Chapter 1

IgA Nephropathy: Discovery of a Distinct Glomerular Disorder

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Introduction

IgA nephropathy (IgAN) is the most common form of primary glomerulonephritis in the developed world and it is an important cause of end stage kidney failure.1,2 Epidemiologic studies have shown that IgAN is nearly universally distributed around the world but the frequency with which it is diagnosed varies, mostly according to local policies regarding the indications for renal biopsy. Prevalence appears highest in Asia (Singapore, Japan, and Hong Kong), Australia, Finland, and southern Europe (20% to 40% of cases of primary glomerulonephritis). In the United Kingdom, Canada, and the United States, prevalence rates are much lower (reviewed by Schena3). This chapter will focus on the early events which preceded and surrounded the discovery of IgAN by Berger and Hinglais more than four decades ago.

History of IgA Nephropathy (Berger’s Disease)

It was the use of the techniques of immunohistochemistry and renal biopsy which led Berger to discover IgAN. The idea of using fluorescent-labeled specific antibodies to detect proteins in tissue was introduced by Coons and Kaplan4 in 1950 and was first used for evaluation of disease
renal tissue by Mellors and Ortega\textsuperscript{5} in 1957. Percutaneous renal biopsy was initially described as a technique to diagnose kidney disease by Iverson and Brun in 1951.\textsuperscript{6} By 1960, there were still only a relatively few sites where percutaneous renal biopsies were performed and even fewer laboratories skilled in the use of the immunofluorescent technique and the antisera used were of poor specificity. In 1963, antibodies against class specific epitopes of the immunoglobulin light chains became commercially available so IgG, IgA and IgM could be identified separately. Tomasi et al.\textsuperscript{7} had discovered the IgA immune system in 1965. Thus two techniques, immunofluorescent tagging of antibodies to detect antigens in tissues and percutaneous renal biopsy, along the discovery of an new immunoglobulin present in serum and in tissue secretions (IgA) all collided to prepare the way for the seminal observations, beginning in 1967 of Jean Berger and Nicole Hinglais at the Necker Hospital in Paris, France concerning a new entity they subsequently called mesangial IgA/IgG deposition. They described their novel observations in a brief paper published in 1968 which described predominant IgA mesangial deposition in some renal biopsies where the immunostaining of IgA strongly outshone the IgG reagent. This was the birth of IgA nephropathy, also subsequently called Berger’s disease.\textsuperscript{8} In the following year in 1969, Berger published another paper “IgA glomerular deposits in renal disease” in the Transplantation Proceedings.\textsuperscript{9} This was a new journal in its first year. Fifty-five patients with various forms of glomerular morphology were described, mostly “focal glomerulonephritis.” These patients had minor proteinuria, but all had microscopic hematuria, of whom 22 had one or more bouts of gross hematuria. It was also already known then that IgA could also be found in patients with nephritis associated with Henoch-Schonlein purpura as well as lupus nephritis. The nephrology world was still sceptical about the “new disease entity.” In 1972, Levy and colleagues\textsuperscript{10} used in print for the first time the term “Berger’s Disease.” It was recorded that Jean Berger was somewhat embarrassed, as one knows he is indeed a very modest man, following appearance of this paper in the US, the UK, the Netherlands, Japan and Australia.\textsuperscript{11} By 1975, “Berger’s Disease” became an established glomerular entity: a condition with moderate proliferative glomerular changes, usually mesangial but often focal or segmental in distribution; associated with microscopic hematuria and about 15% to 20% with macroscopic hematuria. Serum IgA levels were also shown to be elevated in some patients. It was a slowly progressive renal disease with increasing proteinuria, hypertension and renal failure in ~30% of
patient over 25–30 years. The different nomenclature of “Berger’s Disease” is shown in Table 1.1. When such patients were transplanted, Berger showed that about 50% had a recurrence, though not all grafts failed because of recurrent disease.9

First Description of the Broader Clinical Features of “Berger’s Disease”

Clarkson et al.,12 in an impressive collection of cases with “Berger’s Disease” emphasized that “Berger’s Disease” was a syndrome of uniform morphology, diverse clinical features and uncertain prognosis. It is now fully recognized that Berger’s Disease (henceforth called IgA nephropathy) is not always a benign disease. It has a cumulative renal survival of 89% after five years, 81% after ten years and 65% after 20 years.13,14 The data showed that renal deterioration in IgAN is generally slow and progressive over a long period of time (average: 7.7 years). The unfavorable long-term prognostic indices are proteinuria of more than 1 g/day, hypertension, glomerulosclerosis exceeding 20%, presence of crescents, and medial hyperplasia of blood vessels on renal biopsy. A smaller group of patients run a more rapid clinical course progressing to end-stage renal failure within a few years, in which severe uncontrolled hypertension seems to be the major adverse factor.

