ORIGINAL ARTICLE

Hemolytic Uremic Syndrome Following Hemorrhagic Colitis Caused by Verotoxin-producing *Escherichia coli* 0157: H7: Early Signs of Hemolytic Uremic Syndrome

Atsutoshi Tsuji, Michiko Sasaki, Takefumi Kanemitsu, Norio Uehara, Hiroshi Ito¹ and Masatoshi Honda¹

Department of Pediatrics, Urawa Municipal Hospital, Urawa, Saitama and

¹ *Department of Nephrology, Tokyo Metropolitan Kiyose Children's Hospital, Tokyo, Japan*

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Abstract. Ten cases of hemolytic uremic syndrome (HUS) following hemorrhagic colitis caused by verotoxin T₂-producing *Escherichia coli* 0157: H7 (VTEC) occurred in a Kindergarten. Slight changes in results of peripheral blood and blood chemistry studies an average of 4 days after onset suggested HUS, and within the following 12 hours platelet counts and levels of haptoglobin and lactic dehydrogenase decreased. Treatment was mainly directed toward the management of renal failure and included supportive therapy and anticoagulant and antiplatelet treatment. Although neurological complications occurred in some cases, all patients eventually recovered completely. (Keio J Med 45 (1): 44–47, March 1996)

Key words: hemolytic uremic syndrome, hemorrhagic colitis, Enterohemorrhagic *E. coli* 0157: H7, contaminated drinking water, early sign of hemolytic uremic syndrome

Introduction

In October 1990, a sports and games day was held at a Kindergarten in Urawa City. Most of the enrolled children and their siblings and parents participated. That night, many of the participants, mostly children aged 1 to 6 years, were afflicted by acute gastroenteritis. During the next 2 months, 151 children were brought to the outpatient clinic of our hospital with gastrointestinal symptoms. Sixteen children were admitted with hemorrhagic colitis, and complications of HUS were found in 10 cases.

This report describes clinical observations of these patients and laboratory examinations necessary for the early diagnosis of hemolytic uremic syndrome (HUS).

Methods

Patients

The 10 children with HUS were 5 boys and 5 girls ranging in age from 1 year 3 months to 6 years 5 months of age (median, 5 years 1 month).

Clinical and laboratory data

The clinical and laboratory data for these patients were reviewed at the time of admission and those at the time mild signs of HUS developed.

Treatment

Our treatment consisted of 1) management of renal failure, 2) supportive therapy, 3) anticoagulant therapy, 4) antiplatelet therapy, and 5) hemodialysis (Table 1).

Three patients (cases 72, 73, and 82) required dialysis owing to rapidly rising blood urea nitrogen (BUN) levels, two (cases 73 and 82) of these patients had transient convulsions and impaired consciousness but recovered completely.

Results

Past history and family history

Past medical histories and family histories of all chil-

辻 敦敏, 佐々木道子, 金光岳文, 上原紀夫, 伊藤 拓, 本多雅敬

Reprint requests to: Dr Atsutoshi Tsuji, Department of Pediatrics, Urawa Municipal Hospital, 2364 Mimuro, Urawa, Saitama 336, Japan

Table 1 Treatment

Management of Renal Failure	
Supportive Therapy	
Anticoagulant Therapy	heparin, 10 u/kg/hr
Antiplatelet Therapy	gabexate mesilate, 1-2 mg/kg/hr
	human antithrombin III
	dipyridamole, 5 mg/kg/day
Dialysis	

dren were noncontributory.

Clinical course

Ten children were admitted with chief complaints of abdominal pain (90%) and bloody diarrhea (100%) accompanied by severe dehydration (Table 2). Body temperatures ranged from 36.5 to 37.8°C (median, 37.3°C). Eight of the 10 cases were complicated by HUS after admission.

HUS was diagnosed on admission in 2 cases (cases 77 and 78), 9 days and 3 days, respectively after the onset of hemorrhagic colitis. In the other 8 cases, the interval between onset of hemorrhagic colitis and admission ranged from 0 to 2 days (median, 1.5 days). Thus, HUS took 1 to 5 days (median, 3 days) to develop. Three (cases 72, 73, and 82) of the 10 patients needed acute hemodialysis. Neurologic symptoms, such as convulsions and impaired consciousness, were observed after dialysis was started in two (cases 73 and 82) of these three patients. Magnetic resonance imaging revealed an infarction near the lateral aspect of the internal capsule in case 72, and hemosiderin deposits were noted at the site of the pituitary in case 82.¹ However, both children recovered completely.

