Fatal Enteroviral Neonatal Infection, First Omani Case Report of a Twin with Congenital Enterovirus Infection

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Abstract

Introduction: Neonates have immature immune system and are at higher risk for serious complications of bacterial and viral infections, including enteroviral diseases. Evaluating neonates with mild and nonspecific symptoms that are consistent with viral processes can be challenging as it can lead to a wide range of manifestations, from mild febrile illness to severe, potentially fatal sepsis like conditions with multiorgan failure, especially (severe myocarditis and/or hepatitis, often accompanied by encephalitis). Enteroviral disease in neonatal period may be acquired antenatally, intrapartum or postnatally.

Case Presentation: We present a case report of a twin in the first 2 weeks of life with severe encephalitis and systemic enteroviral infection. The diagnosis was confirmed from nasopharyngeal aspirate and blood plasma enterovirus PCR. A maternal infection was highly suspected which can explain that the infection was acquired either prenatally or vertically, more likely at the time of delivery through contact with maternal blood, fecal material, or vaginal or cervical secretions. And, due to the severe illness and the lack of specific antiviral treatment options, the supportive management was provided included ventilation and other medical treatment.

Conclusion: Enteroviral infection is an important differential diagnosis in neonatal encephalitis or severe sepsis like manifestations. Prenatal, intranatal, or early postnatal infection with clinical illness manifested in the first 2 weeks of life is associated with an increased risk of severe neonatal illness.

Keywords: Enteroviral Neonatal Infection; Twin; Congenital Enterovirus Infection

Introduction

Human enteroviruses (HEV) are well-known agents of infection in newborn infants, because of the immaturity of their immune response mechanisms, are considered to be at a higher risk of infection and serious clinical manifestations, complications due to EV infections [1]. EV infections in neonates are common, especially during the summer and fall months [1,2] and lead to a wide range of manifestations, from mild febrile illness to severe, potentially fatal sepsis like conditions with multiorgan failure, especially (severe myocarditis and/or hepatitis, often accompanied by encephalitis) referred to as “neonatal enteroviral sepsis” [2,3]. Factors associated with the increased risk of neonatal EV infection include acquisition of infection transplacentally or from exposure to maternal secretions or blood during delivery, symptomatic EV illness in the mother around the time of delivery, and the lack of preexisting maternal antibodies to an infecting serotype [1-5]. Prenatal, intranatal, or early postnatal infection with clinical illness manifested in the first 2 weeks of life is associated with an increased risk of severe neonatal illness [3,4].

The incidence of enterovirus infection in neonate with systemic infection or in infants with suspected sepsis has been reported by different authors to range from 3% to 50%. Data from the National Enterovirus Surveillance System in the U.S. for the period 1983 - 2003 showed that 11.4% of all reported enterovirus infections occurred in neonates [2,6,7].

Enteroviral disease in neonatal period may be acquired antenatally, intrapartum or postnatally. Typically, the onset of a generalized enteroviral infection occurs at 3 to 5 days post contact, though some may present with a diphasic illness characterized by 1 to 7 days of recovery between initial presentation and disease progression. Early symptoms of an enteroviral infection may include lethargy, decreased feeding and transient respiratory complaints. Substantial mortality rates have been reported, and long-term sequelae may occur among survivors. Risk factors and clinical features associated with severe disease include absence of neutralizing antibody to the infecting serotype, maternal illness prior to or at delivery, prematurity, illness onset within the first few days of life, multi-organ disease, severe hepatitis, positive serum viral cultures, and specific infecting serotype [8].

Newborn EV infection may be acquired vertically from an infected mother in utero, at the time of delivery or postnatally. Alternatively, EV may be transmitted from community sources or through nosocomial spread after birth. Approximately 11% to 22% of serious EV infections are acquired transplacentally, as evidenced by the onset of disease within the first two days of life and the isolation of virus from amniotic fluid or cord blood [9,10]. The dominant mode of transmission of serious neonatal infection (in 63% of serious neonatal echovirus infections) is likely at the time of delivery through contact with maternal blood, fecal material, or vaginal or cervical secretions [9].

The infant acquiring EV from an infected mother is at particularly high risk of severe infection. The close contact with contaminated secretions, the high inoculum size, maternal and transplacental viremia, a lack of transplacentally acquired antibody and impaired neonatal immunity may all contribute to this increased susceptibility of the neonate born to an infected mother [9,10].

