Hemolytic uremic syndrome in a pediatric intensive care unit: a 5-year experience

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To the Editor,

Hemolytic uremic syndrome (HUS) is a disease characterized by microangiopathic hemolytic anemia with fragment erythrocytes (schistocytes), low platelet count and acute renal failure. HUS is most commonly triggered by Shiga-like toxin (Stx) of *Escherichia coli,* is most often presented with acute pallor and oliguria, following bloody diarrhea, and occurs sporadically or in epidemics[1]. Although acute renal failure manifests in over half of the cases, renal function recovers in most of them[2]. Non–Shiga toxin (non–Stx)-associated HUS constitutes a heterogeneous group of patients, and is caused by bacteria, viruses, drugs, or systemic diseases. It can be idiopathic, sporadic or familial, and has a poor outcome[3]. In some HUS cases, due to the severity of symptoms and complications of the disease, there is need of mechanical ventilation and intensive care.

We present a case series of six HUS patients (4 girls, 2 boys) managed in an 8-bed Pediatric Intensive Care Unit (PICU) of a tertiary care hospital in Greece from 2005 to 2009, constituting 1.1% of PICU admissions. In the same period, a total of 16 first-diagnosed HUS patients were admitted to the pediatric wards of North Greece, from which 6 (37.5%) had a need for intensive care. Data of the patients are presented in Table I. The median age was 45 months (range: 13 to 96 months). Five cases presented during hot months (April-September) and 1 case, due to H1N1-2009 strain, presented during November. Diarrhea and oliguria/anuria were present in 4 of the 6 cases with a median of 7 days (range: 1 to 15 days) and 2 days (range: 1 to 8 days), respectively. Other clinical features included seizures (n=4) and pneumonia (n=2), with 2 patients suffering from status epilepticus and 1 patient from both seizures and pneumonia. Neuroimaging studies were performed in all 4 patients with seizures. In 4 of 6 cases, the pathogen recovered from stool cultures was *E. coli*. In the remaining 2 cases, *Streptococcus pneumoniae* and influenza A (H1N1)-2009 strain were isolated. Laboratory investigations revealed in all patients anemia (hemoglobin median, 6.1 g/dl), thrombocytopenia (platelet median, 37,000/mm^3), elevated C-reactive protein (median, 53.2 mg/dl), elevated creatinine (median, 4.8 mg/dl), elevated lactate dehydrogenase (LDH) (median, 4,150 IU/L), depressed albumin (median, 2.3 g/dl), and hyponatremia (median, 123.5 mEq/L). Tracheal intubation was needed in 3 of 6 cases, in 2 due to status epilepticus and in 1 case due to hypoxemia/hypercapnia. Five patients needed dialysis; all had surgically placed Tenckhoff catheters and underwent peritoneal dialysis. All 6 patients survived and were hospitalized in pediatric wards, after staying in the PICU for a median of 7 days (range: 1 to 48 days).

Shiga-like toxin (Stx)-*E. coli* O157:H7 constitutes the dominant cause of HUS worldwide, with other serotypes contributing in different percentages to the overall impact of disease[1]. Stx-*E. coli* colonize the intestine, produce Stx and release it in single or multiple waves. These translocate across the intestinal epithelium resulting in endothelial cell damage, which appears to be the central event in the pathogenesis of renal dysfunction and injury in Stx-associated HUS[4]. All 4 of the *E. coli* isolates from 4 patients were examined by O157 and H7 antisera (MAST Co, UK) to identify O157 or O157:H7 serotypes by using plate agglutination method. Only 1 *E. coli* O157:H7 was detected by serological examination (Patient 2).

S. pneumoniae-associated HUS is different from Stx-associated HUS, and the primary factor appears to be the production of neuraminidase[5]. Influenza A-associated HUS has been very rarely recognized in children[6]; however, both influenza A and *S. pneumoniae* share neuraminidase activity, and influenza A could induce HUS via the same pathway. Unfortunately, the Thomsen Friedenreich antigen (T antigen) test, which investigates the neuraminidase produced by *S. pneumoniae* or H1N1-2009 strain, was not performed in our patients. Although H1N1-associated HUS is rare, there were

Table I. Demographics and Clinical Details of Patients with Hemolytic Uremic Syndrome

