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Atypical hemolytic uremic syndrome in the Colombian Caribbean: its particular characteristics

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Abstract

Introduction Atypical hemolytic uremic syndrome (aHUS) is a rare and genetically mediated systemic disease most often caused by uncontrolled and chronic complement activation that leads to systemic thrombotic microangiopathy, renal and extra-renal damage.

Materials and methods This is descriptive, retrospective and multicenter study, which reports demographic, clinical, laboratory, and genetic characteristics, as well as their treatment response and outcome of 20 aHUS patients diagnosed between 2014 and 2018.

Results Most patients were female adults (75%) and 30% were associated to pregnancy/postpartum, 15% to autoimmune disease, and 65% to infections. Gastrointestinal involvement (75%) was the most frequent extra-renal organ damage. Antenatal mortality and mortality rate were 5% and 10%, respectively. 25% of the patients progressed to end-stage renal disease. In 4/8 of patients treated within 1 week of presentation, eculizumab treatment restored multi-organ function after 4 weeks of treatment. CFH (37%) and CFI (25%) mutations were the most frequent.

Conclusion This is the first series of aHUS cases of Colombian Caribbean region which reports the clinical and epidemiological characteristics of this condition in this region.

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Introduction

Hemolytic uremic syndrome (HUS), characterized by the triad of microangiopathic hemolytic anemia, thrombocytopenia and acute kidney injury (AKI), is a microvascular occlusion disorder that belongs to the category of thrombotic microangiopathy (TMA) [1, 2].

HUS may present primarily or due to secondary causes, such as bone marrow transplant, medication (e.g., anticancer chemotherapy, calcineurin inhibitors and antiplatelet agents), pregnancy or delivery, malignant hypertension, pneumococcal or viral infections and autoimmune diseases. In the case of primary HUS, the atypical form (aHUS) is distinguished from the typical form by the absence of a prior verotoxin-producing *Escherichia coli* infection. aHUS is most often caused by chronic, uncontrolled activation of the complement system, which leads to activation of endothelial

cells, recruitment of platelets and TMA [1–3]. Regardless of the aHUS etiology, patients suffering from this condition may have extra-renal manifestations (e.g., neurological, cardiovascular, pulmonary and gastrointestinal), and poor outcomes: up to 25% of mortality rate, and about 50% of kidney disease progression to end-stage renal disease (ESRD) [2–4]. In this sense, a French cohort of 214 aHUS patients showed that 56% of them progressed to ESRD or died within the first year of follow-up [5].

Genetic or acquired dysregulation of the complement alternative pathway is detected in 40–60% of patients with aHUS, suggesting a genetic predisposition [4, 5]. This dysregulation is caused by mutations in genes that encode complement regulatory proteins: Factor H (FH), Factor I (FI), membrane cofactor protein (MCP), complement 3 (C3), Factor B (FB) or thrombomodulin (THBD) as well as in their combinations, or presence of anti-FH antibody resulting in activation of the complement system [6]. In addition, common single-nucleotide polymorphisms (SNPs) or haplotypes in *CFH*, *CFHR1*, and *MCP* genes are risk factors for aHUS [7–11]. Large patient registries are required to characterize the natural history of this disease and to evaluate the impact of different therapies on it. The aHUS patients' genetic screening from registries has provided an estimation of the mutation frequency in the complement genes [4, 12, 13]. In contrast, our knowledge of the aHUS presentation and outcome in our region is limited. Therefore, the aim of this study was to describe a series of aHUS cases in adult patients from the Colombian Caribbean region.

