Liver Dysfunction in Severe Sepsis from Respiratory Syncytial Virus

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Abstract

A 1-month-old child was admitted at our pediatric intensive care unit (PICU) in a very critical state with generalized cyanosis, grunting, high fever, tachypnea, tachycardia, severe hypotension with capillary refill time > 5 seconds, and no palpable pulse. The child was apparently doing well until a few hours before admission. On admission to PICU, his clinical diagnosis was consistent with severe sepsis with his sequential organ failure assessment scores of 7 to 8 points. We started rapid restoration of circulation with aggressive volume replacement and empiric antimicrobial therapy. Despite optimal supportive therapy, the patient showed severe liver injury leading to liver failure, making the treatment more challenging. His simplex real-time reverse transcriptase polymerase chain reaction assay and enzyme linked immune sorbent assay documented respiratory syncytial virus (RSV) infection. Through our case report we would like to highlight the extrapulmonary manifestations of RSV infections and the importance of liver dysfunction during sepsis.

Keywords

- sepsis
- RSV
- liver dysfunction

Introduction

In healthy children, respiratory syncytial virus (RSV) usually causes mild respiratory infection; however, atypical and severe extrapulmonary manifestations (central nervous system, cardiovascular system, endocrine system, and liver) of RSV infections are described.^{1–7} Likewise, it can present with shock and as a sepsis-like syndrome in young infants.⁸

According to the new consensus definition, sepsis is a life-threatening organ dysfunction caused by a deregulated host response to infection.^{9,10} Sepsis-associated liver dysfunction is traditionally viewed as a late feature of critical illness.^{11–14} Recent studies have revealed liver dysfunction as an early event in sepsis.^{15–17} Liver dysfunction, when culminates into liver failure, becomes a severe complication.¹²

Case Report

A 1-month-old child was admitted at our pediatric intensive care unit (PICU) in critical condition with generalized cyanosis,

grunting, hypoxia (oxygen saturations 84%), high fever (40.4°C), tachypnea (68 breaths/min), tachycardia (226 beats/min), severe hypotension (BP = 54 mm Hg), with capillary refill time > 5 seconds, and no palpable pulse. His medical history revealed delivery at term, appropriate for gestational age (AGA), with a birth weight of 3,750 g. The child was apparently fine till some hours prior to admission and received only one weight-appropriate dose of acetaminophen. As he was clinically diagnosed with sepsis with circulatory compromise, we started immediate fluid resuscitation with crystalloid and colloid parenteral solution (three intravenous boluses of 20 mL/kg). Beside the optimal volume replacement, we started the empiric antimicrobial therapy and oxygen therapy. Patient did not require vasopressor support or positive pressure ventilation. The first laboratory data showed leukocytosis (WBC count of 46,000/mm³) with lymphocytosis, low RBC count (31,80,000/mm³), severe thrombocytopenia (platelet count < 20,000/mm³), normal level of C-reactive protein (persistent even after 2 and 5 days), and high lactates even after 2 hours of fluid resuscitation (4 mmol/L). The chest X-ray revealed only

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peribronchial thickening. After 24 hours of admission despite aggressive supportive therapy, he manifested severe hepatic dysfunction with liver failure—high aspartate transaminase (AST) levels of 2,747 UI/L, high alanine transaminase (ALT) levels of 1,236 UI/L, total bilirubin of 4.6 mg/dL, low total protein of 4.4 g/dL, prothrombin time of 83.1 seconds, activated partial thromboplastin time (APTT) of 46.7 seconds, and fibrinogen level of 119 mg/dL. The peak of AST, ALT, and bilirubin levels was on the 2nd day of admission. The urine routine microscopy and cerebrospinal fluid (CSF) cell count were normal. Blood, urine, and cerebrospinal fluid cultures (obtained prior to antibiotic administration) were negative for any growth. Culture result for *Bordetella pertussis* was negative. Hepatitis A [immunoglobulin M (IgM) and immunoglobulin G (IgG)], hepatitis B superficial antigen, and hepatitis C virus antibodies were negative. Respiratory specimens were tested using validated simplex real-time reverse transcriptase polymerase chain reaction (rRT-PCR) assays. RSV-specific serum antibodies were detected using standard enzyme-linked immunosorbent assay (ELISA) procedures. The result was positive for RSV and negative for other viruses (influenza, rhinovirus, parainfluenza virus, adenovirus, coxsackieviruses, echoviruses, and enteroviruses). Although clinical improvement was apparent in a few days, the liver parameters showed improvement 5 days after admission and returned to normal levels after 2 weeks (► Fig. 1).

