

REVIEW ARTICLE

MEDICAL PROGRESS

Atypical Hemolytic–Uremic Syndrome

Marina Noris, Ph.D., and Giuseppe Remuzzi, M.D.

From the Clinical Research Center for Rare Diseases Aldo e Cele Daccò, Mario Negri Institute for Pharmacological Research (M.N., G.R.), and the Division of Nephrology and Dialysis, Ospedali Riuniti di Bergamo (G.R.) — both in Bergamo, Italy. Address reprint requests to Dr. Remuzzi at the Mario Negri Institute for Pharmacological Research, Via Gavazzeni 11, 24125 Bergamo, Italy, or at gremuzzi@marionegri.it.

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THE HEMOLYTIC–UREMIC SYNDROME IS CHARACTERIZED BY NONIMMUNE hemolytic anemia, thrombocytopenia, and renal impairment.¹ The disorder occurs most frequently in children under the age of 5 years, with an annual incidence of 6.1 cases per 100,000 children under 5 years, as compared with an overall incidence of 1 to 2 cases per 100,000. The presentation is generally heralded by diarrhea, which is often bloody.^{2,3} Most cases (including more than 90% of those in children) are secondary to infection with *Escherichia coli* serotypes O157:H7, O111:H8, O103:H2, O123, O26, or others,¹ which produce Shiga-like toxin (Stx), and several other bacteria, such as *Streptococcus pneumoniae*.⁴

Approximately 10% of cases of the hemolytic–uremic syndrome are classified as atypical, since they are not caused by either Stx-producing bacteria or streptococci.^{1,5} Atypical hemolytic–uremic syndrome has a poor prognosis, with death rates as high as 25%⁵ and progression to end-stage renal disease in half the patients.^{1,4} Research has linked atypical hemolytic–uremic syndrome to uncontrolled activation of the complement system. This article reviews current concepts about the pathobiology of this syndrome and its diagnosis and management.

THE HISTOLOGIC LESION

The lesions of Stx-related hemolytic–uremic syndrome, which are indistinguishable from those of its atypical form on the basis of standard histologic analysis, are characterized by thickening of arterioles and capillaries, endothelial swelling and detachment, and subendothelial accumulation of proteins and cell debris (Fig. 1).^{6,7} The subendothelial space is widened, and platelet thrombi obstruct vessel lumina. Hemolysis occurs, and fragmented or distorted erythrocytes are evident in blood smears. Lesions typically affect the kidney (mainly glomeruli and arterioles), although the brain, heart, lungs, gastrointestinal tract, and pancreas all may be involved.

CLASSIFICATION OF DISEASE

FAMILIAL FORM

Less than 20% of cases of atypical hemolytic–uremic syndrome are familial (Table 1). Patients with the familial form of the disease have a poor prognosis, with a rate of either end-stage renal disease or death of 50 to 80%. In 1965, a combination of hemolytic anemia and azotemia was described in concordant monozygous twins.⁸ Since that time, familial atypical hemolytic–uremic syndrome has been reported in children and, infrequently, in adults. Both autosomal dominant and recessive patterns of inheritance have been reported.⁹

SPORADIC FORM

Atypical hemolytic–uremic syndrome that develops in patients who do not have a family history of the disease is classified as sporadic. Triggers for the sporadic form

include infection with the human immunodeficiency virus, cancer, organ transplantation, pregnancy, and the use of certain anticancer drugs, immunotherapeutic agents (e.g., cyclosporine and tacrolimus), and antiplatelet agents (e.g., ticlopidine and clopidogrel).^{2,6,10}

De novo atypical hemolytic–uremic syndrome has been reported in 3.6 to 14.0% of all kidney-transplant recipients in association with humoral rejection and the use of calcineurin inhibitors.^{11–13} In approximately 10 to 15% of female patients with atypical hemolytic–uremic syndrome, the disorder develops during pregnancy or post partum.^{1,2} Approximately 50% of sporadic cases appear to be idiopathic.

Genetic abnormalities in complement system proteins have been documented in the familial form of the disease^{14–18} and also in the sporadic (mainly idiopathic) form (Table 1).^{14,19–21} Two patients with Stx-related hemolytic–uremic syndrome have been reported to have mutations in complement regulatory genes,^{20,22} but the frequency of the mutations in such patients is not known.

