# Contents

Chapter 1

# A definition, modern classification, and global epidemiology of primary glomerulonephritis

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## Definition

The term *glomerulonephritis* (GN) nominally indicates an inflammation of glomeruli. Not all the glomerular diseases necessarily show an inflammatory component at histologic examination. Accordingly, some investigators feel correct to limit the term GN only to those glomerular diseases that show signs of inflammation (Sethi et al., 2016). On the other hand, primary GN diseases are caused by disorders of the adaptive immunity triggered by the activation of the innate immunity with consequent production of an inflammatory microenvironment. This may legitimate using the term GN to indicate all the diseases that mainly affect the glomeruli of both kidneys. Although the terms GN and glomerulopathy are interchangeable, GN is frequently used more from a traditional and historical perspective, rather than for accuracy.

## Classification of glomerular diseases

Many different criteria exist for classifying the glomerular diseases, including those within the broad term of GN. Many classifications have been based on clinical features at presentation. At the beginning of the twentieth century, Friedrich Müller (1906) proposed the term *nephrosis* to define those kidney diseases characterized by degenerative lesions without any sign of inflammation. In 1914, Franz Volhard and Theodor Fahr introduced a novel classification of renal diseases based on differentiation between degenerative (nephroses), inflammatory (nephritides), and arteriosclerotic (scleroses) diseases. In 1947, Henry Christian of Boston first used the adjectival form of nephrosis—nephrotic syndrome (see Glassock et al., 2015). About ten years later, Berman

and Schreiner (1958) and Derow (1958) proposed that the term *nephrotic syndrome* be used to indicate a condition characterized by marked proteinuria ≥3.5 g/24-hours associated with hypoalbuminaemia, and variable degrees of hyperlipidaemia and peripheral oedema. In contrast, the term *nephritic syndrome* was first used to indicate symptoms and signs that can be associated with inflammation of glomeruli, such as macroscopic or microscopic haematuria, often also associated with variable degree of proteinuria, hypertension and renal function deterioration (Wilson et al., 1947). Thus, according to the presence of either of these two syndromes a clinical classification of glomerular diseases can be based on nephrotic syndrome or nephritic syndrome. However, both syndromes may be concomitant (nephrosis-nephritis) in some instances and in other cases the initial symptoms and signs reliably predict the nature of the underlying glomerular damage.

Another classification of GN was based on the time of appearance and duration of the disease, i.e. acute, subacute or malignant, and chronic GN (Reubi, 1955). However, this classification was also affected by many biases and often led to misunderstanding between clinicians and pathologists (Mihatsch, 1979). Most current students of GN classification agree that the glomerular diseases should be differentiated into primary (the disease is caused by factors intrinsic to the kidney, and which are often unknown or idiopathic) and secondary (the glomerular disease is associated with systemic diseases such as diabetes mellitus or amyloidosis). Accordingly, a classification of glomerular diseases should take into account the possible aetiology and the diseases should be subdivided into primary or secondary forms. A clinical classification of GN can be also based on five major clinical syndromes: acute GN, rapidly progressive GN, chronic GN, the nephrotic syndrome, and asymptomatic urinary abnormalities (Glassock et al., 1991).

In 1946, Bell proposed the term *membranous* glomerulonephritis to describe a new category of glomerular disease. A few years later, kidney biopsy was introduced into clinical practice (Iverson and Brun, 1951; Kark and Muehrcke, 1954). This technique allowed to better elucidate the spectrum of morphologic types of glomerular lesions and their severity. In 1957, David Jones fully illustrated the special features of membranous nephropathy and demonstrated that they were not shared by other renal lesions. Pathologists also demonstrated that the so-called *lipoid nephrosis* in children was associated with minimal glomerular lesions at optical microscopy and by effacement of podocyte foot processes on electron microscopy, without significant deposits of immunoglobulins or complement on immunofluorescence (Joekes et al., 1958; Folli et al., 1958; Caulfield, 1964). In 1957, Arnold Rich reported that, in a number of children, some glomerular tufts in the juxtaglomerular region may show capsular adhesion and

segmental sclerosis. These features were confirmed by other investigators, who proposed to adopt the term focal segmental glomerulosclerosis to define this pathological lesion (Kark et al., 1958; Heptinstall and Joekes, 1959; White et al., 1970; Habib and Gubler, 1973; Cameron et al., 1973). Habib and Kleiknecht (1971) pointed out that the glomerular lesions may be 'minimal', indicating that the glomeruli are normal or slightly modified, 'focal', indicating that, by light microscopy, a limited number of glomeruli are affected, and the remaining are normal, or 'diffuse', indicating generalized glomerular involvement, although not uniform in the degree or type.

