Transplantation in Atypical Hemolytic Uremic Syndrome

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ABSTRACT

Atypical hemolytic uremic syndrome (aHUS) is a disease characterized by over-activation of complement. Recurrence following renal transplantation is determined by a genetic predisposition. Genetic screening of all individuals with aHUS should be performed prior to listing for transplantation. Individuals with isolated mutations in *MCP* have a low risk of recurrence and may be considered for kidney transplantation alone. In individuals with *CFH* and *CFI* mutations, the risk of recurrence following renal transplantation is high. Combined liver/kidney transplantation has been used successfully in individuals with *CFH* mutations following the introduction of perioperative plasma exchange; however, such a procedure is not without its risks. Liver/kidney transplantation has yet to be performed on individuals with *CFI* and C3 mutations but may be predicted to be successful. In individuals with *CFH* autoantibodies, a reduction in titer through plasma exchange and rituximab has been successful. Clinical trials of the complement C5 inhibitor eculizumab may improve prospects for isolated renal transplantation in individuals with complement protein mutations.

KEYWORDS: Transplantation, hemolytic uremic syndrome, complement, factor H, eculizumab

Hemolytic uremic syndrome (HUS) is a thrombotic microangiopathy that consists of microangiopathic hemolytic anemia, thrombocytopenia, and acute renal failure. HUS is classified as either diarrheal associated (D + HUS) or nondiarrheal (atypical; aHUS). The diarrheal form of the disease is most commonly associated with Shiga toxin-like-producing *Escherichia coli*. The atypical form of the disease has been shown to be a disorder of complement dysregulation.[1]

Mutations in genes that encode proteins with complement regulatory functions including factor H (*CFH*),[2–5] factor I (*CFI*),[6–8] membrane cofactor protein (*MCP, CD46*).[9–11] Clusterin[12] and thrombomodulin[13] (*THBD*) have been demonstrated to predispose to disease. Autoantibodies against CFH have also been found in individuals with aHUS.[14–16] In addition to "*loss of function*" mutations in genes encoding complement regulatory proteins, activating mutations in the alternative pathway components C3[17] and factor B[18] (*CFB*) have also been linked to aHUS. Additionally, single nucleotide polymorphisms (SNPs) and haplotypes in the genes encoding regulatory proteins *CFH*,[19,20] *MCP*,[20] C4b-binding protein (*C4BP*),[21] and the factor H–related proteins (*CFHRs*)[22] have also been demonstrated.

The prognosis in those with D + HUS is good, with few patients rapidly progressing to dialysis-requiring

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renal failure, and with most of those who do, regaining renal function. In contrast, in aHUS, the prognosis is poor with ~50% of patients requiring dialysis and 25% dying during the acute phase.[23]

RECURRENCE AFTER RENAL TRANSPLANTATION

In those patients with D + HUS who do progress to ESRF, renal transplantation is associated with a low recurrence rate, < 1%.[24] The 10-year graft survival is similar to those transplanted for dysplasia/uropathies and significantly better than those transplanted for other renal conditions.[25]

In comparison, the outcome for patients with aHUS is poor, although not uniformly so. The reason for this variation has become clear with the elucidation of the genetic mechanism of disease and the genotype-to-phenotype correlations derived subsequently.[26–29] There is no evidence that pretransplant bilateral nephrectomy[26] or avoidance of calcineurin inhibitors is beneficial for preventing post-transplant recurrence of aHUS.[27]

Complement Factor H

In those with mutations in CFH, disease recurrence occurs following renal transplantation in ~80% of cases.[26–29] CFH functions as the most important fluid-phase regulator of the alternative pathway (AP) of complement by acting as a cofactor for CFI-mediated proteolytic inactivation of C3b (CA), competing with factor B for C3b binding, and accelerating the decay of the C3 convertase into its components (decay accelerating activity [DAA]). In addition it serves to control complement on host cells by binding cell surface C3b and glycosaminoglycans via its C-terminal domains (CCP 19 and20).[30] It is this region that is mutated in aHUS, resulting in loss of complement regulation on the renal vasculature.[31,32] Because CFH is predominantly synthesized in the liver, an isolated kidney allograft will not correct the underlying genetic defect predisposing to aHUS.

Renal transplantation in individuals with CFH mutations has been attempted using prophylactic plasma therapy in several cases. Hirt-Minkowski et al[33] report an individual treated with peri- and postoperative plasma infusion who had a successful renal transplant at 1 year. The use of prophylactic plasma exchange (PE) has been described by Olie et al[34] in an individual given perioperative PE and subsequently twice-monthly PE. The graft functioned well; however, aHUS recurrence was seen consequent with cytomegalovirus disease on two occasions with intensification of PE controlling the recurrence. Other reports of recurrent disease in individuals receiving prophylactic PE who did not respond to intensification of PE have been described.[35] If an isolated renal transplant in an individual with a CFH mutation must be attempted, then perioperative PE, postoperative PE, and continued prophylactic PE must be used. Additionally, surveillance must be increased during times of infection with a view to escalation of PE.

