Residência RP Pediátrica
Publicação Oficial da Sociedade Brasileira de Pediatria
ISSN-Online: 2236-6814

Submitted on: 02/24/2022
Approved on: 10/02/2024

CASE REPORT

Hemolytic-uremic syndrome by genetic mutation DGKE: family case report in pediatrics

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Keywords:
Kidney failure, chronic, Hemolytic-uremic syndrome, Atypical hemolytic uremic syndrome, Diacylglycerol kinase.

Abstract

Hemolytic-uremic syndrome (HUS) is an important cause of acute kidney injury (AKI) in childhood and its most common etiology is Shiga toxin-producing *Escherichia coli* colitis. Genetic mutations in the complement system are responsible for rarer cases of HUS and were the only mutations related to this syndrome. New mutations unrelated to the complement system have been described in patients with HUS and the first of these mutations being found in the gene encoding the diacylglycerol kinase epsilon (DGKE). We report two cases of HUS by mutation in the DGKE gene in the first year of life of two related infants, given the rarity of this disease and the progression to chronic kidney disease, thus alerting to the importance of early diagnosis and proper treatment to reduce morbidity and mortality rates. The first one, a 4-month-old female with fever and cough evolved into generalized tonicclonic seizure, severe anemia, thrombocytopenia and acute renal injury. After remaining in serious condition, eculizumab treatment was started. Dialysis was performed for one year, after which there was a partial improvement in the kidney function. Eculizumab was administered for one year and eight months, which was suspended after the result of a genetic test confirmed mutation in DGKE gene. The second one, an 11-month-old female with a history of infection of the upper airways, diffuse rash and periorbital edema, anasarca, oligoanuria, anemia, thrombocytopenia and acute kidney failure. The patient underwent only one session of peritoneal dialysis, since there was an improvement in kidney function.

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Resid Pediatr. 2025;15(1).
DOI: 10.25060/residpediatr-2025.v15n1-849

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INTRODUCTION

Hemolytic uremic syndrome (HUS) is a significant cause of severe acute kidney injury (AKI) in children, characterized by microangiopathic hemolytic anemia, thrombocytopenia, and renal dysfunction[1]. It is one of the main differential diagnoses of thrombotic microangiopathies (TMAs) in pediatrics. HUS is primarily associated with Shiga toxin-producing Escherichia coli colitis (STEC-HUS)[2] in children. HUS can also be linked to genetic alterations, referred to in this study as atypical HUS (aHUS). aHUS was initially associated solely with complement system alterations, but recent studies have identified various genetic causes that vary in pathogenesis, treatment, and prognosis[3-5].

We report the case of two 7th-degree cousins with aHUS in their first year of life, one of whom was confirmed to have a mutation in the diacylglycerol kinase epsilon (DGKE) gene, which is associated with aHUS type 7.

CASE REPORT

First case:

A 4-month-old female infant with no complications during pregnancy or delivery and whose parents are 7th-degree cousins (Figure 1) was initially admitted for suspected pneumonia. She developed severe anemia, irritability, and generalized tonic-clonic seizures. She was referred to a tertiary hospital after presenting with microangiopathic hemolytic anemia, thrombocytopenia, azotemia, hyperkalemia (7 mEq/L), metabolic acidosis (10 mmol/L), and anuria (Table 1). Dialysis along with red blood cell and plasma transfusions was indicated. Clinical and imaging findings ruled out pneumonia.

Seven days later, the patient remained critically ill, experiencing fever, thrombocytopenia, anemia, anuria, and azotemia. Treatment for vitamin B12 deficiency was initiated with cyanocobalamin, and for aHUS, a monoclonal antibody was used to inhibit complement fraction C5 (eculizumab). Cyanocobalamin was discontinued after homocysteine levels normalized (5.4 micromol/L). Congenital thrombotic thrombocytopenic purpura (TTP) was ruled out with a normal ADAMST13 (a disintegrin and metalloproteinase with a thrombospondin motif repeats 13) level (activity 69%). Non-reactive serologies excluded several infections, including toxoplasmosis, rubella, cytomegalovirus, herpes, hepatitis, and human immunodeficiency virus. A diagnosis of aHUS due to genetic mutation was made by exclusion, and eculizumab was administered according to the recommended regimen based on body weight. Vaccination and antibiotic prophylaxis for meningococcus were provided at the start of treatment.

