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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.

Contents

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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.

3. Anti-GBM disease

3.1. Major clinical findings

Goodpasture's disease, also known as anti-GBM disease, is a rare autoimmune disease. The patients develop autoantibodies against the non collagenous domain 1 of the α3 chain of type IV collagen (α3(IV) NC1) leading to glomerulonephritis and lung hemorrhage [8]. Patients experience a rapid progression to renal failure and death if the disease is not recognized and treated early.

The typical presentation is that of a reno-pulmonary syndrome i.e. the combination of renal and pulmonary insufficiency. However, many other types of presentations have been described. In some series, more than 50%, of the patients present with only renal involvement [9]. Virtually all have microhematuria, many have macrohematuria and rapidly progressive renal insufficiency is common. Sometimes the progression is explosive leading to anuria within days, while a minority of cases experience a protracted a course where the renal function is preserved for several months. The presenting symptoms for patients with lung involvement are hemoptysis, exertional dyspnoea, cough and fatigue. The hemorrhage occurs mainly into the alveolar spaces and may result in marked iron deficiency anemia or exertional dyspnoea even in the absence of hemoptysis. In rare cases patients have disease manifestations that are confined to the lungs.

3.2. Histology and pathogenesis

Light microscopy typically reveals general widespread crescent formation. The percentage of glomeruli exhibiting crescents often exceeds 80%, and the percentage usually correlates to renal function as well as outcome after treatment. The typical finding in direct immunofluorescence microscopy is a linear staining of IgG along the GBM, often accompanied by C3 deposition. Other staining patterns are sometimes seen, especially in mild cases with preserved renal function as well as in severely damaged glomeruli.

Numerous animal models have been described showing the pathogenic role of the anti-GBM antibodies. In a classic experiment, primates developed glomerulonephritis after injection of autoantibodies eluted from the kidneys of a nephrectomised patient suffering from anti-GBM disease [10]. Temporal relationships between relapse and reoccurrence of autoantibodies have also been reported. The titer of circulating anti-GBM antibodies, as measured by ELISA, has been shown to have prognostic importance [11]. Patients have a polyclonal immune response and develop autoantibodies to different parts of the antigen [12]. Two major epitopes have been identified [13], but only antibodies against one reflect the toxicity of the antibodies [12]. This epitope is situated near the triple helical junction. The epitope is a cryptotope and accessibility for the anti-GBM antibodies is normally limited. The cryptic properties have recently been shown to be due to cross-linking of the NC1 hexamer of type IV collagen [14]. There is evidence for a T-cell component in anti-GBM disease. The autoantibody IgG subclass distribution is compatible with a T-cell mediated reaction towards a protein antigen. A mononuclear interstitial cell infiltrate is invariably seen in human anti-GBM disease, consisting mainly of $CD4^+$ cells. Animal models indicate a role of autoreactive T-cells and immunization with a short peptide, i.e. the T-cell epitope, can induce florid glomerulonephritis without measurable levels of anti-GBM antibodies [15].

3.3. Geoepidemiology

Published patient series have come from New Zealand, Australia, UK, the US, China, and Scandinavia and estimated frequencies vary from 0.5 to 1 case per million inhabitants per year. No major differences between Asian and Caucasian populations are found, as seen in many other diseases. There are two peaks of age-dependent incidence, in the third and in the seventh decades. The disease is uncommon before puberty and the male to female ratio is about equal [9,16,17].

Genetic studies have revealed a strong link to exist between anti-GBM disease and HLA-DRB1*1501 and DRB1*1502. Most reports stem from Caucasian populations where the DRB1-15 antigen is found in 70–80% of patients, compared to 20–30% of the controls. A negative link is found to HLA-DR7 and DR1, thus acting protective [16].

3.4. Environmental agents

Several attempts have been made to find an association with viral infections but only anecdotal case reports have been published. Some reports describe the development of anti-GBM disease after lithotripsy treatment for renal stones, but this association was not confirmed in a larger study [18]. Exposure to chemical agents, such as organic solvents and cigarette smoke has also been proposed to be implicated [19]. However there is no evidence that any of these factors can induce disease alone, although it is likely that all of them can turn an ongoing subacute disease into an acute one. The limited epitope recognition is compatible with a potential role for molecular mimicry or self-immunization with fragments of the antigen. There are reports that environmental factors such as cigarette smoke or other inhaled fumes may predispose for lung manifestations of the disease [19].

