Overview of Complement-Mediated Kidney Diseases (CMKDs)

INTRODUCTION

- The complement system plays a key protective role in innate and adaptive immunity, but its dysregulation can contribute to CMKDs, which include the following[1-5]:
  - Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis
  - Antiglomerular basement membrane (anti-GBM) disease
  - Atypical hemolytic uremic syndrome (aHUS)
  - C3 glomerulopathy (C3G)
  - IgA nephropathy
  - Immune complex-mediated membranoproliferative glomerulonephritis (IC-MPGN)
  - Lupus nephritis (LN)
  - Membranous nephropathy (MN)

Many CMKDs are rare conditions

In contrast, IgA nephropathy is the most common form of primary glomerulonephritis

aHUS
Global incidence of **0.2 to 1.9 per million** per year[6]

C3G + IC-MPGN
US incidence of **1 to 4 per million** per year[7]

IgA nephropathy
US incidence of **7 to 21 per million** per year[8,9]

PATHOPHYSIOLOGY

The complement system comprises the classical, lectin, and alternative pathways, with activation leading to[5,10,11]:

Inflammation via release of anaphylatoxins

Cell injury via the assembly of the membrane attack complex

Immune-cell targeting and cell injury via opsonization

- In some CMKDs, complement dysregulation is caused by genetic mutations or acquired abnormalities (ie, autoantibodies)[2,3]
- Dysregulated complement activity can progressively damage the kidneys, which may be particularly vulnerable due to their[3,11]:
  - Glomerular structure
  - Immune complex deposition in the mesangium and capillary wall
  - Increased local production of complement proteins
  - Local lack of complement regulator expression

DIAGNOSIS AND PRESENTATION

- Diagnosis can be challenging due to disease rarity, as well as delays in and heterogeneity of clinical presentation[12-15]
- Kidney biopsy is the “gold standard” for diagnostic evaluation of glomerular disease, which can reveal characteristic patterns of injury and complement/immunoglobulin deposits and may be supported by autoantibody, genetic, and serum complement testing[2,16,17]
- Clinical signs are diverse but can involve hematuria, proteinuria, and decreased glomerular filtration rate (GFR)[12,15]

OUTCOMES

Many CMKDs may eventually progress to chronic kidney disease and kidney failure

aHUS

Up to ~50%
of untreated patients develop kidney failure within **5 years**[18]

C3G

30% to 50%
of patients develop kidney failure within **10 years**[19]

IC-MPGN

~40%
of patients progress to kidney failure within **10 years**[20]

IgA nephropathy

~30%
of patients with proteinuria ⩾ 1 g/day develop kidney failure within **10 years**[21]

The role of the complement system in CMKD progression is increasingly recognized but remains to be fully elucidated[5,10]

aHUS, atypical hemolytic uremic syndrome; ANCA, antineutrophil cytoplasmic antibody; C3, complement 3 protein; C3G, complement 3 glomerulopathy; C5, complement 5 protein; C5b-9, membrane attack complex; CMKD, complement-mediated kidney disease; GBM, glomerular basement membrane; GFR, glomerular filtration rate; IC-MPGN, immune complex-mediated membranoproliferative glomerulonephritis; IgA, immunoglobulin A; LN, lupus nephritis; MN, membranous nephropathy.

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