

CLINICAL SPECTRUM, COMPLICATIONS AND OUTCOME OF ATYPICAL HEMOLYTIC UREMIC SYNDROME

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ABSTRACT

Objective: To Determine the clinical spectrum, complications and outcome of atypical Hemolytic uremic Syndrome (aHUS).

Study Design: Case series study.

Place and Duration of Study: The Children's Hospital & The Institute of Child Health Lahore, from Mar 2017 to Jun 2018.

Methodology: Twenty five Children fulfilled the inclusive and exclusive criteria of atypical hemolytic uremic syndrome. Their demographics, clinical characteristics, investigations and treatment modalities used, were documented on the specially designed proforma.

Results: Out of twenty five cases, 15 (60%) were male and 10 (40%) were female with mean age of presentation being 8.47 ± 3.8 years. Seven children (28%) each with preceding history of respiratory tract infection (RTI) and family history of HUS. Twenty four (96%) children presented with anemia, hematuria in 15 (60%). Respiratory distress in 9 (36%) children and seizure in 7 (28%). Fragmented RBCs were present in all children, with thrombocytopenia in 22 (88%). Plasma therapy in 23 (92%) patients and plasma exchange was offered to 2 (8%) while peritoneal dialysis was done in 18 (72%) and hemodialysis was continued in 10 (40%) subjects. Hypertension was persistent in both acute and chronic phase of illness.

Conclusion: Although not uncommon, atypical hemolytic uremic syndrome have variable presentation with high mortality rate. Therefore one should be vigilant in prompt diagnosis as early detection can improve outcome of disease.

Keywords: Atypical hemolytic syndrome, Clinical spectrum, Complications, Outcome.

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INTRODUCTION

Hemolytic uremic syndrome (HUS) is a complex triad of microangiopathic hemolytic anemia, thrombocytopenia and acute kidney injury (AKI). Etiologically, it can be typical when occurring after Shiga like toxin-Escherichia coli (STEC) diarrhea or can be atypical, occurring with other precipitating factors¹. Children less than 18 years are more prone to develop atypical HUS (aHUS) as compared to adults². With kidneys and brain being the two primary target organs. Nearly 40% patients with aHUS require at least temporary renal replacement therapy and up to 20% end up in end stage renal disease (ESRD)³.

aHUS is known to be caused by dysregu-

lation of the alternative complement pathway due to genetic mutations, neutralizing autoantibodies or as gain of functional mutation in factor B^{4,5}. Genetic abnormalities have been recognized in >60% patients and identification of mutations can be helpful for therapeutic interventions⁶. aHUS can be triggered by a variety of precipitating events like upper respiratory tract infections due to *Streptococcus pneumoniae*, drugs, autoimmune conditions, pregnancy and metabolic conditions. Among these non-Shiga toxin diarrhea leading to aHUS was found in about 23% and 28% of French and Italian cohorts respectively⁷.

The overall prognosis for patients with aHUS is poor because of its complications affecting renal and extrarenal organ systems. Renal dysfunction has been reported in about 16% patients even after the first episode with slow progression to ESRD 7 while extra renal

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involvement is reported in 10-20%. Renal and extra renal manifestations of aHUS include anemia (94%), hypertension (68%), hematuria (27%), ARF (28%), seizures (23.5%), pancreatitis (23.1%), cardiac insufficiency (14%), myocardial infarction (3%) and CNS involvement (10%)⁸⁻¹⁰. Although mechanism is still unknown, aHUS can lead to cerebral thrombotic microangiopathy (seizures, vision loss, and nystagmus) and severe hypertension with posterior reversible encephalopathy syndrome².

Eculizumab, a high-affinity humanized monoclonal antibody, prevents generation of membrane attack complex (MAC) and might replace plasma therapy which is the gold standard treatment modality for aHUS.

As mortality and morbidity in patients of aHUS is very grave and limited data is available in our setup, so we focused to collect as much patients with their clinical presentations, to keep them on our regular follow up, monitor disease activity and complications so that early detection and timely intervention can be made available to patients as well to introduce new modalities.

