CASE REPORT

Decreased severity of Shiga toxin-producing *Escherichia coli* haemolytic uraemic syndrome (STEC-HUS) in a child with type 1 von Willebrand diseaseMatthew A Geramita,¹ Johannes Hofer,² James Cooper,³ Michael L Moritz³¹Children's Hospital of Pittsburgh, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA²Department Zahn Mund und Kieferheilkunde und Mund Kiefer und Gesichtschirurgie, Medizinische Universität Innsbruck, Innsbruck, Tirol, Austria³Department of Pediatrics, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, Pennsylvania, USA

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SUMMARY

Shiga toxin-producing *Escherichia coli*-associated haemolytic uraemic syndrome (STEC-HUS) is characterised by haemolytic anaemia, thrombocytopenia and acute kidney injury. Von Willebrand Factor (vWF) is an important mediator of normal thrombi formation and indirect evidence suggests that vWF may play an important role in Shiga toxin-induced thrombi formation. Clinical evidence supporting the role of vWF in STEC-HUS is lacking. A 10-year-old girl with type 1 von Willebrand Disease (vWD) had a mild case of STEC-HUS, with nadir haemoglobin 7.3 g/dL and platelet count 105×10^9 cells/L and peak serum creatinine 0.56 mg/L and lactate dehydrogenase 741 U/L. This is the first report of STEC-HUS in a patient with vWD. We speculate that the quantitative deficiency of vWF associated with type 1 vWD may have attenuated the course of disease by reducing platelet aggregation, complement activation and thrombi formation. This case adds to a growing literature supporting a link between vWF and STEC-HUS.

BACKGROUND

Haemolytic uraemic syndrome (HUS) is characterised by thrombocytopenia, microangiopathic haemolytic anaemia and acute kidney injury. Most cases of diarrhoea-associated HUS are caused by an enteric infection with Shiga toxin-producing strains of *Escherichia coli* (STEC),^{1–3} most commonly O157:H7, a serotype that typically leads to a severe illness course.⁴ In children, STEC-HUS can lead to serious complications, including the need for acute dialysis and blood products, and death in up to 3%–5% of patients.^{4,5}

Multiple studies have traced the sequence of events by which Shiga toxins (Stxs) cause thrombi formation and subsequently thrombocytopenia and haemolytic anaemia and suggest that von Willebrand factor (vWF), a critical element of normal platelet haemostasis, plays an important role. Stx induces endothelial cell secretion of unusually large vWF (ULVWF) multimers^{6,7} and impairs the breakdown of ULVWF multimers by ADAMTS13 (a disintegrin-like and metalloproteinase with a thrombospondin type 1 motif, member 13), the enzyme that normally cleaves vWF.^{7,8} Additionally, vWF was recently shown to be a cofactor in complement activation^{9–11} which is necessary for Stx-induced thrombi formation.^{12–14} Finally, in thrombotic thrombocytopenic purpura (TTP), a

disease with similar clinical manifestations as HUS, large deposits of vWF lead to haemolytic anaemia and thrombocytopenia due to a deficiency in ADAMTS13. However, clinical evidence linking vWF to STEC-HUS is lacking.

Von Willebrand disease (vWD) is the most common hereditary blood clotting disorder and arises from either a qualitative or quantitative deficiency in vWF. vWD type 1, the most common type, is a quantitative defect which is heterozygous for the defective gene. Most cases are either asymptomatic or have mild symptoms. Presented is a case of a 10-year-old girl with type 1 vWD who developed a mild course of O157:H7 STEC-HUS. This case describes an association between vWF and STEC-HUS that may be important for better understanding its pathogenesis.

