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Long-Term Outcomes of Patients with Atypical Hemolytic Uremic Syndrome

Atipik Hemolitik Üremik Sendromlu Hastaların Uzun Dönem Sonuçları

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Abstract

Aim: Hemolytic uremic syndrome (HUS) is the clinical triad of anemia, thrombocytopenia and acute renal injury. Atypical hemolytic uremic syndrome (aHUS) is a rare disease of alternative complement pathways. It is aimed to evaluate long-term follow-up of patients with aHUS in the present study.

Materials and methods: Eleven children diagnosed with aHUS were retrospectively evaluated. Demographic, clinical, and laboratory data and treatment details were reported.

Results: A total of 11 patients were enrolled in the study. The mean age of patients at aHUS onset was 2.9±6 years. The mean follow-up time was 72 ± 4 months All patients had renal involvement. Extrarenal manifestations of aHUS were present in four patients. All patients had eculizumab treatment.

Conclusion: Our study insight into diagnosing and managing aHUS, a very rare disease, in our pediatric patients. Genetic testing is used to improve the diagnosis of aHUS. We demonstrated the long-term efficacy and safety of eculizumab in our aHUS patients. Further studies are needed to determine the optimal time for discontinuation of eculizumab treatment.

Keywords: Atypical hemolytic uremic syndrome; children; complement pathway; eculizumab.

Öz

Amaç: Hemolitik üremik sendrom (HÜS), anemi, trombositopeni ve akut böbrek hasarının klinik üçlüsünden oluşur. Atipik hemolitik üremik sendrom (aHÜS), alternatif kompleman yollarının nadir görülen bir hastalığıdır. Bu çalışmada, aHÜS'lü hastaların uzun dönem takiplerinin değerlendirilmesi amaçlandı.

Gereç ve Yöntemler: Atipik hemolitik üremik sendrom tanısı alan 11 çocuk retrospektif olarak değerlendirildi. Demografik, klinik ve laboratuvar verileri ve tedavi detayları rapor edildi.

Bulgular: Çalışmaya toplam 11 hasta dahil edildi. aHÜS başlangıçlı hastaların ortalama yaşı 2,9±6 idi. Ortalama takip süresi 72 ± 4 aydı. Tüm hastalarda böbrek tutulumu vardı. aHÜS'ün böbrek dışı belirtileri dört hastada mevcuttu. Tüm hastalara ekulizumab tedavisi uygulandı.

Sonuç: Çalışmamız pediatrik hastalarımızda çok nadir görülen bir hastalık olan aHÜS'ün tanı ve tedavisine ışık tutmaktadır. aHÜS tanısını güçlendirmek için genetik testlere ihtiyaç vardır. aHÜS hastalarımızda ekulizumab'ın uzun vadeli etkinliğini ve güvenliliğini gösterdik. Ekulizumab tedavisinin kesilmesi için en uygun zamanı belirlemek için daha ileri çalışmalara ihtiyaç vardır.

Anahtar Sözcükler: Atipik hemolitik üremik sendrom; çocuk; kompleman sistemi; ekulizumab

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Introduction

Atypical hemolytic uremic syndrome (aHUS) is an acute thrombotic microangiopathy and an ultrarare renal disease that involves dysregulation of the alternative pathway (AP) in the complement system (1). Gasser et al. first described the Shiga toxin-producing Escherichia coli (STEC) HUS in 1955 (2) and the term "atypical HUS (aHUS)" was used to describe HUS not triggered by the infection of STEC, so far there has been valuable improvement in understanding of pathophysiology, diagnosis, and treatment of the disease.

