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Gastrointestinal Manifestations of Hemolytic Uremic Syndrome: Recognition of Pancreatitis

S. Grodinsky, A. Telmesani, W. L. M. Robson, G. Fick, and R. B. Scott

Departments of Pediatrics and Community Health, University of Calgary and Alberta Children's Hospital, Calgary, Alberta, Canada

Summary: A restrospective study of 76 children with hemolytic uremic syndrome (HUS) who were admitted to the Alberta Children's Hospital in Calgary, Alberta between January 1982 and December 1988 was undertaken to explore the gastrointestinal manifestations of the syndrome. The children (mean age of 4.0 ± 3.1 years) presented primarily during the summer months with a microangiopathic hemolytic anemia (Hgb 94 ± 26 g/L), thrombocytopenia (platelets 87 ± 83 × 10^9/L), and acute renal failure (oligoanuria with a BUN of 26 ± 15 mmol/L, and a creatinine of 294 ± 90 μmol/L). Forty-three children required dialysis for 10 ± 17 days. The duration of hospitalization was 17 ± 17 days. Four children died of complications attributable to HUS. The following symptoms and gastrointestinal manifestations of HUS were noted: fever (33%), vomiting (80%), abdominal discomfort/tenderness (59%), diarrhea (100%), hemorrhagic colitis (79%), rectal prolapse (13%), colonic stricture (3%), colonic perforation (1%), intussusception (1%), indirect hyperbilirubinemia (49%), and elevated hepatocellular enzymes (58%). Of the last 29 children studied, 19 (66%) had elevated levels of amylase and lipase in the presence of acute renal failure, and six (21%) had a marked elevation of lipase (more than four times normal) with additional supportive evidence of pancreatitis. The additional supportive evidence included persistent elevation of lipase after the resolution of acute renal failure in four children, a marked increment in lipase in association with abdominal pain and an abnormal ultrasound of the pancreas after the initiation of oral feeding in a fifth child, and pancreatic exocrine and endocrine necrosis at autopsy in a sixth child. This study reviews the gastrointestinal manifestations of HUS in a large series of patients and presents data to suggest that pancreatitis is a relatively common complication of HUS. **Key Words:** Hemolytic uremic syndrome (HUS)—Intestinal manifestations—Pancreatitis.

Hemolytic uremic syndrome (HUS) is a common cause of acute renal failure in childhood and is defined by the occurrence of microangiopathic hemolytic anemia and thrombocytopenia in association with acute renal failure (1). Although these features form the basis for the recognition of the syndrome, they do not represent a full description of the clinical presentation of the disorder. Subsequent to the delineation of the syndrome by Gasser et al. (2) in 1955, numerous case reports of scattered or epidemic outbreaks have been documented, but reviews of the clinical course of large patient groups from regions where the disorder is endemic are relatively few in number (3–8). Clinical descriptions of the syndrome have commonly included gastrointestinal symptoms as part of the prodrome. A recent review observed that gastrointestinal symptoms have not been accorded much importance in the disorder, although they are frequently confusing and sometimes morbid accompaniments of the syndrome (9). Since an awareness of the clinical scope of this illness is essential for optimal management, we retrospectively reviewed 76 children with HUS cared for at our institution over a 7-year period. We specifically reviewed the presenting features, clinical complications, and course of the gastrointestinal manifestations of HUS. We present data showing

Address correspondence and reprint requests to Dr. R. B. Scott at Department of Pediatrics, Faculty of Medicine, University of Calgary, 3330 University Drive NW, Calgary, AB, Canada T2N IN4.

that acute pancreatitis is a common complication of HUS, occasionally proceeding to extensive endocrine and exocrine pancreatic necrosis. The difficulty of evaluating serum amylase and lipase measurements in patients with acute renal failure is also discussed.

