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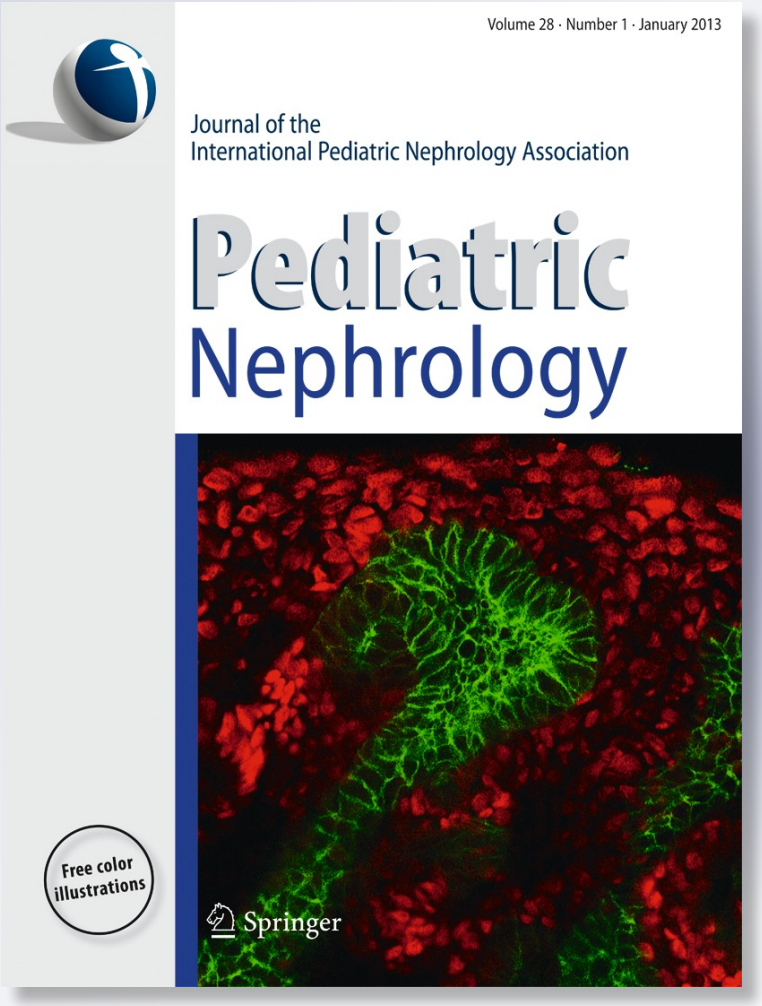

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BRIEF REPORT

Neonatal onset atypical hemolytic uremic syndrome successfully treated with eculizumab

Nesrin Besbas · Bora Gulhan · Diana Karpman · Rezan Topaloglu · Ali Duzova · Emine Korkmaz · Fatih Ozaltin

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Abstract
Background Atypical hemolytic uremic syndrome (aHUS) is characterized by the triad of microangiopathic hemolytic anemia, thrombocytopenia, and renal impairment. Neonatal cases are extremely uncommon. Plasma therapy is the first choice therapy in patients with aHUS based on the belief of an underlying complement dysregulation. Alternatively, eculizumab, which targets complement 5, is used to block complement activation.
Case-diagnosis/treatment Sudden onset macroscopic hematuria, hypertension, and bruises over the entire body were noted in a 5 day-old newborn. Investigations revealed hemolytic anemia, thrombocytopenia, renal impairment, and a low serum C3, leading to the diagnosis of aHUS. Fresh frozen plasma (FFP) infusions and peritoneal dialysis for acute kidney injury were initiated. This approach yielded full renal and hematological remission. The patient was discharged with FFP infusions, but subsequently developed three life-threatening disease recurrences at 1, 3, and 6 months of age. The last relapse presented with uncontrolled hypertension and impaired renal function while the patient was receiving FFP infusions. After the first dose of eculizumab, his renal and hematological parameters returned to normal and his blood pressure normalized. Genetic screening of the *CFH* gene revealed a novel homozygous p. Tyr1177Cys mutation.
Conclusion Eculizumab can be considered as an alternative to plasma therapy in the treatment of specific patients with aHUS, even in infants.

