Clinical characteristics of children with hemolytic uremic syndrome in Hangzhou, China

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Background: **Hemolytic uremic syndrome (HUS) is a main cause of acute renal failure in children. This study aimed to analyze the clinical characteristics of HUS.**

Methods: **A retrospective analysis was performed in 46 children with sporadic HUS.**

Results: **Of the 46 HUS patients, 20 (43.5%) were diarrhea-related HUS, and 26 (56.5%) were atypical HUS. Anemia, edema, oliguria, hemoglobinuria and hypertension were the most common manifestations. Thrombocytopenia, hyponatremia, hypocalcemia, hyperkalemia, metabolic acidosis, increased fibrinogen and hypocomplementemia were found in most patients. The age of onset (younger than 2 years or not, *P*=0.009), the duration of oliguria or anuria (more than one week or not, *P*=0.005), accompanied with extra-renal complications or not (*P*=0.005), dialysis and plasma exchange (*P*=0.04) were associated with the mortality rate.**

Conclusion: **The age of onset younger than 2 years, oliguria/anuria more than 1 week, and associated with extra-renal complications were predictive factors of poor prognosis.**

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Key words: **hemolytic uremic syndrome; prognosis; therapy**

Introduction

The hemolytic uremic syndrome (HUS), characterized by the triad of thrombocytopenia, microangiopathic hemolytic anaemia and acute renal failure, especially in young children, is a main cause of acute renal failure,[1] and was classified as either diarrheal-associated (D^+ HUS) or non-diarrheal/atypical (D^- HUS).

In the present study, the clinical characteristics of 46 patients with D^+ HUS or D^- HUS from March 1996 to October 2015 were retrospectively reviewed in the Department of Nephrology, Children's Hospital, Zhejiang University School of Medicine in China.

Methods

Patients and samples

From 1996 to 2015, 46 patients with HUS were identified, 20 (43.5%) were D^+ HUS and 26 (56.5%) D^- HUS. The median age at diagnosis was 6.3 years (range from 5 months to 14 years). Anti O157 lipopolysaccharide (LPS) antibody was detected routinely. Stool samples or suspected food were cultured for Shigella/Enterohemorrhagic *Escherichia coli* bacterial.

Statistical analysis

Chi-square test (Fisher's exact test) and logistic multiple factor analysis were performed with SPSS software (version 13.0; SPSS GmbH, Munich, Germany). A *P* value of less than 0.05 was considered as statistically significant.

Results

Clinical manifestations and laboratory findings

The course of disease varied from 13 to 28 days (mean: 18.5). Blood routine examination indicated hemolytic anemia. Fragmented red blood cells (schistocytes) were seen in peripheral smears. Anti O157 LPS antibody was found in two children accompanied with bloody diarrhea. Coombs test was negative in all patients. All the lab results had no difference between D^+ HUS and D^- HUS groups. Main lab results are listed in Table 1.

Treatment strategy

Treatment was aimed at controlling mean arterial blood pressure, anemia, and impairment of central nervous system, as well as correcting fluid and electrolyte disturbances and other potentially life-threatening conditions.

Fresh frozen plasma were infused to all patients, and

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red blood cells were given to patients with severe anemia. Plasma exchange and continuous renal replacement treatment (CRRT) were performed in patients whose renal function didn't improve after routine treatment since 2008. Fourteen patients received 2-3 times of plasma exchange treatment, meanwhile 7 of them received CRRT. With the help of plasma exchange and CRRT, the patients' clinical manifestations and laboratory tests improved obviously, the color of urine changed from soy to sandy, till clear, the platelet count, hemoglobin, hepatic function, renal function and myocardial enzyme became normal.

Table 1. Clinical parameters of D^+ HUS and D^- HUS patients

Parameters	D^+HUS	D^-HUS	χ^2	*P*
Gender				
Male	12	16	0.0112	0.916
Female	8	10		
Age less than 2 y				
Yes	7	9	0.0007	0.978
No	13	17		
Decrease of hemoglobin (<60 g/L)				
Yes	4	6	0.0629	0.802
No	16	20		
Edema and oliguria				
Yes	18	24	0.0758	0.783
No	2	2		
Hemoglobinuria				
Yes	12	10	0.0112	0.916
No	8	16		
Hypertension				
Yes	4	6	0.0629	0.802
No	16	20		
Fever				
Yes	4	5	0.0043	0.948
No	16	21		
Convulsion				
Yes	1	2	0.1344	0.714
No	19	24		
Amount of leukocytes greater than 20×10^9/L				
Yes	8	12	0.1742	0.676
No	12	14		
Hyponatremic				
Yes	12	16	0.0112	0.916
No	8	10		
Hypocalcemic				
Yes	12	16	0.0112	0.916
No	8	10		
Hyperkalemia				
Yes	6	9	0.1096	0.741
No	14	17		
Metabolic acidosis				
Yes	5	7	0.0217	0.883
No	15	19		
Increase of fibrinogen				
Yes	6	6	0.2810	0.596
No	14	20		
Hypocomplementemia (low C3 levels)				
Yes	4	5	0.0043	0.948
No	16	21		
Duration of oliguria or anuria exceeding one wk				
Yes	6	10	0.3570	0.550
No	14	16		
Extra-renal complications				
Yes	4	10	1.8200	0.177
No	16	16		
Mortality				
Yes	3	5	0.1408	0.707
No	17	21		

HUS: hemolytic uremic syndrome; D^+HUS: diarrheal-associated HUS; D^-HUS: atypical HUS; C3: complement 3.

