Atypical Hemolytic Uremic Syndrome

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Summary: Hemolytic uremic syndrome (HUS) is a triad of microangiopathic hemolytic anemia, thrombocytopenia, and acute renal failure. The atypical form of HUS is a disease characterized by complement overactivation. Inherited defects in complement genes and acquired autoantibodies against complement regulatory proteins have been described. Incomplete penetrance of mutations in all predisposing genes is reported, suggesting that a precipitating event or trigger is required to unmask the complement regulatory deficiency. The underlying genetic defect predicts the prognosis both in native kidneys and after renal transplantation. The successful trials of the complement inhibitor eculizumab in the treatment of atypical HUS will revolutionize disease management.

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The hemolytic uremic syndrome (HUS) is characterized by the triad of thrombocytopenia, microangiopathic hemolytic anemia, and acute renal failure.[1] The most common form of HUS is secondary to shiga toxin (Stx)-producing bacteria, typically *Escherichia coli* O157:H7. Atypical HUS (aHUS) has been used to classify any HUS not caused by Stx. A variety of precipitating events have been associated with aHUS including infections, drugs, autoimmune conditions, transplants, pregnancy, and metabolic conditions (Table 1). These have frequently been called *secondary aHUS*. With the discovery of the role of complement gene mutations in aHUS, primary aHUS has been used to refer to those cases with documented complement dysregulation. Although a useful aide memoir, these terms do not account for the increasing recognition that patients with an underlying complement risk factor often require a secondary trigger for aHUS to manifest. Classifications that take account of both the genetic background and etiologic trigger are beginning to be introduced.[2] The best estimate of aHUS incidence is 2 of 10^6 in a North American population,[3] although the precise proportion with an underlying complement defect is not known.

PATHOLOGY

In acute aHUS, the pathologic picture is of capillary thrombosis. Glomerular capillary wall thickening is seen as a result of endothelial cell swelling and accumulation of flocculent material between the endothelial cell and the basement membrane. Platelet and fibrin thrombi result in occlusion of the glomerular capillaries. Fibrinoid necrosis of the afferent arteriole associated with thrombosis also may be seen. Mesangiolysis occurs early in the disease process and subsequently is replaced by sclerotic changes. Early arterial changes are variable, ranging from only mild endothelial swelling to fibrinoid necrosis with occlusive thrombus formation. Subsequently, there is mucoid intimal hyperplasia with narrowing of the vessel lumen. Deposition of fibrin or fibrinogen in the glomeruli and in the mesangium, as well as within the vessel walls, are seen on immunofluorescence. Complement and immunoglobulin deposits along the capillary loops of glomeruli may be seen.[4]

THE COMPLEMENT SYSTEM

The complement system is an ancient defense mechanism that stimulates the inflammatory response and destroys pathogens through opsonization and lysis[5] (Fig. 1). In addition to protecting the host against invading pathogens, it bridges innate and adaptive immunity and it disposes of immune complexes and injured tissues and cells.[6]

The alternative pathway of complement (AP), which plays a key role in the pathogenesis of aHUS, is continually activated by a tick-over mechanism, and can also be triggered by the classic and lectin pathways.

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Table 1. Triggers of aHUS

Trigger	Reference
Non-Stx toxin diarrheal illnesses	51,94,95
Norovirus	161,162
Campylobacter upsaliensis	163
Clostridium difficile	164
Respiratory infections	51
Bordetella pertussis infection	10,165
Streptococcus pneumonia	166
Haemophilus influenzae	10
Other bacterial	
Fusobacterium necrophorum	167
Viral illnesses	
Varicella	168
Cytomegalovirus	169
Influenza H1N1	170
Hepatitis A	171
Hepatitis C	172
Human immunodeficiency virus	173
Coxsackie B virus	174
Epstein–Barr virus	175
Dengue	176
HHV6	177
Human parvovirus B19	178
Parasites	
Plasmodium falciparum	179
Pregnancy	51,98,180
Drugs	
Cisplatin	181
Gemcitabine	182
Mitomycin	183
Clopidogrel	184
Quinine	185,186
Interferon-alfa, -beta	187,188
Anti–vascular endothelial growth factor	189
Campath	190
Cyclosporin tacrolimus	191
Ciprofloxacin	192
Oral contraceptives	193–195
Illicit drugs (eg, cocaine, heroin, ecstasy)	196
Autoimmune	
Anticardiolipin	197
C3Nef	198
Systemic lupus erythematosus	199
Vaccination	
Hepatitis B	10
Bone marrow transplantation	200
Malignancy (gastric, breast, prostate, lung, colon, ovarian, pancreatic, lymphoma)	201
Combined methylmalonic aciduria and homocystinuria	202

In the AP, complement C3 undergoes spontaneous hydrolysis, depositing C3b onto the surface of foreign and host cells in the vicinity. On an activating surface such as a bacterium, C3b joins with factor B, which then is cleaved by factor D to form the C3 convertase, C3bBb. The binding of properdin stabilizes this enzyme. This enzyme complex then cleaves more C3 to C3b to initiate a feedback loop. Downstream of this amplification loop, C3b also may join with the C3 convertase to form the C5 convertase. C5 is cleaved to the anaphylatoxin C5a and C5b, which initiates formation of the lytic membrane attack complex (C5b–9) (Fig. 1). To protect host cells from collateral complement damage, many soluble and membrane-associated complement regulatory proteins function to inactivate complement on their surface. It is the imbalance between complement activation and regulation on host cell surfaces that underlies the pathogenesis of aHUS.

COMPLEMENT FACTOR H

Mutations in complement factor H (*CFH*) account for approximately 25% of the genetic predisposition to aHUS (Table 2).[7–15] CFH is the most important fluid-phase regulator of the AP of complement.[16] CFH is composed of 20 complement control protein modules (CCPs)[17] (Fig. 2). The four N-terminal CCPs (CCPs 1-4) mediate the complement regulatory functions of the protein by the following: (1) acting as a cofactor for factor I–mediated proteolytic inactivation of C3b, (2) competing with factor B for C3b binding, and (3) accelerating the decay of the C3 convertase into its components.

In addition to regulating complement in the fluid phase, CFH also can protect host surfaces by binding to polyanions such as the glycosaminoglycans.[18] CFH has two glycosaminoglycan binding domains in CCPs 6 to 8 and CCPs 19 and 20,[17] which have different sulfate specificities resulting in the C-terminal domains (CCP 19 and 20) being predominantly responsible for binding to kidney, and CCPs 6 to 8 being responsible for binding in the eye.[19] Other recent studies have shown that CFH also binds to the lipid peroxidation product malondialdehyde,[20] the acute phase proteins, C-reactive protein,[21–23] and pentraxin 3,[24] as well as necrotic cells.[21]

The majority of mutations in *CFH* are heterozygous, are located in CCPs 19 and 20 (Fig. 2), and do not usually result in a quantitative deficiency of CFH. Structural and functional analysis of the C-terminal mutants has revealed variable consequences on binding to heparin, C3b, and endothelial cells; however, cell surface complement regulation is consistently impaired as measured using sheep erythrocyte lysis assays[25–27] (Table 3). Thus, these C-terminal mutants are predicted to fail to control complement activation at the glomerular endothelium. In keeping with this, renal biopsy data from an aHUS patient with a C-terminal mutant showed reduced CFH binding to renal endothelium compared with wild type.[27] C-terminal *CFH* mutants also have been shown to have impaired binding to platelets resulting in increased complement activation with consequent platelet activation, aggregation, and release of tissue factor–expressing microparticles.[28]

Although *CFH* mutations cluster in the C-terminus, genetic changes are reported throughout the molecule.