

# Seminar Article

## Ig A Nephropathy

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### Introduction

Human kidneys play a pivotal role in excretion of noxious substances from our body. The diseases affecting the kidney are many but early intervention can prevent permanent damage to them. One of the most common structures that get involved in the kidney is the glomerulus. These glomerular diseases have a varied clinical presentation. Ig A nephropathy is a disease process commonly involving the glomerulus.

### Anatomy

Each kidney contains around 0.9 million glomerular capillary tufts each of which is harbored within a Bowman's capsule. This glomerular tuft (Figure 1) is an arteriolar portal system. Each tuft is derived from an afferent arteriole which is continuous as the efferent arteriole and blood from this efferent vessel drains into cortical peritubular capillaries or medullary vasa recta. The glomerular capillaries are lined by the endothelial cells resting on a glomerular basement membrane. The epithelial podocytes seen in the outer surface of these capillaries and their interconnections form the selective filtration barrier. This barrier regulates the filtration mainly by pore size and negative electrostatic charge. Whenever there tends to be a glomerular injury, these regulatory factors are nullified leading to loss of protein especially albumin in large quantities.

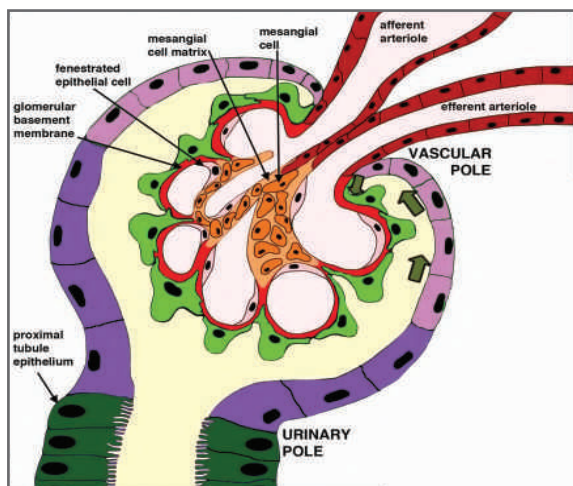


Fig 1: Structure of Glomerulus

### Epidemiology

Overall prevalence of CKD in India is around 17.2% (Stage 1- 5).<sup>1</sup> The leading causes of CKD include Diabetic nephropathy, hypertensive nephrosclerosis, chronic glomerulonephritis, and Polycystic Kidney Disease.<sup>2</sup> Though everyone is aware of the increasing trend in diabetes and hypertension related kidney diseases, the knowledge on chronic glomerulonephritis as a cause of CKD is limited. Ig A Nephropathy is the most common cause of Glomerulonephritis worldwide. Its incidence approximates to 2.5 per 100,000.<sup>3</sup> There is both an increased disease burden and increased risk of progression to End Stage Renal Disease in Asia Pacific region.

### Pathogenesis

The pathogenesis of IgA nephropathy is a multi-hit process (Figure 2) which is influenced by many genetic and environmental factors<sup>4</sup>. The main factor responsible for the disease is the presence of under glycosylated IgA<sub>1</sub> (Figure 3) in both circulation and glomerular immune complex deposits. This is a galactose deficient IgA<sub>1</sub> which may be a heritable trait or induced by an environmental factor. Researchers have found that in mice, exposure to either pathogenic or commensal organisms is sufficient to produce IgA antibodies. The production of antibodies is regulated by APRIL gene. Usually the IgA antibodies are produced in mucosa by T- cell dependent processes, but sometimes T cell cytokines (APRIL) activate B cells to IgA<sub>1</sub> producing plasma cells. A defect in gene encoding for the APRIL deficient IgA<sub>1</sub> which confers susceptibility to IgA nephropathy.<sup>5</sup>

Complement activation is also a risk factor for IgA nephropathy. Defective regulation of alternate complement pathway is linked to IgA nephropathy by some genetic studies.<sup>6</sup> CFHR<sub>1</sub> and CFHR<sub>3</sub> proteins present in CFH(Complement Factor H) gene are responsible for titrating the activity of complement pathway. Absence of these factors enhance the activity of CFH gene which in turn escalates complement activity.<sup>7</sup> Both these mechanisms increase the production of immune complexes which deposit in the mesangium producing glomerulonephritis

