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Retrospective evaluation of patients with diagnosis of atypical hemolytic uremic syndrome: Single center experience

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Abstract

Aim: To evaluate the demographic, clinical, laboratory findings, genetic results and final status of patients followed-up with the diagnosis of atypical hemolytic uremic syndrome (aHUS)

Materials and Methods: Patients who were diagnosed and followed up in our pediatric nephrology center between January 2013 and June 2021 were included in the study retrospectively. Demographic data, history, age at diagnosis, physical examination, laboratory tests, organ involvement, genetic results, treatments, kidney replacement therapies, follow-up and final status were evaluated.

Results: A total of 14 patients, 9 girls (64.3%) and 5 boys (35.7%) were included in our study over a period of 8 years. The mean age at presentation was 66.7±54.1 months (5.5±4.5 years) and the follow-up period in our center was 50.7±37.1 months. Recurrence was detected in 4 patients (28.6%) 18.5±20.4 months after diagnosis. In six of our patients (42.8%) neurological involvement was detected; 5 (35.7%) had hypertensive features and 1 (7.1%) had disease involvement. *MCP (CD46)* mutation was detected in 4 patients (28.6%), *CFH* mutation in 3 patients (21.4%), and *CFHR1-CFHR3* mutation in 3 patients (21.4%). While a total of 4 patients (28.6%) died in our center, 10 patients (71.4%) are still being followed up and treated. From these patients one is followed up with fresh frozen plasma therapy and the rest with eculizumab therapy.

Conclusion: Eculizumab is found to be an effective therapy for patients with aHUS who did not respond to plasmaphresis and/or plasma treatment. We think that eculizumab treatment may be the first choice considering with detailed genetic analysis (including antifactor H antibody) in the light of future multicenter studies with larger of patients.

Introduction

Atypical hemolytic uremic syndrome (aHUS) is a syndrome caused by a heterogeneous group of diseases characterized by hemolytic anemia, acute kidney injury and thrombocytopenia. The etiology of atypical hemolytic uremic syndrome is related to factors that cause dysregulation of the complement system [1]. Genetic mutations in complement regulatory proteins (complement factor H (*CFH*), complement factor I (*CFI*), membrane co-factor protein ie *MCP* (*CD46*) or *CFH-CFHR* hybrid genomic regulators) and complement 3 convertase (*C3* and *CFB*) in the alternative complement pathway mutations or anti-complement factor H antibodies are detected in approximately 60-70% of aHUS patients. In addition recent studies also showed that diacylglycerol kinase-ε (*DGKE*), thrombomodulin (*THBD, CD141*) mutations could be the cause of aHUS [2]. Although mortality is higher in children than adults, it has been reported that after the first episode chronic renal failure is detected at a higher rate in adults than in children [3].

It is reported that recurrence is common and the clinical course is poor in individuals with a family history or the relationship between genetic backgrounds but it is still being investigated genotype phenotype relations in disease [4]. Researchers think that the underlying genetic abnormalities of patients from different ethnic origins may be different and aHUS characteristics may differ in patient populations [4]. Although plasma infusion or plasmapheresis has been used in the treatment of the disease in the past, the availability of a monoclonal antibody eculizumab, has enabled the drug to be used as the first choice of treatment in some countries. However discussions about treatment duration and intervals continue [2].

The incidence of atypical hemolytic uremic syndrome is low but it causes mortality and serious morbidities. Ge-

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netic transmission is important in the onset of the disease. It is known that consanguineous marriages are common in our region. For this reason we planned this study to reveal the clinical and demographic characteristics of our aHUS patients and to review the genetic outcome, clinical course, treatments and the final status of the patients.

Materials and Methods

Pediatric patients diagnosed and followed up in our center between January 2013 and June 2021 was included in the study retrospectively. Exclusion criterias were; patients with *Escherichia coli*, *Shigella dysenteriae*-associated Shiga toxin positivity detected by stool culture, patients with hemolytic uremic syndrome due to systemic disease or drug-related conditions and patients with low level (<5%) activitiy for ADAMTS13 (a disintegrin and metalloprotease with thrombospondin type 1 repeats, member 13) [5]. Atypical hemolitic uremic patients with microangiopathic hemolytic anemia, thrombocytopenia and acute kidney injury with recurrent attacks with a history of sibling or sibling death with the same diagnosis or with a genetic mutation were included in the study [6,7].