COMPLEMENT ABNORMALITIES

Since 1974, reduced serum levels of complement fraction C3 with normal levels of C4 have been reported in patients with atypical hemolytic–uremic syndrome.^{23–25} A low C3 level reflects complement activation and consumption (Fig. 2). Patients with the hemolytic–uremic syndrome who have low C3 levels have high levels of activated complement components, including C3b, C3c, and C3d.²⁶ Granular C3 deposits in glomeruli and arterioles during acute disease are consistent with the activation of complement and local C3 consumption.^{24,27} C9 staining in glomeruli and small arteries with intimal proliferation and thrombosis documents activation up to the final lytic C5b-9 membrane-attack complex.²⁸

The complement system consists of several plasma and membrane-bound proteins that protect against invading organisms.²⁹ Three activation pathways — classic, lectin, and alternative — produce protease complexes termed C3 and C5 convertases that cleave C3 and C5, respectively, eventually leading to the membrane-attack complex (Fig. 1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). C3 hydrolysis in plasma initiates the alternative pathway, leading to the deposition of C3b onto practically all plasma-exposed surfaces (Fig. 2A).³⁰

On host cells, complement activation is controlled by both membrane-anchored and fluid-phase regulators, favoring the cleavage of C3b to inactive C3b (iC3b) by complement factor I (CFI) (i.e., co-factor activity) and dissociating the multicomponent C3 and C5 convertases (i.e., decay-acceleration activity). Without normal regulation, C3b deposition increases by more than a factor of 20³⁰ through the amplification loop and causes activation of the complement cascade, which remains so until complement components are consumed. Foreign targets and injured cells that either do not have membrane-bound regulators or cannot bind soluble regulators are attacked by complement. On the surface of bacteria, C3b binds to specific receptors on neutrophils and macrophages, resulting in phagocytosis of complement-tagged bacteria.

The C3 convertases of the classic and lectin pathways are formed by C2 and C4 fragments, whereas the alternative pathway convertase cleaves C3 but not C4.²⁹ Thus, a low serum C3 level in a patient with atypical hemolytic–uremic syndrome who has a normal C4 level indicates selective activation of the alternative pathway.²⁵

GENETIC ABNORMALITIES

COMPLEMENT PATHWAY MUTATIONS

A variety of mutations in members of the complement pathway have been described in patients with atypical hemolytic–uremic syndrome. These mutations have been found to account for 50 to 60% of cases (Table 2, and Fig. 2 in the Supplementary Appendix).

COMPLEMENT FACTOR H

In 1981, investigators described two brothers with atypical hemolytic–uremic syndrome who did not produce complement factor H (CFH), the plasma regulator of the alternative pathway.³¹ The parents, who were first cousins, had half-normal CFH levels, indicating an inherited defect. Subsequently, complete or partial CFH deficiencies have been reported in patients with atypical hemolytic–uremic syndrome.^{25,32} In 1998, a group of investigators headed by Goodship (Warwicker et al.³³) showed an association between atypical hemolytic–uremic syndrome and the chromosome 1q32 locus, which contains genes for CFH and other complement regulators. The investigators found a heterozygous CFH mutation in patients with the syndrome and obligate carriers in one family and