Membrane Cofactor Protein

Transplantation outcome in those with mutations in MCP is much better, with a recurrence rate of only ~20%.[26] MCP encodes a membrane-bound inhibitor that is highly expressed in the kidney, particularly on endothelium.[36] Membrane cofactor protein (MCP) is an intrinsic complement regulator, protecting the cell to which it is bound, serving as a cofactor for the proteolytic inactivation of deposited C3b and C4b by CFI. Around 75% of MCP mutations described in aHUS lead to reduced surface expression of MCP on peripheral blood; the remaining mutant proteins have decreased complement regulatory activity.[37]

Because MCP is membrane bound, it would be expected that a renal allograft would correct the complement defect and protect against aHUS. It is surprising, therefore, that recurrence has been reported in two patients.

In the series reported by Frémeaux-Bacchi et al,[11] patient 6 lost the graft due to recurrence of disease within a few days of transplantation. Functional analysis of the MCP mutation revealed that functional impairment was only seen in the classical pathway (CP), whereas there was evidence of AP activation in the patient's serum. This suggested that the patient may have another mutant complement protein.

In a second patient, Frémeaux-Bacchi et al[38] described two episodes of mild disease recurrence responsive to PE, and at 2 years renal function was normal. In this individual, they demonstrated patchy endothelial microchimerism in the graft. This is a mechanism whereby some donor graft endothelial cells are replaced by recipient cells. In this case it was hypothesized that this transfer of recipient mutant MCP-bearing endothelial cells transferred the risk of aHUS to the renal allograft.

Despite these two cases, the overall risk of disease recurrence in individuals with isolated MCP mutations is low, although preoperative counseling should highlight that it is possible.

Complement Factor I

Factor I is a serine protease that regulates complement by cleaving C3b and C4b in the presence of cofactors (CA), such as CFH and MCP. Approximately 50% of the CFI mutants associated with aHUS result in low serum levels of complement factor I, with functional

analysis of secreted mutants revealing loss of CP and AP cofactor activity.[39] CFI is predominantly synthesized in the liver, and as would be predicted from a circulating regulator, the recurrence rate following isolated renal transplantation is high (~90%).[26–29] In those individuals with disease recurrence, all lost the graft within the first year.[26]

Activating Mutations in Complement Components (CFB and C3)

More recently, mutations in genes (*CFB* and *C3*) encoding the serum complement activating factors CFB and C3 have been described in aHUS. Activation of the CP, AP, and lectin pathways results in cleavage of C3 to generate C3b and the anaphylatoxin C3a. Factor B interacts with C3b and following cleavage by factor D forms the AP convertase (C3bBb). This set of reactions represents an amplification loop.[36]

Mutations in *CFB* have been demonstrated to enhance the formation of the C3bBb convertase or increase resistance to inactivation by regulators.[18] There is only one reported renal transplant in an individual with a *CFB* mutation, and in this case there was disease recurrence.[18]

Both gain-of-function and loss-of-function mutations have been reported in *C3*.[17] Five mutations had impaired binding to complement regulators with a consequent reduction in CA. Two mutations in *C3* were also shown to result in decreased secretion of C3, although the mechanism through which C3 haploinsufficiency fits into the current complement overactivation model of aHUS remains to be determined. In the six aHUS patients with *C3* mutations who were transplanted, three had recurrent disease.[17]

Thrombomodulin Mutations

Mutations in *THBD* have recently been demonstrated in aHUS.[13] THBD is a transmembrane proteoglycan located on the vascular endothelium. It accelerates thrombin-mediated activation of protein C and enhances thrombin-mediated activation of thrombin activatable fibrinolysis inhibitor (TAFI), which in turn inhibits fibrinolysis and inactivates the anaphylatoxins C3a and C5a. THBD also suppresses leukocyte trafficking. Additionally, THBD has recently been shown to enhance AP cofactor activity. Besides the transmembrane form, THBD also exists in a soluble form in the plasma, generated by proteolytic cleavage of the membrane-bound form of the protein,[40] although the physiological role of the soluble form is unclear. Functional analysis of the mutations described in aHUS demonstrated a decrease in CA and impaired TAFIa generation. Delvaeye et al[13] reported one individual with a mutation with recurrent disease following transplantation. Analysis of

further large panels of aHUS patients will be required to refine the clinical phenotype following transplantation.