METHODS

Patients

We reviewed the case records of 76 children with typical postdiarrhea HUS who were admitted to the Alberta Children's Hospital in Calgary, Alberta over a 7-year period extending from 1982 to 1989. The inclusion criteria for the diagnosis of HUS were the presence of a microangiopathic hemolytic anemia as evidenced by a fall in the hemoglobin with evidence of fragmented red cells and schistocytes on the peripheral smear, thrombocytopenia as evidenced by a platelet count of $<100 \times 10^9$/L, and acute renal failure as evidenced by an elevated blood urea nitrogen (BUN) and creatinine usually associated with oligouria or anuria.

An evaluation of each patient's medical record included age, month and year of presentation, sex, symptoms and signs at presentation, history of antidiarrheal or antibiotic usage, and laboratory, radiologic and pathologic findings. The interval between the onset of gastrointestinal dysfunction and HUS, the duration of intestinal complaints, the pathogenic organisms isolated from the stool, the management, the clinical course, and the outcome were also documented. The onset of HUS was defined as the first day during which there was either a drop in the hemoglobin of >10 mg/L with evidence of hemolysis or a decrease in the platelet count to $<100 \times 10^9$/L.

All values are reported as the mean ± SD. Chi-squared contingency table analysis, analysis of variance, Spearman rank correlation least squares linear regression, and Pearson's correlation coefficients were used where appropriate.

RESULTS

Epidemiology

Over a 7-year period, 76 children with a mean age of 4.0 ± 3.1 years (range of 0.7–13.8 years) were diagnosed with HUS. Eighty percent of the children were <6 years of age and 50% were <3 years of age. The ratio of affected boys to girls was 1.2:1. Although HUS was seen throughout the year, there was a highly significant ($p < 0.001$) seasonal distribution, with 80% of patients presenting between the months of May through September and with July being the month of peak incidence (Fig. 1).

Clinical and Laboratory Features of HUS

Fever >37.5°C axillary or 38.5°C rectally was documented at the time of admission in 25 of 76 children (33%). A history of vomiting was elicited in 61 of 76 children (80%), and 12 of these had bilious emesis. A history of abdominal discomfort and the clinical finding of abdominal tenderness was noted in 45 of 76 children (59%) at the time of the admission.

At the time of presentation, patients had a hemoglobin of 94 ± 26 g/L (normal, >106 g/L), platelet count of $87 \pm 83 \times 10^9$/L (normal, $150–400 \times 10^9$/L), BUN of 26 ± 15 mmol/L (normal, 1.8–5.4 mmol/L), serum creatinine of 294 ± 190 μmol/L (normal, 30–70 μmol/L) and potassium of 4.7 ± 0.9 mmol/L (normal, 3.5–5.5 mmol/L). Forty-three (57%) of the 76 children required dialysis (33 peritoneal and 10 hemodialysis) for an average of 10 ± 17 days. Eighteen children (24%) had a neurologic complication including either focal neurologic signs, convulsions, or a decreased level of consciousness. The hospital stay averaged 17 ± 17 days (range of 2–103 days). The death of four children was directly attributable to the complications of hemolytic uremic syndrome.

Antibiotic therapy was prescribed after admission in 51 of 76 children (67%), with the most common indications being urinary tract infection as a result of prolonged catheterization, peritonitis as a result of peritoneal dialysis, and suspected sepsis.

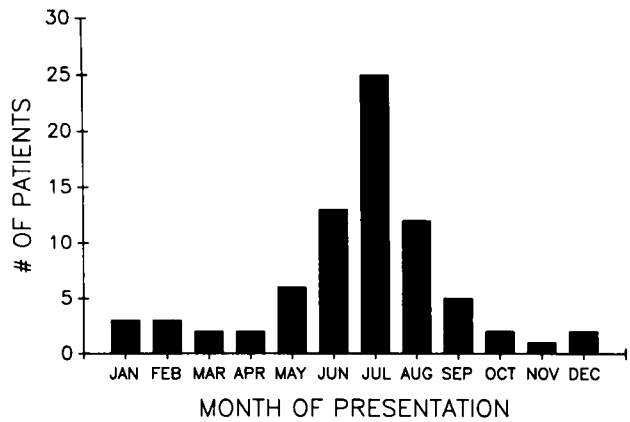

FIG. 1. The seasonal incidence of HUS.

