Nephrotic Glomerular Diseases

Subjects: Urology & Nephrology

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The nephrotic syndrome holds significant clinical importance and is characterized by a substantial protein loss in the urine. Damage to the glomerular basement membrane or podocytes frequently underlies renal protein loss. There is an increasing belief in the involvement of the complement system, a part of the innate immune system, in these conditions. Understanding the interactions between the complement system and glomerular structures continually evolves, challenging the traditional view of the blood–urine barrier as a passive filter. Clinical studies suggest that a precise inhibition of the complement system at various points may soon become feasible.

Keywords: nephrotic syndrome ; podocyte ; complement ; glomerular diseases ; membranous nephropathy

1. Membranous Nephropathy (MN)

MN is the most common nephrotic glomerulonephritis in adults [1]. Specific autoantibodies against podocyte-expressed phospholipase A2 receptor (PLA2R) and thrombospondin type 1 domain-containing 7 A (THSD7A) can explain about 75% of cases [2][3]. Renal biopsies are characterized by depositions of subepithelial IgG and C3, suggesting an activation of the classical complement pathway. Autoantibodies against PLA2R and THSD7A are predominantly of the IgG4 isotype. This isotype has the lowest binding capacity for the complement, so complement activation via the classical pathway is unlikely to be the primary mechanism [4]. Nevertheless, C1q and C4d deposits in the vast majority of MN support the assumption of classical activation [5][6]. On the other hand, other authors have also described the glomerular deposition of MBL in the MN. Since activation of the lectin pathway can also lead to deposits of C4d, one can interpret such findings as the primary activation of the lectin pathway [6]. However, correlations between MBL in the sera of patients and the clinical course were not meaningful. In contrast, correlations between the autoantibody titers and the clinical course are possible [7]. In addition, Bally et al. described cases of MN in patients with a genetic MBL deficiency [8]. There is also discussion about alternative complement activation in MN. Seifert et al. recently addressed the question of primary complement activation [9]. In human kidney biopsies, the authors detected deposits of C1q. As in other studies, IgG4 was the dominant isotype antibody deposition. However, Seifert et al. showed that in addition to IgG4, at least one other IgG isotype that can activate complement is deposited in the kidney. In addition, a proximity ligation assay could demonstrate a dominance of classical activation. The dominance of the classical complement activation contrasts with a study by Manral et al. Based on in vitro studies, an alternative pathway activation is primarily assumed here.

2. Membranoproliferative Glomerulonephritis (MPGN)

MPGN is a morphological pattern of glomerular changes characterized by a thickening of the glomerular basement membrane. The thickening of the basement membrane is caused by deposits of complement factors and, in some cases, immunoglobulins. MPGN can occur in numerous diseases [10]. Depending on the location of the deposits, MPGN type I shows subendothelial and mesangial deposits, type II MPGN intramembranous deposits, and type III MPGN additional subepithelial deposits. Since the composition and the localization of deposits vary, the clinical course of MPGN is very heterogeneous. A nephrotic syndrome occurs in 30–50% of cases [10][11]. The Consensus Report 2013 advocated restructuring the classification of MPGN. The objective was to pivot toward categorization based on immunohistochemical and immunofluorescence characteristics, departing from solely morphological distinctions [12][13]. A novel classification termed C3 glomerulopathy (C3G) was proposed for instances where C3 deposition surpassed that of immunoglobulins. This redefinition of C3G encompassed the patterns noted in MPGN types I and III, along with intramembranous glomerulonephritis/dense deposit disease (MPGN type II). Furthermore, the scope of diagnosing C3G was expanded beyond membranoproliferative patterns to encompass other manifestations of glomerulonephritis, such as mesangioproliferative patterns. In scenarios where immunoglobulin deposition was predominant, the nomenclature transitioned to immune complex-mediated MPGN (IC-MPGN). The evolution of this revised definition stemmed from advancements in comprehending complement-mediated kidney diseases, with C3 glomerulopathy (C3G) serving as a

prototype [14]. Within C3G, an excessive activation of the complement system has been associated with genetic mutations in various complement genes, notably Factor H, C3, and the genes encoding FHR1, FHR2, FHR3, FHR4, and FHR5. A subclass of antibodies known as nephritic factors has been identified, playing a role in stabilizing complement activation by binding to elements such as the alternative C3 convertase, C5 convertase, Factor H, C3, C3b, C3d, or Factor B. These antibodies disrupt the alternative pathway, resulting in its hyperactivation. Numerous additional mutations, predominantly affecting the alternative complement pathway, have also been identified. These mutations involve genes associated with FHR1, FHR2, FHR3, FHR4, FHR5, and C3, which encode components forming C3 or C5 convertases or regulators that govern the timing and site of C3 convertase activity [15]. However, a strict distinction between C3G and IC-MPGN is not always feasible. Patients with IC-MPGN also exhibit genetic and acquired disruptions in the alternative pathway. A retrospective study of 140 patients suffering from idiopathic IC-MPGN or C3G revealed a prevalence of genetic disorders not only in C3G, but also in IC-MPGN. The finding of mutations in the alternative C3 convertase components linked both diseases to alternative complement activation. Antibodies stabilizing the C3 convertase were also detectable in IC-MPGN, not only in C3G [16][17].

