SEVERE ECHOVIRUS 30 INFECTION IN TWIN NEONATES

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Abstract: Although enteroviruses can cause overwhelming and fatal systemic infections in neonates, such severe neonatal infections remain uncommon and rarely involve both of twin neonates at the same time. We report the cases of twin neonates who developed fever initially, and then progressed to disseminated systemic disease with marked thrombocytopenia, coagulopathy, and hepatic failure. One of the neonates died and the other survived. Both neonates were treated with intravenous immunoglobulin and maternal fresh frozen plasma was also given to the neonate who survived. Virus cultures from the nasopharynx, rectum and cerebral spinal fluid of both neonates yielded enterovirus, later typed as echovirus 30. The surviving neonate had normal development without obvious sequelae during a follow-up period of 1 year. The major determinant of the survival from severe neonatal enterovirus infection might have been the pre-existing severity of the disease before treatment, and complete recovery could be expected if the infant survived the acute stage of illness.

Key words: Enterovirus infection; Echovirus 30; Twin; Newborn infant

Enteroviruses can cause a wide spectrum of diseases in childhood, from asymptomatic infection to fatal encephalitis and myocarditis. Neonates are at particularly high risk for developing life-threatening enterovirus infections, and the prognosis of such overwhelming infection is poor. We report the cases of twin neonates who developed echovirus 30 infection, complicated by sepsis, meningitis and hepatitis with hepatic failure.

Case Reports

Twin male infants were born on June 17, 2001, to a 28-year-old, gravida 2, para 2 mother by elective cesarean section due to twin pregnancy with one breech presentation. Apgar scores at 1 and 5 minutes were 9 in both infants and their respective birth weights were 2844 g and 2928 g. Prenatal examinations were unremarkable.

The mother did not have febrile illness nor signs of viral infection within 2 weeks before delivery. Her 2-year-old daughter developed fever one week before the infants’ birth. Vesicles over the left palm and hard palate were noted; hand-foot-mouth disease was diagnosed. She recovered completely without complication.

Case 1

Twin A developed fever at 72 hours of age (temperature 38.5°C) but had a healthy appearance. Laboratory investigation of a presumed infection was begun and antibiotic therapy was initiated empirically. Laboratory results obtained on the 3rd day of life showed a white blood cell (WBC) count of 6.03 x 10⁹/L (2% myelocytes and 3% band forms), a platelet count of 150 x 10⁹/L and a C-reactive protein (CRP) level of 1.52 mg/dL. Cerebral spinal fluid (CSF) analysis was not possible because of a traumatic tap. Liver function test showed elevated aspartate aminotransferase (AST) level at 6.03 x 10⁹/L and normal alanine aminotransferase (ALT) level at 15 U/L. However, intractable severe metabolic acidosis was noted and was not corrected by alkali therapy with sodium bicarbonate. Twenty-four hours later the patient became lethargic and developed poor feeding behavior. The abdomen became distended due to hepatosplenomegaly. Multiple petechiae were noted over the lower back and the skin turned mottled with pallor. No more oral feeding was given and total parenteral nutrition was administered. On the 4th day of life, the platelet count decreased to 5 x 10⁹/L and prothrombin time (PT) / partial thromboplastin time (PTT) level was prolonged (PT > 60 seconds, PTT > 150 seconds). The CRP level rose to 3.59 mg/dL.
Because enterovirus infection was strongly suspected according to the family history and his vital signs became unstable gradually, intravenous immunoglobulin (IVIG) was administered on the 4th and 5th day of life at a dose of 1 g/kg/day. Tachypnea, respiratory distress and irregular respiration progressed from the 5th day of life and he was intubated with ventilator support. Hypotension and oliguria developed and he required inotropic agent support. Thrombocytopenia and coagulopathy progressed despite frequent blood component therapy with platelet and fresh frozen plasma. His liver enzyme levels were elevated and peaked on the 6th day of life (AST 5584 U/L, ALT 427 U/L). Pulmonary hemorrhage, seizure, desaturation and bradycardia developed on the 6th day of life and he died despite aggressive therapy on the 7th day of life. Viral culture developed on the 6th day of life and he died despite aggressive therapy on the 7th day of life. Viral culture of the nasopharynx, rectum and CSF yielded enterovirus 2 days after the death of the patient, and was later typed as echovirus 30.