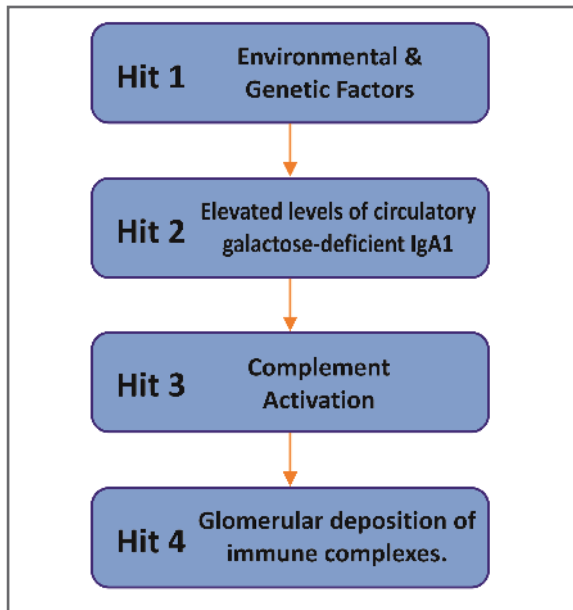


Fig 2: Multiple Hits of IgA Nephropathy

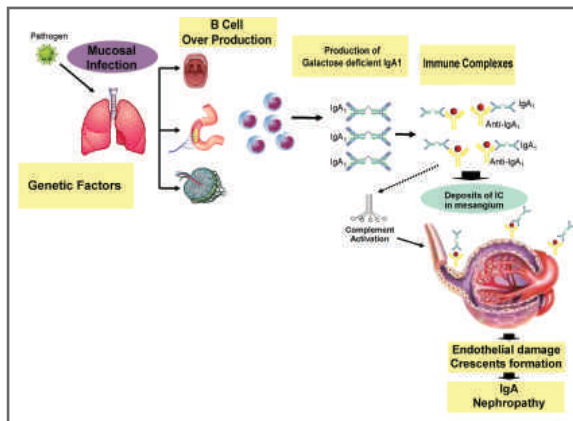


Fig 3: Pathogenesis of IgA Nephropathy

### Pathology

IgA nephropathy is an immune-complex mediated glomerulonephritis. The IgA deposits are mostly seen in mesangium and less commonly in glomerular capillary loops (24-54%) in Immunofluorescence microscopy<sup>8</sup>. Further we should note that 3-16% of normal individuals can have glomerular IgA deposits<sup>9</sup>.

In electron microscopy, mesangial electron-dense deposits are seen in capillary loops and subendothelium. The subepithelial deposits are atypical and presence of this should instigate one to search for other causes of glomerulonephritis.

In light microscopy, 10% of patients had normal architecture. In the remaining 90%, the most common finding was focal glomerulonephritis followed by segmental sclerosis and endocapillary and extracapillary proliferative lesions<sup>10</sup>. The grading of biopsy specimens can be done by one of the two classification systems namely Haas' and Lee's single graded system and Oxford's classification.

CLASS	HAAS'	LEE
I	Minimal or No mesangial hypercellularity	Minimal or No mesangial hypercellularity. Absent tubulo-interstitial inflammation or atrophy
II	Focal Segmental Glomerulosclerosis	Focal and segmental mesangial hypercellularity. Minimal crescents. No tubulointerstitial changes
III	Focal proliferative glomerulonephritis (<50%) ± crescents	Diffuse mesangial hypercellularity. Minimal crescents. Focal tubulointerstitial inflammation and edema
IV	Diffuse Proliferative glomerulonephritis (>50%) ± crescents	Diffuse mesangial hypercellularity and matrix expansion with segmental sclerosis and with 45% crescent formation. Tubulo-interstitial inflammation.
V	≥40% of glomerulosclerosis/ tubular atrophy/ interstitial fibrosis	> 45% crescent formation. Severe tubular atrophy and interstitial fibrosis.

