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Case Report / Приказ болесника

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Hemolytic uremic syndrome complicating whooping cough

Хемолитичко уремички синдром као компликација великог кашља

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SUMMARY

Introduction We are presenting a case of a two-month-old infant who has developed a hemolytic uremic syndrome as an atypical complication of *Bordetella pertussis* infection. The observation that the development of hemolytic uremic syndrome is a late complication of *Bordetella pertussis* infection may be a clue to plan such studies.

Case outline A two-month-old female infant was admitted to our hospital because of fever, intensive cough, shortness of breath and poor feeding. Real-time polymerase chain reaction for *Bordetella pertussis* was positive. A macrolide was introduced in therapy. On the 8th day of hospitalization, the infant's condition improved, she became afebrile and eupneic. On the 16th day of hospitalization, she developed signs of progressive respiratory distress and oliguric acute kidney injury. Hemolytic uremic syndrome was diagnosed, so we started the therapy with the fresh frozen plasma transfusion, therapeutic plasma exchange, and peritoneal dialysis. Levels of ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) were decreased, while the levels of factor H, factor B and factor I were normal. Despite the full supportive and targeted care, severe multiple organ failure developed and on the 24th day of hospitalization the infant died.

Conclusion Further studies are necessary to identify the mechanism of potential interaction between pertussis toxins, pathophysiology of the infection and the interaction of complement activation, coagulation and the regulation of these cascades.

Keywords: hemolytic uremic syndrome; pertussis; infant

САЖЕТАК

Увод Приказан је случај двомесечног одојчета које је развило хемолитичко уремички синдром као атипичну компликацију инфекције бактеријом *Bordetella pertussis*. Чињеница да је развој хемолитичко уремичког синдрома касна компликација инфекције бактеријом *Bordetella pertussis* може бити полазна тачка за планирање даљих студија.

Приказ болесника Двомесечно женско одојче је хоспитализовано на Клинику за педијатрију због повишене температуре, интензивног кашља, диспнеје и одбијања хране. *Real-time polymerase chain reaction* на бактерију *Bordetella pertussis* је био позитиван. Започета је терапија макролидима и осмог дана хоспитализације клиничко стање детета се побољшало, постало је афебрилно и еупноично. Шеснаестог дана хоспитализације дете је развило клиничке знаке прогресивног респираторног дистреса и олигуричног акутног бубрежног оштећења. Дијагностикован је хемолитичко уремијски синдром, те је започета терапија трансфузијама свеже смрзнуте плазме, а затим и терапија изменама плазме и перитонеумска дијализа. Нивои металопротеиназе *ADAMTS13* су били снижени, док су нивои фактора *H, B* и *I* били нормални. Упркос спроведеној терапији, у даљем току, долази до развоја мултиорганске дисфункције и 24. дана хоспитализације долази до смртног исхода.

Закључак Потребне су додатне студије да би се утврдили механизми потенцијалне интерреакције између токсина пертусиса, патофизиологије инфекције и интеракције активације комплемената, коагулације и регулације ових каскада.

Кључне речи: хемолитичко уремички синдром; велики кашаљ; одојче

INTRODUCTION

Typical features of hemolytic uremic syndrome (HUS) are microangiopathic hemolytic anemia and acute thrombocytopenia, accompanied by acute kidney injury. In addition to infections with Shiga-like toxin-producing *Escherichia coli* (STEC-HUS), complement alternative pathway dysregulation may also predispose to atypical HUS (complement mediated aHUS). HUS may also develop in the context of severe infections, including for example Streptococcus pneumoniae, Shigella dysenteriae and *Bordetella pertussis*, various viruses - H1N1 influenza, Cytomegalovirus and

Parvovirus B19 [1, 2, 3]. In addition to thrombotic thrombocytopenic purpura (TTP) and STEC-HUS, aHUS is classified in a group of thrombotic microangiopathies (TMA).

The incidence of aHUS and TTP is around 3/1,000,000 among children younger than 18 years. Patients with TTP have good therapeutic response to plasma exchange (PE), whereas this is not the case in patients with aHUS. Mortality in patients with TTP is around 10%, and 25% in patients with aHUS during the acute phase [4, 5].

Despite the fact that vaccine is widely available, Bordetalla pertussis infections are still very common. The classic symptoms of pertussis are paroxysmal whooping cough, marked leukocytosis and related pulmonary leukostasis. So far, only four cases of HUS associated with *Bordetella pertussis* infection have been described in the literature [6, 7, 8, 9].

CASE REPORT

A two-month old female infant was admitted to our hospital due to fever, intensive cough, shortness of breath and poor feeding. First symptoms have begun two days before admission.

