Rising Enterovirus 71 Threat Compared to Polio

BY MARY ANN MOON
Contributing Writer

Enterovirus 71 infection that results in CNS involvement can induce long-term neurologic sequelae in children, including low intelligence and behavioral problems, reported Dr. Luan-Yin Chang of National Taiwan University Hospital, and associates.

Best known as a cause of benign hand-foot-and-mouth disease and of viral encephalitis, enterovirus 71 has caused several large outbreaks since 1975, including epidemics in Bulgaria, Hungary, and Southeast Asia. A massive outbreak in Taiwan in 1998 led infectious disease experts there to develop a management program, which reduced acute mortality but left lingering concerns about long-term sequelae. "The effect of the virus on subsequent neurodevelopment and cognitive function of the survivors is not known (unlike the effects of other forms of viral encephalitis)," the researchers said.

From 2003 to 2005, they assessed the neurodevelopment and cognitive function of 142 children who had been infected during the epidemic and had CNS involvement.

In an editorial comment accompanying the report, Dr. John F. Modlin noted that unlike other enteroviruses, "enterovirus 71 possesses a unique ability to invade the ventral brain stem, cerebellum, and spinal cord, producing a spectrum of serious neuromotor syndromes."

Dr. Modlin suggested that the experience with EV71 may closely parallel that with poliomyelitis in the first half of the 20th century, and that past outbreaks in Asia may portend future outbreaks in North America and other regions that have been spared so far.

Among the 142 study subjects, 61 had experienced mild CNS involvement (aseptic meningitis) that produced headache and irritability but no altered consciousness or focal signs. Another 53 subjects had experienced severe CNS involvement, including encephalitis with altered level of consciousness, a polio-like syndrome with acute limb weakness and decreased reflex and muscle strength, or encephalomyelitis. The remaining 28 subjects had had severe CNS involvement and developed cardiopulmonary failure caused by medullary damage within 2-36 hours.

The subjects' age at onset of the infection ranged from 1 month to 14 years (median age 2 years); their age at follow-up assessment ranged from 1 to 20 years (median age 5 years).

All subjects with mild CNS involvement recovered fully. One with severe CNS involvement showed residual left facial nerve palsy, and 10 showed unilateral limb weakness and atrophy. In contrast, 21 (75%) of those with severe CNS involvement followed by cardiopulmonary failure showed these sequelae as well as dysphagia necessitating tube feeding, central hypoventilation requiring ventilator support, seizure, or psychomotor retardation.

Cognitive outcomes showed a similar pattern. Neurodevelopment and IQ were unaffected in all patients with mild CNS involvement, and were delayed in only one subject who had had severe CNS involvement alone. Subjects with CNS involvement alone showed deficits in verbal comprehension if they had been younger than 2 years when infected. In contrast, neurodevelopment and IQ were profoundly affected in most of those with severe CNS involvement plus cardiopulmonary failure.

Psychiatric sequelae may be noticed only when children start attending school, and only 47 of these subjects had started school at the time of this assessment. Six of them (13%) were diagnosed as having ADHD requiring medication and, in some cases, special education services. More severe learning and behavioral problems are likely to emerge as the subjects age, Dr. Chang and associates said (N. Engl. J. Med. 2007;356:1226-34).

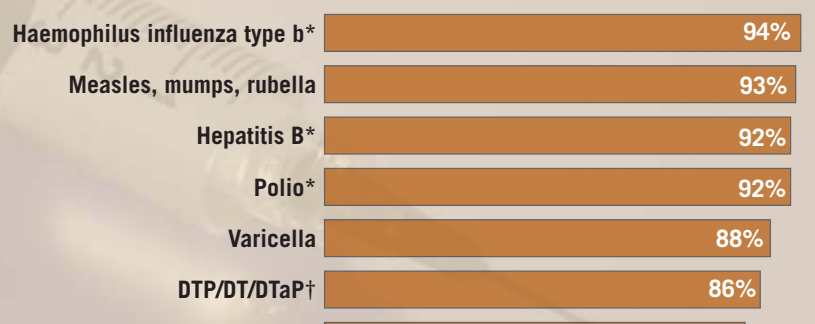
These results show that children who develop CNS involvement with EV71 infection, particularly those who also develop cardiopulmonary failure, would benefit from early evaluation and intervention for cognitive and behavioral problems, they said.

In his editorial comment, Dr. Modlin, chair of pediatrics at Dartmouth Medical School, Hanover, N.H., said that the epidemiologic pattern, clinical disease, and pathologic features of EV71 all are strikingly similar to those of poliomyelitis. Both viruses cause outbreaks "in which acute, severe, and sometimes fatal neuromotor disease occurs as a rare manifestation of common infections, especially in infants and young children."

