TÜRK PEDİATRİ ARŞİVİ
TURKISH ARCHIVES of PEDIATRICS

Case Report / Olgu Sunumu

Candidemia complicating biliary atresia in an infant with hemoglobinopathy

Hemoglobinopatisi olan bir bebekte biliyer atrezi komplikasyonu olarak kandidemi

Ioannis Kyriakidis[1], Maria Palabougiouki[1], Eleni Vasileiou[1], Athanasios Tragiannidis[1], Maria Stamou[1], Tatiani Moudiou[1], Timoleon Vyzantiadis[2], Nikolaos Gombakis[1], Maria Hatzistilianou[1]

[1]Department of Pediatrics, Aristotle University of Thessaloniki, Thessaloniki, Greece
[2]Department of Microbiology, Aristotle University of Thessaloniki, Thessaloniki, Greece

Cite this article as: Kyriakidis I, Palabougiouki M, Vasileiou E, et al. Candidemia complicating biliary atresia in an infant with hemoglobinopathy. Turk Pediatri Ars 2019; 54(2): 129–32.

Abstract

Both biliary atresia and hemoglobinopathies have been associated with a higher incidence of bloodstream infections. We hereby present the case of a female infant of Nigerian descent with extrahepatic biliary atresia and double heterozygocity for sickle cell disease and alpha-thalassemia. Kasai hepatoportoenterostomy was performed in the child's sixth week of life. Bloodstream infections occurred two months post-hepatoportoenterostomy, even though the infant was still in prophylactic antibiotic treatment: the first was due to Candida albicans and was followed by bacteremia due to Escherichia coli. A third infection, confined to the skin only, was due to Acinetobacter spp. Treatment options, predisposing factors, and the pathophysiology of bloodstream infections in patients with biliary atresia and aberrant hemoglobin are discussed herein.

Keywords: Alpha thalassemia, biliary atresia, candida, hemoglobin variants, sepsis, sickle cell disease

Öz

Hem biliyer atrezi, hem de hemoglobinopatilerde, kan dolaşımı enfeksiyonu sıklığı daha fazladır. Burada, ekstrahepatik biliyer atrezisi ve "sickle-cell" hastalığı ve alfa-talasemi için çift heterozigot olan Nijerya kökenli bir kız bebeği sunuyoruz. Çocuğa yaşamının altıncı haftasında Kasai hepatoportoenterostomi uygulandı. Halen profilaktik antibiyotik tedavisi almakta olmasına rağmen, hepatoportoenterostomiden iki ay sonra kan dolaşımı enfeksiyonları ortaya çıkmıştır: birincisi kandida albikansa bağlı iken, bunu Escherichia coli'e bağlı bakteriyemi izlemiştir. Sadece cilt ile sınırlı kalan üçüncü bir enfeksiyon Acinetobacter spp'e bağlı olarak gelişmiştir. Bu yazıda biliyer atrezi ve anormal hemoglobini olan hastalarda, tedavi seçenekleri, predispozan faktörler ve kan dolaşımı enfeksiyonlarının patofizyolojisi tartışılmıştır.

Anahtar sözcükler: Alfa talasemi, biliyer atrezi, hemoglobin varyantları, kandida, sepsis, sickle cell hastalığı

Introduction

Biliary atresia is a rare disease of infancy and its main pathophysiologic hypothesis suggests that a local immune reaction is triggered by an unknown cause, leading to the formation of fibrotic tissue with subsequent obstruction of the bile duct and cholestasis. Bacteremia and fungemia remain a leading cause of mortality and aberrant hemoglobin seems to predispose to infectious complications. Of note, sepsis seems to predict the need for liver transplantation in the context of biliary atresia. Kasai hepatoportoenterostomy (HPE) performed as early as possible can prevent detrimental fibrosis and determine outcomes (1). We hereby present the occurrence of bloodstream infections, but not cholangitis, in a case of an infant with biliary atresia combined with double-heterozygosity for sickle cell disease and alpha-thalassemia, conditions that were not screened prenatally.

