C3 nephritic factors: A changing landscape

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C3 nephritic factors (C3NFs) are a group of autoantibodies that permit continuous overactivation of the alternative complement pathway. They are associated with a range of clinical diseases, including various nephropathies, partial lipodystrophy, and retinal changes, as well as infections. C3NFs can also be identified among patients undergoing complement studies and can be a cause of diagnostic confusion.[1,2] Changes in nomenclature and treatment have prompted a new look at C3NFs.[3,4]

C3NFs AND ALTERNATIVE COMPLEMENT ACTIVATION

The phylogenetically ancient complement system has evolved as a pivotal part of the innate immune system to help protect against infections. It is composed of multiple proteins, which lead to an enzymatic cascade causing lysis of the target cell. The system is activated through the classical pathway, lectin pathway, and alternative pathway (AP). The AP is continuously active at a low rate through generation of C3b molecules, the so-called "tick-over," in which the internal thioester of C3, as hydrolyzed by water, forms an initial convertase with factor B. Factor I and Factor H regulate this pathway, and the short half-life of unstabilized C3bBb ensures the process is tightly controlled (Fig 1).

C3NFs are a group of autoantibodies that bind to the AP C3 convertase (C3bBb), increasing both convertase activity and the duration of the active forms, making it more stable (from minutes to hours).[4-6] These autoantibodies can be detected by using C3 convertase stabilizing activities, semiquantitative hemolytic assays, by measuring autoantibody levels.[6] There are various types of C3NFs, including both IgM and IgG, which can be classified by either being heat sensitive and properdin dependent or heat stable and properdin independent.[7]

C4 and classical complement pathway nephritic factors have been described but are much less well characterized. C4NF targets the classical pathway C3 convertase (C4bC2b), with a similar end point of complement pathway activation. C4NFs have been described as a cause of severe infections resulting from C3 consumption.

C3NFs are found in a small number of healthy subjects[1,2] and can be transiently induced in patients with poststreptococcal glomerulonephritis. C3NFs are most common in patients with membranoproliferative glomerulonephritis (MPGN). More than 80% of patients with dense-deposit disease (DDD) and 40% to 50% with C3 glomerulonephritis (C3GN) have C3NFs.[3,4]

CLINICAL MANIFESTATION

C3 glomerulopathy

MPGN is now classified based on immunofluorescent findings rather than light and electron microscopic findings. This classification groups patients with MPGN into those with immune complex deposition (previously MPGN type 1 and 3) versus those with complement staining with no or almost no immune complex formation (formerly MPGN type 2 [DDD]). The formation of immune complexes is usually secondary to chronic infections, autoimmune disease, or paraproteins, whereas the usually isolated deposition of C3 is secondary to chronic AP activation. Thus DDD with intramembranous isolated C3 deposition by electron microscopy and MPGN is now classified as C3 glomerulopathy.[3,4]

C3GN is a rare cause of glomerulopathy and can present with proteinuria, hematuria, nephrotic syndrome, nephritic syndrome, or nephrotic/nephritic syndrome. It most often occurs in children between the ages of 5 and 15 years. Complement studies (eg, factor levels and function) demonstrate a low serum C3 concentration and positive C3NF results. Historically, more than 50% of patients with DDD have end-stage renal disease within 10 years of diagnosis. After kidney transplantation, disease recurrence occurs in more than 80% of patients, with a graft failure rate of more than 50%. However, patients with C3GN can have a slightly better long-term prognosis than previously described.[3,4] Of note, there have been isolated reports of C3NF in patients with membranous nephropathy and poststreptococcal glomerulonephritis, with both having better clinical outcomes than patients with C3GN.

Partial lipodystrophy

Acquired partial lipodystrophy is a disease that presents in early childhood (mean, 7 years of age) and is more common in girls. It is characterized by loss of upper-extremity and facial fat with sparing of the lower extremities. It can precede kidney disease (in 22%) by 8 years or more. When present, kidney disease manifests as C3GN, with more than 80% of patients having low serum C3 concentrations in the presence of C3NFs. The mechanism of acquired partial lipodystrophy is due to AP complement destruction of adipocytes through Factor D. Prognosis depends on the renal disease, and additional systemic

