Partial Treatment with Exchange Transfusion in Neonatal Atypical Hemolytic Uremic Syndrome: Case Report

Abstract
Neonatal atypical hemolytic uremic syndrome is characterized by hemolytic anemia, thrombocytopenia and thrombotic microangiopathy. Disease caused by a genetic disorder in the alternative complement pathway. Although the traditional treatment methods are plasma infusion and plasmapheresis, C5 complement inhibitor eculizumab is the first treatment option in recent years. Here, we present 5 days old male newborn with direct/indirect hyperbilirubinemia, anemia, thrombocytopenia, hypertension and oliguria. Despite intensive phototherapy hyperbilirubinemia persisted and exchange transfusion was done. After exchange transfusion, his symptoms decreased gradually in 2 days. Two weeks after exchange transfusion, anemia, thrombocytopenia and oliguria occurred again. Hemodiafiltration was started. In genetic analysis, de novo homozygous factor H mutation (c.3493+1G>A) was revealed. Our patient is presented because of its rare occurrence in neonatal period and partly treated with blood exchange.

Keywords: Atypical hemolytic uremic syndrome; Factor H mutation; Exchange transfusion; Eculizumab

Introduction
Neonatal atypical hemolytic uremic syndrome (aHUS) is a rare disease caused by membrane attack complex activation due to hereditary or structural disorder in the alternative complement pathway. Endothelial damage caused by uncontrolled membrane attack complex activation results in thrombotic microangiopathy, hemolytic anemia, thrombocytopenia and renal damage, the classic triad of the disease. 50%-60% of these patients have a genetic mutation related to the complement pathway [1]. The sporadic or familial complement factor H mutation is in 30% of the patients with aHUS but a heterozygous mutation is seen in most cases [2]. Although plasma infusion, plasmapheresis and liver-kidney transplantation have proven treatment options for aHUS. Genetic disorder in the alternative complement pathway. Although the traditional treatment methods are plasma infusion and plasmapheresis, C5 complement inhibitor eculizumab is the first treatment option in recent years. Here, we present 5 days old male newborn with direct/indirect hyperbilirubinemia, anemia, thrombocytopenia and renal damage, the classic triad of the disease. 50%-60% of these patients have a genetic mutation related to the complement pathway [1]. The sporadic or familial complement factor H mutation is in 30% of the patients with aHUS but a heterozygous mutation is seen in most cases [2]. Although plasma infusion, plasmapheresis and liver-kidney transplantation have proven treatment options for aHUS. Monoclonal antibody eculizumab, which blocks the complement pathway by binding to complement protein C5, is the first choice of the treatment in recent years. In our article, neonatal aHUS case report is presented because of its rare occurrence in the newborn period and treated partially with different method.

Case Report
A male infant, born at 34 weeks gestation (birth weight 2.6 kg) to non-consanguineous parents, was hospitalized in a neonatal intensive care unit because of postpartum respiratory distress. On the 5th day after birth, he presented with direct/indirect hyperbilirubinemia, anemia, oliguria and transferred to our hospital for exchange transfusion. The mother had polyhydramniosis and diet-regulated gestational diabetes on antenatal follow-up. There was no family history of kidney disease and mother was taking no medications. On physical examination, skin color, periorbital-pretilial edema was seen. Blood pressure at admission was 137/98 mmHg. Amlodipine treatment was initiated due to hypertension. Because of high level indirect hyperbilirubinemia, intensive phototherapy was started and IVIG therapy (1 g/kg) was given twice in the previous hospital. Initial laboratory values of the patient; hemoglobin: 7.5 g/dL, platelet: 113.000/µL, reticulocyte: 2.27%, urea: 40 mg/dL, creatinine: 2.2 mg/dL, LDH: 1077 IU/L (545-2000 IU/L), total bilirubin: 18.9 mg/dL, direct bilirubin: 2.11 mg/dL, GGT: 209 IU/L, CRP: 0.08 mg/dL, lactate: 13.5 mmol/L ammonia: 109 g/dL. The mother’s blood
type was O, Rh positive, and the infant’s was O, Rh positive, direct coombs (+). G6PDH enzyme level and coagulation parameters were within normal limits. Subgroup incompatibility was not observed between mother and baby. Blood, CSF and urine cultures were taken and antibiotic treatment was started. Renal vein thrombosis was not detected in renal doppler USG. TORCH serology was negative. There was no pathology except for patent foramen ovale on echocardiography. Grade 1 subependymal hemorrhage was observed in transfontanel USG.

