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Assessment of Pediatric Hemolytic Uremic Syndrome Patients Hospitalized in Pediatric Intensive Care Unit

Çocuk Yoğun Bakımda Hemolitik Üremik Sendrom Nedeniyle İzlenen Hastaların Değerlendirilmesi

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Abstract

Aim: It is aimed to describe clinical properties and outcomes of pediatric hemolytic uremic syndrome hospitalized in pediatric intensive care.

Material and Method: Our study was intended as observatory and retrospective. Symptoms before PICU admission, interventions before PICU admission, time period before PICU admission in days were defined as pre-PICU findings. Glasgow Coma Score (GCS) at admission, Pediatric Risk of Mortality Score (PRİSM-III), laboratory parameters, medical treatments, extracorporeal treatments data was collected as PICU interventions. Outcomes were examined as days in PICU, days in hospital and survival.

Results: Twenty-three patients were included into study. Before PICU admission more than half of the patients were treated with antibiotics. Twenty-two were suffered from diarrhea. 3 patients had non-bloody diarrhea. 3 patients had central nervous system involvement presented as seizures. Intravenous diuretics (86.9%) and oral antihypertensives (73.9%) were the most common treatments in PICU. Eculizumab treatment was required for 6 patients. All patients got fresh frozen plasma. Nearly all of the patients required erythrocyte transfusions (95.6%). If we evaluated renal replacement therapies, 2 (8.6%) patients needed CRRT and 12 (52.7%) patients needed IHD. Extrarenal involvement was spotted in 5 patients (21.7%). Most of the patients were survived (95.3%).

Conclusion: Hemolytic uremic syndrome is an important clinic entity. Most patients' blood pressure could be controlled with oral antihypertensive treatments. Antibiotic prescriptions to diarrhetic patients should be more cautiously. There should be transfusion protocols of clinics about HUS patients to prevent over transfusion.

Keywords: Children, hemolytic uremic syndrome, intensive care

Öz

Amaç: Pediatrik yoğun bakımda yatan pediatrik hemolitik üremik sendromun klinik özelliklerinin ve sonuçlarının tanımlanması amaçlanmaktadır.

Gereç ve Yöntem: Çalışmamız gözlemsel ve retrospektif olarak planlandı. ÇYBB'ye yatıştan önceki semptomlar, ÇYBB'ye giriş öncesi müdahaleler, ÇYBB'ye kabulden önceki gün olarak geçen süre ÇYBB öncesi bulgular olarak tanımlandı. Başvuruda Glasgow Koma Skoru (GKS), Pediatrik Mortalite Skoru (PRİSM-III), laboratuvar parametreleri, medikal tedaviler, ekstrakorporeal tedavi verileri ÇYBB müdahaleleri olarak toplandı. Sonuçlar ÇYBB'de gün, hastanede yatış ve sağkalım olarak incelendi.

Bulgular: Yirmi üç hasta çalışmaya dahil edildi. ÇYBB'ye kabul edilmeden önce hastaların yarısından fazlası antibiyotik tedavisi gördü. Yirmi iki kişide ishal mevcuttu. 3 hastada kansız ishal vardı. 3 hastada nöbet olarak ortaya çıkan santral sinir sistemi tutulumu vardı. ÇYBB'de en sık uygulanan tedaviler intravenöz diüretikler (%86.9) ve oral antihipertansifler (%73.9) idi. 6 hastaya ekulizumab tedavisi gerekti. Tüm hastalara taze donmuş plazma verildi. Hastaların tamamına yakınına eritrosit transfüzyonu gerekti (%95.6). Renal replasman tedavilerini değerlendirirsek 2 (%8,6) hastaya CRRT ve 12 (%52,7) hastaya İHD'ye ihtiyaç duyuldu. Beş hastada (%21.7) böbrek dışı tutulum saptandı. Hastaların çoğu hayatta kaldı (%95.3).

Sonuç: Hemolitik üremik sendrom önemli bir klinik antitedir. Çoğu hastanın kan basıncı, oral antihipertansif tedavilerle kontrol edilebilir. İshalli hastalara antibiyotik reçetesi daha dikkatli olmalıdır. Aşırı transfüzyonu önlemek için HÜS hastaları ile ilgili kliniklerin transfüzyon protokolleri olmalıdır.

