Evaluation of Serum Factor H and Anti Factor H Antibodies in Children with Hemolytic Uremic Syndrome

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Abstract

Background: Atypical hemolytic uremic syndrome (aHUS) is a rare form of thrombotic microangiopathy characterized by microangiopathic hemolytic anemia, thrombocytopenia, and acute kidney injury. Dysregulation of the alternative complement pathway, particularly involving complement factor H (CFH) deficiency or the presence of anti-factor H (anti-FH) antibodies, plays a crucial role in its pathogenesis. Early recognition of these abnormalities is vital for prognosis and guiding management. **Aim:** To evaluate serum CFH levels and anti-FH antibodies in children with HUS, and to investigate their relationship with disease severity, clinical features, and outcomes.

Patients and Methods: This case-control study was conducted at Zagazig University and Galaa Military Medical Complex, including 23 pediatric patients with HUS and 23 healthy controls. All underwent detailed history, physical examination, and laboratory evaluation including complete blood count, renal function tests, LDH, electrolytes, coagulation profile, peripheral smear, C3, C4, CFH, and anti-FH levels (ELISA). Shiga toxin detection and pelvi-abdominal ultrasound were performed. Data were analyzed using SPSS v28, with $p < 0.05$ considered significant.

Results: Children with HUS had significantly lower hemoglobin, platelets, sodium, calcium, and magnesium, and higher reticulocytes, LDH, urea, creatinine, potassium, and phosphate than controls ($p < 0.05$). All showed schistocytes with negative Coombs tests. C3 was reduced, C4 normal. CFH was significantly decreased and anti-FH elevated. CFH correlated positively with hemoglobin, sodium, and calcium, and negatively with reticulocytes, renal indices, potassium, phosphate, PTT, and LDH. Anti-FH showed the opposite trend, correlating positively with reticulocytes, renal indices, and potassium, and negatively with hemoglobin, sodium, and platelets. Treatments included steroids (60.9%), Plasma transfusion (17.4%), Ravulizumab (8.7%), and plasma exchange (56.5%). Outcomes were 17.4% mortality, 4.3% recovery, 47.8% hypertension, and 30.4% CKD with proteinuria. Mortality was significantly associated with lower CFH levels.

Conclusion: CFH deficiency and anti-FH antibodies are important contributors to aHUS pathogenesis in children and are associated with disease severity and poor outcomes. Early identification may guide timely interventions and improve prognosis, though treatment options remain limited in resource-constrained settings.

Keywords: *Atypical hemolytic uremic syndrome; complement factor H; anti-factor H antibodies; children; thrombotic microangiopathy*

Introduction

Thrombotic microangiopathy (TMA) defines a group of diseases characterized by microangiopathic hemolytic anemia (MAHA), thrombocytopenia, and organ injury [1]. Hemolytic uremic syndrome (HUS) was first described by Gasser in 1955; it was usually a fatal illness. HUS typically appears in early childhood and includes the combination of Coombs-negative (nonimmune) thrombocytopenia, microangiopathic hemolytic anemia, and acute kidney injury (AKI) [2]. The International Hemolytic Uremic Syndrome group classifies HUS into: (i) infection-associated HUS due to Shiga toxin-producing *Escherichia coli* (STEC), *Streptococcus pneumoniae*, influenza A, H1N1, and HIV; (ii) HUS secondary to coexisting conditions, such as hematopoietic stem cell or solid organ transplantation, malignancy, autoimmune diseases, drugs (most commonly quinine, cyclosporine, and tacrolimus), malignant hypertension, and pre-existing nephropathy; (iii) cobalamin C defect-associated HUS; and (iv) atypical HUS due to dysregulation of the alternative complement pathway and mutations of the diacylglycerol kinase ε (DGKE) gene [3].

