

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

*Pneumokokno povezani hemolitsko-uremički sindrom nakon invazivne
pneumokokne 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 an upper respiratory tract infection. The physical finding was in extremely bad condition with pallor. She was adynamic, confused, dispoic, 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 pneumoniae* 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

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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. Thrombocytopenia is the result of platelet consumption. Some authors published HUS events in children who underwent hematopoietic stem cell transplantation for various malignancies 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-acetylneuraminic 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 reticulocyte count, the evidence of burr cells or schistocytosis on the peripheral blood smear, platelet count below $100 \times 10^9/L$, 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 septicemia 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, adynamic, confused, dyspnoic, 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 $106 \times 10^9/L$; 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, ferritin 2686 ng/ml, haptoglobin 0,113 g/l, blood urea 44.4 ml/l, and creatinin 116 $\mu\text{mol/l}$, acidum uricum 1014 $\mu\text{mol/l}$, 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 $\mu\text{g/ml}$, 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 pleuropneumonia.

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 ceftriaxon) were started. Fluid balance management was ordered because of hypovolemia caused by vomiting. She was treated with high doses (10 mg/kg) of methylprednisolone 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 proteinsukcinate was ordered. After 36 days, she reached complete stable 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.

References

- Huang FY, Lin DS. Pneumococcal meningitis complicated with hemolytic syndrome: report of two cases. *Chung-Hua Min Kuo Hsiao Erh Ko I Hsueh Hui Tsa Chih.* 1998;39:58-61.
- Cabrera GG, Fontenberry JD, Warshaw BL, Chambliss CR, Butler JC, Cooperstone BG. Hemolytic uremic syndrome associated with invasive *Streptococcus Pneumoniae* Infection. *Pediatrics.* 1998;101:699-703.
- McTaggart SJ, Burke JR. *Streptococcus pneumoniae*-induced haemolytic uraemic syndrome. *J Paediatr Child Health.* 1998;34:192-5.
- Morabito S, Karch H, Mariani-Kurkdjian P, Schmidt H, Minelli F, Bingen E, Caprioli A. Enterohemorrhagic, Shiga toxin-producing *Escherichia coli* O111:H2 associated with an outbreak of hemolytic-uremic syndrome. *J Clin Microbiol.* 1998;36:840-2.
- Henning PH, Tham EB, Martin AA, Beare TH, Jureidini KF. Hemolytic-uremic syndrome outbreak caused by *Escherichia coli* O111:H-: clinical outcomes. *Med J Australia* 1998;168:552-5.
- Oshima T. Predictive factors for development of hemolytic uremic syndrome (HUS) and early intensive treatments for prevention of HUS enterohemorrhagic *Escherichia coli* infection. *JPN J Antibiot.* 1997; 50:855-61.
- Karmali MA, Petric M, Lim C, Fleming PC, Arbus G, Lior H. The association between idiopathic haemolytic uraemic syndrome and infection by verotoxin-producing *E coli*. *J Infect Dis.* 1985;151:775-82.
- Neild GH. Haemolytic-uraemic syndrome in practice. *The Lancet.* 1994;343:398-401.
- Kondo M, Kojima S, Horibe K, Kato K, Matsuyama T. Hemolytic uremic syndrome after allogeneic or autologous hematopoietic stem cell transplantation for childhood malignancies. *Bone Marrow Transpl.* 1998;21:281-6.
- Bren AF, Kandus A, Buturović J, Koselj M, Kaplan Pavlović S, Ponikvar R, Kovac D, Lindić J, Vizjak A, Ferlunga D. Cyclosporine-related hemolytic-uremic syndrome in kidney graft recipients: clinical and histomorphologic evaluation. *Transplant P.* 1998;30:1201-3.
- Van der Heijden M, Ackland SP, Deveridge S. Haemolytic uremic syndrome associated with bleomycin, epirubicin and cisplatin chemotherapy - a case report and review of the literature. *Acta Oncol.* 1998;37:107-9.
- Amirlak I, Amirlak B. Haemolytic uraemic syndrome: an overview. *Nephrology. (Carlton)* 2006;11:213-8.
- Klein PJ, Bulla M, Newman RA, Müller P, Uhlenbruck G, Schaefer HE, Krüger G, Fisher R.

- Thomsen-Friedenreich antigen in haemolytic-uraemic syndrome. *Lancet*. 1977;2:1024-5.
14. Agapitos E, Pavlopoulos PM, Vaiopoulos G, Davaris P. Primary Sjogrens syndrome complicated by hemolytic uremic syndrome. *Scand J Rheumatol*. 1996;25:263-5.
 15. Sivamurthy S, Mooney JD, Kenny TD. Atypical haemolytic uraemic syndrome presenting initially as suspected meningococcal disease: a case report. *J Med Case Reports*. 2007;1:122.
 16. Lee CF, Liu SC, Lue KH, Chen JP, Sheu JN. Pneumococcal pneumonia with empyema and hemolytic uremic syndrome in children: report of three cases. *J Microbiol Immunol Infect*. 2006;39:348-52.
 17. Waters AM, Kerecuk L, Luk D, Haq MR, Fitzpatrick MM, Gilbert RD, Inward C, Jones C, Pichon B, Reid C, Slack MP, Van't Hoff W, Dillon MJ, Taylor CM, Tullus K. Hemolytic uremic syndrome associated with invasive pneumococcal disease: the United Kingdom experience. *J Pediatr*. 2007;151:140-4.
 18. Brandt J, Wong C, Mihm S, Roberts J, Smith J, Brewer E, Thiagarajan R, Warady B. Invasive pneumococcal disease and hemolytic uremic syndrome. *Pediatrics*. 2002;110:371-6.
 19. Harel Y, Silva M, Giroir B, Wainberg A, Cleary TB, Beutler B. A reporter transgene indicates renal-specific induction of tumor necrosis factor (TNF) by Shiga-like toxin: Possible involvement of TNF in hemolytic uremic syndrome. *J Clin Invest*. 1993;Vol 92:2110-6.
 20. Vierzig A, Roth B, Querfeld U, Michalk D. A 12-year-old boy with fatal hemolytic uremic syndrome, excessive neutrophilia and elevated endogenous granulocyte-colony-stimulating-factor serum concentrations. *Clin Nephrol*. 1998;50:56-9.
 21. Karpman D, Andreasson A, Thysell H, Kaplan BS, Svanborg C. Cytokines in Childhood Hemolytic Uremic Syndrome and Thrombotic Thrombocytopenic Purpura. *Pediatr Nephrol*. 1995;9:694-9.
 22. Martin AA, Woolven BL, Harris SJ, Keeley SR, Adams LD, Jureidini KF, Henning PH. Plasminogen activator inhibitor type-1 and interleukin-6 in haemolytic uraemic syndrome. *J Paediatr Child Health*. 2000;36:327-31.
 23. Perez N, Spizzirri F, Rahman R, Suarez A, Larrubia C, Lasarte P. Steroids in the hemolytic uremic syndrome. *Pediatr Nephrol*. 1998;12:101-4.
 24. Kalashnikova EA, Kokarovtseva SN, Pakhul'skiĭ AL. Increased proinflammatory cytokine production by human peripheral lymphocytes treated with glucocorticoids. *Vestn Ross Akad Med Nauk*. 2000;(10): 37-45.
 25. Gómez SA, Fernández GC, Camerano G, Dran G, Rosa FA, Barrionuevo P, Isturiz MA, Palermo MS. Endogenous glucocorticoids modulate neutrophil function in a murine model of haemolytic uraemic syndrome. *Clin Exp Immunol*. 2005;139:65-73.