Hemolytic Uremic Syndrome Epidemiological and Clinical Facts

Najla Ibrahiem Ayoub, Ahmed Hameed Mohammed , Jinan Soaod Orabi , Asaad Abdullah Abbas

ABSTRACT:

BACKGROUND:

Hemolytic uremic syndrome is the most common cause of acute renal failure in children and has high mortality rate.

OBJECTIVE:

To study the epidemiology, clinical course, management, complications and the important risk factors that affect the outcome of the patients with hemolytic uremic syndrome.

PATIENTS AND METHOD:

In this retrospective study we collect fifty two patients who were admitted to the Child´s Central Teaching Hospital from the period 1st of Jan. 2005 till 30th May 2008. The data collected from the case records includes: name, sex, age, season, presence of diarrhea, jaundice, family history of HUS, complications, associated clinical features such as: pallor, edema, rash, hypertension, hepatosplenomegaly, and coarse of the disease. Also Laboratory. Findings as Haemlglobin (Hb), Packet Cell Volume (PCV)%, White Blood Cell (WBC), Red Blood Cell (RBC) morphology, platelets counts, blood urea and serum creatinine; and managements were included in the study.

RESULTS:

Of total 52 , there were 21 (40.4%) cases below 2 years, the males account 33 (63.46%) from the total. There were seasonal and annual increments. Eighty four percent had diarrheal prodrome, and 1.91% had familial history of HUS. All patients had pallor and acute renal failure. The mean of the hemoglobin was 8.6 gm/dl, WBC count mean was 18 × 10^9/L, platelets mean was 35 × 10^9/L, blood urea mean was 180 mg/dl, and the mean of serum creatinine was 3.8 mg/dl. The GIT complications was the commonest 23 (44.23%) followed by CNS complication 16 (30.7%), hypertension was present in 25%. During acute phase of disease 12 (23.07%) patients died.

CONCLUSION:

HUS affect mainly age between 3 months and 4 years. There was seasonal variation with peak at wormer months.There were statistically significance correlation between high risk patients and age group below 2 years, CNS complication, and non diarrheal prodrome.

KEY WORD: hemolytic uremic syndrome, epidemiological .

INTRODUCTION:

The hemolytic uremic syndrome(HUS) is the most common cause of acute renal failure in young children and is characterized by microangiopathic hemolytic anemia , thrombocytopenia, and uremia. [1] . It can be classified into two categories :

The typical form account for 90% of cases, affect younger children and in association with prodromal illness usually of bloody diarrhea. The commonest etiological agent being the verocytotoxin producing E.coli. [1] The atypical form account for only 10% of the total number of cases, it is not associated with prodromal illness. [2] . The main target is the gut and the kidney but nearly every organ system can be involved, the most common extrarenal involvement is damage to the CNS[3,4,5] . HUS and thrombotic thrombocytopenic purpura (TTP) share similar clinical features and pathology. Both are defined by hemolytic anemia with fragmented red cell and thrombocytopenia, an association commonly referred to as microangiopathic hemolytic anemia (MAHA). [4,7,8] . Both disorders remained mysterious until the 1980s. In 1982, Moake et al. [5] reported that unusually large multi-mers of

Baghdad Medical City.

von Willebrand factor (VWF) released from endothelial cells were present in the plasma of patients with chronic relapsing TTP and proposed that a failure to process these multimers explained the disorder. In 1985, Karmali et al. [6] demonstrated that HUS in children was associated with enteric infection by Escherichia coli that produce verocytotoxin (VT) (Shiga-like toxin). Subsequent investigations clarified the mechanisms of both disorders. [9]

Twenty years ago it was recognized that childhood HUS could be divided into two main groups according to the clinical presentation and outcome. The importance of a prodrome of diarrhea associated with HUS (D+ HUS) was recognized as a distinguishing feature of the main group. [10] Its infectious origin was confirmed a few years later. D+ HUS represents approximately 90% of cases in children, usually younger than 3 years of age, and is an acquired disease related to the endothelial toxicity of infectious agents, mainly VT-producing Escherichia coli (VTEC). [11]

