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Review Article

Primary glomerulonephritis: A review of important recent discoveries

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Abstract

The publication of the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines on the treatment of glomerular diseases in 2012 marked a milestone in this field, as it is the first time that comprehensive guidelines are provided for such disease entities. The current review focuses on major findings, both pathogenesis related and clinical, in the primary glomerulonephritis that have been made after the guidelines came into effect.

Introduction

Certainly the most important event in 2012 was the publication of the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines for the treatment of glomerular diseases [1]. For the first time evidence-based guidelines are now available in this field. The guidelines have taken a relatively long time to be published and are based on the knowledge available in early 2011 to mid-2011. Thus, in this review I will focus exclusively on important developments in the field of primary glomerulonephritis (GN) in 2012 and early 2013.

Immunoglobulin A nephropathy

Pathogenesis

The year 2012 has seen some advances in understanding the complex pathogenesis of immunoglobulin A nephropathy (IgAN) [2–4]. There is increasing evidence that autoantibodies play a role against poorly galactosylated IgA in the disease. These autoantibodies are largely confined to IgAN and correlate with the clinical prognosis [5,6]. Poor galactosylation of the circulating (and deposited) IgA may, among others, involve altered expression of miR-148b [7]. In addition, a recent study suggests that the fractalkine CX3CR1 contributes to the characteristic hematuria seen in IgAN [8], but the exact mechanism by which it may cause hematuria still remains elusive [9].

In an elegant mouse model, the role of the two IgA receptors, soluble CD89 (sCD89) and transferrin-receptor-1, was studied [10]. Mice with transgenic overexpression of human IgA1 and CD89 develop inflammatory renal changes, hematuria, and proteinuria. In these mice, sCD89 binds mesangial transferrin-receptor-1 and this complex induces transglutaminase-2 in the cells. The latter serves as an amplification loop, favoring the generation of more IgA1-sCD89 complexes and thus further activation of mesangial cells. Transglutaminase-2 thus may be a novel therapeutic target in IgAN, provided that this mechanism can be confirmed in the human disease.

Another rapidly evolving area is the knowledge on the genetic basis of IgAN in large populations. Genome-wide association studies have identified associations of single human leukocyte antigen (HLA) polymorphisms [11] and some proinflammatory genes [12] with the development or course of IgAN. More importantly, using such a genetic approach, we can develop a worldmap of IgAN risk [13] (Fig. 1).

Prognosis

As previously done, in 2011, a number of studies attempted to validate the histological Oxford classification of IgAN [14]. Similar to previous studies, the more recent ones again show that mainly interstitial changes (i.e., the "T" criterion of the

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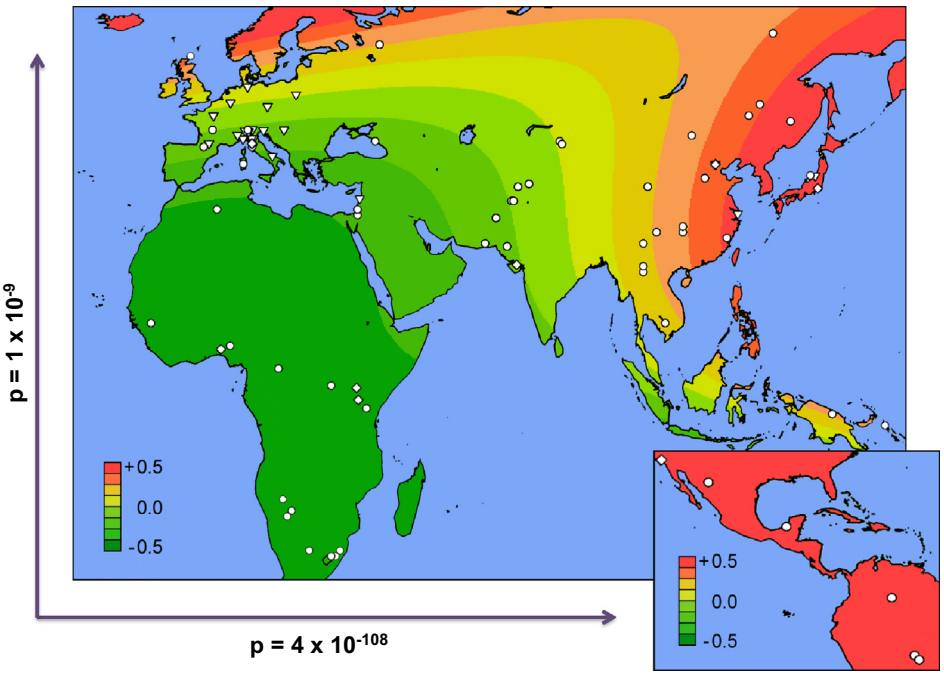

