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DOI link to article:
https://doi.org/10.1093/ckj/sfx030

Date deposited:
20/06/2017
Exceptional Case

Rare genetic variants in Shiga toxin–associated haemolytic uraemic syndrome: genetic analysis prior to transplantation is essential

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Abstract

We present a case of haemolytic uraemic syndrome (HUS) in a 16-year-old female with serological evidence of acute Escherichia coli O157:H7 infection. She progressed to established renal failure and received a deceased donor kidney transplant. Shiga toxin–associated HUS (STEC-HUS) does not recur following renal transplantation, but unexpectedly this patient did experience rapid and severe HUS recurrence. She responded to treatment with the terminal complement inhibitor eculizumab and subsequent genetic analysis revealed a rare variant in a complement gene. This highlights the importance of genetic analysis in patients with STEC-HUS prior to renal transplantation so that management can be individualized.

Key words: atypical haemolytic uraemic syndrome; complement; eculizumab; renal transplantation; STEC-HUS

Introduction

Haemolytic uraemic syndrome (HUS) is characterized by the clinical triad of acute kidney injury (AKI), thrombocytopenia and microangiopathic haemolytic anaemia (MAHA) [1]. The most common form is caused by enteric infection with Shiga toxin–producing bacteria, most frequently Escherichia coli serotype O157:H7 [2], known as STEC-HUS, with an estimated incidence in the UK of 7.1 per million [3]. STEC-HUS is a rare (~5%) self-limiting illness with consequent established renal failure (ERF) [4].

The atypical form of HUS (aHUS) is usually associated with dysregulation of the complement system resulting from inherited or acquired defects. It is rare (UK incidence 0.42 per million [5]), but historically has been associated with a poor outcome (>50% ERF) [6, 7]. Additionally, due to the genetic nature of the disease, aHUS recurrence following renal transplantation and subsequent graft loss was the rule in those with mutations in liver-produced serum complement proteins [1, 8–10]. The development of the terminal complement inhibitor eculizumab has transformed the management and prognosis of aHUS and the outcome following renal transplantation [5, 11].
In contrast, recurrence of HUS after renal transplantation does not occur in STEC-HUS [8, 9].

We report a case of HUS in a 16-year-old female with serological evidence of acute E. coli O157:H7 infection that resulted in ERF; she experienced rapid and severe recurrence of HUS following renal transplantation, and subsequent analysis identified a rare genetic variant in C3.

**Case report**

A 16-year-old female presented with AKI (creatinine 324 μmol/L) and a 4-day history of vomiting without diarrhoea. Her only past medical history was acne, and Roaccutane had been commenced 1 month earlier; blood tests performed at that time were all normal. Her mother had been unwell with a diarrhoeal illness 2 weeks previously.

Blood tests on admission were consistent with a thrombotic microangiopathy (TMA): haemoglobin 9.9 g/dL, platelets 41 × 10^9/L, bilirubin 38 μmol/L, lactate dehydrogenase (LDH) 1865 U/L, reticulocytes 107 × 10^9/L and red blood cell fragmentation on the blood film; Coombs test was negative and coagulation was normal. Treatment with plasma exchange was commenced (total of eight exchanges) and thrombotic thrombocytopenic purpura (TTP) was excluded (ADAMTS13 activity 76%). The National Health Protection Agency (HPA) laboratory reported that immunoglobulin M (IgM) antibodies to E. coli O157 lipopolysaccharide (LPS) were positive, in keeping with acute STEC-HUS [10]. Levels of C3, C4, factor H and factor I were normal. Her renal function deteriorated and she required haemodialysis, as well as ventilatory and inotropic support for ventilatory support and blood pressure control.

A kidney biopsy performed 3 months later, showing features of TMA; immunofluorescence showed segmental C3 deposition in the glomerular tuft. Later, 10 months after presentation, she was admitted to the ICU for management of hypertension and was treated with plasma exchange. Tacrolimus levels were therapeutic. The following day she had multiple generalized tonic–clonic seizures, severe headache, photophobia and blurred vision, which progressed to cortical blindness over the course of 4 h in the context of a blood pressure of 190/113 mmHg. Magnetic resonance imaging (MRI) of the brain was consistent with posterior reversible encephalopathy syndrome (PRES) (Figure 1A). She was admitted to the ICU for management of hypertension and treatment with eculizumab was commenced. The neurological symptoms resolved within 48 h and over the following 2 weeks the renal function improved and haematological parameters normalized. A transplant biopsy performed 15 days post-operatively demonstrated severe acute TMA and borderline acute T-cell–mediated rejection (Figure 1Bii).

