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Paediatric Atypical Haemolytic– Uremic Syndrome on The Ravulizumab Therapy

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Abstract

Introduction: Atypical Haemolytic – Uremic Syndrome (aHUS) is a rare clinical condition made of microangiopathic hemolytic anemia, thrombocytopenia, and acute renal failure. It differs from other hemolytic uremic syndromes in etiology and treatment. In this view, according to the last classification, hemolytic-uremic syndrome (HUS) is divided into hereditary and acquired HUS, whereby the obtained can be: infection-induced HUS and HUS induced by non-infectious agents (aHUS). In any of its forms, HUS is a difficult and life-threatening clinical condition; therefore, it is essential to make a diagnosis and start with treatment.

Objective: Indicate the importance of establishing an early diagnosis and starting with treatment of HUS as soon as possible, which is one of the most common causes of acute renal failure in children. By establishing early diagnosis and rapid therapeutic intervention, we can favorably affect the reduction of severe and chronic consequences of HUS.

Case report: A boy at the age of 11 in poor general condition, aware, tachypneic, bradycardic, hypertensive, edematous, icteric skin, and sclera, was admitted to the Intensive Care Unit (ICU) of our Clinic; he complained of intense abdominal pain and vomited. In the laboratory findings, we verified the indicators of hemolytic anemia, thrombocytopenia, and increased parameters of acute renal failure. Only rare schistocytes were visible at the peripheral blood smear. Proteinuria and macrohematuria were present in the urine. Given the clinical features, it was clear that it was thrombotic microangiopathy and that an urgent and decisive therapeutic approach was needed. Immediately upon arrival to the ICU, the dialysis catheter and central venous catheter were placed in the analgosedation, and the treatment of therapeutic plasmapheresis (TPE) was started on the first day. Plasmapheresis was conducted for the first three days per protocol.

On the third day, due to the progression of renal insufficiency and heavier volume load, we started veno - venous hemodiafiltration (CVVHDF). Further, the blood purification methods (TPE and CVVHDF) were performed one after another until the urination and normalization of the laboratory blood findings were re-established. In the meantime, the microbiological and gene treatment findings arrived, confirming atypical hemolytic uremic syndrome. Given the excessive activity of complement, aHUS have a poor prognosis if not treated with complement inhibitors. Complement component C5 blocker therapy, Ultomiris (eculizumab) manufacturer *Alexion Europe SAS* was prescribed. Before the treatment, meningococcal vaccination was initiated, and antibiotic prophylaxis for pneumococcus was included as the drug increases the risk of infections with encapsulated pathogens. The laboratory findings were normalized gradually. The patient is in excellent general condition and is released home after three weeks of treatment, with standard laboratory parameters and with no signs of disease. According to the treatment protocol, five doses of eculizumab should be received until the subsequent re-evaluation of his clinical condition.

Conclusion: Timely diagnostic treatment is essential in aHUS' clinical approach to avoid severe side effects on the patient's health and life. Monoclonal antibody therapy that inhibits the C5 complement component (eculizumab or eculizumab) should be initiated immediately after diagnosing aHUS. If the drug is not immediately available, the plasmapheresis should be started without any delay until the cure arrives.

Keywords: hemolytic uremic syndrome, acute renal failure, hemolysis, thrombocytopenia, plasmapheresis

Introduction

Hemolytic uremic syndrome (HUS) is a rare clinical condition of microangiopathic hemolytic anemia, thrombocytopenia, and acute renal failure. It is the most common cause of acute renal failure in children **[1]**.

With thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS) belongs to the thrombotic microangiopathies in children. A clinical feature of these conditions is occlusive microvascular thrombosis. In the affected tissue we can find the thickened walls of blood vessels, edema and separation of endothelial cells from the basal membrane, obstruction of the lumen of blood vessels, and fragmentation of erythrocytes **[2]**.

Hemolytic uremic syndromes in children differ in etiology and treatment. According to the last classification, HUS is divided into hereditary and acquired HUS, whereby the obtained can be: infection-induced HUS and HUS induced by non - infectious agents (aHUS and secondary HUS). The most common form of HUS is post-infectious, typical HUS caused by E.coli, which produces Shiga toxin (STEC – Shiga toxin–producing E.coli or EHEC – Enterohemorrhagic E.coli) **[3,4]**. The secondary HUS is often related to malignant disorders, autoimmune diseases, drugs, pregnancy, and septicemia. Atypical HUS is connected to the condition of alternative pathways of complement. About 5-15 % of aHUS cases in children are triggered by streptococcus infection. This form appears most often until the age of two, and it is mainly caused by serotypes of pneumococcus, which are not covered by vaccination **[4]**. The hereditary HUS is the consequence of the gene mutation for regulatory proteins and components of the alternative pathway of complement. The most frequent mutations of the gene, confirmed at aHUS, are the mutations at genes for proteins: C3 and CD46 and mutations at genes for the factors of complements H, B, and I. The modifications of the gene for DGKE - diacylglycerol kinase epsilon also cause the hereditary form of aHUS, but the complement pathway is intact in this form of the disease **[5]**. The mutations, confirmed for regulatory proteins of the complement, represent the risk-bearing factor for the occurrence of the return case of HUS even after kidney transplantation. The particular risk is born by gene mutations, which code the proteins of the component, i.e., CFH, C3, CFB, and CFI mutation **[6]**.