CASE PRESENTATION

A 10-year-old, 44 kg, girl with type 1 vWD was admitted to Children's Hospital of Pittsburgh with 3 days of abdominal pain and profuse bloody diarrhoea. She received supportive care with intravenous normal saline for hydration and Humate-P (replacement vWF) for haemostasis. Stool cultures grew *E. coli* O157:H7. She was discharged on hospital day 2 after diarrhoea improved and stools were no longer bloody. Her renal function tests and complete blood count were normal at discharge (table 1). The patient and her sister were diagnosed with probable vWD according to recent National Institutes of Health criteria¹⁵ when the patient was 7 years old during a previous hospital admission; however, the diagnosis was not genetically confirmed. At the time of diagnosis, she appeared to be mildly affected with vWD as her von Willebrand antigen was 0.39 units/mL (normal 0.5 to 1.5), ristocetin cofactor was 0.38 units/mL (normal 0.5 to 1.5) and factor VIII was 0.45 units/mL (normal 0.6–1.5). The closure times were mildly prolonged in both the epinephrine and adenosine diphosphate cartridges. Her only clinical manifestation was recurrent epistaxis.

Five days following discharge, she presented with a frontal headache, vomiting and severe abdominal pain. On physical examination, she was normotensive, afebrile and haemodynamically stable. She was pale and had mild periorbital oedema. Her abdomen was mildly tender to palpation. Petechiae were absent, but ecchymosis were visible on

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Table 1 Key laboratory values over hospital course

Hospital day relative to current admission	First hospitalisation		Second hospitalisation					Follow-up
	-6	-5	0	+1	+2	+3	+4	+8
Serum levels								
Haemoglobin, g/dL	13.9	13.3	8.5	7.3	7.5	7.5	8.1	10.0
Platelet count, $\times 10^9$ cell/L	381	349	112	105	176	255	359	669
Leucocyte count, $\times 10^9$ cell/L	18.7	17.5	12.4	9.8	9.8	9.2	10.7	8.3
Blood urea nitrogen (BUN), mg/dL	5	7	13	12	9	8	8	14
Serum creatinine, mg/dL	0.39	0.26	0.56	0.46	0.42	0.45	0.52	0.49
LDH, U/L	–	–	741	–	444	393	424	–

LDH, lactate dehydrogenase.

her shins bilaterally. The remainder of the history and physical examination was unremarkable. She was found to be anaemic and thrombocytopenic and was readmitted to the hospital. Other aspects of the patient's medical history were unremarkable.

INVESTIGATIONS

Laboratory studies at presentation revealed a haemoglobin of 8.5 g/dL, platelet count of 112×10^9 cells/L, leucocyte count of 12.4×10^9 cells/L, lactate dehydrogenase (LDH) of 741 U/L and haptoglobin of 31 mg/dL (table 1). Peripheral blood smear revealed red blood cell fragments. Urinalysis revealed 2+ blood, trace protein and no leucocytes, nitrites, white blood cells or bacteria. Biochemistries revealed blood urea nitrogen of 13 mg/dL and serum creatinine of 0.56 mg/dL, elevated from 0.26 mg/dL during the prior admission (table 1). Electrolytes were within normal limits. Direct Coombs test was negative. The patient was admitted for likely STEC-HUS given the haemolytic anaemia, thrombocytopenia and acute kidney injury in the setting of a recent *E. coli* O157:H7 infection.

OUTCOME AND FOLLOW-UP

During the patient's 5-day hospital stay, she was hydrated with normal saline until her haemoglobin, platelet count, LDH and serum creatinine improved (table 1). She did not require blood or platelet transfusions or dialysis. Humate-P was not given. Amylase and lipase were monitored given the patient's abdominal pain and the association of HUS with pancreatitis,¹⁶ and were within normal limits. The patient did not exhibit any other neurological signs or symptoms other than headaches and consequently, no central nervous system imaging was initiated. The patient's headaches and vomiting improved with acetaminophen and ondansetron. She had intermittent systolic blood pressures in the 120s but did not require treatment with anti-hypertensive medications. On discharge, her haemoglobin was 8.1 g/dL, platelet count was 359×10^9 cells/L, serum creatinine was 0.52 mg/dL and LDH was 424 U/dL.

