



Original Research Article

Clinical Profile and Short Term and Long Term Outcome of Childhood Haemolytic Uraemic Syndrome

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ABSTRACT

Objective- To evaluate the clinical and laboratory profile, short term and long term outcome of childhood haemolytic uraemic syndrome (HUS).

Methods- Retrospective study of 33 episodes in 30 patients of HUS over a 11 years. Data on demography, duration of oliguria, requirement for and duration of dialysis, proteinuria, and severe hypertension and CNS involvement was recorded. On follow up the frequency of residual CNS impairment, proteinuria, blood pressure, GFR and deaths were noted.

Results- The patients had a mean age of onset at 5.6 years, 3.6 years for D+ and 6.5 years for D- (p=0.04). Out of total 30 patients, 66% (20/30) were D- and 33% (10/30) D+. D- HUS had longer oliguria 24.7 days versus 9.4 days (p=0.03), dialysis 16.4 versus 7.6 days (p=0.12) and hospital stay 36.4 versus 15.9 (p=0.05) than D+. Overall 50% had nephrotic range proteinuria which was more common in D- than D+ (65% versus 20%, p=0.02).

Conclusion- D- HUS was seen in 66% of cases and in older group and severe hypertension, proteinuria, and CNS involvement was common. They also had longer oliguria and more days on dialysis. Mortality was 20% and 73.6% of survivors had sequelae, proteinuria in 73%, hypertension in 63.5%, eGFR less than 60 ml/min/m² in 26.3%, CNS impairment in 21%. 82% of D- HUS had sequelae.

Key words- Hemolytic uraemic syndrome (HUS), renal failure, outcome

INTRODUCTION

The haemolytic uraemic syndrome (HUS) is characterized by the triad of thrombocytopenia, microangiopathic haemolytic anaemia and acute renal failure.

^[1] It is one of the leading cause of acute renal failure in children in India. ^[1] Two broad subgroups are recognized; diarrhea/dysentery related called D+ or

typical, the other has no relation to enteritis (D- or atypical). ^[2-5] D+ HUS is caused by virulent strains of Shigella dysenteriae that produce shigatoxin 1 or verocytotoxin producing E coli. ^[5] D- HUS is heterogenous and can be familial, drug induced or recurrent. It has been increasingly realized that besides the acute complications and mortality, HUS is known to cause

considerable long term morbidity. Over the decades the epidemiology, management and outcome of HUS has changed considerably in different parts of the world. We undertook this retrospective survey to identify the clinical profile and long term outcome of HUS in western part of India.

Objectives

1. To evaluate the clinical profile and long term outcome of childhood hemolytic uraemic syndrome (HUS)
2. To compare typical with atypical HUS with regards to severity of acute illness and long term outcome.

MATERIALS AND METHODS

A retrospective analysis was made of all children who were admitted with HUS in the nephrology division of Bai Jerbai Wadia Hospital for children over a span of 11 years (1999-2009). Hospital admission records, nephrology proformas, dialysis registers were reviewed to identify patients of HUS defined as the triad of microangiopathic hemolytic anaemia, thrombocytopenia and azotemia. Clinical and laboratory features on presentation (including typical [diarrhoea-positive, D+] or atypical [diarrhoea-negative, D-] presentation), clinical course, treatment and features on subsequent outpatient follow-up (1, 3, 6 and 12 months later), renal outcome on long term follow-up was recorded.

The episodes were categorized into 2 groups D+ and D-. Episodes which were preceded by diarrhoea/dysentery lasting more than 24 hrs in preceding 2 weeks were called D+ or diarrhoeal HUS. D- Patients had no preceding history of diarrhoea. Clinical and laboratory profile of the two groups was reviewed to characterize the severity of renal failure as adjudged by level of serum creatinine at time of admission, maximum creatinine during the hospital stay, duration of oliguria, need for dialysis, duration of dialysis, duration of hospital

stay, presence of hypertension, severity of hypertension (defined as requirement of more than three antihypertensive drugs), presence of proteinuria and severity of proteinuria (mild-when urine albumin creatinine ration is less than 0.5, moderate when it is between 0.5-2, severe or nephrotic range when it is more than 2). Records were screened to identify presence or not of extra renal involvement like encephalopathy, cardiomyopathy and coagulopathy. Both groups were compared with regards to acute mortality (death during first 3 months of onset of symptoms) or during followup. Renal outcomes of both groups was compared to ascertain the numbers who were in mild (defined as eGFR of more than 60 ml/min/m²) or moderate to severe renal insufficiency (defined as eGFR of less than 60 ml/min/m²), those who had residual proteinuria, residual hypertension (blood pressure more than 95th percentile) or neurological sequelae.

RESULTS

Short term outcome

A total 33 episodes of HUS in 30 children over 11 year period were included in the study. 69% (23/33) episodes were of atypical (D-) type. 13% (3) patients in D-group had recurrences. Mean age of presentation of entire group was 5.6 years (6.5 yr for D- versus 3.6 yr for D+). There were 2 females, all of whom had D- HUS. The total 3 boys had a relapsing course with a mean interval of 16 months (8 months-24 months) between the relapses. A seasonal variation in the incidence of D+ HUS was seen. Cases were more common in months of July and August. Except for one patient pneumococcal HUS, no other secondary causes of HUS were seen. None of patients had familial HUS. Prodromal features other than diarrhoea were similar in groups & included pallor, fever, vomiting, jaundice, and hematuria.