4. IgA-nephritis

4.1. Major clinical findings

IgA nephritis was originally described as recurrent macroscopic hematuria and mesangioproliferative glomerulonephritis with IgA deposits in the mesangial area. It was considered as a benign disease occurring preferentially in young males. Later it became evident that a proportion of the patients progressed to end-stage renal disease, and that some patients had progressive disease without episodes of macroscopic hematuria [20]. Other presentations have also been described such as nephrotic syndrome (12%) and acute renal failure (9%) [21].

4.2. Histology and pathogenesis

The defining feature is the depositions of IgA in the mesangium. The IgA is often accompanied by C3 and to a lesser extent by IgG and C4. The degree of hypercellularity differs, but it is usually an increase in the number of cells in the mesangial area as well as an increase of the mesangial matrix. Most of the deposited IgA are of the IgA1 subclass and many patients have also high circulating amounts of this subclass. There are probably many reasons why IgA1 can bind and get deposited in the glomeruli, since this occurs as a secondary phenomenon in many diverse conditions, including liver cirrhosis, HIV and dermatitis herpetiformis [22]. In primary IGAN chemical investigations have revealed that IgA1 molecules from patients differ in their glycosylation pattern as compared to IgA1 from healthy subjects [20]. Short O-linked glycans in the hinge region lack terminal residues, which might reduce hepatic clearance and trigger the formation of IgG anti-IgA autoantibodies and immune complex formation [23]. It's possible that the formation of IgG anti-IgA antibodies is necessary to induce sufficient inflammation for the disease process to lead to permanent renal failure.

4.3. Geoepidemiology

IgA nephropathy is the most common form of primary GN worldwide, but seems to be more dominant in Asia as compared to Europe and North America [22]. In the registry study from China cited in Table 2, IGAN constituted more than half of the cases of biopsy proven GN [3]. IGAN is considerably less common in Europe but figures around 30% of biopsies from patients with primary GN are common in recent reports [6,24]. In the

Table 2
Distribution of selected GN among adults in different biopsy registries.

Country	Period	Disease	All biopsies	Primary GN	NS
China (3)	1993–2007	*n*	5398	3310	
		IGAN	33.5%	54.3%	
		MN	9.3%	15.0%	
		MPGN	0.6%	1.1%	
Korea (33)	1973–1995	*n*	2097	1732	
		IGAN	22.1%	26.8%	
		MN	11.8%	14.3%	
		MPGN	5.9%	7.1%	
USA (25)	2001–2005	*n*		1228	
		IGAN		6.9%	
		MN		6.8%	
		MPGN		1.2%	
Spain (5)	1994–2001	*n*	8439		
		IGAN	13.4%		5.0%
		MN	9.5%		25.2%
		MPGN			6.7%
		GP	(>0.9%)		0.1%
Netherlands (6)	1978–2003	*n*	1209	503	352
		IGAN	12.2%	29.4%	6.0%
		MN	10.1%	26.0%	31.0%
		MPGN	2.4%	5.8%	4.0%
		GP	1.3%	n.a.	0.3%
Serbia (4)	1987–2006	*n*	1626	1042	587
		IGAN	7.7%	12.0%	5.2%
		MN	12.6%	19.7%	32.2%
		MPGN	6.8%	10.6%	15.0%
Italy (24)	1996–2000	*n*	9878	6990	4314
		IGAN	23.4%	33.6%	5.0%
		MN	16.5%	23.4%	32.5%
		MPGN	4.7%	6.6%	6.0%

US substantially lower figures are usually presented, but a recent study found a figure of 14.2% among young adults [25]. Ethnicity has a major impact on the prevalence of IGAN in the US, the disease is rare among Afro-Americans, but seems to be more common among Asians and Caucasians [25]. This suggests that genetic factors are of importance, but a major role for MHC and IgA2 allotypes has been ruled out [26]. Several family clusters of IGAN have been reported but genetic linkage analysis has pointed at different gene loci in different kindred's [23]. IGAN is more common in men than in women, ratios vary between 1.8:1 [25] and 1.14:1 [3] in different reports.

4.4. Environmental agents

There is a strong correlation between exacerbations of the GN and infections, especially upper respiratory infections. This correlation hints that respiratory tract pathogens might harbour an etiological role in this disease, but this is far from proven. Despite many attempts no single microorganism has been singled out as the main culprit. In order to reduce the burden of respiratory pathogens, tonsillectomy has been tried and advocated for [27].

