Rotavirus Meningoencephalitis in a Previously Healthy Child and a Review of the Literature

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Abstract: A 3 1/2-year-old child presented with symptoms of acute gastroenteritis and evidence of central nervous system disease. Evaluation revealed findings consistent with meningoencephalitis and rotavirus detected in the cerebrospinal fluid by polymerase chain reaction. A review of the literature describes 23 cases of central nervous system disease attributed to rotavirus.

Key Words: rotavirus, encephalitis, central nervous system infection

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The primary site of rotavirus infection is the small intestine, although case reports have described detection of rotavirus in the extraintestinal sites of the liver,[1] kidney,[1] and central nervous system (CNS).[2–17] Rotavirus antigen and infectious virus have also been reported in the blood of immunocompetent children with confirmed rotavirus gastroenteritis.[18–21] Most children infected with rotavirus have been viremic, independent of the presence of diarrhea.[21]

CNS involvement associated with rotavirus infections has been determined by electron microscopy (EM), antigen detection via immunologic methods,[2–4] and most recently RNA detection by reverse transcription polymerase chain reaction (RT-PCR) of the cerebrospinal fluid (CSF). Rotavirus RNA has been found in the CSF in rotavirus-infected children with seizures,[3,5–12,14,16] encephalitis,[9,11,14,16,17] aseptic meningitis,[15] cerebellitis,[13,16] and encephalopathy.[8] In the United States, there have been only 3 publications totaling 4 children with CNS complications of rotavirus infection and detection of rotavirus in the CSF.[2,11,13] We describe an older child with rotavirus gastroenteritis and encephalitis, who had a good outcome despite prolonged CNS symptoms.

PATIENT PRESENTATION

A previously healthy 3 1/2-year-old girl presented in March 2004 with mental status changes after a 3-day history of fever, vomiting, diarrhea, decreased appetite, and fatigue. She had been unable to speak or ambulate for several hours.

On examination, the child was somnolent but arousable. She was lethargic and febrile to 38.7°C. She was minimally responsive to stimulation, but occasionally became agitated with intermittent screaming. The liver edge was palpable 1.5 cm below the right costal border. The Glasgow Coma Scale score was 8/15. She was mildly dehydrated but hemodynamically stable. She received intravenous fluid for rehydration and was admitted to the intensive care unit.

Initial evaluation revealed a normal liver function panel and complete blood count: white blood count (WBC) was 4100 with 43% segmented neutrophils, 50% lymphocytes, and 7% monocytes. Electrolyte analysis detected a mild metabolic acidosis with a bicarbonate level of 16 mg/dL and an anion gap of 10. Urine test for toxins was negative. She had a normal CT of the brain without contrast and her CSF revealed a WBC count of 22 cells/mm^3 (97% segmented neutrophils, 1% bands, 1% lymphocytes, and 1% monocytes); red blood cell count of 9 cells/mm^3; glucose level of 48 mg/dL; and protein level of 35 mg/dL. Vancomycin, ceftriaxone, and acyclovir therapy was started empirically.

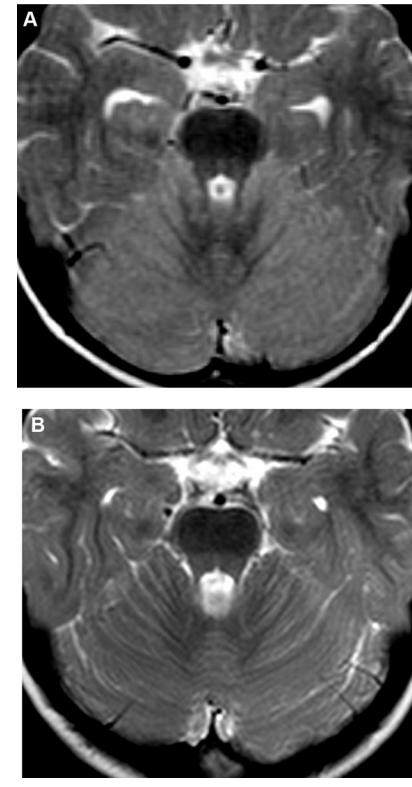

FIGURE 1. T2 weighted MRI image. A, Abnormal; B, Normal.

