

Atypical Hemolytic Uremic Syndrome - A Report of Two Cases.

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Abstract:

Hemolytic uremic syndrome (HUS) is one of the important cause of acute kidney injury in children. There is excellent outcome in patients with typical HUS but atypical HUS is associated with high mortality, risk of recurrence and may lead to end stage renal disease. We report two cases of 5 and 6 year old child having clinical & laboratory characteristics of atypical HUS. These children had a fulminant course of illness with complications involving various systems. The report provides an insight into the etio pathogenesis, diagnoses and treatment of this condition.

Key word: Atypical Hemolytic Uremic Syndrome, End Stage Renal Disease.

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Introduction:

Hemolytic uremic syndrome (HUS) is a disease of the microvasculature. It consists of triad of microangiopathic hemolytic anemia, thrombocytopenia and acute renal failure¹. Hemolytic uremic syndrome is traditionally classified into typical (without diarrhea) and atypical (no diarrhea), according to its etiology. Typical HUS is the common type that results from shiga toxin-producing escherichia coli infection or less commonly shigella dysenteriae type 1 infection. All HUS cases due to other etiologies are classified as atypical HUS². In atypical HUS, patient does not present with previous history of bloody diarrhea within 2 weeks before diagnosis of HUS³. Atypical HUS comprises about 5% to 10% of all cases of HUS in children⁴. There are some causes of atypical HUS like streptococcus pneumoniae (bacterial cause), like human immune deficiency virus (viral cause), drugs (antineoplastic, antiplatelet, immunosuppressive), pregnancy associated, systemic diseases (lupus, scleroderma, antiphospholipid syndrome), idiopathic and genetic(factor H, membrane co factor, factor I) or familial⁵.

Usual presentations are insidious onset. Non specific

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symptoms including pallor , poor feeding , vomiting , fatigue , drowsiness, anuria , oliguria , peripheral edema, impaired kidney function may be present that may lead to end stage renal diseases. Other clinical features are neurological symptoms like stroke and seizure. There can be cardiovascular symptoms such as myocardial infarction and high blood pressure^{6,7}. Atypical HUS commonly develops due to dysregulation of the alternative pathway of complement activation. Mutation in the complement regulatory genes factor H , membrane co factor protein factor I and thrombomodulin are responsible^{8,9}. For diagnosis following investigations should be done including serum level of C3, C4, factor H, factor I, expression of membrane complex protein on peripheral blood mononuclear cells and genetic study for mutation¹⁰⁻¹². It has poor prognosis with a 50% mortality rate¹³. Although we have limited facility regarding modern investigations and treatment of atypical HUS, we are reporting two cases of atypical HUS considering its rarity.

Case 1:

A 5 year old boy, 1st issue of non consanguineous parents got admitted in Bangabandhu Sheikh Mujib Medical University (BSMMU) with the complaints of anorexia, nausea, vomiting, gradual pallor for the last 15 days which was associated with swelling of the whole body for 10 days. Swelling first appeared around the eyes then became

generalized. He had also history of scanty micturition followed by anuria for two days and one episode of convulsion which was generalized tonic clonic in nature and not associated with fever. With this above complaints he initially treated locally with Injection Ceftriaxone, Phenobarbitone and one unit of whole blood transfusion, then referred to BSMMU. He had no history of bloody diarrhea, cough or cold prior to this episode. He had no history of respiratory distress, abdominal pain, headache, bleeding manifestation and no history of drug like cyclosporine intake or family history that may mimic this condition.

During admission he was toxic, irritable, moderately pale, blood pressure was 100/60 mm of Hg and respiratory rate was 30/min. Ascites and hepatomegaly were present. Immediate investigations that showed hemoglobin was 7.1 gm/dl, total count was 8000/mm³ and platelet count was 70,000/mm³. Peripheral blood film showed microangiopathic hemolytic anemia. Serum creatinine was 10.6 mg/dl and blood urea was 273 mgm/dl. There was hyponatraemia 128 mmol/l, lactate dehydrogenase enzyme was 3102, antinuclear antibody was negative, serum C₃ was depressed but serum C₄ was normal. Routine urine analysis, Ultrasonography of renal system, chest X ray and blood sugar was normal. Serum reticulocyte count was 4.3%. On the basis of history, examination findings and investigations he was diagnosed as a case of atypical hemolytic uremic syndrome. But for confirmation of diagnosis, we wanted to do factor H assay, factor I assay, expression of MCP on peripheral blood mononuclear cells and genetic study for mutations of above protein. Due to inadequate facility we could not do those investigations.

