Herpes Involving CNS Poses Diagnostic Challenge

BY BRUCE JANCIN
Denver Bureau

ASPEN, COLO. — A negative cerebrospinal fluid polymerase chain reaction test for herpes simplex virus does not rule out neonatal herpes with central nervous system involvement, Dr. April Palmer said a conference on pediatric infectious diseases sponsored by Children's Hospital, Denver, and the University of Colorado.

That's just one of several reasons why early diagnosis of neonatal herpes simplex virus (HSV) central nervous system (CNS) disease can be so difficult. Another is that 30%-40% of affected babies don't have skin lesions, added Dr. Palmer of the University of Mississippi, Jackson.

Herpes encephalitis in neonates often involves both temporal and extratemporal areas of the brain. It can look in certain respects like bacterial or enteroviral meningitis, cytomegalovirus infection, syphilis, or toxoplasmosis, all of which are in the differential diagnosis.

The sensitivity of cerebrospinal fluid (CSF) polymerase chain reaction (PCR) for HSV in neonates is 75%-100%. The test is most likely to be negative early in the disease course, but it can remain falsely negative on repeat spinal taps as well. Still, PCR is a big improvement over CSF viral culture, which is positive in only about 40% of cases, she continued.

Blood PCR for HSV is useful in ruling in neonatal disseminated HSV infection, which includes CNS disease in 60%-75% of cases. However, blood PCR can't be used to rule out disseminated HSV because the test is sometimes falsely negative in this setting.

As in neonatal CNS herpes, up to 40% of neonates with disseminated HSV don't have skin lesions. They present with a septic picture that may be marked by liver failure, disseminated intravascular coagulation, and respiratory failure. One of the key points in making the diagnosis of neonatal disseminated HSV is the associated extreme elevation of liver enzymes; bacterial sepsis seldom entails such high liver transaminase levels, she said.

For skin lesions the diagnostic test of choice remains viral culture, which is typically positive within several days if the lesions are fresh and the patient hasn't been treated with acyclovir.

If the culture is still negative on day 5, it can be considered a negative result.

Symptoms of neonatal CNS HSV include seizures, lethargy, fever, tremors, irritability, temperature instability, poor feeding, and a bulging fontanelle. Affected babies most often present on days 16-19 of life; however, they can present anytime in the first 3 months. In contrast, neonatal disseminated HSV involving visceral organs almost always presents within the first 2 weeks of life, and disease limited to the skin, eyes, or mucous membranes typically appears on days 10-11.

For skin lesions the test of choice is viral culture, which is typically positive within several days.

DR. PALMER

In the pre–antiviral therapy era, one-third of neonates with HSV presented with CNS disease, compared with 17% today. Similarly, the proportion of neonates presenting with disseminated disease has been cut in half, compared with the 48% prevalence in the pre–antiviral therapy era.

The treatment recommended by the American Academy of Pediatrics for CNS or disseminated neonatal HSV is intravenous acyclovir at 60 mg/kg per day for 21 days.

It's a less than ideal therapy. In the landmark randomized trial that established high-dose acyclovir as the treatment of choice in neonatal CNS and disseminated herpes, only 31% of treated patients with CNS HSV were developing normally at age 12 months (Pediatrics 2001;108:230-8).

Acyclovir is far more effective in older children and adults with CNS disease. The drug is a potent suppressor of viral replication. So the current thinking is that achieving improved developmental outcomes in affected neonates is likely to require adjunctive therapy that addresses apoptosis or the increased cytokine response to HSV that characterizes neonatal CNS infection, according to Dr. Palmer.

An effective vaccine is thought to be a decade or more away, she added.

Dr. Eli Somekh said he knows of investigators who claim they can find a specific immunologic defect in patients with CNS HSV.

"Maybe some neonates are getting HSV encephalitis not because of bad luck but because of a lacunar immunologic problem. [Interferon-α] may be evaluated in the near future as adjunctive therapy to acyclovir to improve the prognosis of HSV in neonates," predicted Dr. Somekh, chairman of the department of pediatrics at Wolfson Medical Center, Holon, Israel. ■

Child Immunization Rates Show Growth

BY JEFF EVANS
Senior Writer

Immunization coverage in 2006 for children aged 19-35 months held steady for most recommended vaccines and grew for several types, but more recent recommendations in coverage for adolescents aged 13-17 years have not yet reached the same levels of success, according to results from the most recent National Immunization Survey.

