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SEIZURE AS THE PRESENTING SYMPTOM FOR ATYPICAL HEMOLYTIC UREMIC SYNDROME

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☐ **Abstract—Background: Atypical hemolytic uremic syndrome (aHUS) is a complement-mediated disease manifesting in thrombocytopenia, microangiopathic hemolytic anemia, and acute kidney injury. It has a higher incidence of extrarenal manifestations, including central nervous system findings like seizure or stroke, pancreatitis, and cardiac manifestations. Case Report: We present a case of an unimmunized 14-month-old girl presenting with generalized seizure and ultimately diagnosed with aHUS. Why Should an Emergency Physician Be Aware of This?: These atypical neurological symptoms can cause the diagnosis to be commonly missed in the emergency department. The etiology of approximately 60% of patients with aHUS can be attributed to genetic mutations in complement regulators including factor H, membrane cofactor protein, factor I, activator factor B, or C3. Although previously treated with plasma transfusion and immunosuppressants, eculizumab is a newer treatment that has been changing prognosis and management of aHUS, but it should be administered within 48 h of symptom onset for best efficacy.**

☐ **Keywords—atypical hemolytic uremic syndrome; seizures; renal**

The parents of the patient gave permission for the authors to publish this report.

INTRODUCTION

Atypical hemolytic uremic syndrome (aHUS) is a rare chronic progressive disease with prevalence of seven per million (1–3). Compared to diarrhea-associated hemolytic-uremic syndrome, which commonly presents after enterocolitis due to infection from Shiga-like toxin-producing bacteria like *Escherichia coli* (O157:H7), aHUS is caused by deregulation and uncontrolled activation of the complement system. Approximately 60% of patients with aHUS have loss-of-function mutations in complement regulators including, but not limited to, factor H, membrane cofactor protein, factor I, or gain-of-function mutations in activator factor B or C3 (4–6). The subsequent systemic thrombotic microangiopathy caused by platelet, leukocyte, and endothelial-cell activation goes on to damage multiple organ systems, including the central nervous system, renal, cardiovascular, and the gastrointestinal tract. aHUS presents more commonly with extrarenal symptoms than typical HUS, in particular with central nervous system involvement. Patients with aHUS may display neurological symptoms such as irritability, drowsiness, seizures, encephalopathy, diplopia, and nystagmus. Cardiovascular presentations include cardiomyopathy, myocardial infarction, myocarditis, and coronary lesions. Although these atypical symptoms commonly lead physicians to consider other diagnoses, aHUS should be included in the list of differential diagnoses (7,8).

Children with HUS who test positive for complement gene mutations have higher mortality rates (9).

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Historically, 65% of such patients reached end-stage renal disease or death 1 year after diagnosis, even with treatment including plasma infusion or plasma exchange. There are worse outcomes with delays in diagnosis or treatment. Additionally, of the patients able to be treated with a kidney transplant, 60–90% of them developed graft failure within a year (1).

CASE REPORT

AC was a 14-month-old, previously healthy, full-term (41 weeks), unimmunized female who presented with a 4-day history of nonbloody, nonbilious emesis, decreased appetite, tactile fever, and a 1-day history of anuria and bilateral periorbital swelling. She was brought to the hospital after a generalized tonic-clonic seizure that lasted for 10–15 min and resolved prior to arrival. Of note, AC had a recent exposure to a gastrointestinal illness from her half-sister and upper respiratory symptoms from her mother.

Past medical history included vaginal delivery birth at home with no complications. Family history was relevant for multiple urinary tract infections in the patient's mother. AC's mother had also been hospitalized for pelvic thrombosis and unspecified liver and kidney issues during pregnancy, suspicious for hemolysis, elevated liver enzymes, low platelet count syndrome. Other family history is negative for renal, cardiac, hepatic, hematological, or neurological disorder.

In the hospital, she had another seizure that resolved with intranasal midazolam. She was hemodynamically stable with an unremarkable physical examination apart from some mild edema. Laboratory studies were notable for hemoglobin 10.5, hematocrit 30.3, platelets 43, schistocytes, sodium 136, potassium 6.8, chloride 97, bicarbonate 14, calcium 8, phosphorus 10.5, blood urea nitrogen (BUN) 106, creatinine (Cr) 2.3, C3 53, C4 10, and lactate dehydrogenase > 2500. Head computed tomography and electrocardiogram were negative. Urine sample from a straight catheter showed spec gravity 1.015, 3+ blood, +protein, +granular casts, no nitrites, no leukocyte esterase, and bacteria 25–50. Renal ultrasound showed mildly echogenic kidneys with no hydronephrosis.

An electroencephalogram was placed to evaluate her seizure activity and showed a slowed background with no epileptiform activity. Subsequent laboratory tests showed negative (2×) stool cultures and negative testing for Shiga, Shiga-like, and *Campylobacter* toxin. A thrombotic microangiopathy panel (molecular and cellular diagnostic testing for atypical hemolytic uremic syndrome) was sent.

The patient's hyperkalemia was treated with calcium gluconate 50 mg/kg/dose and sodium bicarbonate 1 mEq/kg/dose. She also received insulin and glucose infusions. She was given a dose of furosemide i.v. 2 mg/kg dose without effect, and so, based on her critical acute kidney injury, she was started on peritoneal dialysis with appropriate stabilization of her electrolyte and metabolic parameters.