Anahtar Kelimeler: Çocuk, hemolitik üremik sendrom, yoğun bakım

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INTRODUCTION

Hemolytic uremic syndrome (HUS) is an important cause of acute kidney injury in pediatric age.[1] Hemolytic uremic syndrome is characterized with hemolytic anemia, thrombocytopenia and acute renal injury.[1] Hemolytic uremic syndrome primarily affecting children younger than 5-year-old.[2]

Different types of HUS are caused by different factors.[3] Most common type of HUS occurred by Shiga toxin producing E. Coli.[4] STEC HUS is responsible agent for 85-95% of HUS patients in Europa and North America.[2] E Coli serotype 0157:H7is the most common causing agent.[2] Atypical HUS (aHUS) is a complement mediated HUS occurs because of genetic defects or acquired defects in complement system in 50-70% of patients.[2] However, in 30-50% of patients have no mutations spotted.[2]

Thrombotic microangiopathy was the pathologic finding in HUS.[5] Same pathology also seen in thrombotic thrombocytopenic purpura.[5] ADAMSTS-13 deficiency is the main cause of TTP.[5] Hemolytic uremic syndrome and TTP has similar clinical presentation.[5] Physicians can discriminate TTP and HUS with serum ADAMSTS-13 levels in patients.

Hemolytic uremic syndrome give rise to multiple thrombotic occlusions that cause multisystemic involving renal system, central nervous system, gastrointestinal tract and cardiac system.[5]

In this report, we want to describe clinical properties and outcomes of pediatric hemolytic uremic syndrome hospitalized in pediatric intensive care.

MATERIALS AND METHOD

Our study was intended as observatory and retrospective. All patients diagnosed as hemolytic uremic syndrome included into the study. Patients' data was collected from patient's files and computer registries. Patients who were transferred to another hospitals, patients still hospitalized in study period and patients were not meet diagnostic criteria of hemolytic uremic syndrome were excluded.

Patients' demographic data was defined as age (in month), gender, presence of comorbid disease and patients body weight as kg. symptoms before PICU admission (classified as central nervous system symptoms, gastrointestinal system symptoms, cardiovascular system symptoms, respiratory system symptoms and other symptoms), interventions before PICU admission (red blood cell transfusion, platelet transfusion, dialysis, intubation, inotrope requirement, cardiopulmonary resuscitation), time period before PICU admission in days were defined as pre-PICU findings.

Glasgow Coma Score (GCS) at admission, Pediatric Risk of Mortality Score (PRİSM-III), laboratory parameters (blood gas parameters, complete blood count, serum glucose level, liver function tests, renal functions tests, C3 levels, C4 levels, haptoglobin), respiratory support therapies (high flow nasal cannula therapy, non-invasive ventilation, mechanic ventilation), inotrope requirement, medical treatments (antihypertensive treatments, diuretics, eculizumab), abdominal ultrasound findings, transfusions (erythrocyte, thrombocyte and fresh frozen plasma) applied, extracorporeal treatments (renal replacements therapies, plasmapheresis) data was collected as PICU interventions

Outcomes were examined as days in PICU, days in hospital and survival.

Our study was approved by our hospital's Ethic Committee Number 2 (Date:17.08. 2022.Decision Number: E2-22-2246). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Descriptive analysis of the results was conducted by using the SPSS 17.0 software package for Windows (IBM Company, New York, NY). Categorical data expressed as proportions (%). Median and inter quartile range were used for quantitative data.

RESULTS

Throughout the study period 29 patients defined as hemolytic uremic syndrome. 4 patients excluded because of hospitalization in study time. One patient was transferred into another hospital because of previous follow-up was done by another clinic. One patient was not meet HUS criteria. Twenty-three patients were included into study. Demographic data was presented in **Table 1.** Most of the patients were female (52.4%). Only four patients were referred from our emergency department. Nineteen patients were referred from another hospital. Before PICU admission more than half of the patients were treated with antibiotics. Gastrointestinal symptoms were spotted nearly all of the patients (95.6%). Twenty-two were suffered from diarrhea. 3 patients had non-bloody diarrhea. 3 patients had central nervous system involvement presented as seizures. 1 patient had visual impairment. Petechia was seen in 2 patients.