In contrast, HUS not associated with a prodrome of diarrhea (D- HUS) can occur at any age, including the newborn. D- HUS may be familial, with autosomal dominant or, more frequently in children, autosomal recessive transmission. A similar distinction between acquired and intrinsic forms applies in adults. [12] In children, various pathogenic mechanisms, corresponding to distinct subgroups of D- HUS, are described. A neonatal form is associated with methylmalonic acidemia due to intracellular vitamin B12 deficiency. Some D- HUS cases are associated with abnormalities of the complement regulator factor H (fH) or its gene. Another subgroup of children with HUS, often of neonatal onset and running a recurrent TTP-like course, has been shown to have constitutional deficiency of the VWF-cleaving protease (VWF-cp). In spite of these advances, the pathogenesis in many cases of D- HUS remains unknown. [13]

This article aims to study the epidemiology, clinical course, management, complications and the important risk factors that affect the outcome of the patients with hemolytic uremic syndrome.

PATIENTS AND METHODS:

In this retrospective study we reviewed fifty two patients who were admitted to the Child's Central Teaching Hospital from the period 1st of Jan. 2005 till 30th May 2008. The data reviewed include: name, sex, age, season, duration of illness, presence of diarrhea, jaundice, family history of HUS, complications, associated features like: pallor, edema, rash, hypertension, hepatosplenomegaly, coarse and outcome of the disease.

Laboratory finding which were collected include: Hb, PCV%, CBC with RBC morphology, platelet, B.urea, S.creatinine, and stool culture. Management of those patients also discussed briefly and the medications which may be of some value, and times of blood transfusion and peritoneal dialysis are involved in management. The study also showed the fate of the patients and the time of the death. These information were collected from patients files in the hospital.

STATISTICAL ANALYSIS:The statistical method used to analyze the results were: 1.Descriptive statistics: mean, range, ratio, rate, and graphical presentation. 2.Inferential statistic: chi square and P value which is considered significant when it is less than 0.05.

RESULTS:

The total number of patients who were diagnosed as HUS were 52 Age of patients range between 3 months and 13 years with mean age 3.6 years.The peak incidence of HUS at age group < 2 years as seen in (table 1).

Table 1: Distribution of the patients according to the age

Age(years)	No.	%
<2	21	40.4
>2 – 4	13	25.0
>4 – 8	10	19.2
>8 – 13	8	15.4
Total	52	100

Thirty three cases (63.46%) were males, nineteen cases (36.54%) were females.
Male to female ratio : 1.7:1 table 2

Table 2 : Distribution of the patients according to gender.

Gender	NO	%
Male	33	63.46
Female	19	36.54
Total	52	100

Twenty two(42.3%) cases occurred during autumn, as seen in figure 1

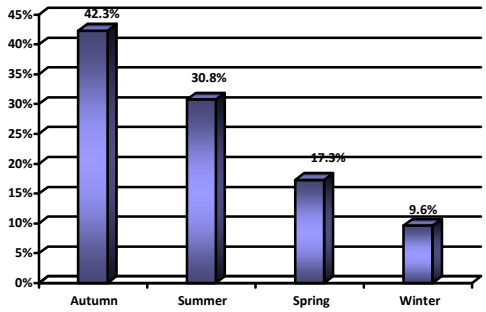

Fig. 1:Seasonal variation of HUS.

Diarrheal prodrome was present in 44 (84%) cases, while patients without diarrheal prodrome were 8 (16%) cases, the latter were divided as fellow: five cases were preceded by respiratory illnesses, one case had positive family history of (HUS), and two cases had no significant prodrome, as seen in (Table 3).

Table 3 : Distribution of the no. of the patients according to family history and history of prodromal symptoms.

Prodrome	NO.	%
Diarrhea	44	84.61
Respiratory	5	9.61
Familial	1	1.92
Drug induced	1	1.92
unknown	1	1.92
total	52	100

All patients (100%) had pallor and acute renal failure, while only 3 (5.76%) patients had jaundice as seen in (table 4).

Table 4 : Distribution of the patients according to the presence of clinical features.