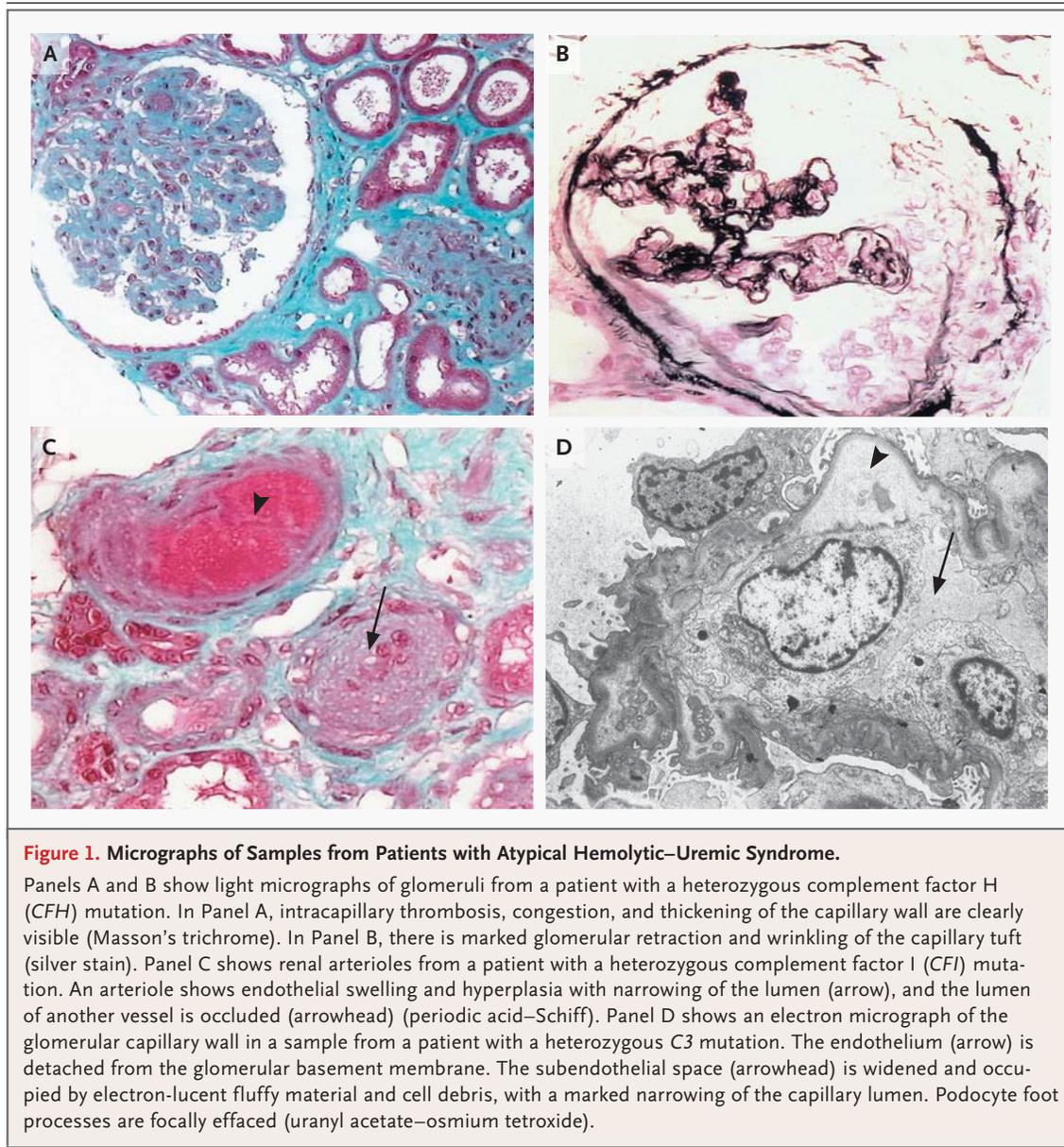


Figure 1. Micrographs of Samples from Patients with Atypical Hemolytic–Uremic Syndrome.

Panels A and B show light micrographs of glomeruli from a patient with a heterozygous complement factor H (CFH) mutation. In Panel A, intracapillary thrombosis, congestion, and thickening of the capillary wall are clearly visible (Masson's trichrome). In Panel B, there is marked glomerular retraction and wrinkling of the capillary tuft (silver stain). Panel C shows renal arterioles from a patient with a heterozygous complement factor I (CFI) mutation. An arteriole shows endothelial swelling and hyperplasia with narrowing of the lumen (arrow), and the lumen of another vessel is occluded (arrowhead) (periodic acid–Schiff). Panel D shows an electron micrograph of the glomerular capillary wall in a sample from a patient with a heterozygous C3 mutation. The endothelium (arrow) is detached from the glomerular basement membrane. The subendothelial space (arrowhead) is widened and occupied by electron-lucent fluffy material and cell debris, with a marked narrowing of the capillary lumen. Podocyte foot processes are focally effaced (uranyl acetate–osmium tetroxide).

another heterozygous mutation in a patient with a sporadic form of the disease, which suggested that sporadic forms of the syndrome had a genetic basis.

CFH POINT MUTATIONS

More than 80 mutations in CFH have been identified in patients with atypical hemolytic–uremic syndrome, with a mutation frequency of 40 to 45% in patients with the familial form and of 10 to 20% in those with the sporadic form.^{14,34–38} (Details about mutations in atypical hemolytic–uremic syndrome are available at www.FH-HUS.org.) CFH, a plasma protein containing 20 homol-

ogous repeats, regulates the alternative pathway by competing with complement factor B (CFB) for C3b recognition by acting as a cofactor for CFI and by enhancing dissociation of C3 convertase (Fig. 2A and 2B).³⁹ These functions are located in the N-terminal region of CFH. In addition, CFH binds to glycosaminoglycans in basement membranes and endothelium through its C-terminal repeats.⁴⁰ CFH down-regulates alternative-pathway activation on structures without other complement regulators, such as glomerular basement membranes, and contributes to endothelial protection when membrane-bound regulators are present.

The vast majority of *CFH* mutations in patients with atypical hemolytic–uremic syndrome are heterozygous and cluster mainly in the C-terminal, causing amino acid changes or translation interruption (Fig. 2 in the Supplementary Appendix). With this abnormality there is a lower density of mutant CFH on cell surfaces and diminished cofactor activity for C3b degradation because of low binding of mutant CFH to glycosaminoglycans on endothelial cells or to surface-bound C3b.^{40–42} Lysis of sheep erythrocytes is a standard test of this system, since these cells have surface glycosaminoglycans and bind CFH. At variance with normal serum, serum from patients with *CFH* mutations lyses sheep erythrocytes through the alternative pathway. The addition of normal CFH stops this lysis (Fig. 2B).⁴³

Most mutant forms of CFH are secreted in plasma. Since CFH forms oligomers,^{44,45} in plasma from heterozygous patients mutant CFH seems to interact with normal CFH and impairs its binding to endothelial cells, suggesting a dominant negative effect,⁴² in which the abnormal gene product acts to block the effect of the wild-type allele. Therefore, even though 50% of CFH molecules are normal, they are not sufficient for preventing atypical hemolytic–uremic syndrome. Homozygous *CFH* mutations, which account for only 15 to 20% of *CFH* mutations in patients with this syndrome, lead to quantitative CFH deficiency and very low C3 levels.³⁵

GENOMIC ABNORMALITIES

A high degree of sequence identity between *CFH* and genes encoding five complement factor H–related proteins (*CFHR1* through *CFHR5*), which are located in tandem to *CFH*, may predispose to non-allelic recombinations.⁴⁶ In 3 to 5% of patients with atypical hemolytic–uremic syndrome, a heterozygous hybrid gene deriving from an uneven crossover between *CFH* and *CFHR1* (which contains the first 21 *CFH* exons and the last two *CFHR1* exons⁴⁷) results in a gene product with decreased complement regulatory activity on endothelial surfaces.

