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Brief report

Familial, atypical hemolytic-uremic syndrome in a premature infant

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Abstract. The hemolytic-uremic syndrome (HUS) typically presents in toddlers or older children after an episode of bloody diarrhea caused by *Escherichia coli* 0157:H7. However, numerous ''atypical'' presentations have been described, including familial cases. Here we describe what we believe to be the first report of familial HUS in a premature infant during the neonatal period.

Key words: Neonate – Prematurity – Hemolytic-uremic syndrome – Anemia – Thrombocytopenia – Renal failure

Introduction

The hemolytic-uremic syndrome (HUS) typically presents in toddlers or older children after an episode of bloody diarrhea caused by *Escherichia coli* 0157:H7 [1]. However, numerous ''atypical'' presentations have been described, including familial and non-diarrhea-associated cases [2]. In this report, we describe the presentation of HUS in a premature infant who had an older sibling who was also affected by HUS in infancy. We believe this to be the first report of familial HUS in a premature infant during the neonatal period.

Case reports

Case 1

Patient 1 was a white female, twin B of a dizygotic pair, born at 32 weeks' estimated gestational age by cesarean section to a 31-year-old gravida 3 para 2 mother, at an outlying hospital. Pregnancy was complicated only by premature onset of labor, which failed to respond to terbutaline and magnesium sulfate tocolysis. The mother was also given betamethasone to promote fetal lung maturity and ampicillin in the immediate prenatal period. The infant weighed 1,675 g at birth, and was noted to have poor color and respiratory effort immediately after delivery, and was therefore intubated and mechanically ventilated. No umbilical catheters were placed. Initial physical examination was remarkable only for evidence of respiratory distress and decreased tone.

Her early course was remarkable for mild respiratory distress syndrome, a negative initial sepsis work-up (ampicillin and cefotaxime were given for 48 h), apnea of prematurity that was treated with aminophylline, and mild non-hemolytic jaundice. Also, due to hypotonia, dysconjugate eye movements, and a static head circumference noted over the first 2 weeks of life, a neurology consultation was requested. The neurologist obtained chromosome analysis, a urine metabolic screen, and an electroencephalogram (EEG). The EEG was read as normal, the metabolic screen was negative, and the chromosome analysis was normal. Cranial ultrasonography had previously revealed a structurally normal brain without intraventricular hemorrhage.

On day of life (DOL) 15 the infant became severely hypertensive, for which an evaluation was performed. Urinalysis revealed hematuria and proteinuria. Blood urea nitrogen (BUN) and creatinine were elevated (Table 1); they had not been previously determined. Renal ultrasonography revealed normal-appearing parenchyma and normal vasculature. The next day she was noted to be thrombocytopenic. A peripheral blood smear showed burr cells, acanthocytes, and schistocytes. Cultures were obtained and antibiotics begun. Over the next 4 days she remained thrombocytopenic (Table 1) and became anemic, for which packed red cell transfusions were given. Neurologically the baby was lethargic and worsening apnea necessitated re-institution of mechanical ventilation. On DOL 17 she experienced a seizure, which was treted with phenobarbital. Repeat cranial ultrasonography was unchanged. Through DOL 19 she maintained a brisk urine output, while her BUN and creatinine continued to rise (Table 1).

From DOL 19 she experienced progressive oliguria, unresponsive to furosemide administration. Worsening hypertension was treated, unsuccessfully, with hydralazine. Concomitant with her decreased urine output was a weight gain of nearly 130 g. Blood cultures were negative.

On DOL 20 the infant was transferred to the University of Michigan Medical Center (UMMC) for management of her refractory hypertension and renal failure. Upon arrival at UMMC, her physical examination was normal except for a blood pressure of 140/93 mmHg. The infant was profoundly anemic and thrombocytopenic. Fibrinogen level was depressed and prothrombin time as well as fibrinogen split products were modestly elevated. Bio-

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Table 1. Selected laboratory values in patient 1