The mean serum creatinine at admission was 3.0 mg/dL. The corresponding values were similar in 2 groups (3.10 mg/dL in D- versus 2.90 mg/dL in D+). Peak serum creatinine of the entire cohort of HUS patients was 6.40 mg/dL (6.50 mg/dL in D- and 6.30 mg/dL in D+). Levels of hemoglobin, white blood count, platelet counts were comparable but D- patients had nephrotic range proteinuria more often than D+ counterparts (p=0.020). The mean duration of oliguria was considerably longer in the D- group than D+ group (24.5 days in D- versus 9.4 days in D+, p= 0.03). Requirement for dialysis was similar in both groups (85% in D- versus 80% in D+). Patients in D- group required dialysis for twice the duration as compared to D+ group but the difference did not reach significance (16.4 days in D- versus 7.6 days in D+, p=0.12). Duration of hospital stay was significantly longer in the D- group than D+ group (35.2 days in D- versus 15.9 days

in D+, p=0.005). Neurologic impairment (74% in D- versus 40% in D+, p=0.14) and cardiovascular dysfunction (48% in D- versus 30% in D+, p=0.51) during acute phase of the disease was commoner in D- group but not significantly. As Tables 1 and 2 illustrate the details of clinical and laboratory features as an entire cohort together and comparative value in D+ and D- groups. There were 6 deaths in total (20%), 5 in D- group and 1 in post diarrhoeal group indicative of higher acute mortality rate in D- group. 2 deaths occurred during the acute phase before discharge from the hospital, 2 patients recovered renal function but died at home within 3 months of presentation due to unknown causes, 2 were late deaths due to CKD. Severe hypertension was seen in all who died and in only 10/24 of the survivors (p=0.05). Fatal cases had longer anuria 42 days than the survivors 23 days (p=0.05).

Table 1: Clinical features during the acute illness

Features	D+	D-	Total	p-value
Duration of Oligoanuria	9.4d	24.7d	19.6d	0.03
Hypertension	60%	90%	80%	0.14
Severe hypertension	30%	70%	53%	0.02
Encephalopathy	75%	40%	63%	0.14
Cardiomyopathy	50%	30%	43%	0.51
Coagulopathy	35%	20%	30%	0.67
Requirement for dialysis	100%	90%	93%	0.59
Duration of Dialysis	7.6d	16.45d	13.5d	0.12
Duration of Hosp. Stay	15.9d	36.4d	29.5d	0.17

Table 2: Lab investigations during the acute illness

Parameters	D+	D-	Total	p-value
Hb (at admission)	6.66	6.03	6.24	0.3
TLC (at admission)	11.5	10.1	10.5	0.5
Plt (at admission)	0.58	0.80	0.73	0.1
Cr (at admission)	2.9	3.4	3.26	0.4
Cr. Max	6.3	7.4	7.0	0.3
Nephrotic range proteinuria	20%	65%	50%	0.02

Long term outcome

Follow up data was available 19 patients out of the initial cohort of 30 for a variable period of 32-120 months. (5 died during

acute phase and 6 were lost to follow up). Overall 73.6% (14/19) of all HUS patients developed sequel. Proteinuria on follow-up was present in 73.6% (14/19), 83.3% of D-

and 43% of D+ (p=0.04). 63.5% (12/19) patients had hypertension, 83% in D- and 28% in D+ (p=0.014). 52.6% (10/19) progressed to various stages of CKD. 21% (4/19) had residual neurological deficit, 25% in D- and 14% in D+. On multivariate analysis, no correlation was found between oliguria of more than 14 days, severe hypertension, severe proteinuria as risk factor for CKD. CNS sequelae range from ADHD, spastic paraparesis, neuroregression, blindness, forgetfulness. The comparative longterm outcome of two groups is given in Table 3. In Table 4 the details of renal outcomes of two groups are compared.

Factors predictive for adverse long term outcome

On univariate analysis-duration of oliguria, presence of severe hypertension and duration of hospital stay were found to be significantly associated with long term outcome. On multivariate analysis none of the acute phase variables reached statistical significance.

Outcome of D- patients who were plasmapheresed

25% patients in D- group (5/20) were treated with plasmapheresis in addition to dialysis. 2 out of these 5 children died (1 after acute phase, 1 late death due CKD). All 3 out of 5 survivors had residual hypertension, 2/5 developed chronic renal insufficiency and 1 had additional development delay.