Materials and methods

This is the first descriptive, retrospective, and multicenter study which included adult patients with aHUS diagnosed during 2014–2018 from the Colombian Caribbean region. The aHUS clinical diagnosis was based on the presence of three criteria, as follows [3, 14]: (a) microangiopathic hemolytic anemia documented by the presence of schistocytes > 2% on peripheral smear, haptoglobin level < 30 mg/dL (normal range 30–200 mg/dL), lactate dehydrogenase (LDH) > 500 U/L (normal range 250–500 U/L), negative Coomb's test, normal ADAMTS13 activity, negative serologic testing, and stool, blood and urine cultures for Shiga-toxin-producing *E. coli* or *Shigella dysenteriae*. (b) AKI defined as serum creatinine increase > 0.3 mg/dL within 48 h in healthy kidney patients (or creatininemia increase > 1.5 times within 7 days in chronic nephropathy patients), and/or urinary output reduction < 0.5 mL/h for 6 h (c) Thrombocytopenia (platelet count < 150×10^3/mm^3 or reduction of > 25% of previous platelet count).

Finally, renal biopsy was just performed in three aHUS patients who were suspected of having another renal disease,

and of course, thrombotic microangiopathy was histologically confirmed in these patients.

In addition, all cases of aHUS secondary to hematopoietic stem cell or solid-organ transplantation, malignancy, drugs, and with ADAMTS13 activity ≤ 5% (the level consistent with thrombotic thrombocytopenic purpura diagnosis) were excluded.

Besides, patients included on the sample were not required to have an identified complement gene mutation or factor H autoantibody, or prior or ongoing eculizumab treatment. Study data were obtained from the medical records of patients with aHUS from the participating medical centers. Relevant clinical and complementary studies data were collected: patient's main demographic and medical antecedents, autoimmune-related diseases, extra-renal clinical manifestations, renal ultrasound, serum and urine biochemical parameters: hemogram, haptoglobin, lactate dehydrogenase (LDH), schistocytes in peripheral blood smear, total bilirubin, aspartate amino transferase (AST), alanine transaminase (ALT), arterial blood gases, serum potassium, serum bicarbonate, urinalysis, 24-h proteinuria, C3-C4 complement, and ADAMTS13 value, associated treatments and concomitant medications, reported clinical outcomes, and genetic test (if available).

All patients were vaccinated against Neisseria meningitides prior to eculizumab initiation and received prophylactic antibiotics up to 2 weeks post-eculizumab [15]. The categorical variables were described through absolute and relative frequencies. Range, mean and standard deviation were used to analyze the continuous variables. Data were stored in a MySQL® database and it was exported to R-CRAN statistical software [16], in which the analysis was performed.

Informed consent was obtained from all individual participants included in the study and this study was approved by the Ethics Committee of the Clínica de la Costa de Barranquilla, Colombia.

Results

Twenty patients suffering from aHUS were diagnosed during the study period. Most patients were female (15/20), with a mean age of 39 years (range 23–62 years). Six (30%) patients had aHUS related to pregnancy/postpartum: 2/6 (10%) were pregnant for the first time and 4/6 (20%) had had a previous normal delivery. Obstetric aHUS appears from 24 weeks of pregnancy to 8 days of postpartum, with 1/6, 3/6, and 2/6 patients presenting obstetric aHUS in second trimester (13–27 weeks), third trimester (28-week delivery) and postpartum, respectively (Table 1). Five pregnancies (25%) resulted in live births and 1 (5%) resulted in fetal death in the third quarter of