Despite improvements in anemia and thrombocytopenia, she remained hospitalized for seven months due to recurring severe infections, primarily related to catheters and reactivations of aHUS. She developed systemic arterial hypertension (SAH) and chronic kidney disease (CKD). She underwent dialysis for one year, during which she showed partial improvement in renal function but continued with conservative treatment. She received eculizumab for one year and eight months, but it was discontinued after a genetic test confirmed aHUS type 7 [DGKE – NM_003647.2 – homozygous likely pathogenic variant c.1068_1071del p (Asn356Lysfs*6)], showing no association with gene mutations of the complement system or the presence of anti-complement factor H antibody (CFH).

She was regularly monitored as an outpatient for four years, presenting stage 3 CKD with conservative treatment, SAH, and significant proteinuria.

Second case:

This case involves an 11-month-old female infant who experienced no complications during pregnancy and delivery. The infant's parents are third-degree cousins on the maternal side and fifth-degree cousins on the paternal side. She is related to the infant described in the first case through her great-great-grandparents (Figure 1). She was admitted 19 months after the patient in the first case. The infant had a history of upper respiratory tract infection symptoms for one month and a diffuse rash for 15 days, along with periorbital edema for three days, which progressed to anasarca, oliguria, choluria, and pallor. Upon admission, she was diagnosed with microangiopathic hemolytic anemia, thrombocytopenia, azotemia, nephrotic syndrome with severe dyslipidemia (total cholesterol: 486 mg/dL; triglycerides: 1127 mg/dL), and microscopic hematuria (Table 1). Peritoneal dialysis (PD) was indicated, requiring only one session. An ultrasound showed hyperechoic kidneys, an enlarged cortex, and preserved cortico-medullary differentiation. A kidney biopsy performed on the 18th day revealed: "two globally sclerotic glomeruli, 23 with signs of glomerular and arteriolar thrombotic microangiopathy with diffuse, organizing mesangiolysis; degenerative tubular epithelial changes with signs of atrophy and discrete interstitial fibrosis, and hyperplastic arteriolosclerosis."

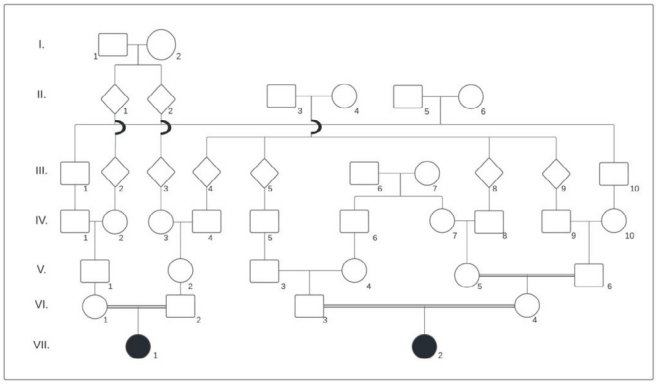


Figure 1. Pedigree of cases 1 and 2. Source: Prepared by the author based on research data.

Table 1. Laboratory tests on admission.

Initial Tests	Case 1	Case 2
Hemoglobin	3.4 g/dL	10.7 g/dL
LDH	1,853 U/L	1,653 U/L
Haptoglobin	Less than 8 mg/dL	Less than 8 mg/dL
Direct Coombs	Negative	Negative
Peripheral blood	Drepanocytes and crenated red blood cells	Schistocytes
Urea	156 mg/dL	120 mg/dL
Creatinine	5.4 mg/dL	2.1 mg/dL
Platelets	128,900/mm^3	109,900/mm^3

Source: Data collected by the author (patient charts).

The patient exhibited clinical and laboratory improvement and was discharged on the 36th day of hospitalization. She continued with regular outpatient follow-up for two years and presented with stage 1 CKD under conservative treatment, hypertension, and proteinuria.

DISCUSSION

TMAs are associated with the histopathological diagnosis of arteriolar and capillary thrombosis. They present as a clinical syndrome of microangiopathic hemolytic anemia, thrombocytopenia, and organ dysfunction. Advances in knowledge about the genetic and pathophysiological processes involved in syndromes associated with TMA have led to changes in its classification, although it is still ambiguous[6-8].

HUS is a syndrome associated with TMA. It primarily affects the kidneys and represents 0.2 to 4.2 out of 100,000 cases of AKI in children. The most prevalent form of HUS in pediatrics is linked to infectious processes, particularly intestinal infections caused by Shiga toxin-producing Escherichia coli (STEC-HUS). Conversely, HUS is associated with genetic alterations that lead to TMA[2].