Case 2

Twin B became febrile at 87 hours of age with body temperature of 38.3°C. The laboratory results obtained on the 4th day of life showed a WBC count of 7.5 x 10⁹/L (1% myelocytes, 5% metamyelocytes and 6% band forms), a platelet count of 128 x 10⁹/L and a CRP level of 1.3 mg/dL. CSF analysis showed unremarkable results (a WBC count of 12/µL, a protein level of 87 mg/dL, and a glucose level above 50 mg/dL). Liver function test showed a mildly elevated AST level of 178 U/L and normal ALT level at 9 U/L. During the following hours the infant developed poor feeding, lethargy and intermittent tachypnea. Coffee-ground substance was aspirated from a nasogastric tube and the abdomen became distended. Oral feeding was stopped and total parenteral nutrition was administered. On the 5th day of life, the platelet count decreased to 9 x 10⁹/L and PT/PTT level was prolonged (PT > 60 seconds, PTT at 15.1 seconds and PT at 61.4 seconds). Liver function tests revealed decreased bilirubin levels (total bilirubin 16.5 mg/dL, direct bilirubin 10.9 mg/dL) and mildly elevated levels of AST and ALT (AST 180 U/L, ALT 91 U/L). Viral cultures of his parents and elder sister were all negative. Repeated viral culture from this infant’s throat, rectum and urine on the 30th day of life was negative. On the 42nd day of life, he was discharged in stable clinical condition. At 4 months old, the infant had mild jaundice (total bilirubin 5.6 mg/dL) with mild hepatomegaly (4 cm below right costal margin). At 1-year-old, the infant had normal development and normal liver function.

Discussion

Enteroviruses can cause overwhelming systemic infections that can be fatal in neonates. Severe enterovirus infection in neonates is often characterized by sepsis-like illness at onset. It cannot be distinguished easily from serious bacterial infections. Because the laboratory examinations are not helpful in the majority of instances, historical data might be crucial. A history of recent febrile or viral-like illness of mother or other family members is often evident in patients with neonatal enterovirus infection.

Among the various types of enteroviruses, more than 50% of neonatal enterovirus infections are caused by echoviruses. Although nearly all 30 echoviruses may cause neonatal diseases, severe diseases are caused by only a portion of these. Sepsis-like illness has been noted most often with echoviruses 5, 11,
and 16; other echoviruses noted include 2, 3, 4, 6, 9, 14, 19, 21, and 22.\(^5\) Severe hepatitis, frequently complicated with liver failure, has been noted with echoviruses 6, 7, 9, 11, 14, 19, and 21.\(^5\) Echovirus 30 is known to be the enterovirus most highly associated with aseptic meningitis in children.\(^6\) However, severe infections in neonates present as sepsis-like illness and hepatic failure is extremely rare.

In the two patients of this report, the initial presentation of the illness was fever without any other symptoms or signs. Twin A developed fever at 72 hours of age and twin B became febrile later, at 87 hours of age. The temperature was only mildly elevated for about 1 day during the course of the illness in these patients. Marked thrombocytopenia and coagulopathy occurred on the second day of illness in both patients. The subsequent course of illness, however, was different between twin A and twin B. Twin A developed severe metabolic acidosis, hypotension and respiratory failure in the following day and he died on the 7th day of life. Twin B never developed metabolic acidosis and was hemodynamically stable. Hepatitis with hepatic failure developed later in the course of illness and the liver function recovered gradually and the patient survived. Growth and development were normal during follow-up for 1 year, with normalization of liver function, platelet count and coagulation.

Treatment with IVIG containing a high level of neutralizing antibodies against specific enterovirus might cause early cessation of viremia and viuria, although Abzug et al\(^7\) found no significant difference between IVIG and control groups with respect to days of fever, days of symptomatic disease, hospital stay, and residual problems at discharge. IVIG was used in both neonates on the second day of illness. The onset of fever was earlier in twin A. Lactic acidosis had already been noted in twin A before administering IVIG, and the acidosis progressed continuously even after using IVIG. On the other hand, twin B did not develop lactic acidosis before or after IVIG administration. This might indicate that the infectious process of twin A was much more fulminant than that of twin B, or that twin A was infected earlier or with higher inoculum than twin B.

Since administration of commercial IVIG may not be successful in all cases because of a lack of specific antibodies to a given virus,\(^1\) administration of maternal plasma is an alternative based on the presumption that neonatal infection is acquired from the mother and the maternal plasma would have a high antibody titer. One report described a patient with echovirus 11 infection who recovered after transfusions with maternal plasma.\(^9\) Twin B received maternal plasma transfusion on the 9th and 10th day of life, but the serum neutralizing antibody titers were not measured. However, in view of the early onset, immediate postnatal infection is likely. This result implies that the survival of twin B was not due to the transfusion of maternal serum, or at least should not be attributed directly to the protective effect of a neutralizing antibody within the maternal serum.

**Conclusions**

Echovirus 30 may cause severe neonatal disease, which is characterized by a sepsis-like presentation with persistent thrombocytopenia and coagulopathy and the development of severe hepatitis with hepatic failure. Although IVIG was administered in both of the twin neonates and maternal plasma was used for the twin who survived, the major determinant of the different outcomes between these twin neonates might have been the pre-existing severity of the disease before treatment.

**References**