Five days before admission, she received a combined five-component vaccine (Diphtheria, Tetanus, Pertussis – acellular component, Poliomyelitis (Inactivated) Vaccine (Adsorbed) and Haemophilus Influenza Type B Conjugate Vaccine). She was second child of the healthy non-consanguineous parents, born at term, birth weight 2900 g. Prenatal and perinatal period went without any complications.

On admission, she was conscious and alert, febrile, with normal vital parameters and normal body weight of 4800 g. Lung auscultation revealed wheezing and bilateral, fine, late-inspiratory crackles on the bases of the lungs. All other physical findings were normal.

Initial laboratory findings are shown in Table 1. All other biochemical findings were within the normal ranges. Chest X-rays revealed pulmonary consolidation in perihilar and basal regions of the right lung and, also, regions of hyperinflation on both lungs. Ultrasound of the brain and abdomen showed normal findings.

The initial treatment included inhaled corticosteroids and bronchodilators and parenteral antibiotic therapy (ceftazidime). Despite the therapy, the child's condition worsened and she became tachydyspnoic, pale, adynamic and continuously febrile. On the 5th day of hospitalization, marked leukocytosis was registered (Table 1). Peripheral blood smear showed prevalence of mature

segmented granulocytes with toxic granulations, with normal red blood cell and platelet count and morphology.

Microbiologic and serologic tests confirmed the diagnosis of *Bordetella pertussis* infection (whooping cough). Real-time polymerase chain reaction (PCR) for B. pertussis was positive. Blood cultures were negative.

A macrolide was introduced in therapy. On the 8th day of hospitalization, the infant's condition improved, she became afebrile and eupneic. This clinical melioration was accompanied with marked improvement of laboratory findings and reduction of WBC count.

On the 16th day of hospitalization, the infant's condition suddenly worsened again. She had frequent attacks of heavy cough and developed signs of progressive respiratory distress with consequent oxyhemoglobin desaturation. She became edematous (gained more than 600g in weight for two days), with a decreased urine output (0.61 ml/kg/h), and hypertensive (BP 128/66 mmHg) so the infant was admitted to Intensive Care Unit (ICU).

On admission to ICU, laboratory tests showed elevated procalcitonin levels, elevated WBC count, signs of hemolytic anemia and mild thrombocytopenia, as well as the signs of renal failure (Table 1). Peripheral blood smear revealed anisocytosis, polychromasia, presence of schistocytes and erythroblasts. Reticulocytes 23%, haptoglobin levels were <0.10 g/l (0.3-2.0 g/l). Lactate dehydrogenase 64.15 μkta/l (< 7.52 μkta/l). Urea 15.8 mmol/L (1.8-6.0 mmol/l), creatinine 328.5 μmol/l (14-34 μmol/l), uric acid 1311 μmol/l (65-319 μmol/l). Blood gas analysis showed decompensated metabolic acidosis. Hemostasis screening tests were normal.

Those clinical and laboratory findings raised suspicion of the presence of HUS, so we started the therapy with the fresh frozen plasma (FFP) transfusion. Hypertension was treated with calcium channel blocker.

Next day (17th hospital day), the infant became extremely tahidyspnoic, hence, she was intubated and mechanical ventilation was initiated. Because the child became anuric, the same day, Tenckhoff catheter for peritoneal dialysis (PD) was inserted and continuous peritoneal dialysis was immediately started. The dialysis solution with 2.3% glucose was used initially, and then after the edema was gone it was replaced with the solution with 1.5% glucose. The initial fill volume of the dialysis solution was 10 ml/kg per exchange and was increasing slowly towards 20 ml/kg. Exchanges were done every 20-30 min at the beginning, and after that - hourly. Dwell time was 10 minutes, same as the drain time.

Also, the same day, two-lumen central venous catheter was inserted and the first session of therapeutic plasma exchange (TPE) was performed. During the hospitalization, we have done a total of 5 TPE sessions. Despite the applied therapy, signs of anuric renal injury, thrombocytopenia, anemia, and elevated lactate dehydrogenase levels continuously persisted.

Additional laboratory tests for the full work-up and differentiation of TMAs were carried out. Findings of immunologic tests of parents and the patient are shown in Table 2.

There was no available material for DNA extraction and genetic analysis of the patient. In both parents, complement profile was normal and the levels of some factors were elevated. Sequencing of the complete CFH gene of both parents was done, and no rare variations were observed, however, both parents turned out to carry the H3 aHUS risk haplotype in heterozygous manner.

Despite the full supportive and targeted care, severe multiple organ failure developed and on the 24th day of hospitalization the infant died.