All data from patients' files; age at diagnosis, gender, family history, presence of family members with a similar history, presence of complaints such as fever, pallor, oliguria, diarrhea, vomiting, jaundice, edema, physical examination findings, central nervous system and/or other organ involvements, requirement of intensive care, mechanical ventilation and inotropic drugs, treatments such as fresh frozen plasma, plasmapheresis, and kidney replacement treatments were noted. From laboratory findings, hemogram parameters hemoglobin (g/dl), hematocrit (%), white blood cell count (x10^3/µL), platelet count (x10^3/µL), serum creatinine (mg/dl), urea (mg/dl), uric acid (mg/dl), lactate dehydrogenase (mg/dl), aspartate aminotransferase (U/L), alanine aminotransferase (U/L), albumin (g/dl), C3 (g/L) and C4 (g/L), reticulocyte levels (%), urinalysis (proteinuria, hematuria), the duration of follow-up time, survival, final status, evaluation of kidney functions and proteinuria, treatments and genetic analysis reports were recorded.

Patients' glomerular filtration rates (eGFR) were calculated using the modified Schwartz formula [8]. Acute kidney injury was defined on increase in basal serum creatinine levels according to the RIFLE criteria (risk; serum creatinine x1.5, damage; serum creatinine x2 and insufficiency; determined by serum creatinine x3) [9]. Hypertension was defined as blood pressure above the 95th percentile on three measurements or the need for antihypertensive medication [10]. Oliguria was defined as daily urine output of less than 0.5 ml/kg/hr and proteinuria as a spot urine protein/creatinine ratio of ≥0.2 mg/mg or above 4 mg/m^2/hr [11]. Complete remission was defined as hemoglobin >10 g/dL, platelet count >150×10^3/µl/L and lactate dehydrogenase below 290 U/L< and normal kidney functions for age. After remisssion if relapse occurs in four weeks and/or later time it was defined as recurrence [12]. Patients with eGFR < 15 mL/min/1.73 m^2 at follow-up or patients requiring dialysis for longer than 3 months were defined as chronic kidney disease (CKD) stage 5 [13].

Plasmapheresis was performed daily in the first 5 days of treatment (x1.5 volume) and then continued every other day while eculizumab treatment was started in cases who did not respond to treatment. Before the eculizumab treatment vaccination and antibiotic prophylaxis were given and the drug treatment dose was given according to the weight of the patient with the approval of the health ministry. Genetic analyzes were performed for *MCP* (*CD46*), *C3, CFB, CFH, CFI, DGKE, CD141, CFHR1-CFHR3* mutations with Sanger sequence analysis.

Ethics committee approval of the study was obtained from Gaziantep University Clinical Research Ethics Committee (2021/206). A pre-study power analysis based on previous data determined a sample size of at least 14 patients to reach the desired power of > 0.8. The incidence of aHUS per million inhabitants was the primary outcome measure for propotional power analysis [14,15].

Statistical analysis

Statistical analysis was performed using the IBM SPSS Statistics for Windows, Version 23.0. (SPSS Inc., Chicago, 103 IL, USA; IBM Corp.) was used for data analysis. All patients with the diagnosis aHUS as the time period mentioned above were included in this study. Kolmogorov–Smirnov test was used for evaluating data distribution. Descriptive statistics were presented as number of observations and percentage (%). Parametric data was expressed as mean±standard deviation (SD) and nonparametric data as median (minimum-maximum).

