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*Original Article*

# Clinical manifestations, pathological findings, long-term follow-up and prognosis in pediatric patients with IgM nephropathy

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**Abstract:** Objective: This study aims to evaluate the clinical manifestations, pathologic findings, therapeutic efficacy, and long-term prognosis of pediatric IgM nephropathy. Methods: Clinical presentations, pathological findings, therapeutic efficacy, and follow-ups in the long-term prognosis of 25 randomly selected biopsy-diagnosed pediatric IgM nephropathy (IgMN) patients were evaluated. Results: In renal biopsy, IgM alone or IgM dominated diffuse deposition was found in the mesangial area. Nineteen patients had nephrotic syndrome (NS) and 11 had refractory nephrotic syndrome (RNS). The incidence of RNS complicated with interstitial lesions was significantly higher than that of non-RNS ($P<0.05$). In six non-NS patients, medical conditions improved to a varied extent after treatment with Baoshenkang, captopril, or dipyridamole. 21 patients were followed for 10 years. Simple hematuria was found in three patients and microscopic hematuria with normal renal function was found in two patients. Hematuria disappeared in one patient. Persistent proteinuria and deterioration after three years occurred in one patient. Among the 17 patients with NS, complete remission occurred in 11 patients, mild proteinuria was found in five patients, and one patient with proteinuria developed renal insufficiency. Dialysis was required after four years of follow-up. Conclusion: Pediatric IgMN patients mainly manifested with NS. The incidence of renal interstitial lesions leading to refractory NS was higher. Patients with NS responded poorly to corticosteroid treatment; hence, this may help identify these patients by more intensive medical examinations. Long-term prognosis was better in patients with simple hematuria.

**Keywords:** IgM nephropathy, nephrotic syndrome, simple hematuria, pathology

## Introduction

IgM nephropathy (IgMN) is an idiopathic glomerulonephritis characterized by mesangial hypercellularity and diffuse IgM deposits [1-5]. Patients with this disease have varied clinical presentations, and there is no standard pathological classification of this disease [1, 2, 6-12]. Furthermore, there is also no consistent treatment strategy. Few studies have evaluated patients with this disease. The purpose of this study was to retrospectively analyze the relationship of pathological changes, clinical presentations, therapeutic intervention, and prognosis in 25 pediatric patients diagnosed with IgMN.

## Materials and methods

### *Subjects*

A total of 166 patients diagnosed with primary glomerulonephritis based on biopsy were admitted to the Department of Pediatrics in our hospital between January 1989 and July 2005. Twenty-five patients had IgMN diagnostic criteria. Membranoproliferative glomerulonephritis, focal segmental glomerulosclerosis (FSGS) and IgA nephropathy were excluded. Among these 25 patients, 19 patients were male and six patients were female, with an average age of 7.1 years (range: 2-13 years). The average disease course after renal biopsy was 7.8 months.

### *Methods*

Laboratory tests: routine urinalysis; 24-hour urinary protein excretion; serum total protein, albumin and cholesterol; serum IgG, IgM, IgA and complement; blood urea nitrogen (BUN); creatinine (Cr); liver function; hepatitis B tests.

Renal biopsy: light microscopy, immunofluorescence and electron microscopy.

**Table 1.** Clinical manifestations of 25 IgM nephropathy patients

| Clinical Manifestation | n | % |
|---|---|---|
| Nephrotic Syndrome | 19 | 76 |
| Simple | 11 | 44 |
| Nephritic | 8 | 32 |
| Simple Hematuria | 3 | 12 |
| Simple Proteinuria | 1 | 4 |
| Hematuria and Proteinuria | 2 | 8 |
| Total | 25 | |