Features	NO.	%
Pallor	52	100
Acute renal failure	52	100
Petechiae	16	30.76
Edema	15	28.84
Hepatomegaly	21	40.83
Jaundice	3	5.76

The hemoglobin range between 4.5 and 10 gm/dl. White blood cell count ranged from 3.6-40 cell X 10^9/L. Platelets count ranged between 15 and 100 X 10^9/L (mean 35±21) and may be normal in some patient. Blood urea level ranged between 60 and 420 mg/dl. Serum creatinine ranged between 0.7 and 7 mg/dl (mean 3.8±1.9). Blood film show fragmented RBC, helmet cell, and burr cell shown in 43 cases. Stool culture showed growth of E.coli in 4 cases only, and negative in the others. Table 5

Table 5: Distribution of the patients according to Laboratory Findings.

labrotary findings	range	mean
Hb gm/dl	4.5-10	8.6
WBC count cell× 10^9/L	3.6-40	18
Platelets count cell×10^9/L	15-100	35
B.urea mg/dl	60-420	180
S.creatinine mg/dl	0.7-7	3.8

Complications of HUS include -GIT 23 (44.23%) cases (hematamesis, malena and rectal prolapse). CNS 16 (25%) cases(convulsion and coma). Hypertension 13 (25%) cases. Hemoglobinuria 7cases (13.46%).

Table 6: Distribution of the patients according to Complications Of HUS.

Complications		NO.	%
GIT	Total	23	44.23
	Malena & Hematamesis	19	36.53
	Rectal prolapse	4	7.69
CNS	Total	16	30.76
	Convulsion	13	25
	Coma	3	5.76
Hypertension		13	25
Hemoglobinuria		7	13.46

Of those 52 cases ,12 cases died on the same admission. (7(58.33 %) males and 5(41.66%) females).

Table 7 A: Relation Between Mortality and Sex.

Gender	NO.	%	% of total
Male	7	58.33	13.46
Female	5	41.66	9.62
Total	12	100	23.08

Table 7 B: Relation Between Mortality and age.

Age(years)	NO.	%	% of total
<2	4	33.33	7.69
>2-4	4	33.33	7.69
>4-8	3	25	5.76
>8-13	1	8.33	1.92
Total	12	100	23.08

The study concentratedon blood transfusion and peritoneal dialysis in management. Forty eight (93.30%) patients received blood transfusion; 39(75%) patients received one time, and 9 (17.30%) patients received more than one time.

Forty one cases were subjected to peritoneal dialysis; 35 (67.30%) cases recovered with single dialysis; while 6 (11.53%) cases needed more than one. Table 8.

Table 8: Number and percentage of the patients and their treatment.

Procedure	No. of Procedure	1 Time	>1 Time
Blood transfusion	48 (93.30%)	39 (75%)	9 (17.30%)
Peritoneal dialysis	41 (78.84%)	35(67.30%)	6 (11.53%)

After statistical analysis the results shows that there was significant association between the younger age (< 2 years); CNS complications; and non diarrheal prodrome with increasing risk of death in HUS cases, as shown in the (table 9).

Table 9 shows that there is no statistically significant association between death and: gender; diarrheal prodrome; GIT complication; hypertension and WBC counts > 20×10^9/L.

Table 9: Distribution of studied group according to outcome status and Risk Factor.

Risk factor	Total	Survived	Died	X^2 value	P value
Age < 2 years	21	13(61.90%)	8(38.09%)	4.48	0.03*
>2 years	31	27 (87.09%)	4 (12.9%)		
Gender ♂	33	26(78.78%)	7(21.21%)	0.18	0.674
♀	19	14(73.68%)	5(26.31%)		
Diarrheal Prodrome	44	36(81.81%)	8(18.18%)	3.86	0.049*
None	8	4(50%)	4(50%)		
GIT complication	23	17(73.91%)	6(26.08%)	0.21	0.646
None	29	23(79.31)	6(20.68)		
CNS complication	11	4(36.3%)	7(63.6%)	12.93	0.001*
None	41	36(87,80)	5(12.19)		
Hypertension	15	9(60%)	6(40%)	3.40	0.065
No	37	31(83.73)	6(8.21)		
WBC > 20×10^9/L	18	15(83%)	3(16%)	0.64	0.425
<20×10^9/L	34	25(73.52)	9(26,47)		

*Significant difference using chi-square test (P<0.05)

DISCUSSION:

In this study we reviewed 52 cases of HUS who were admitted to Child`s Central Teaching Hospital.

