Kathmandu University Medical Journal (2007), Vol. 5, No. 4, Issue 20, 468-474

Original Article

Clinico-laboratory profile of haemolytic uremic syndrome

Jha DK[1], Singh R[2], Raja S[3], Kumari N[4], Das BK[5]
[1,2,3,5]Department of Pediatrics and Adolescent Medicine, [4]Microbiology, B P Koirala Institute of Health Sciences, Dharan, Nepal

Abstract
Objective: To study the clinical profile, the spectrum of functional abnormalities, prognostic factors and outcome of children with haemolytic uremic syndrome (HUS).
Materials and methods: This is a prospective, descriptive, single centre, cohort study, conducted on 42 children during the period of January 2004 to January 2005.
Results: The maximum numbers of cases were below 24 months of age with mean age of 26.6 months and male: female ratio of 2.8:1. Most of the cases (79%) occurred in the warmer months (April-September). The common clinical presentations were bloody diarrhoea, pallor, oliguria & anuria, fever, vomiting, abdominal distension and pain, involvement of central nervous system, chest and cardiovascular system and bleeding manifestations. The common haematological abnormalities were leucocytosis, thrombocytopenia, anaemia and features of haemolysis in the peripheral blood. Electrolyte abnormalities observed were in the form of hyponatremia, hypokalemia and hyperkalemia. Arterial blood gas analysis showed metabolic acidosis in 64% cases, where the estimations were done. The mean blood urea and serum creatinine levels were 113.7 mg/dL and 2.5 mg/dL, respectively. Stool examination showed blood in all cases. Urine examination showed microscopic haematuria and significant proteinuria in 74% and 38% cases, respectively. E. *coli* and Shigella were isolated in stool in three cases each and one case showed mixed growth of E. coli and Salmonella. The mortality rate was 21%. Significantly higher mortality was observed in females, patients presenting with complete anuria, leucocytosis, hyperkalemia and systemic involvement like central nervous system, cardio vascular system and chest.
Conclusions: Female sex, complete anuria, leucocytosis, extra renal involvement and hyperkalemia were associated with poor outcome.

Key words: Haemolytic Uremic Syndrome, Clinical Features, Outcome, Prognostic Factors

Hemolytic Uremic Syndrome (HUS) is defined as microangiopathic haemolytic anaemia, thrombocytopenia and acute renal failure[1]. It is the leading cause of acute renal failure in young children, but can occur in adults as well. Two broad sub groups of HUS have been recognized. The first form is associated with diarrhoea prodrome (D+ HUS) and the second form is not associated with antecedent diarrhoea (D- HUS). D+ HUS are the most common form. It occurs in healthy young children between 6 months to 5 years of age and is preceded by watery diarrhoea that can evolve to hemorrhagic colitis. The diarrhoea precedes the haemolysis and thrombocytopenia by 5 to 7 days; oligo/anuria follows several days later[2]. In developed country, E. coli is the most common organism causing D+ HUS. In the Indian subcontinent, dysentery associated HUS has been chiefly observed[3]. Shigella dysenteriae serotype 1 is the main pathogen responsible.

HUS is a syndrome widely accepted and there are many causes and associations of the disease. There have been enormous advances in defining the aetiology, epidemiology, pathogenesis and histopathological features of shiga toxin associated HUS. However, the review of literature shows no study on the HUS, in this country. So, the study was planned to see the clinico laboratory profile of haemolytic uremic syndrome in this part of the world and to identify some important risk factors in relation to disease severity and outcome.

Correspondence
Dhirendra Kumar Jha
Department of Pediatrics and Adolescent Medicine
B P Koirala Institute of Health Sciences
Dharan, Nepal

Material and methods

The study was conducted in the Department of Pediatrics and Adolescent Medicine, B P Koirala Institute of Health Sciences, Dharan, Nepal during the period January 2004 to January 2005. It is a prospective, descriptive, single centre, cohort study. All the children below 15 years with diagnosis of haemolytic uremic syndrome were included in the study.

Case Definition

Any child presenting with at least three of the following features were enrolled.

1. Oliguria/anuria more than 24 hours with increased blood urea and serum creatinine.
2. Peripheral blood examination suggestive of haemolytic anaemia (haemoglobin < 10 g/dl).
3. Thrombocytopenia (platelet count <1, 00,000/mm^3).
4. History of bloody diarrhoea.

The epidemiological data, detailed history and clinical examination findings were noted in all the cases which met the inclusion criteria. All the children were subjected to the following investigations:

Haemogram (Hb, TLC, DLC, Platelet counts, Reticulocyte counts), Peripheral blood smears for features of haemolysis (i.e. schistocytes, burr cell, fragmented RBC, nucleated RBC), stool routine and microscopic examination, stool culture and sensitivity, urine routine and microscopic examination, urine culture and sensitivity, blood urea, serum creatinine, serum sodium, serum potassium, arterial blood gas analysis and blood culture.