Results

A total of 14 patients, 9 girls (64.3%) and 5 boys (35.7%) were included in our study over a period of 8 years. The mean age of the patients at admission was 66.7±54.1 months (5.5±4.5 years) and the duration of follow-up period was 50.7±37.1 months. The clinical and laboratory findings of the patients are summarized in Table 1. At the time of admission patients complaints were as follows; 9 patients (64.3%) had edema, 8 patients (57.1%) had oliguria ,7 patients (50%) had vomiting, 4 patients (28.6%) had diarrhea, 3 patients (21.4%) had fever, 2 patients (14.3%) had pallor and 1 patient (7.1%) had jaundice. Two patients had a history of sibling death due to the same disease and one of these patients died due to sepsis while being followed up with CKD stage 5 (Table 2-patient number 6) and the other patient died during our follow-up (Table 2- patient number 2). Two sibling patients with the same mutation are still under follow-up in our center (Table 2-patient numbers 5 and 11- family number 1). When laboratory findings were evaluated, the mean hemoglobin was 7.9±1.8 (gr/dl), the mean hematocrit was 23.5±6.0 (%), the mean white blood cell count was 13.83±8.58 (10^3/µl, the mean platelet count was 76±33 (10^3/µl), the mean creatinine was 2.9±1.9 (mg/dl), the mean albumin was 3±0.41 (mgr/dl) and the mean lactate dehydrogenase was (LDH) 2093±1037 (U/L). Reticulocytosis and low haptoglobulin levels were detected in all patients. High levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT) and bilirubin were found in 9 patients

Table 1. Clinical and laboratory results of patients.

Features of patients	Number of patients	Rate (%)
Female/Male	9/5	64.3/35.7
Consanguinity of parents Yes/No	12/2	85.7/14.3
Familial history of the same disease Yes/No	4/10	28.6/71.4
Clinical findings		
Edema	9	64.3
Oliguria	8	57.1
Vomiting	7	50
Diarrhea	4	28.6
Fever	3	21.4
Anemia	14	100
Thrombocytopenia	14	100
Acute kidney injury	14	100
Requirement of dialysis	11	78.6
Hypertension	11	78.6
Requirement of inotrop drugs	3	21.4
Requirement of intensive care unit	9	64.3
Requirement of mechanical ventilation	4	28.6
Central nervous system findings		
None	8	57.2
Hypertensive alterations	5	35.7
Involvement of primary disease	1	7.1
Low level of compleman 3 (C3)	9	64.3
Presence of recurrence	4	28.6
Final status		
Exitus	4	28.6
Follow-up patients	10	71.4

(64.3%) and high level of C-reactive protein was found 8 patients (57.1%). In 9 patients (64.3%) low level of C3 and in 3 patients (21.4%) low level of C4 were detected.

Recurrence was observed 18.5±20.4 months after diagnosis in four patients (28.6%) (Table 2- patient numbers 1,10,12,13). The general characteristics of the patients with recurrence are given in table 3. Growth retardation was detected in 1 patient (7.1%), proteinuria in 3 patients (21.4%) and CKD stage 5 in 1 patient (7.1%). Three patients had proteinuria. One of them was patient number 10 who died due to sepsis when he did not come for follow-up, the other patient was patient number 6 who died due to sepsis while being followed up with CKD stage 5, and the last one was patient number 13 who had nephritic level proteinuria and still had normal kidney function with eculizumab.

Among the patients with recurrence; Patient number 1 had recurrence 45 months after diagnosis and this patient is being followed up monthly with fresh frozen plasma therapy. Patient number 10 had recurrence 24 months after diagnosis who did not come for follow-up and did not receive any treatment. Patient number 12 had recurrence after one month while the patient was receiving fresh frozen plasma with complete remission. Patient number 13 had recurrence 4 months after diagnosis because of a 2-month delay in eculizumab treatment. Patient numbers 1, 12, and 13 were being still followed in complete remission with eculizumab treatment while patient number 10 died due to sepsis (Table 2). The characteristics of patients with recurrence are given in Table 3.

Among all patients 4 patients (28.6%) died and 10 patients (71.4%) are still being followed up and treated in our center. Age, follow-up periods, genetic analysis results, treatments and final status of the 14 patients are summarized in Table 2. The genetic tests of 3 patients who were died during the follow-up period could not be performed. The mutations detected in the genetic analysis reports of the other 11 patients are given in Table 2.