Table 1: Haas' and Lee's Classification System<sup>8</sup>

HISTOLOGICAL PARAMETER	SCORE
M - Mesangial proliferation	0 - Absent, 1 - Present (>50% of glomeruli)
E - Endocapillary hypercellularity	0 - Absent, 1 - Present
S - Segmental Sclerosis	0 - Absent, 1 - Present
T - Tubular atrophy/ Interstitial fibrosis	0 - <25%, 1 - 26-50%, 2 - >50%

Table 2: Oxford's Classification<sup>11</sup>

### Clinical Features

The presentation of IgA nephropathy is varied though one has to have a knowledge over the more common manifestations. Some of the frequently observed manifestations are asymptomatic microscopic hematuria, macroscopic hematuria, rapidly progressive glomerulonephritis. Nephrotic syndrome is a rare presentation of IgA nephropathy. Asymptomatic microscopic hematuria is the most common presentation. Hematuria is defined as presence of 2-3 RBCs/hpf which can be easily detected by a dipstick. A single urine analysis with hematuria may be due to menstruation, allergy, viral fever or trauma. Hence persistent or significant hematuria has to be given importance. Significant hematuria is defined as >3 RBCs/hpf on three occasions or a single episode of hematuria with >100 RBCs/hpf or gross hematuria. Asymptomatic microscopic hematuria with minimal proteinuria (<0.5g/day) suggests a favourable prognosis, especially in white population.<sup>12</sup>

The second common presentation is recurrent episodes of macroscopic hematuria during or following a throat infection<sup>13</sup>. This occurs in 10-15% of patients<sup>14</sup> especially in subjects less than 40 years of age. This usually has a good prognosis provided the patient does not develop proteinuria or progressive renal failure. The development of proteinuria increases the risk for progressive renal failure in these patients<sup>15</sup>.

Among the other manifestations progressive chronic kidney disease is next common presentation. Among the patients presenting as progressive CKD, presence of hypertension, proteinuria, reduced eGFR at diagnosis indicate a poor prognosis.<sup>16,17</sup>

Although nephrotic range proteinuria is not uncommon in IgA nephropathy, nephrotic syndrome per se with edema, hyperlipidemia is rare. In a case series of IgA nephropathy patients, only 306 of 11,885 patients had diffuse IgA-dominant mesangial deposits with minimal changes in glomeruli on light microscopy of biopsy specimens. None of these patients developed end stage renal disease.<sup>18</sup>

IgA nephropathy presenting as a case of acute renal failure and rapidly progressive glomerulonephritis is very rare. In such instances, more than 50% of glomerulus exhibit the presence of crescents. One of such case series showed that around 42.5% developed ESRD even on appropriate immunotherapy.<sup>19</sup>

On evaluation the patients may have raised total count in blood routine due to the precipitating infection. Raised serum urea and S.creatinine are not that common. All levels of proteinuria are seen though nephrotic range is less common. Kidney biopsy is the investigation of choice to prove the diagnosis. Certain case reports<sup>20,21</sup> say that presence of 3 or 4 of the below mentioned markers can help in the diagnosis of patients with IgA nephropathy without kidney biopsy. The markers are

- (i) > 5 RBCs/HPF in urinary sediments,
- (ii) persistent proteinuria (urinary protein of > 0.3 g/d),
- (iii) a serum IgA level of > 315 mg/dL, and
- (iv) a serum IgA/C<sub>3</sub> ratio of > 3.01.

Yanagawa et al<sup>22</sup> compared the serum levels of certain antibodies such as IgA, IgG, Gd-IgA<sub>1</sub>, Gd-IgA<sub>1</sub> specific IgG, and Gd-IgA<sub>1</sub> specific IgA in 135 IgA nephropathy patients, 79 patients with chronic kidney disease other than IgA nephropathy, and 106 controls. In this study it was found that there was an elevation of Gd-IgA<sub>1</sub> specific antibodies in most IgA nephropathy patients. This together with serum levels of Gd-IgA<sub>1</sub>, improved the specificity of the assays. Previously some of them were measuring the antibodies by using a snail helix aspersa agglutinin lectin based Assay. Since the lectin-dependent assay has some serious problems, recently the antibodies are detected by ELISA method developed by Yasutake.<sup>23</sup>