Initially, aHUS was linked only to the dysregulated response of the complement cascade due to mutations in its genes (factor H, I, B, C3, and CD46) or antibodies against complement factor H. However, studies have uncovered autosomal recessive loss-of-function mutations in the gene encoding the DGKE[3-5] protein in patients with aHUS, marking the first identified gene associated with aHUS that does not involve components of the complement cascade[4,9]. A study conducted in England reported a population-year incidence of complement-mediated aHUS of 0.47 per 1,000,000 and of aHUS related to DGKE of 0.009 per 1,000,000 from 2013 to 2019[10].

The mechanism by which mutations in the DGKE gene lead to TMA is not well understood. Nonetheless, it is believed that this gene plays a role in maintaining the integrity of the endothelium of the renal microvasculature and in angiogenesis through the regulation of protein kinase C (PKC), suggesting that these mutations could activate a prothrombotic and proinflammatory state[11-12]. The expression of the DGKE gene has also been found in platelets and podocytes[11], leading to the belief that its dysfunction results in platelet activation and podocyte damage, the latter being associated with proteinuria or nephrotic syndrome observed in these patients[4, 5, 11].

In addition to the clinical signs of TMA, patients with aHUS caused by DGKE exhibit the following traits: onset of the disease in the first year of life, a family history of consanguinity, hypertension, microscopic hematuria, proteinuria, nephrotic syndrome, low to normal complement levels, and a need for dialysis[3,4,13]. Many of these characteristics were observed in the two cases (Table 2). Mutations in the DGKE gene have also been reported in patients with corticosteroid-resistant nephrotic syndrome (CRNS) and those with membranoproliferative glomerulonephritis (MPGN), indicating the association of the DGKE mutation with different phenotypes[5,13].

Table 2. Clinical and laboratory findings.

	Case 1	Case 2
Age at diagnosis	4 months	11 months
Family consanguinity	Yes	Yes
SAH[1]	Yes	Yes
Microscopic hematuria	Yes	Yes
Proteinuria	Anuria [a]	Yes
Nephrotic syndrome	Anuria [a]	Yes
Complement levels	Normal to low	Normal to low
Time on dialysis	One year	One day
Received eculizumab	Yes	No
Admitted to an ICU[2]	Yes	No

Source: Data collected by the author (patient charts).
1. Systemic Hypertension.
2. Intensive Care Unit.
a. The patient was anuric at admission; proteinuria could not be measured.

The specific treatment for aHUS associated with complement gene mutations aims to block the complement cascade using eculizumab. However, the treatment for aHUS due to DGKE remains controversial. Some studies suggest that aHUS caused by DGKE does not respond to eculizumab and recommend against starting the medication in highly suspected cases, as well as discontinuing it when a genetic mutation related to DGKE is diagnosed[1,10,11,] Other reports have shown a favorable response to this medication[15]. A study comparing patients with an isolated DGKE mutation to those with a DGKE mutation associated with complement mutations revealed more severe clinical progression in the latter group, yet a benefit from treatment with plasma and/or eculizumab[3]. Therefore, to date, the treatment for aHUS due to DGKE is supportive only, and further studies are necessary to evaluate the efficacy of blocking the complement cascade in this condition, as well as the impact of the medication when mutations are associated.

This article describes the cases of two seventh-degree cousins with aHUS in their first year of life who came from a

small town where inbreeding was common (Figure 1). The first patient presented a severe initial condition marked by a sudden and significant loss of kidney function. Due to the severity of the condition and the unavailability of genetic testing, eculizumab was prescribed, and prophylaxis against meningococcus was also necessary since this medication can block the complement cascade, thereby increasing the risk of meningococcal disease. Despite early treatment, the patient experienced anuria for 45 days and remained on dialysis for one year, without showing the expected initial improvement from kidney injury. Several factors could explain this progression: (i) the severity of the initial renal impairment, leading to delayed partial recovery, possibly due to the natural development of the kidneys at that age rather than the therapy; (ii) recurrent infections interfering with the treatment response and triggering aHUS; and (iii) the possibility of a mutation that may not respond to eculizumab. This last possibility was considered in this case since the genetic test revealed an isolated mutation of DGKE.

The second child exhibited a less severe condition, but the clinical outcome included CKD, hypertension, and massive proteinuria. Due to service limitations, the genetic study was not performed. Given the family history of aHUS connected to DGKE and the clinical presentation of aHUS with nephrotic syndrome in the first year of life, eculizumab was deemed inappropriate.

Although aHUS is rare, it represents a significant cause of AKI requiring dialysis and has the potential to progress to CKD in pediatric patients. Despite advancements in understanding its pathophysiology and the genetic tests used to identify the various mutations responsible for aHUS, clinical and genetic studies are still necessary to further knowledge and improve treatment for this disease.

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