The study showed that 34 patients (65.38%) were below four years (40.4%) <2 yaers and 25% 2-4 years, and this result was similar to Abbas study[12] and similar to Milford et al. [9] And also this study show that 21 patients (40.38%) were below 2 years; and this result was also similar to Milford et al [9]; this study showed that only eight(15.38%) patients are above eight years, and this is similar to Abbas study.[12]

The study showed that the number of males were thirty three (63.46%), and females number were nineteen

(36.54%) with male to female ratio was 1.7:1, which was similar to Abbas study[12] which showed that (58.2%) of patients were males, and (41.8%) of patients were females. And similar to

Gianviti study[13] which showed that (61.8%) of patients were males, and (39.2%) of patients were females.

This study showed that the number of the cases admitted during summer were sixteen cases (30.76%) and twenty two cases (42.30%) occurred during autumn, this result is similar to the result of Mildford et al.[9] Non diarrheal Hemolytic Uremic Syndrome was not associated with seasonal variation, and the

eight non diarrheal cases in our study were distributed on different seasons. This study showed that only one case has a positive family history, this result is similar to Voyer study.[14]

There was slight yearly increment in the frequency of cases in this study from Jan 2005 till 30 May 2008, this finding was not so similar to Abbas study, may be due to short period of our study as a compared to Abbas study which was eight years.

This study shows that 44 cases (84%) of HUS had diarrheal prodrome, this finding is similar to Seigler et al (90%)[15], and Milford ,et al (95%).[9]

The majority of patients 41 cases (78.84%) had bloody diarrhea ,While only 3 patients had watery diarrhea, this result is similar to Gianviti study.[13]

Non diarrheal prodrome was present in 8 cases (15.38%), 5 cases were preceded by respiratory tract infection, and 2 cases (3.84%) of non diarrheal prodrome were not preceded by any specific illness. Pallor and acute renal failure were present in all cases this fact is similar to Abbas study and Seigler study[14], petechiae occurred in 16 cases(30.76%), edema occurred in 15 cases(28.84%), hepatomegaly occurred in 21 cases (40.83%), and jaundice occurred in 3 cases (5.76%), this result was similar to Gianviti study.[13]

The laboratory findings in this study showed that: the mean of hemoglobin is 8.6 g/dl which is similar to other studies.[13,14,16] The mean of the platelet count is 35 × 10^9 /L which is similar to Gianviti study.[13] Stool culture was positive-without serotype- for E.coli in only 4 cases (7.67%), this result was very poor on comparison with majority of studies which was done in developed countries [17,18] but was similar to Abbas study.[12] the cause may due to lack of laboratory facilities for EHEC and giving the antibiotics before admission. Blood film showed fragmented RBC, helmet cell and burr cell shown in 43 cases(82.69%), this fact is similar to majority of recent studies like Abbas and Seigler study.[12,15]

The GIT complications were the most frequent, followed by CNS complications, followed by hypertension, this result is similar to Gianviti study[13] and Tapper et al study.[16] Hematamesis and malena were the most frequent GIT complications followed by rectal prolapse, while the convulsion was the most frequent CNS complication followed by coma, this result was similar to Tapper et al study.[16] Hypertension was present in 13 cases (25%)only which was low in comparison to Tapper et al [16] study, in which hypertension was 88%. And this could be explain by low rate of the underdiagnosis in our hospital

Twelve cases(23.07%) died during the acute phase of illness, 7 males(58.33%) and 5 females (41.66%), this regarded as a high figure in comparing with Tapper et al[16] study, which is only (8%), this high figure was related to the fact that our patients developed complications because of delay in seeking medical attention so delay in diagnosis; and delay in proper management. Eight of the deaths (66.66%) were below

4 years, this study is similar to Gianviti Study, but not similar to Tapper study[16].

Regarding management 48 cases (93.3%) required blood transfusion, this is high percentage and similar to all studies. Regarding peritoneal dialysis, 41 cases(78.8%) required peritoneal dialysis., this is similar to Abbas study[12] and Gianviti study.[13] Young age(<2 year), and CNS complication and were statistically significant risk factors for death. This finding was similar to Gianviti study.[13] Non diarrheal prodrome was statistically significant risk factor for death, this finding was similar to Abbas study.[12]. Other factors as sex, diarrheal prodrome, WBC count > 20 ×10^9/L, GIT complication and hypertension were statistically not significant as a risk factor for death, this finding is similar to Gianviti study.[13]

CONCLUSION:

HUS is an important cause of acute renal failure in pediatrics age group.HUS affects children mainly between 3months and 4 years. The number of males is exceeding females, with male to female ratio is 1.7:1 . there was seasonal variation in the occurance of HUS with peak at wormer months(Summer and Autumn). There is statistical significance between high risk patients

(those who died) and young age(<2years), CNS complication, and non diarrheal prodrome. Mortality Is much higher than international figures. Low rate of hypertension which may be underdiagnosed.