Hemolytic uremic syndrome (HUS) is the clinical triad of anemia, thrombocytopenia, and acute renal injury. The typical presentation of HUS appears following a diarrhea attack (1,2). Diarrhea is infectious, usually due to STEC.

aHUS is mostly related to noninfectious sources (3). The prevalence of aHUS in children is about 1.0 to 3.3 per million and is approximately 5-10% of HUS patients (3,4). aHUS is more frequently seen in adults (60%) than children (40%) and similar in boys and girls. More than 40% of children are present under age 2 and 25% under 6 months. aHUS may be sporadic or inherited with family members affected in 20% of childhood cases (4-6). Diarrhea or respiratory and gastrointestinal tract infections trigger complement activations. aHUS can range from mild hematologic presentations such as fatigue, and pallor to life-threatening end-organ injuries such as hypertension, acute kidney injury requiring dialysis, blindness, seizure, myocardial infarction, or gastrointestinal bleeding (7). Extrarenal manifestations are constant for up to 40% of patients and neurologic involvement is the most common (8,9). The pathogenesis of aHUS originates from genetic and acquired inadequacy of the AP. 60-70% of the aHUS patients have gene mutations in complement regulatory proteins (e.g. complement factor B (CFB), complement factor H (CFH), complement factor I (CFI), membrane cofactor protein (MCP), complement C3, thrombomodulin (THBD), diacylglycerol kinase-ε (DGKE), or CFH autoantibodies (5,7).

The defect of these regulatory proteins causes exaggerated and dysregulated complement activation and endothelial cell damage. Gene mutations are not identified in the rest 30-40% of patients (7,8).

Eculizumab is the only approved treatment for aHUS by the European Medicine Agency Summary of Product Characteristics (EU SmPC) and Food and Drug Administration (FDA) and the optimal duration of eculizumab therapy for complement blockade in aHUS has not yet been determined (10). It is a monoclonal anti-C5 antibody that stops the switch of C5 into C5 convertase and avoids the formation of C5a and C5b-9 (membrane attack complex-MAC), thus blocking the proinflammatory and prothrombotic effects of complement activation (11).

Here, we report the epidemiological features, clinical characteristics, and follow-up of eleven pediatric aHUS patients who were treated between July 2014 and May 2023 at our Pediatric Nephrology Department.

Methods

The epidemiological and laboratory data, clinical features, pathological findings, treatment, and prognosis of our 11 patients with available file information diagnosed with aHUS in our clinic were investigated retrospectively. Informed consent was obtained from all patients or their parents. This study was done after the approval of the local ethics committee (date: 03/02/2021, approval number: 20.478.486/744).

aHUS was identified as HUS triad (Coombs negative hemolytic anemia, thrombocytopenia, and acute renal injury) negative for Shiga-like toxin (Stx) producing E. Coli (STEC) (12). Stool culture and serologic tests for Stx-producing organisms were carried out for all individuals. The patients considered as thrombotic thrombocytopenic purpura (TTP) were excluded. Also patient with a coexisting disease or drug related aHUS was eliminated.

The Schwartz formula was performed to calculate the estimated glomerular filtration rate (eGFR) (13). Proteinuria was evaluated on spot urine protein to creatinine ratio (spot Uprot/Ucr). Acute kidney injury is determined as an elevation in baseline serum creatinine levels (sCr) according as stated by the pediatric RIFLE criteria (risk, serum creatinine × 1.5; damage, serum creatinine × 2; insufficiency, sCr×3) (14). Anemia is defined as hemoglobin (Hb)<10g/dL and thrombocytopenia is defined as platelet (PLT) levels less than <150 000/mm3.

Genetic study

Genetic testing was not a prerequisite for patient registration, if data is available it is noted. The genomic DNA was obtained in EDTA-anticoagulated venous peripheral blood by using an automatic DNA isolation method (Invitrogen Co. Paisley UK). Oligonucleotide primers specific to each exon and a Platinum Taq polymerase with enhancer buffer were used for PCR amplification for all coding exons of the CFH gene. PCR amplification was done using the Veriti thermal cycler. Enzymatic methods using Exo-SAP enzymes were used to purify the PCR products. Big Dye chemistry sequencing was performed after the purification of the PCR samples. Purified samples were analyzed on the ABI 3130XL Genetic Analyzer automated DNA Sequencing System. Nucleotide sequences and substitutions were analyzed by the SeqScape program and compared with Gene Bank sequences on the web pages of the National Center for Biotechnology Information (https://www.ncbi.nlm.nih.gov/).