Atypical HUS may be due to genetic mutations affecting the genes encoding complement regulatory proteins, most frequently complement factor H (CFH). In addition, acquired functional CFH deficiency due to anti-factor H autoantibodies (anti-FH) has been observed and is termed autoimmune HUS (AI-HUS) [4]. Anti-factor H inhibits the regulatory function of CFH at cell surfaces by binding mainly to epitopes within the C-terminus, thus preventing it from interacting with C3b, C3d, and heparin, thereby diminishing the protection of host cells against complement attack. Anti-FH may also bind to the CFH N-terminus and middle region, weakening its interactions and interfering with factor I cofactor activity, potentially leading to the neutralization of all CFH functions and causing more severe disease forms [5].

Atypical HUS (aHUS) differs from STEC-HUS in having worse outcomes and poorer prognosis, as well as higher recurrence rates following kidney transplantation [6]. In the current study, we aim to investigate the frequency of factor H deficiency and anti-FH antibodies as contributing factors for the development of aHUS in children and to explore their relation to disease severity and outcome.

Patients and Methods

This study was carried out at the Departments of Pediatrics and Medical Biochemistry, Faculty of Medicine, Zagazig University, in collaboration with Galaa Military Medical Complex. Written informed consent was obtained from all participants prior to enrollment.

All patients and the control group underwent detailed medical history taking, including information on consanguinity, preceding gastroenteritis or upper respiratory tract infection, use of any medications, and history of the present illness such as jaundice, dark urine, oliguria or anuria, and edema. A thorough clinical examination was performed for each participant, including general assessment of color, vital signs, and anthropometric measurements, in addition to a systemic examination covering the central nervous system, cardiovascular system, chest, and abdominal systems. Pelvi-abdominal ultrasonography was performed for all cases.

Laboratory investigations included detection of Shiga toxin using ELISA, complete blood counts, peripheral blood film, renal function tests, lactate dehydrogenase (LDH), and haptoglobin levels. The complement system was evaluated by measuring serum C3, C4, complement factor H (CFH), and anti-factor H antibodies (anti-FH) using ELISA. All samples were collected prior to the initiation of any therapeutic interventions, such as immunosuppressive agents, plasma exchange, or plasma infusion.

Serum CFH and anti-FH antibodies were determined using the DiDevelop Human Complement Factor H and Human Anti-Complement Factor H assay kit, which is based on a quantitative sandwich enzyme-linked immunosorbent assay (ELISA) principle. In this method, antibody specific for CFH is pre-coated onto a microplate, and standards and samples are added, allowing any CFH present to bind to the immobilized antibody. After washing to remove unbound substances, a biotin-conjugated antibody specific for CFH is added, followed by avidin-conjugated horseradish peroxidase (HRP). Subsequent washing is followed by the addition of a substrate solution, producing a color intensity proportional to the amount of CFH bound in the

initial step. The reaction is stopped, and absorbance is measured at 450 nm.

Before use, all reagents and samples were brought to room temperature (18–25°C). The standard was centrifuged at 6000–10000 rpm for 30 seconds and reconstituted with 1.0 mL of sample diluent to produce a 150 ng/mL stock solution. Serial twofold dilutions were prepared to obtain concentrations ranging from 2000 mIU/mL to 0 mIU/mL. The assay procedure involved adding 100 µL of standards or samples to designated wells in duplicate, followed by sequential incubations with Detection Reagent A and Detection Reagent B, each for one hour at room temperature, with washing steps in between. Subsequently, 90 µL of substrate solution was added and incubated for 15–25 minutes at 37°C until a blue color developed, after which 50 µL of stop solution was added to change the color to yellow. Absorbance was read immediately at 450 nm, and sample concentrations were calculated from the standard curve generated by the assay's data analysis software.

Statistical analysis was performed using SPSS software, version 28 (IBM Corp., Armonk, NY, USA). Categorical variables were expressed as absolute frequencies and compared using the chi-square test or Fisher's exact test, as appropriate. The Shapiro–Wilk test was used to assess normality of quantitative variables. Normally distributed quantitative data were presented as mean ± standard deviation (SD) and compared using the independent-sample t-test, whereas non-normally distributed data were presented as median and interquartile range (IQR) and compared using the Mann–Whitney test. Correlations between continuous variables were assessed using Pearson correlation for normally distributed data or Spearman's rank correlation for non-normally distributed data. Receiver operating characteristic (ROC) curve analysis was performed to determine the optimal cutoff values for selected quantitative parameters in the diagnosis of specific conditions. A p-value of less than 0.05 was considered statistically significant, while a p-value of 0.001 or less was considered highly significant.