With the exception of nephrotic syndrome in children, which is usually subdivided into steroid-sensitive and steroid resistant forms on the basis of clinical response to glucocorticoids, the most frequently used contemporary classification of glomerular diseases is a pathological one, mainly based on the results of optical microscopy, supplemented by immunofluorescence and electron microscopy. The current classification takes into consideration primary and secondary glomerular diseases. Among primary glomerular diseases, the clinical–pathological classification considers minimal change disease (MCD), focal and segmental glomerulosclerosis (FSGS), membranous nephropathy (MN), membranoproliferative GN (MPGN), infection-related GN, immunoglobulin A nephropathy (IgAN), and pauci-immune (renal limited) necrotizing and crescentic GN (KDIGO, 2012). However, recent advances in the knowledge of mechanisms responsible of GN impose the necessity to review and modify the current pathological classification. In some subtypes of primary GN in which the cause of GN has been identified the term *idiopathic is no longer relevant as a modifier*. For example, the term focal and segmental glomerulosclerosis refers to a phenotypic expression of different disorders that may have different pathogenesis, clinical outcome, and response to therapy. Primary FSGS is now considered as a podocytopathy characterized clinically by the presence of nephrotic syndrome in a patient with an FSGS lesion on light microscopy and widespread foot process effacement on electron microscopy. Thus, FSGS is a lesion, not a specific disease. Many genetic defects localized to the podocyte can be seen in children (Ranganathan, 2016) and adults (Gast et al., 2016) with FSGS. Exome capture has identified many new monogenic causes of familial FSGS. The presence of apoliprotein-L1 (APOL1) variants, related to the increased *APOL1* gene expression (Heymann et al., 2017), in patients of African descent confers seventeenfold higher odds for FSGS and twenty-nine-fold higher odds for HIV-associated nephropathy (Kopp et al., 2011), suggesting the existence of a particular form of APOL1-related FSGS. The cases of FSGS lesions characterized by the absence of nephrotic syndrome and the presence

of segmental foot process effacement by electron microscopy are generally secondary to adaptive haemodynamic changes, infection, or exposure to drugs and should be considered as secondary forms (Sethi et al., 2015). The discovery that in most patients MN is caused by circulating antibodies directed against specific epitopes of some podocyte proteins identifies the disorder as an autoimmune disease and renders the term idiopathic obsolete (Beck et al., 2009; Glassock, 2012; Tomas et al., 2014; Fresquet et al., 2015; Kao et al., 2015). Six different pathologic variants of IgAN have been identified that can help to integrate prognostic significance independent of the clinical data (Working Group of the International IgA Nephropathy Network and the Renal Pathology Society, 2009). Until recently, MPGN has been classified as type I, type II, and type III based upon electron microscopy findings. Type I is characterized by immune deposits in the mesangium and subendothelial space. Type II (also called dense deposit disease, or DDD) is characterized by dense ribbon-like deposits along the basement membranes of the glomeruli and tubules. Type III is characterized by subepithelial deposits in addition to mesangial and subendothelial deposits. However, this classification cannot differentiate between immune complex-mediated and complement-mediated MPGN, an entity characterized by overactivation of the alternative pathway of complement (Servais et al., 2007). Thus, Sethi and Fervenza (2011 and 2012) proposed a new classification based on immunofluorescence results for immunoglobulin and complement deposition. Accordingly, it is now recognized that MPGN is a histological 'pattern of injury' in the same league as FSGS, and not a specific disease. This pattern may be caused either by immune-complexes or by dysregulation of the complement alternative pathway (e.g. C3 glomerulopathy), or, rarely, by chronic relapsing endothelial injury in thrombotic microangiopathy, without deposits of complement or immunoglobulins. Immunoglobulin-dominant MPGN, which is associated with autoimmune diseases, chronic infections, or monoclonal gammopathies with or without cryoglobulins, is now considered as a secondary GN. Instead, the cases in which the sole or dominant immunoreactant in the renal tissue is C3 are classified as primary GN and are defined as C3 glomerulopathy. The morphological phenotypic aspects of C3 glomerulopathy may be either those of DDD, characterized by dense osmiophilic deposits, or those of C3 glomerulonephritis, which shows isolated deposits and a histologic aspect of type I MPGN (Sethi and Fervenza, 2012; Pickering et al., 2013; Cook and Pickering, 2015). Many cases of crescentic GN have been discovered to be ANCA-positive vasculitis with predominant involvement of the kidney (Berden et al., 2010; Quintana et al., 2014). Finally, a number of less frequent primary GN are usually neglected in the different classifications used.