All patients were given eculizumab according to the recommended regimen.

Results

This study included 11 aHUS patients in our pediatric nephrology department. Data from these children and their responses to therapy were retrospectively assessed. Five of our patients were male, and six were female. The mean age of patients at aHUS onset was 2.9±6 years. The mean follow-up period is 72±4 months. Demographical, clinical data, and treatment modalities are summarized in Table 1. All the patients had

Table 1. Demographical, clinical findings and treatment modalities of ten patients with aHUS

Parameters	Patients No.										
	1	2	3	4	5	6	7	8	9	10	11
Age at onset	$16^{5/12}$	0.6	0.9	$2^{6/12}$	0.6	$2^{2/12}$	$7^{3/12}$	$12^{2/12}$	$12^{3/12}$	$7^{5/12}$	4
Sex	Female	Female	Male	Male	Male	Female	Female	Male	Female	Male	Female
Consanguinity	No	No	No	Yes	Yes	No	No	No	No	No	No
Family history of aHUS	No	No	No	No	No	No	No	No	No	No	No
Presenting symptoms	Bloody diarrhea	Bloody diarrhea, vomiting, pallor	Diarrhea without blood, vomiting, pallor	Diarrhea without blood, vomiting, edema	Diarrhea without blood, vomiting,	Bloody diarrhea, edema	Bloody diarrhea	Bloody diarrhea, lethargy	Diarrhea without blood, vomiting, pallor	Diarrhea without blood, vomiting, pallor	Pallor, stomach ache, purpura of the legs
Oliguria/ Anuria	-	Oliguria (for 48 hr)	Anuria (for 24 hr)	Anuria (for 24 hr)	Anuria (for 48 hr)	Anuria (for 24 hr)	-	Anuria (for 48 hr)	-	Anuria (for 24 hr)	Oliguria (for 24 hr)
Hypertension	+	-	-	-	+	-	+	+	+	+	-
Neurologic involvement	+	-	-	-	-	-	-	+	-	-	-
Pulmonary involvement	-	-	-	+	-	-	-	+	-	-	-
Cardiac involvement	-	-	-	-	-	-	-	+	-	-	-
Gastrointestinal involvement	-	-	-	-	-	-	+	-	-	-	-
ICU stay (days)	21	5	27	20	27	9	2	23	10	12	6
Hospitalization (days)	64	17	35	29	37	21	28	23	41	37	23
Number of HD/PD (days)	-	10	18	20	10	10	9	16	-	3	-
Number of PE (days)	4	-	-	-	-	-	1	3	-	5	-

aHUS: atypical hemolytic uremic syndrome, hr hour, ICU intensive care units, HD hemodialysis, PD peritoneal dialysis, PE Plasma Exchange, PI plasma infusion

eculizumab treatment and no complications due to eculizumab or any relapses were detected. The median duration of eculizumab treatment was 60 months (18-96). We did not interrupt the eculizumab treatment of any of our patients.

6 of 11 (%54) patients (Patient no: 1,5,7,8,9,10) had hypertension during hospitalization, and neither of them needed anti-hypertensive treatment after discharge. Three of our patients had hypocomplementemia (Patient no:5,8,11). Extrarenal manifestations of aHUS were present in %36 of our patients. One of the patients had seizures. Two of the patients had respiratory insufficiency requiring mechanical ventilation (Patient no:4,8). Patient no: 8 needed a tracheostomy because of the long-term use of mechanical ventilation. He had a subarachnoid hemorrhage and multiorgan failure occurred and died on the 25th day of his intensive care unit hospitalization after 2 doses of eculizumab treatment.

Eight of the patients had renal replacement therapy (RRT). An average day of RRT was 12 days. Plasma infusion and/or plasma exchange and/or eculizumab treatments were given due to severe extrarenal manifestations, 4 patients had plasma exchange. All patients had eculizumab therapy. They had meningococcal vaccination and prophylaxis and no systemic complications related to eculizumab were observed. Full recovery of hematologic and renal functions was obtained in all patients except patient no: 8 (Table 2,3). Proteinuria disappeared, eGFR increased and complete neurologic recovery was performed after eculizumab therapy.