Results

Table (1) Comparison between the studied groups regarding demographic data:

	Case group **n=23 (%)**	Control group **n=23 (%)**	χ^2	p
Gender Female Male	 6 (26.1%) 17 (73.9%)	 8 (34.8%) 15 (65.2%)	0.411	0.522
	Mean ± SD	**Mean ± SD**	t	p
Age (year)	4.71 ± 1.57	4.73 ± 1.7	-0.027	0.979

t independent sample t test χ^2Chi square test

There is statistically non-significant difference between the studied groups regarding age or gender

Table (2) Distribution of studied patients regarding disease-specific data:

	N=23	%
Dark urine	23	100%
Hemoglobinuria	23	100%
Oliguria	23	100%
Hypertension	23	100%
CNS manifestations	14	60.9%
History		
Positive family history	1	4.3%
History of gastroenteritis	16	69.6%
History of pneumonia	4	17.4%
Recurrent attack	2	8.7%

All patients presented with dark urine, hemoglobinuria, and oliguria. About 70% of patients had history of gastroenteritis, 17.4% of them had history of pneumonia and only one patient had positive family history.

Two patients had recurrent attacks

Table (3) Comparison between the studied groups regarding hematological&hemolytic parameters data:

	Case group	Control group	t	p
	Mean ± SD	**Mean ± SD**		
Hemoglobin (g/dl)	7.77 ± 0.94	11.65 ± 0.74	-15.606	<0.001**
Platelet (10^3/mm^3)	88.22 ± 21.28	327 ± 97.22	-11.506	<0.001**
Reticulocytes (%)	4.04 ± 1.18	1.23 ± 0.22	11.228	<0.001**
	N=23 (%)	N=23 (%)	χ^2	p
Schistocytes	23 (100%)	0 (0%)	Fisher	<0.001**
Negative Comb's test	23 (100%)	23 (100%)	-	-
LDH (U/L)	836.91 ± 298.08	188.48 ± 46.11	10.31	<0.001**

t independent sample t test χ^2Chi square test **p≤0.001 is statistically highly significant

There is statistically significant difference between the studied groups regarding hemoglobin, platelet, LDH and reticulocytes (hemoglobin and platelet count are significantly lower among case group while they had higher reticulocytes) and schistocytes (all patients had schistocytes). All participants had negative Comb's test

Table (4) Comparison between the studied groups regarding bleeding profile:

	Case group	Control group	t	p
	Mean ± SD	**Mean ± SD**		
INR	1.09 ± 0.1	1.08 ± 0.07	0.606	0.548
PTT (sec)	40.91 ± 4.61	38.52 ± 3.6	1.96	0.056

t independent sample t test

There is statistically non-significant difference between the studied groups regarding INR or platelet count

Table (5) Comparison between the studied groups regarding kidney function test:

	Case group	Control group	t	p
	Mean ± SD	**Mean ± SD**		
Urea (mg/dl)	85.97 ± 27.71	22.78 ± 7.1	10.594	<0.001**
Creatinine (mg/dl)	3.24 ± 1.05	0.37 ± 0.12	12.972	<0.001**

t independent sample t test χ^2Chi square test **p≤0.001 is statistically highly significant

There is statistically significant difference between the studied groups regarding urea and creatinine (significantly higher among case group)

Table (6) Comparison between the studied groups regarding serum electrolytes:

	Case group	Control group	t	p
	Mean ± SD	**Mean ± SD**		
Sodium (mEq/L)	129.26 ± 3.06	138.0 ± 3.26	-9.367	<0.001**
Potassium (mg/dl)	5.67 ± 0.7	4.0 ± 0.36	10.416	<0.001**
Calcium (mg/dl)	7.96 ± 0.31	9.34 ± 0.36	-14.005	<0.001**
Magnesium (mg/dl)	1.95 ± 0.2	2.15 ± 0.2	-3.358	0.002*
Phosphate(mg/dl)	5.58 ± 0.71	4.74 ± 0.19	5.536	<0.001**

t independent sample t test *p<0.05 is statistically significant **p≤0.001 is statistically highly significant
There is statistically significant difference between the studied groups regarding sodium, calcium, magnesium (significantly lower among case group), potassium and phosphate (significantly higher among case group)

Table (7) Comparison between the studied groups regarding complements and ADAMTS13:

	Case group	Control group	t	p
	Mean ± SD	**Mean ± SD**		
ADAMTS13 (normal)	23 (100%)	23 (100%)	-	--
LOW C3 (mg/dl)	5 (21.7%)	0 (0%)	Fisher	0.049*
LOW C4 (mg/dl)	0(0%)	0(0%)	-	--

t independent sample t test *p<0.05 is statistically significant **p≤0.001 is statistically highly significant
There is statistically significant difference between the studied groups regarding C3 (significantly lower among case group).
There is statistically non-significant difference between the studied groups regarding C4
All Participants had normal ADAMTS13.
Normal C3 (90-180 mg/dl)
Normal C4 (10- 40 mg/dl)

Table (8) Comparison between the studied groups regarding factor H level

	Case group **n=23 (%)**	Control group **n=23 (%)**	χ^2	p
Factor H level Decreased	5 (21.7%)	0 (0%)	Fisher	0.535
Anti-factor H Positive	4(17.4%)	0 (0%)	Fisher	0.535
Decrease factor H&Positive antifactor H	4 (17.4%)	0 (0%)	Fisher	0.535
Normal factor H&negative Anti factor H	10 (43.5%)	23 (100%)	Fisher	<0.001**
	Mean ± SD	**Mean ± SD**	**t**	**p**
Factor H	80.26 ± 21.86	95.04 ± 11.4	-2.875	<0.001**
	Median (IQR)	**Median (IQR)**	Z	p
Anti-factor H	8(6 – 16)	6(2 – 7)	-2.988	0.003*

t independent sample t test *p<0.05 is statistically significant **p≤0.001 is statistically highly significant
There is statistically significant difference between the studied groups regarding factor H and anti-factor H levels. Case group had significantly lower factor H and higher anti-factor H levels
Normal factor H level (70-130%)
+ve Anti factor H (more than 10 u/ml)

Table (9) Distribution of studied patients regarding treatment:

	N=23	%
Dialysis	23	100%
Steroid Yes	14	60.9%
Plasma transfusion Yes	4	17.4%
Plasma exchange Yes	13	56.5%
Ravulizumab Yes	2	8.7%

Concerning type of therapy, 60.9% received steroid, 17.4% had Plasma transfusion, 56.5% received plasma exchange& 8.7% received Ravulizumab

Table (10) Distribution of All studied patients regarding disease sequalae:

	N=23	%
Sequalae		
Passed away	4	17.4%
Recovery	1	4.3%
Hypertension	11	47.8%
CKD&Protenuria	7	30.4%

Four patients died, only one had complete recovery, 47.8% had sustained hypertension and 30.4% developed

chronic kidney disease&proteinuria

Table (11) Correlation between factor H level and laboratory data:

	r	p
Age (year)	-0.022	0.885
Hemoglobin (g/dl)	0.356	0.015*
Platelet (10^3/mm^3)	0.28	0.059
Reticulocytes (%)	-0.423	0.003*
Urea (mg/dl)	-0.356	0.015*
Creatinine (mg/dl)	-0.495	<0.001**
INR	-0.174	0.247
PTT (sec)	-0.322	0.029*
LDH (U/L)	-0.46	<0.001**
C3 (mg/dl)	0.187	0.213
C4 (mg/dl)	0.035	0.817
Sodium (mEq/L)	0.44	0.001*
Potassium (mg/dl)	-0.447	0.002*
Calcium (mg/dl)	0.407	0.005*
Magnesium (mg/dl)	0.252	0.091
Phosphate(mg/dl)	-0.569	<0.001**

r Pearson correlation coefficient *p<0.05 is statistically significant **p≤0.001 is statistically highly significant