DISCUSSION

In the European cohort, 16% of aHUS cases were reported as a secondary HUS [10]. When a secondary HUS occurs, such as in the setting of different diseases, signs and symptoms of the primary disease can confound the diagnosis of aHUS [11].

Non-deficient ADAMTS13 activity (over 5-10%) supports the diagnosis of aHUS (under the condition that STEC test is negative). Of course, in these conditions, a differential diagnosis must be distinguished between aHUS and secondary HUS. Secondary HUS may be associated with different infections and sepsis, use of medications (anticancer molecules, immunotherapeutics- cyclosporine, tacrolimus, and antiplatelet agents), malignancies and other underlying medical conditions such as autoimmune diseases, scleroderma and antiphospholipid syndrome. Familial aHUS occurs in about 10-20% of cases, the remaining patients having sporadic disease. Hypocomplementemia with a low level of C3 but normal C4 is a sign of alternative pathway dysregulation and activation, however, in 60-80% of the patients with aHUS levels of C3 are normal [12, 13, 2].

Due to the underlying immune-mediated, auto-inflammatory mechanisms and missing complement regulators, transfusions of FFP and plasmapheresis are therapeutic options for this syndrome. The aim of plasma therapy is to replace the mutant elements of the complement with normal elements in order to eliminate the pro-inflammatory and thrombogenic factors responsible for the symptoms. It is assumed that injections of fresh frozen plasma alone are sufficient in the case of quantitative deficits [14]. But the long-term outcomes for this treatment are still not well known [15].

In the case of the treatment failure (FFP, TPE), application of eculizumab (humanized monoclonal antibody against complement protein C5 terminal) is recommended [16, 17]. Studies that reported the benefits of these therapeutic choices in patients with aHUS are accumulating, but further evaluation is required to guide early and late therapeutic decisions like up-front treatment, treatment duration and discontinuation [18, 19, 20]. Baskin et al. reported 10 paediatric patients with aHUS who did not respond to PE. Eculizumab improved their renal function and quality of life [18]. Greenbaum et al. prospectively evaluated efficacy and safety of eculizumab in paediatric patients with aHUS. Their findings establish the efficacy and safety of eculizumab for the paediatric patients with aHUS and the recommendation is to start the therapy with it as soon as possible after establishing the aHUS diagnosis [19]. Considering the cost of the treatment, the cost/benefit of this cure should be estimated more thoroughly in the future.

This drug was neither registered nor available in our country in the time of our patient treatment.

B. pertussis produces a number of virulence factors that are involved in the pathogenesis and manifestations of the disease. Toxins of B. pertussis and other virulence factors enable adhesion of bacteria, locally injure epithelium, cause leukocyte dysfunction and macrophage cytotoxicity, increase release of proapoptotic and pro-inflammatory cytokines such are TNF-alpha and IL-6. In addition to the damage to the epithelium, those factors injure the endothelium what causes a pro-coagulant pathway activation [21].

The infant presented in our report has received the first dose of pertussis vaccine two days prior getting the disease, so she has not developed the immunity.

So far, only four cases of HUS associated with *Bordetella pertussis* infection have been described in the literature [6, 7, 8, 9]. The association of *Bordetella pertussis* infection and HUS was first described by Berners et al. in a newborn with complement factor H (CFH) mutation, which was treated with peritoneal dialysis and ended fatally [6]. In this patient, an abnormal band was identified on Factor H Western-blot, indicative for the presence of an abnormal complement regulator. After that, Pela et al. described the case of a 42 days old infant treated with hemodiafiltration and FFP infusions. In this case mutations in the genes encoding factor H and MCP were not detected. This patient survived with a completely recovered renal function [9]. Chaturvedi et al. described the case of a 28 days old baby who was treated with FFP infusions and did not require dialysis. Similarly to previously mentioned case, mutations in the genes encoding factor H, factor I, factor B and ADAMTS13 were not identified. The patient survived, fully recovered and maintained a normal renal function [7]. The most recent case was reported by Cohen-Ganea et al. In this case, complement (C3, C4, CH50) and factor H levels were within the normal range [8].

Our patient was a two-month-old infant who developed HUS three weeks after starting the whooping cough, and who was treated by peritoneal dialysis and TPE without a favorable response. Death of the patient was caused by HUS and severe sepsis which resulted in multiple organ dysfunction.