AUTOANTIBODIES AGAINST CFH

In approximately 6 to 10% of patients with atypical hemolytic–uremic syndrome, anti-CFH autoantibodies develop.^{48–50} These antibodies bind to the CFH C-terminal, reduce CFH binding to C3b, and enhance alternative-pathway–dependent lysis of sheep erythrocytes without influencing fluid-phase

Table 1. Classification of Atypical Hemolytic–Uremic Syndrome.*

Form of Disease	Complement Abnormalities
Familial	Mutations in <i>CFH</i> , 40–45%; in <i>CFI</i> , 5–10%; in <i>C3</i> , 8–10%; in <i>MCP</i> , 7–15%; in <i>THBD</i> , 9%; and in <i>CFB</i> , 1–2%.
Sporadic	
Idiopathic	Mutations in <i>CFH</i> , 15–20%; in <i>CFI</i> , 3–6%; in <i>C3</i> , 4–6%; in <i>MCP</i> , 6–10%; in <i>THBD</i> , 2%; and in <i>CFB</i> , 2 cases; anti-CFH antibodies: 6–10%
Pregnancy-associated	Mutations in <i>CFH</i> , 20%; in <i>CFI</i> , 15%
HELLP syndrome	Mutations in <i>CFH</i> , 10%; in <i>CFI</i> , 20%; and in <i>MCP</i> , 10%
Drugs	Rare <i>CFH</i> mutations (mostly unknown)
Organ transplantation	Mutations in <i>CFH</i> , 15%; in <i>CFI</i> , 16%
Human immunodeficiency virus infection	Unknown†
Cancer	Unknown†

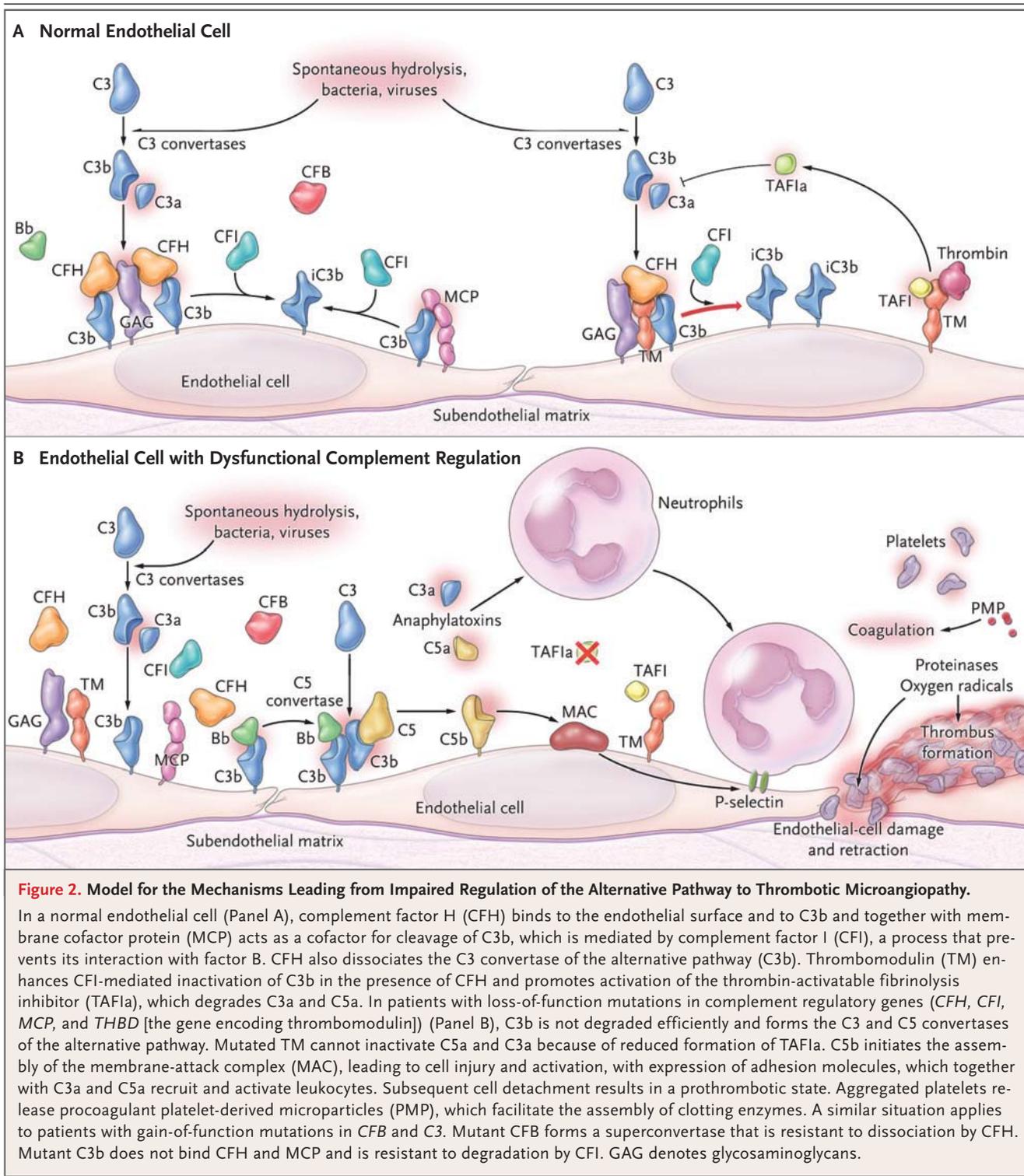
* HELLP denotes hemolytic anemia, elevated liver enzymes, and low platelet count.