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TABLE 1. Clinical Symptoms and Outcomes

Patient Number	Reference	Year	Country	Sex	Age in Months	Days of Illness	Presenting Symptoms				CNS Diagnosis	Seizures	Outcome
							Diarrhea	Vomiting	Fever	CNS			
1	Wong[2]	1984	United States	M	6	6	Yes	Yes	No	Irritability	Aseptic meningitis	No	WNL*
2	Ushijima[3]	1986	Japan	M	9	2	Not Stated	Yes	Yes	Seizures	Infantile spasms	Yes	Infantile spasms developmental delay
3	Keidan[4]	1992	Israel	M	24	3	No	Yes	Yes	Lethargy	Encephalopathy	No	WNL*
4	Nishimura[5]	1993	Japan	M	10	Not Stated	Yes	Yes	Not Stated	Seizures	Seizures	Yes	WNL*
5	Nishimura[5]	1993	Japan	F	12	Not Stated	Yes	Yes	Not Stated	Seizures	Seizures	Yes	WNL*
6	Nishimura[5]	1993	Japan	F	12	Not Stated	Yes	Yes	Not Stated	Seizures	Seizures	Yes	WNL*
7	Nishimura[5]	1993	Japan	M	12	Not Stated	Yes	Yes	Not Stated	Seizures	Seizures	Yes	WNL*
8	Nishimura[5]	1993	Japan	M	12	Not Stated	Yes	Yes	Not Stated	Seizures	Seizures	Yes	WNL*
9	Nishimura[5]	1993	Japan	M	12	Not Stated	Yes	Yes	Not Stated	Seizures	Seizures	Yes	WNL*
10	Nishimura[5]	1993	Japan	M	36	Not Stated	Yes	Yes	Not Stated	Seizures	Seizures	Yes	WNL*
11	Yoshida[6]	1995	Japan	F	24	3	Yes	Yes	Yes	Seizures	Encephalitis	Yes	WNL*
12	Pang[7]	1996	Finland	F	9	1	Yes	Yes	Yes	Febrile seizure	Febrile seizures	Yes	WNL*
13	Makino[8]	1996	Japan	F	21	1	Yes	Yes	Yes	Seizure	Encephalopathy	Yes	Moderate left hemiparesis, borderline mental retardation
14	Hongou[9]	1998	Japan	M	24	2	Yes	Yes	No	Seizures	Encephalitis	Yes	WNL*
15	Pager[10]	2000	South Africa	M	<1	1	Yes	Yes	Not Stated	Seizures	Seizures	Yes	Died
16	Lynch[11]	2000	United States	M	72	4	Yes	Not Stated	Yes	Agitation, confusion	Encephalitis	Yes	Died 3 mo later
17	Lynch[11]	2000	United States	F	30	5	Yes	Not Stated	Not Stated	Agitation, weakness	Encephalitis	No	WNL*
18	Iturriza-Gomara[12]	2002	United Kingdom	M	22	2	Yes	Yes	Yes	Seizures	Seizures	Yes	WNL*
19	Nigrovic[13]	2002	United States	F	36	2	Yes	Yes	Yes	Loss of speech	Cerebellitis	No	Wide-based gait, moderate expressive aphasia
20	Keble[14]	2003	Germany	F	9	1	Yes	Yes	Yes	Seizures	Meningo-encephalitis	Yes	WNL*
21	Furuya[15]	2007	Japan	F	43	3	Yes	Yes	Yes	Decreased consciousness	Aseptic meningitis	No	WNL*
22	Shiihara[16]	2007	Japan	F	31	3	Yes	Yes	Yes	Decreased consciousness	Encephalitis Cerebellitis	Yes	Right hand tremor, slow speech, and dysarthria
23	Goto[17]	2007	Japan	M	35	3	Yes	Yes	Yes	Decreased consciousness	Meningo-encephalitis	No	WNL*
24	Dickey	2008	United States	F	42	3	Yes	Yes	Yes	Mental status changes	Encephalitis Cerebellitis	No	WNL mild speech and fine motor incoordination

*WNL indicates within normal limits.

Results of blood, urine, and CSF cultures were negative and antibiotics were discontinued. CSF polymerase chain reaction (PCR) assays for enterovirus, adenovirus, herpes simplex virus 1 and 2, lymphocytic choriomeningitis, rubeola, mumps, varicella, and arbovirus were negative. Epstein-Barr virus and mycoplasma serologic titers were negative. Rotavirus antigen was detected in the stool by enzyme immunoassay. The CSF was evaluated and rotavirus RNA was detected by RT-PCR.[22] By genotyping the stool and CSF isolates were G1 serotypes.

An electroencephalogram (EEG) showed no seizure activity, but generalized slowing compatible with encephalopathy. By the fourth day after admission, the child was transferred out of the intensive care unit. Diarrhea, vomiting, and fever had resolved, and irritability had improved. The frequency of screaming episodes had decreased. She remained hypotonic, minimally interactive, aphasic, and had difficulty swallowing. Nasogastric feedings and occupational and physical therapy were initiated.