The Centers for Disease Control and Prevention estimated that the percentage of children aged 19-35 months who have received the recommended series of childhood vaccines grew from 76% in 2005 to 77% in 2006 (MMWR 2007;56:880-5).

"While we're very pleased with how high the complete series coverage is, we know we still have a way to go to reach the 80% goal for [the Healthy People 2010 target] and the 90% coverage for individual vaccines," Dr. Melinda Wharton, deputy director for the National Center for Immunization and Respiratory Diseases at the CDC, said during a teleconference.

Adolescents aged 13-17 years—who were included in the survey for the first time—fulfilled the recommended immunizations at high percentages for measles, mumps, and rubella vaccine (87% for 13-15 years of age) and hepatitis B vaccine (82%). But recommendations made in 2005 for vaccination with tetanus-diphtheria or tetanus, reduced diphtheria, and acellular pertussis vaccines (Tdap) and meningococcal conjugate vaccine (MCV4) reached levels of only 60% (after age 10 years) and 12%, respectively (MMWR 2007;56:885-8).

Any new vaccine recommended by the Advisory Committee on Immunization Practices has a target coverage of 90% or higher within 5 years of the recommendation, according to the CDC.

The survey did not report on human papillomavirus (HPV) vaccination because it was conducted before HPV vaccination recommendations were published.

The survey estimated immunization coverage through a quarterly, random-digit-dialed sample of telephone numbers in each of the 50 states, plus 30 local areas (counties and cities). The household responses are then corroborated with vaccination records from their health care providers. The household response rates for the child and adolescent surveys were 65% and 56%, respectively. The 21,044 children with provider-reported vaccination records represented 70% of all children with completed household interviews, whereas the 2,882 adolescents with provider-reported vaccination records represented 53% of adolescents with completed household interviews.

For children aged 19-35 months, the levels of coverage rose significantly from 2005 levels for pneumococcal conjugate vaccine (from 83% to 87%, for three or more doses), varicella vaccine (from 88% to 89%), and poliovirus vaccine (from 92% to 93%).

Across the states, the percentage of children who received the recommended series of childhood vaccines ranged from 84% in Massachusetts to 60% in Nevada. These rates also varied across local areas, ranging from 81% in Boston to 65% in Detroit.

Coverage for the recommended series of childhood vaccines was significantly lower for black children than white children (74% vs. 78%), but after adjustment for income the difference in coverage was no longer significant.

"Vaccination funding through the federal Vaccines for Children program has contributed to record coverage levels among children who are uninsured or underinsured, but additional measures are needed to deliver vaccines to children who live below the poverty level," according to the CDC.

"Clearly we need to do more to get information to parents and health care providers, and to make sure that everyone has a good understanding of the recommendations and the health benefits that the vaccines provide," Dr. Wharton said.

Dr. Wharton suggested that physicians can use immunization registries or electronic medical records to track the immunization status of individual children. Such systems "can really be part of the solution because many children may move from provider to provider or community to community," and may have already received vaccines even though it has not been recorded. ■

Histoplasmosis Pericarditis Common In Endemic Regions

ASPEN, COLO. — Think of histoplasmosis pericarditis when encountering pericarditis in a patient who has been in an endemic area, Dr. Matthew Zahn said at a conference on pediatric infectious diseases sponsored by Children's Hospital, Denver, and the University of Colorado.

Histoplasmosis accounts for up to one-quarter of all cases of pericarditis in the Ohio River Valley and other endemic regions, noted Dr. Zahn, a pediatrician who is medical director of the Louisville (Ky.) Metro Department of Public Health and Wellness.

Histoplasmosis is endemic in the central United States, including the Mississippi River Valley.

However, histoplasmosis pericarditis does not call for antifungal therapy. Rather, it is a reactive inflammatory process that occurs weeks to months following acute pulmonary histoplasmosis with infection of the mediastinal lymph nodes. The appropriate treatment is an NSAID, added Dr. Zahn, who is also at the University of Louisville (Ky.).

"There are two aspects to histoplasmosis disease. There's the illness from the fungus itself, and then there's the immune response. And the immune response sometimes can be quite big. Pericarditis is one of the immune-response illnesses," he explained.

The other common and sometimes debilitating postinfectious complications of histoplasmosis are reactive arthritis, erythema multiforme, and erythema nodosum. None require treatment other than NSAIDs.

At least one-quarter of patients with histoplasmosis pericarditis present with tamponade. Many will need drainage of the effusion.

Eventually 15% of patients with histoplasmosis pericarditis develop constrictive pericarditis.

—Bruce Jancin