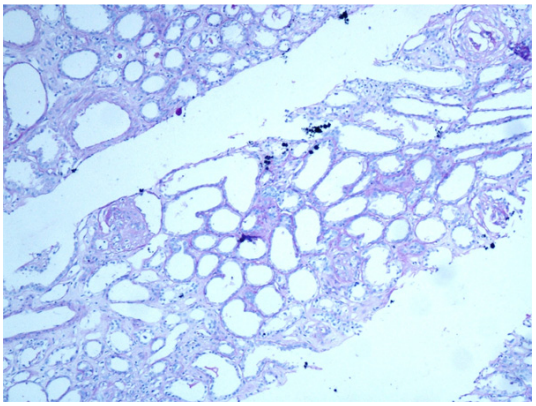

**Figure 1.** Mesangial proliferation and focal segmental sclerosis [periodic acid Schiff (PAS) × 40].

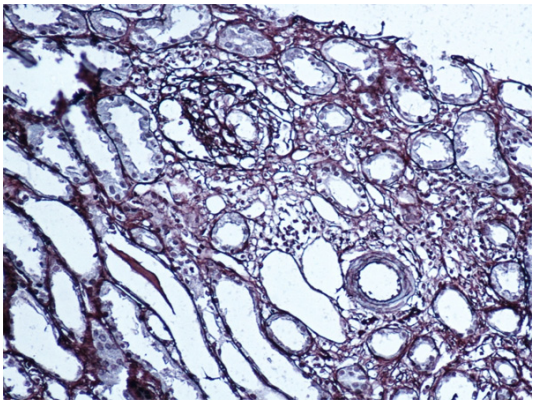

**Figure 2.** Interstitial fibrosis. Silver staining × 100.

Treatment and evaluation: national pediatric unified treatment program and treatment efficacy evaluation standards were used. Long-term prednisone therapy was given to standard patients. Cyclophosphamide (CTX) or other immune-inhibitors were combined with steroids in steroid-resistant, dependent, or frequently recurrent (repeated) refractory NS patients.

Statistical methods: chi-square test for differences.

*Diagnostic criteria*

IgMN diagnostic criteria: (1) glomerular mesangial IgM deposition, with or without other immunoglobulins and/or C3 deposition by immunofluorescence examination; (2) varying degrees of glomerular mesangial proliferation with normal glomerular basement membrane morphology under light microscopy [6, 13, 14]. Membranoproliferative glomerulonephritis, focal segmental glomerulosclerosis, and IgA nephropathy were excluded.

## Results

*Clinical manifestations (**Table 1**)*

A total of 19 patients manifested with NS, in which 11 patients were simple type and eight patients were nephritic type. Furthermore, three patients had simple hematuria, one patient had persistent proteinuria, and two patients had hematuria with proteinuria. Moreover, three patients were admitted to the hospital with hypertension.

*Laboratory routine test*

Among the 25 patients, elevated serum IgM was found in nine patients and decreased C3 was found in five patients. Renal function was normal in all 25 patients. In the 19 NS patients, average plasma albumin level was 21.6 ± 4.9 g/L and 24-hour urinary protein excretion was 5.3 ± 2.9 g/L.

*Renal histopathology examination*

Light Microscopy (**Figures 1** and **2**): varying degrees of mesangial proliferation, which appeared as focal segmental mesangial proliferation or diffuse mesangial proliferation, were found by light microscopy. Eight patients had glomerular-capsule adhesion, four patients had tubular degeneration and/or atrophy, four patients had interstitial inflammatory cell infiltration, one patient had interstitial fibrosis, two patients had mesangial sclerosis, two patients had glomerulosclerosis, and two patients had vessel wall thickening with hyalinization (**Table 2**).

**Table 2.** Light microscopic examination of 25 patients

| Histology | Nephrotic Syndrome | | Persistent Proteinuria | Hematuria+ Proteinuria | Simple Hematuria |
|---|---|---|---|---|---|
| | Simple | Nephrotic | n=1 | n=2 | n=3 |
| | n=11 | n=9 | | | |
| Glomerular minor lesion | 6 | 2 | 1 | 1 | 1 |
| Glomerular-capsule adhesion | 3 | 5 | 1 | 1 | 0 |
| Glomerulosclerosis | 1 | 0 | 1 | 0 | 0 |
| Mesangial proliferation (minor) | 11 | 7 | 1 | 2 | 2 |
| Mesangial proliferation (medium) | 0 | 2 | 0 | 0 | 0 |
| Mesangial sclerosis | 0 | 2 | 0 | 0 | 0 |
| Interstitial tissue | | | | | |
| Tubular atrophy | 2 | 2 | 0 | 0 | 0 |
| Interstitial inflammatory cell infiltration | 2 | 2 | 0 | 0 | 0 |
| Interstitial fibrosis | 0 | 1 | 0 | 0 | 0 |
| Blood vessel hyalinization | 1 | 1 | 0 | 0 | 0 |