In the acute phase, very low C1q levels with decreased C3 concentration and combined (classical and alternative pathway) complement consumption were observed. We apprehended that as a result of ongoing severe infection, not as dysregulation of the alternative pathway. In line with this, there was no evidence of Factor H mutation in this patient, since the parents did not carry rare variations in CFH. Hence, we consider the possibility of a cause-effect relationship between B. pertussis infection and HUS in our patient. B. pertussis infection may be capable to stimulate the inflammatory cells to release the cytokines which determine microangiopathy and HUS. No abnormalities of factor H were found in the parents of our patient, however, due to the lack of available samples for DNA extraction we were unable to completely sequence all of the important genes of complement regulators and factors. Therefore, we can only assume that B. pertussis may cause HUS in the children without any predisposing factors. The infant developed HUS in the later phase of the infection after a brief period of clinical improvement (from the eighth to the fourteenth day of hospitalization). From this aspect our patient was similar to the three previously reported patients who had HUS in the context of an infection caused by B. pertussis. These patients also developed a severe HUS after a period of clinical improvement – in the period between 6th and 42nd day of hospitalization [6, 7, 9]. The patient described by Cohen-Ganelin et al. was in very difficult condition with paroxysmal coughing and extreme excitability, all the time until the moment of HUS diagnosis (the 10th day of hospitalization) [8]. So far, all described cases have developed HUS between 12th and 45th day since the start of the illness (first symptoms of a whooping cough).

Further studies are necessary to identify the mechanism of a potential interaction between pertussis toxins, pathophysiology of the infection and the interaction of complement activation, coagulation and the regulation of these cascades. The observation that the development of HUS is a late complication of B. pertussis infection may be a clue to plan such studies.

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REFERENCES

1. Besbas N, Karpman D, Landau D, Loirat C, Proesmans W, Remuzzi G, et al. A classification of hemolytic uremic syndrome and thrombotic thrombocytopenic purpura and related disorders. Kidney Int. 2006; 70:423–31. DOI: 10.1038/sj.ki.5001581 PMID: 16775594
2. Salvadori M, Bertoni E. Update on haemolytic uremic syndrome: diagnostic and therapeutic recommendations. World J Nephrol. 2013; 2(3):56–76. DOI: 10.5527/wjn.v2.i3.56 PMID: 24255888
3. Siegler R, Oakes R. Hemolytic uremic syndrome; pathogenesis, treatment, and outcome. Curr Opin Pediatr. 2005; 17(2):200–4. doi: 10.1097/01.mop.0000152997.66070.e9
4. Ariceta G, Besbas N, Johnson S, Karpman D, Landau D, Licht C. European Paediatric Study Group for HUS. Guideline for the investigations and initial therapy of diarrhea-negative haemolytic uremic syndrome. Pediatr nephrol. 2009; 24(4):687–96. DOI: 10.1007/s00467-008-0964-1 PMID: 18800230
5. Noris M, Remuzzi G. Atypical haemolytic uremic syndrome. N Engl J Med. 2009; 361:1676–87. DOI: 10.1056/NEJMra0902814 PMID: 19846853
6. Berner R, Krause MF, Gordjani N, Zipfel PF, Boehm N, Krueger M, et al. Haemolytic uremic syndrome due to an altered factor H triggered by neonatal pertussis. Pediatr Nephrol. 2002; 17:190–2. DOI: 10.1007/s00467-001-0798-6
7. Chaturvedi S, Licht C, Langlois V. Haemolytic uremic syndrome caused by Bordetella pertusis infection. Pediatr Nephrol. 2010; 25:1361–4. DOI: 10.1007/s00467-010-1449-6 PMID: 20145955
8. Cohen GE, Davidovits M, Amir J, Prais D. Severe *Bordetella pertussis* infection associated with hemolytic uremic syndrome. IMAJ. 2012; 14:456-458. PMID: 22953627
9. Pela I, Seracini D, Caprioli A, Castelletti F, Giammanco A. Hemolytic uremic syndrome in an infant following Bordetella pertusis infection. Eur J Clin Microbiol Infect Dis. 2006; 25:515–7. DOI: 10.1007/s10096-006-0171-6 PMID: 16871374
10. Noris M, Caprioli J, Bresin E, Mossali C, Pianetti G, Gamba S, et al. Relative role of genetic complement abnormalities in sporadic and familial aHUS and their impact on clinical phenotype. Clin J Am Soc Nephrol. 2010; 5(10):1844–59. DOI: 10.2215/CJN.02210310 PMID: 20595690
11. Nester CM, Thomas CP. Atypical hemolytic uremic syndrome: what is it, how is it diagnosed, and how is it treated? Hematology. 2012; 2:617–23. DOI: 10.1182/asheducation-2012.1.617 PMID: 23233643
12. Laurence J. Atypical hemolytic uremic syndrome (aHUS): making the diagnosis. Clin Adv Hematol Oncol. 2012; 10(Suppl 17):1–12. PMID: 23187605
13. Noris M, Mescia F, Remuzzi G. STEC-HUS, atypical HUS and TTP are all diseases of complement activation. Nat Rev Nephrol. 2012; 8:622–33. DOI: 10.1038/nrneph.2012.195 PMID: 22986360
14. Loirat C, Garnier A, Sellier-Leclerc AL, Kwon T. Plasmatherapy in atypical hemolytic and uremic syndrome. Semin Thromb Hemost. 2010; 36(6):673–81. DOI: 10.1055/s-0030-1262890 PMID: 20865645
15. Lapeyraque AL, Wagner E, Phan V, Clermont MJ, Merouani A, Frémeaux-Bacchi V, et al. Efficacy of plasma therapy in atypical hemolytic uremic syndrome with complement factor H mutations. Pediatr Nephrol. 2008; 23(8):1363–6. DOI: 10.1007/s00467-008-0803-4 PMID: 18425537
16. Magen D, Oliven A, Shechter Y, Elhasid R, Joseph GB, Zelikovic I. Plasmapheresis in a very young infant with atypical haemolytic uremic syndrome. Pediatr Nephrol. 2001; 16:87–90. PMID: 11198613
17. Szarvas N, Szilagyi A, Tasic V, Nushi-Stavileci V, Sofijanova A, Gucev Z, et al. First-line therapy in atypical hemolytic uremic syndrome: consideration on infants with a poor prognosis. Ital J Pediatr. 2014; 40(1):101. DOI: 10.1186/s13052-014-0101-7 PMID: 25496981
18. Baskin E, Gulleroglu K, Kantar A, Bayrakci , Ozkaya O. Success of eculizumab in the treatment of atypical haemolytic uremic syndrome. Pediatr Nephrol. (2015); 30(5):783–9. DOI: 10.1007/s00467-014-3003-4 PMID: 25384530

