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ORIGINAL ARTICLE

# Adolescence-onset atypical hemolytic uremic syndrome: is it different from infant-onset?

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## Abstract

**Background** Atypical hemolytic uremic syndrome (aHUS) is a rare, mostly complement-mediated thrombotic microangiopathy. The majority of patients are infants. In contrast to infantile-onset aHUS, the clinical and genetic characteristics of adolescence-onset aHUS have not been sufficiently addressed to date.

**Methods** A total of 28 patients (21 girls, 7 boys) who were diagnosed as aHUS between the ages of ≥10 years and <18 years were included in this study. All available data in the Turkish Pediatric aHUS registry were collected and analyzed.

**Results** The mean age at diagnosis was 12.8±2.3 years. Extra-renal involvement was noted in 13 patients (46.4%); neurological involvement was the most common (32%). A total of 21 patients (75%) required kidney replacement therapy. Five patients (17.8%) received only plasma therapy and 23 (82%) of the patients received eculizumab. Hematologic remission and renal remission were achieved in 25 (89.3%) and 17 (60.7%) of the patients, respectively. Compared with the infantile-onset aHUS patients, adolescent patients had a lower complete remission rate during the first episode ($p = 0.002$). Genetic analyses were performed in all and a genetic variant was detected in 39.3% of the patients. The mean follow-up duration was 4.9±2.6 years. At the last visit, adolescent patients had lower eGFR levels ($p = 0.03$) and higher rates of chronic kidney disease stage 5 when compared to infantile-onset aHUS patients ($p = 0.04$).

**Conclusions** Adolescence-onset aHUS is a rare disease but tends to cause more permanent renal dysfunction than infantile-onset aHUS. These results may modify the management approaches in these patients.

**Keywords** Atypical hemolytic uremic syndrome · Adolescence · Genetics · Complement · Turkish aHUS registry

## Introduction

Atypical hemolytic uremic syndrome (aHUS) is a rare, life-threatening systemic disease generally resulting from dysregulation of the alternative complement system. Previous studies reported genetic and/or autoimmune abnormalities causing complement dysregulation in 45–70% of aHUS patients [1–3]. Loss of function mutations in complement regulatory genes [complement factor H (*CFH*), complement factor I (*CFI*), membrane cofactor protein (*MCP/CD46*), *CFH-CFH*-related proteins (*CFH-CFHR* genomic rearrangements), thrombomodulin (*THBD/CD141*)], gain of function mutations of complement activator proteins [complement factor B (*CFB*), complement 3 (*C3*)], and anti-CFH antibodies are identified genetic or acquired abnormalities that cause over-activation of the alternative complement system, formation of C5b-9/membrane attack complex on endothelial cells, and thereby endothelial damage [4]. Diacylglycerol kinase ε (*DGKE*), plasminogen (*PLG*), and recently identified tRNA splicing endonuclease 2 (*TSEN2*) mutations also cause aHUS independent of complement system [5, 6]. Eculizumab and the recently introduced long-acting form of C5 blocking agent, ravulizumab, are effective FDA-approved, complement-blocking humanized monoclonal antibodies for aHUS in all age groups [7].

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aHUS can occur in both children and adults at any age. In different aHUS registry studies that included patients from all age groups, approximately 60% of the patients were adults and 40% were children [1, 3, 8]. Half of the pediatric patients participating in these studies were under 2 years of age [3, 8, 9]. Previous studies have shown that there are differences in terms of gender, genetics, and long-term outcome between pediatric and adult-onset patients [1, 3]. In the literature, information regarding patients with aHUS occurred firstly in the adolescence period, which constitutes approximately 6.5–11% of the aHUS group, are limited [8–10]. In large registry studies, *CFH* and *CD46* mutations were reported as the most commonly identified aHUS mutations during childhood. However, anti-CFH antibodies were more frequently reported as the cause of aHUS in adolescents, and *CFI* mutations were more commonly associated with older age cases [1, 3]. Our clinical observations as well as the available limited data in the literature suggest that the characteristics of aHUS triggered during adolescence, which is the transition period from early childhood to adulthood, may differ from both infantile and adult-onset aHUS. However, to the best of our knowledge, there is no study in the literature that focuses specifically on adolescence-onset aHUS to date. We therefore conducted a multicentric, nationwide study to better define clinical, genetic, and prognostic features of aHUS occurred in adolescents. Our study also includes a comparative analysis with infantile onset cases from our registry to gain more insight of the condition across different age groups.