Keywords Atypical hemolytic uremic syndrome · Complement factor H mutation · Eculizumab · Newborn

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Introduction

Atypical hemolytic uremic syndrome (HUS) is a rare disease and is characterized by the triad of microangiopathic hemolytic anemia [hemoglobin (Hb) <10 g/dL] with fragmented erythrocytes (schistocytes), thrombocytopenia ($<150\times10^9$/L), and renal impairment (serum creatinine > upper limit of normal age) [1, 2]. Atypical HUS (aHUS) accounts for 5–10 % of all HUS cases and often results from complement dysregulation and mutations in genes encoding complement regulatory proteins or complement factors [2, 3]. These include mutations in genes encoding complement factor H (CFH), complement factor I (CFI), membrane cofactor protein (MCP), and factor B and C3, which are detected in more than 50 % of patients with aHUS. In certain patients antibodies against factor H may contribute to the disease, and these have been associated with deletions in factor H-related proteins 1 and 3 [4]. Mutations in the thrombomodulin gene have also recently been uncovered [5]. Inborn errors of cobalamin metabolism can also cause aHUS [6]. Cobalamin disorders form a large group of diseases that can appear from the first days or weeks of life to significantly later stages in childhood. There is a wide spectrum of clinical signs and symptoms related to cobalamin disorders, from neurological or psychiatric problems to multisystem disease with a more complex clinical picture. Among these, aHUS is the least common and has been

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described only in a small group of patients [6]. Patients with factor H mutations have the worst prognosis, with up to 60 % reaching end-stage renal disease within the first year after onset of the disease, and mortality is high among these patients [7]. Eculizumab, a new treatment modality for aHUS, is a recombinant, humanized monoclonal immunoglobulin G (IgG) antibody that targets complement 5 (C5) and blocks the cleavage of C5 to C5b, ultimately preventing the generation of the proinflammatory peptide C5b and the cytotoxic membrane attack complex C5b-9. Eculizumab has been described as an effective therapeutic strategy in the management of refractory aHUS that has failed to respond to plasma therapy [8].

Here we describe a newborn presenting with aHUS with a novel *CFH* mutation that was successfully treated with eculizumab.

Case report

A Caucasian male infant born at a gestational age of 40 weeks with a birth weight of 3.410 kg was admitted on day 3 of life with neonatal jaundice for phototherapy. He was the first born child of consanguineous parents, and the antenatal scans had revealed oligohydramnios. The complete blood count was normal at admission. On day 5, he developed macroscopic hematuria with bruises over his entire body and was noted to be significantly hypertensive at 150/90 mmHg. Laboratory parameters were as follows: Hb 6.2 g/dL; platelet count 66×10^9/L; white blood cell count 10,400/μL; blood urea nitrogen (BUN) 62.3 mg/dL (normal range 5–18 mg/dL); serum creatinine level 1.81 mg/dL (normal range 0.24–0.41 mg/dL). Serum electrolytes were within normal limits. Urinalysis showed hematuria and proteinuria, and renal ultrasound revealed patent renal blood vessels. His peripheral blood smear showed hemolysis, and the direct Coombs' test was negative. An increased blood level of lactate dehydrogenase (4,303 U/L) and a low level of haptoglobulin confirmed intravascular hemolysis, supporting the diagnosis of aHUS. The serum C3 level was low at 60.6 mg/dL (normal range 79–152 mg/dL); however, serum CFH and CFI levels were normal.

Genetic screening [the study was approved by the Hacettepe University Ethics Committee (FON 10/03–22) and the parents gave informed consent] detected a novel homozygous mutation in the gene encoding factor H, c.3530A>G (p. Tyr1177Cys) (sequence including the signal peptide), in which tyrosine was exchanged for cysteine (Fig. 1a). The parents were heterozygous for the same mutation (Fig. 1b). One hundred healthy Turkish children screened by direct sequencing showed only the wild-type sequence. No mutation was detected in the genes encoding factor I, MCP, C3, or factor B. No anti-CFH antibodies were detected. ADAMTS13 activity was normal. Urine methylmalonic acid test was also negative.

