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Characteristics and Outcome of Pediatric Hemolytic Uremic Syndrome

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Abstract

Introduction. Hemolytic uremic syndrome (HUS) is one of the most common causes of renal failure in pediatric population. It is characterized by renal failure in association with microangiopathic hemolytic anemia and thrombocytopenia.

Methods. This was a retrospective study. All children with the diagnosis of HUS in "Dr Sheikh Children Hospital" diagnosed from January 2006 to December 2016 were included in the study. They were divided into two groups: diarrhea positive HUS (D^+HUS) and diarrhea negative HUS (D^-HUS). We assessed demographic characteristics, laboratory data and outcome of patients.

Results. Thirty-six patients were identified; 70% were D^+HUS and 30% were D-HUS. Mean age of patients with D^-HUS was significantly higher than in D^+HUS patients. Oligo/anuria and unconsciousness were significantly more common in D^+HUS patients, while D-HUS patients more frequently had hematuria. Frequency of hypertension and duration of hospitalization were not significantly different between two groups.

Conclusion. Our cases of pediatric hemolytic uremic syndrome had a high rate of complications and we experienced many sequelae in these patients, including: renal, central nervous system, cardiac, respiratory, gastrointestinal complications and sepsis. It is a condition with significant mortality and morbidity. Prevention and early recognition is important.

Keywords: diarrhea, hemolytic uremic syndrome, renal failure, pediatrics

Introduction

One of the most common causes of pediatric renal failure is hemolytic uremic syndrome (HUS). It consists of the triad of microangiopathic hemolytic anemia, thrombocytopenia and acute renal failure [1]. HUS in its acute phase is a condition with significant mortality and morbidity. It has also chronic complications that can extend well beyond the acute phase of the condition [2]. Two main categories of this condition are:

- Typical HUS or classic HUS, also called diarrhea-associated HUS (D+HUS). This form is usually caused by Shiga toxin-producing Escherichia coli (STEC).
- Atypical HUS or D-Hus, which is usually due to genetic factors like complement system abnormalities.

Additionally, HUS may be associated with pneumococcal infection and is mediated by neuraminidase [3]. In cases of D+HUS, patients often present with diarrhea which is often bloody and/or watery. They may show other signs of gastrointestinal infection like abdominal tenderness and low-grade fever, followed by decreasing urine output and oligo/anuria. However, a temporary renal involvement and decreased glomerular filtration rate (GFR) might be seen due to dehydration in STEC gastroenteritis without HUS. Extrarenal involvement may occur in the acute phase of the condition including central nervous system (CNS), often accompanied by respiratory, cardiac and gastrointestinal complications. D-HUS may present with various atypical symptoms [4].

All clinical features of HUS results from the microangiopathic lesions and they are termed as thrombotic microangiopathy (TMA). TMA most often affects arterioles and capillaries of the kidneys and the CNS and the resultant decreased blood flow to the affected organ causes ischemic damage [4,5]. A large meta-analysis has estimated that renal complications without end-stage renal disease (ESRD) occurred in around 25% and ESRD in 3% of D+HUS cases [6].

HUS related mortality is 3-5% and is always due to severe extrarenal complications [2,3]. Long- term complication of HUS is usually related to kidneys and is manifested as hypertension and long-term proteinuria [7]. The mainstay of treatment in HUS is supportive therapy that includes: fluid therapy, dialysis and plasma exchange depending on the etiology of the condition [4,8]. Eculizumab is a C5 monoclonal antibody that has been used in the treatment of atypical HUS [4].

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In the present study we evaluate the epidemiologic and clinical features of childhood HUS in our population.

Materials and methods

We retrospectively reviewed chart and medical records of all children with a diagnosis of HUS admitted to "Dr. Sheikh Children Hospital" during the period from January 2006 to December 2016. This hospital is the pediatric kidney reference center in East of Iran and is affiliated with Mashhad University of Medical Sciences. Demographic data, symptoms, laboratory data, duration of dialysis, length of hospital stay, complications during hospitalization and outcome of patients were assessed. Statistical analysis was performed using SPSS16 statistical package. Data was expressed as mean± standard deviation. Chi square test and Student t-test were used for group comparisons. A P value <0.05 was considered as significant.

Results

A review of patient's records revealed 36 patients diagnosed with HUS during the study period. They were classified into two groups: D+HUS (25 patients, 14 male) and D-HUS (11 patients, 6 male). Mean age of patients in the D+HUS group was 40.3±27.6 months and 70.1±62.3 in D-HUS group (P=0.09). No significant difference was noted regarding patients gender.
Clinical characteristics of the patients are shown in Table 1.

Table 1. Clinical characteristics

Characteristic	D^+ HUS (n= 25)	D^- HUS (n= 11)	P value
Hypertension	6 (24%)	5 (45.5%)	0.198
Oligo/anuria	13 (52%)	2 (18%)	0.035
Hematuria	17(68%)	9 (81%)	0.0285
Seizure	9 (36%)	5 (45%)	0.592
Edema	17 (68%)	6 (54%)	0.439
Unconsciousness	11 (44%)	1 (9%)	0.041

The mean duration of hospitalization was 13.6 days in the first group and 14.9 days in the second group (P=0.6). Sixteen (64%) of patients in the D^+HUS group needed dialysis in the acute phase of the condition whereas dialysis was necessary in 8(73%) patients from the D^-HUS group (P=0.184). Majority of them underwent peritoneal dialysis. Plasma exchange and plasma infusion were used in 24% and 48% patients from the D^+HUS group and 27% for each one in the D^-HUS group. Hyperuricemia was detected in 12% and 36% of patients, respectively. It resolved in all patients after treatment of kidney failure or with administration of rasburicase. Mortality in the acute phase of the condition was 28% and 18% in the two groups, respectively.

