

Rotavirus-Induced Seizures in Childhood

Marc P. DiFazio, MD, Loranee Braun, MD, Scott Freedman, MD,
and Patrick Hickey, MD

Rotavirus infection is a frequent cause of gastroenteritis in children, and accounts for significant morbidity and mortality, especially in the developing world. Less well recognized is the association of Rotavirus-induced central nervous system dysfunction, which has been associated with seizure, encephalopathy, and death. Symptoms may vary widely, however, and children can experience short afebrile convulsions as the only

manifestation of rotavirus encephalopathy. We report 4 further cases of Rotavirus-induced seizures with mild neurologic manifestations. The condition is reviewed and practical management strategies are suggested.

Keywords: rotavirus; seizure; encephalopathy; virus; epilepsy

Rotavirus infection is a frequent cause of severe gastroenteritis in children, and accounts for a large number of deaths in the developing world.^{1,2} Severe diarrheal illness, vomiting, and resultant dehydration commonly require fluid resuscitation and hospitalization. Less well recognized is the phenomenon of central nervous system involvement in rotavirus infections, which has been associated with seizures, severe encephalopathy, and death.³ Disease severity varies widely however, and children with well tolerated clusters of seizures, early in the diarrheal illness represent a mild form of the disorder. We report several further cases of Rotavirus-induced seizures, with mild neurologic manifestations. The condition is reviewed, and practical management is suggested.

Case Summaries

The first patient is a 19-month-old white female who presented after a 4-minute generalized convulsive seizure. She was previously well, with no significant medical, developmental, or neurologic history. The seizure was characterized as clonic movements of all extremities, accompanied by leftward gaze deviation and head movement and orofacial automatisms. She was afebrile, and serum chemistries and glucose were normal. The recent medical history was notable

for a febrile illness over the 3 days prior with vomiting, and on the day of presentation, she had a single watery stool. Family history was notable for an uncle with a history of a single simple febrile seizure.

She was admitted and underwent extensive diagnostic evaluation. Stool was positive for rotavirus antigen. Stool culture was also positive for enterovirus. Spinal fluid bacterial culture, reverse transcriptase-polymerase chain reaction (PCR) for rotavirus, enterovirus, and DNA PCR for herpes simplex virus 1 and 2 were negative. Additional normal studies included a brain magnetic resonance imaging, as well as an electroencephalogram (EEG) obtained on the day of admission. During the course of her evaluation, she experienced 3 more generalized, afebrile convulsions, lasting 1–2 minutes. Her seizures were treated with lorazepam and fosphenytoin without recurrence.

After initiation of treatment, she returned to her normal neurologic baseline, without further seizures. She continued to experience 2 to 3 watery stools per day for a total of 1 week. Anticonvulsants were discontinued after 5 days, and she has remained free of neurologic symptoms over more than 20 months of follow-up. The first and 3 additional cases of seizures associated with rotavirus are summarized in Table 1.

Discussion

The occurrence of convulsions associated with rotavirus infections or an undifferentiated presumably viral diarrheal illness has been reported.^{1,4–8} Of interest, a preponderance of these publications are from Asian centers, and a recent publication from Great Britain laments the lack of guidance on this topic in major textbooks of pediatrics and neurology.⁹

From the Uniformed Services University of the Health Sciences, Bethesda (MPD, LB, PH); Shady Grove Hospital for Children, Rockville, Maryland (SF); and Walter Reed Army Medical Center, Washington, DC (LB, PH).

Address correspondence to: Marc P. DiFazio, MD, 9715 Medical Center Dr., Suite 233, Rockville, MD 20850; e-mail: mddfazio@aol.com.

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Table 1. Characteristics of cases of Seizures Associated With Rotavirus

	Case 1	Case 2	Case 3	Case 4
Age	19 mo	33 mo	20 mo	2 y
Sex	Female	Female	Male	Female
Race	Caucasian	Hispanic	Asian	Asian
Febrile seizure	No	No	No	No
Seizure type	GTC + leftward gaze deviation & automatisms	GTC	GTC	GTC
Number of seizures	4 in 24 h	3 in 24 h	5 in 24 h	>2 in 24 h
Past medical history	Healthy	Healthy	Healthy	Afebrile seizure during diarrheal illness 2 mo prior; otherwise healthy
Admitted	Yes	Yes	Yes	Yes
Diarrhea	+ watery	+ watery	+ watery	+ watery
Rotavirus studies	Stool antigen positive; CSF PCR negative	Stool antigen positive	Stool antigen positive	Stool antigen positive
Electrolytes	Normal	Normal	Normal	Normal
CSF studies	Normal to include PCR for enterovirus and HSV	None	None	None
CNS radiographs	CT & MRI normal	CT & MRI normal	CT normal	MRI normal
EEG	Normal	Normal	Normal	Normal
Anticonvulsants	Lorazepam × 1 d Fosphenytoin × 1 d Phenytoin × 5 d	Fosphenytoin × 1 d Levetiracetam × 3 wk	Fosphenytoin × 1 d	Levetiracetam × 1 mo (lost to follow-up)
Follow-up	20 mo	6 mo	6 mo	6 mo

Abbreviations: GTC, generalized tonic-clonic; CSF, cerebrospinal fluid; PCR, polymerase chain reaction; HSV, herpes simplex virus; CNS, central nervous system; CT, computed tomography; MRI, magnetic resonance imaging; EEG, electroencephalogram.