Plasma therapy (20 mL/kg/d) was initiated using fresh frozen plasma (FFP). Furosemide and nifedipine were given for hypertension. On day 10, the patient became oliguric and his creatinine level went up to 3.17 mg/dL; peritoneal dialysis (PD) was therefore initiated. These therapies yielded renal and hematological remission. He was discharged with daily FFP treatment. The frequency and dose of FFP was tapered according to the renal and hematological parameters. He developed three life-threatening disease recurrences at 1, 3 and 6 months of age during tapering of the frequency of FFP infusions. The first relapse was successfully treated by increasing the frequency of FFP infusions, and the second relapse was treated with FFP and PD for 10 days. The third relapse presented with severe hemolytic anemia (Hb 7.2 g/dL), hyperkalemia (6.3 mEq/L), and severely impaired renal function (BUN 78.2 mg/dL, creatinine 1.77 mg/dL). The frequency of FFP infusions was increased and PD was started due to impaired renal function and oliguria. Life-threatening hypertension had to be controlled with five different antihypertensive drugs (intravenous furosemide, intravenous nitroprusside, nifedipine, enalapril, and propranolol). As plasma exchange could not be performed due to technical difficulties, eculizumab treatment was initiated. It was given weekly for the first 3 weeks at a dosage of 300 mg and was thereafter continued every other week at

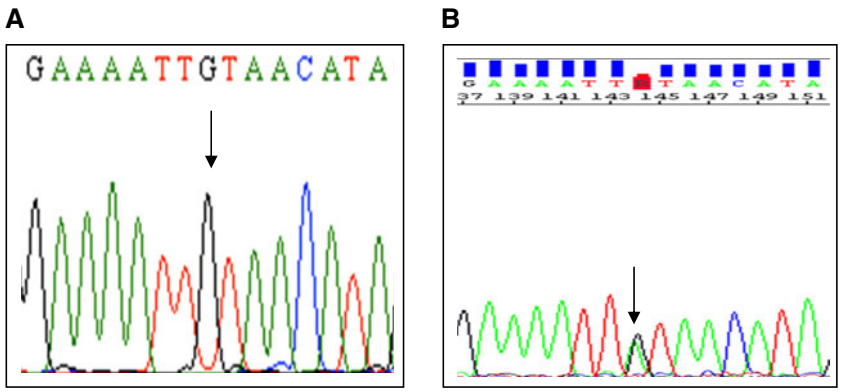

Fig. 1 Electropherograms of the patient (**a**) and one of the heterozygous parents (**b**). *Arrows* indicate the site of the c.3530A>G (p. Tyr1177Cys) mutation

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a dosage of 600 mg. Five days following the first dose, renal and hematological parameters returned to normal range and blood pressure normalized. FFP infusions were gradually decreased and eventually stopped. At the time of this report, the patient is 20 months of age and currently on eculizumab treatment every other week with completely normal renal and hematological parameters (Fig. 2).

Discussion

Although aHUS can affect patients of all ages, its prognosis correlates to a certain extent with the identified genetic defects. Here, we describe a case of neonatal onset aHUS with a novel homozygous *CFH* mutation that was successfully treated with eculizumab.

One of the possible diagnoses in our patient was congenital thrombotic thrombocytopenic purpura, which was excluded by normal ADAMTS13 activity. Methylmalonic aciduria-associated HUS was excluded due to a negative test for urine methylmalonic acid. He was not given any drug that could cause aHUS.

Atypical HUS is characterized by overactivation of the alternative complement pathway. Mutations have been found in genes encoding both complement regulators (CFH, CFI, and MCP) and complement activators (factor B and C3) in more than 50 % of patients [4]. Mutations in *CFH* are the most frequent genetic abnormality in aHUS patients. Complement factor H is a serum glycoprotein that is composed of 20 short consensus repeats. It is a cofactor for factor I-mediated proteolytic inactivation of C3b, competes with factor B for C3b binding, and accelerates the rate of decay of the C3 convertase. The majority of factor H mutations are heterozygous and located in the exons that encode the C-terminal domain of the protein [3, 8] responsible for host recognition. Mutations in *CFH* cause either quantitative or functional deficiency in CFH. A quantitative deficiency is defined as CFH levels below half of the normal range [9]. The majority of mutations in *CFH*, as detected in our patient, are associated with normal plasma levels of CFH (type 2 mutations). The plasma C3 level is decreased in 30–50 % of patients with heterozygous mutations of *CFH*. Our patient also had moderately decreased C3 levels [8].