Figure 1. World-wide genetic risk for immunoglobulin A nephropathy (IgAN). Gene-wide association studies indicate different worldwide risks for IgAN. (Reprinted with permission from Kiryluk K, Li Y, Sanna-Cherchi S, Rohanizadegan M, Suzuki H, Eitner F, Snyder HJ, Choi M, Hou P, Scolari F, Izzi C, Gigante M, Gesualdo L, Savoldi S, Amoroso A, Cusi D, Zamboli P, Julian BA, Novak J, Wyatt RJ, Mucha K, Perola M, Kristiansson K, Viktorin A, Magnusson PK, Thorleifsson G, Thorsteinsdottir U, Stefansson K, Boland A, Metzger M, Thibaudin L, Wanner C, Jager KJ, Goto S, Maixnerova D, Karnib HH, Nagy J, Panzer U, Xie J, Chen N, Tesar V, Narita I, Berthoux F, Floege J, Stengel B, Zhang H, Lifton RP, Gharavi AG. Geographic differences in genetic susceptibility to IgA nephropathy: GWAS replication study and geospatial risk analysis. *PLoS Genet* 8:e1002765, 2012)

Oxford classification) allow a prognostic assessment, whereas all other parameters, in particular the more inflammatory changes ("M" and "E") performed less reliably ([15–20], Table 1). Similarly, the presence of glomerular crescents, which is not a part of the four Oxford criteria, is of inconsistent prognostic power.

Apart from histological predictors of IgAN, a Korean study demonstrated that low circulating C3 levels can also herald an adverse prognosis in IgAN patients [21]. Similarly, extraglomerular C3 deposits in Bowman's capsule and/or arterioles signal an adverse prognosis [22].

Of clinical importance is a Chinese study that describes histological features of 90 IgAN patients, who had received a kidney biopsy for isolated microhematuria [23]. Not surprisingly, these patients exhibited mostly mesangial hypercellularity ("M" in the Oxford classification) and endocapillary proliferation ("E" in the Oxford classification), i.e., mostly early and inflammatory changes. However, and very remarkably, within these relatively young patients (mostly 20–30 years old) 50% had some focal or global glomerulosclerosis, 20% had tubulointerstitial damage, and 25% had isolated glomerular crescents. Thus, the important insight gained here is that IgAN patients with a clinically excellent prognosis can exhibit even crescents and vice versa; not every crescent in IgAN necessitates immunosuppression.

Clinical aspects

A Spanish study reported on the long-term course of 141 IgAN patients, who, similar to the Chinese patients discussed earlier, had received kidney biopsies despite only minor urinary abnormalities [i.e., microhematuria or mild proteinuria with a normal glomerular filtration rate (GFR)] [24]. No patient received immunosuppression. An increase in serum creatinine of 50% or more was observed in 3.3% of cases at 10 years follow-up and in 8.9% of cases at 20 years follow-up. Of the patients, 38% developed a full clinical remission after a median duration of 48 months. However, six patients developed a proteinuria of more than 1 g/d and 42% of patients subsequently received blockers of the renin–angiotensin system (RAS).

This Spanish study therefore confirms that mild IgAN has an excellent overall prognosis. However, a few patients will progress, and currently it is not possible to identify them prospectively. It is therefore imperative that such early diagnosed IgAN patients receive annual or biannual checkups.

Based on the literature, a nephrotic syndrome is a rare manifestation of IgAN (unless there is an overlap with minimal change nephropathy). It is therefore notable that in Korea about 10% of a large patient series exhibited a nephrotic syndrome [25]. Such patients had a poor prognosis, and almost a quarter of them experienced a doubling of their serum creatinine within the subsequent 4 years. Surprisingly, however, others exhibited spontaneous remissions, a good prognosis (in particular women and patients with low initial serum creatinine levels, and a decrease of the proteinuria of $>50\%$ in 3 months). Again, these observations stress the importance of regular controls after the diagnosis.

Yet another Korean study contradicts the widespread opinion that Henoch-Schönlein purpura in adults runs a more severe course than primary IgAN [26]: when patients were matched for baseline characteristics, the course of the two diseases was not different. This study supports the general assumption that the two diseases are very similar and likely manifestations of the same disease process.