Statistical Method:

The data collected was compiled and entered in MS - Excel and analysis was done using EPI 2000 version and SPSS CP+11.5 version software to find chi - square values. P value <0.05 is taken as statistically significant.

Results

Forty two children admitted to the Paediatric ward, B.P. Koirala Institute of Health Sciences, Dharan, Nepal during the period January 2004 to January 2005 with a diagnosis of haemolytic uremic syndrome were enrolled for the present study.

The demographic profile of the patients studied is depicted in Table 1. The maximum numbers of cases were below 24 months of age (69%). There was predominance of males (73.8%) and most cases were observed during summer months (April–September). Majority of the patients were Non vegetarian (69%).

Table 2 shows the clinical presentations of haemolytic uremic syndrome patients. All the patients (100%) presented with history of blood mixed stools and oliguria/anuria. However, complete anuria was noted in 48% cases. Other common presentations were fever (94%), vomiting (86%), abdominal distension (83%) and abdominal pain (71%). About 17% patients presented with generalized seizures and 14% had bleeding manifestations like skin and mucous membrane bleeds

Anaemia was noted in all the patients and in 10 (24%) patients, it was of severe degree. Edema was noted in 93% of patients. Ascites was noticed in 31% patients. Hepatomegaly was noted in 11 (26%) cases and in 10 (24%) cases, the bowel sounds were absent. Central nervous system involvement in the form of seizures, altered sensorium and irritability was noted in 16 (38%) cases. Examination of chest showed crepitations in 14 (33%) patients. Cardiovascular system was involved in 8 (19%) cases in the form of cardiomegaly and features of congestive cardiac failure.

Table 3-4 show the laboratory investigations of the cases studied. Leucocytosis (> 15000/mm^3) was found in 95% cases. Counts more than 30,000 per mm^3 were observed in 62% of cases. The mean total leucocytes count was 38021 (range 9100-80,000 per mm^3) and polymorphs percentage was 75 (range 44-93). The mean platelet count was 84500 with a range of 13400-303000 per mm^3. The platelet count was below 50,000 per mm^3 only in 9 (21%) cases. Six patients presented with skin and mucous membrane bleeds. The mean platelet count of these patients was 42833 ± 13151. Four out of these six patients had platelet count less than 50,000 per mm^3. The mean haemoglobin was 6.7 g/dL (range 3-9.8 g/dL). However, severe anaemia (< 5 g/dL) was observed in only 9 (21%) cases. The mean reticulocyte count was 2.26 and was more than 2% in 19 (45%) cases. Peripheral blood smear showed features of haemolysis 81% cases. The blood culture was positive only in two patients; enterococcus in one case while in other Streptococcus pneumoniae was grown.

The mean serum sodium was 126.6 m mol/L (Range 107-161mmol/L). Hyponatremia (<135 m mol/L) was found in 91% cases. Similarly, mean serum potassium was 4.12 m mol/L (range 2.1-8.7 m mol/L). The level was low (<3.5 m mol/L) in 45%

cases and high (>5 m mol/L) in 26% cases. Arterial blood gas analysis showed the mean pH as 7.3 and mean bicarbonate as 12.4 m mol/L. Bicarbonate less than 10 m mol/L was observed in 25% cases where it was estimated. Most of the cases were of metabolic acidosis (64%). The mean serum creatinine level was 2.5 mg/dL (range 0.9-5.8 mg/dL). In 40 (95%) cases serum creatinine level was above 1 mg/dL. The blood urea was high in all cases with a mean of 114 mg/dL (range 56-187 mg/dL).

Routine examination of stool showed RBC in all (100%) cases and pus cells in 81% cases. In 7 (17%) patients, cysts were found; E. histolytica in 6 and Giardia in 1 patient. Stool culture was positive in 7 (17%) cases; E. coli in 3, Shigella in 3 and in one case mixed organisms were grown.

Urine examination showed significant albuminuria (> ++) in 16 (38%) cases while in 11 (26%) cases, the proteinuria was mild. Microscopic haematuria (> 5 /hpf) and pyuria (> 5/ hpf) were observed in 29% and 24% cases, respectively. Epithelial cells and casts were observed in 19% and 7% patients, respectively. Urine culture was positive in 11 (26%) cases; E. coli in 7, Citrobacter and Enterobacter in 1 each. In 2 patients urine culture showed growth of Candida.

All the patients received antibiotics in the form of ceftriaxone. In 55% of patients, additional antibiotics were needed. Thirty two patients (76%) needed blood transfusion and 15 (36%) patients were subjected to peritoneal dialysis. Out of 42 patients, 30 (71%) improved while 9 (21%) died during hospital stay. Three (7%) patients left against medical advice.