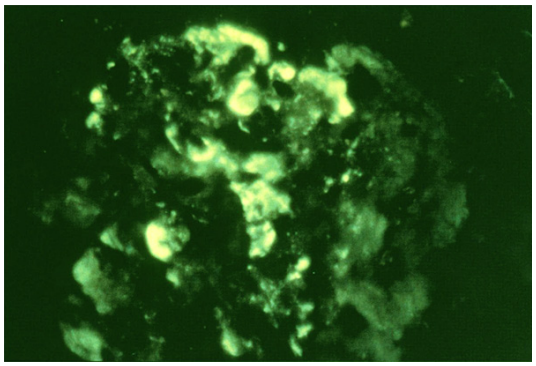

**Figure 3.** IgM deposits along the glomerular mesangial field and capillary wall.

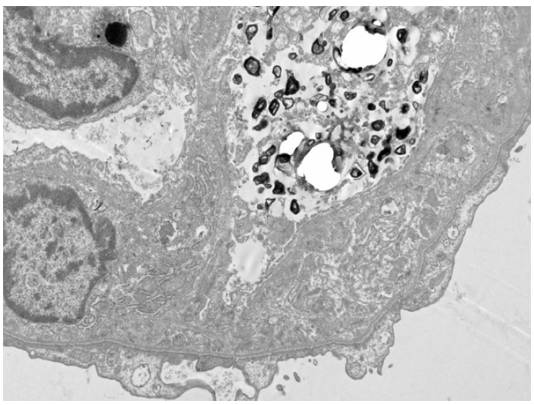

**Figure 4.** Electron dense deposits × 12000.

Immunofluorescence (**Figure 3**): granular or lumpy IgM deposition was observed in the mesangial area in all patients. IgM was present in nine patients, IgG deposition was present in five patients, IgA deposition was present in three patients, and IgG ang IgA deposition was present in eight patients. Furthermore, C3 deposition was found in 11 patients, C1q deposition was found in three patients, and fibrin deposition was found in one patient.

Electron microscopy (**Figure 4**): electron microscopic examination was performed in six patients. Electron dense deposits were visualized in the mesangial and partial basement membrane or subendothelial areas in five patients.

Relationship of IgMN immunoglobulin deposition pattern and clinical manifestations: simple hematuria was mainly associated with IgM. NS or hematuria combined with proteinuria was associated with not only mesangial IgM deposition, but also IgG, IgA and complement deposition (**Table 3**).

*Analysis of therapeutic efficacy and prognosis*

Among the 19 NS patients, 11 patients had simple NS; in which seven patients accounted for 63.6% and were sensitive to the initial eight weeks of steroid treatment, two patients were steroid resistant, and two patients were steroid-dependent. Eight patients had nephritic type NS. Among these patients, one patient was steroid-sensitive (12.5%), one patient was steroid-dependent, and six patients were resistant to steroids. Simple nephropathy patients were more sensitive to steroids than nephritic nephropathy patients, and the difference was

**Table 3.** relationship of immune globulin deposition pattern in IgM nephropathy and clinical manifestations

| Clinical manifestations | Patient number | IgM | IgMG | IgMA | IgM+C3 | IgM+C1q | IgMG+C3 | IgMA+C3 | IgMGA+C3 |
|---|---|---|---|---|---|---|---|---|---|
| Simple hematuria | 3 | 2 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| Persiatent proteinuria | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| Hematuria plus proteinuria | 2 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 1 |
| Nephrotic syndrome | 19 | 3 | 2 | 3 | 1 | 2 | 1 | 0 | 7 |

statistically significant ($P<0.05$); indicating that nephritic nephropathy patients were more likely to be resistant to steroids. Furthermore, 11 patients (accounting for 57.8% of NS patients) clinically manifested with refractory NS, and were treated with a combination of steroids and CTX. Eight patients had complete remission, two patients had partial remission, and one patient revealed no response. Eight of 11 (72.7%) children with refractory NS had combined renal interstitial lesions, while two of eight patients (25%) with non-refractory NS had the same lesion; and the difference was statistically significant ($P<0.05$). In non-NS patients, medical condition improved in varying degrees after treatment with Bao shenkang (a Chinese herbal medicine), captopril, or dipyridamole.