On the basis of the current knowledge, an aetiopathogenetic classification has been proposed by Mayo Clinic/Renal Pathology Society (Sethi et al., 2016). Five classes have been recognized:

1. Immune-complex GN
2. Pauci-immune GN
3. Anti-glomerular basement membrane GN
4. Monoclonal immunoglobulin GN
5. C3 Glomerulopathy

This classification is etymologically correct since it considers only GN characterized by increased glomerular hypercellularity caused by proliferation of indigenous cells and/or leukocyte infiltration. However, it does not include a number of proliferative GN, e.g. pure mesangial proliferative GN, IgM GN, C4 GN, and nonproliferative glomerular diseases, e.g. MCD, FSGS, MN, that may be considered as podocytopathies, but that are usually classified as GN (KDIGO, 2012). On the other hand, most glomerular diseases, including the so-called podocytopathies, are considered to be immune-related diseases (Couser and Johnson, 2014). It is now accepted by immunologists that the immune response is initiated by the activation of innate immunity with production of an inflammatory micro-environment. Thus, from a pathogenetic point of view, the immune-mediated glomerular diseases, including those without signs of inflammation at optic microscopy, might be classified as GN. Finally, the Mayo Clinic/Renal Pathology Society does not separate primary GN, in which the immune attack is limited to the kidney (Box 1.1), from secondary GN, in which the glomerular disease may be associated with systemic autoimmune diseases, infection, malignancy, or may be triggered by exposure to drugs or toxins. In this book we maintain the standard pathologic classification of primary GN, but the term C3 glomerulopathy and idiopathic MPGN will be used instead of MPGN.

## Epidemiology of primary glomerular diseases

Little is known about the worldwide epidemiology of primary glomerular diseases. A large source of information comes from McGrogan and colleagues (2011), who conducted a systematic review of studies published between 1980 and 2007. The inclusion criteria were that the studies reported original work, that the study reported incidence of specific forms of glomerular disease with reference to a denominator population, that the estimates of population size and person-time contributed were accurate, and that efforts had been made to ascertain all incident cases. In most cases, primary GN was classified by renal

## Box 1.1 List of primary glomerular diseases

- Minimal change disease
- Focal segmental glomerular sclerosis (excluding the histological pattern of FSGS secondary to well-defined causes)
- Membranous nephropathy
- Immunoglobulin A nephropathy
- C3 Glomerulopathy (DDD, C3 GN) and Idiopathic Immune Complex Membranoproliferative GN
- C4 Glomerulopathy (extremely rare)
- Infection-related and Renal-limited GN
- Renal Limited Vasculitis
- Collagenofibrotic glomerulopathy
- Thin basement membranes nephropathy
- Lipoprotein glomerulopathy
- 'Pure' mesangial proliferative GN
- IgM nephropathy
- C1q nephropathy
- Idiopathic nodular glomerulosclerosis (diabetic nephropathy without diabetes)

DDD = Dense Deposit Disease, GN = Glomerulonephritis

biopsy. From their large analysis McGrogan and colleagues (2011) found that the reported incidence rates of primary GN in adults varied between 0.2 and 2.5/100,000/year, depending on the specific disease considered. More recently, in children, the annual incidence of GN has been steady at five to ten cases per 100,000 population, with the peak incidence ranging between one and eight years of age (Grenbaum, 2012). In a retrospective cohort study using two large US administrative datasets, Wetmore and colleagues (2016) found a prevalence of primary GN of 306/100,000 persons.

Among the primary glomerular diseases, *minimal change disease* (MCD) accounts for over 75 per cent of cases of nephrotic syndrome in children. According to McGrogan and colleagues (2011), the incidence rates in children were between 0.23/100,000/year and 15.6/100,000/year, being between

0.23–2.8/100,000/year in Caucasian children, 2.4/100,000/year in Hispanic children, 3.4/100,000/year in Afro-Caribbean children, 7.2–11.6/100,000/year in Arabian children, and 6.2–15.6/100,000/year in Asian children who resided in the UK. The exact prevalence is unknown, but it may be estimated at approximately ten to fifty cases per 100,000 children (Vivarelli et al., 2017). A systematic review on the epidemiology of histologically proven glomerular diseases in Africa between 1980 and 2014 reported that MCD was the most frequent primary GN accounting for 16.5 per cent (Okpechi et al., 2016). Another report showed that the incidence of idiopathic nephrotic syndrome in Japanese children is approximately three to four times higher than that in Caucasians (Kikunaga et al., 2017). This illustrates the great importance of geography, ancestry, and environment in determining the epidemiologic features of GN. In adults, MCD accounts for 10–15 per cent of all primary nephrotic syndrome cases undergoing renal biopsy (Waldman et al., 2007). In adolescents the incidence of MCD is similar to that observed in adults (Hogg et al., 1993).

