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Original Article

Diagnosis and treatment of pediatric hemolytic uremic syndrome

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Abstract: This study is aimed to observe clinical characteristics of pediatric hemolytic uremic syndrome (HUS) and evaluate clinical efficacy of glucocorticoid, gamma globulin, plasma exchange (PE) and dialysis in treating pediatric HUS. Thirty five HUS children admitted to Shengjing Hospital of China Medical University between January 2002 and January 2014 were recruited. Laboratory examination, medication therapy, PE and dialysis were delivered. Oral administration of glucocorticoid was given after HUS symptoms were alleviated. Clinical characteristics of all participants were observed and followed up for 0.5-12 years. Five cases with normal blood platelet count had dual HUS symptoms, C3 decrease in 26, complement C3 reduction in 16, C3 and C4 decrease in 1 case and digestive tract symptoms in 5 upon onset. Ten were effectively treated after hormone or combined use of hormone and gamma globulin. Nineteen had to undergo PE and 6 received dialysis. Efficacious rate of conservative therapy did not differ over complement or D-D dimer levels. One case had chronic renal insufficiency, one with long-term hypertension, two with urinary protein and the parameters of the remaining patients returned to normal. All children survived. Alternative pathway of complement is activated in most children and classical pathway of complement for a minority of individuals. Combined use of glucocorticoid and gamma globulin, and PE are efficacious treatment of HUS. Sequential oral administration of glucocorticoid reduces urinary protein. Chronic renal insufficiency and hypertension are potential complications. Long-term follow-up is urgently required.

Keywords: Plasma exchange, child, hemolytic uremic syndrome, complement

Introduction

Hemolytic uremic syndrome (HUS) is clinically manifested as a triad of microangiopathic hemolytic anemia, thrombocytopenia and acute renal insufficiency [1]. Approximately 10% of HUS cases may present with dual symptoms. HUS is characterized with acute onset, severe symptoms and high mortality. Early diagnosis and treatment determine the clinical prognosis. European Paediatric Study Group for HUS recommend rapid administration of plasma exchange (PE) or infusion, intensively administered daily for 5 days and then with reducing frequency [2]. However, the American Society for Apheresis provides less recommendation for PE to treat HUS considering the “low” or “very low” quality of evidence supporting its use. Although some patients experienced improvements in red blood cell and platelet counts, plasma therapies generally did not lead to full remission [3]. Currently, scholars’ opinions upon the therapy of HUS tend to be divergent. In this clinical trial, 35 children diagnosed with HUS were observed for clinical manifestations, diagnosis, treatment and prognosis, aiming to investigate the effective therapy of HUS.

Materials and methods

Baseline data

According to the diagnostic criteria of pediatric HUS [4, 5], a total of 35 children admitted to the Department of Pediatric Nephrology of our hospital between January 2002 and January 2014 were diagnosed with HUS. Among 35 children, 15 cases were diagnosed with D+HUS (post-diarrhea HUS) and 20 with D-HUS (non-diarrhea HUS), 21 male and 14 female. Six children were aged ≤1 year, 9 aged 1-3 years and 20>3 years.

In the D-HUS group, 7 cases had the onset of HUS between January and March, 7 between April and June, 1 between July and September and 5 between October and December. In the D-HUS group, 2 cases had the onset of HUS between January and March, 11 between April and June and 2 between October and December. Informed consents were obtained from all patients or their parents. The study procedures were in accordance with the ethics committee of our hospital.

Methods

Laboratory examinations: Thirty five HUS children received routine blood and urine test, quantitative detection of urinary protein, liver and renal function, myocardial enzyme spectrum, complement C3C4, Coombs test, DIC, blood and stool culture test, radiography and CRP. Nine children underwent routine renal biopsy.

Clinical treatment: The infusion amount was strictly controlled to maintain water electrolyte balance. Twenty four children were administered with prostacyclin E1 at a dosage of 10 μg/time, 1-2 times daily. Those with severe anemia were given with red cell infusion. Upon admission, methylprednisolone shock treatment was delivered at a dose of 15-20 mg/kg/d for 1-2 courses of treatment (3 d for one course of treatment). Twenty six cases were administered with hormone combined with gamma globulin via intravenous route at a dose of 400 mg/kg/d for consecutive 3 d. If untreated with the medication therapy, PE (n=19) or peritoneal dialysis/hemodialysis (n=6) was subsequently performed. Initially, all affected children received sequential oral administration of glucocorticoid (prednisone or methylprednisolone) at a dose of 1-1.5 mg/kg/d for 2-8 weeks and then with every other day after the urinary protein detection was negative. During the following 6 months, the dose was gradually reduced and discontinued eventually.