FACTOR H AUTOANTIBODIES

Autoantibodies to CFH were first reported to be associated with aHUS in 2005 by Dragon-Durey et al.[16] This observation has been confirmed in three independent cohorts of aHUS patients at a frequency of ~10%.[14,16,41] Most auto-antibodies to CFH bind to the C-terminal end of CFH.[14,41] Moreover, it has been demonstrated that CFH autoantibodies impair the binding of CFH to C3b and are associated with enhanced hemolysis of sheep erythrocytes in patient plasma.[16,17,41] These antibodies have been shown to block the C-terminal recognition domain of CFH (CCP 19 and 20), an area where it is known that *CFH* mutations associated with aHUS cluster.

Factor H autoantibodies have been associated with recurrent disease following renal transplantation. Le Quintrec et al[42] reported an individual in which rapid loss of an allograft due to aHUS recurrence was associated with anti-CFH autoantibodies prior to transplantation. In a subsequent renal transplant, PE was instigated immediately postoperatively and maintained six times weekly to maintain a low titer of CFH autoantibodies, and at 36 months renal function was normal with no recurrence of disease. Kwon et al[43] also reported an individual with CFH autoantibodies in which early detection of anti-CFH autoantibodies allowed their preemptive removal using a regime including the anti-CD20 monoclonal antibody, rituximab, PE, and prednisolone and azathioprine. This, in combination with pre- and postoperative PE continued for 4 weeks, resulted in a successful transplant at 2 years. A recent report by Moore et al[14] described three individuals with factor H autoantibodies who had been previously transplanted and had only been found to have autoantibodies through retrospective analysis of historical serum samples. These patients had no recurrence of disease, with follow-up ranging from 2 to 6 years in the absence of specific therapy aimed at reducing CFH autoantibody titer.

A suggested approach, in light of our current understanding of pathogenesis, is to monitor CFH autoantibody titer and administer rituximab to those with persistently elevated titers in conjunction with PE perioperatively.

LIVING RELATED TRANSPLANTATION

Live related renal transplantation should not currently be attempted in aHUS. As we have discussed, graft loss due to recurrent disease is common in those individuals with mutations in *CFH*, *CFI*, *CFB*, and *C3*. Additionally, in four reported cases, the donors themselves have gone on

to develop de novo HUS within a year of donation.[44–46] It has been suggested that the hyperfiltration induced in the remaining kidney following donation triggered aHUS in the genetically susceptible donor. In at least one of these families, a mutation in *CFH* was subsequently described.[44,47]

If live donation is considered, it is essential that the donor and recipient undergo genotyping to identify previously unsuspected carriers, given the high reported rates of incomplete penetrance for mutations. One explanation for the ∼50% penetrance is that other genetic factors act as modifiers of disease penetrance. In addition to mutations, several SNPs and haplotypes in complement genes have been associated with disease. Pedigrees have been reported in which co-segregation of three independent genetic risk factors was required for disease to manifest. Thus only when an unfavorable collection of complement genes is present will aHUS develop, and even then only following a triggering event.[48] Given that a related donor will carry many of the same susceptibility factors, many of which have still to be determined, screening will not completely eliminate the risk for the donor.

LIVER/KIDNEY TRANSPLANTATION

Because CFH and CFI are predominantly synthesized in the liver, combined liver/kidney transplantation is a potential treatment. Three initial reports describing this procedure in individuals with *CFH* mutations were not promising.

In 2002 Remuzzi et al[49] reported the first combined liver/kidney transplant in a child with a *CFH* mutation who was failing on dialysis. The liver failed due to hyperacute rejection, and the child developed hepatic encephalopathy and progressed to coma. He underwent a second liver transplant with normalization of liver function; however, there was only partial recovery of his neurological abnormality, which resulted in his death 3 years later. Despite this poor outcome, there was no recurrence of aHUS, supporting a theoretical benefit of this approach.

In the second combined liver/kidney transplant, the child died from primary nonfunction of the liver with autopsy demonstrating widespread microvascular thrombosis with evidence of complement activation.[50] Because activation of the complement cascade is an unavoidable consequence of organ transplantation, it was suggested that unless there was adequate complement regulation at the time of organ transplantation, the ensuing complement activation would result in graft failure.