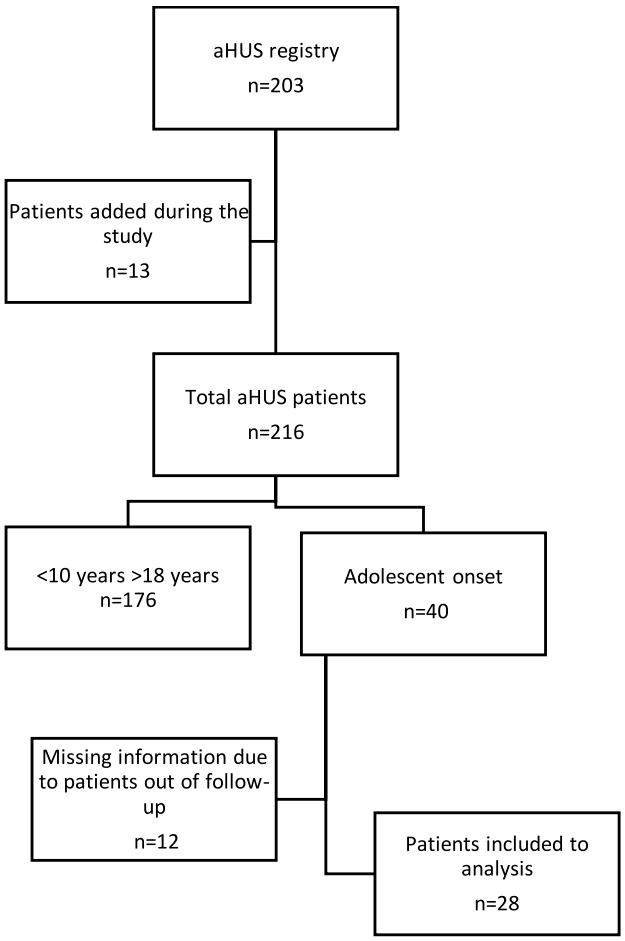


**Figure 1** The distribution of the patients in this study

## Materials and methods

### Definitions and data collection

The Turkish Pediatric aHUS registry is a web-based national registry system established in November 2013 that collects data on both retrospective and prospective pediatric aHUS patients (www.ahusnet.org). The details and objectives of the Turkish Pediatric aHUS registry have been reported previously [9, 11]. Patients with adolescent onset aHUS who were recorded between November 2013 and January 2022 and were followed for more than 3 months were selected from this registry. As the World Health Organization defines the adolescence as the period between 10 and 19 years of age [12], we included all data of those patients whose age of diagnosis was ≥10 and <18 years and who did not have previous aHUS history (Figure 1). A written informed consent was provided by the patients and/or parents. This study was approved by the Hacettepe University Ethics Committee (2019/02-18).

The triad of aHUS was defined as microangiopathic hemolytic anemia (i.e., hemoglobin level <10 gr/dL, negative direct Coombs test, presence of schistocytes, and fragmented erythrocytes in peripheral blood smear), thrombocytopenia (< 150.000/mm$^3$), and acute kidney injury (AKI). AKI was defined according to the Kidney Disease Improving Global Outcomes (KDIGO) serum creatinine criteria [13]. The baseline plasma creatinine level was defined as the lowest level in the 3 months before admission. When the baseline plasma creatinine level was unavailable, the estimated GFR (eGFR) was assumed to be 120 mL/min/1.73m$^2$, as validated previously [14]. Oliguria was defined as daily mean urine output less than 1 mL/kg/h for more than 4-h period; anuria was defined as complete absence of urine production [15, 16]. HUS cases with secondary causes (i.e., Shiga-toxin-producing *Escherichia coli* infection and other infections, drugs, autoimmune disorders, bone marrow or solid organ transplantation, or cobalamin C deficiency) and those with ≤ 10% of ADAMTS13 activity were excluded [17]. Extra-renal system involvements such as central nervous system, gastrointestinal system, cardiovascular system, respiratory system were recorded. If available, kidney biopsy results that were performed in the acute phase

with the primary physician's decision to confirm the diagnosis were also recorded. Anti-CFH antibodies were analyzed by using Human Complement Factor H Antibody (CFH-ab) ELISA Kit (YLbiont, Shanghai, China), in the Gazi University Nephrology Laboratory. The assay was performed according to the manufacturer's recommendations, with a detection limit of 6000 pg/mL. The anti-CFH antibody result of one patient, which was published in our group's previous study [9], was analyzed using the CFH IgG ELISA Kit (Abnova™) according to the manufacturer's recommendations, with a detection limit of 0.6 AU/mL.

The patients were categorized into three groups based on the treatment regimens they received: (1) Those who received only plasma, (2) Those who received initial plasma but did not respond adequately and subsequently were started eculizumab (plasma + eculizumab), and (3) those who were initially started on eculizumab as the first-choice treatment. The treatment choices were made by the primary physician. All clinicians had used the same eculizumab dosage regimen [18].