İnterventions and treatments which applied to patients were presented in **Table 2.** Intravenous diuretics (86.9%) and oral antihypertensives (73.9%) were the most common treatments in PICU. Intravenous antihypertensive treatments required for one patient. Esmolol and nitroglycerin infusions applied to that patient. Eculizumab treatment was required for 6 patients.4 patient who needed eculizumab was defined with clinic decision as aHUS. 2 patients with typical HUS also treated with eculizumab. All patients got fresh frozen plasma. Nearly all of the patients required erythrocyte transfusions (95.6%). Mechanical ventilation applied to two patients. If we evaluated renal replacement therapies, 2 (8.6%) patients needed CRRT and 12 (52.7%) patients needed IHD. Peritoneal dialysis was not performed to any patient. Plasmapheresis applied to 3 patients. Neuroimaging was done for two patients. One of the patients who suffered from mental motor retardation with renal biopsy result as thrombotic microangiopathy cranial magnetic resonance imaging resulted as posterior reversible encephalopathy. The other patient who suffered from status epilepticus cranial MRI was resulted as restriction of diffusion in lenticular nucleus and corticospinal tract. Continuous renal replacement therapy applied to two patients because of hemodynamic instability of two patients.

Table 1. Demographic data and pre-PICU findings and interventions of pediatric HUS patients, (n=23)

Age (month), median (IQR)	23.0 (16.0-63.0)
Gender, n (%)	
Female	12 (52.1)
Weight (kg), median (IQR)	14.0 (10.0-20.0)
Co-morbid disease presence, n (%)	1 (4.3)
Patient's referral to PICU, n (%)	
Another hospital	19 (82.7)
Emergency department	4 (17.3)
Time before PICU admission in days, median (IQR)	4 (3-7)
Interventions before PICU admission, n (%)	
IV antibiotic usage	7 (30.4)
Oral antibiotic usage	7 (30.4)
No intervention	4 (17.3)
Maintenance hydration	3 (13.0)
Fluid resuscitation	3 (13.0)
Diuretics	2 (8.6)
Inotrope	1 (4.3)
RBC transfusion	1 (4.3)
Fluid restriction	1 (4.3)
Eculizumab	1 (4.3)
Antiepileptic	1 (4.3)
Symptoms of patients, n (%)	
Gastrointestinal system,	22 (95.6)
Cardiovascular system,	4 (17.3)
Central nervous system,	3 (13.0)
Dermatologic	4 (17.3)

HUS: Hemolytic uremic syndrome; IQR: Inter quartile range; IV: Intravenous; PICU: Pediatric intensive care unit; RBC: Red Blood Cell.

Table 2. Treatment and interventions of pediatric HUS patients in pediatric intensive care unit

GCS at PICU admission, median (IQR)	15 (15-15)
PRISM-III scores, median (IQR)	8 (5-8)
Urinary ultrasound findings, n (%)	
Increased renal parenchyma echogenicity	16 (69.5)
Normal renal parenchyma	7 (30.5)
Medical treatments, n (%)	
Diuretics,	20 (86.9)
Oral antihypertensive	17 (73.9)
Inotrope,	4 (17.3)
Eculizumab,	6 (26.0)
Transfusions, n (%)	
RBC transfusion,	22 (95.6)
Number of RBC transfusions, median (IQR) (n=22)	4 (2-8.25)
FFP,	23 (100.0)
Number of FFP transfusions, median (IQR), (n=23)	8 (3-19)
Thrombocyte transfusion,	15 (65.2)
Number of thrombocyte transfusions, median (IQR) (n=15)	1 (1-3)
Mechanical ventilation, n (%)	2 (8.6)
Plasmapheresis, n (%)	3 (13.0)
Renal treatments, n (%)	
IHD,	12 (52.1)
CRRT,	2 (8.6)

CRRT: Continuous renal replacement therapy; FFP: Fresh frozen plasma; GCS: Glasgow Coma Scale; HUS: Hemolytic Uremic Syndrome; IHD: Intermittent hemodialysis; IQR: Inter quartile range; PRISM: Pediatric risk of mortality; RBC: Red blood cell

Extrarenal involvement was spotted in 5 patients (21.7%). Four patients had CNS involvement. Three of them had seizures, one patient had visual impairment. İntestinal perforation was spotted in another patient.

Laboratory parameters were demonstrated in **Table 3.** Serum ADAMS-TS 13 test was performed to 6 patients and all ADAMS-TS13 level results was above 10%. Enterohemorrhagic E Coli was spotted in only 1 patient's stool culture. 20 patients stool culture was negative.