Table 1 Clinical data, treatment, genetic, and renal outcomes of aHUS patients

	Age (years)	Sex	Pregnancy (weeks)	Affected organs						Infections	Focused therapy	Genetic mutation	Outcome
				Kidney	CNS	Lungs	Heart	Liver	GI				
1	35	F	24	+	+	+	+	+	+	Urinary sepsis	PE, steroids, eculizumab	N/A	Slight proteinuria
2	23	F	31	+	+	+	+	−	+	Pulmonary sepsis	PE, steroids, eculizumab	C2 Gene (US)	Slight proteinuria
3	54	F	No	+	−	+	+	−	+	Pulmonary sepsis	PE, cyc, RTX, steroids	N/A	Slight proteinuria
4	48	F	No	+	+	+	+	−	+	Pulmonary sepsis	PE, cyc, steroids	N/A	Died
5	54	M	N/A	+	−	+	−	−	+	Urinary sepsis	PE, steroids	C3	ESRD
6	34	F	37	+	−	+	−	+	+	SSI	PE, steroids, eculizumab	N/A	Slight proteinuria
7	67	M	N/A	+	−	+	−	−	+	Urinary sepsis	PE, steroids, eculizumab	N/A	Recovered
8	45	F	No	+	−	+	−	−	+	Urinary sepsis	PE, steroids	N/A	ESRD
9	33	F	PP	+	−	+	+	−	−	Pulmonary sepsis	PE, steroids, eculizumab	Negative panel	Recovered
10	32	F	No	+	+	−	−	−	+	No	PE, steroids, cyc	N/A	Died
11	34	F	PP	+	−	−	−	−	−	No	PE, steroids, eculizumab	Factor B heterozygous	Recovered
12	22	M	N/A	+	−	−	−	−	+	No	PE, steroids, cyc	N/A	ESRD
13	33	F	No	+	−	+	−	−	+	Pulmonary sepsis	PE, steroids	N/A	ESRD
14	57	F	No	+	−	+	−	+	+	Urinary sepsis	PE, MFM, steroids	CFI y CFH	CKD
15	23	F	36	+	−	−	−	+	+	No	PE, steroids	N/A	Fetal death
16	57	M	N/A	+	+	−	−	−	+	Varicella zoster virus	PE, steroids	N/A	CKD
17	62	F	No	+	+	−	−	−	−	No	PE, MFM, steroids	CFHR3 Heterozygous	Proteinuria
18	51	M	N/A	+	+	−	−	−	+	No	PE, steroids, eculizumab	CFI Heterozygous	Recovered
19	31	F	No	+	+	−	−	+	−	No	PE, steroids	N/A	Slight proteinuria
20	44	F	No	+	−	+	+	−	−	Pulmonary sepsis	PE, steroids, eculizumab	CFHR1–CFHR3 heterozygous	ESRD
Patients with affected organ, n (%)					8 (40%)	12 (60%)	6 (30%)	5 (25%)	15 (75%)				

PP postpartum, *CNS* central nervous system, *GI* gastrointestinal, *SSI* surgical site infection, *PE* plasma exchange, *CYC* cyclophosphamide, *MFM* mycophenolate mofetil, *ESRD* end-stage renal disease (GFR < 15 mL/min/1.73 m^2), *CKD* chronic kidney disease (GFR < 60 mL/min/1.73 m^2 longer than 3 months), *N/A* no available

− Organ not affected. slight proteinuria: <500 mg/day, proteinuria: ≥500 mg/day, + organ affected

