 38 cases of IgA nephropathy were found with more cases of the former among the children and more cases of the latter among the adults.

DISCUSSION

For the most part, in ML glomeruli appear normal, but ML may be accompanied by a slight increase of mesangial matrix or by mesangial proliferation, and thickening of the basement membrane, and there is a history of upper respiratory infection (Habib and Kleinknecht 1971), allergy, immunization (Zollinger and Mihatsch 1978; Grupe 1983) in most cases.

This lesion may be difficult to differentiate from the lesions of early stages of other forms of glomerulonephritis including mesangioproliferative glomerulone-

Table 7. Response of patients with MLNS to steroid treatment

	Children	Adults	Total
Responded	70	30	100
Nonrelapser	23	11	34
Relapsed infrequently	38	16	54
Relapsed frequently	8	3	11
Subsequently failed to respond	1		1
Initially failed to respond	5	4	9
Continued to fail to respond	1	4	5
Responded late	4		4
Total	75	34	109

Table 8. Comparison of diagnoses after follow-up biopsies

Age at first biopsy (years)	Sex	Diagnosis, first biopsy	Diagnosis, second biopsy	Length of time between first and second biopsy
1. 3	F	MLNS with IgM/G-C3	MLNS with IgM-C3	2 months
2. 13	M	MLNS with IgM-C3	MLNS with IgM	11 months
3. 11	F	MLNS with IgM/G-C3 & mes prolif	MLNS with IgM/G-C3 & mes prolif	9 months
4. 13	M	MLNS with C3 & mes prolif	MLNS with IgA-C3 & mes prolif	2 years

phritis (MsPGN) and membranous glomerulonephritis, but it is regarded as a distinct entity by virtue of characteristic age distribution, symptoms, glomerular morphology, and good response to steroids.

Minimal lesion frequently occurs in children, is reported to be associated with NS in 53.6 to 88.0% of children with NS (White *et al.* 1970; Habib 1973; ISKDC 1978) and with NS in 10 to 43% of all persons (Bohle *et al.* 1969; Seymour *et al.* 1971; Györkey *et al.* 1973; Hayslett *et al.* 1973). In our study NS was found to be associated with ML in 52.7% of the total number of cases of ML and its incidence was not significantly different between that in children and that in adults. Mesangial proliferation was less commonly associated with NS than not. These were two possibilities: one, that mesangial proliferation per se had no primary pathogenic role in the expression of massive proteinuria or edema, but was simply the cumulative results of minor injuries, and two, that our ML with mesangial proliferation group was so heterogeneous as to include an early stage of MsPGN. Some investigators have insisted upon considering idiopathic MsPGN as an entity, in view of the higher frequency of hematuria, hypertension, diffuse mesangial proliferation, and poorer therapeutic response and prognosis than that of ML (Cohen and Border 1983). However, this has been a matter of dispute, and some have emphasized the correlation and continuation between ML and MsPGN (Habib *et al.* 1978; Waldherr *et al.* 1978; Migone *et al.* 1980). We did not regard MsPGN as a separate entity in this study and included the cases with mesangial proliferation with ML, except for Henoch-Schönlein purpura and IgA nephropathy, because most of the mesangial proliferation amounted to less than 25% in the extent of its occupancy in a glomerular tuft.

Immunopathologically most cases of ML have previously been reported to have neither immunoglobulin nor complement deposits (Grupe 1983), but in over half of our cases a minor amount of either immunoglobulin or complement deposit was found in the mesangium. The most frequently found deposit was C3, but IgM was prominent in the deposits and most frequently accompanied by NS. It was unclear whether these deposits had some roles in immunologically mediated glomerular injury or were mere trappings in the mesangium.

In the cases in which C3 was the only deposit found, C3 could have been directly activated and deposited without interaction between antigens and antibodies (Berger *et al.* 1971); therefore, C3's being the only deposit can not necessarily be interpreted as being immunological in origin.