Case

A 31-day-old female infant of Nigerian descent was initially admitted to the emergency unit of our department

Corresponding Author / Sorumlu Yazar: Ioannis Kyriakidis E-mail / E-posta: kyriakidis@auth.gr
Received / Geliş Tarihi: 14.12.2016 **Accepted / Kabul Tarihi:** 01.03.2017

DOI: 10.14744/TurkPediatriArs.2019.67674

with jaundice of both skin and conjunctival membranes. Detailed physical examination revealed pruritus, decoloring of stools, dark urine, and hepatosplenomegaly along with omphalocele. Her family history suggested the presence of aberrant hemoglobin: her mother was diagnosed as having double-heterozygosity for sickle cell anemia and alpha-thalassemia, her father with heterozygosity for hemoglobin S (HbS), and both of her two sisters were being regularly transfused for alpha-thalassemia.

Blood biochemistries confirmed cholestasis with total bilirubin levels at 12.76 mg/dL and its direct form at 10.24 mg/dL (>80% of total). Liver function tests were abnormal with elevated serum levels for aspartate transaminase (AST or serum glutamic oxaloacetic transaminase i.e. SGOT), alanine transaminase (ALT or serum glutamate-pyruvate transaminase i.e. SGPT), gamma-glutamyl transferase (γ-GT), and alkaline phosphatase (ALP). Anemia was prominent with hemoglobin (Hb) at 10.8 g/dL, mean corpuscular volume (MCV) at 83.7 fL, mean corpuscular hemoglobin (MCH) at 29.9 pg, and red blood cells count (RBC) at 3.61 M/μL. Sickle cells were present in the blood film. Hemoglobin electrophoresis revealed 32% HbS, 11.2% HbF, and 2.4% HbA2.

As regards imaging studies, ultrasonography of the abdomen implied the presence of biliary atresia and subsequent hepatobiliary iminodiacetic acid (HIDA) scanning documented this diagnosis. Surgical intervention was planned fifteen days after the initial admission; atresia was determined as extrahepatic after liver biopsy and Kasai portoenterostomy was conducted at the infant's sixth week of life. The infant followed normal post-operative course and neomycin was added as prophylaxis against cholangitis. In the short-term after the Kasai operation, the infant presented with marginal but persistent hyponatremia and hypoproteinemia.

At the age of 3.5 months, the infant presented with low-grade fever and malaise. Blood cultures obtained were positive for Candida albicans and the patient was put on antifungal treatment with liposomal amphotericin B (LAMB). The ultrasound examination of the abdomen showed no evidence for cholangitis, but hypoechoic lesions in the spleen increased suspicion of bloodstream infection. Immediate clinical response was achieved thereafter and two subsequent blood cultures were negative. Seventeen days later, and while the infant was on treatment with both neomycin and LAMB, onset of spontaneous vomiting and decreased milk intake led to blood tests that revealed bacteremia due to Escherichia coli. The infant initially received amikacin and amoxicillin/clavulanic acid. Four days after this second bloodstream infection, the infant developed a skin lesion in her right foot, which developed to an eschar positive for Acinetobacter spp in swab culture, but not in blood. At this point, the infant was put on meropenem, adhering to the respective antibiogram, and the subsequent clinical course was uneventful. Interestingly, no other infection was recorded thereafter i.e. till her eleventh month of age.

The infant is a candidate for liver transplantation and is currently well with no other events in her history that would require hospitalization.
Written informed consent was obtained from both parents as regards this publication.