19. Greenbaum LA, Fila M, Ardissino G, Al-Akash SI, Evans J, Henning P, et al. Eculizumab is a safe and effective treatment in pediatric patients with atypical hemolytic uremic syndrome. Kidney Int. 2016; 89(3):701–11. DOI: 10.1016/j.kint.2015.11.026 PMID: 26880462
20. Picard C, Burtey S, Bornet C, Curti C, Montana M, Vanella P. Pathophysiology and treatment of typical and atypical hemolytic uremic syndrome. Pathol Biol. 2015; 63(3):136–43. DOI: 10.1016/j.patbio.2015.03.001 PMID: 25845294
21. Heininger U. Recent progress in clinical and basic pertussis research. Eur J Pediatr. 2001; 160:203–13. PMID: 11317640

Table 1. Laboratory findings and clinical course

Parameter	Day 1	Day 5	Day 10	Day 14	Day 16	Day 17
Hemoglobin (g/l)	111	105	93	83	61	76
Platelet count (10^9/l)	552	778	1137	481	95	46
White blood cell (10^9/l)	18	90	32	18	32	29
Creatinine (μmol/l)	/		/	/	328.5	398.47
CRP (mg/l)	45.9	36.7	negative	negative	13.34	/
Procalcitonine (ng/ml)	/	/	0.38	/	4.39	75.0
Clinical development	Coughing, heavy breathing	Tachydyspnoic, febrile, coughing, adynamic	Better overall condition, coughing	Paroxysmal whooping cough	Oliguria, oedema, dyspnea	Anuria
Therapy	Antibiotic therapy (ceftazidime)	Antibiotic therapy (macrolide)	Antibiotic therapy (macrolide)	Antibiotic therapy (macrolide)	Intensive Care Unit	FFP, CAPD, TPE

FFP – frozen fresh plasma; CAPD – continuous ambulatory peritoneal dialysis; TPE – therapeutic plasma exchange

Table 2. Findings of immunologic tests of parents and the neonate

Parameter (reference range)	Patient before FFP infusion (16th hospital day)	Patient after FFP infusion (17th hospital day)	Father	Mother
Classical pathway activity CH50/mL (48-103)	51	42		
C3 g/L (0.9-1.8)	0.88	0.54		
C1q mg/L (60-180)	36	40		
C4 g/L (0.15-0.55)	0.38	0.21	0.27	0.42
Alternative pathway activity % (70-105)	60	54		
Factor B % (70-130)	139	125	128	186
Factor H mg/L (250-880)	429	358	882	1209
Factor I % (70-130)	138	99	146	162
ADAMTS13 activity % (67-147)	43	50		