The mortality was significantly higher in female sex ($p < 0.05$) and in those who had anuria ($p<0.01$), abdominal distension ($p<0.001$), CNS ($p<0.001$), CVS ($p<0.001$) and chest ($p<0.05$) involvement. Similarly, the mortality was significantly higher in those who had TLC more than 30,000 per mm^3 ($p < 0.05$) and serum potassium of more than 5 m mol/L ($p < 0.05$). The mortality was significantly higher in patients treated with peritoneal dialysis ($p<0.001$). In the peritoneal dialysis group, mortality was higher ($p<0.01$) in patients who developed secondary infection after the peritoneal dialysis.

Table 1: Demographic profile of Haemolytic uremic syndrome (N=42)

Parameters	Number (%)
Age (Months)	
< 12	03 (07)
13-24	26 (62)
25-36	08 (19)
> 37	05 (12)
Sex	
Male	31 (74)
Female	11 (26)
Season	
April – June	21 (50)
July – September	12 (29)
October – December	03 (07)
January – March	06 (14)
Feeding habit	
Vegetarian	13 (31)
Non vegetarian	29 (69)

Table 2: Clinical presentation of haemolytic uremic syndrome (N = 42)

Sign and symptoms	Number (%)
Bloody Diarrhoea	
≤ 10 days	22 (52)
> 10 days	20 (48)
Fever	
Absent	03 (07)
≤ 10 days	22 (52)
> 10 days	17 (41)
Urine Output	
Oliguria	22 (52)
Anuria	20 (48)
Vomiting	36 (86)
Abdominal distension	35 (83)
Abdominal pain	30 (71)
Bleeding manifestations	06 (14)
Seizures	07 (17)
Pallor	
Moderate	32 (76)
Severe	10 (24)
Edema	39 (93)
Ascites	13 (31)
Hepatomegaly	11 (26)
Absent bowel sound	10 (24)
CNS involvement	16 (38)
CVS involvement	08 (19)
Chest involvement	14 (33)

Table 3. Haematological Findings of Haemolytic Uremic Syndrome (N=42).

Parameter	Number (%)	Mean ± 1 SD (Range)
TLC (10^3/mm^3)	42 (100)	38.02±17.05 (.91 -80.0)
<15000	02 (05)	
15000 - 30,000	14 (33)	
>30,000	26 (62)	
Polymorphs (%)	42 (100)	75.4 ± 13.7 (44-93)
Platelet count (lac/mm^3)	42 (100)	.845 ±.516 (.134-3.03)
<50,000	09 (21)	
50,000-1,00,000	24 (57)	
>1,00,000	09 (21)	
Haemoglobin (g/dL)	42 (100)	6.7 ± 1.9 (3.0-9.8)
< 5	09 (21)	
5-8	19 (45)	
>8	14 (33)	
Reticulocyte count	42 (100)	2.26 ± 1.4 (0.8-7.3)
PBS features of haemolysis	34 (81)	

Table 4. Blood Biochemistry of Haemolytic Uremic Syndrome (N=42).

Parameter	Number (%)	Mean ± SD (range)
Sodium (m mol/L)	42 (100)	126.6 ± 9.5 (107-161)
<135	38 (91)	
135-145	03 (07)	
>145	01 (02)	
Potassium (m mol/L)	42 (100)	4.12 ± 1.58 (2.1-8.7)
<3.5	19 (45)	
3.5-5	12 (28)	
>5	11 (26)	
Bicarbonate (m mol/L)	28 (100)	12.46 ± 3.98 (6.4-20.5)
pH	28 (100)	7.30 ± 0.05 (7.2-7.51)
Creatinine (mg/dL)	42 (100)	2.51 ± 1.59 (0.9-5.8)
Urea (mg/dL)	42 (100)	113.7 ± 45.2 (56-187)

Discussion

Haemolytic uremic syndrome (HUS) is an important cause of acute renal failure in young children leading to significant morbidity and mortality. The present work was designed to investigate and correlate clinical presentation, laboratory findings, functional abnormalities and the outcome of HUS patients. The study was conducted in a tertiary care centre in Eastern Nepal over a 12 months period.

In the present study, majority (69%) of the patients were below the age of two years; while most (95%) were below the age of five years. The mean age of presentation was 26.6±13.6 months. Srivastava et al[3] also observed that 59% of their patients were below the age of two years while 92% were below five years. Tozzi et al[4] from Italy reported higher incidence in children less than five years of age (mean = 0.75 cases per 1, 00,000 population, range = 0.33-1.10). Elliott et al[5] from Australia reported HUS in children under five years as 1.35 (95% CI 1.06 to 1.72) per 10^5 population. The annual incidence is highest in young children with an age specific incidence per 1,00,000 children as 3.1 for Canadian children less than five years of age[6] and 7.1 for children of Utah, aged 1 to 2 years[7].