† There are no published data on the frequency of complement gene mutations or anti-CFH autoantibodies in patients with this condition.

cofactor activity.⁵¹ The lack of complement control on cells, despite control in the fluid phase, mimics the course of the disease in patients with *CFH* mutations. Anti-CFH autoantibodies develop mainly in young children who, unlike their heterozygous mothers, lack *CFHR1* and *CFHR3* because of homozygous deletions of the corresponding genes.^{50,52,53} Interestingly, the antibodies appear to recognize *CFHR1* and *CFHR3*,⁵⁰ which suggests that they may arise from an immune reaction against maternal *CFHR1* and *CFHR3* (Dragon-Durey MA: personal communication). *CFHR1/3* deficiency itself may also predispose to atypical hemolytic–uremic syndrome, since patients with this deficiency who do not have anti-CFH antibodies have been described previously.^{53,54}

MEMBRANE COFACTOR PROTEIN

Mutations in the gene encoding membrane cofactor protein (*MCP*), a widely expressed transmembrane regulator, have been described in 10 to 15% of patients with atypical hemolytic–uremic syndrome.^{14–16} *MCP* serves as a cofactor for *CFI* to cleave C3b and C4b on cell surfaces (Fig. 2A and 2B).⁵⁵ Intact *MCP* is pivotal in preventing C3 activation on glomerular endothelium. In one study, an anti-*MCP* antibody completely blocked cofactor



activity in cell extracts.⁵⁶ Most mutations are heterozygous, though about 25% are either homozygous or compound heterozygous. Such mutations usually cluster in extracellular domains that are critical for regulation (Fig. 2 in the Supplementary Appendix). Expression on blood leukocytes was reduced in 75% of mutants. Other mutants showed low C3b-binding capability and decreased cofactor activity.^{14,57}

CFI
CFI is a plasma serine protease that regulates the

Table 2. Genetic Abnormalities and Clinical Outcome in Patients with Atypical Hemolytic–Uremic Syndrome.*

Gene	Protein Affected	Main Effect	Frequency %	Response to Short-Term Plasma Therapy†	Long-Term Outcome‡	Outcome of Kidney Transplantation
<i>CFH</i>	Factor H	No binding to endothelium	20–30	Rate of remission: 60% (dose and timing dependent)	Rate of death or ESRD: 70–80%	Rate of recurrence: 80–90%§
<i>CFHR1/3</i>	Factor HR1, R3	Anti-factor H antibodies	6	Rate of remission: 70–80% (plasma exchange combined with immunosuppression)	Rate of ESRD: 30–40%	Rate of recurrence: 20%¶
<i>MCP</i>	Membrane cofactor protein	No surface expression	10–15	No definitive indication for therapy	Rate of death or ESRD: <20%	Rate of recurrence: 15–20%¶
<i>CFI</i>	Factor I	Low level or low cofactor activity	4–10	Rate of remission: 30–40%	Rate of death or ESRD: 60–70%	Rate of recurrence: 70–80%§
<i>CFB</i>	Factor B	C3 convertase stabilization	1–2	Rate of remission: 30%	Rate of death or ESRD: 70%	Recurrence in one case
<i>C3</i>	Complement C3	Resistance to C3b inactivation	5–10	Rate of remission: 40–50%	Rate of death or ESRD: 60%	Rate of recurrence: 40–50%
<i>THBD</i>	Thrombomodulin	Reduced C3b inactivation	5	Rate of remission: 60%	Rate of death or ESRD: 60%	Recurrence in one case

* ESRD denotes end-stage renal disease.

† Remission was defined as either complete remission or partial remission (i.e., hematologic remission with renal sequelae).

‡ The long-term outcome was defined as the outcome 5 to 10 years after onset.

§ Patients in this category were eligible for combined liver and kidney transplantation.