pregnancy. Three babies were premature (26-, 28- and 33-week gestation) after emergency cesarean section due to severe preeclampsia resulting in premature delivery within 96 h of aHUS appearance. Three (15%) patients presented aHUS related to autoimmune disease: 2 (10%) had systemic lupus erythematous, and 1 (5%) had scleroderma, while 13 cases (65%) were associated to infection, being pulmonary sepsis the most frequent one (30%) (Table 1). Regarding the main hematologic parameters, hemoglobin (Hb) levels were low in all patients: mean Hb 8.2 g/dL (range 5.4–12.1 g/L), as well as mean platelets count, which was $67 \times 10^3/mm^3$ (range $9–140 \times 10^3/mm^3$). Besides, low serum C3 levels were observed in 12 cases (60%): mean 84.2 mg/dL (range 45–150 mg/dL). The rest of the main laboratory parameters of the aHUS patients are outlined in Table 2. In regards to the renal manifestations, 15 patients (75%) presented hypertension, 12 of them were on angiotensin-converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARA), in combination with beta-blocker in 2 patients, and with calcium channel blocker in 2 patients, and 3 patients were on methyldopa. Eighteen patients (90%) presented several degrees of AKI. Nine patients (45%) showed oliguria or anuria, and required hemodialysis sessions for up to 5 days (cases 4, 5, 8, 10, 12, 13, 14, 16 and 20). AKI was related to high serum potassium levels in 40% (n: 8) of patients (serum potassium 5.3 ± 0.9 mmol/L, range 3.6–6.3 mmol/L in the study group), as well as metabolic acidosis in 50% (n: 10) of patients (serum pH: 7.30 ± 0.3, range 6.5–7.4, and serum bicarbonate 19.7 ± 3.9 mmol/L, range 12.6–26 mmol/L, in the study group). In addition, 10 patients (50%) had proteinuria, and 8 (40%) had microscopic hematuria in spot urine samples. Renal ultrasounds were informed as normal, except for one who showed signs of acute nephropathy, and three presented renal changes of chronicity. It is worth mentioning that an additional glomerular pattern was found in three aHUs patients (15%) in renal biopsy, as follows: one case had a membranoproliferative glomerulonephritis pattern associated with fibrinoid thrombi and vasculopathy (case 13). The second case had a diffuse proliferative lupus nephritis (class IV–G), activity and chronic index was 14/24 and 2/12, respectively (case 10). Lastly, the third case had a pauciimmune rapidly progressive glomerulonephritis associated to ANCA (case 5). All patients experienced extra-renal manifestations as outlined in Table 1 and most experienced multiple organ failure. Seventeen patients (85%) had ≥ 2 extra-renal manifestation and 4 patients (15%) had ≥ 4 extra-renal manifestations (Table 1). Concerning the gastrointestinal involvement, it was the most frequent one (n = 15, 75%): 10 patients (50%) had abdominal pain, 2 (10%) diarrhea, and 5 (25%) gastrointestinal bleeding (melena or hematochezia). Liver injury was present in 5 patients (25%), and 3 patients (15%) had jaundice with high mixed serum bilirubin levels.

With respect to patients' respiratory symptoms, 12 (60%) presented dyspnea, 5 were associated to acute respiratory distress syndrome (ARDS), while 4 were associated to acute pulmonary edema.

Finally, CNS involvement (n = 8, 40%) included loss of consciousness (25%) and generalized seizures (15%). Ischemic or hemorrhagic cerebrovascular disease was present in 2 cases (15%) with pregnancy-associated aHUS. Cardiac involvement (n = 6, 30%) mainly manifested as acute cardiac failure with dilated cardiac chambers and decreased ejection fraction (minimum 22%). One patient had a noncoronary acute myocardial infarction, since absence of coronary artery lesions was confirmed by coronary angiogram.

Concerning to aHUS treatment and outcomes, an overview of them is outlined in Table 1. Plasma therapy, both small volume infusion of fresh–frozen plasma (n = 15, 75%) and plasmapheresis (n = 20, 100%), was initiated in all patients. In addition, some patients received immunosuppressant (cyclophosphamide or mycophenolate), low molecular weight heparin, antibacterial, and dialysis therapy). Twelve patients were on antiproteinuric agents, such as ACEI or ARA. Regarding eculizumab treatment, it induced clinical and laboratory normalization, and full reversal of TMA manifestations with restoration of renal and extra-renal functions after 4 weeks of its initiation in 4/8 patients treated within 1 week of presentation (Table 1). Eculizumab was discontinued following the induction phase in two patients who achieved clinical remission (renal and hematologic) as local availability was restricted. Despite initial decrease in the severity of renal and extra-renal manifestations after the first two infusions of the drug, 3/8 patients whose eculizumab initiation occurred at least 3 weeks postpresentation remained with slight proteinuria (> 500 mg/day) being on ACEI or ARA (Table 1). No side effects were observed with eculizumab treatment in this study. Heterozygous mutations in CFHR1–CFHR3 were detected in 1/8 genetic screening available (Table 1). This patient received eculizumab 1 month after initial disease presentation and reached complete remission of TMA and extra-renal aHUS manifestations. However, kidney function was not restored, ESRD developed possibly due to delayed initiation of eculizumab treatment. Antenatal mortality and mortality rate were 5% and 10%, respectively. Patients who died had higher LDH levels (1344 versus 1222 U/L) and more severe thrombocytopenia (12 versus 75 $10^3/mm^3$) than survivors. Five patients (25%) progressed to ESRD (Table 1). Genetic screening to assess alterations in complement regulatory proteins was available in 8/20 (40%) patients as outlined in Table 1. CFH 3/8 (37%) and CFI 2/8 (25%) mutations were the most frequent. One case reported C2 gene mutation as an alteration of uncertain significance for aHUS [13].