Plasma exchange procedures: Seldinger technique was adopted to obtain safe access to blood vessels. Internal jugular or femoral venous puncture was conducted under topical anesthesia. Dual lumen catheterization was performed by using single needle. The quantity of PE was 50 ml per kilogram of body weight with a maximum quantity of 2000 ml, 2-3 h for each cycle of PE at a speed of 3-5 ml/min. For 500 ml of PE, 10 ml of 10% calcium gluconate was supplemented to the children. A dose of 0.5-1 mg/kg heparin was utilized for anticoagulation. Nineteen affected children underwent PE, once for 9 and twice for 10. Two cases received PE in combination with hemodialysis.

Dialysis treatment: Four children received peritoneal dialysis alone due to body weight <20 kg, 2 with hemodialysis alone and another 2 cases underwent combined therapy of PE and hemodialysis.

Follow-up

The follow-up endured from 0.5 to 12 years. During the first year, blood and urine examination and kidney function were monitored every 3 months, and then once every 6 months after the second year.

Statistical analysis

SPSS 16.0 statistical software was utilized for data analysis (SPSS Inc., Chicago, IL). Enumeration data were statistically analyzed using *chi*-square test. Measurement data were processed by using *t*-test.

Results

Clinical manifestations

Primary symptoms: in the D+HUS group (n=15), 5 children had simple digestive tract symptoms including diarrhea, abdominal pain and vomiting, 8 presented with both digestive and urinary symptoms, such as hematuria, edema and uropenia and 2 cases had digestive, urinary symptoms and hemorrhagic spot upon onset of HUS. Two children had hematuria observed by naked eye. In the D-HUS group (n=20), four children had skin hemorrhagic spots upon onset and 16 presented with urinary system symptoms. In the D-HUS group, 8 children were characterized with urinary symptoms complicated with abdominal pain and vomiting, 2 with fever and 6 with hematuria observed by naked eye. All HUS affected children had hematuria under microscope.

Table 1. Accessory examination of 35 children affected by HUS

HUS	D-HUS group (n=20)	D+HUS group (n=15)
HB	(63±4) g/L	(67±18) g/L
PLT	79±60/mm^3	75±52/mm^3
WBC elevation	N=6	N=5
C3 decline	N=15	N=11
Significant C3 decline (< normal value 50%)	N=9	N=7
C4 decline	N=1	N=0
Albuminuria	10 cases with nephrosis, 5 with negative urinary protein and 5< nephrosis albuminuria level	4 cases with nephrosis, 3 with negative urinary protein and 8< nephrosis albuminuria level
Hypertension	N=5	N=5
Uropenia	N=7	N=9
Anuria	N=0	N=0
Radiography	6 cases with bronchitis and 2 with pneumonia	6 cases with bronchitis and 5 with pneumonia
Stool culture	Negative	Negative
Routine stool test	20 cases with normal results	3 with red and white cells
Coombs	Negative	Negative
Creatinine	61-398 μmol/L	77-503 μmol/L
LDH	545-3165 μmol/L	373-2378 μmol/L
CRP elevation	N=4	N=2
D-D	322-9999/L	807-2084/L
Pathogeny	3 cases infected with mycoplasma and 3 with chlamydia	2 with CMV and 1 with rotavirus

Table 2. Comparison of clinical efficacy of medication therapy for HUS children with different C3 levels

	Efficacious medication therapy	Inefficacious medication therapy	Total
Significant C3 decline	3 (18.75)	13 (81.3%)	16
No significant decline in C3	7 (37.7%)	12 (62.3%)	19
Total	10	25	35

P>0.05.

Table 3. Comparison of clinical efficacy of medication therapy for HUS children with different levels of D-D dimer

	Inefficacious medication therapy	Efficacious medication therapy	Total
D-D>1000	14 (87.5%)	2 (12.5%)	16
D-D<1000	11 (57.9%)	8 (42.1%)	19
Total	25	10	35

P>0.05.

Table 4. Comparison of PLT and LDH levels in HUS affected children before and after plasma exchange

	PLT	LDH
Before plasma exchange (n=19)	71.6±63.8	2183.8±963.2
After plasma exchange (n=19)	168.3±131.6	784.2±545.2

P<0.05.

Auxiliary examination

In the D+HUS group, 3 children had normal blood platelet count and 2 in the D-HUS group, manifested as incomplete HUS. These 5 cases were diagnosed with thrombotic microangiopathy confirmed by renal biopsy. All HUS children had hematuria under microscope. Eight affected children had negative urinary protein, as illustrated in **Table 1**.