Subsequent genetic analysis identified a heterozygous rare genetic variant in C3: c.4855A>C p.(Ser1619Arg). The functional significance has not been assessed, however, the amino acid is well conserved, in silico analysis suggests that the variant is possibly deleterious and structural modelling (Figure 1C) demonstrates that this is in the same C3 domain as the variant c.4973T>C p.(Val1658Ala) demonstrated by Sartz et al. to be functionally significant [12].

A transplant biopsy performed 3 months post-operatively for proteinuria (urine protein:creatinine ratio 243 mg/mmol) showed no significant abnormality. A fourth transplant biopsy was performed 5 months post-operatively because the creatinine rose from 130 to 180 μmol/L. This showed acute T-cell–mediated rejection (Banff IB) (Figure 1Biii) and she was treated with intravenous methylprednisolone. Immunofluorescence, including kappa and lambda, was negative. She remains on eculizumab, prednisolone, tacrolimus and MMF, and 3 years after transplantation she is well and creatinine is 157 μmol/L.

**Discussion**

This patient presented with a TMA and normal ADAMTS13 activity, and although she had no history of diarrhoea, she had serological evidence (positive IgM) of recent E. coli O157:H7 infection consistent with a diagnosis of STEC-HUS. However, a faecal specimen was not analysed and the serodiagnosis is sensitive but not specific for verocytotoxin-producing E. coli (VTEC) [15]. In addition, serum antibodies to the LPS of E. coli O157 have been detected in healthy people in rural communities in the UK [10]. The absence of diarrhoea does not preclude STEC-HUS [2] and –5% of people with STEC-HUS may not have diarrhoea [13]. We recommend that all patients with HUS, even those without a history of diarrhoea, be investigated for STEC infection by culture and Shiga toxin polymerase chain reaction on a faecal specimen, as well as serological testing, to optimize sensitivity [17, 18].

STEC-HUS is said not to recur following renal transplantation [8, 9]; however, a severe TMA evolved within 1 week of transplantation, resulting in AKI and neurological manifestations. She responded promptly to treatment with the terminal complement inhibitor eculizumab. Subsequent genetic analysis revealed the p.(Ser1619Arg) heterozygous rare genetic variant in C3 [12].

Historically, aHUS recurrence following transplantation has occurred in 60% of patients, with the highest risk observed in patients with mutations in CFH and C3 [1, 19, 20]. This patient had seizures 10 months after the initial presentation and neurological symptoms during the recurrence after transplantation; it is not known whether extrarenal manifestations occur consequent to AKI, hypertension, TMA or complement dysregulation [21].

Very rare cases of STEC-HUS infection unmasking latent complement defects and triggering aHUS have been described [22–25] and Alberti et al. [26] also reported post-transplant recurrence leading to graft loss in two patients with STEC-HUS who were subsequently found to have complement gene mutations.

In this case, due to ongoing proteinuria, for disease resolution we looked for evidence of eculizumab deposition in the renal biopsy as described by Herlitz et al. in C3G [27]. That we were unable to detect immunoglobulin G (IgG) kappa deposition may reflect the differing nature of complement activation in aHUS compared with C3G.

In summary, as ERF following STEC-HUS is rare and a priori knowledge of an underlying complement mutation allows prophylactic eculizumab to be given, genetic screening should be performed in all individuals who develop ERF following STEC-HUS and who are being considered for transplantation, as
recommended in a 2015 Kidney Disease: Improving Global Outcomes consensus document [21]. This personalized approach to HUS will prevent the morbidity and mortality associated with recurrent disease [28].

**Funding**

V.B has received funding from the Northern Counties Kidney Research Fund.

**Conflict of interest statement**

Newcastle University has received honoraria for consultancy work (D.K.) from Alexion Pharmaceuticals, and D.K. is a director of and scientific advisor to Gyroscope Therapeutics.

**References**