HUS is a problematic and life-threatening clinical condition; therefore, it is essential to make a diagnosis in time and start with treatment as soon as possible to avoid severe and chronic consequences of this syndrome for the life and health of the patient.

Case Report

A boy at the age of 11, who was ill just one day before he was admitted to the Intensive Care Unit (ICU), of poor general condition, febrile up to 40°C, aware, tachypneic, with breathing frequency of 35/min, bradycardic, with a pulse frequency of 48/min, hypertensive, arterial pressure 150/80 mmHg, edematous, icteric skin and sclera, was admitted at the Intensive Care Unit (ICU) of our Clinic; he complained of intense abdominal pain and vomited, he was oliguric (0.5 ml/kg/h). In the laboratory findings, we verified the indicators of hemolytic anemia (E 3.2 T/L, Hgb 91 g/L, Hct 0.24 L/L, haptoglobin 0.030 g/L, LDH 1710 U/L, total bilirubin 119 umol/L), thrombocytopenia (Trc 19 G/L) and raised parameters of acute renal failure (urea 27.3 mmol/L, creatinine 474 umol/L). Only rare schistocytes were visible at the peripheral blood smear. Proteinuria and macrohematuria were present in the urine.

Coagulogram was normal, d-dimers >4.25 mg/L. The results of immunological tests were also expected (ds-DNA, C-ANCA, P-ANCA, Anti-GBM, Atvs. b2 glycoprotein, Atvs. cardiolipin); C4 test result was expected, while C3 was on the lower level of the reference value (0.9 g/L). Given the clinical features and laboratory test results, it was clear that it was thrombotic microangiopathy and that an urgent and decisive therapeutic approach was needed. Immediately upon arrival to the ICU, the dialysis catheter and central venous catheter were placed in the analgosedation, and the treatment of therapeutic plasmapheresis (TPE) was started on the first day. The plasmapheresis was conducted for the first three days per protocol. On the third day, due to the progression of renal insufficiency, anuria, and heavier volume load, we started veno - venous hemodiafiltration (CVVHDF) with systemic anticoagulation with heparin. In the next ten days of treatment, the blood purification methods (TPE and CVVHDF) were performed one after another until the urination and normalization of the laboratory blood findings were re-established. The boy was repeatedly receiving fresh frozen plasma.

Antibiotics, gastro prophylaxis, and antihypertensive were included in the therapy. In the meantime, the microbiological and gene treatment findings arrived, which excluded the infection-caused HUS. The smears of upper breathing airways, hemoculture, urine culture, a spot of the rectum, coculture, and verotoxin, and the rapid virus infection tests all arrived with negative values. Gene analyses of the mutations of genes and factors of complements related to the occurrence of aHUS resulted in no pathological deviations. Further laboratory tests indicate dysregulation and excessive activity of alternative pathway of the addition, C3 is on the lower level, and sC5b-9 (terminal complex of complement) is multiplied increased – 829 ng/mL (ref. 110-252 ng/mL). With all those above clinical and laboratory indicators, the level and activity of protease are average, which breaks the von Willebrand factor (ADAMS 13 – the action of 53 %), which indeed excludes thrombotic thrombocytopenic purpura and confirms another thrombotic microangiopathy, i.e., atypical hemolytic uremic syndrome at the boy. Given the diagnosis, we indicated the therapy with inhibitors of the complement system and started the treatment with eculizumab (Ultomiris, produced by *Alexion Europe SAS*).

The drug increases the risk of infections by encapsulating pathogens such as N. meningitidis and S. pneumonia, because of which the meningococcal vaccination was initiated before the therapy, and antibiotic prophylaxis for pneumococcus was included until the pneumococcal vaccination arrived. The first loading dose of ravulizumabwas applied according to the treatment protocol. The laboratory findings were normalized gradually. The second maintenance dose was applied two weeks after the first dose with previously planned vaccinations. The patient is in excellent general condition, and the laboratory parameters are normal (E 4,1 T/L, Hgb 118 g/L, Hct 0.33 L/L, Trc 268 G/L, haptoglobin 0,68 g/L, LDH 300 U/L, total bilirubin 21 umol/L, urea 5.9 mmol/L, creatinine 72 umol/L, C3 1,68, C4 0,36 g/L), and shows no signs of disease.