Discussion

Hemolytic uremic syndrome is the leading cause of acute renal failure in children between 1-4 years and the second most common cause in children younger than one year and older than 4 years [1,9]. In this study we evaluated 36 patients with the diagnosis of hemolytic uremic syndrome. 69.5% had a history of diarrhea before presentation and were categorized as D^+HUS while 20.5% were categorized as D-HUS or atypical HUS. This proportion is similar to that presented in the study of Micheletti *et al*. [10]. Most studies have reported the prevalence of D^+ about 90% [1,2]. In the study by Jennsen *et al.* in Norway, the prevalence of D^+HUS was reported to be 80% [3]. The lower incidence of D^+HUS in our study could be due to the small sample size and more probability of genetic defects due to the prevalence of consanguine marriage in our population. Also, STEC infection may present without diarrhea in some cases [11,12]. The mean age of our patients in the D^- HUS group was similar to that of examined patients by Micheletti *et al.* [10], but in the D^+ group was similar to Jenssen's study [3]. Duration of hospitalization in our patients was similar to that reported in the Jenssen's study in Norway [3]. Duration of hospitalization in D+HUS was similar to previous studies [13], but for the D^-HUS it was different which could be due to different treatment modalities and complexity of the nature of disease.
Hypertension is one of the most common presentations of HUS and is present in 50% of cases. It could be due to elevated renin activity and other factors like volume overload [3,14]. In Micheletti' s study the prevalence of hypertension in the D+HUS and D^-HUS was reported to be 46% and 66%, respectively. Jenssen also reported the prevalence of hypertension in their study population: 24% for D^+HUS and 33% for D^-HUS at presentation and 83% and 100% during hospitalization period [3]. The lower incidence of hypertension in our study population may be due to the time of blood pressure measurement. Our patients' blood pressures were measured in the acute phase of the condition and could be affected by conditions like dehydration and sepsis. 52% of our patients in the D+ HUS group developed oligo/anuria and 64% needed dialysis. It was 18% and 73% in the D-group, respectively. Prevalence of oligo/anuria was 76% and 56% in Jenssen's study and 84%, and 100% in Michelet's study. Loos *et al*. reported an incidence of oligo/anuria in HUS patients following an outbreak of E-coli104: H4 infection producing shigatoxin to be 66% [15]. Similar to our study, a large number of other studies have reported the need for dialysis in HUS patients between 47-68% [16-20]. Central nervous system (CNS) involvement is common in HUS. CNS involvement in HUS has been reported between 0-50%

in different studies. The most common presentation is seizure, either generalized or focal; loss of consciousness, personality changes, transient hemiparesis and coma have also been reported. CNS involvement in HUS seems to be sometimes due to electrolyte abnormalities or hypertension, but these conditions sometimes cannot explain the severe neurologic manifestations in HUS [21,22]. Pathologic evaluation of the CNS in HUS patients who died due to HUS and neurologic dysfunction has showed nonspecific changes like hypoxic-ischemic changes or brain edema [21-24]. In our study 36% of D^+HUS and 45% of D^-HUS patients had seizures. There was no statistically significant difference between the two groups. In Micheletti's study, the prevalence of seizure was 15% and 22% respectively, and like in our study there was no difference between the two groups. In a study by Sheth *et al*., 27% of patients presented with seizures [24]. In our study 16% of patients in D^+ HUS group needed plasma exchange and 64% received plasma infusion. This percentage was 45% and 36% in D^-HUS group respectively, which is similar to a study by Loos *et al*. [5]. Of patients who had hyperuricemia, 7.4% received rasburicase which resulted in reduction in serum uric acid and improvement of renal function. In a study by Esmaeeli *et al*. including 15 patients with acute renal failure and concomitant hyperuricemia, they showed that treatment with rasburicase resulted in uric acid reduction and improvement of renal failure [25]. Acosta reported one-month-old infant with HUS and serum uric acid elevation who experienced complete renal function improvement and normalization of serum uric acid following therapy with one dose of rasburicase [26]. Mortality of D^+HUS has been reported between 3-50% and is slightly higher during the outbreaks [4]. In our study mortality was 28% and was due to complications of dehydration, renal failure complications, and neurologic involvement. In a study in North India, mortality was reported to be 60% and was due to renal failure and cortical necrosis [27]. Patients' mortality in D^-HUS in our study was 18% during the acute phase of the condition. It has been reported to range between 0- 25% in other studies [28,29].

Conclusions

Results of this study show that hemolytic uremic syndrome (HUS) is a condition with significant mortality and morbidity. Attempts should be made in prevention and early recognition of the condition.

Conflict of interest statement. None declared.

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