

# Atypical hemolytic uremic syndrome due to factor H autoantibody

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Atypical hemolytic uremic syndrome (aHUS) is a disease caused by pathologies in the alternative complement system. The prevalence of aHUS is 10% of all aHUS cases. The subgroup of aHUS designated as DEAP (DEficiency of CFHR Proteins and CFH Autoantibody Positive)-HUS because of autoantibody to complement factor H (CFH) and CFH-related protein deficiency is seen very rarely, and the prevalence is 6% of all aHUS cases in the literature. We present here a female patient with DEAP-HUS. A 7.5-year-old girl with recurrent attacks of HUS had low C3 level. We initiated plasmapheresis treatment. After further analysis of the complement system, the result was compatible with DEAP-HUS, so we initiated immunosuppressive treatment. There were also family members with deficiency of CFHR-1 and CFHR-3, but they had no CFH autoantibody and no symptoms of HUS. In atypical cases of HUS, we should investigate complement status, especially for factor H autoantibody, for which treatment options differ from those of the other types of aHUS.

**Key words:** atypical hemolytic uremic syndrome, complement, autoantibody, complement factor H, complement factor H-related protein.

Hemolytic uremic syndrome (HUS) is a predominantly pediatric condition that consists of the triad of hemolytic anemia with fragmented erythrocytes, thrombocytopenia and acute renal failure. The underlying histological lesion is thrombotic microangiopathy<sup>1</sup>. The typical or post-diarrheal (D+) form of HUS is the most frequent (90% of patients), and the remaining 10% of HUS are categorized as atypical form (D-negative)<sup>2</sup>. The atypical form of HUS (aHUS) may be sporadic or familial and has a poor prognosis, as approximately 50% of patients progress to end-stage renal disease (ESRD)<sup>1</sup>.

A subgroup of aHUS, which consists of deficiency of complement factor H-related (CFHR) proteins and autoantibodies to complement factor H (CFH), is defined as DEAP-HUS (DEficiency of CFHR Proteins and CFH Autoantibody Positive)<sup>3</sup>. This subgroup is seen very rarely; the prevalence is 6% of all aHUS cases in the literature<sup>4</sup>.

Here we present a patient with DEAP-HUS.

## Case Report

A 7.5-year-old female presented to the Emergency Department with fever, vomiting, abdominal pain for four days, and dark urine for one day. She had no diarrhea or any other infection in the past month. She had no oliguria. Her past history was unremarkable. There was third-degree consanguinity between the parents. No kidney disease was defined in her family. Her weight was 20 kg (50-75 percentile), height 126 cm (75-90 percentile), blood pressure 115/70 mmHg (95P: 116/76 mmHg), body temperature 37.2°C, heart rate 96/min, and respiratory rate 28/min. She appeared very pale. On physical examinations, she had hepatomegaly, palpated 1-2 cm below the costal margin. On laboratory investigation, she had anemia and thrombocytopenia (hemoglobin: 6.7 g/dl, platelet: 18.000/mm<sup>3</sup>). The peripheral smear disclosed many fragmented erythrocytes. Direct Coombs test was negative. Lactate

**Table I.** The Factor H Antibody Titers and Time of Analysis

Time of analysis	The titer of factor H antibody (arbitrary unit/ml)
At the beginning of the 2nd attack	395
At the beginning of the 3rd attack	1750
After 30 sessions of plasmapheresis after the 3rd attack	512

