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ORIGINAL ARTICLE

IgM Nephropathy in India: A Single Centre Experience

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Abstract
Objective To find out the incidence and natural history of IgMN in India.
Methods Renal biopsies of children ≤12 y age of last 6 y were retrospectively evaluated. Their clinical and biochemical presentation were correlated. Patients with systemic diseases/disorders were excluded from the study.
Results Immunoglobulin M nephropathy (IgMN) constituted 11.9% (n=28) of 236 renal biopsies. Mean age was 10 y, predominant in boys (n=24), most of the patients presented with proteinuria and edema. The most common associated histopathological finding was mesangial proliferative glomerulonephritis (MePGN) in 60.7% (n=17) followed by minimal change disease (MCD) in 28.6% (n=8) and focal segmental glomerulosclerosis (FSGS) in 10.7% (n=3). In 85.7%, IgM appeared as the sole immunoglobulin deposit mainly in mesangial regions, followed by accompanied C3 in 3.6% (n=1) and C1q+C3 in 10.7% (n=3) biopsies.
Conclusions IgMN was observed in 11.9% biopsies with commonest morphology of MePGN followed by MCD and FSGS; proteinuria was bad prognosticator in addition to FSGS and co-deposition of other immunoglobulins had no significance.

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Keywords IgM nephropathy · Focal segmental glomerulosclerosis · Minimal change disease · Renal biopsy · Nephrotic syndrome in children

Abbreviations

FSGS	Focal and Segmental Glomerulosclerosis
IF	Immunofluorescence
IgMN	IgM Nephropathy
LM	Light Microscopy
MCD	Minimal Change Disease
MePGN	Mesangial Proliferative Glomerulonephritis
SCr	Serum Creatinine

Introduction

Nephrotic syndrome (NS) is one of the commonest renal affection of pediatric population and the commonest kidney biopsy finding in childhood NS is MCD without immune deposits. One of the presentations can be Immunoglobulin M nephropathy (IgMN) characterized by primary mesangioproliferative glomerulonephritis (MePGN) on light microscopy with sole or dominant diffuse, granular deposits of IgM within the mesangium on immunofluorescent microscopy and clinically presenting with steroid resistant/dependent proteinuria, having no associated systemic disorders/disease [1–3]. Morphological presentation in IgMN may vary from unremarkable to segmental /global glomerulosclerosis. Cohen et al described IgMN for the first time in 1978 [1]. IgMN can be disturbing to the child/ family due to its steroid dependence/ resistance, yet little is known about this entity.

The authors carried out a retrospective analysis of native renal biopsies of children to find out the incidence and natural history of IgMN in India.

Table 1 Incidence pattern and clinical presentation

Parameter	MCD	MePGN	FSGS
N=28	8 (28.6%)	17 (60.7%)	3 (10.7%)
M: F	8: 0	14:3	2:1
Mean age (y) ±1 SD	8±6	10.1±2.6	9.7±2.6
Mean disease duration (mo) ±1 SD	2.46±1.68	10.1±21.8	3.7±2.52
24 h urine protein leak (m/kg BW) ±1 SD	47.2±9.8	85.96±127.1	139.9±59.5
Mean SCr(mg%) ±1 SD	0.67±0.41	1.17±1.88	0.49±0.2

Material and Methods

This was a retrospective analysis of 236 native renal biopsies of patients up to the age of 12 y who presented at the authors center from January 2004 through December 2009. Inclusion criteria were pediatric patients with steroid resistant/dependent nephrotic/nephrotic-nephritic syndrome. Exclusion criteria were age above 12 y, associated/other systemic diseases like systemic lupus erythematosus, diabetes mellitus, hepatitis, HIV infection and congenital NS.

Clinical history and findings of age, gender, hypertension, quantitative proteinuria, renal function tests were evaluated. Steroid-resistant NS was defined as per standard International Study of Kidney Diseases in Children (ISKDC) as "no response to prednisone, 2 mg/ kgBW/ d within 4 wk of starting treatment" [4].

All the children were subjected to biopsy. The tissues were processed, 3 μ thick paraffin sections were subjected to light microscopy (LM) and stained by hematoxylin and eosin, periodic acid Schiff, Jone's silver methaneamine, and Gomori's trichrome stains. Biopsy was considered adequate if it contained 7 glomeruli. Biopsies were evaluated for mesangial cell proliferation, focal segmental/global sclerosis, tubular atrophy/degeneration, interstitial fibrosis/ inflammation, and fibrointimal proliferation in vessels. Changes were graded as unremarkable, mild, moderate or marked. For direct immunofluorescence (IF) studies anti-human IgA, IgG, IgM, C1q, C3, albumin and fibrinogen antisera (Dako, USA) were used on 3 μ thick frozen sections. Glomerular IF findings were graded as trace, +1, +2, +3 and +4 and intensity of ≥+2 was considered positive.

Results

Out of 236 biopsies performed in children between the age of 1 to 12 y, 28 (11.9%) were diagnosed as IgMN. The disease had male predilection with ratio of 3.1:1 with common presentation at the age of 10±3.6 y. (Table 1)

There were three morphological patterns noted, minimal change disease (MCD), MePGN and focal segmental glomerulosclerosis (FSGS). The mean blood pressure (BP) was 110/70 mm Hg (range: 90/64 to 130/84 mm Hg). There was no significant difference in BP between the three groups. They were all being treated with prednisone, 20 to 40 mg/d.

MCD was noted in 28.6% (*n*=8) patients, all males, with mean age of 8±6 y (range: 6–12 y). The mean disease duration was 2.46±1.68 mo (range:1–6 mo) with mean 24 h urinary protein loss of 47.2±9.8 mg/kg BW (range: 17.6–90 mg/kg BW). Their mean SCr was 0.67±0.41 mg/dl (range: 0.32–1.5 mg /dl).

