## IgA Nephropathy

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IgA nephropathy (IgAN) is a relatively young disease among primary glomerulopathies, but has emerged as the most common primary glomerular disease world wide.<sup>1</sup> 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.<sup>2</sup> As such, its diagnosis requires pathologic evaluation of invasive renal biopsy by light microscopy (LM) and immunoflourescence microscopy (IF). 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 worldwide have proved both the above assumptions wrong. Epidemiological studies from different parts of the world have proved that IgAN has global distribution and is the most common primary glomerular disease.<sup>1,3-9</sup> There is however, significant variability in the reported incidence and prevalence in different countries.<sup>3-9</sup> High rates of 20 to 47 percent have been reported in biopsy studies from Western Europe, parts of Asia and Australia.<sup>3</sup> On the other hand, very low rates have been reported from US, Africa. Middle East and some parts of Asia.4-7 The apparent variable rates most probably reflect differences in medical practice, biopsy policies and lack of IF facilities in some countries rather than true ancestral differences in the prevalence of this disease.7

There are no population based incidence and prevalence data on IgAN in Pakistan. However, a few hospital based studies are available during recent past on the prevalence of this disease in renal biopsies in this country.<sup>7</sup> The reported frequency has ranged from 2 to 20.8% of all biopsies. These studies do not reflect the true prevalence and the full spectrum of disease in the population and likely represent only the severe forms of the disease.<sup>7</sup> A community urine analysis survey by dipstick testing conducted in a locality of Karachi had observed hematuria in 25% and proteinuria in 15% of asymptomatic individuals including both children and adults.<sup>8</sup> If these cases are further investigated, some may turn out to be the cases of latent IgAN.

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The etiology of this enigmatic disorder remains unclear. 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,<sup>9</sup> which is still largely unknown. Numerous studies carried out on animal models and humans during the past three decades have shed light on some of the steps involved in the pathogenesis of sporadic IgAN.<sup>9</sup> The final common pathway in the process appears to be the accumulation of aberrantly glycosylated polymers of IgA1 (plgA1) molecules and/or complexes in the glomerular mesangium.<sup>9</sup> It is possible that numerous pathogenetic pathways are involved and converge on this central and unifying stage in the pathogenesis.9 A complete understanding of the pathogenesis along with etiology holds key to the specific therapy for the disease. Future molecular biologic studies will certainly help unravel the missing steps in the pathogenesis.

Although this disease was initially considered 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 twenty years after diagnosis.<sup>10</sup> Long-term outcome data show variable rates of disease progression throughout the world.3 Attempts have been made in identifying clinical, laboratory and morphologic features in renal biopsies which can predict the outcome.<sup>10</sup> Controversy still exists, however, about the histologic prognostic factors in patients with IgAN, and factors of importance in the progression of renal impairment in these patients. A few investigators attempted to incorporate the various histological features into a pathologic classification of IgAN, but none has succeeded in achieving widespread acceptance.<sup>10</sup> More recently, an international collaborative group of nephrologists and pathologists with special interest in IgAN have proposed a new pathology based classification of IgAN, termed "The Oxford classification of IgAN".10 This scheme has employed a novel approach to the pathologic classification of IgAN. It is clinically pre-validated, evidence based classification with good interobserver reproducibility among researchers with special interest in IgAN, with a limited number of cases and in the research setting.<sup>10</sup> However, it remains to be validated in real clinical practice in different parts of the world with a wide variety of cases of this disease.

As regards treatment, there is no specific therapy for this condition primarily due to unknown etiology and unclear

pathogenesis and nephrologists are forced to use less specific disease modifiers.<sup>9</sup> Future research into the pathogenesis may yield specific, targeted therapy for IgAN.

In conclusion, although significant developments have taken place during recent past regarding pathogenesis and pathologic classification of IgAN, much remains to be discovered, especially with regard to etiopatho-genesis. Molecular biologic studies hold considerable promise in this scenario. This will hopefully lead to the development of specific targeted therapies for this disease in near future.

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