Patient	1	2	3	4	5	6
Gender	Female	Female	Female	Female	Male	Male
Age (months)	13	24	42	48	84	96
Weight (kg)	9	11	14	20	24	25
Duration of diarrhea if present (days)	5	15	–	1	–	9
Duration of oliguria/anuria if present (days)	1	8	2	–	1	3
Hematuria/proteinuria	Yes	Yes	Yes	Yes	No	Yes
Acute hypertension	No	Yes	No	Yes	Yes	No
Pathogen	*Escherichia coli*	*Escherichia coli*	*Streptococcus pneumoniae*	*Escherichia coli*	H1N1-2009 strain	*Escherichia coli*
Laboratory diagnosis	Stool cultures	Stool cultures	Pleural fluid cultures, Ag in urine	Stool cultures	PCR in respiratory specimens	Stool cultures
Complications	Seizures	Seizures	Pneumonia	–	Seizures, pneumonia	Seizures
Acute phase MRI findings	Abnormalities of the basal ganglia, increased signal intensity on T1- and T2-weighted images, representing hemorrhage	Abnormalities of the basal ganglia, dorsolateral portion of the lentiform nucleus	Not performed	Not performed	Multiple lesions in the white matter, situated in the temporo-parieto-occipital regions	Bilateral hyperintense lesions in the thalami and dorsolateral lentiform nuclei, increased signal intensity on T1- and T2-weighted images, representing hemorrhage
WBC count (/mm^3)	17,350	9,740	23,420	8,230	14,840	12,300
Hemoglobin (g/dl)	5.2	4.1	6.4	7.6	7.5	5.8
Platelet (/mm^3)	11,000	33,000	45,000	52,000	30,000	41,000
CRP (mg/dl)	58.4	18.2	135	99	37	48
Creatinine (mg/dl)	5.7	6.8	3.9	2.6	3.4	5.8
Albumin (g/dl)	2.8	1.2	2.5	1.4	2.1	2.4
Total/direct bilirubin (mg/dl)	4.1/3.0	1.2/0.4	3.2/1.4	4.5/3.1	3.7/2.6	1/0.3
LDH (IU/L)	9,320	4,350	3,950	6,760	2,330	1,990

BUN (mg/dl)	94	142	36	50	223	88
GFR (ml/min per 1.73 m^2)	13	4	88	7	4	11
PT/PTT (sec)	15.2/47.4	16.2/52.1	12.8/31.2	16.7/47.8	13.1/30	13.7/39.2
Serum K^+ (mEq/L)	2.7	5.2	2.8	2.9	3.1	2.3
Serum Na^+ (mEq/L)	118	123	127	129	124	121
Duration of dialysis (days)	2 (cont'd)	48 (cont'd)	–	12	12 (cont'd)	2 (cont'd)
Tracheal intubation due to (duration-days)	Status epilepticus (1)	Status epilepticus (28)	–	–	Hypoxemia, hypercapnia (10)	–
PICU stay (days)	2	48	1	13	12	2
Outcome	Discharged	Discharged	Discharged	Discharged	Discharged	Discharged

BUN: Blood urea nitrogen. CRP: C-reactive protein. GFR: Glomerular filtration rate. LDH: Lactate dehydrogenase. MRI: Magnetic resonance imaging. PCR: Polymerase chain reaction. PICU: Pediatric Intensive Care Unit. PTT: Partial thromboplastin time. PT: Prothrombin time. WBC: White blood cells.

no statistical differences in clinical and laboratory findings, complications or prognosis as compared with the other HUS cases presented in this case series.

The value of magnetic resonance imaging (MRI) in HUS has been well studied, and various imaging findings have been described. It is interesting that in 4 patients in whom MRI studies were performed in the acute phase of HUS, all had pathological imaging findings. However, the only 2 patients with hemorrhagic lesions on the acute MRI studies (Patients 1 and 6) had very low serum levels of sodium and potassium (Patient 1, Na=118 mEq/L, K=2.7 mEq/L; Patient 6, Na=121 mEq/L, K=2.3 mEq/L) as compared to the other HUS patients.

The role of PICU in the management of HUS may be substantial in improving patient outcome, especially in cases with complications such as refractory status epilepticus and respiratory distress with hypoxemia and/or hypercapnia. Hyponatremia and associated encephalopathy are common in post-diarrheal HUS patients, as seen in the present and previous studies[7]. Noticeable in our study is the fact that all HUS patients with seizures had hyponatremia. Mortality among pediatric patients with HUS decreased with the availability of dialysis as well as after the introduction of intensive care facilities[8]. This is supported by the findings of our study, in which, despite the critical condition of patients, the use of peritoneal dialysis and intensive care resulted in favorable outcomes.

The etiology of HUS is multifactorial, with the majority of cases associated with diarrheal illness by Stx-*E. coli*. Although *S. pneumoniae* has been recognized as a common cause of non-enteropathic HUS in children, influenza A virus-associated HUS has been very rarely recognized. HUS constitutes a challenge for intensivists because early transfer of complicated HUS cases in PICUs can improve outcome.

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