Discussion

After the early-onset neonatal sepsis, most common infections that can cause sepsis in neonates include RSV (as in our case), *Cytomegalovirus*, *Escherichia coli*, *Candida*, herpes simplex virus, and *Listeria monocytogenes* infections.^{18,19}

RSV infection is common in children. Virtually all children have had at least one RSV infection by the age of 3.²⁰ RSV infection usually causes a mild respiratory infection and is the leading cause of lower respiratory tract infections in infants and young children manifested as bronchiolitis or viral pneu-

monia.^{20,21} It is interesting that recently different atypical and severe extrapulmonary manifestations of RSV infection are described, including central apneas, status epilepticus, ventricular tachycardia, fibrillation, heart block, pericardial tamponade, and hyponatremia, which suggest that RSV may infect organs other than the lungs.^{1–7} Additionally, features of “sepsis syndrome” have been described in the literature in a significant proportion of infants with RSV infection.⁶ However, RSV sepsis syndrome and septic shock are rare consequences of RSV infection, generally occurring only in newborns and young infants.²² The risk of bacterial infection in children infected with RSV is low (0.6–1.1%).²

The pathophysiology of viral infections may be attributed to the degeneration and cellular necrosis of the infected cells, leading to local and systemic inflammatory responses. The body's defense mechanisms include phagocytosis, humoral and cell-mediated responses, and the production of interferons. Interferons prevent the local spread of the virus, whereas antibodies prevent viremia. During RSV infection, the interferon-response factor pathway is inhibited. Severe RSV disease is associated with a misdirect immune response, characterized by enhanced release of mediators and infiltration of a range of macrophages and polymorphonuclear cells.²³

In our case, besides sepsis, we faced significant hepatic dysfunction with liver failure. Eisenhut et al have described elevated transaminase levels in 46 to 49% of ventilated children with RSV bronchiolitis.^{3,4} Severe hepatitis with alanine aminotransferase levels of nearly 3,000 UI/L associated with coagulopathy has also been noted.³ Considering the new consensus for sepsis definition,⁹ looking at the clinical situation and the complementary investigation, we think that our case had sepsis with severe liver injury (liver failure), not RSV hepatitis. Liver dysfunction generally is a late feature of sepsis, but is not uncommon and is well established.¹⁷ Liver dysfunction was commonly viewed only as a consequence of shock and initial tissue hypoperfusion. As a matter of fact, the injured liver may be considered one of the main factors in the genesis and amplification of multiple organ failure. Clinical features of

Fig. 1 Evolution of liver parameters. (a) Bilirubin values (b) AST and ALT values. ALT, alanine transaminase; AST, aspartate transaminase.

liver dysfunction during sepsis are hypoxic hepatitis and jaundice or sepsis-induced cholestasis.^{11–14,17}

The pathophysiological aspects of liver dysfunction in sepsis are complex. During sepsis, the liver has many functions to accomplish. It plays a critical role in endotoxin and bacteria scavenging, detoxification, and synthesizing proteins for metabolic, immune, and coagulation functions. During sepsis and septic shock in humans, the liver seems to be characterized by a state of relative ischemia, in which the increased metabolic requirements are not matched by an adequate increase of blood flow.²⁴ Liver perfusion represents 25% of the cardiac output. This flow is regulated by the hepatic arterial buffer response, which tends to compensate any reduction in portal blood flow.²⁵ In the early stages of the disease after severe shock states, probably due to inadequate oxygen delivery to the liver, centrilobular hepatocellular necrosis occurs, since centrilobular zones are the most sensitive to hypoxic damage (ischemic hepatitis).¹⁴ Clinically, an elevation of plasma aminotransferase and alanine aminotransferase, usually greater than 1,000 U/L, is found (in our case, the peaks were 3,747 and 2,332 U/L, respectively). On the other side, sepsis induces a profound alteration of hepatobiliary transport mechanisms, impairing the hepatic ability to transport bile acids and bilirubin into the hepatic canaliculi, thereby causing cholestasis with jaundice, which represents the classical liver alteration during sepsis.

The precise incidence of liver dysfunction during sepsis remains difficult to establish, because of the lack of a precise and consensus definition and the various observation times. In the 2001 International Sepsis Definition Conference, sepsis liver dysfunction was defined as a plasma total bilirubin of greater than 4 mg/dL (a higher cutoff than before—2 mg/dL). Except for severe sepsis or septic shock in which an acute elevation of serum aminotransferase level 20-fold the upper limit of normal permits the diagnosis of hypoxic hepatitis, serum bilirubin could be assumed to be the most widely used and proposed biomarker to diagnose hepatic dysfunction/failure during sepsis.^{26,27} In our case, the peak bilirubin level was 5.6 mg/dL.

Despite the huge progress in the management of sepsis, it remains a challenge for pediatricians.¹⁸ Sepsis morbidity and mortality rate remain high. Despite advances in diagnosis and treatment, almost half of neonatal deaths are caused by sepsis. For this reason, sepsis needs to be suspected and recognized as early as possible, because any delay in treatment increases the risk of death. Patient in our case recovered completely.

Conclusion

Extrapulmonary manifestations of RSV infection can be life threatening. RSV sepsis syndrome and septic shock are rare consequences of RSV infection. Generally occurring only in newborns and young infants, these manifestations need to be suspected and recognized as quickly as possible. We should also keep in mind that liver dysfunction can be an early event in sepsis.

Conflict of Interest

None.

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