Table 2 Symptoms

Case No.	Age (yrs)	Sex	Max. Fever (A)	Max. Fever (B)	Bloody Diarrhea (A)	Bloody Diarrhea (B)	Vomiting (A)	Vomiting (B)	Abdominal Pain (A)	Abdominal Pain (B)	Annotation
70	6	M	36.5	37.6	1	f	+	+	+	+	
71	4	F	37.2	37.5	f	f	-	+	+	-	
72	1	F	37.5	37.6	f	f	-	-	+	+	dialysis
73	5	M	37.3	38.1	f	f		+	+	+	dialysis
											neurological symptom
75	5	M	37.8	37.6	f	1	-	-	+	+	
76	6	F	37.3	38.2	f	2	-	-	+	+	
77*	5	M	37.3		1		-		-		
78*	4	M	37.4		f		-		+		
79	4	F	37.2	37.9	f	f	-	-	+	+	
82	3	F	37.6	37.6	f	f	-		+	+	dialysis
											neurological symptom

(A); at the time of admission. (B); at the time of mild sign of HUS. f; frequently, +; noted, -; none, *: diagnosis of HUS was established on admission.

Laboratory results

Enterohemorrhagic *Escherichia coli* (EHEC) 0157: H7 was isolated from feces, and verotoxin VT₂ was detected in all 10 cases.²

Tables 3 and 4 show laboratory findings at the time of admission, a median of 1.5 days after onset of hemorrhagic colitis, and those at the time the first signs of HUS appeared, a median of 4 days after onset.

Complete blood counts on admission showed mild leukocytosis in 5 cases and increased numbers of neutrophils in all cases.

In eight patients admitted after the acute phase, platelet counts fell abruptly by the time the possibility of HUS was suggested by clinical findings. Tables 3 and 4 show changes in the levels of hemoglobin, total serum bilirubin, and serum haptoglobin, which indicated hemolysis. By a median of 4 days after the onset of hemorrhagic colitis, a slight decrease in hemoglobin levels had occurred. The haptoglobin level was elevated in most cases before the onset of HUS, possibly owing to infection, but decreased to less than 10.5 mg/dl in each case by the time HUS was diagnosed. Elevation of direct serum bilirubin and lactic dehydrogenase (LDH) in serum were also indicated hemolysis. The BUN and serum creatinine levels rose abruptly by the time the first signs of HUS appeared in most cases. The fibrinogen levels decreased to less than 150 mg/dl in 4 cases, then returned to normal by the time the patient recovered.

Discussion

The occurrence of 151 cases with diarrhea in a Kindergarten in Urawa City in October and November 1990 led to recognition of an outbreak of hemorrhagic colitis and HUS due to verotoxin-producing EHEC.

Table 3 Laboratory Data

Case No.	WBC $\times 10^3/\text{mm}^3$		Neutrophil %		Hemoglobin g/dl		Platelet $\times 10^4/\text{mm}^3$		AST IU/L		LDH IU/L		Annotation
	(A)	(B)	(A)	(B)	(A)	(B)	(A)	(B)	(A)	(B)	(A)	(B)	
70	8.7	12.4	67	61	13.5	13.4	32.0	4.5	20	82	330	2955	
71	21.2	14.8	74	65	15.1	10.7	34.7	6.2	16	107	393	4930	
72	13.1	12.4	66	49	12.2	12.0	42.8	13.1	23	98	537	2606	dialysis
73	14.0	28.1	71	75	14.8	13.8	34.9	5.1	17	100	352	3403	dialysis
75	10.2	9.3	60		12.1	10.3	27.2	10.9	19	24	365	705	
76	8.4	11.7	80	76	13.5	10.4	30.2	6.0	18	25	307	1004	
77*	8.8	18.8	56	93	7.3	8.2	24.2	48.5	22	20	1241	857	
78*	24.5	12.0	75	66	12.7	5.7	4.4	14.8	45	19	2441	1553	
79	7.8	9.6	67	59	13.4	8.0	30.1	2.6	21	59	334	2043	
82	9.5	12.5	51	69	13.9	12.0	29.4	7.5	17	313	313	4056	dialysis

(A); at the time of admission. (B); at the time of early signs of HUS. *, HUS was diagnosed on admission.