Discussion

Atypical hemolytic syndrome usually occurs after gastroenteritis or an upper respiratory tract infection [16]. It is known that infectious diseases are more common in childhood than in adults. For this reason aHUS has a more critical importance in patients in the age group from newborn period to the age of 2 years. In the Turkish aHUS registry 36% of all aHUS patients were diagnosed before the age of two [12]. In a study of aHUS involving two hundred and fourteen patients it was reported that 58% of the patients were diagnosed in adulthood [3]. Although it is known that it is more likely to be seen in the childhood age group, the number of patients diagnosed in adulthood is quite high. The age of the patients included in the Turkish aHUS registry system was 4.82±4.4 years at the time of diagnosis [2]. Similarly in our study the age of the patients at admission was 5.5±4.5 years. In our study the number of patients diagnosed less than 2 years of age was 4.

In terms of gender, it has been reported that the first episode of aHUS in childhood is more common in boys (56%) [17]. When considering the adulthood period it has been reported that aHUS is more common in women than men because pregnancy is accepted to be an important triggering factor for aHUS [18]. In the Turkish aHUS registry system which included 146 patients sent from 26 pediatric nephrology centers, it was reported that the number of female patients (84 female patients) was higher than the number of male patients [2]. Similarly we found a higher number of female patients in our study.

Neurological involvement is the most important mortality and morbidity of extra-renal involvement that can be seen in 20-50% patients with atypical hemolytic uremic syndrome [19]. Neurological symptoms ranging from irritability to coma may occur due to cerebral microangiopathy, cerebral edema or the delay in treatment. Activation of complement cascade and C5a formation play an important role in the appearance of central nervous system findings [20]. Central nervous system lesions can be visualized by computed tomography (CT) and magnetic resonance (MR) imaging as bilateral symmetrical thalamus

Table 2. Treatments, final status and genetic analysis of patients.

Number	Gender	Age at diagnosis (month)	Follow-up duration (month)	PH	FN	FFP	KRT	Eculizumab	CKD stage 5	Recurrence	Treatment	Final status	Genetic analysis
1	F	87	109	+	1	+	-	+	-	+	Eculizumab	Follow-up	*CFH* c.307 C>T heterozygous
2	F	28	5	+	2	+	+	-	-	-	-	Exitus	Not performed
3	F	66	100	+	3	+	+	+	-	-	Eculizumab	Follow-up	*CFH* c.921 A>C heterozygous
4	M	20	40	+	4	-	+	+	-	-	Eculizumab	Follow-up	*CFH* c.1204 C>T heterozygous, *CFH* c.3148 A>T heterozygous
5	M	34	26	+	5	-	+	+	-	-	Eculizumab	Follow-up	*CD46* c.565 T>G homozygous
6	M	9	39	+	6	-	+	+	+	-	Eculizumab	Exitus	No mutation
7	F	120	51	+	7	-	+	+	-	-	Eculizumab	Follow-up	*CFHR1/CFHR3* total gene deletion
8	F	51	48	+	8	-	+	+	-	-	Eculizumab	Follow-up	*CFHR1/CFHR3* total gene deletion
9	F	166	2	+	9	-	+	+	-	-	-	Exitus	Not performed
10	M	150	40	+	10	+	+	+	-	+	-	Exitus	Not performed
11	F	72	122	+	5	+	+	-	-	-	FFP	Follow-up	*CD46* c.565 T>G homozygous
12	M	11	17	-	11	+	-	+	-	+	Eculizumab	Follow-up	*CD46* c.565 T>G homozygous
13	F	117	70	+	12	-	+	+	-	+	Eculizumab	Follow-up	*CD46* c.565T>G homozygous
14	F	3	42	-	13	+	-	+	-	-	Eculizumab	Follow-up	*CFHR1/CFHR3* total gene deletion

F: Female; M: Male; PH: Plasmapheresis; FFP: Fresh frozen plasma; KRT: Kidney replacement therapy; CKD: Chronic kidney disease; FN:Family number.

Table 3. The characteristics of patients with recurrence.