dehydrogenase (LDH) was 2553 U/L (N: 135-214 U/L). She had renal failure (blood urea nitrogen [BUN]: 71 mg/dl, serum creatinine 1.2 mg/dl, uric acid 9.2 mg/dl, estimated glomerular filtration rate [eGFR]: 43.3 ml/min/1.73m<sup>2</sup>), hematuria (3+ blood on dipstick test and many erythrocytes in urine sediment), and proteinuria (3+ on dipstick test, 58 mg/m<sup>2</sup>/hour). Plasma complement C3 level was low (59 mg/dl; N>90). With a diagnosis of aHUS, plasmapheresis with 50 ml/kg was initiated on alternate days. After four sessions of plasmapheresis, both hematological and renal remission was achieved and she was discharged on the 10th day of admission. One month after discharge, when she presented with malaise and pallor, her serum creatinine was 1.76 mg/dl, eGFR 29 ml/min/1.73m<sup>2</sup>, hemoglobin 4.9 g/dl, and platelet count 66,000/mm<sup>3</sup>. As she had recurrent attacks of HUS with low C3 level, a blood sample was sent for factor H levels to Leibniz Institute for Natural Product Research Laboratory. After a total of 14 sessions of plasmapheresis (first 5 sessions daily and following 9 sessions on alternate days), serum creatinine was 1 mg/dl, eGFR 52 ml/min/1.73m<sup>2</sup>, hemoglobin 9.9 g/dl, and platelets 190.000/mm<sup>3</sup>. She had a third attack 10 days after discontinuing plasmapheresis therapy. At this time, serum creatinine was 4 mg/dl, eGFR 13 ml/min/1.73m<sup>2</sup>, hemoglobin 6.8 g/dl, and platelets 81,000/mm<sup>3</sup>. Plasmapheresis was re-initiated. Meanwhile, the complement results were attained and we found that she had autoantibodies to factor H with a deficiency of CFHR-1 and CFHR-3 levels, compatible with DEAP-HUS. As immunosuppressive treatments were recommended for patients with DEAP-HUS to suppress the formation of autoantibodies<sup>3</sup>, an immunosuppressive treatment containing high-dose intravenous methylprednisolone followed by prednisolone, intravenous cyclophosphamide (500 mg/m<sup>2</sup>/dose, monthly) and azathioprine (2 mg/kg/day) was introduced in addition to plasmapheresis. Hemodialysis was also

administered for a total of 30 sessions because of hypervolemia and uremia. After 30 sessions of plasmapheresis with immunosuppressive treatment, serum creatinine was 2.1 mg/dl, cystatin C 3.92 mg/dl, and eGFR 20 ml/min/1.73 m<sup>2</sup> with hematological remission; 37 sessions of plasmapheresis were performed in total, after which fresh frozen plasma (FFP) was administered every two weeks. The antibody titer dropped from 1750 arbitrary unit/ml to 512 after 30 sessions of plasmapheresis (Table I).

Four months after the first admission, she had a generalized tonic-clonic convulsion. A brain magnetic resonance imaging (MRI) revealed changes in the cortical intensity at the left temporal and bilateral parietal lobes without diffusion restriction on diffusion MRI. Electroencephalogram was compatible with encephalopathy. As she had central nervous system involvement of HUS, intravenous immunoglobulin (IVIG, 1 g/kg) was given; convulsion did not recur. At follow-up, azathioprine was changed to cyclosporine (CsA) because of leukopenia. After six months of therapy with CsA, it was changed to mycophenolate mofetil because of the cosmetic side effects of CsA. After a total follow-up period of 20 months, her serum creatinine was 2.1 mg/dl and cystatin C was 3.3 mg/dl, with an eGFR of 23 ml/min/1.73m<sup>2</sup>. She was receiving prednisolone 5 mg/day and mycophenolate mofetil 1 g/day for five months in addition to FFP bimonthly. The course of serum creatinine is shown in Figure 1.

## Discussion

The guidelines recommend checking for alternative causes of HUS for the disorders of complement regulation in patients without diarrhea or with diarrhea having any one of the following: age younger than six months, a relapse of HUS, suspected previous HUS, previous unexplained anemia, or a family

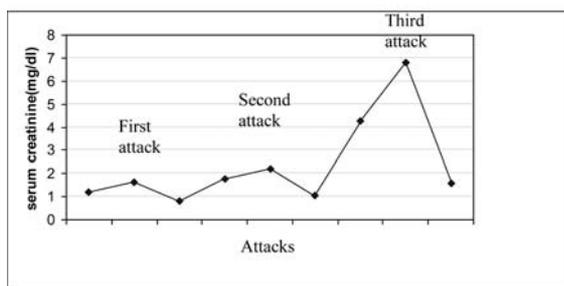


Figure 1. Serum creatinine levels during the attacks.

history of HUS<sup>5</sup>.