Table 4 Laboratory Data

Case No.	BUN mg/dl		Creatinine mg/dl		Total Bilirubin mg/dl		Haptoglobin mg/dl		Fibrinogen mg/dl		Annotation
	(A)	(B)	(A)	(B)	(A)	(B)	(A)	(B)	(A)	(B)	
70	9.8	25.0	0.46	0.46		3.8		<10.5		126	
71	9.3	37.1	0.46	1.43	0.5	2.4	442	<10.5		200	
72	17.2	20.6	0.62	1.30		0.9		<10.5		238	dialysis
73	9.8	69.3	0.57	2.22	0.4	0.7	351	<10.5	282	276	dialysis
75	4.7	30.1	0.60	1.00		1.0	119	<10.5		131	
76	7.4	50.7	0.55	0.86	0.3	2.8	404	<10.5		198	
77*	25.3	33.7	0.81	1.00	0.3		<10.5				
78*	34.1	30.7	0.90	0.86	1.6		<10.5		222	122	
79	5.8	52.5	0.50	2.01	0.5	1.7	261	<10.5	259	148	
82	6.3	90.8	0.57	3.95	0.4	1.0	222	<10.5		261	dialysis

(A); at the time of admission. (B); at the time of early signs of HUS. *, HUS was diagnosed on admission.

157: H7; to our knowledge, this outbreak was the first reported in Japan. This type of HUS is usually referred to as classic HUS; it begins with frequent bloody diarrhea and is occasionally accompanied by vomiting, abdominal pain, and fever.³ Because of this prodrome symptom of frequent bloody diarrhea, the management of dehydration is emphasized; maintenance of appropriate fluid levels is important. The pathologic features of HUS include formation of platelet and fibrin thrombi owing to endothelial injuries in the microvasculature of the kidney and hemolysis due to a reduction in renal blood flow. Therefore, if HUS occurs following hemorrhagic colitis, the kidney may not be able to deal with the large volume of fluid administered to counteract dehydration, and body fluid levels may become difficult to adjust.⁴ Because of these differences in pathogenesis and treatment between hemorrhagic colitis and HUS, an index of the risk of HUS following hemorrhagic colitis would be of clinically useful.

Pavia suggested an increase in peripheral blood leukocytes and fever as predictive signs of HUS,⁵ but in our study there were no significant differences in symptoms or laboratory findings between HUS and non-HUS patients before the onset of HUS. In the HUS group, all but two patients (cases 77 and 78) were hospitalized 1.5 days (median) after the onset of hemorrhagic colitis due to 0157: H7 (A in the table). When these eight cases were reviewed, changes that suggested the onset of HUS were found in results of peripheral blood and blood chemistry examinations performed 4 days (median) after the onset of hemorrhagic colitis (B in the table). These changes indicate a very early stage of HUS, and if they are identified early measures can be taken against HUS in children admitted owing to hemorrhagic colitis.

In the early stage of HUS, marked changes were observed in the platelet count. On admission, platelet counts in the eight patients (excluding cases 77 and 78, in whom HUS had already developed) decreased from

$31.1 \times 10^4/\text{mm}^3$ (median) to $6.1 \times 10^4/\text{mm}^3$ (median). The hemoglobin concentration, which is an index of hemolytic anemia, decreased only slightly from 13.5 g/dl (median) to 11.3 g/dl, but decreased further to 8.7 g/dl (median, range; 4.2 ~ 9.9 g/dl) 1.5 days later. The haptoglobin level, which is another index of hemolytic anemia, decreased, and was 10.5 mg/dl or less in all cases. The LDH level also changed markedly, increasing rapidly from 343 IU/L (median) to 2780.5 IU/L. This increase far exceeded the change in the value of aspartate aminotransferase. In this period, BUN was higher than 80 mg/dl in only one case (case 82; 92.8 mg/dl). The serum potassium concentration reached a peak of 5.0 mEq/l (case 72).

To summarize these results: A marked decrease in the platelet count, a sudden decrease in the haptoglobin level, and a marked increase in LDH are signs of a very early stage of HUS in children admitted owing to hemorrhagic colitis. A marked decrease in hemoglobin and an increase in BUN occur later. These changes are considered to reflect the onset of HUS. None of the clinical symptoms of hemorrhagic colitis suggested the future development of HUS.

Hemodialysis was performed in three cases. None of the clinical or laboratory findings during the period of hemorrhagic colitis predicted a need for the dialysis. Symptoms in the central nervous system are common in HUS.^{4,6} One of two patients with neurologic symptoms (case 82) had a mild metabolic disorder (serum Na^+ ; 139 mEq/l, K^+ ; 4.7 mEq/l, Cl^- ; 99 mEq/l, Ca^{2+} ; 8.0 mg/dl, phosphorus; 9.8 mg/dl, arterial pH; 7.315, base excess; 6 mmol/l) and had convulsions; pituitary hemorrhage was demonstrated by magnetic resonance imaging.

Because we were extremely mindful of the danger of

overhydration due to fluid therapy in the treatment for HUS,⁷ hypertension did not develop in any of our patients.

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