Meningitis Due to Parainfluenza Virus Type 3: Report of Two Cases and Review

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We report the cases of two infants with meningitis due to parainfluenza virus type 3. This is the first time that documented clinical and laboratory details have been reported for a 1-month-old infant with meningitis due to parainfluenza virus type 3 (our second case). We reviewed the literature and determined that CNS involvement by parainfluenza virus type 3 appears rare. Clinicians should be aware that parainfluenza virus type 3, one of the most common causes of viral respiratory infection in infancy, can also produce infection of the CNS and that hemadsorption testing of CSF specimens submitted for viral culture is necessary for detecting these paramyxoviruses.

The parainfluenza viruses, types 1–4, are frequent causes of acute upper and lower respiratory tract disease in infants and young children. Parainfluenza virus type 3 closely mimics respiratory syncytial virus in its clinical manifestations and is second only to respiratory syncytial virus as a cause of pneumonia and bronchiolitis in infants [1]. Parainfluenza virus type 3 is generally considered a pathogen of the respiratory tract, and infection of other organs, including the CNS, rarely has been documented [2–9].

We report the isolation of parainfluenza virus type 3 from the CSF of two infants with aseptic meningitis and review the literature to determine the clinical and laboratory features associated with CNS infection by this virus. In addition, we emphasize the importance of hemadsorption testing of CSF specimens submitted for viral cultures for detecting paramyxoviruses.

Case Reports

Case 1. A 2-month-old male infant was admitted to the hospital with a 2-day history of fever (temperature of 38.3°C), slight cough, and nasal congestion. His mother had had upper respiratory symptoms and cough for 2 weeks. Both the mother and patient were seropositive for the human immunodeficiency virus. The infant was the product of an uncomplicated spontaneous vaginal delivery at term and his medical history was unremarkable.

Physical examination revealed an alert but irritable patient with a rectal temperature of 37.8°C. There was clear nasal discharge, and upper airway sounds were transmitted on auscultation of the chest. The rest of his examination was unremarkable. Initial laboratory studies revealed a white blood cell count of 17,300 cells/mm^3 (25% neutrophils, 1% band forms, 62% lymphocytes, 9% monocytes, and 3% eosinophils) and a platelet count of 464,000/mm^3. The result of a urinalysis was normal. A lumbar puncture yielded clear, colorless CSF with 17 white blood cells/mm^3 (1% neutrophils and 99% lymphocytes). The glucose level was 53 mg/dL, and the protein level was 66 mg/dL. No organisms were seen on a gram-stained smear. A chest radiograph (equivocally) showed prominent central bronchial markings that were suggestive of airway disease. Cultures of blood, CSF, and urine subsequently did not yield bacteria. CSF, but no respiratory sample, was submitted for viral culture.

The patient was hospitalized with a diagnosis of upper respiratory tract infection and suspected sepsis. Therapy with iv ampicillin and cefotaxime was administered until the bacterial cultures became negative (day 4 of hospitalization). On day 2 he became less irritable and was taking oral feedings well. On day 3 he was afebrile, he had no new medical problems, and his lungs remained clear. He was discharged from the hospital in good condition on day 5. Culture of a CSF specimen subsequently yielded parainfluenza virus type 3. At a follow-up visit 2 months later, findings on physical examination and on a chest radiograph were normal.

Case 2. A 1-month-old male infant was admitted to the hospital with a 24-hour history of coryza, irritability, (subjective) fever, and emesis (several times per day). He had not had known contact with persons who were ill. He was a full-term infant with no perinatal problems and his medical history was unremarkable.

On admission the patient was in no apparent distress. His temperature was 38.1°C, and he had a dry crusted nasal discharge. The rest of his physical examination was normal. A white blood cell count revealed 5,700 white blood cells/mm^3, with 30% neutrophils, 8% band forms, 44% lymphocytes, 8% atypical lymphocytes, 8% monocytes, 1% basophils, and 1% eosinophils. Examination of CSF yielded clear, colorless fluid with 65 white blood cells/mm^3 (65% neutrophils, 22% lymphocytes, and 13% monocytes). The glucose level was 52 mg/dL, and the protein level was 85 mg/dL. No or-

Received 24 February 1993; revised 11 May 1993.

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Clinical Infectious Diseases 1993;17:995–7
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1058-4838/93/1706-0005$02.00

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ganisms were seen on a gram-stained smear. Findings on a chest radiograph did not reveal any abnormalities, and the result of a urinalysis was normal. A latex agglutination test with urine was negative for antibodies to *Haemophilus influenzae* type b, *Neisseria meningitidis*, and *Streptococcus pneumoniae* but positive for group B streptococcus. Cultures of blood, CSF, and urine subsequently did not yield bacteria. CSF, urine, and stool specimens, but no respiratory sample, were submitted for viral culture.

The patient was hospitalized and received iv ampicillin and cefotaxime. While it was possible that the group B streptococcus antigen detected in the urine represented contamination of the urine with group B streptococcus that was present on the infant's skin, the patient's physicians believed that a systemic bacterial infection could not be excluded, and the patient received a 10-day course of antibiotics. Over the course of hospitalization, the patient did well. Emesis was no longer noted and the patient became afebrile; he was discharged from the hospital on the 10th day. Cultures of the CSF specimen subsequently yielded parainfluenza type 3.