## Treatment

Management of IgA nephropathy targets to reduce proteinuria, slow the progression of renal failure and to improve the clinical outcome. ACE inhibitors or Angiotensin receptor blockers are useful in treatment of proteinuria. Combination of these agents is to be avoided due to increased risk of hyperkalemia.<sup>24</sup> In a trial of 21 patients with S. creatinine <1.8 and with absence of severe lesions in renal biopsy, fluvastatin reduced proteinuria after treating for a period of 6 months. Lifestyle modifications such as weight loss reduced proteinuria<sup>25</sup> and smoking cessation reduced the progression of renal disease.<sup>26</sup>

Corticosteroids have reduced proteinuria and improved clinical outcome in many clinical trials. According to the Evidence-based Clinical Practice Guideline for CKD (Japanese Society of Nephrology, 2013)<sup>27,28</sup>, steroids are useful for patients with proteinuria > 1 g/day and CKD Grade 1, 2. Steroids have been given as pulse therapy 1 g intravenously for 3 days at months 1, 3, and 5, and followed by oral prednisone at 0.5 mg/kg per day on alternate days for 6 months in one of the randomised trials<sup>29</sup> and found to be much beneficial.

In STOP - IgAN study, patients were treated with immunosuppressants such as steroids and cyclophosphamide. In this study, patients would receive corticosteroids if the eGFR was >60 ml/min per 1.73 m<sup>2</sup> whereas those with eGFR of 30–59 ml/min per 1.73m<sup>2</sup> would receive steroid and cyclophosphamide, followed by maintenance immunosuppression with azathioprine. After 3 years, patients treated with immunosuppression had full clinical remission. The term full clinical remission means protein-to-creatinine ratio of <0.2 and stable renal function with a decrease in the eGFR of <5 ml/min per 1.73 m<sup>2</sup> from the baseline eGFR. Unfortunately there was an increase in infection rate and weight gain in the patients. Hence risks have to be weighed against the benefits before starting the patients on immunosuppressive therapy. Other immunosuppressants such as mycophenolate mofetil<sup>30</sup> and rituximab<sup>31</sup> are not useful in IgA nephropathy. Further in patients with IgA nephropathy Kawamura et al<sup>32</sup> reported that tonsillectomy with steroid pulse therapy reduced proteinuria.

## Conclusion

IgA nephropathy being the most common cause of chronic glomerulonephritis, its pathogenesis have been clarified by many researchers especially the role of galactose deficient IgA<sub>1</sub> in the disease. The classifications developed would help in deciding the treatment. The role of immunosuppressants in IgA nephropathy has been only in studies and no recommendations are presently available. Further researches are required in finalising the treatment of this disease.

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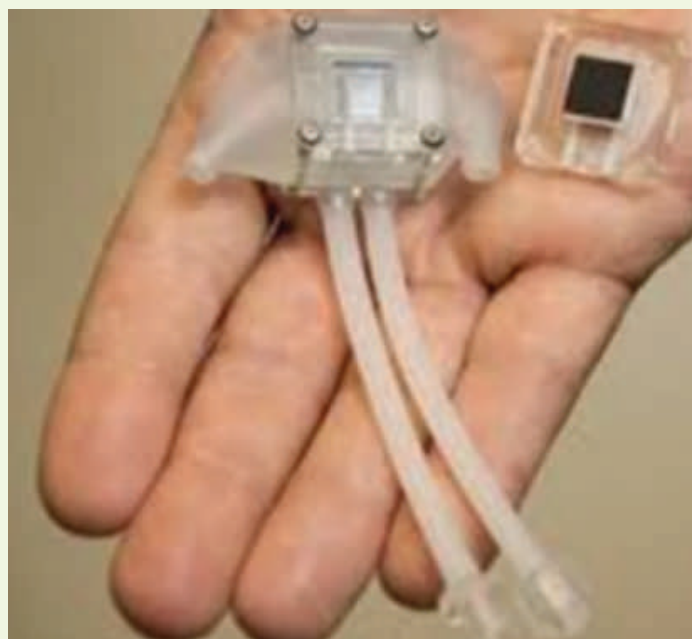


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