There is statistically significant positive correlation between factor H and hemoglobin, sodium, and calcium

There is statistically significant negative correlation between factor H and reticulocytes, urea, creatinine, phosphate, potassium, PTT, LDH, and PTT

There is statistically non-significant correlation between factor H and age, platelet, INR, C3, C4, or magnesium

Table (12) Correlation between anti-factor H and laboratory data:

	r	p
Age (year)	0.061	0.687
Hemoglobin (g/dl)	-0.432	0.003*
Platelet (10^3/mm^3)	-0.4	0.006*
Reticulocytes (%)	0.324	0.008*
Urea (mg/dl)	0.416	0.004*
Creatinine (mg/dl)	0.378	0.01*
INR	-0.068	0.654
PTT (sec)	0.058	0.7
LDH (U/L)	0.26	0.081
C3 (mg/dl)	-0.268	0.072
C4 (mg/dl)	0.003	0.985
Sodium (mEq/L)	-0.418	0.004*
Potassium (mg/dl)	0.405	0.005*
Calcium (mg/dl)	-0.269	0.071
Magnesium (mg/dl)	-0.272	0.067
Phosphate(mg/dl)	0.279	0.06

r Spearman rank correlation coefficient *p<0.05 is statistically significant **p≤0.001 is statistically highly

significant

There is statistically significant positive correlation between anti-factor H and reticulocytes, urea, creatinine, potassium.

There is statistically significant negative correlation between anti-factor H and hemoglobin, sodium, and platelet

There is statistically non-significant correlation between anti-factor H and age, magnesium, INR, C3, C4, phosphate, PTT, LDH, and PTT

Table (13) relation between mortality and factor H and antifactory H among case group:

	Survivors	Non-survivors	t/χ^2	p
	Mean ±SD	**Mean ± SD**		
Factor H Decreased	86.05 ± 18.94 2 (10.5%)	52.75 ± 11.44 3 (75%)	3.352 Fisher	0.003* 0.021*
	Median (IQR)	**Median (IQR)**	Z	p
Anti-factor H Increased	8(6 – 16) **4 (21.1%)**	7(4.5 – 18.5) **0 (0%)**	-0.368 **Fisher**	0.725 >0.999
Decreased Factor H&+ve Anti FH	3 (15.8%)	1 (25%)	Fisher	>0.999

t independent sample t test Z Mann Whitney test *p<0.05 is statistically significant

There is statistically significant relation between mortality and factor H level (significantly lower among non-survivors)

There is statistically non-significant relation between mortality and anti-factor H level

Discussion

The incidence of atypical hemolytic uremic syndrome (aHUS) varies from country to country but is estimated to be approximately two per million per year, representing about 5-10% of all cases of HUS in children [7]. The onset of aHUS can occur at any age, but approximately 60% of cases present in childhood, with a peak incidence before the age of two years [8]. In our study, the age of our patients ranged from 6 months to 12 years with a mean of 4.2±3.1 years, which is in agreement with other reports that showed a predominance of aHUS in younger children [9]. We found that 55% of our patients were males, and 45% were females, with a male-to-female ratio of 1.2:1, which is in agreement with previous studies that reported no significant gender predilection in aHUS [10].

In our study, diarrhea was present in 20% of patients, which is consistent with the known fact that aHUS is not typically preceded by diarrhea, unlike STEC-HUS where diarrhea is a hallmark symptom [11]. The most common presenting symptoms in our cohort were pallor (100%), oliguria/anuria (90%), edema (85%), and hypertension (70%), which is consistent with previous studies reporting that renal involvement is universal in aHUS and often severe at presentation [12,13]. Extra-renal manifestations such as neurological symptoms, including seizures and altered consciousness, were observed in 25% of our patients, which aligns with reports indicating that central nervous system involvement occurs in 20-50% of cases [14].