Gastrointesinal Manifestations of HUS

Although diarrhea was reported in all children prior to admission, bloody diarrhea was present in 60 children (79%). The stool smears of those children were remarkable in that they generally contained only occasional white blood cells. The interval between the onset of bloody diarrhea and the subsequent diagnosis of HUS was 4 ± 3 days (range of 0–13 days) and was <5 days in 80% of patients. The duration of the hemorrhagic colitis was 7 ± 8 days, with a range of 0–62 days. Stool tests for culture and sensitivity, and ova and parasites were performed in all children, but virology was requested only sporadically. Fifty stool cultures were negative. Bacterial pathogens were isolated in 26 children (34%). *Escherichia coli* O157:H7 was the organism identified in 25 children, and *Campylobacter jejuni* was identified in the remaining child. Stool virology identified cytomegalovirus (CMV) on two occasions, adenovirus 1 on five occasions, and adenovirus 2 on one occasion. Prior to admission, antidiarrheal medications had been administered to 22 children and antibiotics to 25 children. The prior prescription of an antidiarrheal medication was associated with a significantly increased ($p < 0.05$; $r = 0.3$) duration of hemorrhagic colitis (7.1 ± 2.8 days vs. 5.4 ± 2.8 days). The prior prescription of an antibiotic had no effect on the duration of colitis. Of the 60 children with hemorrhagic colitis, 10 experienced rectal prolapse, two developed colonic strictures with intestinal obstruction, one developed a colonic perforation, one experienced an ileocecal intussusception, and one was felt to have the colonoscopic appearance of pseudomembranous enterocolitis (culture for *C. difficile* and toxin assay were negative).

TABLE 1. *Gastrointestinal manifestations of HUS*

	Number studied	Number affected	Percentage
Fever	76	25	33
Vomiting	76	61	80
Abdominal discomfort/ tenderness	76	45	59
Hemorrhagic colitis	76	60	79
Rectal prolapse	76	10	13
Colonic stricture	76	2	3
Colonic perforation	76	1	1
Intussusception	76	1	1
Indirect hyperbilirubinemia	47	23	49
Hepatocellular injury	43	25	58
Pancreatitis[a]			
Suspected on the basis of elevated amylase/lipase	29	19	66
Confirmed	29	6	21
Pancreatic endocrine insufficiency	78	2	3

[a] Assessed in only those 29 patients evaluated since January 1987.

Children were typically nonicteric; however, several with severe hemolysis were clinically jaundiced at the time of admission. The total bilirubin was assessed in 47 children and averaged 28 ± 23 μmol/L (normal, 5–23 μmol/L). It was modestly elevated (range of 25–150 μmol/L) in 23 children (49%) (Fig. 2). No child had an elevated direct bilirubin. Biochemical evidence of hepatocellular injury was sought in 60 children. At the time of admission, serum aspartate transaminase (AST) was 149 ± 166 U/L (normal, 12–50 U/L), serum alanine transaminase (ALT) was 74 ± 72 U/L (normal, 5–40 U/L), and serum γ-glutanyl transpeptidase (GGT) was 28 ± 37 U/L (normal, 5–32 U/L) (Fig. 2). The elevation of the hepatocellular enzymes beyond five times normal occurred in only six (10%) of those children studied. No child developed hepatic failure or chronic hepatitis. No child had a liver biopsy, and of the four children who died none had hepatocellular enzymes elevated beyond five times normal, or liver abnormalities at autopsy.