Discussion

Both biliary atresia and hemoglobinopathies are conditions that predispose to invasive infection and thus sepsis. Impaired liver function affects host defense and has been linked with mononuclear phagocytosis, reduction of Kupffer cells and neutrophil function, along with decreased complement levels. Malnutrition beyond the context of hypoproteinemia has also been associated with secondary immunodeficiency. Administration of antibiotic chemoprophylaxis for long periods and long hospitalization periods may also contribute to the increased rates of nosocomial Candida infections, even in patients that have no central venous catheter placed (2). In addition, corticosteroids after hepatoportoenterostomy seem to bear only small clinical benefit but their administration may increase bacteremia and fungemia rates by impairing the function of mononuclear macrophages and chemotaxis of neutrophils, and by lowering the synthesis of immunoglobulin (2, 3). Apparently, our patient may not bear central venous catheters, but had multiple reasons to develop candidemia and E. coli sepsis: biliary atresia, underlying hematologic condition, liver dysfunction, preceding corticosteroid treatment, young age, prolonged hospitalization, malnutrition, prior antibiotic use, and being of Nigerian descent plus with low socioeconomic status.

Beyond cholangitis, biliary atresia has been associated with increased infection rates and sepsis. Notably, sepsis occurrence has been used in a scoring system predicting the need for liver transplantation after HPE. In a retrospective study, 15% of patients with HPE but no transplantation had experienced at least one episode of sepsis, while this percentage was significantly greater (43%; $p<0.05$) among both liver transplant recipients and negative outcomes (1).

Studies from national registries demonstrated that bloodstream infections and septicemia were important

causes of mortality and morbidity in patients with biliary atresia, especially during the period between HPE and liver transplantation. A retrospective study from Switzerland reported that 44% (19/43) of patients had at least one episode of cholangitis, either suspected or proven with positive blood cultures. In this study, 8% of patients died while waiting for liver transplantation; however, better survival rates were recorded for patients who underwent HPE in their first 45 days of life (4). Sepsis was the prevailing direct cause of death in patients with non-transplanted biliary atresia (13/44, 30%) according to a retrospective study from the Netherlands. In the latter study, sepsis was also the most common cause of death (5/13, 38%) for patients waiting for liver transplantation (5).

Decreased candidacidal activity of neutrophils has long been known for sickle cell disease and seems to correlate with disease severity (6). Nowadays, the occurrence of bacteremia in patients with sickle cell disease seems to be much lower than previous estimates according to a large American retrospective study. Blood cultures obtained during 9 out of 1118 febrile episodes grew a pathogen (0.8%; 95% CI: 0.3–1.3), two of which referred to E. Coli bacteremia. Pathogens other than Pneumococcus seem to be responsible for most episodes of bacteremia and prompt evaluation remains warranted for the febrile child with sickle cell disease (7). In febrile children with sickle cell disease, an absolute neutrophil count of more than 20 x109 /L, a higher proportion of band cells, and the presence of vomiting were associated with an increased likelihood of bacteremia. Specifically for vomiting, which was also present in our case, it seemed to be an independent predictor (OR 2.9; 95% CI: 1–8.4) of bacteremia. Escherichia coli bacteremia accounted for 5% of all documented bloodstream infections, but no positive blood culture for Candida species was reported (8). As described above, our patients had Nigerian descent. Nigeria is the second African country with the most combinations (circa 23%) of significant hemoglobin variants per 1000 conceptions and an increased risk of invasive bacterial infections in African people with sickle cell disease has been repeatedly documented; the pooled odds of sickle cell disease for all-cause laboratory-confirmed that bacteremia was 19-times greater than controls (9).

The selection of the proper antifungal agent was another intriguing point in our case. The Candida antibiogram was sensitive to both micafungin and LAMB, and although micafungin has been approved for administration in infants, its hepatotoxicity issues (i.e. 'black box' warnings) led us to use LAMB instead (10). In a recent clinical trial, use of steroids after HPE was linked with 5 cases of fungemia (7%) and 31 cases of bacteremia (44%) in a cohort of 70 subjects. Likewise, the control group, which consisted of 70 subjects, presented 2 cases of fungemia (3%) and 27 cases of bacteremia (39%), suggesting only a minimal burden (3).