Mortality and prognostic factors influencing mortality

Eight (3/5 D^+/D^-) patients died with a mortality rate of 17.4% (8/46). The causes of death included pulmonary edema (2 patients), cerebral edema (1), cardiogenic shock (2), multiorgan failure (2) and disseminated intravascular coagulation (DIC) (1).

We followed up 2-6 years (mean: 4.2 years) after experiencing HUS. Thirty-eight patients survived after treatment, of which most patients (69.6%) showed complete recovery, a few patients (8.7%) showed proteinuria in different extent and hypertension at the same time, 1 patient with chronic renal insufficiency (creatinine clearance: 30 mL/min/1.73 m^2), and 1 patient finally developed with end stage renal disease. Relative risk factors are listed in Table 2.

Discussion

In its most common form, HUS is associated with a diarrheal prodrome and is defined as D^+HUS, meanwhile, D^-HUS, is less common and more frequently encountered in children. In the present study, 20 out of 46 patients were associated with a prodrome of diarrhea. The percentage of D^+ HUS in the present study was different from the studies reported by Rock et al,[2] but was consistent to the report of Zhang et al.[3] To our knowledge, difference of catering culture between eastern and western country may account for the discrepancy of incidence of D^+/D^-HUS in these studies. People in western countries and Japan are used to eat undercooked food, like raw beef, raw pork in sandwiches and sashimi, meanwhile in traditional Chinese diet, uncooked beef and vegetable were rarely eaten, and cooking habit for thousands of years in China reduced the possibility of *Escherichia coli* O157:H7, O26, O121, O145 or Shigella type I contamination in food.

Recent advances have shown that atypical HUS

Table 2. Analysis of risk factors of 46 cases with HUS

Parameters	Death	Survival	χ^2	*P*
Gender				
Male	5	23	0.0108	0.917
Female	3	15		
Age less than 2 y				
Yes	6	10	6.9050	0.009
No	2	28		
Amount of leukocytes greater than 20×10^9/L				
Yes	4	14	0.4804	0.488
No	4	24		
Duration of oliguria or anuria exceeding one wk				
Yes	6	9	7.9190	0.005
No	2	29		
Extra-renal complications				
Yes	6	8	9.0840	0.003
No	2	30		
Plasma exchange and CRRT				
Yes	0	14	4.2370	0.040
No	8	24		

HUS: hemolytic uremic syndrome; CRRT: continuous renal replacement treatment.

(familial or sporadic) is predisposed to genetic mutations in complement factor H (CFH).[4] Furthermore, CFH is also associated with the recurrent HUS. There were 4 patients in the present study with recurrent HUS each having 1-3 episodes of HUS, respectively. No familial history was found in these patients, though we did not do mutation screening for gene coding CFH. Complementemia plays a great role in the pathogenesis of HUS, especially in D^- HUS. D^- HUS is caused by dysregulation of the complement alternative pathway, leading to persistent cleavage of complement protein C5, generation of C5a and C5b proteins, and the formation of the membrane attack complex (C5b-9), which in turn leads to endothelial cell activation, injury, and death. Eculizumab, known as humanized monoclonal antibody against C5 became the first and only approved treatment for D^- HUS both in adults and children.[5]

The therapy of HUS was still controversial. Plasma exchange and plasma infusion were the first-line therapy in treating D^- HUS.[6,7] Overall, following the introduction of plasma exchange and plasma infusion, the mortality rate had dropped from 50% to 25%. Patients with renal insufficiency should receive dialysis as soon as possible. Hemodialysis is more efficient than peritoneal dialysis in reducing the possibility of pulmonary edema and cerebral edema.[8,9] Eight dead patients all occurred because of pulmonary edema, cerebral edema, cardiogenic shock, multiple organ failure and DIC before 2008, when plasma exchange and hemodialysis were not introduced in our hospital. Since 2008, 21 patients of HUS were diagnosed from then on, and 14 of them received plasma exchange, 7 received CRRT at the same time; all the 21 survived. Plasma exchange has an active effect on the recovery of renal function, preventing of complication and improving prognosis in clinical use. The European Association of HUS in Children recommended that active plasma exchange was the first choice D^- HUS treatment.

The risk factors for mortality and prognosis of D^+ HUS and D^- HUS were controversial.[10-12] Young incident age, without diarrhea, long duration of ogliurai/anuria, dialysis continued for long time, significantly low hemoglobin and/or high white blood cell count at onset, complicated with multiple organ disfunction were reported to be important risk factors of poor prognosis. In the present study, the age onset younger than 2 years, ogliura/anuria lasting for long time and extra-renal complications were risk factors, which was consistent with other studies. The need for initial dialysis was strongly associated with worse outcome. No one achieved full renal recovery when dialysis therapy exceeded 4 weeks.

In conclusion, age of onset younger than 2 years, long-time lasting oliguria or auria, and severe extra-renal complications, were strongly associated with a worse long-term prognosis in the present study. Early dialysis and CRRT may be helpful to control the progress of disease and improve the prognosis of HUS.

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Competing interest: None.
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