Pancreatitis has not been recognized as a common gastrointestinal complication of HUS and was not screened for at our institution prior to 1987. In 1987, two children with HUS developed persistent abdominal pain and vomiting during the period of their hospitalization. Both were found to have elevated pancreatic enzyme levels consistent with pancreatitis, and, in one child who died, the autopsy findings

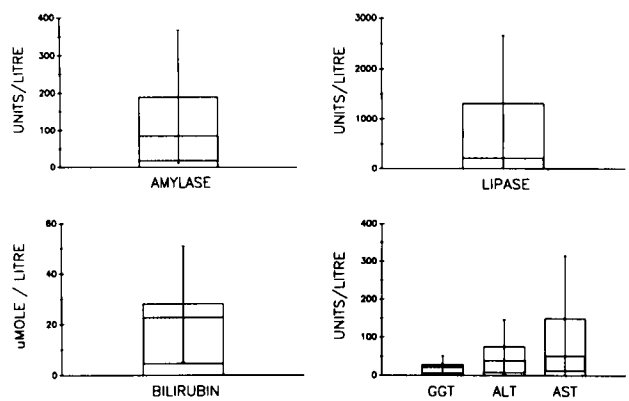

FIG. 2. A graphic presentation of the $\bar{x}$ ± SD of the serum amylase, lipase, bilirubin, γ-glutamyl transpeptidase (GGT), alanine transaminase (ALT), and aspartate transaminase (AST) in patients with HUS. The stippled area represents the normal reference values in our laboratory.

demonstrated extensive pancreatic endocrine and exocrine necrosis. These two children were the index cases that caused us to initiate routine evaluation of serum amylase and lipase as part of the evaluation of children with HUS. From June 1987 to the present, 29 children have had their serum amylase [normal, 20–80 U/L; performed using a drimarene red Z2B technique on a Kodak ektachem 700 (10)] and lipase [normal, 20–200 U/L; performed using a Kodak ektachem 700 (11)] assessed at the time of admission and followed during the course of their hospitalization. Seven of the 29 children had elevated values at the time of admission, and a total of 19 of 29 children (65%) had an elevated amylase and/or lipase during the course of their illness. The peak value was 189 ± 178 U/L for amylase and 1,308 ± 1,349 U/L for lipase (Fig. 2). The peak values occurred 7 ± 7 days after the diagnosis of HUS and 11 ± 7 days after the onset of the hemorrhagic colitis. The duration of elevation was 10 ± 10 days. All children with biochemical evidence of pancreatitis had a history of vomiting, abdominal discomfort, and the clinical finding of abdominal pain. These symptoms and signs were common clinical features of all the children with HUS, and did not discriminate between those with and without elevated values of serum amylase and/or lipase. The majority of children with biochemical evidence of pancreatitis were already nil per os and on total parenteral nutrition because the symptoms related to the hemorrhagic colitis precluded an adequate caloric intake. In patients with elevated values of serum amylase or lipase, total parenteral nutrition was discontinued and feeding was reinitiated after 10–14 days if there was no fever, vomiting, or abdominal pain. The amylase before (134 ± 132 U/L) and after (154 ± 134 U/L) feeding, and the lipase before (708 ± 778 U/L) and after (849 ± 791 U/L) feeding were not significantly different. However, in one child the reintroduction of oral feeding was associated with an increase in amylase (20 to 192 U/L) and lipase (112 to 1,303 U/L), and a recurrence of abdominal pain. This was conservatively managed with a further delay in the reintroduction of oral feeding. Four children had biochemical evidence of pancreatitis (amylase of 150 ± 56 U/L and lipase of 856 ± 601 U/L), which persisted after the BUN and creatinine normalized. Eleven of the 19 children with elevated pancreatic enzymes had ultrasounds performed. The pancreas was enlarged and sonolucent or hypoechoic consistent with pancreatitis in three children, one of whom had biochemical evidence of pancreatitis that persisted even after the BUN and creatinine had normalized. No child was found to have a pseudocyst. Hyperglycemia and severe glucose intolerance developed in two children during the course of their illness and was sufficiently severe to require exogenous insulin administration. At autopsy, one of the four children who died had diffuse hemorrhagic infiltration and extensive coagulative necrosis of the exocrine and endocrine pancreas. The presence of biochemical pancreatitis did not correlate with severity of HUS as assessed by the degree of abnormality of the admission hemoglobin, platelet count, BUN, creatinine, or the duration of colitis, dialysis, or hospitalization.

