Human Herpesvirus 6 Detection during the Evaluation of Sepsis in Infants Using the FilmArray Meningitis/Encephalitis Panel

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We used the FilmArray meningitis/encephalitis panel for evaluation of sepsis in febrile neonates. We detected human herpesvirus 6, a virus we did not routinely test for previously, in the cerebrospinal fluid of 7 neonates. In all 7 cases, detection of the virus did not warrant antiviral treatment. *(J Pediatr 2020;223:204-6).*

New multiplex molecular diagnostic panels allow rapid detection of organisms and may improve our ability to provide optimal care for patients.[1] However, many of these panels are expensive and include target organisms of unclear clinical significance, leading to additional testing and cost.[1] In 2 infants, we detected human herpesvirus 6 (HHV-6) in cerebrospinal fluid (CSF) specimens using the FilmArray meningitis/encephalitis panel. Therefore, we reviewed all infants <90 days of age with HHV-6 detection from CSF using the meningitis/encephalitis panel at our institution, where all febrile infants <60 days of age undergo a full sepsis evaluation including lumbar puncture for CSF analysis. Over a 13.5-month period from May 2018 - June 2019, 242 infants underwent meningitis/encephalitis panel testing, 53 (22%) had detection of any organism and 5 (2.1%) had detection of HHV-6. We summarize the clinical and laboratory characteristics of these 7 infants with HHV-6 detection in the CSF. This study was approved by the Vanderbilt University Institutional Review Board.

Cases

Patient A

A 4-week-old term girl who presented in the summer with fussiness and temperature of 38.1°C. As part of a sepsis evaluation, CSF cell count and chemistries were normal, but the meningitis/encephalitis panel was positive for enterovirus and HHV-6 (Table). The infant was admitted and monitored for 48 hours while receiving empiric ceftriaxone. She remained afebrile and her CSF, blood, and urine cultures were negative.

Patient B

A 5-week-old term girl presented in the fall with 1 day of fever (38.3°C) and nasal congestion. As part of a sepsis evaluation, she had a bloody lumbar puncture; the meningitis/encephalitis panel was positive for enterovirus and HHV-6 (Table). CSF, blood, and urine bacterial cultures were negative. She was given a dose of ceftriaxone and discharged home as her symptoms resolved.

Patient C

A 5-week-old term boy presented in the winter with increased work of breathing, requiring supplemental oxygen. He had a fever (38.6°C) and evidence of bronchiolitis on his chest radiograph. Because of apnea, a sepsis evaluation was initiated and ceftriaxone was started. The lumbar puncture was bloody; HHV-6 was detected on meningitis/encephalitis panel (Table). The infant improved, cultures remained negative, and antibiotics were discontinued before discharge.

Patient D

A 4-week-old term girl presented in the winter with weight loss and temperature of 38.3°C. As part of a sepsis evaluation, a lumbar puncture was performed and ceftriaxone was started; CSF had no pleocytosis and the meningitis/encephalitis panel was positive for HHV-6 (Table). No pathogens were detected from multiplex PCR testing of a respiratory specimen. The infant was thrombocytopenic (platelet count 59 000 cells/μL) and developed a rash, both of which improved over 2 days. Cultures remained negative, and she was discharged without antibiotics. Two weeks later, the infant re-presented with a fever (38.2°C), cough, congestion, and diarrhea. A sepsis evaluation was performed again; the meningitis/encephalitis panel was negative and respiratory panel testing revealed rhinovirus/enterovirus. She received ceftriaxone and was admitted for observation. All cultures remained negative.

ciHHV-6	Chromosomally integrated HHV-6
CRP	C-reactive protein
CSF	Cerebrospinal fluid
HHV-6	Human herpesvirus 6

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Table I. Clinical presentation and laboratory findings of neonates with HHV-6 detection by FilmArray meningitis/encephalitis panel

