Pneumococcal associated haemolytic uremic syndrome following invasive pneumococcal disease in a 2-year-old girl

Pneumokokno povezani hemolitsko-uremički sindrom nakon invazivne penumokokne bolesti kod dvogodišnje djevojčice

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--- Summary ---

The haemolytic uremic syndrome is characterized by microangiopathic haemolytic anaemia, thrombocytopenia and acute renal failure and is the most common in children under the age of 4. The etiology can be associated with some infectious agents like Streptococcus pneumoniae. We review the case of a 2-year-old girl presenting with invasive pneumococcal disease followed by the haemolytic uremic syndrome. The onset of the haemolytic uremic syndrome clinical manifestation was preceded by un upper respiratory tract infection. The physical finding was in extremely bad condition with pallor. She was adinamic, confused, dispnoic, dehydrated with peripheral circulatory failure. Tubular breath sounds with moist rales on both sides of the lung were registered as well as liver and spleen enlargement. Presenting clinical and laboratory data we confirmed that, in our case, following the invasive pneumococcal disease (pleuropneumonia, sepsis and septic shock), Streptococcus pneumoniae was the trigger of HUS. High doses of corticosteroids, fresh frozen plasma, antibiotics, and intravenous immunoglobulins were a successful treatment.

Key words: haemolytic uremic syndrome; invasive pneumococcal disease; child

--- Sažetak ---

Hemolitičko-uremički sindrom karakterizira mikroangiopatska hemolitička anemija, trombocitopenija i akutno zatajenje bubrega. Najčešće se javlja u djece u dobi mlađoj od 4 godine. Etiologija je povezana s nekim infektološkim agensima kao što je Streptococcus pneumoniae. Prikazali smo slučaj dvogodišnje djevojčice s invazivnom pneumokoknom bolesti s hemolitičko-uremičkim sindromom. Bolest je počela infekcijom gornjeg respiratornog trakta. Djevojčica je primljena u vrlo teškom stanju, ekstremno blijeda, adinamična, konfuzna, dispnoična, dehidrirana u kolapsu periferne cirkulacije. Obostrano nad plućima čuli su se brojni bronhitički hropci, a jetra i slezena su bile uvećane. Klinički i laboratorijski potvrdili smo da je u djevojčice pneumokokna invazivna bolest (pleuropneumonija, sepsa i septički šok) uzrokovana Streptokokom pneumonije potaknula nastanak hemolitičko-uremičkog sindroma. Uspješno izlječenje postignuto je primjenom visokih doza kortikosteroida, svježe smrznute plazme, antibiotika i intravenoznih imunoglobulina.

Ključne riječi: hemolitičko-uremički sindrom, invazivna pneumokokna bolest, dijete

Introduction

The haemolytic uremic syndrome (HUS) is an acquired hematological disorder largely affecting infants and young children. Microangiopathic hemolytic anemia, acute renal failure, and thrombocytopenia are the symptoms of this syndrome. HUS with unknown etiology is most common in children under the age of 4. It has most often been associated with enterohaemorrhagic Escherichia coli O157:H7 and some infectious agents like Streptococcus pneumoniae.[1,2,3,4,5,6,7,8] Renal

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biopsy samples show vasculopathy as a consequence of the thrombosis of the arteriolar and glomerular microcirculation. Trombocytopenia is the result of platelet consumption. Some authors published HUS events in children who underwent hematopoietic stem cell transplantation for various malignances and others cyclosporine or chemotherapy related.[9,10,11]

HUS is the most common cause of acute renal failure in childhood resulting from mechanical damage to the red blood cells as they pass through the altered vasculature. Some divide the HUS Clinical syndrome into two groups: diarrhoea-associated HUS (D+HUS) mainly affecting children under the age of 5 years, while non-diarrhoea-associated HUS (D-HUS) are rare in children. D-HUS characterised triad of HUS without diarrhoeal prodrome, and some authors define it as atypical HUS (aHUS).[12]

Streptococcus pneumoniae associated HUS (SP-HUS) may occur in all seasons.[2] Pneumococci produced neuraminidase and remove the N-acetyl-neuraminic acid from cell membrane surfaces exposing the Tomsen-Friedenreich antigen present on erythrocytes, platelets, and glomerular capillary walls to circulating blood elements.[2,13] Antigen-antibody interaction results in hemolysis, thrombocytopenia and renal microangiopathy. Immune complexes may have contributed to the endothelial injury and the pathogenesis of HUS.[14] HUS diagnosis can be established by clinical and laboratory findings such as normocytic and normochromic anemia with high reticulocite count, the evidence of burr cells or schistocytosis on the periferal blood smear, platelet count bellow 100×10^9/L, marked elevation of blood urea nitrogen and serum creatinine. Depending on the degree of haemolysis, there is an increase in reticulocytes, plasma lactate dehydrogenase, unconjugated bilirubin, ferritin, with a decrease in serum haptoglobin levels. Those parameters are very sensitive and it is a way to control the intensity of haemolysis.