Number	Gender	Age at diagnosis (month)	Recurrence (after the time of diagnosis-month)	Follow-up duration (month)	Low level of C3	Neurological involvement	CKD stage 5	Recurrence	Treatment	Final status
1	F	87	45	109	-	+	-	+	Eculizumab	Follow-up
2 (Patient number 10)	M	150	24	40	-	-	-	+	-	Exitus
3 (Patient number 12)	M	11	1	17	+	+	-	+	Eculizumab	Follow-up
4 (Patient number 13)	F	117	70	4	+	+	-	+	Eculizumab	Follow-up

and white matter involvement or as hypertensive posterior reversible encephalopathy (PRESS) [21]. We also performed cranial CT and cranial MR in 6 patients (42.8%) with neurological findings. Of these patients one (7.1%) had disease involvement, five (35.7%) had hypertensive changes. Neurological involvement rate (42.8%) in our

study was similar to the literature [1]. While 2 patients with severe hypertensive findings with coma died, the remaining 4 patients completely recovered during the treatment process.

Low level of C3 is seen in one third of aHUS cases which indicates dysregulation in the complement cascade but it is not necessary for diagnosis of aHUS [3]. Different rates have been reported in the literature on the presence of low level C3 in atypical hemolytic uremic syndrome. In the study conducted by Conkar et al., which included 19 patients, low C3 level was found to be 10.5%, while in the study of 15 patients by Baskin et al., low C3 level was found to be 50% [1,4]. In a large study including the Turkish aHUS registry system, hypocomplementemia was found 48.5% of the cases [2]. In a study conducted in our country, which included aHUS patients under 2 years of age the rate was reported as 57% [12]. Štolbová Š et al. reported low C3 levels in 71% of 21 pediatric aHUS patients [14]. Similar to this study, we found low C3 level in 9 patients 64.3%.

Complement dysregulation at cellular level is the main mechanism causing aHUS and approximately 20% of cases are familial cases. Although sporadic cases are more common but genetic transmission is still very important in the disease. Familial HUS is defined as the diagnosis of aHUS in at least two family members within six months. In atypical hemolytic syndrome the inheritance may be as follows; autosomal dominant, autosomal recessive, pathogenic variants in a single gene or rarely polygenic [22]. While *CFH* and *MCP* (*CD46*) mutations are generally detected in familial cases, *CFI* and *C3* mutations are less common [4]. In our study, there are two siblings with same genetic mutation (patient numbers 5 and 11) who are still being followed and two of our patients who died at the time of diagnosis in our center had a history of sibling death with the same diagnosis. While no mutation was detected in one of the deceased patient, genetic analysis could not be performed in the other. Membrane co-factor protein (*MCP*, *CD46*) mutation was detected in two siblings who are still under follow-up.

Recurrence has been reported in some cases of atypical hemolytic uremic syndrome. It is recommended that all cases be followed carefully, especially in the first year after the disease. In a study by Fremaux Bacchi et al., it was reported that the recurrence rate decreased to 25% after 1 year, except for pediatric patients with *MCP(CD46)* mutation. The recurrence rate was reported as 40% in this study [3]. Therefore the therapeutic strategy must be as a reduction in treatment instead of sudden interruption. In addition the determination of mutations will be useful to confirm the diagnosis of complement-mediated aHUS, to determine the prognosis and to determine the treatment plan for prevention of recurrence before kidney transplantation in patients with CKD stage 5 [3]. We also conducted a genetic analysis study in patients with or without recurrence but genetic studies could not be performed in 3 patients who did not come for follow-up. In our study recurrence was detected in 4 patients. While *MCP(CD46)* mutation was detected in two patients, *CFH* was detected in one of these patients unfortunately genetic study could not be performed in one patient. Disease causing mutations are generally heterozygous which detected in 44-60% of all cases and of which approximately 30% are *CFH* mutations [3,16].

Genetic mutations of our patients were as follows; *MCP*(*CD46*) mutations were detected in 4 patients (28.6%), *CFH* mutations in 3 patients (21.4%) and *CFHR1-CFHR3* mutations in 3 patients (21.4%). Membrane co-factor protein (16.3%) and *C3* (11.4%) mutations are the most frequently detected mutations in patients in the Turkish aHUS registry [2]. Similarly *MCP*(*CD46*) mutation (28.6%) was the most common mutation in our study. While the group with the lowest recurrence rate after kidney transplantation in patients with chronic renal failure is *MCP*(*CD46*) mutations, this rate is reported to be 90% in patients with *CFH* mutations [14]. In a study by Bresin et al., it was determined that the combined variants may have a potential role in the development of aHUS due to the possible low pathogenicity of *MCP(CD46)* and CFI variants [23]. In the study of Štolbová Š et al., *MCP(CD46)* mutation was detected in 3 patients without other variant carriers [14]. In our study *MCP(CD46)* homozygous mutation was detected in 4 patients. There were no other variant mutations in the genetic analysis results. While recurrences were detected in two of these patients one patient is being followed up with fresh frozen plasma infusion and the other 3 patients are being followed up with eculizumab treatment. All have normal kidney functions.