Thirty-two of the 76 children with HUS required parenteral nutritional support including intravenous lipid (Intralipid) administration. Elevation of serum triglycerides above 4 μmol/L in response to lipid infusion was common. Only two of the 34 children (6%) who required total parenteral nutrition achieved the recommended rate of infusion (4 g/kg/day). To maintain serum triglyceride levels at values of <4 μmol/L, 23 children (72%) were maintained on infusion rates of ≤2 g/kg/day. There was no predictive association between serum levels of triglyceride and amylase or lipase.

DISCUSSION

This article reviews the epidemiologic, clinical, and laboratory features of HUS, with particular reference to the gastrointestinal manifestations, in a large series of 76 children. The clinical presentation and course of HUS in the children in our study is consistent with previous descriptions (1,12,13) of this disorder and is characterized by multiorgan involvement (12–15). The mortality rate of 5% that we report is comparable to that reported in a recent epidemiologic study (16), although higher rates have been reported in the immunocompromised, the very young, or in seniors (17–19).

Hemorrhagic colitis is the most common and widely recognized gastrointestinal manifestation of HUS (9,20–23). *E. coli* O157:H7, an enterohemorrhagic *E. coli* that produces verotoxin (24), is now recognized as the most common pathogen associated with hemorrhagic colitis and HUS in North America (6,17,18,21,22,25–30). The organism has been linked to sporadic outbreaks of bloody diarrhea in both children and adults, and in some localities it is recognized as one of the most common

causes of bacterial enterocolitis (6,29,31). Since 1986, when techniques were established for identification of this serotype of verotoxin producing *E. coli* at our hospital, 25 of the 26 children with both HUS and a positive stool culture grew *E. coli* O157:H7. Transmission of *E. coli* O157:H7 is thought to be due to the ingestion of contaminated beef, although poultry, dairy products, and fomites have also been implicated (20,24,30). Cimolai et al. (32) recently reported that prolonged use of antidiarrheal and, more specifically, "antimotility" agents may be a significant risk factor in the progression of *E. coli* O157:H7 enteritis to HUS. In our series, the 22 children who had an antidiarrheal medication prescribed prior to admission had a significantly prolonged diarrheal illness compared to those who did not receive an antidiarrheal medication. A definite cause-and-effect relationship has yet to be established.

Several reviews (1,9,12,33) and case reports (20,21,23,34–37) have documented the potential complications of the hemorrhagic colitis associated with HUS. Prolapse of the rectum in association with HUS was first described by Tochen and Campbell (23) in 1977. Although it has not been widely noted since, it occurred in 10 of the 60 children with hemorrhagic colitis in this series. Ischemic colonic strictures with obstruction occurred in two of the children in our study and has been previously reported with HUS (35). Ileocecal intussusception and colonic perforation each occurred in one child, and both are previously recognized complications of HUS (12,23).

In accordance with Whitington's (9) findings, we found only mild and transient elevations of the hepatic transaminases. Slight elevation of serum aminotransferase activity is consistent with hemolysis (38) and might also develop if the diffuse microangiopathy characteristic of HUS involved the liver. No child developed cholestasis, chronic hepatitis, or hepatic failure.