According to the protocol, our patient needs to receive 3 more doses of keeping eculizumab in the internals for 8 weeks until the subsequent re-evaluation of his clinical condition.

Discussion

The hemolytic uremic syndrome also affects adults but is more frequent in children. It equally appears in male and female children, and infective causes of the upper respiratory tract or gastroenteritis most often trigger it. Although diarrhea is closely connected to infection-induced HUS, in about 24% of cases, patients with atypical HUS can have infective gastroenterocolitis **[7]**. Atypical HUS mainly causes renal dysfunction even though extrarenal complications are also possible, including neurological symptoms and hypertension in about 10-30 % of patients. Neurologic symptoms are more often at TTP **[8]**. Symptoms of CNS dysfunction during the aHUS are anxiety, cerebral seizures, diplopia, hemiplegia, blindness, stupor, and coma. About 3 % of patients had a myocardial infarction **[7]**. Since no specific markers would indicate immediately at the beginning of the disease's clear atypical HUS, we use a wide range of the laboratory tests mentioned above and microbiological and gene analyses to come to an accurate diagnosis as quickly as possible. While waiting for the results, we definitely must not delay the beginning of the treatment because it may lead to chronic kidney disease and the need for long-lasting replacement renal therapy. Significant pathophysiologic developments at aHUS are dysregulation and disorder of the activation of the alternative pathway of the complement. About 30-40 % of the patients have no gene changes in the base of the hemolytic uremic syndrome, while approximately 20 % have normal renal function **[8]**. In the late stage of the aHUS, the disease may also affect the lungs, which has not been described so far in the case of TTP **[9]**. For a long time, the core part of treating atypical hemolytic uremic syndrome was the therapy with plasma and plasmapheresis. In 70 % of cases, the plasmapheresis leads to the remission of aHUS. The procedure of the exchange of plasma needs to be started within 24 hours after setting the diagnosis, and it needs to be conducted every day until the hematologic parameters are recovered, i.e., primarily thrombocytes, LDH, and hemoglobin. The remission usually develops in 7 to 10 days with plasmapheresis. If, even after 3 to 5 days, the thrombocytopenia and hemolysis persist – the disease is considered to be resistant to the plasma therapy; therefore, the treatment needs to be modified, and the application of the monoclonal blocker of the C5 component of complement needs to be started. The patients with the form of the aHUS, caused by mutation of the membrane cofactor protein (MCP) gene, have no favorable clinical response to the plasma therapy because the MCP protein is not the protein of plasma. The secondary HUS can also have an inadequate response to plasma therapy **[10]**.

Atypical HUS is treated today with monoclonal antibody therapy that inhibits alternative pathways of the complement on the level of C5 protein. The drug that was most often used was eculizumab. In the last years, in the therapy of this clinical entity – also the drug eculizumab appeared, which has the same effects as its predecessor, but for four times longer half-life, and it is applied in longer time intervals because of which it is at the forefront of the eculizumab in the choice of therapy for atypical pediatric HUS **[5]**.

The therapy is mostly well endured, and the primary defect is the risk of infection with encapsulated bacteria, especially meningococcus and pneumococcus since it blocks the terminal component of complement; because of this, it was indicated to carry out the vaccination against these causes before the therapy as well as to include antibiotic prophylaxis during the first two weeks until adequate immunology response of the organism matures. The prevention is most often conducted by penicillin/cephalosporin antibiotics **[11]**. Ravulizumabis dosed according to weight, and it is given in one loading dose; after that, the first maintenance dose is given after 15 days; after that, the same three more doses are given in intervals of 8 weeks.

Conclusion

Since it is about a child with aHUS diagnosis, which was successfully resolved to its end at our Clinic regarding diagnosis and therapy, our objective was to show that timely diagnostic and therapeutic treatment was essential in the clinical approach of the atypical hemolytic uremic syndrome. Severe and complicated side effects to the health and life of the patient were avoided by such an approach. Our recommendation is to start immediately with the therapy with a monoclonal antibody that inhibits the components of C5 complement (eculizumab or eculizumab) upon diagnosing the aHUS. If the drug is unavailable immediately, the plasmapheresis must be started with no delay until the cure arrives, which we have also done for our patient while guided by such instructions.

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