METHODOLOGY

This case series study was conducted at the Nephrology ward at The Children's Hospital and The Institute of Child Health Lahore between March 2017 and June 2018 which enrolled 25 newly diagnosed children with aHUS of both genders between 3 months to 18 years of age. Informed written consent was taken from all parents and approval was obtained from institutional review board. As aHUS is rare entity and we had very less numbers of patients, so we enrolled all those subjects in our study that had features suggestive of disease during study duration through non probability consecutive sampling technique. The inclusion criteria were non diarrheal infections, Platelet count less than $150 \times 10^3/\mu\text{L}$, Peripheral blood smear showing helmet cells/burr cells/schistocytes, Renal injury in the form of Acute Kidney Injury (AKI), Kidney Disease: Improving Global Outcomes (KDIGO)^{11,12} defined AKI as renal failure divided into 3

stages depending upon the severity of derangement of serum creatinine and urine output of patients. Patients with common childhood malignancy (acute myeloid leukemia), scleroderma, medications (immunosuppressant/ chemotherapy) and Kasabachmerritt syndrome were excluded from the study. All those patients having history of diarrhea associated HUS was excluded from study.

All children were admitted and underwent complete clinical examination with strict vitals and input output monitoring during hospitalization. Complete blood count with peripheral smear, reticulocyte count, peripheral blood film for malarial parasite, renal function tests, serum electrolytes, complement levels, anti double stranded-DNA antibodies, serum haptoglobin, lactate dehydrogenase, Chest X-ray, renal ultrasound, mycoplasma antibodies and urine complete examination were performed and all the information documented on specially designed proforma. Hypertension was managed with IV/oral antihypertensive medications and plasma-therapy was offered to all patients. Platelets were transfused only in those patients who had active bleeding or had platelet counts $<20,000/\text{cmm}$. Fresh frozen plasma was transfused in all patients after excluding respiratory tract infection. Peritoneal dialysis was performed in all those patients who presented in emergency with AKI. Hemodialysis was continued in children who failed to show complete renal recovery. These subjects were followed up after discharge for 3 months, monitored by serial estimation of hemoglobin, platelet counts, serum LDH, haptoglobin and RFTs while outcome was measured by response to treatment, relapse of disease, and development of End Stage Renal Disease (ESRD).

Response was defined as full resolution of renal failure/stabilization of RFTs with recovery of normal platelet count ($\geq 150,000/\text{cmm}$). **Relapse** was defined as reappearance/worsening of renal failure with thrombocytopenia (indicating disease activity). Chronic Renal insufficiency: Estimated GFR $\leq 60\text{ml}/\text{min}/1.73\text{m}^2$ present for ≥ 3

months (calculated by Schwartz formula). **ESRD** Estimated GFR $\leq 15\text{ml}/\text{min}/1.73\text{m}^2$ present for ≥ 3 months (calculated by Schwartz formula). **Familial HUS** Patient having family history of HUS¹¹⁻¹⁴.

This study was analyzed by using computer software SPSS version 21. Mean and standard deviation were calculated for quantitative variables while percentages and frequencies for qualitative variable.

RESULTS

Twenty five children who fulfilled the clinical and laboratory criteria of aHUS were selected. Male patients were more commonly affected than females with mean age of presentation being 8.47 ± 3.8 years. Complete clinical data at the onset of illness was obtained in which consanguinity was a common factor in 23 (92%) subjects followed by familial HUS in 7 (28%) subjects. aHUS caused by preceding history of respiratory tract infections account for another 7

samples for laboratory evaluation were collected during acute phase of illness in all patients. Renal functions were deranged in 25 (100%) patients with mean serum urea $226.3 \text{ mg}/\text{dl} \pm 150$, mean serum creatinine $6.5 \text{ mg}/\text{dl} \pm 4.27$, hemoglobin

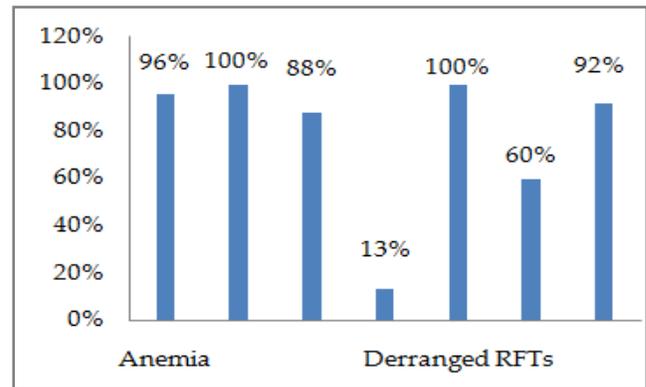


Figure-1: Results of various Laboratory parameters in our patients of aHUS.

