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Autoimmune kidney diseases

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ABSTRACT

The second most common cause of chronic renal failure is glomerulonephritis, which is a collective term used for numerous diseases with the common denominator of histological renal inflammation emanating from the glomerular tuft. Whether all forms of glomerulonephritis should be considered as autoimmune disease is debatable, but immune mechanisms are important in all of them. This review focuses on four relatively well delineated forms of primary glomerulonephritis: Goodpastures or anti-GBM disease, IgA nephritis, membranous nephropathy and membranoproliferative glomerulonephritis. The autoantibodies are directed either to molecules within the glomeruli, such as the glomerular basement membrane in anti-GBM disease and to the podocytes in membranous glomerulonephritis, or to components of the immune system such as C3 convertase in membranoproliferative glomerulonephritis and IgA in IgA nephritis. Differences in diagnostic practices and classification controversies obscure comparative epidemiological studies, but there seem to be huge differences between incidence rates between countries and over time, both genetic factors and infections seem to matter but strong indications for a role of other environmental factors are still lacking.

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1. Introduction

The immune system is involved in many types of renal disease, but there is no universally accepted definition of the term autoimmune kidney disease. The most common cause of kidney failure worldwide today is diabetes mellitus, and at least for type I diabetes the origin is considered to be autoimmune. The renal damage in diabetic nephropathy is not caused by autoimmunity, however, and Type 1 diabetes is covered in Chapter 24 in this issue. The second most common cause of chronic renal failure is glomerulonephritis, which in turn is a collective term used for a substantial number of diseases with the common denominator of histological renal inflammation emanating from the glomerular tuft. Whether all forms of glomerulonephritis should be considered as autoimmune disease is debatable, but immune mechanisms are important in all of them. Immune mechanisms also participate in the pathogenesis of several forms of tubulointerstitial diseases, but here autoimmunity is considered to be less important in the majority of cases. Consequently we will focus this review on glomerular diseases

Glomerulonephritis is usually separated into primary and secondary forms. Secondary glomerulonephritis can be seen in systemic inflammatory diseases such as small vessel vasculitis (see Chapter 20 in this issue) and systemic lupus erythematosus (see Chapter 14 in this issue), in infectious diseases (malaria, HIV, hepatitis etc.) and in malignancies. The classification of primary glomerulonephritis is debatable and confusing. A major cause of confusion is the poor correlation between histological and clinical findings, causing considerable overlaps between diseases defined by clinical features and diseases defined by histological features. With this in mind we have chosen to focus this review and four relatively well delineated forms of primary glomerulonephritis, all with histological definitions which are widely accepted: Goodpastures disease (GP), IgA nephritis (IGAN), membranous nephropathy (MN) and membranoproliferative glomerulonephritis (MPGN).

2. General aspects glomerulonephritis

2.1. Clinical findings and diagnosis

The clinical hallmarks of glomerulonephritis are hematuria, proteinuria, urinary casts and a reduced glomerular filtration rate (GFR). The presence and severity of each of these signs vary considerably between disease categories as well as between individual patients. However, it is common to lump different combinations of these hallmarks in clinical syndromes, a list of six commonly used terms for glomerulonephritis syndromes is presented in Table 1. There is a correlation between histological findings and clinical signs, but the correlation is not good enough to allow diagnosis without a renal biopsy. A direct consequence of the central role for renal biopsies is that indications and contraindications for this procedure have an immense affect on the number of individuals who receive a diagnosis of glomerulonephritis. This blurs the picture for anyone interested in genetic or environmental influence on glomerular diseases.

Table 1
Syndromes of glomerulonephritis.

Syndrome	Proteinuria	Hematuria	Reduced GFR
Urinary abnormalities (UA)	+–++	+–++	–
Recurrent macroscopic hematuria (RMH)	0–+	++	0–+
Chronic glomerulonephritis (CGN)	+–++	+–++	+++
Rapidly progressive glomerulonephritis (RPGN)	+–++	++–+++	+++
Acute glomerulonephritis (AGN)	+–+++	++–+++	+–++
Nephrotic syndrome (NS)	+++	0–++	0–++

2.2. Renal biopsy

Renal biopsy registries are major sources of information, when trying to analyze differences in the epidemiology of glomerular disease, but there are several caveats to consider. A needle biopsy is an invasive procedure, which is accompanied with a small, but potential risk of a major bleeding. A renal biopsy is only justified if the information gained may alter the medical care for the individual patient. When new therapies are introduced, this affects the diagnostic practices. Renal biopsies are rarely performed in outpatients, and renal pathology service is usually restricted to tertiary referral centres and university clinics. Socioeconomic factors influence the likelihood to get access to biopsies when needed, which limits the possibilities to study the effect of such factors on the incidence of glomerulonephritis.

Patient age has a major impact on the decision to perform a biopsy [1]. The percentage of patients being elderly at the time of biopsy varies considerably between centres and over time. In a study based on a Chinese registry the percentage of patients >60 years with primary glomerular disease increased from 0% in 1993 to 9% in 2007 [2,3]. In Serbia during the period 1987–2006 only 8.5% of the 1626 patients were above 60 at the time of biopsy [4], while in Spain 26% of the adult patients were above 65 [5].

Persistent urinary abnormalities (UA) are common, and surveys indicate that low-grade hematuria and/or proteinuria are to be found in 2–5% of the population. Only a small fraction of these individuals will eventually progress to end-stage renal disease, and biopsy is not generally indicated [6,7]. There exist, however, substantial variations between countries, in the Limburg region in the Netherlands 46% of the biopsies were done with UA as the indication [6], while in Serbia [4] and China [3] the corresponding figures were 29% and 16%. For other indications such, as the nephrotic syndrome in young adults, one can assume smaller variations in clinical practices between hospitals and regions. Consequently, when trying to compare incidence between countries it is more reliable to compare the proportion of patients with a certain diagnosis with the nephrotic syndrome, than to compare the proportion of patients in a total registry having this diagnosis.

Furthermore the renal biopsies are usually examined not only by light microscopy but also by immunofluorescence (IF) and electron microscopy (EM). Even though IF is absolutely required for some diagnoses, not all biopsies are subjected to this examination in some series [4], while in other series such specimens are considered inadequate and not counted. In a similar fashion certain diagnoses, such as thin basement membrane disease, cannot be made without EM.

Renal biopsy is not considered to be indicated, when the diagnosis can be made with reasonable certainty without histology. This is the case for acute tubular necrosis in acute renal failure, minimal change disease in young children with the nephrotic syndrome and diabetic nephropathy in patients with diabetes mellitus and chronic proteinuric renal failure. In such cases most nephrologists order a needle biopsy only if there are inconsistent signs. However, huge differences exist on what emphasis to put on different signs of inconsistency.

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