MePGN was noted in 60.7% (*n*=17) patients, 14 males and 3 females, with mean age of 10.1±2.6 y (range: 3–12 y). The mean disease duration was 10.1±21.8 mo (range: 1 to 72 mo) with mean 24 h urinary protein loss of 85.96± 127.1 mg/kg BW (range:11.8–235.3 mg/kg BW). Their mean SCr was 1.17±1.88 mg/dl (range: 0.38–8.58 mg /dl).

FSGS was noted in 10.7% (*n*=3) patients, 2 males and 1 female, with mean age of 7.5±4.6 y (range: 2–12 y). The mean disease duration was 3.7±2.52 mo (range: 1–6 mo) with mean 24 h urinary protein loss of 139.9±59.5 mg/kg BW (range: 90.9–175 mg/kg BW). Their mean SCr was 0.49±0.2 mg/dl (range: 0.38–0.71 mg /dl).

IgM was the predominant immunoglobulin deposited in diffuse pattern in all glomeruli with the intensity ranging from +2 to +4 (Fig. 1). IgM alone was noted in 78.6% (*n*= 22) biopsies, associated C3 in 10.7% (*n*=3), with intensity of +1 to +2 and C3+C1q in 10.7% (*n*=3) biopsies. No other

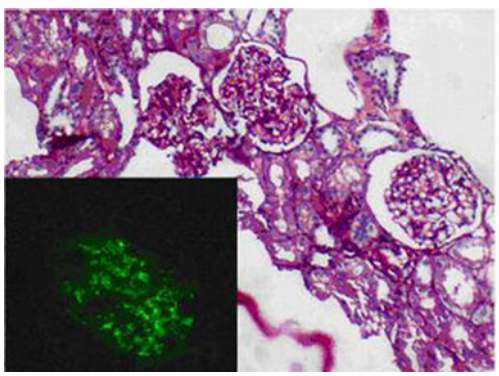

Fig. 1 Photomicrograph of Mesangial proliferative glomerulonephritis in a 7-y-old boy with nephrotic syndrome of 6 wk duration. Periodic acid Schiff Stain, ×100, with 3 glomeruli showing mild mesangial prominence and fairly open capillary lumina lined by membranes of normal thickness and inset, immunofluorescence staining with anti-human IgM antiserum showing +3 fine granular fluorescence across 70–80% mesangial regions and occasional capillaries of the glomerulus

immune deposits were sighted. There was no correlation between co-deposits of immunoglobulins and clinical or histopathological presentation of the disease. Electron microscopy was not performed.

Proteinuria was significant finding, and was poor prognosticator whereas BP, age and disease duration had no prognostic significance. Statistical analysis was performed by analysis of variance (ANOVA) and difference between MCD and FSGS was significant ($p=0.007$), the difference between MePGN and FSGS was also significant ($p=0.008$). No difference was observed between MCD and MePGN.No statistically significant difference was noted between the three groups with respect to disease duration, BP and SCr.

Over a mean follow-up of 4 y, one child (12.5%) with MCD was put on MMF, 6 (35.3%) children with MePGN required CsA and 3 (17.7%) required MMF. All these children with MCD and MePGN were maintaining stable renal functions with decreased urinary protein leak of <300 mg/24 h (range: 0 to 450 mg) and SCr of 0.6±0.53 mg/dl (range: 0.52–1.01 mg /dl) with addition of cyclosporine, 2 mg/ kgBW/d or Mycofenolate mofetil (MMF) 360 mg BD given for 1 y. Out of 3 children with FSGS 1 child was put on CsA and other on MMF, however both developed end stage renal disease at the end of 2 y and 1 was lost to follow up (he was also put on CsA).

Discussion

IgMN in children is a less known clinicopathological entity predominantly affecting male children [5]. To the authors' knowledge, this is the first Indian study of IGMN in children. The authors have seen higher incidence of IgMN in children (11.9%) as compared to adults (4.3%) in Indian population. Researchers have tried to study the IgM deposits in mesangium and their pathogenesis, whether these patients were steroid dependent/ resistant, and whether there was any role of IgM deposits or complement fixation in therapeutic management [6–8]. No consensus has been reached so far. It was only observed that patients with IgMN had very high levels of circulating complement fixing IgM immune complexes, which were significantly heavier than IgM molecule as compared to controls. It has been observed that hypertension and proteinuria were the clinical bad prognosticators and interstitial fibrosis and tubular atrophy along with FSGS were bad pathological prognosticators [7–9]. In the present study undertaken in children the authors have not observed any correlation with hypertension. However majority of the present patients were steroid dependent. Proteinuria was more severe in FSGS group than MCD or MePGN in the present study. The mean SCr in FSGS group was appearing disproportionately low due to small sample size and one boy who was 3 y old had SCr of 0.38 mg%. Some authors have placed IGMN in category between MCD and FSGS [10]. However, the authors propose that just as IgAN has been recognized as an independent entity, IGMN also should be recognized as independent entity especially since these children are likely to be steroid resistant/ dependent and although they have not been able to correlate with long term prognosis, steroid dependence and presence of FSGS are themselves harbingers of guarded long term prognosis. The present findings correlate with meta-analysis done by Bagga et al that longer remission is achieved by using CNI and other drugs in NS and also MCD patients respond better than others [11]. Children with IgMN may be offered alternative safe regimes like MMF at least to delay their chronic renal failure.

Conclusions

IgMN was observed in 11.9% pediatric patients with commonest morphology of MePGN followed by MCD.FSGS may be considered as an independent entity. Proteinuria is bad prognosticator in addition to FSGS and co-deposition of other immunoglobulins have no significance.

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