Homozygous mutations in factor H are uncommon but have been reported in a few aHUS patients [10]. Homozygous mutations affecting cysteine bridges will affect the tertiary structure of the protein. As is evident in our patient, the mutation did not affect the secretion of factor H, as levels were normal, but it most probably affected its function, leading to early-onset of the disease.

Plasma infusion and plasma exchange therapies are the mainstay of treatment in aHUS. Plasma therapy can normalize soluble factors CFH, CFI, CFB, and C3. Plasmapheresis is a highly technical, complicated treatment and should be instituted in specialized centers only. On the other hand, it is known that the three pathways of the complement system converge at the level of C3, leading to the activation of C5 that is necessary for the development of aHUS [8]. Eculizumab is a monoclonal IgG antibody that targets C5 and prevents the generation of C5b and membrane attack complex C5b-9. To date, 17 patients treated with eculizumab have been published and presented at scientific meetings [8]. Among these, eight patients (six <18 years of age) were treated for aHUS with functional native kidneys, and the remainder were treated to prevent or treat post-transplant recurrence. In four of these six pediatric cases no mutation was identified; two patients had *CFH* mutations. The age

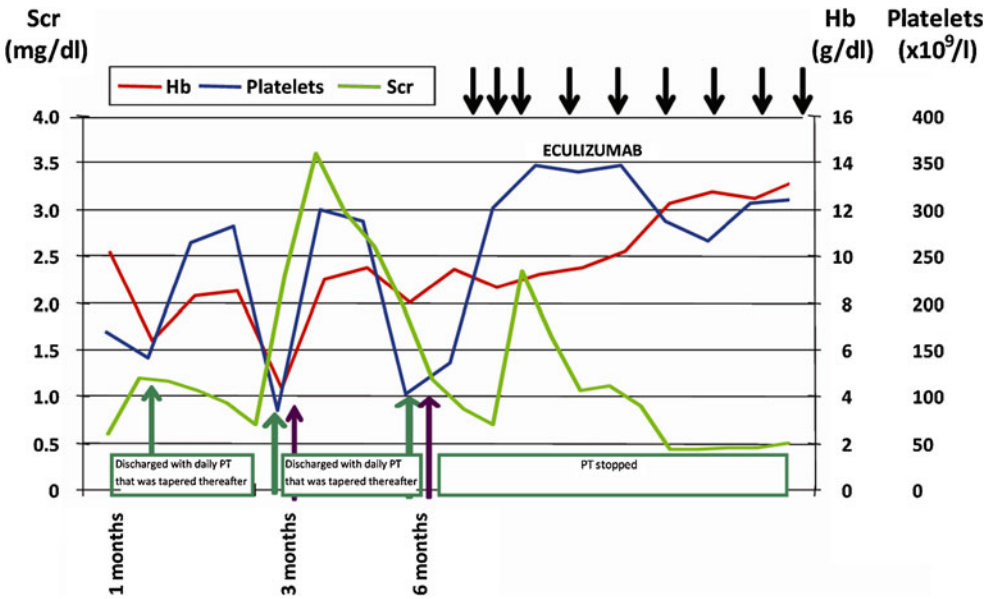

Fig. 2 Serum creatinine (*Scr*) and hemoglobin (*Hb*) levels and platelet counts of the patient before and after eculizumab treatment. Eculizumab was started at the third relapse and resulted in dramatic increases in both Hb levels and platelet count and was associated with a dramatic decrease in Scr levels. *PT* Plasma therapy

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range of eculizumab initiation in these patients was between 11 days and 18 years [11–15]. Our patient is one of the youngest patients in whom eculizumab therapy has been initiated. Our patient suffered from three life-threatening disease recurrences and was on chronic FFP therapy that failed to induce remission at the last recurrence. Therefore, eculizumab had to be initiated, and a very rapid response in terms of renal function, hematological parameters and normalization of blood pressure was observed after the first dose.

In conclusion, we identified a novel homozygous C terminal factor H mutation in neonatal aHUS. Eculizumab seems to be an effective therapy and can be used safely even in neonatal onset aHUS patients who fail to respond FFP treatment. However, the optimal duration and frequency of eculizumab therapy remain to be determined.

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