Day of life	BUN	Creatinine	Hematocrit	Platelet count	LDH
12	–	–	44.5	306,000/mm^3	–
15	58 mg/dl	1,3 mg/dl	–	–	–
16	–	–	–	59,000/mm^3	–
18	115 mg/dl	3.2 mg/dl	–	–	–
20	116 mg/dl	2.8 mg/dl	24.3	10,000/mm^3	2,966 IU/l
22	72 mg/dl	1.8 mg/dl	32.4	26,000/mm^3	937 IU/l
26	20 mg/dl	1.0 mg/dl	36.3	137,000/mm^3	282 IU/l
30	15 mg/dl	1.0 mg/dl	30	182,000/mm^3	251 IU/l
43	9 mg/dl	0.4 mg/dl	34.7	489,000/mm^3	–
Second admission	45 mg/dl	0.3 mg/dl	35.5	18,000/mm^3	2,289 IU/l

BUN, Blood urea nitrogen; LDH, lactate dehydrogenase

chemical analysis of serum revealed: sodium 130 mEq/l, potassium 3.0 mEq/l, calcium 8.2 mg/dl, and phosphorus 11.1 mg/dl. Serum protein was 4.0 g/dl, albumin 2.2 g/dl. BUN, creatinine, and lactate dehydrogenase (LDH) were elevated (Table 1). The diagnosis of HUS was made shortly after the infant's arrival. A familial variant was suspected based on a positive family history; a sibling with HUS had been cared for at UMMC 14 months prior to patient 1's admission (this history had not been obtained at the referring hospital).

Initial management consisted of a double volume exchange transfusion of red blood cells and plasma, as well as a platelet transfusion. Infusions of fresh-frozen plasma (10 ml/kg), given twice daily, were started and continued for several days after the exchange. The hypertension was treated with labetalol and hydralazine infusions. The next morning, discussions were held with the family and a dialysis catheter and central vascular catheter were placed and peritoneal dialysis begun. Due to the poor prognosis of the disease, the option of discontinuing support was offered to the family, but they wished to continue maximal medical management.

On dialysis the patient's hypertension resolved, which allowed rapid weaning of all antihypertensives. Urea nitrogen, creatinine, and LDH consistently decreased (Table 1). She required only one further packed red blood cell transfusion, and no further platelet transfusions. Hypoalbuminemia and edema were treated with a 25% albumin infusion. The only sign of central nervous system abnormality was her persistent dysconjugate gaze. Seizures did not recur and phenobarbital was discontinued. Dialysis was discontinued on DOL 30, due to leakage of dialysate around the Tenckhoff exit site. During the next few days off dialysis, the infant experienced increasing urine output and decreasing urea nitrogen and creatinine. She was extubated on DOL 34. On DOL 36 hypertension recurred and was treated with oral antihypertensives. On DOL 43 her Tenckhoff was removed. She was discharged soon thereafter with stable renal function (Table 1) and was thriving.

C3 values, measured during the acute phase of her illness (53 mg/dl), remained low (61 mg/dl) months after her first episode of HUS. However, her total CH_{50} values were normal during her hospitalization and during convalescence.

At approximately 7 months of age, the patient presented to her local physician with extreme irritability and dark urine, and was readmitted to UMMC. Laboratory studies were significant for hematuria, proteinuria, and thrombocytopenia (Table 1). The diagnosis of recurrent, familial HUS was made, and extensive discussions were held with the family regarding therapeutic options, including plasmapheresis. Given her poor long-term prognosis, it was decided to provide comfort care only, and she died 3 days after admission. No autopsy was performed.

The patient's twin sibling, who did not experience any signs or symptoms suggestive of HUS in the neonatal period, was last seen in follow-up at UMMC at 6 months of age. At that time she was developing normally and had no evidence of renal disease. C3 and CH_{50} determinations have not been performed in her case.

Case 2

Patient 2, the older sister of patient 1, presented at 4 months of age with feeding intolerance and irritability approximately 2 weeks after surgical placement of a feeding gastrostomy. There was no history of vomiting or diarrhea, but she did have a low-grade fever and symptoms of an upper respiratory infection. Past medical history was significant for microencephaly, a Dandy-Walker malformation, and failure to thrive. Physical examination was remarkable for tachycardia, hypertension, pallor, and mild peripheral edema. Initial laboratory studies revealed mild anemia, hyponatremia, and a normal platelet count. Creatinine was 0.6 mg/dl, up from 0.2 mg/dl 2 weeks previously.