Response to different treatment choices was evaluated in terms of acute and long-term outcomes (>3 months). In the acute episode, assessments included hematologic remission, renal remission, and complete remission. Hematologic remission was defined as normalization of hemoglobin (>10 gr/dL), platelet count (≥150.000/$mm^3$), and lactate dehydrogenase (LDH) (≤ upper normal limit of the laboratory) with cessation of hemolysis. Renal remission was defined as the normalization of eGFR( >90 mL/min/1.73 $m^2$) according to the modified Schwartz formula [19]. Complete remission was defined as achieving hematological and renal remission (including no/trace proteinuria via urine dipstick test or a random urine protein to creatinine ratio (UPCR) ≤0.5 mg/mg). Long-term outcomes included patients' eGFR levels, the presence of proteinuria (i.e., ≥1+ via urine dipstick test or a random urine protein to creatinine ratio (UPCR) ≥0.5 mg/mg), hypertension, and the need for dialysis at their last visit. Chronic kidney disease staging was conducted in accordance with the KDOQI Clinical Practice Guidelines for Chronic Kidney Disease [20]. Hypertension was defined according to 2016 European Hypertension Guidelines for children and adolescents [21]. A new episode after 4 weeks of aHUS was defined as aHUS recurrence [2, 11]. The outcome of the patients was compared with the infantile-onset aHUS patients of the same registry [11].

### Genetic analysis

Genetic analyses were performed at the Hacettepe University Nephrogenetics Laboratory. All patients were run with a gene panel containing the relevant complement system genes (i.e., complement *C3*, *CFH*, *CFB*, *CFI*, *CD46*, *CFHR1,2,3,4,5*) as well as other relevant genes (i.e., *THBD, PLG,* and *DGKE*) via next-generation sequencing method using Ion S5 System® (Thermo Fisher Scientific) according to the manufacturer's recommendations. All variants that deemed pathogenic were confirmed by Sanger sequencing. *CFHR1-3* deletion was also evaluated via multiplex ligation-dependent probe amplification (MLPA).

### Statistical analysis

The analysis of data was performed by IBM SPSS statistics for Windows version 22. Baseline demographics and the clinical features of the cases were summarized by using descriptive statistical methods as mean ± standard deviation or median (interquartile range (IQR, 25–75p). Frequency tables were used to demonstrate the categorical data. GraphPad PRISM version 8.0 was used to compare current data with published data results. Unpaired *t*-tests were used to compare the mean values of parametric data. Fisher exact test was performed to compare the categorical results of groups. A $p$ value less than 0.05 was considered as statistically significant.

## Results

### Patient characteristics

A total of 28 patients (21 girls, 7 boys) from 16 pediatric nephrology centers were included in this study. The mean age at the time of aHUS diagnosis was 12.8±2.3 years. Extra-renal involvement was observed in 13 patients (46.4%) and central nervous system involvement was the most common one ($n = 9$, 32%). Demographic and clinical characteristics of the patients are presented in Table 1.

### Initial treatment

As a first-line therapy, 20 patients (71.4%) were treated with plasma-based therapy. While 5 patients (25%) received only plasma-based therapy, 15 patients (75%) received both plasma-based therapy and eculizumab (Table 2). A summary of the patients' treatments and their responses is presented in Supplementary Figure 1.

Hematologic remission and renal remission were achieved in 4 (80%) and 3 (60%) of the patients receiving only plasma-based therapy, respectively. One of them achieved complete remission. All five patients who received plasma-based therapy alone required renal replacement therapy (CRT) during their hospital stay, and one of them was discharged on dialysis. The mean dialysis time was 13±10.5 days, and the mean eGFR at the last visit of the patients whose dialysis treatment was discontinued was 117.6±26 2 mL/min/1.73$m^2$.

**Table 1** Demographic and clinical characteristics of the patients during the first aHUS episode

| Parameters | |
|---|---|
| Age at diagnosis, (years), (mean± SD) | 12.8±2.3 |
| Parental consanguinity, *n* (%) | 12 (42.8) |
| Triggering event, *n* (%)[a] | 11 (39.3) |
| Diarrhea | 6 (21.4) |
| Respiratory infection | 6 (21.4) |
| Extra-renal involvement, *n* (%) | 13 (46.4) |
| Central nervous system | 9 (32) |
| Seizure | 8 (28.5) |
| Loss of vision | 1 (3.6) |
| Cardiac | 6 (21.4) |
| Hearth failure | 4 (14.3) |
| Dilated cardiomyopathy[b] | 2 (7.1) |
| Gastrointestinal | 3 (10.7) |
| Abdominal pain | 2 (7.1) |
| Gastrointestinal bleeding | 1 (3.6) |
| Urine output, *n* (%) | |
| Oliguria | 16 (57.1) |
| Anuria | 7 (25) |
| Normal | 5 (17.9) |
| Duration of oliguria (days) (median) (IQR) | 7 (4-30) |
| Duration of anuria (days) (median) (IQR) | 7.5 (2.5–37.5) |
| Hemoglobin (g/dL), (mean±SD) | 7.8±1.4 |
| Platelet count ($10^9$/L) (median) (IQR) | 69.5 (38.5–92.0) |
| LDH (IU/L) (median) (IQR) | 1313 (784–1946) |
| Complete triad[c] | 25 (89.3) |
| Decreased C3 levels, *n* (%) | 11 (39.3) |
| Kidney biopsy, *n* (%) | 14 (50) |
| TMA | 11 (39.2) |
| FSGS+TMA | 2 (7.1) |
| MPGN | 1 (3.6) |