$8.1 \text{ g}/\text{dl} \pm 2.76$ and serum LDH $14582 \text{ IU}/\text{dl} \pm 896$ (fig-1). Patients were managed conservatively with packed RBCs transfused in 21 (84%), fresh

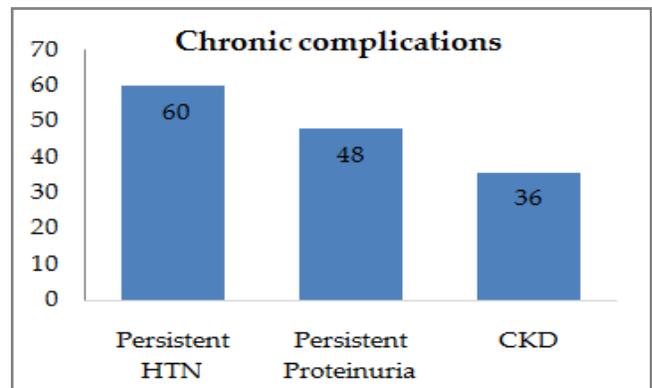
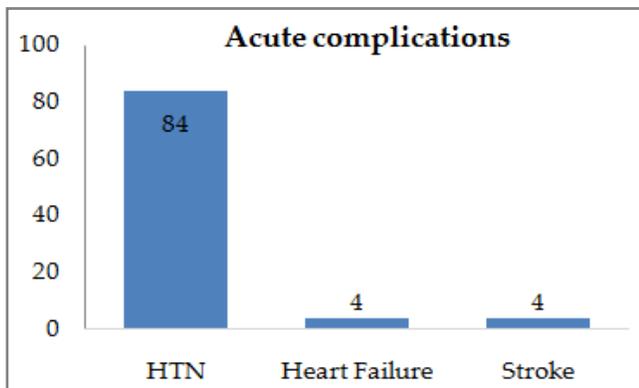


Figure-2(a&b): Demonstrates both acute and chronic complications of all patients with aHUS included in our study.

(28%) subjects. The putative triggering events recognized in less than 12 (48%) patients, but those children having familial cases were 7 (28%) while aHUS caused by each malaria, systemic lupus erythamatosus and mycoplasma pneumonia turned out to be 1 (4%).

The clinical manifestations of patients were variable and the most consistent feature of pallor was seen in 24 (96 %) while oliguria/anuria was found in 13 (52%) children (table-I). Blood

frozen plasma was received by 23 (92%) and platelet extract given in 3 (12%) children. Peritoneal dialysis and hemodialysis were performed in 18 (72%) and 10 (40%) subjects respectively while plasmapheresis was offered to all subjects but due to non-availability of this facility in our hospital and non-affordability of majority of patients it could be done only in 5 (20%) children. Acute and chronic complications encountered were described in fig-2a & 2b, while effects of different treatment modalities on the outcome of

disease observed during the 3 month follow up period were shown in table-II.

Complete remission was achieved in 2 (13%) and 2 (11%) patients who were treated with PD and FFP transfusion, retained normal renal functions with no residual hematological abnor-

Table-I: Illustrates various clinical manifestations in patients of aHUS in order of decreasing frequency.

Clinical Features	Frequency (n)	Percentage (%)
Pallor	24	96
Edema	15	60
Hematuria	15	60
Oliguria/anuria	13	52
Bruises	4	16
Respiratory distress	9	36
Seizures	7	28
Altered state of	3	12

malities. Relapse of disease was observed in only 1 (8%) subject who was being hemodialysed. CKD being outcome of most of treatment modalities. Out of 15 patients who undergone peritoneal dialysis, 7 (46.7%) subjects developed CKD and out of 12 patients who were hemodialysed, 6 (50%) children developed CKD. Likewise out of 18 children treated with plasma infusion and 5

hemodialysis 5 (41.7%) and plasma infusion 7 (38.9%).

DISCUSSION

Atypical HUS (aHUS), also called non-Shiga-toxin HUS, is primarily a disorder of complement dysregulation and accounts for about 10% patients with HUS. Its onset varies from neonatal period to adulthood and most patients presenting with renal involvement while others show extra renal manifestations. The overall prognosis is poor 10% patients die and one-third end up in end-stage-renal-disease (ESRD) even after one episode^{15,16}.

In our study we determined the clinical spectrum, complications and outcome of aHUS in pediatric population. We found a male predominance (male: female, 1.5:1) unlike the report by Leclerc *et al*¹¹ study that which showed equal frequency in both genders.

Familial aHUS was reported to be 24% by Geerdink *et al*¹⁷ study that which corroborates with our results of 7 (27%). Among all the characteristics only a positive family history predicts the presence of a genetic mutation¹⁸. In the former study, majority of patients (53%) presented between 1 and 7 years of age with 22% children

Table-II: Illustrates outcome of various treatment modalities in management of patients of aHUS.