Elevated serum levels of amylase of lipase activity are useful as laboratory aids to assist in the confirmation of a clinical diagnosis of pancreatitis. Lipase has several advantages over amylase as a diagnostic assay. Lipase is produced only by the pancreas, and its elevation is specific for pancreatitis (39). Since lipase has a longer half-life, the lipase remains elevated as a marker of pancreatitis for a longer period of time than amylase (39–41). Although each enzyme is excreted in a different manner, amylase and lipase are both eliminated at least partially by the kidney (42). Under normal conditions, the half-lives of amylase and lipase are reported to be 10 h and 15 h, respectively (42). Patients with renal failure tend to develop elevated levels of serum amylase and lipase (43–46). Vaziri et al. (45) recently compared the serum levels of amylase and lipase in 34 patients with end-stage renal disease (without pancreatitis) maintained on hemodialysis to those of healthy controls. There was a significant elevation in the serum activity of both amylase and lipase in patients with end-stage renal disease (without pancreatitis) as compared to controls. The serum activity of amylase exceeded the upper limits of the normal range in 94% of patients and reached values that were two to four times the upper limit of normal in 56%. The serum activity of lipase exceeded the upper limits of the normal range in 79% of patients and reached values that were two to three times the upper limit of normal in 59%. Vaziri et al. (45) concluded that marked increases of serum amylase or lipase above these elevated baseline values (i.e., values of greater than four times the upper limits of normal) should suggest the diagnosis of pancreatitis in patients with renal disease. Clearly, not all of the 19 patients with elevated serum levels of amylase and lipase reported in this article had pancreatitis. However, nine of the 19 children in our study had levels of serum lipase elevated four to 28 times the upper limit of normal. Of these nine children, the lipase levels remained two to nine times normal in four children even after dialysis was discontinued, and the BUN and creatinine were normal. A fifth child, whose maximal lipase level reached 5.5 times normal, died and was found to have extensive necrosis of the exocrine and endocrine pancreas at autopsy. A sixth child, whose serum lipase was greater than four times normal during the early phase of his illness, experienced a marked elevation in lipase (112 to 1,303 U/L) and increased abdominal pain in response to the reintroduction of oral feedings. Thus, since 1987, 19 of 29 children with HUS have had elevated serum amylase or lipase activity suggestive of pancreatitis. In at least six of the 29 children (21%), the elevated lipase was due to pancreatitis and was not due renal failure. Pancreatitis has not previously been recognized as a common gastrointestinal complication of HUS, although anecdotal occurrences have been reported (47–49). Andreoli et al. (49) reported that pancreatic involvement during the acute phase of HUS may ultimately result in exocrine insufficiency requiring pancreatic enzyme replace-

ment therapy. The pathophysiologic mechanism predisposing to pancreatitis in HUS is not yet defined. It is hypothesized that both the pancreatitis and HUS are endotoxin-initiated effects. In several animal models, the infusion of endotoxin from an enteropathogen (for example, verotoxin from *E. coli* O157:H7) causes thrombocytopenia, hemolytic anemia, and fibrinoid deposition in the glomeruli (50–53). The endotoxin triggers endothelial damage, microthrombi formation, and ischemic necrosis, which may affect a number of organs including the kidney, gastrointestinal tract, brain, and, to a lesser extent, the liver, heart, adrenals, spleen, pancreas, and other organs (13,15,54). Support for this mechanism in humans comes from the work of Koster et al. (55), which documents endotoxemia in patients with HUS.

Two children in our series had hyperglycemia and severe glucose intolerance indicative of pancreatic endocrine insufficiency or peripheral insulin resistance. One of the children who died of the complications of HUS had evidence of inflammation and necrosis of the islets of Langerhans at autopsy. The association between pancreatic endocrine insufficiency (56,57), inflammation, hemorrhage, and coagulative necrosis of the islets of Langerhans (3,13,14,58,59) and HUS has been previously reported.

Lipid intolerance, a prominant feature of the children in our study, prevented the optimal delivery of parenteral nutrition and is a recognized complication of HUS (33,60). The mechanism remains unclear, but it is suggested that diffuse endothelial cell damage in HUS may lead to lipoprotein lipase deficiency (60) and hypertriglyceridemia. Although hypertriglyceridemia has been implicated as a pathogenetic factor for the development of acute pancreatitis, we found no predictive association between serum levels of triglyceride and the amylase or lipase.

In summary, this study reviews the gastrointestinal manifestations and complications in a large series of children with HUS. We also present new data which suggests that pancreatitis is a relatively common complication of HUS, occurring in ~20% of cases. The acute pancreatitis seen in HUS is generally mild and responsive to conservative medical management, but may on occasion progress to extensive endocrine and exocrine pancreatic necrosis.

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