An adverse reaction to food antigens has been suspected. In support of this notion it has been shown that a correlation between celiac disease and IGAN exists [28]. There are reports about improvement after dietary changes, such as the exclusion of gluten. The higher frequency in men can be explained by genetic or hormonal factors, but is also compatible with the assumption that industrial occupational exposures play a role. There are also reports about an association between organic solvent exposures and at least the progression rate of IGAN [29].

5. Membranous nephropathy

5.1. Major clinical findings

The vast majority of patients diagnosed with MN have a nephrotic syndrome (NS). This is evident in Table 1, and in the Italian registry 86% of the patients with MN had a biopsy performed because of NS [24]. MN can sometimes occur secondarily to other disease processes such as infections and cancer, and it can develop as a complication to certain drugs [30]. Idiopathic MN constitutes around 2/3 of all MN, at least in the industrialized world. Most patients have normal renal function at the time of diagnosis but in those with persistent nephrosis a substantial number progress to end-stage renal disease.

5.2. Histology and pathogenesis

The key pathological feature is the deposition of immune complexes on the urinary side of the glomerular basement membrane. These deposits can be seen directly by light microscopy as small spikes when using silver stains, but they are better visualized using EM or IF. The typical IF finding in idiopathic MN is a course granular staining of IgG which distinguish it from the membranous variant of Lupus nephritis, where typically all classes of immunoglobulin are present. An animal model of MN, called Heyman nephritis, was developed more than 50 years ago [31]. This model is driven by autoantibodies raised against tubular epithelial cells. For a long time searches for pathogenic autoantibodies in human MN were fruitless, but recently compelling evidence was published pointing to the presence of autoantibodies directed against a podocyte antigen named phospholipase A2 receptor [32].

5.3. Geoepidemiology

The prevalence of MN secondary to infection varies in accordance with the epidemiology of the infections. In countries where Hepatitis B and malaria are endemic, secondary MN is the leading cause of NS among children and young adults [30]. For idiopathic MN there are no clear differences in the incidence between countries, as shown in Table 2, MN constitutes between 12 and 23% of the patients with primary GN. Most of the variations can be explained by different case mix between UA and NS. Yearly incidence rates are in the range of 1 per 100,000 inhabitants per year. Most reports show a male preponderance, with a ratio that varies between 1.3:1 [3] and 2.2:1 [33].

5.4. Environmental agents

It is clear that exogenous chemicals may induce MN. The two anti-rheumatic drugs gold salts and penicillamine are well known to be associated with MN as a side-effect. To what extent idiopathic MN is caused by occupational exposures is unknown.

6. Membranoproliferative glomerulonephritis

6.1. Major clinical findings

MPGN is not a diagnostic label for one disease, but rather a description of a pattern of glomerular reactions to a variety of causes, i.e. infections, complement activation in systemic diseases, mutations of components of the complement system, and autoantibody formation. It most often affects young adults and children with 50% being primary and the other half being secondary due to infections, cryoglobulinemia, or systemic autoimmune disease [34]. MPGN typically manifests with proteinuria, hematuria, acute nephritic or nephrotic syndrome. MPGN patients have a poor prognosis and many progress to end-stage renal failure already during childhood. The most common clinical symptoms of MPGN are nephrotic syndrome (35%), nephritic syndrome (17%) or gross hematuria [35]. Negative predictors for outcome are the percentage of crescents, impaired renal function, hypertension and nephrotic range proteinuria.

The diagnosis is based on kidney biopsies (see below) but serological characteristics are low levels of complement factors C1q, C3 and C4 and sometimes the presence of the nephritic factor (C3Nef).

6.2. Histology and pathogenesis

Three distinct types of primary MPGN have been described on the basis of histological findings, MPGN I, II and III. The light microscopy features and clinical presentation are similar among the three types of MPGN. Morphological changes seen in light microscopy are typically hypercellular glomeruli with proliferation of endothelial and mesangial cells leading to a lobular aspect of the capillary tuft. In recent years disturbances of the complement system and its regulatory factors were found to be important in the pathogenesis [36]. Types I (MPGN I) and III (MPGN III) are variants of immunocomplex-mediated diseases, and characterized by persistently low C3 serum level and in about 30% of the cases by the presence of C3NeF. Other disturbances of the complement system include factor H dysfunctions or deficiencies, dysfunctional C3 molecules and reduced factor B levels.