3. Lupus Nephritis (LN)

LN occurs in approximately 50–75% of cases of systemic lupus erythematosus [18]. It significantly determines the morbidity and mortality of the disease. The presence of autoantibodies, such as those against dsDNA, leads to the formation of immune complexes that can deposit in the kidneys. LN exhibits diverse clinical and morphological manifestations. Morphologically, there are six distinct types, with LN Type VI characterized by advanced sclerosis and, consequently, unresponsiveness to therapy. The focal LN (Type III) and diffuse LN (Type VI) often present a nephritic syndrome with a rapid decline in GFR. Type V LN morphologically shows a membranous pattern and frequently presents clinically as a nephrotic syndrome. Overall, LN demonstrates deposits of immunoglobulins and complement factors, often referred to as a “full-house pattern” [19]. Reduced serum levels of C3 and C4 serve as activity markers of LN [20]. Accordingly, the serum has elevated corresponding cleavage products such as iC3d, C4d, and C5b-9 [21][22]. The deposition of immunoglobulins and complement factors immediately suggests activation of the classical complement pathway in LN. This is supported by C4d deposits, which are frequently diffuse in Type III/IV LN but are subepithelial in Type V LN [23][24]. Thus, the location of complement activation and various dysregulations may lead to different types of LN [25]. Activation of the lectin pathway via increased MBL levels has also been described [26]. Another indicator of lectin pathway activation is the alteration of MASP1 and MASP2 in LN, which was observed in LN type III and IV compared to the membranous form [27]. Consequently, activation of the lectin pathway might contribute to the manifestation of different types of LN.

4. Focal Segmental Glomerulosclerosis (FSGS)

FSGS represents a histopathological description of morphological changes within glomeruli, predominantly characterized by segmental sclerosis. The challenge lies in recognizing that this histopathological pattern can emerge from many glomerulopathies. Often, FSGS represents the common endpoint of vastly different conditions mediated by adaptation (a mismatch between glomerular load and capacity), genetics, viral association (such as HIV), or medication-induced factors (e.g., lithium). In the primary form, akin to minimal change disease (MCD), there is an assumption of a circulating factor responsible for the disease [28]. Deposits of immunoglobulins like IgM and C3 are generally perceived as nonspecific. However, evidence is mounting regarding the involvement of the complement system in FSGS [29][30][31][32]. Serum studies in patients have revealed indications of complement activation, where complement cleavage products such as C3a, C5a, sC5b-9, C4a, and C4d were elevated [30][31][32]. The local regulation of complement becomes particularly intriguing. Angeletti et al. identified CD55/DAF as a crucial regulator of local complement activation in a mouse model of adriamycin-induced FSGS. A podocyte-specific knockout of DAF resulted in an increased C3b deposition in the glomeruli. The authors argue that C3a signaling in podocytes reduced nephrin expression [33]. Indeed, mutations in nephrin have been described in humans with FSGS [34]. Another study demonstrates a reduced DAF expression in FSGS patients, establishing a potential link to the human condition [35]. Even in the frequently described deposits of IgM, they might serve as effectors of the disease rather than nonspecific deposits. Trachtmann et al. describe IgM deposits in FSGS patients, correlating with deposits of complement products from the classical complement pathway. Furthermore, the authors speculate that IgM antibodies are not deposited nonspecifically but bind to glomerular antigens. It remains unclear whether antibody binding and complement activation contribute to disease onset or if these occur secondarily to glomerular damage. However, complement activation potentially contributes to disease progression.

5. Minimal Change Disease (MCD)

MCD is the most common cause of nephrotic syndrome in childhood. The disease was explicitly named due to the absence of morphological changes in light microscopy, including the absence of complement factors [36]. It is important to note that diagnosing MCD in childhood often relies not on biopsy, but on clinical criteria and response to cortisone. Biopsy for MCD is commonly performed in cases of atypical presentations or during adolescence or adulthood. This fact makes scientific analysis challenging. However, due to an immunologically mediated pathophysiology, interaction with the complement system is at least conceivable [37]. Nevertheless, current data regarding complement activation do not extend beyond measuring complement cleavage products in patients' blood. Elevated levels of C5b-9 have been observed, while serum levels of C3 and C2 were reduced [35][38]. Even measurements of serum levels of C4a were inconclusive in different studies [39]. Therefore, a clear hypothesis regarding the involvement of complement in MCD cannot be conclusively generated.

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