Table 2 Main laboratory parameters of aHUS patients

ID	Hemoglobin (g/dL) (M: 13.5–17.5; F: 12–15.5)	Platelets (10³/mm³) (150–450)	LDH (U/L) (250–500)	Total bilirubin (mg/dL) (0.2–1.3)	AST (U/L) (0–40)	ALT (U/L) (0–40)	Creatinine (mg/dL) (M: 0.9–1.3; F: 0.6–1.1)	24-h proteinuria (mg/day) (<150 day)	Serum C3 (mg/dL) (>90)	Serum C4 (mg/dL) (>10)
Normal range										
1	11.0	60	1993	12.9	945	980	1.4	520	52	25
2	5.4	58	2150	1.2	32	45	1.6	450	125	30
3	6.3	10	569	1.6	32	35	1.15	320	150	36
4	8.6	9	1018	1.5	29	30	1.72	300	95	15
5	9.1	16	575	0.5	16	15	4.76	120	46	16
6	7.9	140	2141	1.08	820	365	1.57	356	85	16
7	6.2	25	1900	1	35	38	1.62	140	48	22
8	5.4	115	1011	1	46	44	11.2	120	95	16
9	9.7	75	871	0.31	43	29	1.28	116	120	32
10	7.1	15	1670	0.4	52	48	2.58	1100	55	12
11	9.3	54	712	0.85	32	27	1.55	140	78	16
12	8.6	80	1589	3.7	57	48	2.65	115	65	30
13	9.2	97	785	0.6	19	64	5.17	300	76	16
14	12.1	45	567	1.13	547	439	3.12	130	69	20
15	9.5	110	555	0.6	598	560	1.7	893	72	13
16	9.0	77	1888	0.8	31	30	2.16	145	95	16
17	7.1	46	1930	2.3	45	42	1.56	2055	123	19
18	8.1	130	1125	0.3	52	43	1.52	120	130	16
19	6.5	64	697	5.5	109	41	1.66	450	60	25
20	8.5	120	942	0.7	42	40	10.7	130	45	30

LDH lactate dehydrogenase, *ALT* alanine transaminase, *AST* aspartate amino transferase

Discussion

This study describes a series of 20 adult cases with aHUS from the Colombian Caribbean region. Since all the evaluated patients had a preserved ADAMTS13, thrombotic thrombocytopenic purpura was ruled out as the cause of their TMA [1]. Some conditions are known to amplify complement and unmask latent complement defects resulting in aHUS manifestation in predisposed individuals. These potential precipitating factors include autoimmune diseases, transplants, infections, drugs, and metabolic conditions [2, 3, 6]. In the present study, 3 (15%) cases had aHUS autoimmune-related disease and 13 (65%) had bacterial or viral infection. Pregnancy is also a powerful complement activator, accounting for 7% of aHUS cases [17]. In this report, six (30%) had aHUS related to pregnancy/postpartum: 2/6 (10%) were pregnant for the first time and 4/6 (20%) had previously given birth to healthy children. Under physiological conditions, complement activation in pregnancy is regulated by three proteins which are present in the trophoblast membrane: decay-accelerating factor (DAF), membrane cofactor protein (MCP), and CD59. When complement system activation exceeds the regulatory ability of the previously mentioned proteins, injury is produced specially in the endothelial cells of human placenta. This phenomenon leads to the potential risk of premature deliveries and fetal loss, as observed in the present study [4, 18, 19].