Both viruses also "target gray matter in the spinal cord and brainstem, causing acute neuronal destruction and inflammation," although EV71 appears to cause more extensive and severe CNS damage, he said (N. Engl. J. Med. 2007;356:1204-5). It would be presumptuous to predict that EV71 infection will behave like poliomyelitis and cause large, annual summertime outbreaks in the West. However, "it would also be foolish not to be better prepared than we are now," Dr. Modlin noted. ■

DATA WATCH

Vaccination Rates of Children Aged 19-35 Months



*3 or more doses
†4 or more doses
Note: Based on 2004 data from the National Immunization Survey.
Source: Centers for Disease Control and Prevention

ELSEVIER GLOBAL MEDICAL NEWS

Consider Babesiosis in Transfused Infants With Liver Problems

BY MICHELE G. SULLIVAN
Mid-Atlantic Bureau

PHILADELPHIA — A single split unit of infected blood was the source of *Babesia microti* infections in four very-low-birthweight babies in Rhode Island, Dr. Kari Simonsen reported at the annual meeting of the Eastern Society for Pediatric Research.

The first case was seen in an acutely ill 35-day-old infant born at 25 weeks' gestation. The other three cases were identified after a search for other recipients of the suspect blood. None of these infants was seriously ill. Unlike the index case, who had a parasitemia level of 17%, the other three infants had low levels of parasitemia, said Dr. Simonsen, a pediatric infectious disease fellow at Brown University, Providence, R.I.

B. microti is an erythrocytic parasite similar to *Plasmodium*—the cause of malaria. The parasite is transmitted via tick bite to a human. It is endemic in the Northeast and upper Midwest of the United States, where up to 10% of the population is infected, Dr. Simonsen said.

Blood banks do not routinely screen for the parasite in donations, despite the prevalence of infections in some regions. "Up to 1.4% of blood donated in hyperendemic regions is seropositive and up to 53% [of the seropositive blood] is positive by [polymerase chain reaction]," she said.

Up to 1.4% of blood donated in hyperendemic regions (such as the Northeast U.S.) is seropositive.

DR. SIMONSEN

The index infant weighed 760 g at birth, and on day 2 received a transfusion for anemia. On day 35, the infant developed worsening apnea, respiratory distress requiring reintubation, fever, edema, hepatosplenomegaly, hemolytic anemic, and thrombocytopenia.

The initial workup, which was unrevealing, included blood, urine, and cerebrospinal fluid cultures, and viral studies. The patient was managed with ampicillin, gentamicin, and amphotericin B.

When the infant was 50 days old, a blood smear was done; a laboratory technician noted the typical intraerythrocytic "Maltese cross" formation of the *Babesia* parasite, with 17% of the red blood cells parasitized. "The infant immediately received a double-volume exchange transfusion, and clindamycin and quinine were started," Dr. Simonsen said.

By treatment day 6, the infant still had a parasitemia of about 6%. Another double volume exchange transfusion was performed; azithromycin and atovaquone were added to the existing medical therapy. By day 9, the parasitemia had decreased to 0.09%, and quinine was discontinued. A week later, the infant's blood smear was negative, but parasitemia increased to 0.03% on day 20. "This patient experienced a long period of low, but not absent, parasitemia," Dr. Simonsen said. Medical therapy was continued until two consecutive negative smears were obtained (days 24 and 27). On day 28, antibiotics were discontinued.

A blood bank investigation identified three additional infants who had received transfusions from the same unit of blood, all of whom were asymptomatic or mildly symptomatic. Case 2 had only a single organism on blood smear, and was managed with clindamycin and quinine. The smear was negative after just 1 day of treatment. Case 3 had a parasitemia of 0.9%, received clindamycin and quinine, and had a negative smear after 14 days. The final case had a parasitemia of 1.5%, and also was negative after 14 days of clindamycin and quinine.

Epidemiologists could find no reason for the large load in the index case, Dr. Simonsen said. "That infant did not receive a larger share of the blood than our other cases."

Dr. Peter J. Krause, director of the division of infectious diseases in the department of pediatrics at the University of Connecticut, Farmington, commented on the identification of infants with suspected babesiosis.

"It's probably not worth a routine smear, but if you have a neonate who has been transfused and is not doing well, with increasing liver enzymes or splenomegaly, it might be something to order." The incubation period in transfusion-related cases is typically 6-9 weeks, he said at the meeting. ■