In the present study, males (74%) were more affected with a male: female ratio of 2.8: 1. Srivastava et al[3] also reported HUS more in males (72.6%) with a male: female ratio of 2.5: 1. However, other workers[6, 8, 9] reported that female gender is a modest risk factor; while Cimolai et al[10] refute gender predisposition.

In the present study, maximum number of cases occurred in summer months (April to September), which is similar to other studies where the authors[11-15] observed haemolytic uremic syndrome more frequently during warmer months. However, Brandt et al[16] report that North West epidemic did not occur in summer.

The common clinical presentations of patients in our study were bloody diarrhoea (100%), oliguria / anuria (100%) and fever (93%). Other presentations were vomiting (86%), abdominal distension (83%) and abdominal pain (71%). About 17% patients presented with generalized seizures and 14% had bleeding manifestation like skin and mucous membrane bleeds. Srivastava et al[3] reported bloody diarrhoea in 80% of their patients and 12% had watery diarrhoea. Oliguria/anuria was documented in 86% patients. Elliott et al[5] in their study found that all patients had diarrhoea prodrome while vomiting was observed in 80% of patients. Tozzi et al[4] reported bloody diarrhoea in 48% cases while 30% presented with non bloody diarrhoea. Siegler et al[7] reported that majority of their patients had oliguria and almost half were anuric. They also reported that vomiting usually accompanied the diarrhoea. Patients had fever and occasionally petechiae or purpura, while 10% of patients presented with seizures. In our study also about 17% of patients presented with seizures. Chang et al[17] reported bloody stool in 82%, fever in 64% and vomiting in 54% of cases.

In the present study, CNS involvement in the form of seizures, altered sensorium and irritability was noted in 38% cases. Other systemic involvement included chest (33%) and cardiovascular system (19%). Siegler[18] reported that the brain was the most commonly involved extra renal organ. These include alteration of consciousness and disorder of movement, muscle tone and posture. Seizure was common and was generalized in nature.

Common laboratory findings of the present study were leucocytosis, thrombocytopenia, anaemia, reticulocytosis and features of haemolysis in peripheral blood smear. Common electrolyte disturbances were hyponatremia, hypo and hyperkalemia. The cause of hyponatremia could be dilutional. Hypokalemia may be due to excessive loss of potassium in the stool while the hyperkalemia may be due to renal failure. Similar to the present study, Srivastava et al[3] also reported leucocytosis in 85% of cases. Chang et al[17] in their study found thrombocytopenia in 95% of cases and 85% had haemolytic anaemia with microangiopathic changes on peripheral blood smear. Brilliant et al[19] reported haemolytic uremic syndrome without evidence of microangiopathic haemolytic anaemia on peripheral blood smear.

In the present study, urine microscopy showed significant albuminuria (38%) and haematuria (26%). Stool culture was positive in about 17%cases. E. coli and Shigella were the common organisms. Chang et al[17] in their study found haematuria in 80% and protein in urine in 80% cases. In our study, previous antibiotic therapy and a delay in stool examination for several days after the onset of dysentery could account for the low isolation rate of organisms. Srivastava et al[3] in their study showed that out of 73 patients, 27 (37%) were stool culture positive; E. coli and Shigella being the main pathogens.

Fifteen (36%) of our patients were subjected to renal replacement therapy and 32 (76%) patients received blood transfusion. Almost all patients received antimicrobial therapy. During the treatment, three (7%) patients left against medical advice, 30 (71%) patient's improved and 9 (21%) died. Srivastava et al[3] from India reported mortality in 60% of cases while other authors[7, 17, 20] from reported mortality between 4-10%.

In the present study, poor outcome was significantly associated with female sex, patients presenting with anuria, systemic involvement, high leukocyte count and hyperkalemia. Those patients subjected to peritoneal dialysis had significantly higher mortality. The high mortality in peritoneal dialysis group may be due to the fact that very sick patients had received the peritoneal dialysis. Other reason could be the secondary infections following peritoneal dialysis. Srivastava et al[3] reported that the mortality was chiefly related to the duration of renal failure and presence of renal cortical necrosis, whereas persistent dysentery and infections were complicating factors. The presence of convulsions and coagulation defects had no relation to the outcome. Walters et al[21], observed that polymorph nuclear cell count was significantly higher in their diarrhoea associated HUS patients who had a poor outcome. Trompeter et al[20] observed that younger age, presentation in the summer months, diarrhoea at onset and, in those patients who were dialyzed, a short prodromal illness were associated with a good outcome. They also

reported that diarrhoea favoured a good outcome among boys but not girls.

D' Souza et al[22] reviewed literature and reported bad prognostic factors as higher age (>3 years) at presentation, leucocytosis, systemic involvement, anuria or prolonged oliguria, and prolonged duration of prodromal illness.

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