A repeat lumbar puncture and MRI of the brain were performed on the sixth hospital day. The CSF examination was normal. The MRI had diffuse abnormal signals involving predominantly the gray matter of the cerebellar hemispheres bilaterally (Fig. 1) and parenchymal volume loss. MRI spectroscopy findings of a single voxel in the left cerebellar hemisphere were consistent with encephalitis. By the ninth day of admission, her neurologic status had improved. Although interactive and able to tolerate soft solids, she remained aphasic.

She was transferred to the rehabilitation unit for 20 days, where she received intensive physical, occupational, and speech therapy. She was nonverbal and dysphagic with a videofluoroscopic swallowing study showing aspiration of thin liquids. Bilateral upper extremity movements were dysmetric; she had significant ataxia precluding ambulation. She inconsistently followed 1-step commands. At discharge, she followed 2-step commands, was able to swallow thin liquids and had resumed speaking in 2–4 word sentences, although speech was dysarthric and slow. Dysmetria and ataxia improved but she still required supervision with ambulation. Outpatient therapies continued for 5 months after discharge. At a 1-year follow-up visit, she was attending preschool. She had mild disarticulation in speech and mildly decreased fine motor coordination. A neuropsychological evaluation at 14 months postinfection showed overall normal cognitive functioning, with strength in visual relative to verbal reasoning skills. Skills ranged from comprehension of complex oral instructions that was mildly below average to motor-free matching of letter-like forms that was above average.

DISCUSSION

In the United States, our case is the fourth publication and the fifth case documented of a child with rotavirus and CNS involvement. Table 1 and online Table 2 (Supplemental Digital Content, http://links.lww.com/A757) review the characteristics of our case and the other 23 reported cases. Most cases (63%) occurred in the high-risk age group for serious rotavirus disease (6–24 months of age). Of the 24 reported cases, including ours, there were 9 children outside that range. The mean age of cases was 22.6 months with a median age of 21.5 months and a range of 1 day to 72 months. Fifty-six percent of cases were male.

Nearly all children had symptoms of diarrhea (96%) and vomiting (92%). Although fever was present in our case, fever was not consistently reported in other cases (only 54%). Of the 17 children with available data, the mean number of days of symptoms before presentation was 2.6 days. The most common neurologic presentation was seizures, occurring in 67% of the 24 children; however, 1 large case series solely focused on children with seizures.[5] Other presentations included irritability, altered consciousness, inability to speak, ataxia, and shock. Of the 11 children with neuro-imaging done, 7 (64%) had abnormal studies. Of the 11 children with EEGs done, 10 (91%) had abnormal EEGs.

All cases had rotavirus detected in the stool by enzyme-linked immunoassay (ELISA) or latex agglutination. All 24 children had CSF studies done, although specific WBC counts were stated for only 13 children; another 8 children had studies reported as within normal limits, and the WBC was not stated for 3 children. CSF WBC count was reported in 21 cases, with CSF pleocytosis seen in 48%. In earlier reports, rotavirus was detected in CSF by EM alone,[4] by ELISA alone[3] or ELISA and immune EM.[2] In 83% of cases, however, rotavirus was identified using RT-PCR.[5–17] G1 serotypes were the most commonly identified serotype, detected in 65% of children.

Overall, outcomes for most children were good, with 75% returning to baseline. However, the 2 children at either end of the age range, a newborn and a 6-year-old, died. The newborn died shortly after becoming ill, and the 6-year-old died of intractable seizures 5 months after presentation. Four additional children had poor neurologic outcomes. Our case appears to be the first with prolonged neurologic deficits who ultimately had only mild deficits by 5 years of age.

Our case had extensive neuropsychological evaluations over a 14-month period. It is unclear if children who reportedly returned to baseline had comparable neuropsychological testing; however, it is unlikely. Many of the cases may have had subtle deficits in motor and cognitive function upon more extensive and prolonged neuropsychological testing. Based on our findings, a more complete functional assessment should be considered for children with rotaviral CNS involvement.

A limitation in assessing children for rotaviral CNS infection and possibly in our case report, is that the CSF could be contaminated if the overlying skin comes in contact with diarrheal stool. This contamination is, however, very unlikely because CSF is obtained under sterile conditions, and in our case there was a CSF pleocytosis and both routine and uncommon causes of CNS infection were excluded.

Our case report combined with other published cases and recent reports of rotavirus antigenemia and viremia suggest that extraintestinal involvement of rotavirus occurs. In children with rotavirus gastroenteritis, CNS disease may be present and should be considered when CNS symptoms are present. An appropriate evaluation includes a lumbar puncture with routine studies and a CSF RT-PCR for rotavirus should be performed. Additional studies are needed to fully assess the true spectrum and burden of rotavirus disease in children, and to determine if a national rotavirus immunization program prevents cases of extraintestinal rotavirus disease.

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