Nonpolio EV infection occurs in a spectrum of illness ranging from asymptomatic viral shedding to fatal multisystem disease. The majority (79%) of EV infections are asymptomatic, and most symptomatic neonates are hospitalized [2]. The approximate distribution of clinical manifestations among hospitalized infants is reflected in a recently published retrospective series [8] of 146 hospitalized patients completed over a nine-year period in Taiwan, in which 30% of patients had a clinical syndrome of nonspecific febrile illness, 40% had aseptic meningitis, and 30% had severe infection or hepatic necrosis and coagulopathy (HNC). No fatalities occurred among infants with nonspecific febrile illness or isolated aseptic meningitis, whereas the mortality rate in the group with HNC was 24%. In the subgroup of seven patients who also had myocarditis, the mortality rate reached 71% [8]. These data illustrate that the common manifestations of EV infection have a low mortality, while the potentially fatal complications (i.e. HNC and myocarditis) are much less common. Figure 1 summarizes the data from these two studies to illustrate the relative incidence of various neonatal (Adapted from references [2,8]).

Because EV infections vary greatly in severity, understanding the risk factors for severe infection may help clinicians identify infants at risk for adverse outcomes to institute early and aggressive management. In the largest case series to date [8], involving 146 patients with EV infection and 42 cases of HNC, features independently and significantly associated with severe infection or HNC were prematurity (37 weeks or less), maternal history of illness, early age of onset of illness (younger than seven days of age), higher WBC count (15 ×
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10^9/L or greater) and low hemoglobin (107 g/L or lower) [9]. Maternal illness and early-onset disease were identified as risk factors in other studies [9,12], which reflects the higher mortality associated with vertical as opposed to postnatal transmission. An elevated WBC count may reflect a higher degree of inflammation and consequent hepatic and/or myocardial damage, and low hemoglobin may signal a bleeding diathesis.

Table 1 outlines these risk factors along with the odds ratio for severe (HNC) versus milder (febrile illness and aseptic meningitis) disease [8].

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>OR (95% CI)*</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prematurity</td>
<td>6.6 (1.5 - 29)</td>
<td>0.012</td>
</tr>
<tr>
<td>Maternal illness</td>
<td>6.0 (1.2 - 29)</td>
<td>0.027</td>
</tr>
<tr>
<td>Onset before one week of age</td>
<td>49 (8.4 - 290)</td>
<td>0.001</td>
</tr>
<tr>
<td>Elevated white blood cell count</td>
<td>6.8 (1.1 - 27)</td>
<td>0.006</td>
</tr>
<tr>
<td>Low hemoglobin</td>
<td>29 (5.2 - 160)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

*For hepatic necrosis and coagulopathy versus febrile illness or aseptic meningitis. Data from reference 10.

Table 1: Risk factors for severe enteroviral disease.

Case Presentation

We report a twin, who were delivered prematurity by a cesarean section to primi mother 26 years old after IVF conception and an eventual pregnancy with no risk factors of sepsis, at 36 weeks of gestation. They were Di chorionic Di ammonitic twin.

Just after delivery, both of them were admitted to neonatal intensive care unit, because of respiratory distress, required non-invasive positive airway pressure ventilation for a period of 24 hours followed by a spontaneous breathing with impression of transient tachypnea of newborn. Broad spectrum antibiotic therapy (Gentamycin and Ampicillin) was started. They were improving but on day 4 post delivery, the twin 1 was noted to be hypoactive, having temperature instability with prolonged severe apnea episodes, required mechanical ventilation. He was evaluated for sepsis in this unexpected deterioration. His Labs revealed leucopenia (white blood cells (WBC) of 4.3) with thrombocytopenia (plt = 16). A Lumbar puncture was performed due to this clinical picture of encephalitis showing an elevation of CSF protein level (1.68 g/L) with normal cell counts and CSF Bacterial culture was sterile. CSF viruses multiplex PCR was negative for HSV1, HSV 2, HZV and enterovirus. So, antibiotics were upgraded and acyclovir was added. On day eight post delivery, he deteriorated more as started to have poor perfusion, hypotension, required inotropes and became oedematous and US showed ascites. In addition, an echocardiogram done showed mild pericardial effusion 3 - 4 mm with poor contractility and ejection fraction (EF) [10]. Then, on day 9 post delivery, the patient developed acute renal failure and became anuric for which he required Peritoneal dialysis and for that PD fluid also was sent for culture.

The diagnosis of Enteroviral infection was confirmed from nasopharyngeal aspirate initially and then from peritoneal fluid and blood plasma enterovirus PCR.