As in the time of Berger, the cause remains unknown in the majority of IgAN. However, cases of familial IgAN and secondary IgAN have been reported and these have provided insights into underlying genetic and environmental triggers for this common glomerular disease.
Secondary IgAN is seen most commonly in patients with liver disease or mucosal inflammation, in particular affecting the gastrointestinal tract. A number of dietary and microbial antigens have been identified in circulating IgA immune complexes and mesangial IgA deposits, suggesting that environmental factors may play a role in the pathogenesis of IgAN. Whether these reports represent chance associations or genuine shared pathophysiology remain to be confirmed.

The Recognition of Disease Progression and Proteinuria

At the time of its discovery, IgAN was believed to be a “benign” disorder. We now recognize that the majority of cases will progress to renal failure although at a widely varying rate. A small subset of patients with heavy proteinuria behaves clinically like minimal change disease. Their proteinuria responds to steroid and this subset was recognized as “an overlapping syndrome of IgA nephropathy and lipoid nephrosis.” Otherwise, severe nephrotic-range proteinuria is not common in IgAN, but nephrotic-range proteinuria in the absence of minimal change disease is associated with poor prognosis.

Evolution of Beliefs Regarding Treatment of IgAN

Initially, IgAN was not thought to require any treatment. However, upon recognition that progression to renal failure was not uncommon, interest in attempting therapy became of significant importance. However, early attempts were reported mainly as anecdotes, small prospective, uncontrolled trials or retrospective observational analyses. This, whether truly beneficial and safe forms of therapy for IgAN existed was quite uncertain. The paucity of controlled clinical trials of therapy for IgAN during the past three decades contrasts with the number of recent reviews, illustrating frustrations in obtaining new, reliable long-term data on treatment for IgAN. Scrutiny and evaluation of other regimens can only be good for patients, but current recommendations are polarized and sometimes changeable, supporting or denying use of corticosteroids when proteinuria exceeds 1 g/24 h. The quality of
randomized, controlled trials is substantially influenced by design parameters, so retrospective interpretation using a mathematically insufficient approach is a likely source of discrepancy between reviews. Recent commentaries address how disparate opinion may have risen and quantify existing data to balance recommendations.\textsuperscript{17,18}

In sum, the paucity of good clinical trials highlights the remaining uncertainty persisting from the early 1970s concerning what is best treatment and for how long must treatment be continued. History has taught us that good clinical trials are difficult to conduct in IgAN because of the slow progressive nature of the disease, diverse clinical features, different biopsy criteria for determining prognosis, and selection of end-points.

\textbf{Conclusion}

It is now four decades since Berger’s observation and description of this distinct clinico-pathological entity first called Berger’s Disease and now called IgA nephropathy. The coalescence of immunohistochemistry, percutaneous renal biopsy and discovery of the IgA molecule in 1950–1965 set the stage for this discovery. We now know that IgAN is characterized immunologically by the presence of IgA immune complexes deposition in the mesangium in the clinical setting of diverse clinical features, but primarily asymptomatic hematuria and proteinuria. Histologically, most patients have a diffuse mesangial proliferative glomerulonephritis, whilst others have focal proliferative lesions and a very small minority develop acute renal failure with crescents as in “malignant” IgAN. We now recognize, not well understood in the initial years following the discovery of IgAN, that in the majority of patients, IgAN is a smouldering disease of a slowly progressive nature. Up to the present, there is no universally agreed-upon definitive therapy for IgAN, though renin-angiotensin system blockade can slow the progression to end stage renal failure.\textsuperscript{19} Ever since Berger, investigators in the field of IgAN have pursued the underlying mechanisms responsible for the disease with a view to seeking a cure, yet the gap between the bench and the patient’s bedside does not seem to be closing very rapidly. Slow progress has been made, particularly in the understanding of the abnormalities of the IgA molecule itself in subjects with IgAN (reviewed in Chapter 12). Seekers of the Holy Grail or the final chapter of the IgAN story which began in
Paris so many years ago will have to continue to persevere and hopefully one day harness a solution for the commonest form of primary glomerulonephritis worldwide.

References