¶ Patients in this category were eligible for single kidney transplantation.

three complement pathways by cleaving C3b and C4b in the presence of cofactor proteins (Fig. 2A). *CFI* mutations affect 4 to 10% of patients with atypical hemolytic–uremic syndrome.^{14,58–60} All mutations identified to date have been heterozygous, and 80% cluster in the serine protease domain (Fig. 2 in the Supplementary Appendix). Approximately 50% of mutations result in low CFI levels.^{14,58–60} Others disrupt cofactor activity.⁵⁹

CFB AND C3

Gain-of-function mutations can affect genes encoding the alternative pathway C3 convertase components, CFB and C3 (Fig. 2A).^{17,18} *CFB* mutations, which lead to chronic alternative-pathway activation, occur in only 1 to 2% of patients with atypical hemolytic–uremic syndrome (Fig. 2 in the Supplementary Appendix).¹⁷ Mutants have excess C3b affinity and form a hyperactive C3 convertase that is resistant to dissociation, enhancing C3b formation.¹⁷

About 4 to 10% of patients have heterozygous mutations in *C3*, usually with low C3 levels.¹⁸ Most

mutations reduce C3b binding to CFH and MCP, which severely impairs degradation of mutant C3b (Fig. 2B).¹⁸

THROMBOMODULIN

A recent study has shown that about 5% of patients with atypical hemolytic–uremic syndrome carry heterozygous mutations in *THBD*, the gene encoding thrombomodulin, a membrane-bound anticoagulant glycoprotein that facilitates complement inactivation by CFI in the presence of CFH (Fig. 2A).⁶¹ Cells expressing these variants are less efficient in degrading C3b and in generating activated thrombin-activatable fibrinolysis inhibitor (TAFIa), a plasma carboxypeptidase B that cleaves C3a and C5a (Fig. 2A and 2B).⁶¹

INCOMPLETE GENETIC PENETRANCE

Mutations in complement genes confer a predisposition rather than cause atypical hemolytic–uremic syndrome, and penetrance among carriers of *CFH*, *MCP*, and *CFI* mutations appears to be

40 to 50%.¹⁴ Healthy carriers of *CFB* and *C3* mutations also have been reported.^{17,18} Thus, the presence of these mutations cannot be used to predict future cases of the syndrome.

About 5% of patients have combined mutations, usually in *CFH* with either *MCP* or *CFI*, each inherited from a healthy parent.¹⁴ In some family pedigrees, atypical hemolytic–uremic syndrome has occurred in family members with a *CFH* mutation on one allele and two or three predisposing *CFH* polymorphisms on the other allele, whereas the syndrome has not developed in family members carrying just one affected allele.³⁷ Similarly, in a large pedigree with *CFI* and *MCP* mutations and the risk-associated *MCPggaac* haplotype, the syndrome occurred only in family members who had all the risk factors.⁶² In another study,⁶³ carriers of a common *CFH* mutation that is associated with the hemolytic–uremic syndrome had disease penetrance of 30%, and most patients also carried at least one additional genetic risk factor. These data indicate that the concurrence of both mutations and risk polymorphisms may be required for the development of the syndrome.

Even in patients with multiple genetic risk factors, the syndrome may not occur until middle age, which suggests an environmental effect. Infections may precede clinical cases of the hemolytic–uremic syndrome in many such patients, including in 35% of those with mutant *CFH*, in 50% of those with mutant *MCP*, in 55% of those with mutant *CFI*, and in 22% of those with mutant *C3*.¹⁴ Pregnancy and the use of contraceptive pills were reported to trigger disease in 8% of patients with *CFH* mutations and in 20% of those with *CFI* mutations.¹⁴

Given such data, unaffected carriers should be monitored during pregnancy and episodes of infection, and precipitants, such as drugs that trigger the hemolytic–uremic syndrome, should be avoided.

FROM COMPLEMENT
ABNORMALITIES TO THROMBOTIC
MICROANGIOPATHY

Several factors that contribute to complement regulation are expressed on or bound to endothelium (Fig. 2A). Normally, complement regulation remains intact even when the activities of one or two regulators are partially reduced. However, triggers, such as infections and pregnancy, that are associated with inflammation and complement acti-

vation may lead to problems in such persons,⁶⁴ since the vascular endothelium may require multiple regulators for protection. Certain vascular beds may be at increased risk. For example, the glomerular capillary bed has a fenestrated endothelium, which continually exposes the subendothelial matrix to a variety of circulating proteins and peptides. Thus, anyone lacking complement regulatory proteins is particularly vulnerable to complement attack. Persons with gain-of-function mutations in *C3* or *CFB* are similarly at risk, since these mutations lead to C3-convertase hyperactivity.

