Primary Immunoglobulin A (IgA) nephropathy in Western India

AV Vanikar¹, KV Kanodia¹, RD Patel¹, HL Trivedi²
¹Department of Pathology, Laboratory Medicine & Transfusion Services; ²Department of Nephrology & Transplantation Medicine, Institute of Kidney Diseases & Research Centre and Institute of Transplantation Sciences, Ahmedabad.

Abstract
Background: Although primary IgA nephropathy (IgAN) is a common glomerulonephritis there are few documented studies of its prevalence and evolution in India. This 6 year retrospective study aims at finding out its incidence and natural history in western India.

Material and methods: We studied 4132 native renal biopsies, using hematoxylin and eosin, periodic acid Schiff, Jone's silver methamine and Gomori's trichrome stains on paraffin sections. Immunofluorescence studies were performed using anti-human IgA, IgG, IgM, C1q, C3, albumin and fibrinogen antisera. Patients with hematuric nephrotic/nephritic presentation were selected, their biopsies studied and those with predominant IgA deposits were labeled as IgAN. We studied their morphological pattern, (classified as per IgAN databank) clinical, lab parameters and correlated them.

Observations: Incidence of primary IgAN in patients with nephrotic/nephritic syndrome is 16.2 % in western India; more common in young males in second/third decade of life, pure mesangiopathy being the commonest pattern, C3 and IgG were common co-deposits. Patients with combined lesions had more frequent relapsing episodes of hematuria. Nephritic syndrome was more common presentation and older patients had more aggressive disease with vicious injury.

Conclusion: IgAN is a neglected disease in India, this study may direct towards new efforts in clinical research for its treatment.

Key words: IgA nephropathy, renal biopsy, incidence, natural history

Introduction
Primary or idiopathic immunoglobulin A (IgA) nephropathy is characterized by predominant IgA deposits in glomeruli, in absence of systemic or other non-renal diseases. In 1968 Berger and Hinglais described IgA nephropathy (IgAN) for the first time in 300 human renal biopsies by applying fluorescein conjugated antibodies against IgA. However this entity was not well accepted outside France until seventies. Today IgAN is recognized as one of the common glomerulonephritis in the world. There are few documented studies about the incidence or natural history of this entity in India. Extensive clinical, immunologic, pathological and epidemiologic studies of primary glomerulonephritis with IgA as the predominant or co-dominant immunoglobulin deposit in the glomerular mesangial regions have given it a distinct position. IgAN progresses relentlessly to end stage renal disease requiring renal replacement therapy however the basic molecular mechanisms responsible for mesangial matrix expansion and cell proliferation are still poorly understood.

Aims
We carried out a retrospective evaluation of native renal biopsies performed at the Institute of Kidney Diseases and Research Centre, a tertiary care center for renal diseases in Ahmedabad, India, to find out the incidence and natural history of IgAN in Western India.

Material and methods
We studied 4132 native renal biopsies of patients who presented themselves at our center from 1st June, 1998 to 30th June, 2004, using hematoxylin and eosin, periodic acid Schiff, Jone’s silver methamine and Gomori’s trichrome stains after procuring 3 μm size paraffin
sections. Immunofluorescence studies were performed on their frozen sections using anti-human IgA, IgG, IgM, C1q, C3, albumin and fibrinogen anti-sera (Dako, USA). All the patients with indications for biopsy in case of hematuric nephrotic/nephritic presentation were separated out from others. Biopsies with predominant IgA deposits were labeled as IgAN. Their morphological patterns were classified as per IgAN databank by Wyatt et al. Presence of associated immunoglobulins was also studied.

The natural history of patients with each pattern was evaluated by recording the demographics including urinary protein leak and serum creatinine at the time of presentation. Twenty four hours urinary proteins were measured by the standard Biuret method.

**Observations**

**Incidence and morphological pattern**

There were 740 (17.9%) patients out of 4132, with hematuric nephrotic/nephritic presentation with at least 1 episode of micro/macrohematuria. Out of these 740 biopsies, 120 (16.2%) had primary IgAN. Figure 1 shows the distribution pattern of all lesions. Pure mesangiopathy (class B+C) was the most common pattern found in 73 (60.8%) biopsies, followed by focal segmental endocapillary proliferation superimposed on mesangial proliferation (class D1) in 19 (15.8%), combined/unclassified lesion in 15 (12.5%), diffuse endocapillary proliferation (class E) in 11 (9.2%) and normal/minimal glomerular lesions in 2 (1.7%) biopsies respectively. Class A lesions had unremarkable morphology except acute tubular necrosis. In pure mesangiopathy (class B+C), there was segmental to diffuse mesangial expansion with mild to moderate mesangial hypercellularity and rare leucocytes (lymphocytes/neutrophils) infiltrating the glomeruli. Tubules were moderately degenerated and interstitium revealed mild to moderate edema with scanty mononuclear cellular infiltration. No tubular atrophy or interstitial fibrosis was recorded. Blood vessels were unremarkable (Fig 2A). In class D1 there was focal segmental endocapillary proliferation superimposed on mesangial proliferation. Focal global sclerosis (FGS) involving less than 30% glomeruli, was also noted. Occasional leucocytes were noted infiltrating glomerular capillaries in these lesions. Tubules were focally atrophied along with focal interstitial fibrosis in this set of biopsies.