Outcome	Peritoneal dialysis (n=5)	Hemodialysis (n=12)	Fresh frozen plasma infusion (n=18)	Plasma exchange (n=5)
No sequelae	2 (13.3%)	-	2 (11.1%)	-
Extra Renal complications	-	-	-	-
Relapse	-	1 (8.3%)	-	-
Chronic renal insufficiency	5 (33.3%)	5 (41.7%)	8 (44.4%)	1 (20%)
ESRD	2 (13.3%)	1 (8.3%)	1 (5.6%)	-
Death	6 (40%)	5 (41.7%)	7 (38.9%)	4 (80%)

patients undergoing plasma exchange also developed CKD in proportion of 9 (50%) and 1 (20%) respectively.

Mortality in our subjects treated with plasma exchange were 4 (80%), while we observed almost similar mortality rate in all subjects who were treated with peritoneal dialysis 6 (40%),

presenting before 1 year of age (youngest being 1 month old). Our study observed majority of patients presenting between age of 3 and 8 years, with only 1 (4%) child below one year of age (3 months old). In Geerdink *et al*¹⁷ study that also reported 84% patients with a triggering event like diarrhea (74%), upper RTI (45%), and fever (32%) in contrast to our study showing diarrhea in 2

(8%) and URTI in 7 (28%) children. Among the infectious etiology, our study demonstrated one patient each with mycoplasma infection and malaria as triggering factors, while streptococcal, Bordetella pertussis and Haemophilus influenza infections and Hepatitis B vaccination have also been documented in literature¹⁷.

aHUS exposes individuals to the risk of involvement of various organs, renal as well as extra renal. Renal manifestation in our study were reported to be haematuria in 15 (60%), edema 15 (60%), oliguria/anuria 13 (52%) and petechial rash/bruises 4 (16%), in contrast to haematuria documented in 27% and oliguria/anuria in 28% children in literature⁹.

In Kavanagh *et al*⁸ study that described extra-renal manifestations in many patients of aHUS including seizures (23.5%) and pancreatitis (23.1%) patients 8 with almost similar results reported by Dragon *et al*⁹ study that cardiac insufficiency 14% and rare complications like peripheral gangrene, retinal involvement and stroke were observed in other trials^{10,19}. In contrast our study demonstrated that respiratory distress due to volume overload/pneumonia/acidosis was seen in 9 (36%) patients, seizures 7 (28%), altered state of consciousness (ASOC) 3 (12%) and cardiac insufficiency in only 1 (4%) children.

In Nester *et al* study that observed that neurological involvement was most common extra-renal manifestation of aHUS 6 (more than 10%) while almost similar results were noted by In Geerdink *et al* 17 (13%). The neurological manifestations included irritability, drowsiness, seizures, diplopia, cortical study that blindness, hemiparesis or hemiplegia, stupor, and coma. Comparatively another recent trial of Turkish pediatric aHUS registry and our study revealed similar results of (28%) and 7 (27.7%) 20 patients with CNS complications.

Regarding complications of aHUS, hypertension (blood pressure >95th percentile for age, sex and height) was reported in 21 (84%) patients in our study in contrast to other reports of 71%

and 68% of patients^{17,20,21}. Similar results were obtained for persistent proteinuria by Geerdink *et al*, 19 (48%) and in our subjects 12 (47%). The most common GIT complication seen in an international cohort of patients with aHUS was pancreatitis/pancreatic insufficiency in 23 (8%) while none of our children had pancreatic involvement¹⁷. Pediatric case reports have described ocular complications like retinal hemorrhage, optic disc edema and retinal ischemia, but we did not encounter any visual manifestations in our subjects²³.

In Geerdink *et al*¹⁷ study that, Managed 60% patients with plasma therapy (plasma infusion and/or plasma exchange), while we administered plasma infusion in 23 (92%) children and platelet extract in 3 (12%) patients with active bleeding. Plasma exchange was performed in 2 (8%) patients only.

Our study reported 7 (28%) children with familial HUS, only 1 (14%) developed CKD, 6 (86%) remained in remission, while another study²⁴ reported familial HUS in 83% subjects, 91% children achieving complete remission almost similar to our study.

LIMITATION OF STUDY

Our study has certain limitations. Due to limited resources and high cost of screening/diagnostic investigations, we couldn't ruled out differentials like Thrombotic thrombocytopenic purpura, aHUS due to cobalamine deficiency and antiphospholipid syndrome requiring ADAMTS 13, homcysteine and cardiolipin antibody respectively. Likewise we could not offer plasma exchange and Eculizumab as gold standard treatment to our all patients, possibly explaining the grave prognosis.

CONCLUSION

Though not uncommon, aHUS has variable presentation with high mortality, so high index of suspicion should be considered so that prompt diagnosis could be made, as early intervention can altered the course of illness.

CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any authors.

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