Table 3. Laboratory parameters at pediatric intensive care admission,

Venous blood gas parameters, median (IQR)	
pH,	7.39 (7.35-7.44)
pCO2, mm Hg	30.5 (26.6-35.5)
BE, mmol/L	-4.7 (-9.0-0.0)
Bicarbonate, mmol/L	19.3 (17.0-23.4)
Lactate, mmol/L	1.30 (1.01-1.53)
White blood cell, $\times 10^9$/L median (IQR)	13670(10660-17800)
Hemoglobulin, g/dl median (IQR)	9.10 (7.70-10.30)
Platelets, x10^9/L median (IQR)	63 (28-107)
Biochemical parameters, median (IQR)	
BUN, mg/dl	146(81-190)
Creatinine at admission, mg/dl	1.72 (1.07-2.72)
Creatinine at discharge, mg/dl	0.46 (0.37-0.67)
AST, U/L	105 (69-214)
ALT, U/L	30 (21-71)
LDH, U/L	1961 (1333-3002)
Sodium, meq/L	135 (132-139)
Potassium, meq/L	4.5 (3.9-4.9)
Calcium, mg/dl	8.4 (8.10-8.79)
C3, (n=19)	0.85 (0.76-1.00)
C4, (n=17)	0.20 (0.103-0.203)
Haptoglobin, (n=20)	0.300 (0.291-0.308)

ALT: Alanine amino transferase; AST: Aspartate amino transferase; BE: Base excess; BUN: Blood urea nitrogen; IQR: Inter quartile range; LDH: Lactate dehydrogenase

If outcomes evaluated, most of the patients were survived (95.3%). Only one patient was died. 3-year-old boy admitted to emergency service with hematuria one week after upper respiratory tract infection. After the clinical evaluation patient was referred to our PICU with HUS diagnosis. Supportive therapy and 3 hemodialysis sessions performed, and patient was transferred to ward. Atypical HUS was the probable diagnosis because of medical history. Diagnostic blood tests and genetic tests could not be done because of laboratory insufficiencies. Eculizumab therapy applied to the patient because of continuation of renal dysfunction in ward. He suffered from sudden cardiac arrest and cardiopulmonary resuscitation (CPR) was applied for forty-five minutes. Patient transferred back to PICU. After a long CPR, multi-organ failure developed in the patient. After 7 day follow up, patient was died.

Table 4. Outcomes of pediatric HUS patients	
Days in PICU, median (IQR)	5 (3.0-12.0)
Days in hospital, median (IQR)	19 (14.0-22.0)
Mortality, n (%)	1 (4.3)

HUS: Hemolytic uremic syndrome; PICU: Pediatric intensive care unit

DISCUSSION

HUS is a clinical condition defined with triad that includes microangiopathic hemolytic anemia, thrombocytopenia and acute kidney injury.[7] Hemolytic uremic syndrome is major cause of acute kidney injury in children.[8] In children infectious causes are the commonest reason of HUS.[7] Most common cause of HUS is E. Coli O157:H7.[8] Despite that in our patient group, only in one patient's stool culture we could detect EHEC. Patient with diarrhea positive HUS (D+HUS) E Coli 0157:H7 could be generable 100% in first two days.[9] After 7 days this ratio decreases to 30%. Our patient groups referral to our center was nearly 7 days. We could only see E Coli presence in 1 patient. This condition may be related with late PICU referral or deficient microbiological examination.

Stool culture with selective and differential media such as MacConkey agar effectively identifies O:157 in USA.[01] Polymerase chain reaction or immunoassay for toxin is now uniformly recommended to support stool culture.[10]

Complement regulation problems could cause aHUS.[5] In our country there are limited number of laboratories which studies factors causing aHUS like Factor H, Factor I.[5] So, we could not correctly describe aHUS patients in our population. Maybe some results may not be correctly recorded into patient files because nephrology and pediatric intensive care departments advices patient family about laboratory restrictions. Patient with bloody diarrhea in our patient group could be accepted as STEC+HUS because of their milder clinical aspects. But bloody diarrhea may be a symptom of aHUS due to gastrointestinal involvement of aHUS.[10]

Studies also showed that early antibiotic prescription also aggravates HUS development.[11,12] Antibiotics induce shigatoxin production and release.[8] In our patient population a large number of patients got antibiotics before HUS development. Antibiotic prescription should be more carefully in patients with diarrhea.