To our knowledge, this is the first reported case of candidemia in a child with biliary atresia after successful HPE. This infant had many factors predisposing to infections: biliary atresia, hemoglobinopathy, liver dysfunction, post-HPE corticosteroid treatment, and low socioeconomic status. Timely vaccinations and antibiotic prophylaxis did not prevent our patient from developing bloodstream infections and all these facts impose the need for liver transplantation.

Informed Consent: Written informed consent was obtained from both parents as regards this publication.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - M.H., N.G.; Design - A.T.; Supervision - M.H., N.G., M.S.; Data Collection and/or Processing - M.P., E.V.; Analysis and/or Interpretation - M.S., T.M., T.V.; Literature Review - I.K.; Writing - I.K.; Critical Review - A.T.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

Hasta Onamı: Her iki ebeveynden de yazılı bilgilendirilmiş onam alınmıştır.

Hakem Değerlendirmesi: Dış bağımsız.

Yazar Katkıları: Fikir - M.H., N.G.; Tasarım - A.T.; Denetleme - M.H., N.G., M.S.; Veri Toplanması ve/veya İşlemesi - M.P., E.V.; Analiz ve/veya Yorum - M.S., T.M., T.V.; Literatür Taraması - I.K.; Yazıyı Yazan - I.K.; Eleştirel İnceleme - A.T.

Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Mali Destek: Yazarlar bu çalışma için mali destek almadıklarını beyan etmişlerdir.

References

1. Jiang CB, Lee HC, Yeung CY, Sheu JC, Chang PY, Wang NL, et al. A scoring system to predict the need for liver transplantation for biliary atresia after Kasai portoenterostomy. Eur J Pediatr 2003;162: 603–6.
2. de Marie S. Diseases and drug-related interventions affecting host defence. Eur J Clin Microbiol Infect Dis 1993;12 Suppl 1: S36–41.
3. Bezerra JA, Spino C, Magee JC, Shneider BL, Rosenthal

P, Wang KS, et al. Use of corticosteroids after hepatoportoenterostomy for bile drainage in infants with biliary atresia: the START randomized clinical trial. JAMA 2014; 311: 1750–9.
4. Wildhaber BE, Majno P, Mayr J, Zachariou Z, Hohlfeld J, Schwoebel M, et al. Biliary atresia: Swiss national study, 1994-2004. J Pediatr Gastroenterol Nutr 2008;46: 299–307.
5. de Vries W, de Langen ZJ, Aronson DC, Hulscher JB, Peeters PM, Jansen-Kalma P, et al. Mortality of biliary atresia in children not undergoing liver transplantation in the Netherlands. Pediatr Transplant 2011;15: 176–83.
6. Anyaegbu CC, Okpala IE, Akren'Ova YA, Salimonu LS. Peripheral blood neutrophil count and candidacidal activity correlate with the clinical severity of sickle cell anaemia (SCA). Eur J Haematol 1998; 60: 267–8.
7. Baskin MN, Goh XL, Heeney MM, Harper MB. Bacteremia risk and outpatient management of febrile patients with sickle cell disease. Pediatrics 2013; 131: 1035–41.
8. Savlov D, Beck CE, DeGroot J, Odame I, Friedman JN. Predictors of bacteremia among children with sickle cell disease presenting with fever. J Pediatr Hematol Oncol 2014; 36: 384–8.
9. Ramakrishnan M, Moïsi JC, Klugman KP, Iglesias JM, Grant LR, Mpoudi-Etame M, et al. Increased risk of invasive bacterial infections in African people with sickle-cell disease: a systematic review and meta-analysis. Lancet Infect Dis 2010;10: 329–37.
10. Wang JL, Chang CH, Young-Xu Y, Chan KA. Systematic review and meta-analysis of the tolerability and hepatotoxicity of antifungals in empirical and definitive therapy for invasive fungal infection. Antimicrob Agents Chemother 2010; 54: 2409–19.