Following delivery, mothers lose these placental protective mechanisms. This and the presence of inflammation, an extensively wounded uterus, influx of fetal cells into maternal blood, bleeding, and infection can lead to the systemic activation of the alternative complement pathway, and postpartum aHUS [18, 20]. Evidence of microangiopathic hemolytic anemia should be confirmed with a peripheral blood smear showing schistocytes and helmet cells [2, 17]. However, in this study, two patients showed no schistocytes in peripheral blood smear. This phenomenon could be explained since there are patients with intact reticuloendothelial system, which has the ability to rapidly remove peripheral blood schistocytes.

In addition, no significant alteration in serum transaminases, bilirubin levels, and haptoglobin levels were documented. Even though these values were not the theoretically expected ones in a setting of hemolysis, they represent the balance between production and removal of these substances, and not the presence or absence of hemolysis; thus, they could actually have any serum value [10]. Therefore, it is recommended to perform a serial sample on peripheral blood smear, and to be interpreted by an expert in hematologic cytopathology to confirm the presence of fragmented red blood cells [1, 21, 22]. Other

laboratory parameters consistent with hemolytic anemia are an elevated serum LDH level and a low serum haptoglobin concentration [17, 23]. In addition, Coombs test should be performed to rule out the presence of an autoimmune hemolytic anemia, therefore, being negative in cases of aHUS [9, 23, 24]. Kidney biopsy is not considered necessary to diagnose primary TMA, although it can be useful when secondary aHUS is suspected [3, 23]. In this study, biopsy was performed in patients with active systemic lupus erythematous or other suspected glomerular disease. A membranoproliferative glomerulonephritis pattern, a diffuse proliferative lupus nephritis (class IV–G) and a pauci-immune rapidly progressive glomerulonephritis associated to ANCA were detected. There is an established correlation between aHUS and membranoproliferative glomerulonephritis (C3 glomerulopathy) whose physiopathology involves genetic alterations in the regulatory proteins of the alternative complement pathway. Based on this finding, it has been hypothesized that both conditions could be the same entity with different phenotypes, varying from aHUS to C3 glomerulopathy (DDD or C3 glomerulonephritis) [4, 14, 23, 25]. Hypocomplementemia was seen in 60% of the cases; however, this finding is not very sensitive or specific, being reported in only 30–50% of cases [25]. Fakhouri et al. reported 85% of cases with disorders in the complement regulatory proteins, being CFI mutation frequently documented [18]. Huertas et al. [26] reported in his study cohort genetic disorders in 41% of cases, notably without MCP protein and anti-HF antibody mutations. Despite aHUS diagnosis is mainly clinic, and its treatment initiation does not depend on any genetic mutation identification, its presence should be ruled out because of its influence on nephropathy progression to ESRD, and the aHUS recurrence risk in kidney transplantation [2, 4, 23, 24]. In the present study, the different aHUS inducing identified mutations are detailed in Table 1. Because of the high morbidity and mortality associated with aHUS, it is crucial to have an understanding of the potential clinical manifestations of the disease and its associated laboratory findings to ensure prompt diagnosis and treatment [17]. aHUS typically is characterized by renal involvement [24]; however, medical literature is increasingly reporting extra-renal complications of the disease, including cardiovascular, neurological, pulmonary, and gastrointestinal [4, 19, 27]. Gastrointestinal complications of HUS are quite exclusive of Shiga-toxin-producing E. coli-associated HUS, whereas aHUS have usually mild or absent intestinal involvement [28]. In our study, gastrointestinal involvement ($n = 15$, 75%) was the most frequent extra-renal manifestation. Recent studies have evidenced that gastrointestinal complications and symptoms, as well as pancreatitis, are more common in aHUS with anti-factor-H autoantibodies [3,

