

Seizure as First Manifestation of Hemolytic Uremic Syndrome with Bacteremia due to Shiga Toxin-Producing *Escherichia coli*

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ABSTRACT

Hemolytic uremic syndrome (HUS) often causes neurologic symptoms, but they typically occur as a later symptom of the syndrome. In addition, the Shiga toxin-producing *E. coli* (STEC) which causes HUS rarely causes bacteremia. We present the case of a 10-year-old male with Smith-Magenis syndrome who was admitted to the hospital due to STEC gastroenteritis, who was initially improving with supportive care, and then subsequently developed fever and had multiple seizures which were different from his typical seizure semiology. Over the subsequent 48 hours he gradually developed microangiopathic hemolytic anemia consistent with HUS. His course was further complicated by *E. coli* bacteremia and oliguric renal failure requiring renal replacement therapy, depressed mental status, and difficult-to-control hypertension. This case demonstrates the importance of neurologic manifestations as a harbinger of developing HUS.

KEYWORDS: hemolytic uremic syndrome; Shiga toxin; seizures; bacteremia

CASE REPORT

A 10-year-old male with Smith-Magenis syndrome (a neurodevelopmental disorder caused by 17p11.2 deletion, with primary symptoms of autism, developmental delay, and epilepsy) was admitted to a large New England tertiary care children's hospital due to abdominal pain, bloody diarrhea and non-bloody emesis. A stool PCR panel was positive for Shiga toxin-producing *E. coli* (STEC). The patient had no recent travel, unusual food intake, ill household members, or livestock exposures. Thus, the source of his infection was unknown. His admission workup was otherwise significant for normal hemoglobin, mildly low platelets (196,000/ μ L), and normal renal function. He was initially admitted to the Pediatric Hospital Medicine service for intravenous (IV) hydration and supportive care, appropriate standard of care for symptomatic STEC infection. Complete blood counts and basic metabolic panels were monitored twice daily due to the etiology of the stool pathogen and to monitor for laboratory findings of HUS. He remained hospitalized due to the persistence of his pain and stool output requiring IV fluid replacement. His hemoglobin and renal function remained

normal for the first five days of his admission. Platelets decreased to 127,000/ μ L on the morning of hospital day three but then improved to >190,000/ μ L and were stable on multiple rechecks between hospital days three and five.

Overnight on hospital day five, the patient became febrile for the first time during his illness, to a temperature of 104 degrees Fahrenheit. Shortly thereafter, he had two episodes of loss of consciousness with associated tachycardia and eyelid fluttering, followed by somnolence. These episodes were concerning for seizures with post-ictal periods. Although the patient had seizures at baseline, his typical semiology was absence seizures with preserved consciousness; he had no history of seizures with associated loss of consciousness. The patient had not missed any doses of his anti-epileptic medications. Additionally, he was outside the age typically seen with febrile seizure.

Repeat laboratory examinations drawn following the event showed a mild decrease in platelets to 137,000/ μ L from 191,000/ μ L, a slight increase in serum creatinine from 0.4mg/dL to 0.5mg/dL, and a mildly elevated INR to 1.4. His urine output was normal. However, due to the acute change in his neurologic status, the patient was transferred to the pediatric intensive care unit (PICU) for closer monitoring.

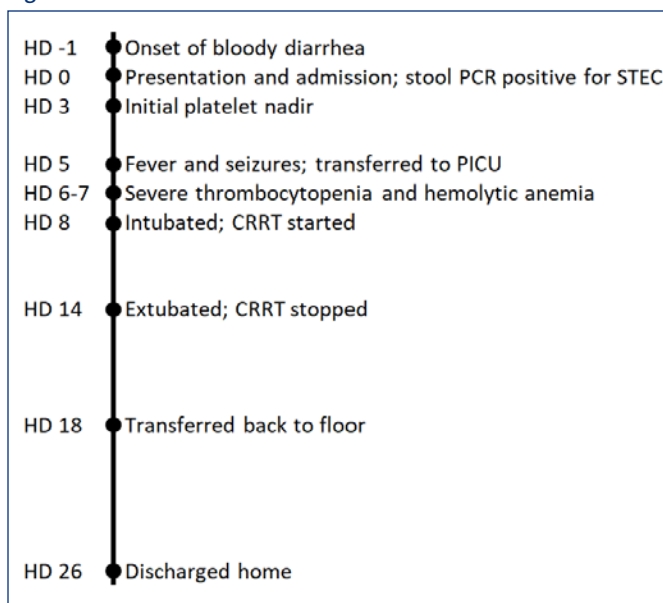
In the PICU, over the next 48 hours, the patient developed worsening thrombocytopenia to a nadir of 37,000/ μ L, as well as epistaxis. He then developed anemia with schistocytes and non-oliguric acute kidney injury, all consistent with HUS. He also remained febrile to a maximum temperature of 106 Fahrenheit, and significantly somnolent. An MRI brain without contrast, performed due to somnolence, was unremarkable. A lumbar puncture was not performed. Subsequently, blood cultures collected on the day of PICU transfer resulted with Gram negative rods, found to be pan-sensitive *Escherichia coli* (*E. coli*). Despite the risk of worsening HUS, ceftriaxone was started on hospital day seven due to the greater risk of untreated gram negative sepsis. Antibiotics were narrowed to ampicillin after sensitivities resulted.