Table 3: Comparison of long term outcome

Parameters	D+	D-	Total	p-value
Hypertension	2/7 (28%)	10/12 (83%)	12/19 (63.5%)	0.014
Proteinuria	3/7(43%)	10/12(83%)	14/19(73.6%)	0.04
CNS Sequele	1/7 (14%)	3/12 (25%)	4/19 (21%)	0.01

Table 4: Details of the long term renal outcome in 30 pts of HUS

Outcome	D+	D-	Total
Acute Deaths	1	4	5/30 (16.6%)
Late Deaths	0	1	1
Lost to FU <3mts after onset	2	3	5/30 (16.6%)
Complete renal recovery	3/7 (42.8%)	2/12(16.6%)	5/19 (26.3%)
Stage 1 (GFR>90ml/min/1.73m2 but HT/proteinuria/both)	2/7(28.5%)	2/12(16.6%)	4/19 (21%)
Stage 2 (GFR 60-90ml/min/m2)	2/7(28.5%)	5/12(41.6%)	7/19 (36.8%)
Stage 3,4 and 5 (GFR<60ml/min/1.73 m2)	0/7	3/12(25%)	3/19(15.8%)

DISCUSSION

The current concept divides childhood HUS into post diarrhoeal D+ HUS and non diarrhoeal or atypical D-HUS. [2-5] D+ HUS accounts for >80% of cases in children. [3-13] Most cases of D+ HUS are caused by VTEC in developed countries and shigella dysentrae in developing nations. [15] For patients with D+ HUS, supportive therapy including dialysis is still the most effective treatment. [26 ,27 ,28] Previous reported studies predict a variable

prognosis. [3-13] with mortality of 5-10% in the acute phase and 25% risk of developing chronic kidney disease many years later. [16] The D+ patients in our study had acute mortality rate of 10% and 40% of survivors had sequelae after a variable follow up of 3.5-11 years. Atypical HUS, in contrast, comprises a heterogeneous group of varied epidemiology, pathophysiology and outcome. [14] A number of previous publications have reports that D- HUS is generally associated with a greater

morbidity and mortality than D+ HUS, [3-10,13,17] as was also seen in our study (Table 2). However a few studies reported that outcome in D- HUS and D+ HUS is not significantly different and that D- is not invariably associated with a poorer prognosis than D+ HUS. [11,18,19] Another large study by Fitzpatrick et al found that D- had a superior outcome in terms of mortality and sequel than D+ counterparts. The patients in their study had a milder clinical illness with only 21% requiring dialysis, which is far less than in the other series, ranging from 53 to 80%. [6, 8-10] However 92% of their patients had D+ HUS which could have contributed to overall better outcome. Our study is comparable to the studies of Renaud et al, [20] Neuhaus et al [21] in having similar number of patients, a higher proportion of D- HUS and a similar clinical profile. The mortality and morbidity in terms of sequel were significant in both the studies and also in our study.

A unique finding in our study was the significantly high proportion of D- patients. Two third of our patients with HUS were of D- subtype, which is higher than previously quoted, [3-13,17,18] except for an Italian study (34% D- HUS). [22] The absence of D+HUS outbreaks and epidemics in our referral area partly accounts for the high percentage of patients with D- HUS. Another possibility is that our population may be genetically predisposed to disorders of complement dysregulation and antibody production putting it at a greater risk for non enteric form of HUS. [23] None of our HUS patients were familial, 3 had a recurrent course and only had post pneumococcal subtype. This is at variance with studies from Taiwan, Spain [24, 25] and other parts of the world where post pneumococcal HUS constitutes a sizable chunk of D- patients. This boy had a pneumococcal empyaema, followed by a fulminant acute phase of HUS. He survived

the acute phase but was left with residual nephropathy and hypertension.

Plasma exchange was not found useful in the management of D- patients in our study. We used plasmapheresis in only 5/20 of our D- patients. 2 out of these 5 patients, died, 2 had sequelae on followup. One patient was found to be in stage 4 CKD with severe hypertension and the other had residual proteinuria and hypertension. This is again at variance with a number of studies which have found plasma exchange to be a useful standard modality in the management of D- patients. [28-31] A possible explanation may be the delayed initiation of plasma exchange in our patients. At the time of study we use to offer plasma exchanges as a rescue therapy only to patients who failed to improve with renal replacement therapy and other supportive therapy by end of 2 weeks of admission and those who could afford it. Studies which endorse the use of plasmapheresis for D- HUS insist on initiating it very early on in the treatment course. We tried to identify factors in the acute phase which could predict prognosis. On univariate analysis, we found duration of oliguria, presence of severe hypertension and duration of hospital stay to be significantly associated with long term outcome. However on multivariate analysis none of the acute phase variables reached statistical significance. A number of studies have found anuria of more than 1 week or oliguria of more than 2 weeks to be a useful predicting factor. [32-34] Others have found neurological involvement, duration and severity of thrombocytopenia, high leucocyte count during acute phase in acute phase to be a strong determinant of adverse long term outcome. [21, 35, 36]

CONCLUSION

We conclude by saying that in the last decade, D- HUS was seen twice as frequently as D+ in our centre in western

India. Childhood HUS was associated with overall mortality of 20% (16.6% acute phase deaths, 3.3% late deaths due to CKD) and 52% incidence of chronic renal insufficiency. 63% developed persistent hypertension, 68% residual proteinuria and 20% were left with permanent neurological deficits. Patients with atypical HUS had a more severe acute nephropathy & higher rates of residual hypertension, proteinuria & neurological sequelae as compared to children with typical disease.

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