Exceptional Case

Novel complement factor H gene mutation causing atypical haemolytic uraemic syndrome: early Eculizumab prevents acute dialysis

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Abstract

We describe the clinical course and response to treatment of atypical haemolytic uraemic syndrome (aHUS) in two sisters presenting to our hospital 6 years apart with a novel complement factor H mutation that has not been described previously in literature and demonstrates the genetic complexity of this ultra-rare disease. The contrast in course and outcome of disease between the two sisters highlights the rapid evolution of management of aHUS, the importance of rapidly establishing a diagnosis, and how minimizing time to eculizumab therapy significantly reduces associated morbidity and mortality.

Key words: AKI, complement, dialysis, gene expression, thrombotic microangiopathy

Background

Emerging evidence suggests environmental triggers and genetic predisposition play a role in atypical haemolytic uraemic syndrome (aHUS) disease activation, well demonstrated in this unique example due to the novel genetic link between the two cases.

Case

Sister A presented in 2008 at age 21 years with diarrhoea and evidence of a thrombotic microangiopathy (TMA) with microangiopathic haemolytic anaemia (MAHA), thrombocytopenia (platelets $75 \times 10^9/L$) and renal failure. Relevant clinical features and investigations excluded other causes of TMA and supported a clinical diagnosis of aHUS (see Table 1). She was commenced urgently on haemodialysis. aHUS is genetically determined and steroids and immunosuppressive medications have no role in this context, however, due to ADAMTS13 testing only being available retrospectively, she was heavily immunosuppressed (see Table 1). Apart from an initial brief recovery, she remained dialysis dependent.

About 21 months after initial presentation and 15 months without evidence of ongoing haemolysis, she received a related living donor kidney transplant (from her mother) and had low-level Human leukocyte antigen (HLA) Class II donor-specific antibodies. The donor had no prior evidence of MAHA and genetic testing was unavailable at the time. Pre-transplant conditioning involved three Plasma exchanges (PEXs) over 1 week...
and Intravenous immunoglobulin (IVIg). Post-transplant immunosuppression included anti-thymocyte globulin induction, IVIg and PEXs along with tacrolimus, mycophenolate mofetil and oral prednisolone. She had two early steroid-responsive acute cellular rejection and relapse of MAHA 5 weeks into the transplant. Tacrolimus level was therapeutic at 9.7 μg/L, 2 days later. Due to family history and ruling out other causes, aHUS was diagnosed. PEXs were commenced on the day of admission and first dose of eculizumab (900 mg) was administered within 75 h of presentation, followed weekly for 4 weeks and 1200 mg fortnightly, thereafter. Serum creatinine peaked at 580 μmol/L, 8 days post-admission with the patient never requiring dialysis support and after 17 months of treatment with eculizumab, her serum creatinine declined to 100 μmol/L.

Genetic testing of both sisters revealed heterozygosity for c.3493+2T>G splice variant in intron 21 of the CFH gene (NM_000186.3). This pathogenic variant abolishes the consensus splice donor site and is predicted to result in skipping of exon 21, and has not been reported previously. The variant was identified via a targeted exome-sequencing panel performed on Sister B (TruSight One panel on an Illumina HiSeq 2500) that included CFH, CFI, CD46, CFB, C3, MMACHC, THBD and C5_21. Cascade testing demonstrated that Sister A carried the same variant and that both sisters had inherited the variant from their mother, who remains clinically well since the time of donation.

### Discussion

These cases highlight the variable disease penetrance seen in families with disease-causing CFH variants. The mother never displayed evidence of aHUS. This variability emphasizes the complexity and phenotypic variability in families with the same gene mutation. Within this family, mutations within other known aHUS-related genes were not identified. There is a suggestion that multiple gene mutations may increase disease penetrance [1].

There is limited evidence available to clinicians to predict occurrence and timing of disease onset in clinically well family members who are heterozygous for a familial CFH variant [2], highlighting the importance for genetic counselling and informed consent prior to performing cascade testing in extended families with known CFH gene variants. In patients who are appropriately counselled, knowledge of increased risk for aHUS within a family offers the benefit of rapid access to appropriate treatment, as occurred in Sister B. There is a third male sibling who has never displayed evidence of disease.

Although the time from presentation to administration of eculizumab is linked to likelihood of renal recovery [3], our case...
also highlights that it can prevent the need for dialysis in the acute setting. In a recent case series of 19 patients, median time between aHUS onset and eculizumab therapy initiation was 6 days and only three patients received eculizumab in a shorter time frame after onset of aHUS [4]. The proposed model of care emphasizes minimizing time to eculizumab therapy as the overriding goal when aHUS is suspected, as evidenced by the distinct advantage that Sister B had, with known family history affecting the decision to commence eculizumab as soon as the drug could be procured.

This case demonstrates the evolution of our understanding and treatment of aHUS over the last 10 years. Here we report a novel, as yet not described, CFH gene mutation and highlight the importance of a high index of suspicion in achieving a rapid diagnosis and early eculizumab administration to prevent the need for acute dialysis and enhance renal recovery.

Conflict of interest
B.B. has received a travel grant and honorarium from Alexion Pharmaceuticals, Inc. The other authors have no other conflict of interests to declare.

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