Genetic analysis was performed in seven of our patients. 4 of 8 of the patients had heterozygous CFH mutations (pGlu936Asp), and one patient had a homozygous CFH mutation (pHis402Tyr). Patients 6 and 9 were negative for disease-causing mutations of aHUS.

Discussion

The incidence of aHUS in children under 18 years of age is approximately 1.0 to 3.3 per million and it is related to defective regulation of the AP in %50-60 cases (4,14). aHUS is a life-threatening disease with a mortality or end-stage renal disease rate of 25% (15). RRT is required for renal failure in more than 50% of cases despite the cause (7,16). No direct diagnostic test for aHUS exists. Although it is a complement pathway disease, only 30% of aHUS patients have hypocomplementemia, and 50-60% of aHUS patients have complement gene variants (17,18). Herein, the long-term follow-up and safety of eculizumab treatment are reported in our aHUS patients. In this report, we have examined eleven patients with aHUS. The mean follow-up time was 70±4 months. Gastroenteritis was the most common precipitating factor in this study as earlier reports (7,17,19). This clearly shows that post-diarrheal onset does not rule out the possibility of aHUS also normal complement concentrations do not exclude complement-negative hemolytic uraemic syndrome. Similarly, diagnosis of the atypical hemolytic uraemic syndrome should not be

Table 2. Laboratory data of patients with aHUS

Parameters	Patients No.										
	1	2	3	4	5	6	7	8	9	10	11
Hb (g/ dL)	7.6	5	6.7	7.6	6.9	7.3	9.6	7.6	6.5	9.3	6.6
PLT ($x10^3$/mm3)	61	30	45	46	73	45	81	95	85	80	39
WBC ($x10^3$/mm3)	17.6	14.4	26.2	12.9	17	7.3	10.6	33.8	5.2	12	19.8
Schistocytes	+	+	+	+	+	+	+	+	+	+	+
Creatinine (mg/ dL)	1.6	2.7	4.2	4.3	3.7	6.1	4.9	3.1	0.5	3.1	1.59
LDH (IU/L)	822	2837	2958	1808	1738	2481	2085	2507	571	950	2765
AST (IU/L)	51	107	74	120	136	52	104	133	26	34	114
ALT (IU/L)	31	86	90	149	55	99	32	175	16	45	19
CRP (mg/L)	3,5	1	3	1.8	5.6	2.1	0.8	5.6	6.7	3.2	0.33
C3 (mg/dL)	142	110	114	112	70	86	97	62	71	80	65.9
C4 (mg/dL)	34	15	23	13.6	30	17	14	7.4	69	25	30
Albumin (mg/L)	2.6	2.3	2.5	2.6	3	2.3	3.4	2.5	3	3.8	3.7
eGFR (mL/min/1.73 m^2)	55.2	11.3	7.3	11.6	8	7.8	13.1	14	85	20	25
Proteinuria	-	+	+	+	+	+	+	+	+	+	+
ADAMTS-13 activity (%)	48	59	68	91	95.4	56.9	94	55.5	69	87	94
Genetic screening	CFH mut(+) pGlu936Asp hetero.	NA	CFH mut(+) pGlu936Asp hetero.	CFH mut(+) pGlu936Asp hetero.	CFH mut(+) pGlu936Asp hetero.	No mut.	NA	NA	No mut.	CFH mut(+) p.His402Tyr homozy.	NA

aHUS atypical hemolytic uremic syndrome, hr hour, ICU intensive care units, HD hemodialysis, PD peritoneal dialysis, PE Plasma Exchange, PI plasma infusion