After conducting follow-ups on 21 patients for an average of 10 years, two of three simple hematuria patients continued to have microscopic hematuria. Hematuria disappeared in one patient with normal renal function, and the patient was married. One patient with persistent proteinuria had renal deterioration after three years. Among the 17 patients with NS, complete remission was achieved in 11 patients and mild proteinuria was found in five patients. One patient with proteinuria developed renal insufficiency, which required dialysis treatment after four years follow-up.

## Discussion

IgMN was first reported by and named after Bhasin and Cogen in 1978 [1, 15]. It is currently accepted as an independent disease by most domestic and foreign researchers. IgMN is an idiopathic glomerulonephritis with mesangial hypercellularity and diffuse IgM deposits, which manifests mainly as mesangial proliferative glomerulonephritis. Most studies have reported that the prevalence of IgMN was from 2% to 18.5% in native biopsies [5, 16-19]. The incidence of IgMN in primary glomerular diseases in this study was 15.02%, and was consistent with previous reports.

The etiology and pathogenesis of primary IgM nephropathy remains unclear. It has been proposed that there may be a variety of pathogenic pathways such as the deposition of circulating immune complexes or *in situ* immune complex formation [18, 20-24]. Histologic findings mainly occur in the mesangial membrane as IgM deposition, which is shown by immunofluorescence. Furthermore, this is common in young people, and more common in males than in females. There are no obvious symptoms except for asymptomatic hematuria or proteinuria in the early stages. Major clinical manifestations are massive proteinuria or NS [5, 18, 19, 23, 25-28]. Seventy-six percent of our patients presented with NS, which was consistent with an early domestic study (80.3%). In addition, we found that there was some correlation of IgM deposition pattern with clinical manifestations. For example, there were mainly IgM depositions in simple hematuria patients. In NS patients, IgG and/or IgA and complement depositions were observed, in addition to mesangial IgM deposition.

There are controversial reports on the responsiveness of IgMN to prednisone treatment, which manifest as NS [5, 18, 19, 27, 29-31]. Our study comprised of 11 simple hematuria patients and eight NS patients. Simple nephropathy patients were significantly more responsive (63.6%) than nephritic nephropathy patients (12.5%) ($P<0.05$). This result indicates that the nephritic type is more likely resistant to steroid treatment. This study also includes 11 patients with refractory NS (57.8%). The incidence of renal interstitial lesions in patients with refractory NS (72.7%) was significantly higher than in non-refractory NS patients (25%) ($P<0.05$), suggesting that complicated renal

interstitial changes can be used as a checking index for prognosis.

A study conducted by Myllymaki J *et al.* revealed that in 110 primary IgMN patients, 29% of NS patients were resistant to steroid treatment and 80% of these initially steroid-responsive patients eventually became steroid-dependent. Hypertension associated with the onset of this disease was a risk factor for progression to renal insufficiency, and renal interstitial fibrosis was also an important parameter for evaluating prognosis [5, 13, 18, 23]. We repeated the renal biopsy in 11 patients after eight years follow-up, and found that five patients had advanced to FSGS. We followed-up this group of patients for 15 years, and found that 36% of these patients developed renal insufficiency and 23% progressed to end-stage renal failure. Those patients with renal interstitial changes were more likely to clinically present with refractory NS. One patient with renal insufficiency had hypertension at the time of diagnosis. Pathologic examination revealed glomerular-capsule adhesions, interstitial inflammatory cell infiltration, and interstitial fibrosis. Three other patients with these biopsy findings clinically presented with simple hematuria. These findings suggest that patients with less pathological damage (such as the mild proliferation of mesangial cells and the mesangial matrix) were more likely to have milder clinical manifestations (asymptomatic hematuria or proteinuria), while patients with severe pathological damage (such as mesangial cell sclerosis, renal interstitial fibrosis or inflammatory cell infiltration) were more likely to present with refractory NS, in which prognosis was relatively poor.

Further clinical observations and follow-ups would be performed in these patients to evaluate the natural history of treated pediatric IgMN. We propose that nephritic nephropathy patients should be treated actively, and repeated renal biopsy should be performed, when indicated; in order to prevent renal insufficiency.

In conclusion, pediatric IgMN patients mainly manifested with NS. The incidence of renal interstitial lesions leading to refractory NS was higher. Patients with nephritic nephropathy responded poorly to corticosteroid treatment, which may help identify these patients by less intensive medical examinations. Long-term prognosis was better in patients with simple hematuria.

## Disclosure of conflict of interest

None.

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