In the presence of events that enhance alternative-pathway activation, carriers of complement mutations undergo excess C3b formation and deposition on vascular endothelium. An uncontrolled level of C3 convertase leads to more C3b molecules and to more C5 convertase, initiating the formation of the membrane-attack complex. Complement-mediated endothelial injury creates a prothrombotic state through exposure of subendothelial collagen, von Willebrand factor, and fibrinogen (Fig. 2B). Moreover, it has been shown that mutant *CFH* has defective binding to platelets, allowing C3 and C9 deposition and platelet activation.⁶⁵

CLINICAL COURSE AND OUTCOME

Among patients with atypical hemolytic–uremic syndrome who have genetic mutations, 67% are affected during childhood,^{14,22} and the disease is diagnosed in almost all patients with anti-*CFH* antibodies before the age of 16 years.⁴⁹ Acute episodes manifest with severe hemolytic anemia, thrombocytopenia, and acute renal failure. Extrarenal (i.e., central nervous system or multivisceral) involvement occurs in 20% of patients.^{14,22}

Both short-term and long-term outcomes vary according to the underlying complement abnormality. About 60 to 70% of patients with *CFH*, *CFI*, or *C3* mutations and 30% of children with anti-*CFH* autoantibodies lose renal function or die during the presenting episode or have end-stage renal disease after relapses^{14,22} (Table 2). *CFB* mutations are associated with particularly poor renal outcomes, with a loss of renal function in 88% of patients in one study.¹⁷

About 20% of patients with *CFH* mutations have cardiovascular complications and excess mortality.²² Chronic complement dysregulation can contribute to the formation of atheromatous lesions.⁶⁶

Long-term survival of patients with *CFH* mutations (50% at 10 years) is poorer than that of patients with *CFI* or *C3* mutations or anti-*CFH* autoantibodies (80 to 90% at 10 years^{14,22}).

Carriers of *MCP* mutations have a good prognosis, with a complete remission rate of 80 to 90% (Table 2). Recurrences are frequent, but the long-term outcome appears good, with 80% of patients remaining free of dialysis.^{14,22} Rarely, concurrent genetic abnormalities may lead to exceptionally severe disease.^{14,67}

TREATMENT

Early reports of successful treatment with plasma in atypical hemolytic-uremic syndrome date back 30 years.^{68,69} Since then, plasma exchange or infusion has been associated with a decrease in mortality from 50% to 25%.^{70,71} Guidelines suggest that plasma therapy should be started within 24 hours after diagnosis, with an exchange of one to two plasma volumes per day or an infusion of 20 to 30 ml per kilogram of body weight.^{72,73} (For details, see the case reports in the Supplementary Appendix.) Plasma exchange allows for the provision of larger amounts of plasma than would be possible with infusion while avoiding fluid overload. However, trials of plasma therapy in patients with the hemolytic-uremic syndrome are few and not current.^{74,75} A recent meta-analysis^{76,77} suggesting that plasma offers no significant benefit over simple supportive therapy may be misleading, since the trials that were evaluated did not distinguish between *Stx*-related and atypical hemolytic-uremic syndrome.^{74,75}

Since *CFH* is a plasma protein, plasma infusion or exchange provides normal *CFH* to patients with homozygous mutations and complete *CFH* deficiency and induces disease remission (Table 2).^{14,22,78,79} However, since such patients are plasma-dependent, unresponsiveness may develop after long-term therapy.⁷⁹⁻⁸¹ Carriers of heterozygous *CFH* mutations usually have normal levels of *CFH*, but half is dysfunctional. The beneficial effect of plasma strongly depends on the amount, frequency, and method of administration, with plasma exchange having been shown to be superior to plasma infusion for remission and prevention of recurrences, possibly through the removal of mutant dysfunctional *CFH* molecules^{82,83} (case reports in the Supplementary Appendix). Overall in patients with *CFH* mutations, either complete remission or partial remission (which was defined

as hematologic normalization with renal sequelae) occurred in 60% of plasma-treated patients^{14,22} (Table 2).

Plasma exchange appears to be effective in removing anti-*CFH* antibodies.^{22,48} However, the effect is usually transient. The combination of plasma exchange with the use of immunosuppressant drugs (e.g., corticosteroids and azathioprine or mycophenolate mofetil) and an anti-*CD20* antibody (rituximab) resulted in long-term dialysis-free survival in 60 to 70% of patients.^{49,51,84,85}

Patients with *CFI* mutations have only a partial response to plasma therapy; remission occurred in only 30 to 40% of patients.^{14,22,86} Since *MCP* is a cell-associated protein, plasma exchange or infusion is unlikely to be effective in patients with *MCP* mutations. Indeed, 80 to 90% of such patients have remission without plasma treatment.^{14,22,86} Plasma exchange or infusion resulted in a response in 30% of patients with *CFB* mutations and in 50% of those with *C3* mutations.^{17,18} Possibly, patients with either *CFB* or *C3* mutations need more frequent plasma exchanges to clear the hyperfunctional mutant *CFB* and *C3* (Table 2).