On hospital day eight, he developed oliguric renal failure, hyperkalemia, and volume overload, with respiratory distress requiring intubation. A tunneled dialysis catheter was placed on hospital day nine and he was started on continuous renal replacement therapy (CRRT). Repeat blood cultures prior to central access placement were negative.

Despite multiple complications during his PICU course including extensive thrombophlebitis (requiring broadening antibiotics to ampicillin-sulbactam for better Staphylococcal coverage in addition to *E. coli*), profound thrombocytopenia and anemia (requiring multiple transfusions), and persistent electrolyte abnormalities, the patient was ultimately extubated and CRRT was discontinued on hospital day 14. He received one hemodialysis session while his renal function was still recovering, but did not require further renal replacement therapy after hospital day 16. He was transferred back to the floor on hospital day 18.

The patient's course after return to the pediatric hospital medicine service was significant for hypernatremia, refractory hypertension, and poor oral intake. Hypertension management was complicated by behavioral disturbances around blood pressure measurements. Ultimately, after a 26-day total hospitalization, the patient was discharged home with oral amoxicillin-clavulanic acid to complete a four-week total antibiotic course, as well as lisinopril and amlodipine for ongoing blood pressure control. When he was seen in nephrology follow-up one month later, his renal function had fully normalized and he was able to stop anti-hypertensive therapy. He has had no other sequelae of this acute illness to date. (Figure 1)

Figure 1.



DISCUSSION

Hemolytic-uremic syndrome occurs in 15–20% of pediatric patients with STEC infection, and on average occurs approximately seven days after onset of diarrhea.¹ Rapidly progressive thrombocytopenia is typically the cardinal manifestation, followed by other signs of intravascular

hemolysis. Approximately 25% of patients with STEC-associated HUS develop neurologic manifestations,² with these manifestations being associated with more severe disease.³ There is a paucity of objective data in pediatrics, but in adult patients, neurologic symptoms have typically followed onset of hemolytic symptoms by a mean of four days.⁴ The timing of this patient's symptoms was unusual in that his seizure activity and acute change in clinical status on hospital day five preceded other signs and symptoms diagnostic for HUS, thus posing a diagnostic challenge. While his platelets and creatinine were each slightly worse when rechecked after his seizure, neither was yet outside normal limits. Another challenge was interpreting the clinical meaning of a seizure in a patient with known epilepsy, but who had never had a seizure with loss of consciousness before, even with prior illnesses and fevers. Only over the next 48 hours did it become clear that the patient had indeed developed HUS.

Additionally, bacteremia is highly unusual in STEC gastrointestinal infections. STEC is typically considered a non-invasive infection whose serious sequelae are caused by microvesicular toxin spread.⁵ This non-invasive nature is important in that it allows for avoidance of antibiotics, as there is evidence that antibiotics can worsen clinical outcomes.¹ There are case reports of STEC-associated bacteremia in adults,^{6,7} as well as of HUS associated with verocytotoxin-producing *E. coli* bacteremia⁸ and non-toxin-producing *E. coli* bacteremia.⁹ Of the two adults mentioned above with STEC, only one had *E. coli* O157:H7, and that adult had a urinary tract infection rather than a diarrheal illness.⁶ The other adult patient with STEC-associated bacteremia had a novel hybrid strain of *E. coli*, O80:H2, and presented with seizure, posterior circulation cerebral infarcts, and non-bloody diarrhea.⁷ To our knowledge, this is the first case reported of a pediatric patient with bacteremia associated with Shiga toxin-producing *E. coli*. Unfortunately, serotyping of our patient's strain was not available. It is possible that our patient was infected with a more virulent serotype such as O80:H2, which has been increasingly common in Europe,¹⁰ although the patient had no recent travel.

It is also possible that our patient's underlying diagnosis of Smith-Magenis syndrome played a role in the development of bacteremia. Smith-Magenis syndrome is caused by 17p11.2 deletions which can have immunologic consequences, including impaired antibody production and decreased response to vaccination.¹¹ However, our patient underwent testing of his IgA, IgG, and IgM levels the year prior to his illness, all of which were normal. He also had hepatitis B surface antibody testing which was within the expected range for protective immunity after vaccination. In addition, the infections to which individuals with Smith-Magenis syndrome are more prone tend to be sinopulmonary infections¹¹ rather than invasive gastrointestinal infections.

CONCLUSION

Hemolytic uremic syndrome due to Shiga toxin-producing *E. coli* is a well-known clinical entity which frequently causes neurologic symptoms. However, seizure as the initial sign of developing HUS is uncommon. In addition, bacteremia associated with STEC HUS is quite rare. In a patient with known STEC infection, an acute clinical change such as new fever, change in neurologic exam or mental status, or seizure should prompt immediate workup for developing HUS, as well as consideration of escalation of care given the risk of rapid decompensation.

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