Renal biopsy

Pathological biopsy revealed the signs of endotheliocytic swelling, capillary cavity stenosis and glomerulus capillary vascular shrinkage in 9 cases. Meantime, 3 patients were complicated with renal tubular thrombosis, 3 with arteriole wall thickening, 1 with local segmental glomerulus sclerosis and partial glomerulus sclerosis and 2 patients were accompanied by mild mesangial cell proliferative lesions and 1 with cellular fibrous crescent. Four patients presented with renal stromal edema and renal tubular epithelial cell abnormality. Immunofluorescence: 1 case with IgG (+), 2 with IgM (+), 1 with C3 (++) and 1 with C1q (+).

Clinical treatment and follow-up

Clinical efficacy: all 35 affected children survived. Ten cases recovered after combined use of hormone and gamma globulin (IVIG), manifested as no hemolysis, steady levels of hemoglobin, PLT elevation and recovery of kidney function. Twenty five patients were not healed after conservative medication therapy, 19 of whom undergoing PE (combined with hemodialysis in 2 cases) and another 6 receiving dialysis alone. Approximately 81.3% patients were untreated by conservative therapy in those with significant decline in complement C3, and 62.3% for their counterparts with no apparent decrease in complement C3 level. No statistical significance was noted between two groups (P> 0.05), as illustrated in **Table 2**. Almost 87.5% HUS affected children were untreated by conservative therapy among those with D-D dimer >1000, and 57.9% for their counterparts with D-D dimer <1000 with no statistical significance (P>0.05), as shown in **Table 3**. Except 1 child presenting with transient PLT decline, the others had significant PLT elevation with statistical significance before and after PE (P<0.05). However, LDH levels were significantly decreased after PE in all children (P<0.05), as illustrated in **Table 4**.

PE was successfully performed. During PE, 2 children had plasma allergy manifested as 1 case with rash and 1 with cough, and recovered after use of hormone and clarityne. Two children presented with hypotension and returned to normal after physiological saline supplement. Two cases had transient hematuria detected by naked eye, probably resulted from hemodynamic changes and anticoagulation. Six children who underwent dialysis alone gradually restored their kidney function and prevented hemolysis, one of whom presenting with uropenia for consecutive 4 weeks. Upon discharge, 28 children had normal kidney function and routine blood test.

Seven cases had normal routine blood test whereas relatively high levels of serum creatinine, 6 with no RBC in the urine and 3 with no urinary protein. All children presented with decreasing levels of albuminuria.

Subsequent follow-up

At 2.5-year follow-up, 2 children had no albuminuria, 1 with chronic renal insufficiency at compensatory phase, 1 with long-term hypertension, 1 recurred half a year after discharge and the remaining cases had normal routine urine examination during half a year and restored normal renal function within 3 months after discharge.

Discussion

HUS is characterized with endothelial cell injury secondary to thrombosis, microvascular hemolysis and kidney function damage [4, 5]. Approximately 90% of HUS cases present with a triad of hemolytic anemia, thrombocytopenia and renal insufficiency [6]. In this study, 5 among 35 HUS children had normal blood platelet, who were manifested as dual symptoms. Renal biopsy indicated the incidence of renal microvascular lesions, hinting that the possibility of HUS should be excluded for those children with hemolytic anemia complicated with renal insufficiency whereas with normal blood platelet count. Normal values of creatinine differ among the children of different ages. In our investigation, one 6-month-aged child presented with 61 μmol/L of creatinine and it was likely to be misdiagnosed with Evans syndrome. A majority of HUS affected children were accompanied by low levels of complement, which was consistent with the classification criteria of systemic lupus erythematosus (SLE) by ACR in the year of 2009. However, the levels of antinuclear antibodies in the affected children were normal, excluding the possibility of SLE. Hence, the diagnostic criteria of SLE should not be applied in these cases.

Among 35 HUS cases, 5 presented with digestive tract symptoms alone. It was likely to make a misdiagnosis if routine blood and urine tests were not performed. The signs of hematuria were observed under microscope in 35 HUS children, indicating the importance of routine urine test. Combined use of routine urine and blood tests predicts the possibility of HUS. Though the diagnosis of HUS does not totally depend upon pathological findings, renal biopsy contributes to validating the diagnosis of incomplete or suspected HUS cases. In current clinical trial, 9 children underwent renal biopsy. Four cases had immune material deposition in the kidney, 4 with stromal edema and 1 with cellular fibrous crescent, probably due to efficacious combined therapy of hormone and gamma globulin. Renal biopsy was conducted after hemolysis was alleviated and physical signs stabilized, which probably led to less pathological changes compared with that upon early onset. One HUS child had C1q deposition whereas failed to progress into SLE during subsequent follow-up.