*aHUS* atypical hemolytic uremic syndrome, *SD* standard deviation, *IQR* interquartile range, *GFR* glomerular filtration rate, *LDH* lactate dehydrogenase, *C3* complement 3, *TMA* thrombotic microangiopathy, *FSGS* focal segmental glomerulosclerosis, *MPGN* membranoproliferative glomerulonephritis.

[a]One patient had both diarrhea and respiratory tract infection.

[b]One patient with dilated cardiomyopathy also had craniofacial and teeth malformations. The other patient with dilated cardiomyopathy was diagnosed with 3M syndrome with short stature, unusual facial features, and skeletal abnormalities three years prior to the diagnosis of aHUS.

[c]Three patients did not have a complete triad of aHUS at the onset. The hemoglobin level was >10 g/dL in a patient who had microangiopathy signs in the peripheral blood smear, uremia, and thrombocytopenia, and the platelet count was > 150.000/$mm^3$ in two patients who had microangiopathic hemolytic anemia and uremia.

Eculizumab was administered to 23 patients (82%). Eight (34.8%) patients received eculizumab as a first-line therapy and 15 (65.2%) patients due to insufficient response to plasma therapy (Table 2). Eculizumab treatment was initiated at median 28 days (IQR,12–65) in plasma + eculizumab group and at median 6.5 days (IQR, 1.3–46.8) in first-line eculizumab group ($p$=0.07). Hematologic remission was achieved in 21 patients (91.3%), while renal remission was attained in 14 patients (60.8%) with eculizumab. Complete remission was achieved in nine patients (39%) of the eculizumab-treated group. Despite eculizumab treatment, complete hematologic and renal remission could not be achieved in one patient. Of 23 patients received eculizumab, sixteen (69.5%) required KRT during the hospital stay and eight (34.7%) were discharged with KRT; three of them (13%) progressed to chronic kidney disease stage 5 on dialysis (CKD 5D). The median duration of dialysis were 9 days (IQR, 5–90). The duration of dialysis was not statistically different between eculizumab and only plasma-based treatment groups ($p$=0.51). Hematologic ($p$=0.23) and renal remission rates ($p$=1.0) were not different between patients with or without identifiable mutation. The complete remission rate of adolescence aHUS group was significantly lower when compared to the infant aHUS patients [10 (35.7%) vs. 39 (74%), $p$=0.002] (Table 3).

**Table 2** Treatment and outcome of the patients at the first aHUS episode

| Parameters | *n* = 28 |
|---|---|
| aHUS treatment, *n* (%) | |
| Only plasma-based therapy | 5 (17.8) |
| Only eculizumab therapy | 8 (28.5) |
| Plasma + eculizumab therapy | 15 (53.5) |
| Plasma-based therapy, *n* (%) | 20 (71.4) |
| PI | 4 (14.3) |
| PE | 11 (39.3) |
| PI+PE | 5 (17.8) |
| Kidney replacement therapy, *n* (%) | 21 (75) |
| Hemodialysis | 19 (67.9) |
| Peritoneal dialysis | 2 (7.1) |
| KRT at the time of discharge from the hospital, *n* (%)* | 9 (33.3) |
| Outcome, *n* (%) | |
| Complete remission | 10 (35.7) |
| Hematologic remission | 25 (89.3) |
| Renal remission | 17 (60.7) |
| Proteinuria | 13 (46.4) |
| Time to achieve remission, days (median) (IQR) | |
| Hematologic remission | 26 (14.3–49.5) |
| Renal remission | 57 (32.5–112) |
| Mortality during the first attack, *n* (%) | 1 (3.6) |

*aHUS* atypical hemolytic uremic syndrome, *PI* plasma infusion, *PE* plasma exchange, *KRT* kidney replacement therapy