Type II (MPGN II), also known as dense-deposit disease (DDD), has no known association with immune complexes, but is caused by dysregulation of the alternative complement pathway either via the presence of C3NeF, or by defects of regulatory proteins, e.g. Factor H. In MPGN II hypocomplementemia is often observed with low C3 levels in the fluid phase, but normal C1q and C4 levels. EM analysis demonstrates the presence of electron-dense deposits along the glomerular basement membrane, which is the diagnostic hallmark for MPGN II. IF shows deposition of complement proteins, including C3, properdin and terminal complement components and generally the absence of IgG [37]. MPGN II characteristically progresses to end-stage renal failure and the recurrence rate in kidney transplants is also near 100% [38]. C3NeF is an autoantibody found in 80% of cases and which represents a major factor for the autoimmune pathogenesis. C3NeF is directed against the C3 convertase C3bBb, one of the focal points of complement activation. This C3-converting enzyme cleaves and activates C3 and has a short half-life. C3NeF prolongs the half-life of the convertase and makes the enzyme less susceptible for Factor H- and Factor I-mediated inactivation [39]. Increased C3 convertase activity results in enhanced C3b and C3a generation and C3 consumption, resulting in low C3 and factor B plasma levels. C3NeF represents a heterogeneous group of IgG and IgM antibodies and in some cases the function may also be properdin-dependent.

MPGN III shows a similar pattern as in MPGNII on immunofluorescence and immunohistology with the exception that also subepithelial immune complex deposits occur. On electron microscopy, however, usually a more marked distortion of the GBM by massive amounts of electron-dense deposits on both sides of the GBM is seen and this aspect is clearly different from the findings in the other types of MPGN [40]. Type III of MPGN is rare (approximately 15% of all MPGN) and it is related to C3 and properdin and invariably also to immune complex and C1q depositions mostly due to secondary causes (i.e. hepatitis B and C).

6.3. Geoepidemiology

Data from kidney biopsy registers show that MPGN is the most common type of GN in Eastern Europe, Africa and parts of Asia with a prevalence of up to 30% [35]. In Western Europe the prevalence of MPGN lies around 6% of patients with biopsy proven GN [6,24] with a marked decrease in the prevalence over the last decade probably due to a better therapeutic management of underlying diseases. In a report from China MPGN constituted only about 1% of primary GN [3] and in a recent retrospective US study in 1228 kidney biopsies from patients with primary GN a percentage of 1.2% in adults and 0.2% in young adults (20–39 years) was found for MPGN [25]. Another US study reported an age- and sex-adjusted incidence rate for MPGN of 0.1–0.6 per 100.000 residents between 1974 and 2003 [21].

6.4. Environmental agents

MPGN can be divided into conditions with or without mixed cryoglobulinemia. MPGN with cryoglobulinemia is likely to develop in conjunction with Hepatitis C infections (70–90% of patients) or other infections, i.e. bacterial endocarditis or hepatitis B. It is also associated with systemic vascular diseases, i.e. SLE or in situations of malignancies. MPGN without cryoglobulinemia is associated with other bacterial infections, i.e. endocarditis or abscess, infected ventriculo shunt, or viral infections, i.e. HBV, HCV, HGV, HIV and Hantavirus. It can also be found together with other diseases such as SLE, hypocomplementemic vasculitis and malignancies. Other common reasons are hereditary and acquired complement deficiencies

7. Summary

Autoantibodies of IgG class can be found in several forms of primary glomerulonephritis and seem to be of paramount importance for pathogenesis, which entitles these diseases to be considered to be of autoimmune origin. The autoantibodies are directed either to molecules within the glomerular tuft, such as the GBM in GP and to the podocytes in MN, or to components of the immune system such as C3 convertase in MPGN and IgA in IgAN. 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.

Take-home messages

- Autoantibodies are important in the pathogenesis of glomerulonephritis.
- In MN and anti-GBM disease the autoantibodies are directed against components within the kidney.
- In MPGN and IGAN autoantibodies are found against components in the immune system, i.e. complement and Ig molecules.
- Different indications for taking a biopsy in different countries make it hard to compare results from different countries.
- Epidemiological figures calculated from biopsy-based studies are very similar when comparing Europe and China, but very different from studies performed in the US.

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