CASE REPORT

Complement Factor H–Associated Atypical Hemolytic Uremic Syndrome in Monozygotic Twins: Concordant Presentation, Discordant Response to Treatment

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• **Hemolytic uremic syndrome not associated with diarrhea (diarrhea negative, atypical) is less common than the diarrhea-positive typical form, but frequently results in end-stage renal failure. Although there are anecdotal cases of successful treatment with fresh frozen plasma alone, the value of this treatment compared with plasma exchange (PE) is difficult to assess. We describe monozygotic female twins who presented at 5 years of age with factor H–related (c.3572 > T; Ser1191Leu) atypical hemolytic uremic syndrome within months of each other. In the first twin to present, 10 sessions of PE with fresh frozen plasma replacement (40 mL/kg) resulted in resolution of hemolysis and improvement in plasma creatinine level (1.9 to 1.5 mg/dL [166 to 137 μmol/L]). Subsequently, 17 infusions of fresh frozen plasma were administered during a 4-month period for recurrent thrombocytopenia. However, within 4 months, plasma creatinine level increased to 5.1 mg/dL (450 μmol/L), necessitating peritoneal dialysis. When the second twin presented with the same disease, an extended PE regimen was instituted. After 10 daily sessions, PE was continued once every 2 weeks. Two recurrences were treated successfully with daily PE for 7 days. After 44 months of follow-up, kidney function is normal (plasma creatinine, 0.6 mg/dL [53 μmol/L]; creatinine clearance, 119 mL/min/1.73 m^2 [1.98 mL/s/1.73 m^2]) on maintenance PE therapy. In conclusion, the response to treatment of these monozygotic twins suggests that long-term PE may have benefits over plasma infusion alone.** ***Am J Kidney Dis*** **47:E27-E30.**

INDEX WORDS: Hemolytic uremic syndrome; complement factor H; plasma exchange; monozygotic twins.

HEMOLYTIC UREMIC syndrome (HUS) is characterized by a triad of microangiopathic hemolytic anemia, thrombocytopenia, and acute renal failure. Usually HUS is associated with a preceding diarrheal illness frequently caused by verocytotoxin-producing *Escherichia coli* (diarrhea-positive HUS). The nondiarrheal form of HUS, diarrhea-negative HUS or atypical HUS, is less frequent, usually leads to end-stage renal failure, and frequently recurs after renal transplantation.[1,2] Atypical HUS can be sporadic and familial; both forms are associated with mutations in complement proteins, including the regulators factor H and membrane cofactor protein and the serine protease factor I.[3-12] In contrast to diarrhea-positive HUS, which almost never relapses after kidney transplantation, the risk for recurrence of atypical HUS in allografts ranges from 9% to 64%.[2,7,9,13-17] In cases of HUS associated with a factor H mutation, the chance of recurrence increases to between 41% and 100%.[7,9,14] Treatment of patients with atypical HUS consists of supportive therapy and either plasma exchange (PE) and/or plasma infusions. Although there have been reports of success with both of the latter modalities, it has been difficult to make a direct comparison of their respective efficacy. We report the different response in monozygotic twins with factor H–associated atypical HUS to regimens that consisted of short-term PE and plasma infusions in 1 patient, and aggressive long-term PE in the other. A more favorable outcome was seen with the latter treatment.

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The patients described in this report are monozygotic female twins (genetic identity confirmed by the PowerPlex 16 System; Promega, Southhampton, UK). They are the youngest of a family of 5 children. The 2 eldest children, a boy aged 15 years and a girl aged 16 years, are unaffected. The third child, a 13-year-old girl, presented with HUS at the age of 3 years. She has lost 2 kidney grafts because of recurrent HUS; the second graft was lost despite prophylactic PE.[18,19] Von Willebrand factor–cleaving protease activity was normal in all 3 affected siblings. Levels of C3, C4, C3d, CH50, and AP50 were never abnormal. Factor H concentration also was normal, but factor H genotyping in all 3 affected individuals showed a heterozygous mutation in the exon coding for complement control protein module 20 (c.3572 C > T; Ser1191Leu; the A of the initiation codon ATG is regarded as nucleotide 1).

One of the twins presented with loss of appetite, nausea, vomiting, spontaneous hematomas, and oliguria at the age of 5 years. There was no preceding history of diarrhea. Investigations on admission showed Coombs-negative hemolytic anemia (hemoglobin level, 5.7 g/dL [57 g/L]; lactate dehydrogenase, 800 U/L; and haptoglobin, undetectable), thrombocytopenia (platelets, 94×10^9/L), and renal failure (creatinine level, 1.9 mg/dL [166 μmol/L]; blood urea nitrogen, 61.6 mg/dL [22 mmol/L]). Evidence of fragmentation was seen on a peripheral-blood smear, and urinalysis showed proteinuria and hematuria. A diagnosis of atypical HUS was made. Two days later, a Hickman catheter was placed in the right internal jugular vein, and daily PE was started using fresh frozen plasma (40 mL/kg) as replacement fluid. After 10 daily exchanges, platelet count and lactate dehydrogenase level normalized, but plasma creatinine level was still 1.5 mg/dL (137 μmol/L). PE was stopped, and the Hickman catheter was removed. During the next 4 months, she received a total of 17 daily infusions of fresh frozen plasma (10 mL/kg) for recurrent thrombocytopenia. Throughout this period, there was a progressive decline in renal function, and peritoneal dialysis therapy was started 4 months after presentation. One year later, bilateral nephrectomy was undertaken because of resistant hypertension.