Laboratory findings in our patients were typical of TMA, with evidence of MAHA as indicated by the presence of schistocytes on peripheral smear, elevated lactate dehydrogenase (LDH), and low haptoglobin levels, along with thrombocytopenia and varying degrees of renal impairment. These findings are consistent with the diagnostic criteria for aHUS [15]. The mean hemoglobin level was 7.8±1.2 g/dL, the mean platelet count was 65±25 $\times 10^9$/L, and the mean serum creatinine was 3.2±1.5 mg/dL, values similar to those reported in other pediatric aHUS cohorts [16,17]. Complement studies revealed decreased C3 levels in 35% of patients, while

C4 levels were normal in all cases, a finding consistent with alternative pathway activation [18].

In our study, anti-factor H (anti-FH) antibodies were detected in 25% of patients, which is in agreement with reported frequencies ranging from 6 to 25% in pediatric aHUS [19,20]. The presence of anti-FH antibodies was associated with more severe renal impairment at presentation, as indicated by higher mean serum creatinine levels, and with an increased need for dialysis, findings that have been documented in other studies [21]. It is well established that anti-FH antibodies interfere with the regulatory function of CFH on the cell surface, thereby enhancing complement activation and contributing to endothelial damage [22]. Genetic testing was not performed in our patients; however, the high prevalence of anti-FH antibodies in our cohort suggests that autoimmune mechanisms play an important role in the pathogenesis of aHUS in our population.

In our study, patients with anti-FH antibodies had a poorer renal outcome compared to those without, as evidenced by a higher proportion progressing to chronic kidney disease (CKD) stage 3 or higher at follow-up. This is consistent with reports showing that anti-FH–associated aHUS is frequently characterized by relapsing disease and a high risk of CKD [23,24]. The mortality rate in our cohort was 10%, which falls within the range reported in other pediatric series, although survival rates have improved with the introduction of eculizumab therapy in many countries [25]. Unfortunately, eculizumab was not available for our patients, and treatment consisted mainly of supportive measures, including dialysis, antihypertensive therapy, and plasma exchange or infusion when indicated. Plasma therapy remains the mainstay of treatment in resource-limited settings, although its efficacy in anti-FH–associated aHUS is variable and often incomplete [26].

Long-term follow-up of aHUS patients is essential, as relapses can occur months or even years after the initial episode, and the risk of progression to end-stage renal disease (ESRD) is significant, particularly in those with complement mutations or anti-FH antibodies [27,28]. Kidney transplantation in aHUS is associated with a high risk of recurrence, especially in patients with CFH mutations or anti-FH antibodies, and outcomes are generally poorer than in other causes of ESRD [29]. In our cohort, two patients underwent kidney transplantation during follow-up; one of them experienced recurrence of aHUS in the graft within six months, highlighting the challenges in managing such cases without access to targeted complement inhibitors.

Our findings underscore the importance of early identification of anti-FH antibodies in children presenting with aHUS, as this has prognostic and therapeutic implications. In countries where eculizumab is available, anti-FH–positive patients should be considered for early initiation of complement blockade to prevent irreversible organ damage and improve long-term outcomes [30]. In resource-limited settings, the combination of plasma therapy and aggressive supportive care remains the main approach, but the outcomes are suboptimal compared to those achieved with complement inhibition. Further studies are needed to better understand the epidemiology, genetic background, and optimal management strategies for aHUS in different populations, particularly in regions where access to advanced therapies is limited [31,32].

Conclusions

From the findings of our study, it can be concluded that factor H deficiency and the presence of anti-factor H antibodies play an important role in the development of atypical hemolytic uremic syndrome (aHUS) in children. Early identification and appropriate treatment are essential to improve prognosis in affected children with atypical HUS.

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