She rapidly developed progressive thrombocytopenia and azotemia, as well as a markedly elevated LDH of 1,863 IU/l. Hyptension persisted, and she developed progressive oliguria. Because of extreme irritability, a head computed tomographic (CT) scan was obtained, and revealed a left posterior fossa hemorrhage. A Tenckhoff catheter was placed 4 days after admission and dialysis was initiated. Renal function returned after approximately 9 days of peritoneal dialysis. She required multiple transfusions of packed red cells during her course. Hypertension remained difficult to control throughout her hospitalization, ultimately requiring a combination of three antihypertensives. Neurological status remained stable, with no further hemorrhages seen on follow-up CT scanning. Discharge was delayed because of feeding difficulties, but she was eventually discharged on hospital day 25 with a stable creatinine of 0.2 mg/dl, hemoglobin of 10.6 g/dl, and platelet count of 513,000/mm^3.

Discussion

HUS, first described by Gasser in 1955, has since been shown to occasionally occur in multiple members of the same family. Fison [3], in 1956, reported what is thought to be the first occurrence of HUS in siblings. Kaplan et al. [2], in 1975, examined HUS in 83 siblings from 41 families. They described two groups: the siblings from group one families had onset of their disease within a short time of each other and a good prognosis; while group two patients had more than 1 year between occurrences of the disease in family members and a much worse prognosis. They postulated that there was a genetic predisposition to the disease in the patients in group

two. This classification has been further refined to typical or diarrhea-associated HUS (Kaplan's group one, D+) and atypical HUS (group two, D–). Two subtypes of atypical HUS are now recognized: sporadic and familial [3]. Autosomal dominant and recessive forms of the familial disease have been described [4]. Although the pathogenesis of inherited HUS remains unknown, complement abnormalities [5] and defects in the metabolism and function of prostacyclin have been implicated [6]. Autosomal recessive cobalamin C defect has also been associated with HUS; the pathophysiologic mechanism is thought to be endothelial damage as a result of accumulation of homocysteine in the plasma of these patients [7]. Kaplan and Kaplan [4] have recommended, due to the abnormal complement profiles demonstrated in many families with inherited HUS, that a serum C3 and CH_{50} be obtained in patients suspected of this diagnosis.

Diagnosis of a familial variant of HUS rests on the history of another family member affected with HUS at a remote time, or recurrence of the disease in the patient or a family member, both of which characterized patient 1. Other clues that HUS may be familial include an atypical or no prodromal illness, predominantly arteriolar changes on renal biopsy specimens, a slowly progressive course, or recurrence after renal transplantation [4]. The absence of the disease in the parents and an older brother of patient 1, as well as her twin, leads us to believe that this is a case of autosomal recessive transmission of the disease. The parents in this case are not related.

HUS has been previously described in term neonates, with onset as young as 2 days of age [8]. The differential diagnosis of thrombocytopenia, hemolytic anemia, and renal failure in this age group should include sepsis with acute renal failure and disseminated intravascular coagulation, bilateral renal vein thrombosis, and thrombotic thrombocytopenia purpura (TTP). Sepsis was excluded in this case on the basis of negative cultures and no antecedent hypotension before onset of the acute renal failure. Bilateral renal vein thromboses were unlikely, based on a negative renal ultrasound examination. TTP has been seen in infants [4]. However, it typically affects adults, and consists variably of hemolytic anemia, thrombocytopenia, mild renal disease, fever, and prominent neurological symptoms. The renal failure and the lack of both fever and severe neurological symptomology in this patient mitigate against the diagnosis of TTP.

Treatment of familial HUS focuses on the acute phase of the illness, and is primarily supportive. The hypertension is often severe and is thought to be mediated by the renin-angiotensin system. Angiotensin converting enzyme inhibition may be necessary [9]. Plasma infusions [10] and plasmapheresis [11] have been advocated, but without much evidence to support their potential benefit. An exchange transfusion was performed during patient 1's first episode because plasmapheresis was not technically feasible.

The prognosis in familial, non-diarrhea-associated HUS is dismal. The mortality rate is greater than 90% in the autosomal dominant form and 70% in patients with the autosomal recessive form [3]. Many patients have relapses, or a progressive course in some cases requiring renal transplantation [4]. Genetic counselling should be offered to the family of the child with the diagnosis of familial HUS. DNA testing is not yet available for this disorder, but a registry has been established and blood samples are being collected for future analysis (B. Kaplan, personal communication).

In summary, we present what we believe to be the first case report of a premature infant with familial HUS presenting in the neonatal period. Diagnosis of this disease in a premature baby expands the age spectrum of this disease and adds to the differential diagnosis of the triad of renal failure, thrombocytopenia, and hemolytic anemia in the premature neonate.

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