IgA nephropathy (IgAN) is a relatively young disease among primary glomerulopathies, yet it has emerged as the most common primary glomerular disease worldwide. Numerous studies carried out during last four decades have unravelled many aspects of this enigmatic disease. In this review, recent developments in the diagnosis and prognosis of IgAN are discussed with particular emphasis on a recent clinicopathological classification developed through international collaboration by the members of International IgAN network in conjunction with renal pathology society (RPS).

Historical perspective
IgAN was first described by Berger and Hingalis in France in 1968 and is defined by the predominant or co-dominant IgA containing immune complex deposits in the kidney. As such, its diagnosis was and continues to be based on histopathologic and immunofluorescence (IF) evaluation of the invasive procedure of renal biopsy. It was initially thought of as a benign disease as is evident from its earlier synonym of benign familial hematuria and confined to France. However, subsequent long term follow-up studies from different parts of the world have proved both assumptions wrong, as will be evident below in the discussion of epidemiology and prognosis.

Epidemiology
Epidemiological studies from different parts of the world have proved that IgAN has worldwide distribution and is the most common primary glomerular disease. There is however, significant variability in the reported incidence and prevalence rates from different countries. High rates of 20-58% have been reported in biopsy studies from Western Europe, parts of Asia and Australia. On the other hand, very low rates have been reported from US at 2-10%, with the exception of a 38 percent incidence in the Navajo Indians in New Mexico. Similarly, low rates are reported from Africa, Middle East and some parts of Asia. The apparent variable rates most probably reflect differences in biopsy policies and lack of IF facilities in the later countries rather than true ancestral differences in the prevalence of this disease. There are no population based data on the prevalence and incidence of this disease in Pakistan. A few single center biopsy series have been published in last few years. Earlier biopsy reports were based on light microscopic studies only and obviously missed this diagnosis. More recently, a few centers have started performing IF study on renal biopsies and cases of IgAN nephropathy have begun to be reported in the literature. These, however, represent only the tip of the iceberg; the actual prevalence is likely to be considerably higher if population-based studies are conducted. A community urine analysis survey by dipstick testing conducted in a locality of Karachi had found hematuria in 25% and proteinuria in 15% of asymptomatic individuals including both children and adults. If these cases are further investigated, some may turn out to be the cases of latent IgAN.

Etiology
The etiology of this enigmatic disorder remains as unclear today, as it was at the time of discovery. IgAN is predominantly a sporadic disorder. However, cases of familial and secondary IgAN are well documented and these have provided insights into the underlying pathogenesis of the disease.

Pathogenesis and pathology
The pathogenesis of IgAN is still largely unknown. Numerous studies conducted on animal models and humans during the past four decades have shed light on some of the steps involved in the pathogenesis of sporadic IgAN. The final common pathway in the process appears to be the accumulation of aberrantly glycosylated polymers of IgA1 (pIgA1) molecules and/or complexes in the glomerular mesangium. It is possible...
that numerous pathogenetic pathways are involved and converge on this central and unifying stage in the pathogenesis.31

The likely events of pathogenesis implicated in different studies run the whole gamut of IgA immune system abnormalities from increased production of aberrantly glycosylated plgA1 molecules by a putative abnormal subclone of B lymphocytes, to decreased clearance, to host immune response to abnormal plgA1 molecules to physicochemical mechanisms leading to abnormal accumulation of plgA1 in the mesangium,33,34 These bind to and interact with mesangial cells leading to their activation and proliferation. Activated mesangial cells not only proliferate but also produce pro-inflammatory cytokines, chemokines and growth factors, which initiate tissue injury. A number of cytokines have been studied not only proliferate but also produce pro-inflammatory cytokines, chemokines and growth factors, which initiate tissue injury. A number of cytokines have been studied in detail including platelet derived growth factor (PDGF) β-chain and transforming growth factor-β (TGF-β) for their roles in the ultimate expression of the disease. There is also evidence of local complement activation induced by alternative pathway triggered by plgA1 molecules in the mesangium.

There are species differences in the molecular structure of IgA and unique features of human IgA1 have prevented development of satisfactory animal models for the early stages of IgAN. A fully humanized mouse model of disease would be a welcome addition to the investigative armamentarium of the pathogenesis. It is likely that events after plgA1 deposition which result in glomerular inflammation and scarring are not specific to IgAN but generic to many forms of glomerulonephritis (GN). A complete understanding of the pathogenesis along with etiology holds the key to the specific therapy for the disease. Future molecular biologic studies will certainly help unravel the missing steps in the pathogenesis.