Management of D+ HUS is supportive therapy, appropriate fluid infusion, electrolyte management and blood pressure control.[13] Hypertension in HUS patient's is result of activation of renin-angiotensin-aldosterone system activation due to renal vascular thrombosis.[9] Hypertension is quite common in HUS patients.[14] Nearly ¾ of our study group patients required oral antihypertensives. Intravenous antihypertensives were used only in 1 patient.

Neurological involvement is reported in approximately 30% of all types of HUS.[15] Seizures, irritability, lethargy, encephalopathy are the most common CNS findings.[15] In pediatric age group CNS involvement rate is 3-53%.[16] Single centered study from Turkey showed that CNS involvement seen in 13% of HUS patients.[1] Another single centered study with 64 HUS patients demonstrated that CNS involvement in 37.5% of patients.[6] We had an CNS involvement ratio (17.4%) similar to the rates found on other studies in our population.

Eculizumab is the monoclonal C5 antibody.[5] Eculizumab is the most effective therapy option in aHUS patients.[17] Due to recent published articles, eculizumab is also effective in long term treatment of aHUS.[17] Eculizumab in STEC HUS is controversial.[8] Studies also showed that complement overactivation in STEC HUS.[8] In HUS epidemic in Germany, eculizumab was used in patients with neurological involvement. There are small series and case reports demonstrated that STEC HUS patients were successfully treated with eculizumab. In our HUS patients 6 patients with HUS treated with eculizumab. 4 of them without bloody diarrhea and extrarenal involvement but their diagnostic test was not done. One of them had cecal perforation. Others had neurological symptoms. 2 of them with D+HUS findings. D+HUS patients got the eculizumab to improve renal functions. One patient was lost despite eculizumab treatment.

Endothelial and thrombocyte activation, HUS process continues and progressive renal failure is formed.[9] Two thirds of patients required dialysis during acute stage.[13] In our cohort, half of the patient required intermittent hemodialysis similar with literature.

Thrombocyte transfusions should be done in before surgical procedures or active bleeding in HUS patients.[5] Hemoglobulin level should be supported below 7 gr/dl.[5] Nearly all of the patients in our cohort got thrombocyte or erythrocyte suspensions repetitively. This result was the absence of transfusion protocol in HUS patients. Plasma therapy was used to replace and remove circulating factors causing to HUS.[8] Plasma therapy was advised in HUS patients despite lack of large trials.[18] There is no evidence to support to give plasma therapy to patients for improve outcomes.[2,10]

Mortality rate of STEC HUS is 3-5%.[8] Morbidity including hypertension and proteinuria of STEC HUS is up to 30%.[2] Mortality rate is higher in aHUS than STEC HUS up to 25%.[2] Only one patient died in our study. His clinic was progress rapidly despite eculizumab treatment.

Our study has several limitations. Our study was single centered and retrospective. We could not perform tests for atypical HUS because of inaccessibility of laboratory work so treatment decisions were made according to clinical judgements. We could not reach urine output of patients from files so we could not classify renal injury due acute kidney injury scores. Transfusion decisions were not taken by a treatment protocol. Some patients would be suffered from unnecessary transfusions. Classification of HUS were not correctly done because of lack of laboratory tests required for differential diagnosis in our hospital.

CONCLUSION

Despite lack of limitations, we want to show a picture of important clinical entity. Hemolytic uremic syndrome is an important cause of renal failure under five years of age. D+ HUS has a good prognosis in our patient group. Renal replacement therapies often required in these patient group. Blood pressure follow-up is important. Most patients' blood pressure could be controlled with oral antihypertensive treatments. Antibiotic prescriptions to diarrhetic patients should be more cautiously. There should be transfusion protocols of clinics about HUS patients to prevent over transfusion. Hemolytic uremic syndrome patients without bloody diarrhea's clinical process could be severe. Physicians could be more careful in those patients' follow-up. Eculizumab treatment may improve outcomes.

ETHICAL DECLARATIONS

Ethics Committee Approval: Our study was approved by our hospital's Ethic Committee Number 2. (Date:17.08. 2022. Decision Number: E2-22-2246).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The author has no conflicts of interest to declare.

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