Isolation and Identification of Virus

The specimens of CSF were inoculated directly into human foreskin fibroblast (HFF), Rhesus monkey kidney (RhMK), human epidermoid laryngeal carcinoma (Hep2), and human lung carcinoma (A549) cell culture monolayers and were visually inspected each day under the light microscope for evidence of viral cytopathic effect. No cytopathic effect was detected in any cell line. A hemadsorption test, performed with a 0.4% suspension of guinea pig red blood cells onto RhMK cell monolayers, was positive for case 1 on day 7 and for case 2 on day 14 of incubation [10]. The hemadsorbing isolates were identified as parainfluenza type 3 by immunofluorescence with use of type-specific antibody reagents (Microscan, Bartels Viral Respiratory Screening and Identification, Baxter Laboratories, West Sacramento, CA). Both isolates were identified during an outbreak of parainfluenza virus type 3 in Houston in the spring of 1992.

Discussion

The parainfluenza viruses are members of the paramyxovirus family, which includes parainfluenza virus types 1, 2, 3, and 4 as well as respiratory syncytial virus, mumps virus, and measles virus. Infection with the parainfluenza viruses is common, and infection with parainfluenza virus type 3 usually occurs early in life. One-half to two-thirds of the infants have been infected by 12 months of age, and almost all children have acquired infection by 3 years of age [1, 11].

Despite the frequency with which parainfluenza virus type 3 infection occurs, it rarely has been documented as a cause of CNS infection. We reviewed the literature for reports of patients for whom parainfluenza virus type 3 was isolated from CSF (table 1). After reviewing these reports, we found that the virus can cause CNS infection in individuals of all ages, from newborns to middle-aged adults, who are either immunocompetent or immunocompromised. We also found that when parainfluenza virus type 3 infects the CNS, it most commonly causes benign, self-limited aseptic meningitis. However, severe illness—even death—can occur in immunocompromised patients.

For six patients whose cases were reported, detailed CSF findings were documented. For two of these patients, one of whom was our patient, the ratio of polymorphonuclear cells to mononuclear cells was higher than 1, probably indicating an early stage of viral meningitis. For three other patients, CSF findings were typical for aseptic meningitis; there was a predominance of mononuclear cells, levels of protein and glucose were normal, and cultures were negative for bacteria. The one patient who had Guillain-Barré syndrome associated with parainfluenza type 3 infection had no cells in the CSF.

Unquestionably, enteroviruses are the most common cause of viral meningitis, and these viruses are isolated from the CSF in up to 90% of cases of aseptic meningitis in which a virus is identified [12–14]. However, the relative frequency with which other viruses cause viral meningitis is less clear. Of 787 CSF samples submitted to our laboratory from 1 January 1990 through 31 December 1992 for viral culture, 72 (9.1%) yielded a virus. Enteroviruses were isolated from 64 samples and accounted for 88.8% of the positive cultures. Hemadsorbing viruses (one mumps and three parainfluenza type 3 isolates) accounted for 5.6% of positive CSF cultures and were the next most common group of virus isolated from CSF, followed by herpes simplex virus (three isolates [4.2%]) and adenovirus (one isolate [1.4%]) (our unpublished data). It is interesting that in our laboratory parainfluenza virus type 3 was isolated more often than was mumps virus, traditionally thought to be the paramyxovirus most commonly isolated from CSF.

Enteroviruses grow quickly and produce a characteristic cytopathic effect in several different cell cultures. However, parainfluenza viruses grow relatively slowly, often without producing a cytopathic effect in cell culture, and their presence can be recognized only if hemadsorption with guinea pig red blood cells is performed. Since laboratories may not routinely perform hemadsorption on CSF samples submitted for viral culture, the presence of parainfluenza viruses and other hemadsorbing viruses may go undetected and the relative frequency of CNS infection with these viruses may be underestimated.

The decision to routinely test all CSF samples for the presence of hemadsorbing viruses rests with the individual laboratory. Our hospital cares for many chronically and acutely ill children, many of whom are immunocompromised or present difficult diagnostic dilemmas. Since hemadsorbing viruses are the second most common group of viruses isolated

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Table 1. Features of 14 patients with parainfluenza virus type 3 isolated from CSF (including the present report).

Patient no.	Age/sex	CSF findings: WBC (mm^3)	CSF findings: PMNL/MONO	CSF findings: Glucose (mg/dL)	CSF findings: Protein (mg/dL)	Diagnosis	Reference
1	8 mo/M	Unknown	Unknown	Unknown	Unknown	Severe combined immunodeficiency, disseminated disease*	[3]
2	19 y/M	0	0/0	79	66	Guillain-Barré syndrome	[4]
3	11 mo/F	155	36/64	59	30	Otitits media, meningitis	[5]
4	Unknown/Unknown	WNL	Unknown	Unknown	Unknown	Febrile seizure	[6]
5	2 mo/F	60	40/60	59	41	Meningitis	[7]
6	16 mo/M	32	69/31	50	15	Meningitis	[7]
7	64 y/M	Increased	Unknown	Unknown	Unknown	Meningitis	[8]
8	37 y/F	0	0/0	Unknown	Unknown	Demyelinization syndrome	[8]
9	1 y/M	Increased	Unknown	Unknown	Unknown	Meningitis	[8]
10	1 mo/F	Increased	Unknown	Unknown	Unknown	Meningitis	[8]
11	Neonate/M	WNL	Unknown	Unknown	Unknown	Hypotonia	[8]
12	10 mo/F	10	Unknown	Unknown	Unknown	Bronchopneumonia, meningoencephalitis, coma	[9]
13	2 mo/M	17	1/99	53	66	Seropositive for HIV, URI, meningitis	[PR]
14	1 mo/M	65	63/35	52	85	URI, meningitis	[PR]

NOTE. WBC = white blood cells; PMNL/MONO = polymorphonuclear leukocytes/mononuclear cells; M = male; F = female; WNL = within normal limits; PR = present report; HIV = human immunodeficiency virus; URI = upper respiratory infection.
* This patient died.

from the CSF of children in our hospital, we routinely test all CSF samples for their presence and will continue to monitor the relative frequency of these agents as CNS pathogens in children.

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