Pathologically, IgAN is quite heterogenous. The range of morphologic patterns seen in the glomeruli spans the whole spectrum from minor changes to full blown crescentic GN. The unifying and defining feature of IgAN is the predominant or co-dominant IgA deposition in the glomerular mesangium on IF microscopy.30

**Risk of progression and classification systems**

Although this disease was initially thought of as benign, it is now known to lead to a slowly progressive decline in renal function with end stage renal disease (ESRD) developing in upto 30% of patients 20 years after diagnosis.36,37 Long-term outcome data show variable rates of disease progression throughout different parts of the world.38 Numerous attempts have been made in identifying clinical, laboratory and morphologic features in renal biopsies which can predict the outcome. Many pathologic studies done in different parts of the world have produced conflicting results. A few investigators attempted to incorporate the various histological features into a pathologic classification of IgAN, but none has succeeded in achieving widespread acceptance.39-41 More recently, an international collaborative group of nephrologists and pathologists with special interest in IgAN proposed a new pathology-based classification of IgAN, termed “The Oxford classification of IgAN”.42,43 This scheme employed a novel and unique approach to the pathologic classification of IgAN, in that no arbitrary classes or grades are formulated. Instead, specific histopathologic features of prognostic importance independent of clinical data at the time of biopsy and follow-up have been identified and scored by a rigorous iterative process of first defining the lesions and then testing for reproducibility and ease of scoring. This approach has never been employed previously in the classification of renal pathology.42 This classification is based on detailed analysis of retrospective clinical data obtained on 265 adults and children with IgAN from eight different countries of the four continents, followed for a median of 5 years in concert with intense detailed review of their renal biopsy material.

Six pathology variables were identified on the basis of reproducibility among pathologists, least susceptibility to sampling error, and the ease of scoring in routine practice while avoiding strong co-linearity (mesangial hypercellularity score, segmental glomerulosclerosis or adhesion, endocapillary hypercellularity, cellular or fibrocellular crescents, tubular atrophy/interstitial fibrosis, artery score). Four of these (mesangial hypercellularity score, segmental glomerulosclerosis or adhesion, endocapillary hypercellularity, and tubular atrophy/interstitial fibrosis) were shown to have independent value in predicting renal outcome even after taking into account all clinical indicators available at the time of biopsy as well as during follow-up. These features along with their proposed scoring, which are recommended by the Oxford group, to be included in the pathology report of renal biopsy specimens from patients with IgAN, are shown in Table I. The value of crescents could not be addressed due to their low prevalence in the enrolled.

**Table I:** The four key pathological features that are recommended by the Oxford group to be included in the pathology reports for patients with IgA nephropathy.42

<table>
<thead>
<tr>
<th>Pathological features</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mesangial hypercellularity</td>
<td></td>
</tr>
<tr>
<td>Present in ≤ 50% of the glomeruli</td>
<td>M0</td>
</tr>
<tr>
<td>Present in &gt; 50% of the glomeruli</td>
<td>M1</td>
</tr>
<tr>
<td>Segmental glomerulosclerosis</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>S0</td>
</tr>
<tr>
<td>Present</td>
<td>S1</td>
</tr>
<tr>
<td>Endocapillary hypercellularity</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>E0</td>
</tr>
<tr>
<td>Present</td>
<td>E1</td>
</tr>
<tr>
<td>Tubular atrophy/interstitial fibrosis</td>
<td></td>
</tr>
<tr>
<td>≤ 25% of the cortex</td>
<td>T0</td>
</tr>
<tr>
<td>26-50% of the cortex</td>
<td>T1</td>
</tr>
<tr>
<td>&gt; 50% of the cortex</td>
<td>T2</td>
</tr>
</tbody>
</table>
Future prospects

In recent years, a series of important breakthroughs in the areas of molecular pathogenesis and experimental therapy have emerged, reflected in a molecular paradigm shift in the techniques and approaches applied to the study of IgAN. Ongoing and future investigations in this area will lead to the development of promising areas of new investigation and approaches to the identification of disease susceptibility genes involved in the development and progression of IgAN, the application of these discoveries through the development of clinically useful molecular diagnostic tests, and the rational design of specific therapeutic agents. With further refinements, such molecular tests may provide new tools for the diagnosis and monitoring of patients with IgAN that is more sensitive than current standard clinical testing and may obviate the need for invasive renal biopsy.

REFERENCES