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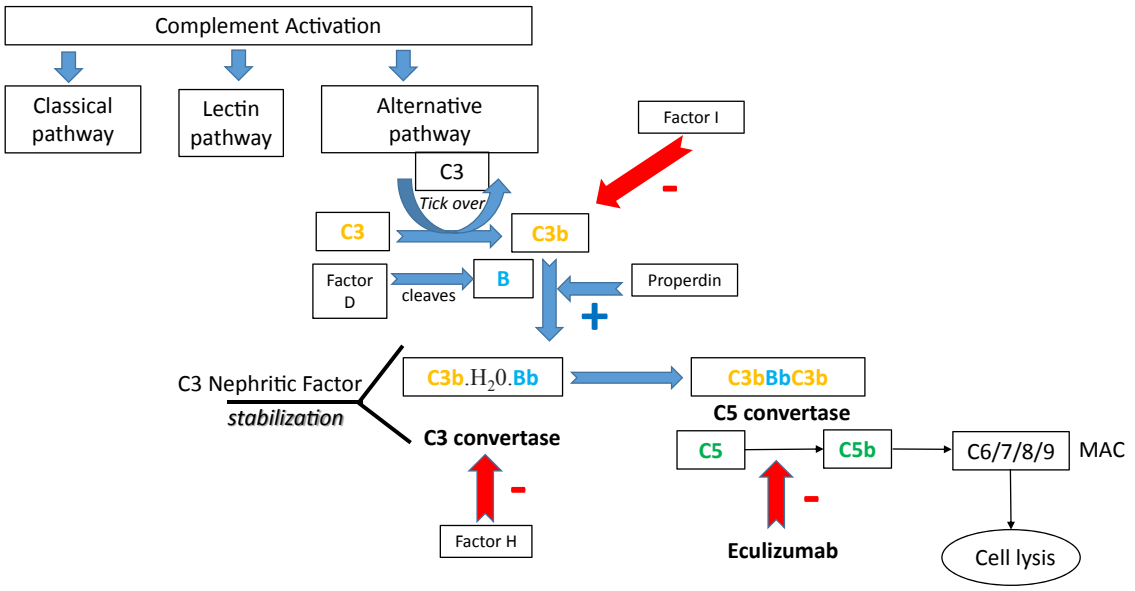

FIG 1. Alternative complement pathway activation. The AP is activated continuously by hydrolysis of C3 ($C3{\bullet}H_20$), which binds Factor B. The so called "tick-over" process involves the internal thioester of C3, as hydrolyzed by water, forming an initial convertase with Factor B subsequently cleaved by Factor D to produce the enzyme C3 convertase ($C3b[H_2O]Bb$). This fluid phase C3 convertase can be stabilized by properdin *(P)* and cleaves additional C3. Factor H binds host cell surfaces, protecting them by competing for C3b and displacing Factor B. Factor I regulates the AP by cleaving C3b and inactivating it. The enzyme C3bBbC3b is termed the AP C5 convertase. Cleavage of C5 catalyzes the assembly of C5b-C9, and this is termed the membrane attack complex *(MAC)*, a pore capable of driving cell lysis. C3NFs bind to the AP C3 convertase and by doing so increase its activity duration. Eculizumab inhibits C5 cleavage.

TABLE I. Laboratory findings among various phenotypes presenting with C3NFs

Clinical phenotype	Prevalence of C3NFs in disease state	Laboratory findings
C3 glomerulopathy		
DDD	80%	Low C3, low CH50, normal C4
C3 glomerulonephritis	50%	Low C3, low CH50, normal C4
Partial lipodystrophy	80%	Low C3, low CH50, normal C4
Macular degeneration	Unknown	Low C3, low CH50, normal C4
Healthy general population	Rare/unknown	Unclear
C4NF	Unknown	Low C3, low CH50, low C4
C3 classical NF	Unknown	Low C3, low CH50, normal C4

manifestations can include pancreatitis, liver dysfunction, diabetes mellitus, and retinitis pigmentosa.[8]

Ocular manifestations

Macular degeneration can be present in patients with C3GN. Common findings on fluorescein angiography include macular hyperpigmentation, drusen, and neovascularization. Genetic polymorphisms in the AP proteins are also associated with macular degeneration, highlighting the importance of complement in endothelial protection.[9] The pathophysiologic mechanism of macular degeneration with C3NFs is not yet clear.

DIAGNOSTIC APPROACH

C3NFs are associated with low CH50 and low C3 levels and preserved C4 levels. The presence of C3NFs is sought by means of direct autoantibody analysis and/or by using a semiquantitative hemolytic method to analyze the stability of C3 convertase.[5] The tests for C3NFs can be requested through reference laboratories as part of a complement pathway workup or through available complement study panels (Table I).

THERAPEUTIC MODALITIES

Asymptomatic patients should undergo monitoring of renal function and periodic eye examinations. Treatment of MPGN depends on the clinical presentation, with an early decrease in kidney function requiring more aggressive therapy. First-line therapy includes glucocorticoids, cyclophosphamide, mycophenolate mofetil, and tacrolimus, although success has been limited with these approaches.[3,4] Plasmapheresis with use of rituximab to remove these autoantibodies in patients with C3GN has shown conflicting results.[4]

The recent emergence of a specific humanized mAb C5 inhibitor (eculizumab) holds therapeutic promise. Multiple case

Box 1. Key points

- C3NFs are autoantibodies that activate the AP and can be found as part of a glomerulonephritis workup, as well as among asymptomatic subjects.
- MPGN has been newly classified, leading to a grouped syndrome of C3 glomerulopathy, which encompasses DDD and C3GN, both with predominant C3 deposition in the glomerulus.
- The phenotype can include lipodystrophy, pancreatitis, and macular degeneration.
- New treatment modalities, such as eculizumab, can alter the course of C3 glomerulopathy.

reports have shown benefits either before or after recurrence in the renal allograft.[10] Despite promise, further studies are required to determine long-term outcomes.

CONCLUSIONS

C3NFs are a heterogeneous group of autoantibodies that results in a secondary AP hypocomplementemia and are associated with a variety of clinical conditions (Box 1). New treatments show promise.

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