*One of the patients died during the hospital stay

**Table 3** Comparison of the clinical features of infant aHUS study [11] and adolescent-onset aHUS

| Variables | Infant aHUS $n = 53$ (11.6±6 months) | Adolescent aHUS $n = 28$ (12.8±2.3 years) | $p$ value |
|---|---|---|---|
| Female gender, *n* (%) | 30 (56.6) | 21 (75.0) | 0.15 |
| Triggering event, *n* (%) | 44 (83.0) | 11 (39.3) | <0.001 |
| Extra-renal involvement, *n* (%) | 33 (62.2) | 13 (46.4) | 0.24 |
| CNS | 21 (63.6) | 10 (79.6) | 0.8 |
| KRT, *n* (%) | 38 (71.6) | 21 (75.0) | 0.8 |
| Treatment, *n* (%) | | | |
| Plasma therapy | 42 (79.2) | 20 (71.4) | 0.58 |
| Eculizumab therapy | 33 (62.3) | 23 (82.1) | 0.08 |
| First line | 5 (9.4) | 8 (28.5) | 0.05 |
| Second line | 28 (84.8) | 15 (53.5) | 1 |
| Response to treatment | | | |
| Complete remission, *n* (%) | 39 (73.6) | 10 (35.7) | 0.002 |
| Hematologic remission, *n* (%) | 49 (92.4) | 25 (89.3) | 0.7 |
| Renal remission, *n* (%) | 42 (79.2) | 17 (60.7) | 0.11 |
| Mean follow-up, years, (mean±SD) | 2.6±2.5 | 4.9±2.6 | 0.0002 |
| eGFR >90 mL/min/1.73m$^2$ at the last visit, *n* (%) | 38(82.6)* | 13(48.1)# | 0.03 |
| CKD 5D, *n* (%) | 1 (2.2)* | 4 (14.8)# | 0.04 |
| Proteinuria, *n* (%) | 17 (37.0)* | 12 (44.4)# | 0.82 |
| Hypertension, *n* (%) | 20 (43.5)* | 12 (44.4)# | 1 |
| Mutations, *n* (%) | 14 (35.8)¶ | 11(39.3) | |
| *CFH* | 3 (21.4) | 2 (18.2) | |
| *C3* | 2 (14.2) | 2 (18.2) | |
| *CD46*§ | 2 (14.2) | – | |
| *CFB* | 3 (21.4) | 1 (9.0) | |
| *CFI* | 1 (7.14) | 1 (9.0) | |
| *CFHR1-3* | – | 4 (36.4) | |
| *DGKE* | 4 (28.5) | – | |
| *TSEN2* | – | 1 (9.0) | |

*aHUS* atypical hemolytic uremic syndrome, *CNS* central nervous system, *C3* complement 3, *KRT* kidney replacement therapy, *CKD 5D* chronic kidney disease stage 5 on dialysis, *eGFR* estimated glomerular filtration rate, *CFH* complement factor H, *C3* complement 3, *MCP* membrane cofactor protein, *DGKE* diacylglycerol kinase ε, *TSEN2* tRNA splicing endonuclease 2.

*Data are available for 46 patients

#Data are available for 27 patients

¶Data are available for 39 patients

§Combined with *CFB* mutation in a patient

During the acute stage, 21 (75%) of all the patients required KRT (Table 2). One of those patients died in the acute period due to multi-organ failure. Nine of the remaining patients (33.3%) were discharged with KRT and four (14.8%) of them progressed to CKD 5D (Table 2). After 3 months, proteinuria and hypertension persisted in 13 patients (46.4%) for each.

## Genetics

In 11 (39.3%) of 28 patients, a genetic variant was found in genes associated with aHUS: *CFHR 1–3* deletion ($n = 4$, 14.3%), *C3* ($n = 2$, 7%), *CFH* ($n = 2$, 7%), *CFI* ($n = 1$, 3.5%), and *CFB* ($n = 1$, 3.6%). A newly defined syndromic atypical hemolytic uremic syndrome due to homozygous *TSEN2* splice site mutation was diagnosed in a patient with craniofacial abnormalities accompanied by central nervous system malformations [6]. In 2 patients who presented with complete aHUS triad and progressed to end-stage renal disease, *COQ8B* variant was detected simultaneously with *CFH* in one and *COQ6* variant in the other. The genetic variants of the patients and their clinical features are given in Supplementary Table 1.

### Anti-CFH antibody

Fifteen patients could be searched for anti-CFH antibodies. Of them 14 could be screened during the remission period and none of them had anti-CFH antibodies. Three out of 4 patients with homozygous *CFHR1-3* deletion were screened for anti-CFH antibodies; among them, only 1 patient was able to be screened in the acute phase and was found to have high titer of anti-CFH antibody (327.43 AU/mL, cut-off value<0.6 AU/mL) detected by CFH IgG ELISA Kit (Abnova™).