Given suspicion for aHUS and 5-day history of anuria, planning was made for treatment with eculizumab. She received vaccines for encapsulated bacteria, including meningococcal, pneumococcal, and *Haemophilus influenzae*, and prophylactic treatment with antibiotics (amoxicillin 10-mg/kg/dose once daily and rifampin 10–20-mg/kg/dose once daily for 10–14 days) prior to starting eculizumab (300 mg i.v. over 30–60 min). Her second dose of eculizumab was given 1 week later, with subsequent doses every 3 weeks.

On hospital day 8, she began to show recovery with urine output. She was discharged on hospital day 15 with glomerular filtration rate 25–30 and peritoneal dialysis catheter in place with a plan to continue eculizumab infusions every 3 weeks given her substantial risk of relapse. She eventually showed a full remission, with normalization of her hemoglobin, platelets, and renal function.

AC was healthy for the subsequent 9 months, receiving her eculizumab infusions as scheduled every 3 weeks, and once she reached 20 pounds, every 2 weeks. She then developed a fever of 39.66°C (103.4°F) and upper respiratory symptoms and was diagnosed with influenza A. Three days later she presented to her local emergency department (ED) with nystagmus and a generalized tonic-clonic seizure. AC's notable laboratory values included Cr 0.7 mg/dL (increased from 0.2 mg/dL 3 days prior), BUN 67 mg/dL (compared with 15 mg/dL 3 days prior), and platelets 87 (decreased from 149 just a few hours prior).

Because her seizure presentation and laboratory abnormalities were most consistent with a recurrence of her aHUS, secondary to influenza infection, she was given a 600-mg i.v. weekly dose of eculizumab as emergent treatment. Given weight loss and vomiting, she was given isotonic fluids without potassium at 80 mL/h. She also received lorazepam 0.05 mg/kg/dose every 8 h for seizure prophylaxis. Her treatment course resulted in improved health status, complicated only by hypertension on hospital day 4 that was treated successfully with furosemide and amlodipine, and she was discharged on hospital day 8. She has since had a full recovery and remission, with normalization of her kidney function (Cr 0.2–0.3 mg/dL), blood pressure, hemoglobin, and platelets. She continues to receive eculizumab infusions 300 mg every 2 weeks.

DISCUSSION

We report on a case of a 14-month-old unimmunized girl presenting with neurological symptoms (seizures and nystagmus) secondary to aHUS. In both her initial presentation and her subsequent relapse, she had an evaluation for

epilepsy before aHUS was considered. In addition to microangiopathic hemolytic anemia, thrombocytopenia, and acute kidney injury, aHUS presents more commonly with atypical symptoms such as seizure, as compared with HUS (7). It is important for physicians to recognize the presentation of aHUS, including neurological manifestations, because its treatment differs significantly from epilepsy and also from typical diarrhea-associated HUS. Delays in diagnosis and treatment result in worse clinical outcomes, including an increased risk of end-stage renal disease and death, making it especially important for emergency physicians to be aware of aHUS.

The previous standard of care for aHUS included plasma infusion or plasma exchange. This often improved hematologic measures transiently by removing circulating antibodies, but was unable to address the underlying systemic disease and was inadequate at preventing recurrences (2). However, management and prognosis of aHUS is evolving now with the availability of eculizumab. Eculizumab is a monoclonal antibody that directly blocks C5, the terminal point in the alternative activation pathway cascade. A recent study examining patients over age 12 years with aHUS found eculizumab had significant time-dependent improvement in platelet count with no toxic side effects (1). Patients who test positive for certain genetic mutations have a high rate of relapse, even with eculizumab treatment. AC's genetic panel returned negative; however, 40% of patients with aHUS continue to have negative genetic testing, most likely due to mutations in genes not yet discovered or abnormalities in known genes that are not testable at present.

Eculizumab is well tolerated and has very few side effects. Serious adverse effects are rare, though they include fatal meningococcal infections (0.5% annual rate), in patients who are partially immunized. This is especially important in patients unvaccinated against encapsulated bacteria, and prompted both vaccination and the use of prophylactic antibiotics in AC's case while waiting for the vaccination to take effect. Other adverse effects include hypertension, influenza, and peritonitis (10). Eculizumab has been previously used safely for treatment of paroxysmal nocturnal hemoglobinuria (PNH), but dosages for aHUS are 30% higher than PNH (1). Another factor requiring careful consideration prior to the use of eculizumab is cost. The average wholesale price is $7827.60 per 300-mg vial. Eculizumab is a rarely used medication, and therefore, prescribers should include careful documentation regarding its indication and benefits. Direct communication with the pharmaceutical company can assist in its approval and delivery. Of note, eculizumab is a life-saving and life-altering therapy for patients with aHUS and prevents long intensive care unit admissions, long-term morbidity, end-stage renal disease, and death. Given these results, many physicians believe eculizumab should be the standard of care despite the lack of large studies demonstrating safety efficacy and cost-effectiveness of long-term therapy (1). Studies have also found that eculizumab treatment can be discontinued in some patients with no relapse of symptoms. In the patients who had relapse, rapid remission was achieved with treatment of eculizumab within 48 h (11–13).

WHY SHOULD AN EMERGENCY PHYSICIAN BE AWARE OF THIS?

It is important to recognize the presenting atypical features of aHUS in the ED and the pediatric intensive care unit. In addition to the microangiopathic hemolytic anemia, thrombocytopenia, and acute kidney injury commonly also seen in typical HUS, patients with aHUS commonly display neurological symptoms such as nystagmus and seizures. Rapid diagnosis of aHUS is especially important to optimize long-term prognosis, which can be done through administration of eculizumab within 48 h of symptom onset.

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