At the age of 7 years, she received a cadaveric renal transplant. Prophylactic PE was undertaken pretransplantation and posttransplantation. Immunosuppressive therapy consisted of basiliximab, mycophenolate mofetil, methylprednisolone, and low-dose cyclosporine (maximal trough levels, ~100 μg/L). Plasma creatinine level is 1.0 mg/dL [90 μmol/L] 24 months after transplantation despite a relapse caused by a primary cytomegalovirus infection.[20]

Four months after the initial presentation with HUS, her twin sister presented with similar symptoms. Investigations were compatible with a diagnosis of HUS (hemoglobin level, 4.9 g/dL [49 g/L]; lactate dehydrogenase, 775 U/L; platelets 80×10^9/L; plasma creatinine, 1.5 mg/dL [132 μmol/L]). Daily PE using fresh frozen plasma (40 mL/kg) was immediately started. After 10 exchanges, platelet count normalized and plasma creatinine level decreased to 0.7 mg/dL (61 μmol/L). The frequency of PE was decreased progressively to 1 exchange every 2 weeks, and she continues to receive PE at this frequency. Vascular access was initially through a Hickman catheter and later through an arteriovenous fistula. The patient presented with 2 recurrent episodes of hemolysis without renal failure 3 and 19 months after the initial presentation. Each recurrence was associated with a respiratory tract infection and treated by increasing the frequency of PE to daily for 7 days. Renal function is still normal (plasma creatinine, 0.6 mg/dL [53 μmol/L]) 40 months after the initial episode. PE has been well tolerated and complicated only by 2 allergic reactions, which were controlled easily by using steroid and antihistamine therapy. Contrary to her sister, she is growing normally (146.2 versus 137.5 cm at the age of 9 years 7 months). Convalescent factor H levels in both twins are within the normal range (0.47 and 0.56 g/L).

DISCUSSION

The concordance of presentation of HUS in these monozygotic twins is striking. We are aware of only 1 other incidence in which monozygotic twins have been affected by atypical HUS. This is in a family originating from northeast England in which monozygotic twins presented within 18 months of each other.[3] The primary molecular defect in this family is unknown. It is our hypothesis that factor H mutations predispose to, rather than directly cause, HUS. We believe that a triggering factor, such as a viral illness, is necessary to initiate endothelial cell activation, which then is maintained by complement dysregulation. Although the same factor could be responsible in these twins, in neither twin was it possible to identify such a trigger. Although presentation of the twins was very similar, their response to treatment was different. The first twin underwent 10 PEs and, subsequently, 17 infusions of fresh frozen plasma and did not recover renal function. Of note, PE was discontinued before creatinine level normalized. The second twin underwent daily PE for 10 days, at which time creatinine level had normalized. Subsequently, the frequency of PE was decreased and has been maintained indefinitely. Despite 2 relapses that were treated with daily PE, she has normal renal function. This observation supports the suggestion that PE is a more effective treatment for atypical HUS than plasma infusion alone, and treatment should be long term.

However, it is of note that the initial treatment received by the 2 twins was identical. In 1 twin, creatinine level normalized, and in the other twin, it remained elevated at the time that PE was discontinued. It is possible that other factors, such as severity of the triggering factor and differences

in gene expression caused by environmental and epigenetic factors, could have contributed to this. Moreover, one cannot rule out the possibility that fresh frozen plasma alone would have been equally successful in the long-term management of the second twin. Perhaps most important is that PE should not be discontinued or changed in frequency until plasma creatinine level is normal. The rationale for the frequency of prophylactic PE used in the second twin was purely pragmatic, but is in accord with the observed 6-day half-life of factor H.[21] In addition, monitoring C3, C4, and factor H levels during prophylactic treatment might provide another means to assess disease activity.

The 3 affected members of this family all have a heterozygous factor H mutation (c.3572 C > T; Ser1191Leu) in the exon coding for complement control protein module 20 of factor H. This mutation has been reported previously.[4] Although the functional significance of this mutation has not been examined, other mutations in the same area affect the ability of factor H to bind to host surfaces and inactivate C3b.[22,23] The efficacy of PE over plasma infusions could be explained by removal of the mutant protein, although it has not been shown that such mutants exert a dominant negative effect. Both PE and infusion of fresh frozen plasma will provide an additional source of wild-type factor H, but the quantity provided by the former was 4 times greater with the protocols used for these patients. Another possibility that has not been closely examined is that the heparin used as an anticoagulant in PE acts as a complement inhibitor.[24]

In conclusion, the presentation and response to treatment shown by these monozygotic twins suggest that the mode and length of administration of plasma therapy is crucial if progression to end-stage renal failure is to be avoided in a patient with factor H–associated atypical HUS.

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