Table 3. The last physical and laboratory evaluations of our patients

Parameters	Patient No.									
	1	2	3	4	5	6	7	9	10	11
Age at last follow-up visit	$23^{6/12}$	$5^{10/12}$	$10^{6/12}$	10	8	$8^{4/12}$	$11^{9/12}$	$16^{1/12}$	$13^{3/12}$	$5^{6/12}$
Hypertension	-	-	-	-	-	-	-	-	-	-
Hemoglobin (g/dL)	13.1	12.4	12.6	11.6	11.6	12.8	12.7	11.6	15.7	12.5
PLT ($x10^3$/mm3)	268	430	272	225	341	214	597	229	240	203
Creatinine (mg/dL)	0.55	0.19	0.38	0.32	0.28	0.37	0.43	0.43	0.8	0.31
LDH (IU/L)	219	277	316	234	273	245	256	224	173	226
eGFR (mg/min/1.73m^2)	142	123	129	161	118	116	126	110	117	127
Proteinuria	-	-	-	-	-	-	-	-	-	-

attributed to the revealing of complement gene variants, which are detected in only 40–60% of patients or less (16). A genetic diagnosis is not required but obviously would confirm the diagnosis of aHUS. This makes the distinction between typical HUS and aHUS even more difficult and may delay adequate treatment in these patients. Low levels of C3 may designate complement dysregulation in aHUS, but this is not an exact indication (15,18). We had three patients (27%) with low levels of C3.

73% of our patients required RRT during the first episode of aHUS with an average dialysis duration of 12 days. Ten of them have fully recovered. Patient no:8 died. It might be related to multiple extrarenal manifestations and the delay in eculizumab access of the patient.

In a nationwide French series, disease-causing mutations in genes encoding CFH, CFI, MCP, THBD, CFB, DGKE, and CFH autoantibodies have been presented in aHUS in 60-70% of the patients (17). All these changes lead to the overactivation of the alternative pathway (18). Patients with childhood presentation were significantly less likely to have complement factor I (CFI) and more likely to have MCP mutations. Complement factor B (CFB) mutations are the rarest mutations, whereas CFH and antiCFH antibodies mutations were the most common mutations seen in both pediatric and adult patients. Genotype determines the prognosis, with MCP mutations carrying the best prognosis (17,19-21). Mutations in CFH, CFI, or C3 all are related to poor outcomes. MCP gene mutation is related to a significantly earlier onset of the disease than CFH, CFI, or no identified mutation in the 2017 Turkish pediatric atypical hemolytic uremic syndrome registry (19). Frequent CFH mutations usually have poor outcomes, with recurrence rates of 50% and combined ESRD or mortality rates of 50% to 70% in a 273-patient Italian study (20). Most mutations were found in CFH (80%) in our study. CFH mutations were reported for 21% in the 2018 global aHUS registry (8), 56% for Turkish (19) and Indian (22), 29% for South Korean (23) pediatric aHUS cohorts, pGlu936Asp heterozygous mutation in CFH was detected in four of our patients. pGlu936Asp mutation was reported in the 2001 Italian series (24) and the 2004 German series (25). Our patients had complete

remission although CFH mutations have poor outcomes in the French series (17), Italian (24), and German registries (25). More studies are needed to explain the relationship between the genotype and phenotype of aHUS.

It is considered to stop eculizumab treatment to minimize the risk of adverse reactions and meningitis, reduce significant treatment costs, and improve the quality of life. But the risk of recurrence of atypical HUS after eculizumab discontinuation has been presented to be 20-30% (26). The relapse risk after discontinuation of eculizumab was the highest in patients with MCP and CFH variants (26,27). Eculizumab discontinuation seems safe after 6–12 months of treatment in patients with no documented mutations (27,28).

The main limitation of this study is its retrospective nature with a small sample size. Also, some data are missing, such as genetic mutations of some patients. Our study has several strengths. First of all, this study captures the progression of aHUS in a well-characterized pediatric population. It is a single-center study where the patients were followed up and managed by the same researchers.

Conclusion

Atypical hemolytic uremic syndrome is a very rare disorder seen in the pediatric age, thus, long-term outcomes are still controversial due to the small number of patients. Therefore, we demonstrated the long-term follow-up, safety, and efficacy of eculizumab treatment in our aHUS patients. Further studies are required to determine the optimal time for discontinuation of eculizumab treatment.

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