### Follow-up

After a mean follow-up period of 4.9±2.6 years, 27 patients were evaluated. One patient died during the acute phase. At the last visit 13 patients (48.1%) had an eGFR over 90 mL/min/1.73m$^2$ (Table 3). There was no difference in eGFR at the last visit between patients with an identified genetic variant and those without ($p$=0.54). CKD 5D was developed in 4 patients (14.8%), which was significantly higher when compared to those in the infant aHUS patient cohort [$n$ = 1 (2.2%); $p$=0.04] (Table 3). After a median 1.2 years (IQR, 0.4–2.2), eculizumab treatment was discontinued in 15 of the 23 patients (65.2%) with the primary clinician's decision. Eculizumab therapy was discontinued after a median of 5.3 months (min-max, 1–6.5 months) in three patients who progressed to CKD 5D. At the last visit, the eGFR values of eculizumab discontinued and continued groups were not different ($p$=0.73). One patient who progressed to CKD 5D in the pre-eculizumab era was transplanted from a deceased donor with eculizumab prophylaxis and no recurrence was observed during the 9-year follow-up period. The treatment of a patient with a *C3* variant was interrupted due to the unavailability of the eculizumab. Afterward eculizumab could be re-initiated after aHUS recurrence.

At the last visit, three of the patients were on chronic dialysis and one of them had a functional transplanted kidney. The patient with *TSEN2* mutation was followed up on chronic dialysis for 2 years and died due to heart failure. Follow-up details are presented in Table 4.

**Table 4** Treatment and outcome of the patients during follow-up

| Parameters | $n$ = 27 |
|---|---|
| Duration of follow-up, (years) (mean±SD) | 4.9 ±2.6 |
| Eculizumab treatment, $n$ (%) | |
| Continued | 8(29.6) |
| Discontinued | 15(55.5) |
| Duration of follow–up with eculizumab, (years), median (IQR) | 2.1 (0.9–4.8) |
| Eculizumab free follow-up, (years), median (IQR) | 2.3 (1.3–3.9) |
| Relapse after eculizumab discontinuation[#], $n$ (%) | 1 (6.6) |
| Overall relapse, $n$ (%) | 1 (3.7) |
| Proteinuria, $n$ (%) | 12 (44.4) |
| Non-nephrotic range | 9 (33.3) |
| Nephrotic range | 3 (11.1) |
| Hypertension, $n$ (%) | 12 (44.4) |
| CKD 5D, $n$ (%) | 4 (14.8) |
| eGFR at last visit (mL/min/1.73m$^2$), $n$ (%) | |
| >90 | 13 (48.1) |
| 60–89 | 5 (18.5) |
| 30–59 | 5 (18.5) |
| 15–29 | 1 (3.7) |
| <15 | 3 (11.1) |

eGFR, estimated glomerular filtration rate; CKD 5D, chronic kidney disease stage 5 on dialysis

[#]analyzed with 15 patients

## Discussion

While this study describes, for the first time, the clinical and genetic characteristics of patients with aHUS diagnosed between the ages of 10 and 18 years, it also provides an opportunity to compare the short- and long-term outcomes of adolescence- and infantile-onset aHUS. The prevalence of adolescence-onset aHUS has not been reported in the literature so far but is estimated to comprise 10% of pediatric aHUS patients [8, 9, 22, 23]. In the present study, we showed, by analyzing Turkish Pediatric aHUS registry data, that adolescence-onset aHUS patients account for 18.5% of the pediatric aHUS cases.

The present study demonstrated that while hematologic remission rate of adolescence-onset aHUS patients was comparable with infantile aHUS, renal remission rate was lower (60% vs. 79%). Most prominently, the complete remission rate during the first attack was significantly lower in adolescence-onset aHUS when compared with infantile onset (35.7% vs. 74%) [11]. Moreover, the rate of discharge from hospital with dialysis was significantly higher in adolescents than in infants (32% vs. 7.5%). These results reflect that adolescents have more severe kidney damage and require longer periods of dialysis. There is no conclusive data in the literature about clinical course and the outcomes of the adolescence-onset aHUS patients. Greenbaum et al. reported that 60% of the patients (3 out of 5 patients) under 2 years of age and 75% of patients (3 out of 4 patients) aged 12–18 years who received eculizumab treatment achieved hematological improvement and ≥25% of serum creatinine reduction after 4 weeks [22]. In the Brazilian aHUS study, dialysis dependency at 3 months after diagnosis was reported to be 47% and 50% in those under 2 years and 2–18 years of age, respectively [24]**.** In our study renal remission rate was 60%. Although these studies may not be comparable due to

heterogeneous patient population with aHUS, when taken together one can suggest that adolescent patients have poorer renal outcome when compared to infantile-onset aHUS patients and therefore should be managed and followed up meticulously.