17, 28]. Diarrhea is also observed in approximately 50% of patients preceding or during the acute phase of aHUS [17]. Thus, a further anti-factor-H autoantibodies assessment is required to identify a possible association in our population. Neurological manifestations (seizures, confusion, diplopia, blindness, hemiparesis, etc.) are usually described in 20–48% of the cases in the literature [21]. In the present investigation, it was documented that 11 patients (55%) presented some neurological manifestation, from altered state of consciousness, seizures to ischemic/hemorrhagic stroke. Cerebrovascular events occurred in three pregnancy-associated aHUS cases. Fakhouri et al. reported 4 patients (18%) with neurological manifestations in a cohort of 22 cases with pregnancy-associated aHUS [18]. In a collaborative work between the United Kingdom and Italy, Bruel et al. [29] described neurological involvement in 7 out of 87 cases (8%), similarly to another study published by Huertas et al. [26] describing 7 cases of neurological involvement. However, it should be pointed out that the study performed by Huerta et al. [26] was a specific descriptive study of only patients with aHUS associated with pregnancy, where 22 cases were studied, with 7 patients with neurological symptoms (7/22: 31.8%). On the other hand, in the present study, only six were associated with pregnancy, and two cases had neurological symptoms (2/6: 33%). Therefore, the frequency of neurological symptoms in our cases with pregnancy-associated aHUS was in fact similar to that reported by Huerta et al. [26]. Even more, the frequency of neurological symptoms was similar in this study to that reported in the literature, if all the reported patients are taken into account [6, 9, 21]. Thus, it seems that our population did not present more neurological compromise compared to other published reports. Pulmonary complications of aHUS are typically seen in cases of multiple organ dysfunction and pulmonary edema associated with cardiac dysfunction and/or systemic volume overload [17]. Bruel et al. [29] reported three cases, two had acute pulmonary edema, and one had pulmonary thromboembolism. In our study, progressive respiratory failure occurred in 12 patients due to pulmonary edema caused by acute respiratory distress syndrome or pulmonary sepsis. Most of the patients developed and required hemodialysis (59% of children and 81% of adults). Other manifestations of aHUS induced renal damage, aside from an elevated serum creatinine, were the presence of hematuria, proteinuria, and edema [3, 6, 30]. Kidney involvement, defined by an elevated serum creatinine, presence of dysmorphic hematuria, proteinuria, or/and altered renal imaging, occurred in all the studied patients. Those aHUS patients who required dialysis were the ones whose clinical presentation was a severe acute kidney injury. Clinical outcomes in aHUS were historically poor: over half of patients managed with plasma sustained permanent renal damage, progressed to ESRD, or died within 1 year of diagnosis [17]. Eculizumab, a monoclonal humanized antibody directed against C5, is the mainstay of treatment for aHUS [10], and it was initiated within 1 week of aHUS diagnosis in 4/8 patients. Hematological signs normalized and the function of damaged organs, including the kidneys, brain, and lungs, was fully restored after 4 weeks of treatment initiation. In those 3/8 cases whose eculizumab initiation occurred at least 3 weeks postpresentation remained with slight proteinuria. When eculizumab treatment was started later (1-month post-diagnosis) the outcomes in 1/8 case were ultimately unfavorable resulting in ESRD. Even our findings demonstrated the benefit of early treatment of aHUS with eculizumab, still it has certain limitations, the main one being the lack of available genetic screening, which would identify mutations in the genes of the complement system. However, identification of a complement mutation or anti-CFH inhibitory antibody is not required to make aHUS diagnosis nor to initiate therapy, still it does inform on prognosis and risk of recurrence.

Conclusion

This is the first series of atypical hemolytic uremic syndrome (aHUS) cases of Colombian Caribbean region being reported, and this study documented that aHUS in this region presented the classical clinical and epidemiological characteristics which characterize this condition, even presenting similar extra-renal manifestations than previously reported cases in the literature. This report also reinforces the concept that the delay in early diagnosis and effective treatment of this condition can lead to poor outcomes.

Declarations

Conflict of interest All the authors declare that they have no conflict of interest.

Ethical approval All the procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all the participants included in the study.

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