Patient was treated conservatively with fluids, fruits and salt restriction and intermittent peritoneal dialysis was given for 72 hours. As the plasma exchange is one of the modalities of renal replacement therapy we counselled the patient regarding plasma exchange but due to financial cause they denied. After 03 days of peritoneal dialysis serum creatinine was 7.8 mg/dl and serum urea was 250 mg/dl. Then 3 times per week hemodialysis was initiated through central venous line (left internal jugular vein).

After 05 days of hospital admission patient developed severe abdominal pain, fever and malena. On examination the child was febrile and bowel sound was sluggish. Septic screening was done which showed septicemia. Prothrombin time (PT), activated partial prothrombin time (APTT), fibrinogen degradation product and D-dimer was increased. Then patient was kept on nothing per oral, given fresh frozen plasma infusion, injection ceftazidime, Injection amikacin. Then the boy developed uncontrolled hypertension which was managed by 6 different groups of antihypertensive drugs including angiotensin converting enzyme inhibitor, angiotensin receptor blocker, nifedipine, carvedilol, diuretics and alpha receptor blocker.

After 25 days of hospital admission patient develop infection in the central venous line evident clinically by fever, discharging pus from the site of catheter. He was evaluated which showed growth of enterobacteriaceae sensitive to ceftazidime. Then a new catheter was introduced in other vein and give sensitive antibiotics for 21 days. After 03 months of hemodialysis, patient died due to septicemia.



Fig-1: Picture of case 01

Case 2:

A 6 years old boy, 1st issue of his non consanguineous parents was admitted in BSMMU with the complaints of vomiting and high grade continued fever for 10 days, abdominal pain and alteration of bowel habit for 05 days. Informant mother also gave history of swelling of whole body for last 05 days which first appeared around the eyes then gradually became generalized. The boy also developed scanty micturition, followed by anuria for 03 days. On query, mother also told that baby became progressively pale. For those above complaints he was initially admitted in a local hospital, where he was suspected as a case of enteric fever and treated with injection Ceftriaxone for 05 days but the condition was not improved.

He had no history of diarrhea, respiratory tract infection before this episode. No history of drug intake or family history that may mimic this condition. On examination he was puffy, edematous, temperature was 102.0 F, blood pressure was 130/100 mm of Hg (more than 99th centile of CDC chart) and respiratory rate was 30/min. Ascites and hepatomegaly were present.

Immediate investigation showed hemoglobin 6 gm/dl, total count 8000/cumm, platelet count was 50,000/cumm, Peripheral blood film shows microangiopathic hemolytic anemia. Serum reticulocyte count was 6.3%, serum creatinine 6 mg/dl, blood urea 100 mg/dl, serum electrolyte was normal except Tco2 which was 17mmol/L. LDH was raised (3102 IU/L), ANA was negative, serum C₃ was low (6mg/dl), but serum C₄ was normal. Blood sugar, blood culture and alkaline phosphatase were normal. Basing on history and investigation we diagnosed the case as atypical hemolytic uremic syndrome.

Patient was treated conservatively by fluids, fruits and salt restriction and intermittent peritoneal dialysis was given for 72 hours. After 03 days of peritoneal dialysis serum creatinine was 5 mg/dl and serum urea was 72 mg/dl. Then hemodialysis was initiated through central venous line (right internal jugular vein).

After 3rd days of hospital admission the boy became restless developed generalized convulsion. That time

blood pressure was 140/110 mm of hg. Serum electrolyte and CT scan was normal. Convulsion was managed by injection Phenobarbitone and sub lingual nifedipine gel. Different groups of antihypertensive drugs including nifedipine, angiotensin converting enzyme inhibitor, angiotensin receptor blocker, diuretics and alpha receptor blocker were added but patient remained hypertensive and restless.

On 7th day of hospital admission the boy developed malena and haematemesis and bleeding through central venous line catheter. on examination he was febrile, severely pale and hypertensive (BP 140/90 mm of hg). Investigations shows hemoglobin 6.6 gm/dl, total count 8000/cumm, neutrophil 88%, platelet 150000/cumm. PT and APTT were elevated. FDP and D-dimer were increased. Blood culture was negative. We considered these features of septicemia. We managed this condition with broad spectrum IV antibiotic meropenem and for the management of anemia 02 units of PRBC was transfused. Even after these treatment the boy died due to cardio respiratory failure.