An attempt was made by Cohen *et al.* in 1978 to designate glomerular lesion with prominent and diffuse mesangial IgM deposits as a new disease entity, as "IgM nephropathy" (Bhasin *et al.* 1978; Helin *et al.* 1982; Hsu *et al.* 1984; Kim *et al.* 1985), but there was much controversy, and no consensus on this term was reached (Vilches *et al.* 1982; Kim *et al.* 1983; Yang *et al.* 1984; Pardo *et al.* 1984). We could find no remarkable differences in ML with prominent IgM deposit comparable with other groups, and therefore, it is our opinion that "IgM nephropathy" could not be accepted as a specific entity in our present study.

Fifty-three cases of ML with definite but minimal mesangial IgA deposits were less likely to be associated with NS than other cases in which other kinds of immune deposits were found. Twenty cases of ML with minimal but definite mesangial IgA deposits were accompanied by NS, but in these cases, a possibility of Berger's nephropathy could be excluded, because of the presence of NS and other clinical features. The remaining 33 cases without NS had no supporting laboratory or clinical evidences of IgA (Berger's) nephropathy, but it was considered necessary for them to be followed up carefully and continuously in order that a differential diagnosis could be made and confirmed.

According to previous reports steroids had produced excellent therapeutic results in MLNS, especially in children, in which the results were reported to be up to 90-98% successful (77-85% successful in adults) (Cameron *et al.* 1964; Cameron 1968; White *et al.* 1970; ISKDC 1978).

Factors reported to be influencing the results of steroid therapy in MLNS were hematuria, hypertension, decreased C3 level in the serum, nitrogen retention, and mesangial proliferation (Habib and Kleinknecht 1971; Jao *et al.* 1973; ISKDC 1981; Allen *et al.* 1982). Therefore, we studied the significance of age, hematuria, mesangial proliferation, and immunoglobulin deposits as to their influence on the predictability of response to steroid therapy (Table 6).

The steroid regimen used was prednisone given by the conventional method with or without cytotoxic agents, but the course became irregular due either to complications which developed during therapy or poor cooperation of the patient or the patient's parents.

Of 109 cases followed, 93.3% which occurred in children and 88.2% which occurred in adults responded to treatment with steroids. This finding is similar to findings reported previously (Cameron *et al.* 1964; Cameron 1968; ISKDC 1978; ISKDC 1981). Mesangial proliferation seemed to signal prognosis, but

hematuria, presence of type of immunoglobulin deposit had no significance in this regard in this study. The better response in children might be interpreted in two ways: first, it was simply because they were, as children, young, and second, it was only apparently better because the composition of our ML cases in adults was heterogenous. Mesangium has been said to be the last recovery site in glomerular injury and it has been speculated that this might be related to the disease progression or to persistent immunologic or nonimmunologic glomerular injury (ISKDC 1981).

Hematuria has less commonly occurred in MLNS (White *et al.*, 1970; Habib and Kleinknecht 1971), but some investigators have reported a 31-41% association of hematuria with ML (Habib 1970; Bohle *et al.* 1974). Hematuria was present in 39.5% of our cases of MLNS, mostly of microscopic, and of intermittent or persistent nature. However, there were no cause-effect relationships between hematuria and age, mesangial proliferation, or treatment response.

Complications during therapy were largely of drug origin, but minor upper respiratory infection was often present. The death rate has been reported to be 2.3-6.7% (White *et al.* 1970; Habib and Kleinknecht 1971; ISKDC 1984; Trompeter 1985), and the causes of death have been complications of treatment, pulmonary artery embolism, chronic cardiac failure than chronic renal failure (Zollinger and Mihatsch 1978; ISKDC 1984). A 51-year-old female patient who had frequently suffered relapses died during follow-up, but on her entire course of ML was superimposed hypertension, diabetes mellitus, and HBs antigenemia; she actually died of meningo-encephalitis after 21 months of follow-up.

Henoch-Schönlein purpura and IgA nephropathy had characteristic clinical and pathological findings, and in our study the former commonly affected children, the latter, the adults. These two diseases were similar in many aspects; sometimes could be differentiated on a clinical basis only. It has been thought that they may represent different stages of one disease spectrum (Weiss *et al.* 1978; Levy *et al.* 1982; Waldherr *et al.* 1982; Meadow and Scott 1985). Although this consideration is outside the purpose of this study, further inquiry into it and further study on this particular subject would be very interesting; at any rate, their relationship should be clarified.

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