Many factors may be responsible for severer disease course in adolescents than in infants. The lower incidence of aHUS diagnosis in adolescent patients may have caused it not to be prioritized among differential diagnoses in similar presentations. We did not have any data on the duration between the onset of the first symptoms and the diagnosis of aHUS. However, renal biopsy, which is not a routine diagnostic procedure in aHUS, performed in half of the patients may suggest that the diagnostic evaluation took time that might be associated with delaying in initiation of specific therapy. On the other hand, age-related differences of the immune system may affect the complement response and disease severity. Complement proteins are known to belong to the innate immune system, and also have been demonstrated to have a key role in the regulation of adaptive immune response [25]. The effect of genetic variants of complement genes, the so-called complotype, is thought to provide an advantageous response to infection before adaptive immunity is fully developed, predisposing to complement-mediated tissue injury from lifelong environmental inflammatory stimuli in advancing ages [26].

In previous studies, it has been reported that overall 45–70% of aHUS patients carry an identifiable mutation in complement genes or have anti-CFH antibodies. These mutations lead to loss of regulation of the alternative complement pathway, resulting in a great amount of membrane attack complex formation on endothelial cells resulting in endothelial damage [1–3]. Specific mutation rate and distribution in adolescent patients remain unknown. In the present study, comprehensive complement gene analysis was performed in all patients. Mutation detection rate in the adolescence-onset aHUS study was similar to that of our infant study (39.3% vs. 36%, respectively) considering the fact that genetic analyses could have been done in only 75% in latter [11]. In our study, hematological and renal remission rates were not different in patients with or without genetic variants. These figures suggest that there may be other yet-to-be identified genetic abnormalities or other non-genetic triggers in adolescent patients that need to be investigated. *CFH* mutation has been reported as the most common genetic abnormality in all pediatric ages in comprehensive studies [1, 3]. Anti-CFH antibody associated aHUS presents predominantly in older pediatric age group and is closely associated with *CFHR1* and *CFHR3* deletions [27, 28]. Jozsi et al. reported the presence of anti-CFH antibodies in 73% of the aHUS patients with *CFHR1-3* deletions [28]. In Global aHUS study, anti-CFH antibodies were reported as the most common cause of aHUS etiology in children aged 6 to 17 years; however, *CFH-CFHR* genomic rearrangements were not screened. In our study we detected homozygous *CFHR1-3* deletion in 4 (14.3%) of adolescent patients. Of them we could screen anti-CFH antibody levels in 3 patients and detected it in 1 patient during the acute phase. In the entire cohort, 15 patients except for 1 could be screened for the anti-CFH antibodies during the remission phase and none of them had anti-CFH antibody. It remains unknown whether we could detect more patients with anti-CFH antibody if these patients could have been screened during the acute phase as 20 patients receive plasma-based therapies including plasma exchange during the acute phase. If this speculation is true, then anti-CFH antibodies may be the leading cause in adolescent patients, which deserves further research. Indeed, studies showed that anti-CFH antibody titers could decrease to undetectable levels with immunosuppressive and plasma treatments in time [27, 29]. Plasma exchange is also a recommended therapy in anti-CFH antibody-related aHUS. In 2016 consensus report for management of aHUS in children [30], eculizumab is recommended as a first-line treatment within 24–48 hours after onset. While homozygous deletion of *CFHR1* without anti-CFH antibody was identified in 11% of the aHUS cases [27], heterozygous *CFHR1* deletion has been reported as a genetic polymorphism at a frequency of 4% in healthy Caucasians and is not well correlated with the prevalence of anti-CFH antibody-related aHUS [31, 32]**.** In our cohort, all patients with *CFHR1-3* deletion were homozygous.

Reports about the prognosis of anti-CFH antibody associated aHUS are controversial. Bacchi et al. reported that the prognosis of anti-CFH antibody associated aHUS in children is favorable and similar to *CD46* mutation associated aHUS, whereas the others showed a high rate of CKD 5D [1, 3, 27]. Although we could not look at anti-CFH antibody at the acute phase, all patients with *CFHR1-3* deletions assuming to have anti-CFH antibodies had preserved kidney functions at the last visit. This outcome may be related to combined plasma exchange with steroid ($n = 1$) or eculizumab ($n = 3$) therapy.

In our infant group the most common disease causing variants were on *DGKE (10%)*, *CFH* (7.6%), *CFB* (7.6%), and *CD46* (5%) [11]. However, we did not detect *DGKE* and *CD46* variants in adolescent cohort. At the last visit, approximately half of adolescent-onset aHUS patients had normal eGFR($\geq$90 mL/min/1.73m$^2$). In comparison with infants, adolescent group had a significantly lower preserved eGFR rate [13 (48.1%) vs. 38 (83%)] [11]. This situation may be related to different genetic and non-genetic triggers between these age groups. Indeed, *CD46* mutations have been associated with better outcomes in previous studies and may enhance the rate of complete remission [1]. While in our infantile group *CD46* variants comprises 5% of all genetic abnormalities, in the adolescent cohort we did not detect

