Factor H autoantibody is associated with atypical hemolytic uremic syndrome in children in the United Kingdom and Ireland

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Factor H autoantibodies can impair complement regulation, resulting in atypical hemolytic uremic syndrome, predominantly in childhood. There are no trials investigating treatment, and clinical practice is only informed by retrospective cohort analysis. Here we examined 175 children presenting with atypical hemolytic uremic syndrome in the United Kingdom and Ireland for factor H autoantibodies that included 17 children with titers above the international standard. Of the 17, seven had a concomitant rare genetic variant in a gene encoding a complement pathway component or regulator. Two children received supportive treatment; both developed established renal failure. Plasma exchange was associated with a poor rate of renal recovery in seven of 11 treated. Six patients treated with eculizumab recovered renal function. Contrary to global practice, immunosuppressive therapy to prevent relapse in plasma exchange–treated patients was not adopted due to concerns over treatment-associated complications. Without immunosuppression, the relapse rate was high (five of seven). However, reintroduction of treatment resulted in recovery of renal function. All patients treated with eculizumab achieved sustained remission. Five patients received renal transplants without specific factor H autoantibody–targeted treatment with recurrence in one who also had a functionally significant *CFI* mutation. Thus, our current practice is to initiate eculizumab therapy for treatment of factor H autoantibody–mediated atypical hemolytic uremic syndrome rather than plasma exchange with or without immunosuppression. Based on this retrospective analysis we see no suggestion of inferior treatment, albeit the strength of our conclusions is limited by the small sample size.

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Atypical hemolytic uremic syndrome (aHUS) is commonly a consequence of complement dysregulation[1] and is characterized by the triad of microangiopathic hemolytic anemia, thrombocytopenia, and acute kidney injury.[1] It is rare, with an incidence of 0.42 per million in the United Kingdom,[2] but associated with significant morbidity and mortality.

aHUS is associated with mutations in genes encoding complement regulatory proteins, complement factor H (*CFH*), complement factor I (*CFI*), and membrane cofactor protein (*CD46*)[1] and in genes encoding the complement components complement factor B (*CFB*) and C3 (*C3*).[1] For all of these complement mutations, penetrance is incomplete and influenced by genetic modifiers in addition to environmental triggering events.[1]

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aHUS is also associated with acquired complement dysregulation, occurring consequent to the development of autoantibodies directed against complement factor H (FH)[3] and factor I.[4] Anti-FH–associated aHUS predominantly presents in childhood.[3] The proportion of children with aHUS who have anti-FH autoantibodies has been reported as 5% to 25% in European cohorts[5] and as high as 56% in a large Indian cohort.[6] Anti-FH autoantibodies have been shown to be directed against different epitopes, in some reports exclusively[7,8] but in others predominantly[9–11] located at the C-terminal of FH; a polyclonal response to both N and C termini has also been reported,[10,12] and functional analyses have demonstrated disruption of complement regulation by multiple mechanisms.[12]

A strong association has been observed between anti-FH autoantibodies and a homozygous deletion of *CFHR1* and *CFHR3*, which encode complement FH–related proteins 1 and 3. A deletion encompassing *CFHR1* and *CFHR4* has also been reported in anti–FH- associated aHUS, suggesting that it is the absence of FH-related protein 1 that is most important in the development of FH autoantibodies,[1,9,12–19] and homozygous deletion of *CFHR1* has been identified in 79% to 89% of affected individuals.[5]

Recent international consensus recommendations on the management of aHUS highlight the uncertainty regarding optimal management in patients with anti-FH autoantibodies.[20] In the United Kingdom and Ireland, our management regimen, in contrast to practice in other countries, has not incorporated immunosuppression. We report here our experience of the management of pediatric FH autoantibody–associated aHUS.

RESULTS

Patient details

A total of 175 children younger than 16 years of age from the United Kingdom and Ireland who were referred to the UK National aHUS center between 2000 and 2015 were examined for FH autoantibodies. Twenty-two children (13%) had positive FH autoantibody results; 17 of 22 children (9.7% of the total cohort) had titers higher than the international standard[21] (100 relative units) on serum samples obtained at the time of the initial presentation and were included in this study (mean follow-up was 6 years, 5 months; range, 7 months to 13 years, 7 months). Five of 22 children did not meet the inclusion criteria (details in Supplementary Methods). In all patients, a clinical diagnosis of aHUS was made based on the presence of microangiopathic hemolytic anemia, thrombocytopenia, and acute kidney injury and the absence of Shiga toxin and secondary causes.[2] In 7 patients, a renal biopsy was performed that demonstrated thrombotic microangiopathy. The median age at presentation was 8 years (range, 1–15 years), and there was a male preponderance (male:female ratio = 11:6) (Figure 1).

Clinical presentation

Clinical features at the time of presentation are shown in Table 1. Prodromal gastrointestinal symptoms were commonly observed, including abdominal pain (9/16 patients), vomiting (9/16 patients), and diarrhea (8/16 patients). Infection was reported as a triggering event in 7 of 17 patients. Extrarenal manifestations were reported in 8 of 16 patients and included central nervous system involvement, hepatitis, and pancreatitis. The serum creatinine and platelet values at presentation are shown in Supplementary Figure S1.

Complement analysis ($N = 17$)

Initial complement levels are shown in Table 2 and Supplementary Figure S2 ($N = 17$). Thirteen patients had normal C3 levels and 12 had normal C4 levels; 3 patients (patients 2, 20, and 24) had both low C3 and low C4. Two patients (patients 5 and 15) had low FH levels (Figure 2a), and neither was found to have a rare genetic variant in *CFH*. No patients had abnormal levels of CD46 or factor I.

Anti-FH autoantibodies ($N = 17$)

The anti-FH autoantibody titers at presentation are shown in Figure 2b (range, 277–4000 relative units; median, 1594 relative units). In 9 of 17 patients, circulating FH/autoantibody immune complexes were detected, and these patients had lower C4 levels (Supplementary Figure S3). In 10 patients, anti-FH autoantibody titer measurements at multiple time points up to 163 months after the first presentation were available (Figure 3). In only 1 patient did the FH autoantibody titer decrease to less than the international standard. In 3 patients treated with eculizumab only, the titer increased. In 5 patients who received immunosuppression in association with current ($n = 4$) or previous ($n = 1$) transplantation, 1 of whom was also treated with eculizumab, the titers decreased, but 4 of 5 remained higher than the international standard. In 2 patients (patients 2 and 17) who did not receive eculizumab or immunosuppression and recovered renal function and remain in remission, the titers remain positive 12 (patient 2) and 9 (patient 17) years after the first presentation.

The binding epitopes of the anti-FH autoantibodies were determined (Figure 4 and Supplementary Table S1). In 15 of 17 patients, the antibodies bound to the C-terminal; 14 of these 15 patients had homozygous deletion of *CFHR1*, whereas the 2 patients (patients 6 and 22) with antibodies that did not bind to the C-terminal did not have a deletion of *CFHR1*. In 12 of 15 patients with antibodies that bound to FH short consensus repeats 19 and 20, there was also positive binding to the C-terminal short consensus repeats 4 and 5 of FH-related protein 1. In 2 patients, the autoantibodies apparently cross-reacted with FH-related proteins 2 through 5 (Supplementary Table S2), but this was not confirmed on Western blotting (not shown), suggesting this interaction was nonspecific or low-affinity binding.