Fig-2: Picture of case 02

Discussion:

Atypical HUS is a rare disease. The incidence of atypical HUS in children is approximately 2 cases per 1000,000 population per year^{14,15}. Seventy percent of patients with atypical HUS can present at extremes of age like less than 2 year and more than 40 year¹⁶. Arnaud lionet showed a case of adult atypical HUS at the age of 42 years⁵. Our case 01 presented at the age of 4 year and case 02 presented at the age of 06 year. Usually atypical HUS

cases have no previous history of diarrhoea¹⁷ like both of our cases. Siddharta Sivamurthy et al reported a case of atypical HUS, confused with meningococcal diseases due to presence of petechial rash, tachycardia and hypothermia. Later on, it was diagnosed as a case of atypical HUS on the basis of peripheral blood film, biochemistry, complement level and genetic study⁷. Our case 2 was initially suspected as a case of enteric fever due to high grade fever, abdominal pain and alteration of bowel habit. Hypertension is frequent in atypical HUS and is often expected to be severe¹⁸. Both of our patients had hypertension and it was very difficult to manage despite use of the 06 different classes of anti hypertensive drugs. Arterial hypertension is frequent and often severe, due to volume overload in case of oliguria/anuria and to hyperreninemia secondary to renal thrombotic microangiopathy¹⁹. D'Souza KD et al observed a case of atypical hemolytic uremic syndrome with severe hypertension not controlled with optimum doses of calcium channel blockers, angiotensin converting enzyme inhibitors, alpha blockers (Prazosin), beta blockers and Minoxidil²³.

Extra renal involvement is common in atypical HUS and may even be the cause of death or sequelae²³. CNS dysfunction may be seen in up to 50% of the cases. This could present as drowsiness, agitation, irritability, lethargy, seizures or coma. CT scan of brain may show infarcts or hypodensities more commonly in the basal ganglia²⁴. D'Souza KD et al described a patient with atypical HUS who had seizure and CT scan of brain revealed multiple infarcts²³. On the contrary our case 2 had seizure but CT scan was normal. Seizure of our patients may be attributed to uncontrolled hypertension.

Diagnosis depends on assay of complement factors and mutational analysis like assay of serum level of C3, C4, factor H, factor I, expression of membrane complex protein on peripheral blood mononuclear cells and genetic study for mutation. In developing countries like ours, we have lack of these diagnostic facilities. So, we diagnosed these cases based on history, clinical examinations and some related investigations¹.

In 2 independent cohort of atypical HUS patients, C3 level of 26 patients were persistently below the lower end

of normal range^{1,13}. Both of our patients had depressed C3 and normal C4. Carla et al showed a patient with atypical HUS with mildly depressed C3 and level of C4 were normal¹.

Plasma exchange, Eculizumab therapy, renal transplantation and both liver and renal transplantation are the most advance management regarding atypical HUS. Treatment facilities are limited in Bangladesh. Now a days Plasmapheresis has been used the most important modalities of the treatment of atypical HUS. In our country this type of treatment is only available for adults. Gianviti et al found that the evolution of renal function treated with plasma exchange and untreated patients are not significantly different, but chronic renal failure and end stage renal disease are present only in untreated patients²¹. Eculizumab and rituximab have been successfully used for control of atypical HUS and severe central nervous system manifestations^{7,13}. Carle nester used eculizumab and plasmapheresis pre-emptively as part of a renal transplant protocol for the treatment of atypical HUS in 12 years old patient with no relapse up to 04 months¹. In a meta analysis Rathbone J showed that eculizumab was clinically effective in patients with atypical HUS with reduced thrombotic microangiopathic activity as measured by thrombotic microangiopathic activity event-free status, and normalised platelet count in the majority of patients¹².

Final outcome of atypical HUS is usually poor, as 25 % die during the acute phase and 50% need long-term renal replacement therapy¹². In a recent report on 29 children with atypical HUS, only 24.1% had normal kidney function during long-term follow up²⁵. Renaud et al reported that 17 out of 21 children (81%) with atypical HUS had ESRD (end stage renal disease) in comparison to 18/21 (86%) patients with typical HUS having a good outcome²⁰. After plasma exchange was introduced, the mortality rate has been dropped from 50 to 25%²⁴. Both of our patients developed ESRD and we provided renal replacement therapy by haemodialysis along with other supportive measures.

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