Erythrocyte and platelet transfusions were given. Despite intensive phototherapy, direct and indirect bilirubin level rising and double volume blood exchange was performed on postnatal 6th day. 24 hours after exchange transfusion, blood pressure values returned to normal and oliguria of the patient was improved. TANDEM, galactosemia panel, renin, aldosterone test results were normal. Hemolytic process was not considered in the patient because no schistocytes were seen on peripheral blood smear and normal serum LDH level. After 14 days of blood exchange (postnatal 21st day), patient had recurrence of anemia, thrombocytopenia with hypertension, edema and decreased urine output. Serum LDH 1077 IU/L and schistocytes were found on peripheral smear. The patient was diagnosed with neonatal atypical hemolytic uremic syndrome (aHUS) with current clinical and laboratory findings. Peritoneal dialysis was started. After 48 hours of peritoneal dialysis, no urine output was seen. Plasmapheresis was started. Plasmapheresis therapy continued for 14 days, his clinical and laboratory findings were improved. Genetic analysis revealed homozygous factor H mutation (c.3493+1G>A). ADAMTS-13 activity was determined as 87, 86% (40%-130%). Eculizumab treatment was started after the patient was in remission on the postnatal 54 days. Eculizumab was administered 300 mg once a week for the first two weeks, 300 mg once every three weeks (Alexion pharmaceuticals www.alex.com). One week after the first dose of eculizumab (postnatal 61st day), the 13- valent conjugated pneumococcal, polysaccharide meningococcal ACY and W-135, Haemophilus inf. type b tetanus toxoid vaccines were administered, followed by a prophylactic dose of amoxicillin (20 mg/kg/day) for 2 weeks. aHUS is predominantly susceptible to encapsulated bacterial infections due to blockade of the complement pathway. In our patient, no infection was seen other than urinary tract infection was found due to K. pneumoniae.

Although eculizumab treatment is a safe treatment option in infants with aHUS, optimal dose-related studies are needed.

Homozygous factor H mutation is rarely reported in patients with aHUS, and the complement factor H is not completely seen in these patients and C3 levels are low [9-11]. These patients often experience failure after relapse and plasma exchange [12]. Although plasma replacement is still the first recommended treatment in the guidelines for the complete lack of complement factor H, the possibility of recurrence of the disease and inability to improve renal function may persist after treatment. Complement factor H homozygote mutation was also detected in our patient and had a partial response to the first blood exchange procedure. Our patient who was diagnosed with aHUS at the youngest age in the literature is 14 months old now, still taking eculizumab treatment and no relapse has been observed so far.

Discussion

Although eculizumab is the first choice in the treatment of aHUS, peritoneal dialysis and plasmapheresis can be applied. Because indirect bilirubin level didn’t decrease by intensive phototherapy and IVIG treatment, blood exchange was considered as the first choice. With blood exchange, we performed partial plasmapheresis inadvertently. The temporary well-being period after blood exchange lasted approximately 14 days. Considering this remission period, blood exchange in newborns with suspicion of aHUS may provide a safe approach until transport to the center of hemodialysis. The appropriate dose range for newborns is not known for eculizumab, which is the first choice for the treatment of the disease [3,4]. In the patient treated by Ariceta et al., eculizumab dosing of 150 mg resulted in a sub-therapeutic eculizumab level of 19.1 µg/mL (goal=50-100 µg/mL) and hematological relapse that responded to dosing at 300 mg [4]. We also applied 300 mg eculizumab in hematologic relapse after blood exchange and received clinical response 48 hours after treatment. No side effects were observed.

As a result of immunosuppression due to the use of eculizumab, the need for vaccination and use of prophylactic antibiotics against N. menigitidis is required [5-7]. Antibiotic prophylaxis is recommended for 2 weeks if eculizumab is administered within 2 weeks after meningococcal vaccination [8]. One week after the first dose of eculizumab treatment, 13-valent conjugated pneumococcal, polysaccharide meningococcal ACY and W-135, Haemophilus inf. type b tetanus toxoid vaccines were administered, followed by a prophylactic dose of amoxicillin (20 mg/kg/day) for 2 weeks. aHUS is predominantly susceptible to encapsulated bacterial infections due to blockade of the complement pathway. In our patient, no infection was seen other than urinary tract infection was found due to K. pneumoniae. Although eculizumab treatment is a safe treatment option in infants with aHUS, optimal dose-related studies are needed.

Recommended immunization schedule for persons aged 0-18 years is recommended for 2 weeks if eculizumab is administered within 2 weeks after meningococcal vaccination [8]. One week after the first dose of eculizumab treatment, 13-valent conjugated pneumococcal, polysaccharide meningococcal ACY and W-135, Haemophilus inf. type b tetanus toxoid vaccines were administered, followed by a prophylactic dose of amoxicillin (20 mg/kg/day) for 2 weeks. aHUS is predominantly susceptible to encapsulated bacterial infections due to blockade of the complement pathway. In our patient, no infection was seen other than urinary tract infection was found due to K. pneumoniae. Although eculizumab treatment is a safe treatment option in infants with aHUS, optimal dose-related studies are needed.

References

6. Centers for Disease Control and Prevention (2014) Recommended immunization schedule for persons aged 0
through 18 years.