Complement is activated by three pathways: the classical pathway, the lectin pathway and the alternative pathway. These three pathways converge at the point of cleavage of C3. There are also regulatory proteins that control the complement system. There are many soluble and membrane-associated complement regulatory proteins. CFH is the most important protein in the regulation of the alternative pathway. CFH inhibits the formation of the alternative C3-convertase and accelerates its decay. CFH and CD46 serve as cofactors for the complement factor I, which is the other regulatory protein. Both genes encoding CFH and CD46 are localized on the long arm of chromosome 1, a locus called regulators of complement activation (RCA) that contains genes encoding different regulatory proteins of complement activation<sup>1</sup>. CFH captures C3b, which is generated by the alternative pathway and prevents formation of C3 convertase. This activity causes the prevention of the amplification in the complement cascade and is the major defensive mechanism of host cell surfaces from alternative pathway activity. The acquired type of complement regulation was shown due to autoantibody to CFH. In this group of patients, the plasma concentration of CFH and the CFH gene were normal<sup>2</sup>. In the present patient, CFH level was normal but antibody to CFH was detected.

Zipfel et al.<sup>3</sup> defined the acquired type of complement regulation with autoantibody to CFH as DEAP-HUS. In these patients, there is absence or deficiency of CFHR proteins CFHR-1 and CFHR-3 in the plasma. This subgroup of HUS is characterized by the combination of acquired and genetic factors. The acquired factor is the autoantibodies to CFH, which is the central complement inhibitor. The genetic factor

causing the production of antibodies to CFH is the absence or deficiency of CFHR-1 and CFHR-3 plasma proteins as a result of homozygous chromosomal deletion on chromosome 1. In the present patient, the family members were also screened for aHUS, and it was found that her father and one of her sisters were also deficient for CFHR-1 and CFHR-3 without autoantibodies. It is not known what triggers the formation of antibodies in patients lacking CFHR-1 and CFHR-3.

The autoantibodies in DEAP-HUS patients are of the IgG3 and/or IgG1 subclass and characterized to bind the C- terminal surface binding region of CFH<sup>6</sup>. As a result, these autoantibodies block the surface binding of CFH and cause the reduction in the protective function of CFH on the cell surface<sup>3</sup>. It was demonstrated that deficiency in CFHR-1 and CFHR-3 was strongly associated with CFH autoantibody<sup>6</sup>. The data suggest that the onset of disease or disease recurrence correlates with the presence of CFH autoantibody<sup>7</sup>.

In the present patient, hemolysis could be stopped by four sessions of plasmapheresis at the first admission. At the 2nd and 3rd attacks, we had to prolong the number of the plasmapheresis sessions. An intense immunosuppressive treatment was also administered to prevent the formation of autoantibodies and to avoid further renal injury, which protected her from ESRD. The rate of ESRD in aHUS differs according to etiology. It was reported as 30-40% in DEAP-HUS<sup>7</sup>.

Interestingly, autoantibodies exist in the plasma of patients with DEAP-HUS in two forms: a free form and a form bound to CFH as autoantibody-factor H complexes. The common enzyme-linked immunosorbent antibody (ELISA) assays identify the level of free antibodies, but they do not detect autoantibodies complexed to CFH. Thus, the actual level of autoantibodies may be even higher than the value obtained using the assay<sup>3</sup>. In the present patient, as the antibody titers decline, she might have higher bound antibody to CFH causing renal damage.

Rapid diagnosis of DEAP-HUS is important to initiate appropriate therapy. The primary focus of treatment is to reduce the autoantibody titers. The overall treatment goal is restoration of a physiological balance between activation and control of

the alternative pathway<sup>3</sup>. Plasmapheresis treatment for these patients should be enhanced to eliminate circulating autoantibodies and immunosuppressive treatments should also be started. Immunosuppressants like corticosteroids, azathioprine, mycophenolate, cyclophosphamide, and rituximab have been used<sup>8,9</sup>. However, there has been no consensus in the literature regarding the immunosuppressive therapy in patients with DEAP-HUS. Thus, it is difficult to treat this group of patients.

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