The incidence of *FSGS* in prospective or retrospective studies, was between 0.2/100,000/year and 1.1/100,000/year (McGrogan et al., 2011). An Australian retrospective review reported higher rates of 2.5/100,000/year in males and 1.8/100,000/year in females (Briganti et al., 2001). In New York, the frequency of FSGS increased from 19.3 per cent (1986–1991) and 16.6 per cent (1992–1997) to 58.5 per cent in the period from 2002 (Dragovic et al., 2005). Recent reviews from different countries also reported that FSGS was the most common cause of nephrotic syndrome (Polito et al., 2009; Woo et al., 2010; Alwahaibi et al., 2013; Golay et al., 2013; Chavez-Valencia et al., 2014; Jegateesan et al., 2016; Murugapandian et al., 2016). A survey of renal biopsies performed in the US in adults with primary glomerulopathies found that FSGS was the most common lesion (38.9 per cent) across all race and ethnic groups. The lesion of FSGS was much more frequently seen in African-Americans and patients with FSGS had the highest rate of poverty (Sim et al., 2016). In the analysis from the NEPTUNE study, FSGS was the most frequent cause of nephrotic syndrome (Gipson et al., 2016). Even in children in the last 30 years the incidence of FSGS increased by three- to fivefold (Srivastava et al., 1999; Filler et al., 2003). It should be noted, however, that in an undefined number of cases, FSGS was secondary to other diseases or pathologic conditions.

The incidence of *membranous nephropathy* in children and adolescents ranged between 0.02/100,000/year to 0.09/100,000/year (McGrogan et al., 2011); in adults, MN develops between 50 and 60 years of age, with 2:1 male predominance (Couser, 2017). The estimated incidence of MN in adults is around 1.2/100,000/year (McGrogan et al., 2011; Couser, 2017). Surveys in

different countries reported that MN was the most frequent cause of nephrotic syndrome among primary GN (Polenakovic et al., 2003; Zhou et al., 2011; Ozturk et al., 2014), particularly in elderly subjects (Moutzoris et al., 2009; Yokoyama et al., 2012; Jin et al., 2014; Rollino et al., 2014; Maixnerova et al., 2015), while in other series it was the second cause of nephrotic syndrome after FSGS (Chavez-Valencia et al., 2014; Gipson et al., 2016; Sim et al., 2016; Jegateesan et al., 2016; Murugapandian et al., 2016). It is generally assumed that MN is more frequent in males but McGrogan and colleagues (2011) determined that there was insufficient information to conclude reliably whether there is a difference in risk between males and females.

*IgA nephropathy* often presents with asymptomatic microscopic haematuria and mild or absent proteinuria. The different policies used for renal biopsy in patients with isolated microscopic haematuria may render difficult to estimate the real incidence of IgA nephropathy. At any rate, studies in children based on renal biopsy estimated an incidence ranging between 0.31 to 0.57/100,000/year (Sehic et al., 1997; Coppo et al., 1998), while a Japanese study based on screening reported an incidence of 4.5/100,000/year (Utsunomya et al., 2003). In McGrogan and colleagues (2011), most of the studies in adults were prospective, reporting rates from 0.2/100,000/year to 2.8/100,000/year; the retrospective studies reported a similar range of rates, from 0.4/100,000/year to 2.9/100,000/year. Taken together the available results, IgAN seems to be the most common histological feature in Europe, Asia, and the US (Gesualdo et al., 2004; Nair et al., 2006; Hanko et al., 2009; Riispere et al., 2012; Zaza et al., 2013; Xie et al., 2013; Sugiyama et al., 2013, Floege and Amann, 2016). IgAN is rare in subjects of African ancestry.

Until few years ago, the diagnosis of *membranoproliferative glomerulonephritis* was based on ultrastructural findings, namely interposition of the mesangium and a double contoured appearance of the glomerular basement membrane. As mentioned, today a histological appearance of MPGN associated with immunoglobulin deposits is generally secondary to infection or systemic diseases, while primary cases are generally associated with dysregulated activation of the alternative pathway of complement, hence the term *C3 glomerulopathy*. McGrogan and colleagues (2011) found that most cases defined as MPGN were actually secondary to acute post-infection glomerulonephritis or hepatitis B infection, making it difficult to evaluate the incidence of primary disease. According to the old classification, the general impression is that the incidence of this lesion among renal biopsies is decreasing in Western countries, while it seems to be increasing in the Danish and North-eastern Rumanian registries (Heaf et al., 1999; Volovat et al., 2013). However, the available data are deeply biased by the inclusion of cases associated with infection, cryoglobulinemia, or malignancy.