On day 15 post delivery, baby’s condition deteriorated and he developed multi-organ failure (renal, hepatic and cardiac) died on the same day.

The twin 2 also on Day 6 post delivery, started to become more hypoactive, having poor feeding and temperature instability with increased work of breathing. So, she was suspected also to have sepsis and evaluated for that. Her labs revealed also thrombocytopenia (Plt = 95) with normal white blood cells (WBC) count 13.2. The diagnosis of Enteroviral infection in twin 2 was confirmed from nasopharyngeal aspirate initially and then from blood plasma. Unfortunately, her condition deteriorated quickly within 2 days, required mechanical ventilation, multiple inotropes, upgrading of antibiotics and suddenly arrested. An echocardiogram was done as and revealed small pericardial effusion along with poor contractility and ejection fraction (EF) 30%. Lumbar puncture was not performed as hemodynamically she was not stable.

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Discussion

In the two cases that we report, the twin had severe enteroviral infection in the first 2 weeks of life, which is a risk factor for increasing the severity of EV infection. The fact that the twin were born premature at 36 weeks of gestation and because both of them acquired the infection during almost same time, maternal infection was highly suspected which could be acquired either prenatal or vertical transmission, more likely at the time of delivery through contact with maternal blood, fecal material, or vaginal or cervical secretions.

Because of the clinical pictures of sepsis like condition, a complete assessment, including full septic workup: blood, urine culture, lumbar puncture, basic work up for inborn error of metabolism, was collected and the twin were empirically started on broad spectrum antibiotic and antiviral (acyclovir).

Usually the diagnosis of enterovirus infection is performed by viral isolation in cell culture, Viral culture and PCR are effective methods for the detection of Enterovirus. Advantages of using a PCR over a viral culture included faster results and improved sensitivity; however, the use of PCR is laboratory dependent [14]. PCR has been demonstrated to be highly sensitive, specific and rapid [14]. Duration and level of detectable viral RNA in blood specimens are positively correlated with disease severity [15].

Treatment of enteroviral disease in neonates is supportive, including addressing complications of diseases such as hepatitis and myocarditis, and initiating antibiotics such as ampicillin, gentamicin or cefotaxime along with the consideration of vancomycin in the very ill-appearing infant. Use of intravenous immunoglobulin (IVIG) and Pleconaril in infected neonates as therapy remains experimental [16].

There is no approved treatment regimen for enterovirus infections. Intravenous immune globulin (IVIG) is often administered to infected neonates, but without satisfactory evidence of efficacy [8,17,18]. Pleconaril was developed in the 1990s as a capsid-binding antiviral agent that prevents virion uncoating of all susceptible enteroviruses following cell entry, and also inhibits attachment to cells for a subset of enteroviruses. The drug exhibits potent in vitro activity against many enterovirus and human rhinovirus serotypes and a favorable pharmacokinetic profile when administered orally [19,20]. An uncontrolled study of patients given pleconaril under a treatment Investigational New Drug application (IND), including 6 neonates, suggested efficacy against serious enterovirus infections [21]. Other drugs designed to treat enterovirus infections are advancing through clinical development, including pocapavir (V-073, formerly SCH 48973), another orally administered capsid inhibitor with a slightly limited spectrum of enterovirus activity compared with pleconaril [22]. Pocapavir, which is under development to treat chronic enterovirus infection in immunocompromised patients, significantly reduced the duration of oral poliovirus vaccine excretion in a recent randomized trial in healthy Swedish adults [23]. Therefore, the Therapy with IVIG and/or pleconaril in the neonate with EV infection is of unproven efficacy but may be considered among infants with severe, life-threatening disease.

Conclusion

Enteroviruses are common neonatal pathogens associated with high risk of infection and death. The present case report demonstrated that EV are important neonatal pathogens associated with high risk of morbidity and mortality. The spectrum clinical manifestation of EV infection includes the common but generally benign syndromes of asymptomatic infection, nonspecific febrile illness and aseptic meningitis, as well as the uncommon but potentially fatal syndromes of HNC and myocarditis. So, an awareness of the various clinical syndromes associated with EV infection, as well as the appropriate diagnostic testing, will help clinicians to recognize this common viral infection in neonatal period. In addition, the recognition of the risk factors for severe disease will help clinicians to exercise vigilance when managing neonates at high risk of an adverse outcome. It also enlightened the understanding of physicians that enteroviral infections should be taken seriously and that rapid deterioration leading to death can happen in neonates.

Bibliography


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