n 1998, a linkage analysis in three families with atypical hemolytic uremic syndrome (aHUS) demonstrated segregation to the RCA (regulators of complement activation) cluster of genes on 1q32 (1). In one of these families, a missense mutation was found in the gene (CFH) encoding the soluble complement regulator factor H. Subsequently, more than 50 different CFH mutations have been described both in sporadic and familial aHUS (details at the FH Associated HUS Database (www.biochem.ucl.ac.uk/~becky/FH/submit.php) (2). The majority of these are heterozygous missense mutations that cluster in the exons encoding the C terminal region of the protein. The secreted protein product of CFH consists of 20 repetitive units (each approximately 60 amino acids) named short consensus repeats (SCR). Factor H downregulates the activity of the alternative complement pathway by increasing the rate of dissociation of the alternative pathway convertase C3bBb (decay accelerating activity) and by acting as a cofactor for the serine protease factor I, which cleaves C3b (cofactor activity). In addition, factor H is able to inactivate membrane-bound C3b by binding to anionic residues on cell surfaces and basement membrane. The complement regulatory activity of factor H is localized in the N-terminal region (SCR 1 to 4) while the cell-binding activity is localized in the C-terminal region (SCRs 19 and 20). Various series suggest that CFH mutations are found in 15 to 30% of aHUS patients. In the remaining patients and families, evidence of complement activation suggested that other complement regulatory genes might be implicated in the pathogenesis of aHUS. Membrane cofactor protein (MCP; CD46) is a widely expressed transmembrane complement regulator. It is highly expressed within the kidney, particularly on endothelium. MCP has 4 SCRs and has cofactor activity for both the classical and alternative pathways. The gene encoding MCP consists of 14 exons and also lies within the RCA cluster. This made it an ideal candidate in the two remaining unsolved families from Warwicker’s original study (1). Mutation screening in one of these showed that affected individuals carried a heterozygous 6-bp deletion leading to the deletion of two amino acids (D237/S238) in SCR 4. Functional studies showed that the mutant protein was retained intracellularly (3). At the same time, two other families were found to carry a missense mutation (T822C, S206P) in the exon encoding SCR 4. The mutant protein was found to be expressed but lacked C3b binding and cofactor activity. In another family reported at the same time, a heterozygous 2-bp deletion was detected in the same exon (4). This resulted in a premature stop codon and reduced cell surface expression to approximately 50%. Because both factor H and MCP act as cofactors for the serine proteinase factor I, it was logical to look for mutations in the gene (IF) encoding factor I. In initial studies, mutations were detected in six families/individuals. All were heterozygous and in five serum factor I levels were decreased (5–7). Two recent reports, one in this issue of the JASN (8) from the French cohort (120 patients), and the other published in Blood (9) from the Italian cohort (156 patients), make substantial additional contributions to our understanding of complement dysregulation in aHUS. MCP mutation screening was undertaken in both cohorts; 10% of the French and 13% of the Italian cohorts were found to have MCP mutations. Functional characterization of many of these mutations was undertaken in the Atkinson Laboratory at Washington University (St Louis, MO). Adding these MCP mutations to those previously described (3,4,6) gives a total of more than 20 different mutations and allows several generalizations to be made. The majority of MCP mutations (75%) are associated with reduced cell surface expression of MCP. Most of these are heterozygous but a few are either homozygous or compound heterozygotes. In these, very low levels of cell surface expression are detected. In the remaining 25%, cell surface expression of MCP is normal but there is a reduction in either cofactor activity or ligand binding. The clinical phenotype of MCP-associated HUS differs from that of factor I and factor H. Most patients do not develop end-stage renal failure; in the Italian cohort 86% of patients retained normal renal function compared with 23% and 33%, respectively, of patients with CFH and IF mutations. In those patients that do develop end-stage renal failure, the outcome of transplantation is much better in patients with MCP mutations. To date, 10 such patients have been transplanted and in only one has there been recurrence of HUS within the allograft. In this patient the MCP mutation was found to only affect classic pathway activity, yet there was evidence of alternative pathway activation with low levels of both C3 and factor B (8). This patient is likely to have an additional mutation in a gene encoding another complement protein. The outcome of transplantation in patients known to have either a CFH or IF mutation is poor, with a >80% risk of graft loss due to recurrent disease within 2 years of transplantation (10). Because both factor H and factor I are predominantly produced by the liver,
combined liver–kidney transplantation is a logical option for patients known to have a mutation in the genes for either of these proteins. To date there have been two reports of this procedure in aHUS. One was complicated by irreversible liver failure necessitating a repeat liver transplant within a month (11). In the second case, death resulted from primary nonfunction of the liver (12). There has also been a third report where auxiliary, partial, orthotopic liver transplantation alone was complicated by death from infectious causes at 11 months posttransplant (13). Despite this, Saland et al. documented a case of aHUS with a compound heterozygous CFH mutation where combined liver–kidney transplantation has been successful with a >2 yr dual graft survival (14). It is interesting to note that in this case plasma exchange with fresh frozen plasma replacement was undertaken immediately before surgery.

These recent reports also show that some patients will have mutations in more than one complement regulator and this may determine penetrance of the disease (Esparza-Gordillo, unpublished observations, 2006). What are the implications of these recent studies in the management of patients with aHUS? First, all patients with end-stage renal failure who are being considered for transplantation should undergo CFH, IF, and MCP mutation screening. Details of laboratories offering this service are available on the GeneTests website (www.genetests.org). Second, those patients known to have either a CFH or IF mutation should be considered for combined liver-kidney transplantation.

References


Please see the related article, “Genetic and Functional Analyses of Membrane Cofactor Protein (CD46) Mutations in Atypical Hemolytic Uremic Syndrome,” on pages 2017–2025.