DISCUSSION

Recent work has begun to trace the molecular events by which Stxs lead to thrombi formation, haemolytic anaemia and thrombocytopenia. Indirect, *in vitro*, evidence suggests that vWF plays a role in this process, but clinical evidence is lacking. This case of a 10-year-old girl with type 1 vWD and a mild course of STEC-HUS is the first report of STEC-HUS in a patient with vWD and provides a clinical, although speculative, link between vWF and Stx-induced thrombi formation.

The clinical course of STEC-HUS in this patient would be considered mild when compared with a prospective study of almost 400 paediatric patients with O157:H7 STEC-HUS in Germany and

Austria.⁴ This patient's most severe laboratory values were less severe than the 25% IQR reported, and this patient did not require interventions such as blood transfusions, platelet transfusions or dialysis that were necessary in 75%, 16% and 60% of patients reported.⁴ This patient was hospitalised for 5 days, which is less than the median length of hospital stay of 11 days in a large US sample of adult and paediatric patients with STEC-HUS.¹⁷ These studies from large hospital centres may overestimate the severity of STEC-HUS given that less severe cases may be treated at smaller community hospitals. The prevalence of mild cases of STEC-HUS may also be higher than is currently reported.

In vitro studies provide evidence that reductions in vWF, as seen in type 1 vWD, may be associated with a mild course of STEC-HUS. The complement system plays an important role in Stx-induced thrombi formation^{12–14} and recent work indicates that vWF is not only important for haemostasis-thrombosis but also a cofactor in complement activation.^{9–11} Importantly, Stx induces endothelial cell secretion of ULVWF multimers^{6,7} and impairs the ADAMTS13 breakdown of ULVWF multimers.^{7,8} Therefore, during an acute episode of STEC-HUS, there are likely increased amounts of vWF released onto endothelial cell membranes due to a combination of increased secretion and decreased breakdown. Consequently, we suggest that, in the patient presented here, reduced levels of vWF led to a more benign disease course due to reductions in platelet aggregation, complement activation and thrombus formation. As a caveat, recent work has also speculated that vWF factor has a protective effect on endothelial cells as endothelial cells from patients with type 3 vWD showed more pronounced complement C3c deposition and cytotoxicity compared with endothelial cells from control patients.¹⁸ Therefore, the effects of vWF on endothelial cells may be multifactorial and depend the size on vWF multimers.¹¹ The case presented here only describes a potential association between vWD and a mild case of STEC-HUS and is unable to provide direct evidence that the mild course of STEC-HUS is due to reduced vWF. Future *in vitro* work studying Stx-induced thrombi formation in vWF-deficient mice¹⁹ will be important for providing direct evidence of vWF's role in STEC-HUS.

Understanding the mechanisms that lead to Stx-induced thrombi formation and mediators of less severe presentations of STEC-HUS will help reduce the high morbidity and mortality typically seen in STEC-HUS. The case presented here of a mild course of STEC-HUS in a patient with vWF supports *in vitro* data that suggest an association between vWF and STEC-HUS. Future *in vitro* work could build on this clinical observation and aim to create experimental paradigms that directly address the causal relationship between vWF and STEC-HUS and work towards potential novel therapies for STEC-HUS such as the use of anti-vWF antibodies.

Learning points

- ▶ Von Willebrand Factor (vWF) is an important mediator of normal thrombi formation and complement activation and indirect evidence suggests that vWF plays a role in Shiga toxin-induced thrombi formation in Shiga toxin-producing *Escherichia coli*-associated haemolytic uraemic syndrome (STEC-HUS).
- ▶ Presented is a case of a 10-year-old girl with type 1 von Willebrand Disease (vWD) who developed a mild course of O157:H7 STEC-HUS. This is the first report of STEC-HUS in a patient with vWD.
- ▶ We speculate that reduced levels of vWF in this patient may lead to a more benign course of STEC-HUS due to reductions in platelet aggregation, complement activation and thrombus formation in STEC-HUS.

Contributors MAG wrote the first draft of the manuscript. MLM cared for the patient, outlined the topic and edited the final draft. JC and JH provided their expertise in the critical review and editing of the manuscript.

Competing interests None declared.

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