![Figure 1: Morphological patterns of IgA nephropathy in western India](image1)

![Figure 2A: Pure mesangio-pathy in IgA nephropathy, H & E stain (x 200).](image2)

![Figure 2B: Immunofluore-scence micrograph showing mesangial and capillary IgA deposits (x 100).](image3)
Blood vessels showed mild fibrointimal proliferation. In class E lesions, there was predominant endocapillary proliferation in glomeruli with accompanying occasional leucocytes infiltrating and tubular degenerative changes with interstitial inflammation. No irreversible changes were noted in this class. In biopsies with combined lesions (class H) there were acute and chronic changes involving all components of the renal parenchyma. The glomeruli revealed well developed cellular/fibro-cellular crescents along with endocapillary proliferation, focal segmental necrotizing lesions and FGS of less than 30% glomeruli. Tubules were focally atrophied along with degenerative changes. Interstitium also showed focal fibrosis with overlying edema and scattered lymphocytic infiltration. Blood vessels revealed mild to moderate fibrointimal proliferation with partial luminal obliteration.

Clinicopathological correlation (Table 1)

All the patients had presented with at least one episode of micro/macrohematuria with variable proteinuria. Almost all patients had upper respiratory tract infection 7 to 10 days preceding micro/macrohematuria. This disease was found to affect more commonly young patients, in the second or third decade of life, with a wide range, between 10 to 81 years of age. Combined lesions (class H) were noted in patients above 30 years more commonly than other lesions which were noted in the age group below 30 years. The disease affected males more commonly (2.6 times) than females. Pure mesangiopathy and combined lesions had more frequent male predominance (M:F: 3:1) than other patterns (M:F: 2:1). Patients above 30 years of age had a tendency of longer duration of symptoms, more frequent relapsing hematuria episodes and more vicious lesions than those below the age of 30 years. The disease duration with all patterns ranged between 10 days to 20 years. Urinary protein leak measured in terms of 24 hours urinary protein estimation was variable with different morphological patterns of injury ranging from 300 mgs to 6 grams. The degree of proteinuria was more in patients with minimal lesion. Patients with all other patterns of injury had presented with nephritic syndrome. Patients with pure mesangiopathy (class B+C) had lesser degree of proteinuria and lesser serum creatinine than others. Serum creatinine values ranged from 0.74 to 16.0 mg %. These values were higher in patients with combined lesions (class H) and lowest in patients with pure mesangiopathy (class B+C).

Associated immunoglobulins

IgA was the predominant immunoglobulin deposited in all glomeruli with the intensity ranging from +2 to +4 (Figure 2B). IgA alone was noted in 38 (31.6%) biopsies. The other associated deposits were; IgG in 44 (36.7%),
IgM in 26 (21.7%) and IgG + IgM in 12 (10%) biopsies. Complement C3 deposits were noted in 87 (72.5%) biopsies. There was no correlation between co-deposits of immunoglobulins and natural history of the disease.

Discussion

Epidemiologically IgAN is found in 2% to 40% of renal diseases depending upon the geographical location. It is found to be affecting any age ranging from 10 years to 81 years, with most common onset in second or third decade of life. We have seen the same pattern in Indian population. We have observed an incidence of 16.2% primary IgAN in patients presenting with nephrotic/nephritic syndrome. This correlates with its prevalence in other Asian countries.

Cause and Genetic Factors

We have not been able to study the relationship of IgAN either with HLA antigens or their subtypes, however its onset is often associated with upper respiratory tract infection similarly noted in other studies. We have an interesting observation that there is a correlation between intensity and frequency of upper respiratory bacterial infection and the viciousness of the clinical syndrome. The prevailing hygienic conditions and familiar clustering might be augmenting microbial environmental injury.

The pathogenic mechanism is given below in the form of flow chart (Figure 3).

Pathogenesis

Potential mechanisms by which mucosal T-cell defect produces increased IgA deposits in mesangial regions is explained below.

Microbial environment stimuli

Figure 3: Pathogenesis of IgA deposit in mesangium

Pathology

The pathological presentation varies with the disease progression. The lesions are not homogeneous. Emanicipator et al designed a scheme for classification of these lesions. There may be no morphological alteration observed on light microscopy and foot process dissolution may be seen on electron microscopy. This pattern is the least common. In present study this pattern had an incidence of 1.7%. Class B and C which reveal mesangial prominence in glomeruli with mild tubular and interstitial involvement is the most common presentation noted in about 63% biopsies in other studies and 60.8% in our biopsies. Class E lesions were observed in 9.2% of our biopsies, fairly similar to other studies. Class D1 was observed in 15.8% of our biopsies. Class H lesion noted in 12.5% of all biopsies was more common in our set up unlike in other studies.

Clinical features

Microscopic/episodic macroscopic hematuria and proteinuria are detected for many years which may coincide with upper respiratory tract infection. There are no consistent genetic, immunologic, clinical or morphological markers that predict progressive disease in patients who have no symptoms except minor urinary abnormalities.

Outcome

Primary IgAN eventually progresses to chronic renal failure with variable course ranging from benign condition to a rapidly progressive renal failure in 15 to 40% of patients. In children as well as adults, hypertension, high glomerular histopathological scores, persistent microscopic hematuria, proteinuria of more than 1 gm/24 hrs and impaired renal function at the time of diagnosis stand out as consistent strong predictors of poor renal survival.

Conclusion

We believe that IgAN is a significant problem in India, and there is need to increase efforts in clinical research including role of hematopoietic stem cell transplantation to treat this enigmatic disease.

Abbreviations

IgAN: Immunoglobulin A nephropathy
GN: Glomerulonephritis
FGS: Focal global sclerosis
References