Patient	Age	Sex	Clinical presentation	Infectious disease consultation	Meningitis/encephalitis panel results	CSF studies	Complete blood count	Other laboratory tests
A	4 weeks	Female	Fussiness and fever	Yes	Enterovirus, HHV-6	WBC 8,* RBC 0,* N 11%, L 21%, M 68%, glucose 42,† protein 71†	WBC 9400, Hbg‡ 8.7, Plt 494 000, N 20%, L 65%, M 11%	
B	5 weeks	Female	Fever and nasal congestion	No	Enterovirus, HHV-6	WBC 287, RBC 2750, N 24%, L 16%, M 54%, glucose 51, protein 85	WBC 12 700, Hbg 12.4, Plt 721 000, N 25%, L 56%, M 17%	
C	5 weeks	Male	Fever, respiratory distress, and apnea	No	HHV-6	WBC 123, RBC 5445, N 12%, L 7%, M 45%, glucose 49, protein 50	WBC 5500, Hbg 13.1, Plt 812 000, N 28%, L 42%, M 17%	
D	4 weeks	Female	Fever and weight loss	No	HHV-6	WBC 2, RBC 1120, N 9%, L 68%, M 23%, glucose 29, protein 171	WBC 14 100, Hbg 14.2, Plt 59 000, N 9%, L 80%, M 7%	Meningitis/encephalitis panel at 6 weeks of age negative
E	6 weeks	Female	Fever, cough, and congestion	No	HHV-6	WBC 1, RBC 2700, N 18%, L 73%, M 5%, glucose 55, protein 61	WBC 13 700, Hbg 15.1, Plt 656 000, N 32%, M 7%, M 14%	Second meningitis/encephalitis panel on same specimen positive for HHV-6
F	1 day	Male	Respiratory distress and elevated CRP	Yes	HHV-6	WBC 0, RBC 11, glucose 39, protein 85	WBC 19 900, Hbg 20.8, Plt 125 000, N 73%, L 18%, M 5%	Plasma HHV-6 PCR§ >999 000
G	4 days	Male	Elevated CRP on sepsis screen and maternal chorioamnionitis	Yes	HHV-6	WBC 2, RBC 15 512, N 38%, L 29%, M 28%, glucose 46, protein 290	WBC 12 300, Hbg 20.3, Plt 111 000, N 63%, L 25%, M 7.8%	

Hbg, hemoglobin; *L*, lymphocytes; *M*, monocytes; *N*, neutrophils; *PCR*, polymerase chain reaction; *Plt*, platelets; *RBC*, red blood cell count; *WBC*, white blood cell count.
*WBC, RBC, and platelets are expressed in cell/μL.
†Glucose and protein are expressed in mg/dL.
‡Hemoglobin is expressed in g/dL.
§PCR is expressed in copies/mL.

Patient E

A 6-week-old girl born in the spring at 36 weeks gestational age presented with fever (38.2°C) and emesis. After blood and urine cultures were obtained, she was admitted for observation and developed increased work of breathing, congestion, and hypoxia. A chest radiograph revealed bronchiolitis vs left lower lobe pneumonia. She was given ceftriaxone and a lumbar puncture was obtained; CSF analysis was normal except for detection of HHV-6 on the meningitis/encephalitis panel (Table). Owing to rapid clinical improvement and negative cultures, the infant was discharged without antibiotics.

Patient F

A 1-day-old term male infant was born in the summer via spontaneous vaginal delivery, which was complicated by meconium-stained fluid. On his first day of life, after circumcision, he became tachypneic and hypoxic, requiring respiratory support with high-flow nasal canula. White blood cell count was elevated, C-reactive protein (CRP) was 119.7 mg/L, and CSF cell counts and chemistries were normal (Table). The meningitis/encephalitis panel was positive for HHV-6, and the infectious diseases team recommended ordering plasma HHV-6 quantitative polymerase chain reaction, which revealed >999 000 copies/mL of virus. The high viral load was thought to be due to chromosomally integrated virus, and antiviral treatment was not recommended. CSF and blood cultures were negative, and the infant received 5 days of ampicillin and gentamicin for culture-negative sepsis. He was weaned off respiratory support quickly and the white blood cell count normalized and CRP trended down to 15.1 mg/L before discharge on day of life 7.

Patient G

A 4-day-old term boy was born in the summer via cesarean delivery to a mother with chorioamnionitis. Delivery was complicated by meconium-stained fluid and fetal tachycardia. The infant's CRP was 72.6 mg/L at 12 hours of life, so a blood culture was obtained, and he was started on empiric ampicillin and gentamicin. On day of life 4, CRP was still elevated at 32 mg/L, so CSF was obtained, which was bloody but revealed 2 white blood cell count cells/μL, normal glucose, 290 mg/dL protein, and HHV-6 on the meningitis/encephalitis panel (Table). CSF and blood cultures remained negative, and ampicillin and gentamicin were continued for 7 days for culture-negative sepsis. The infant did well clinically and was discharged off antibiotics.