it. This may be a factor that might explain better outcome in our infantile aHUS cohort when compared to those in adolescent cohort. In addition, adolescent patients required a longer duration of dialysis, had lower complete remission rate, and had a more tendency to progressive kidney disease. The CKD 5D rate was 14.8% in adolescent-onset aHUS patients, which is also significantly higher than the CKD 5D rate reported in the infant study (2.2%, $p$=0.04) [11]. The CKD 5D rate was even higher (27%) for pediatric aHUS patients of all ages reported in the Global aHUS Study [3]. This difference was thought to be due to the use of data from the pre-eculizumab era in the Global aHUS study [3]. As generally accepted, eculizumab has significantly improved the outcome of complement-mediated aHUS and decreased the CKD 5D rate from 60–70% to 10–15 % in children [33]. In the present study, three of the patients with CKD 5D were received eculizumab and did not respond to treatment. These patients had either homozygous *COQ8* variant accompanied by a heterozygous *CFH* variant, or homozygous *COQ6* variant without an identifiable complement gene abnormality, or a genetic abnormality that was not related to complement system (*TSEN2* variant). These observations suggest that in those patients who do not respond to complement-blocking therapies, other factors should also be looked for in order to provide rational treatment approach.

The infections are well known triggering factor for aHUS. In the present study aHUS onset was preceded by a triggering event in 40% of the cases and the rate was significantly lower when compared to infantile-onset aHUS**.** Fremeaux-Bacchi et al. reported a higher rate of aHUS triggered by infections in children (47%) than in adults (16%) [1]. Brazilian aHUS group observed a higher rate of diarrhea as a triggering event at infant age than at other ages [24]. In adult age, pregnancy and autoimmunity are the most common precipitating factors [34]. Although the triggering role of infections on aHUS seems to decrease with age, the cause is unknown. It may be possible that community-acquired infections that have been easily diagnosed may be replaced by unidentified or subtle infections with age and therefore remain undiagnosed.

It has been reported that complete aHUS triad may be missing at the presentation, and 15% of the children may also have normal serum creatinine and present with isolated proteinuria or hematuria or hypertension [35, 36]**.** This may cause a delay in the diagnosis of aHUS and thereby delayed initiation of a complement-blocking treatment. One of the patients presented with renal dysfunction, hypertension, and proteinuria. A kidney biopsy was performed due to unusual course; thrombotic microangiopathy (TMA) and focal segmental glomerulosclerosis were reported. Since the clinical presentation was atypical, eculizumab was only able to be given at the 7$^{th}$ month of the presentation after histopathological evidence of TMA. In this patient, we could not achieve complete hematological and renal remission despite eculizumab therapy, no mutation was detected. In the last visit, her eGFR was compatible with CKD 2. This delay may be one reason of ineffectiveness of eculizumab in this case. Another possibility would be C5 mutation; however, we could not look for. Delayed treatment may compromise ultimate renal recovery and increase the risk of early progression to CKD 5D [30]. In our study, 3 patients (10%) did not have the classical aHUS triad; therefore, the eculizumab was initiated for an average of 26.7±11.6 days. At the last visit, one of these patients was CKD 5D, and the other two were CKD 4 and CKD 3. Therefore, a high index of clinical suspicion is critical in patients with incomplete diagnostic criteria to timely initiate specific therapy that will prevent sustained renal damage.

There are some limitations of this study due to nature of retrospective studies. Firstly, we could not enroll 30% of adolescent patients due to lack of sufficient information. Secondly, we could not look at anti-CFH antibody during the acute phase, but searched during the remission. This may not reflect the real prevalence of anti-CFH antibody associated aHUS in adolescent cohort. Thirdly, as treatment approaches were not homogeneous, we could not compare them to suggest a therapeutic plan.

## Conclusions

In conclusion, adolescent-onset aHUS patients constitute approximately one–five of the pediatric cases therefore should be kept in mind in differential diagnosis. Its presentation, course and outcome seem to be different when compared to younger patients. Moreover, presentation of the disease may not fulfill the classic triad. In the long term, adolescents may have significant permanent loss of renal functions and higher CKD 5D rates. Therefore, adolescence-onset aHUS should be timely and meticulously managed during the acute phase and should be closely followed up in the long term. Further studies focusing on this age group will provide more insight regarding the age-specific clinical and genetic features as well as therapeutic strategies.

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of the manuscript. All authors made substantial contributions to the conception of the work, revised it critically, approved the final version, and agree to be accountable for all aspects of the work.

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**Data availability** The datasets during and/or analyzed during the current study available from the corresponding author on reasonable request,

## Declarations

**Ethical standards** This study was approved by the ethics committee of Hacettepe University (2019/02-18). Written informed consent was obtained from the parents of all the patients.

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