TRANSPLANTATION

It has long been debated whether kidney transplantation is appropriate for the treatment of end-stage renal disease in patients with atypical hemolytic-uremic syndrome. The disease recurs in around 50% of patients who undergo transplantation, and graft failure occurs in 80 to 90% of those with recurrent disease.^{87,88} The type of mutation may predict the outcome after transplantation (Table 2). The recurrence rate after transplantation is 70 to 90% in patients with genetic abnormalities in the circulating complement regulators *CFH* and *CFI*, mainly of hepatic origin.^{58,87,88} Intensive long-term plasma prophylaxis was thought to prevent recurrence in one patient with a *CFH* mutation⁸⁹ but failed in another patient.⁹⁰ Atypical hemolytic-uremic syndrome recurred in 40 to 50% of patients with *C3* mutations.¹⁸ A patient with a *CFB* mutation who underwent renal transplantation had recurrence of disease.¹⁷

The outcome of single kidney transplantation is more favorable in patients with *MCP* mutations than in those with other mutations. More than 80% had no recurrence, with a rate of long-term graft survival that was similar to that of patients who underwent transplantation for other causes.^{22,87,88} The *MCP* gene product, membrane

cofactor protein, is a transmembrane protein that is highly expressed in the kidney, so kidney transplantation, not surprisingly, corrects the defect.

Living-donor transplantation is contraindicated in patients with atypical hemolytic–uremic syndrome because of the high risk of recurrent disease.^{91,92} In addition, such procedures may be risky to donors, who may be mutation carriers. For example, *de novo* atypical hemolytic–uremic syndrome developed in a man with a heterozygous *CFH* mutation after he donated a kidney to his affected child.⁹² If living-donor transplantation is considered, the donor and recipient should undergo genotyping of complement genes to identify hitherto unsuspected mutation carriers.

Simultaneous kidney and liver transplantation was performed in two children with atypical hemolytic–uremic syndrome and *CFH* mutations with the rationale of correcting the genetic defect and preventing recurrence.^{93,94} However, both cases were complicated by early failure of the transplanted liver. The first child recovered after a second liver transplantation and had no symptoms of the hemolytic–uremic syndrome for 3 years but ultimately died from hepatic encephalopathy.^{93,95} This case offered the proof of concept that liver transplantation cures atypical hemolytic–uremic syndrome associated with *CFH* mutations. The second case was also complicated by failure of the transplanted liver, with concomitant widespread microvascular thrombosis and complement deposition.⁹⁴ The investigators who reported the case speculated that surgical stress with ischemia–reperfusion induced complement activation in the liver that could not be regulated because of functional *CFH* deficiency. A modified approach that included extensive plasma exchange before surgery to provide a sufficient amount of normal *CFH* until the liver graft recovered synthetic function was applied in eight subsequent cases^{95–97} and succeeded in seven; severe hepatic thrombosis and fatal encephalopathy developed in the eighth patient.⁹⁵ Thus, the substantial risks of dual kidney and liver transplantation require a careful assessment of possible benefits for any candidate patient.

Screening for mutations may help patients and clinicians to make more informed decisions regarding listing for transplantation on the basis of the risk of recurrence. A position paper reporting the conclusions of a 2007 conference on atypical hemolytic–uremic syndrome⁹⁵ listed groups of patients for whom isolated kidney transplantation

would be extremely risky and for whom combined kidney–liver transplantation would be worth considering. They also suggested which patients would be most likely to benefit from isolated kidney transplantation (Table 2).

EVOLVING APPROACHES

The identification of complement genetic abnormalities may facilitate treatments that down-regulate complement activation. A human plasma-derived *CFH* concentrate is being developed. (For details, see the European Medicines Agency Web site at www.emea.europa.eu/pdfs/human/comp/opinion/52123506en.pdf.) A humanized anti-C5 monoclonal antibody, eculizumab, which had undergone phase 3 trials involving patients with paroxysmal nocturnal hemoglobinuria,⁹⁸ was reported as promising in patients with atypical hemolytic–uremic syndrome in two single-case reports.^{99,100} An 18-month-old boy with a plasma-resistant congenital form of the disease achieved remission after the initiation of treatment with eculizumab,⁹⁹ although a possible effect of previous plasma therapy could not be ruled out because markers of hemolysis began to decrease before the administration of eculizumab. A 30-year-old woman with a *CFH* mutation who had a recurrence of the hemolytic–uremic syndrome in a kidney graft¹⁰⁰ had resolution of hemolysis and improved transplant function after receiving eculizumab. Results concerning 14 additional eculizumab-treated patients, 10 of whom achieved stable remission, have been reported recently (Nurnberger J: personal communication). The efficacy of eculizumab in the treatment of atypical hemolytic–uremic syndrome is being evaluated in controlled trials that are either ongoing or planned (ClinicalTrials.gov numbers, NCT00844545, NCT00844428, NCT00838513, and NCT00844844). (For details regarding international registries of patients and addresses of the main laboratories that perform genetic screening, see the Resources section in the Supplementary Appendix.)

SUMMARY

During the past decade, multiple and complex genetic abnormalities that are associated with atypical hemolytic–uremic syndrome have been described. Although of disparate origin, disease-associated abnormalities have in common the

overactivation of the alternative complement pathway, which has opened perspectives for complement inhibitor therapies in the future.

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