Discussion

In all of these cases, the detection of HHV-6 was unexpected and thought to be due to congenital or postnatally acquired infection with minimal clinical relevance. Infants A and B likely had coinfection with enterovirus and HHV-6, infants C and E potentially had postnatally acquired infection, because their respiratory symptoms may be explained by

HHV-6. Interestingly, infant D tested positive for HHV-6 at 4 weeks of age, but CSF testing was negative at 6 weeks of age. Her initial presentation with fever and rash may be explained by HHV-6 infection, and her second presentation may be explained by either enterovirus or rhinovirus (our respiratory pathogen panel cannot distinguish between the 2 viruses). We believe that infants F and G who presented within the first week of life likely had asymptomatic congenital HHV-6 infection.

First discovered in 1986, HHV-6 is a common cause of febrile illness and affects the majority of children at <2 years of age, with peak incidence between 9 and 21 months of age.[2] In 2012, the virus was distinguished as 2 different subspecies, A and B; HHV-6B is responsible for most postnatally acquired infections.[3] Clinical manifestations of primary HHV-6 infection in children include fever, fussiness, rhinorrhea, cough, diarrhea, and rash.[2] We suspect that HHV-6 clinical detection among febrile infants has increased since the FilmArray meningitis/encephalitis panel became clinically available in 2015, compared with periods before routine testing for this virus was available. HHV-6 detection can reflect acute or postnatally acquired infection; reactivation of latent infection, which is unlikely in neonates; or chromosomally integrated virus, which accounts for the majority of congenital infections.[4]

Congenital HHV-6 occurs in approximately 1% of all newborns.[5] Hall et al found that the majority of infants with congenitally acquired HHV-6 infection do not have clinical manifestations after birth, which may be due to the presence of transplacental maternal immunity.[4] However, congenital HHV-6 infection has been associated with slight cognitive impairment by 12 months of age.[6] Congenital HHV-6 infection can be acquired by 2 different mechanisms: germline passage of chromosomally integrated HHV-6 (ciHHV-6), which accounts for 86% of infections, or transmission of maternal HHV-6, including biologically active ciHHV-6, across the placenta, which accounts for the remaining 14% of infections.[5,7] Chromosomal integration results in a copy of the HHV-6 genome in every cell of the body, and typically, individuals with ciHHV-6 have higher viral loads, >5.5 $\log_{10}$ copies/mL[8]; therefore, we suspect that patient F, who had an extremely high plasma viral load had ciHHV-6.[9]

In a performance evaluation of the FilmArray meningitis/encephalitis panel in infants 1-60 days of life undergoing sepsis evaluations, HHV-6 detection was rare, being found in only 4 of 145 patients (2.8 %), and infants with detection of HHV6 infrequently had pleocytosis, which is similar to our findings.[10] Among 242 infants <3 months of age who received meningitis/encephalitis panel testing at our institution over 13.5 months, only 5 infants (2.1%) had HHV-6 detected. Aside from patients B and C, who had traumatic lumbar punctures, none of the other patients had pleocytosis.

Acute infection can be distinguished from ciHHV-6 by convalescent serology (an increase in the immunoglobulin titer can be associated with acute infection), qualitative polymerase chain reaction of hair or nail, or droplet digital polymerase chain reaction of cellular specimens (to assess for chromosomal integration).[4,11] In either case, treatment with ganciclovir or foscarnet is only indicated for individuals who are either immunocompromised, have a significantly elevated viral load in the absence of ciHHV-6, or present with severe disease.[3] None of our patients met these criteria or received antiviral treatment.

Our study is limited by the lack of testing for ciHHV-6 or HHV-6 subspecies. However, we can conclude that routine use of the meningitis/encephalitis panel has led, in some cases, to detection of HHV-6 in CSF from febrile infants. This can be challenging to interpret, but seems to be due to asymptomatic congenital infection or self-limited postnatal infection, neither of which require antiviral treatment.[6] Providers should be aware that most cases of congenital HHV-6 are due to inherited chromosomally integrated virus or transplacental transfer of the virus, and among young infants HHV-6 infection generally is asymptomatic.[7] ■

Acknowdements available at www.jpeds.com (Appendix).

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Appendix

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