Additionally, a child with preserved renal function but recurrent episodes of hemolysis and thrombocytopenia underwent an auxiliary liver transplant from his father but died 10 months after transplant from

lymphoproliferative disorder and infection with some evidence of HUS.[51]

To correct the underlying complement regulatory defect prior to combined liver/kidney transplantation, in a 5-year-old child with aHUS and a compound *CFH* mutation, Saland et al[52] performed PE perioperatively and gave plasma infusion intraoperatively. Enoxaparin and aspirin were also given postoperatively. This resulted in excellent graft function at 4 years with no recurrence of aHUS during this time. A second child with a *CFH* mutation successfully underwent a combined split liver/kidney transplant at the same center.[53] Using a rather similar protocol, successful combined transplants were performed on three patients (2.5, 16, and 22 years of age) with a heterozygous R1215Q mutation in *CFH*[54] (and unpublished results). No disease recurrence occurred in these patients, and both liver and kidney functions are excellent 2 to 3.5 years after the operation. Post-transplantation lymphoma was successfully treated in one, but otherwise the postoperative course has been quite uneventful in all three cases. Altogether, we are aware of 11 recent liver/kidney and one liver transplantation due to *CFH* mutations as well as one liver/kidney transplantation due to a *CFB* mutation, with an overall patient survival of 70%. Based on this limited experience, treatment guidelines for the use of liver/kidney transplantation in aHUS were recently proposed by a consensus conference.[55] To minimize complement activation during the operation, extensive PE (at least 1.5 plasma volumes) preoperatively is recommended. Also, mini-heparin and aspirin soon after the operation are suggested for thrombosis prophylaxis. It is clear that even in experienced centers, combined transplantation is associated with surgical and medical risks, and the treatment modality must be chosen on an individual basis. However, in an aHUS patient with terminal renal failure, the use of combined transplantation instead of solitary renal transplantation is beneficial in two ways: the recurrence of renal or neurological problems after the combined operation is very unlikely, and the outcome of the kidney graft is often excellent due to the protective effect of the liver graft (fewer rejections).

Analogously, in those with activating mutations in *C3*, a combined liver/kidney transplant has been suggested as potential treatment for disease. This is complicated by substantial extrahepatic generation of C3 from the recipient endothelium. Whether this extrahepatic generation of these mutated proteins is sufficient to cause aHUS in an allograft is unclear.

ECULIZUMAB

Eculizumab is a monoclonal antibody directed against the complement protein C5. It prevents activation of the terminal complement cascade and the generation of the effector molecules C5a and C5b-9. This complement

Table 1 Genotype-to-Phenotype Correlation in Atypical Hemolytic Uremic Syndrome

Mutation	Complement Function	Distribution	Frequency in aHUS (%)	Recurrence Rate after RTx (%)
CFH	Regulator CA, DAA (AP)	Serum	15–30	~80
CFI	Regulator CA (protease)	Serum	5–14	~90
MCP	Regulator CA (AP/CP)	Membrane	10–15	~20
C3	Activating component	Serum	5–10	~50
CFB	Activating component	Serum	0–3	100*
THBD	CA Inactivation of C3a and C5a	Serum/Membrane	~5	100*

*Only one individual transplanted with a mutation.
aHUS, atypical hemolytic uremic syndrome; RTx, renal transplant; CFH, factor H; CA, cofactor activity; DAA, decay-accelerating activity; AP, alternative pathway; CFI, factor I; MCP, membrane cofactor protein; CP, classical pathway; CFB, factor-B; THBD, thrombomodulin.

inhibitor has recently been reported to salvage a transplanted kidney in an individual with a CFH mutation in whom PE had been unable to stop recurrent aHUS.[56] Chatelet et al have also reported an individual with a C3 mutation who had received a renal transplant but was dependent on PE to prevent aHUS recurrence.[57] Long-term treatment with eculizumab in this individual kept the patient in remission. Although treatment with this complement inhibitor may supersede current transplantation protocols in aHUS, systematic trials of eculizumab are required before its use can be universally adopted and recommended for renal transplantation in aHUS.

SUMMARY AND CONCLUSION

Atypical HUS is a disease of complement overactivation, and recurrence following transplantation is determined by a genetic predisposition (Table 1). Renal transplantation is associated with an activation of complement both at the time of the operation and in the context of acute rejection/infection. Isolated renal transplantation in those with CFH and CFI mutations cannot be recommended currently, due to an unacceptably high rate of primary disease recurrence in the allograft (80 to 100% in case series). In the limited experience of transplantation in individuals with CFB, C3, and THBD mutations, the recurrence rate also appears to be high. This risk may be modified in the future by the use of pre/postoperative PE or the use of eculizumab, but as yet there are no randomized controlled trials to support these approaches. Combined liver/kidney transplantation has proved successful in treating individuals with CFH mutations following the introduction of perioperative PE, although the risks are not inconsiderable. Liver/kidney transplantation has yet to be performed on individuals with CFI and C3 mutations but may be predicted to be successful. Individuals with isolated mutations in MCP have a low risk of recurrence and can be considered for isolated renal transplantation. In individuals with CFH autoantibodies, a reduction in titer through PE and rituximab has been successful.

In conclusion, we would recommend that comprehensive genetic screening and tailored preoperative counseling of all individuals with aHUS must be performed prior to listing for transplantation,[58–60] and we suggest that live-related transplantation not be undertaken at the present time.

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