Measuerment of blood pressure and follow up. .Special attention should be paid by physician to patient with HUS who have one of those risk factors include: young age, non diarrheal prodrome, and presence of CNS complication. Improve the laboratory facilities to detect the pathogenic strains that cause HUS and to demonstrate the pathological changes in the blood smear. Further researches for regular follow up of the survival patients is recommended.

REFERENCES:

1. Davis I D, Avner E D. Hemolytic uremic syndrome. In Behrman R E, Klegman R M, Jenson H B(editors). Nelson text book of pediatrics ,18th Ed, 2007:2181-83.
2. .Gord J N, Suter AH, Zimmerhack1 LB, Brandis M, HUS in childhood. Semew - Thrombo-Hemest 1997: 281-91.
3. Samson M., Audia S, Leguy V, et al. Haemolytic-uraemic syndrome during severe lupus nephritis: efficacy of plasma exchange, Internal Medicine Journal, January 2012;42: 95–98.
4. Moschcowitz E. An acute febrile pleochromic anemia with hyalin thrombosis of the terminal arterioles and capillaries. An undescribed disease. Arch Intern Med 1925;36:89-93.
5. Moake J, Rudy C, Troll J, et al. Unusually large plasma factor VIII: von Willebrand factor multimers in chronic relapsing thrombotic thrombocytopenic purpura. N Engl J Med 1982;307:14.
6. Karmali MA, Petric M, Lim C, et al. The association between idiopathic hemolytic uremic syndrome and infection by verocytotoxin-producing Escherichia coli. J Infect Dis 1985; 151:775-82.
7. Moake J. Thrombotic microangiopathies. N Engl J Med 2002; 347:589-600.
8. Levin M, Barratt JM. Haemolytic uraemic syndrome. Arch Dis Child 1984;59:397-400.
9. Milford D, Taylor C, Guttridge B, et al. Haemolytic uraemic syndromes in the British Isles 1985-1988: association with verocytotoxin producing Escherichia coli. Part 1: clinical and epidemiological aspects. Arch Dis Child 1990;65:716-21.
10. Melnyk AM, Solez K, Kjellstrand CM. Adult hemolytic-uremic syndrome. A review of 37 cases. Arch Intern Med 1995;155:2077-84.
11. Ruggenenti P, Noris M, Remuzzi G. Thrombotic microangiopathy, hemolytic uremic syndrome, and thrombotic thrombocytopenic purpura. Kidney Int 2001;60:831-46.
12. Al-azzawi S E, Abbas A T, Al-Naddawi N M. HUS epidemiological and clinical study. J Fac Med Baghdad 2000;42.
13. Gianviti A, Tozzi A E, Petris L D, Caprioli A et al; Risk factors for poor renal prognosis in children with HUS J; Springer Berlin and Heidelberg (edits); 2004;18:1262-66.
14. Voyer L E , Wainsztein R E, et al; in HUS in families- an Argentinian experience J; Springer Berlin and Heidelberg (editors); 2004;10:70-72
15. Siegler RL: Spectrum of extrarenal involvmemnt in post diarrheal HUS. J. Pediatrics. 1994;125:511-18.
16. Tapper D, Tarr P, Avner E, et al: Lessons learned in the management of HUS in children. J pediatrics-Surg. 1995; 30:158-63.
17. Craig S. Wong1, Jody C. M, John R. , et al , Risk Factors for the Hemolytic Uremic Syndrome in Children Infected with *Escherichia coli* O157:H7: a Multivariable Analysis, Clinical Infectious Disease ,2012;55:33-41.
18. Ann R. Punnoose, MD, Writer; Cassio Lynm, MA, Illustrator; Robert M. Golub, MD, Hemolytic Uremic Syndrome, JAMA. 2012;307:1098-98.