HUS usually is not associated with plasma coagulation abnormalities or diffuse intravascular coagulopathy (DIC). DIC is rare in HUS, and plasma coagulation abnormalities are highly suggestive of septicaemia as the cause of HUS.[8] The mortality rate during the acute phase is high (3-5%), but early recognition and proper treatment may result with a favourable outcome.[15]

Case report

We review the case of a previously healthy 2-year-old girl presented in extremely bad condition at the time of admission. An upper respiratory tract infection and bilateral pneumonia eight days earlier, with persistent fever, pallor, and weakness preceded the onset of clinical manifestation. At home she was treated with a cephalexin and azitromycin, but aggravation of the symptoms proceeded.

Physical examination on admission to hospital revealed lethargy, and dehydration. She was extremely pale with jaundice, adinamic, confused, dysponic, dehydrated with a pallor and peripheral circulatory failure. On both sides of the lung tubular breath sounds with moist rales were confirmed. The liver was enlarged by 5 cm, and the spleen by 3 cm. Initial laboratory findings were ESR 160 mm./hr.: WBC $98,6 \times 10^9$/L; RBC $1, 8 \times 10^{12}$/L; haemoglobin 5,1 g/dl; haematocrit 15,0%; platelet count 106×10^9/L; reticulocytes 115‰. There was no evidence of burr cells or schistocytosis on the peripheral blood smear.

Direct, indirect and monospecific Coombs test was negative, AST 110 U/l, ALT 69 U/l, LDH 2247 U/l, feritin 2686 ng/ml, haptoglobin 0,113 g/l, blood urea 44.4 ml/l, and creatinin 116 umol/l, acidum uricum 1014 umol/l, prothrombin time (PT 3) 26,8", APTV 27", fibrinogen 4,0 g/l, Factor II 25%, Factor V 30%, Factor VII 21%, Factor VIII 55%, fibrin degradation products (FDP) 256 ug/ml, potassium 2,8 mmol/l, sodium 131,0 mmol/l, chloride 92 mmol/l, calcium 2, 47 mmol/l, magnesium 0,98 mmol/l. Streptococcus pneumoniae grew on blood culture and on pharyngeal swab. Urinalysis showed mild proteinuria.

Ultrasound showed enlargement of the kidneys with hyperechogenic changing in parenchyma. A chest radiograph showed that the child had clinical and radiographic evidence of both sided pleuro-pneumonia.

A bone marrow examination confirmed normal megakaryocytopoiesis with erythroid hyperplasia with dyserythropoietic elements.

Three days after admission she manifested melena. Intravenous antibiotics (vancomycin, amycacin, ceftazidim, and eight days after ceftriakson) were started. Fluid balance management was ordered because of hypovolemia caused by vomiting. She was treated with high doses (10 mg/kg) of methyl-prednisolone for nine days, with subsequent tapering till the 42nd day. She received transfusion of packed erythrocytes and fresh frozen plasma for the first two days. Supportive therapy such as alopurinol, furosemid, intravenous immunoglobulins (IVIG), and multivitamines were given. Because of iron deficiency, oral administration of ferrous proteinsukci-nilate was ordered. After 36 days, she reached complete stabile remission. Ten years later, our patient was healthy without any consequences.

Discussion

HUS occurs with some systemic conditions and treatment of the triggering cause is very important.[8] It is a rare but severe complication of invasive pneumococcal infection in children. Patients with SP-HUS commonly have a pneumonia or meningitis and have poor clinical outcome.[16]

An increased incidence of SP-HUS has been noted in the United Kingdom between January 1998 and May 2005. Its frequency has increased compared with historic surveys, and early mortality remains high.[17]

In children with SP-HUS, pneumococcal pneumonia with empyema is the most common precipitating illness (67%), while pneumococcal meningitis (17%), pneumonia with bacteremia (8%), and pneumonia with meningitis (8%) are less frequent. SP-HUS patients have more severe renal and hematologic disease than D+ HUS patients. However DIC can also occur in these children.[18]

Some authors revealed cytokine disturbances in patients with HUS. Tumor necrosis factor (TNF) may play the role in the pathogenesis of HUS.[19] Elevated granulocyte-colony-stimulating-factor (G-CSF) serum concentrations with leucocytosis may be found.[20] Several studies of cytokine levels such as IL-6 and TNF-α in the serum of the HUS patients suggested that IL-6 plasma levels were significantly elevated.[21,22] The exact consequences of elevated IL-6 serum concentrations are still unknown, such as the cause of those elevations.

New investigations indicate that corticosteroids are immunomodulators that inhibit the action of various cytokines.[23] Steroids seem to be associated with a more rapid decline in serum creatinine levels.[24] Endogenous glucocorticoid secretion attenuates HUS severity in mice.[25]

Acute mortality remains high in patients with SP-HUS (18.9%).[16] Most patients die in the early phase. High doses of corticosteroids (10 mg/kg) were beneficial in the presented HUS case, and our patient achieved a complete remission without any impairment approved after ten years of follow up.

Conclusion

Our report suggests that it is extremely important to recognize SP-HUS very early, and start adequate treatment. This complication, associated with DIC, our patient expressed following invasive bilateral pneumococcal pleuropneumonia, sepsis and septic shock. High doses of corticosteroid, fresh frozen plasma, antibiotics, and IVIG were a successful treatment. Such therapeutic approach may increase the survival rate and prevent renal impairment.

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