Complement factor H mutations generally have a poor prognosis. Chronic renal failure and mortality rates are 50-70%, while the recurrence rate is 50% [4]. While recurrence was detected in one of our 3 patients with complement factor H mutation, no recurrence was observed in the other two patients. All of these patients are receiving eculizumab treatment and are followed up with normal kidney functions.

It is accepted that homozygous *CFHR1-CFHR3* mutation is significant only in the presence of anti-factor H. The *CFHR1–CFHR3* deletion in the absence of anti-factor H antibody is not considered as a pathogenic variant [24]. Detection of the anti-factor H mutation, which plays an important role in the etiopathogenesis of atypical hemolytic uremic syndrome, is very important because the treatment options include plasma exchange, immunosuppressive therapy, and rituximab [25]. In the study by Palma et al., *CFHR1-CFHR3* homozygous mutation was detected in 2 patients, but anti-factor H antibody could not be performed. Recurrence was detected after eculizumab treatment was stopped in one patient and proteinuria and hypertension were detected in the other patient during the period when the eculizumab dose should be increased but it was determined that the patients responded well to eculizumab treatment. It has been recommended in the study to check anti-factor H antibody as soon as possible [24]. We could not look for anti-factor H antibodies in our study, but we obtained a good response to eculizumab treatment in 3 of our patients.

Eculizumab, which binds C5 in the terminal complement pathway, has been used since 2011. The safety and efficacy of the drug in children has been proven by case reports and clinical trials [2,12]. Although there are stud-

ies recommending the use of the drug as first-line [1], the European pediatric hemolytic uremic syndrome working group in 2014 recommends plasma therapy as first-line therapy [26]. In addition, in the study of Beşbaş et al. including patients with aHUS from our country, it is seen that plasma therapy and/or plasma exchange are still a valid option for our country [2]. In our study plasma exchange and/or plasma infusion was performed as the first line therapy and eculizumab was started in patients who did not respond or had a delay in response. There was no serious problem in the follow-up of any of the patients with eculizumab treatment and 9 patients are still on eculizumab. Only one patient is followed up with fresh frozen plasma infusion. There are studies on the safety of eculizumab treatment and the continuation of the treatment period. In a study of 93 patients by Menne et al. 42 patients (45%) discontinued treatment at follow-up. It has been reported that recurrences are more common especially in patients with a history of recurrence and/or genetic or auto-immune complement abnormalities before eculizumab therapy was started. In addition, only 3 patients in this study had proven meningococcal infection that had completely resolved with treatment [27]. In our study any serious infection was not detected in 9 patients receiving eculizumab treatment and all patients were followed up with normal kidney functions.

Our study is with limitations such as retrospective methodology, small sample size of patients and also the lack of long-term renal outcomes.

Conclusion

In conclusion we wanted to present our patients who were diagnosed with aHUS in a period of eculizumab availability in our country. It is seen once again in our study that family history is valuable. Patients with aHUS should be followed-up regularly due to high recurrence rate. We think that testing anti-factor H antibody in patients with *CFHR1-CFHR3* mutations is important. Satisfactory results were obtained with eculizumab treatment who did not respond to plasmapheresis and/or plasma infusion therapy We think that eculizumab treatment may be the first choice based with detailed genetic analysis (including antifactor H antibody) in the light of future multicenter studies with larger numbers of patients. There is a necessity of clinical trials on the effectiveness of the drug, its long-term results, the optimal duration of treatment.

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Ethics approval

Ethics committee approval of the study was obtained from Gaziantep University Clinical Research Ethics Committee (2021/206).

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