Based upon the presence of diarrhea, HUS can be classified into typical (post-diarrhea HUS; D+HUS) and atypical HUS (non-diarrhea HUS, D-HUS). D+HUS, accounting for approximately 90% of all HUS cases, can be sporadically distributed or prevail. Patients constantly present with blood stool mainly infected by the pathogen of escherichia coli 0157:H7. Among 35 children in this study, 20 cases were diagnosed with D+HUS and 15 with D-HUS. No signs of escherichia coli or shigella were detected during stool test, probably resulted from varying geographic locations, epidemiological characteristics and constituent ratio of HUS. Previous studies have demonstrated that a variety of pathogens, such as shigella, salmonella, escherichia coli, streptococcus pneumoniae, coxsackie virus, enterovirus, chickenpox virus [7], influenza virus [8], ADV and EBV [9] are correlated with the incidence of HUS. In this study, 3 children were infected with mycoplasma pneumonia (MP), 3 with pneumonia chlamydia, 2 with CMV and 1 with rotavirus. As an inherent specific immune complex of antibody formation, MP is capable of inducing immune inflammatory injury via activating complement and immunocytes [10]. However, whether MP and pneumonia chlamydia could cause the incidence of HUS remains to be further elucidated.

Previous investigations have indicated that excessive activation of alternative pathway of complement participates in the occurrence of D+ and D-HUS [11-13]. In current study, 26 HUS children had decreasing C3 levels and 16 presented with significant decline in complement

C3, which is consistent with the findings above. Meantime, 1 child had simultaneous decline in C3 and C4, prompting that the activation of classical complement pathway is probably involved with the incidence of HUS. Whether cortical hormone should be used to treat HUS remains to be elucidated.

For patients with uncontrollable hemolysis and severe symptoms, early administration of methylprednisolone could suppress the progression of hemolysis, inhibit immunologic function, decrease the cascade of inflammation reactions and mitigate the kidney injuries, which is especially efficacious for D+HUS patients [14]. It has been widely accepted that a large dose of gamma globulin (IVIG) is an efficacious therapy of HUS. Use of IVIG is able to neutralize toxin, remove latent infection, enhance immunologic function, act on macrophage, inhibit antigen presenting, suppress T-lymphocyte RECEPTOR, inhibit THE secretion of inflammatory factors and compete to bind with Fc receptor [15]. Among 35 HUS children, 10 were effectively treated by use of hormone or combined use of hormone and gamma globulin. However, 25 cases gradually progressed and had to receive hemodialysis. Currently, it is challenging to identify which type of HUS patients are suitable for conservative medication therapy. In this study, 81.3% of HUS patients with significant C3 decline were untreated by conservative therapy, significantly higher compared with 62.3% for those without apparent C3 decline. In addition, approximately 87.5% of HUS children with D-D dimer >1000 were untreated by medication therapy, considerably higher compared with 57.9% for their counterparts with D-D dimer <1000. Nevertheless, due to relatively small sampling, whether C3 and D-D dimer levels can serve as the predictors of clinical efficacy of conservative medication therapy remains to be further confirmed by large sample size investigations.

In the year of 2003, British Society for Haematology proposed standard guidelines of PE for thrombotic microangiopathy and recommended PE immediately after HUS was diagnosed [16]. In 2009, Guideline for the Investigation and Initial Therapy of Diarrhea negative HUS recommended intensified PE as the primary therapy for HUS [17]. PE is able to eliminate multiple pathogenic factors. It can reduce the pathogenic materials in the plasma, such as antigen, antibody, immune complex and endotoxin. In addition, it is capable of eliminating the serum inflammatory factors. Moreover, it is able to regulate immune system function by improving monocyte macrophage system function and maintaining the balance between idiotype and anti-idiotype antibody system. Eventually, PE may eliminate the materials which inhibit the synthesis of prostacyclin, restore it activity, supplement plasma factors which stimulate the production of prostacyclin 12 and thus decrease the incidence of microthrombosis. In this study, 25 children were untreated by combined use of hormone and IVIG, 19 of whom undergoing PE (once PE for 9 and twice for 10). Two children had dialysis indications and then PE in combination with hemodialysis was conducted. HUS children were successfully treated after receiving PE with blood platelet elevation, significant LDH decline, alleviated hemolysis and stead recovery of renal function. Blood platelet and LDH significantly differed before and after PE and no serious complications were documented, hinting high efficacy and ensured safety of PE for HUS. Six cases with low body weight, untreated by medication therapy and refusing to receive PE subsequently underwent dialysis and survived. Blood purification treatment significantly decreased the HUS mortality from 40-50% to approximately 5%.

Clinical prognosis of HUS mainly depends upon early diagnosis and timely improvement of kidney function. In this study, no albuminuria was noted in 2 cases during 2.5-year follow-up, 1 with chronic renal insufficiency at compensatory phase, 1 with long-term hypertension, the others with normal routine urine test half a year after discharge and normal kidney function within 3 months. Elevated understanding, early diagnosis and effective therapy play a pivotal role in the treatment of HUS.

Disclosure of conflict of interest

None.

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