Rotavirus infection associated with short-lived seizures, with or without additional neurologic symptoms such as encephalopathy, represents the largest number of reported cases of seizures associated with afebrile diarrheal illness.^{6,8} Typically, such cases do not have serious electrolyte or metabolic disturbance, and patients are usually afebrile. The virus itself has, therefore, been implicated as a cause of seizure and encephalopathy, independent of fluid and electrolyte abnormalities. It is believed that the most probable mechanism of seizure associated with rotaviral infection is direct central nervous system infection.^{10,11} This explanation has been further substantiated by several studies demonstrating rotavirus reverse transcriptase-PCR positivity on testing of spinal fluid.¹² Although some have attributed this finding to contamination of the spinal fluid sample with fecal material, the number of studies identifying rotavirus in the cerebrospinal fluid speaks against this.¹³ Additionally, animal studies have identified rotaviral involvement in nonintestinal fluids after experimental inoculation.¹⁴ Direct inoculation of primate brains results in neurologic compromise and histologic evidence of infection.¹⁵ However, not all children have demonstrated evidence of Rotavirus on testing of the spinal fluid.

Another fascinating possibility is a remote or secondary effect of the virus. In 1 report, nitric oxide was demonstrated to be significantly elevated in the spinal fluid of patients with rotavirus-induced convulsions. Controls or patients with other mechanisms for seizure, such as febrile convulsions or meningitis had much lower levels.¹⁶ This

finding has led to proposals that seizures might be induced by elevation of nitric oxide during rotavirus infections inducing neurotoxicity.^{16,17} In vitro, rotavirus has been shown to infect and replicate within neurons, and viral proteins such as NSP4 have been identified in dendritic processes.¹⁸ NSP4 has been shown to stimulate intracellular calcium mobilization in infected gastrointestinal epithelial cells.¹⁹ Calcium dysregulation causes cytolysis in gastrointestinal cells, and NSP4-induced calcium channel fluctuations may result in neurotoxicity and neurotransmitter dysregulation. NSP4 has also been shown to have inherent membrane destabilizing properties.²⁰ The ultimate etiology might have clinical and research importance in the setting of newly diagnosed epilepsy and may explain the development of an apparent fixed epileptic state in some individuals after rotavirus infection.⁷ Of interest, it has been hypothesized that exposure to enteric infections may cause epilepsy in some individuals, and a remote effect of neuroenteric proteins has been postulated as a mechanism.²¹ Additionally, the irritability associated with several of our cases and those reported in the literature may be attributable to the remote effect of a neurotoxin, especially because obvious central nervous system inflammation is not evident in most children.

The reported clinical presentation varies widely, and some case series probably include children with convulsions due to febrile seizures, Reye syndrome, as well as first presentations of epilepsy.^{3,7,22,23} This finding has complicated

attempts to identify the natural history and prognosis, and these remain ill defined. Severity varies from serious encephalopathic manifestations and fever, consistent with encephalitis to short convulsions, clustering in the first few days of a diarrheal illness, without serious disruption otherwise in neurologic functioning.^{3,9} These seizures are usually described as short and generalized, although other types of seizures have been reported.⁹ The wide variation in clinical presentation and course can be confusing for clinicians. It may be particularly problematic when encountering a mildly affected child, without evidence of significant encephalitis or fever, who experiences a cluster of seizures without apparent provocation, especially if the diarrhea is mild or has begun to resolve. Additionally, because children may experience recurrent bouts of rotavirus over several seasons, and if seizures are associated, some may appear to have recurrent episodes of “unprovoked” seizures, and, therefore, meet criteria for epilepsy.

All of our cases returned to normal in the interictal period (although 3 patients had transient mild to moderate irritability), and have had no neurologic residual. Because of the potentially mild nature of rotavirus-induced diarrheal illnesses, this may be overlooked as a cause for recurrent seizures. When children present with apparently unprovoked afebrile seizures, especially (as in our case 4) on multiple occasions, treatment with an anticonvulsant may be initiated on the basis of a clinical diagnosis of epilepsy. Current treatment of children with 2 or more unprovoked seizures usually involves anticonvulsant treatment for a 2-year period. However, anticonvulsant use in children is not uncommonly associated with side effects, potentially causing a broad range of medical and neurologic complications. Because of the potential for side effects, and the infrequent nature of some seizures, Aicardi has proposed symptomatic or as-needed therapies for nonfebrile, occasional seizures.²⁴ In fact, “Nonfebrile Illness Seizures” has recently been proposed as a separate category of childhood seizures.²⁵ Although this report did not identify particular causes of infectious illness-associated seizures, diarrhea was strongly associated. Overall, nonfebrile illness-associated seizures represented 12% of their sample of first time seizures in children. A uniform recommendation for management requires more deliberation among experts in epilepsy and seizure management in children.

Our cases had mild gastrointestinal illnesses, and aside from mild irritability, they had no evidence of encephalopathy. In fact, case 4 had experienced a previous gastrointestinal illness in association with several seizures, prompting admission to another center, where diagnostic testing for viral provocation was not carried out. This finding raises questions regarding the awareness of gastrointestinal-associated neurologic disorders such as rotavirus-induced seizures among pediatricians and neurologists alike.

Our current method for addressing such patients who experience a cluster of recurrent seizures is to screen

carefully for ongoing or recent gastrointestinal illnesses, and if present, stool testing for rotavirus is carried out. If positive, the parents are instructed regarding the possible association of seizures and rotavirus, although definitively excluding the possibility of epilepsy is impossible without further diagnostic study, and clinical follow-up. Several of our children had experienced multiple seizures within a short period of time and required treatment with fosphenytoin to prevent further occurrence. This treatment appears to be effective, as all children responded to anticonvulsants without recurrence subsequent to institution of medication. However, others have reported a clustering of seizures in the first 72 hours of diarrheal illness, which may have accounted for the apparent response to medication.⁷ Because the literature regarding rotavirus-induced seizures is unclear regarding the short-term risk of recurrence after initial presentation of multiple seizures requiring hospitalization and anticonvulsant treatment, we believe that a short course of anticonvulsants is prudent and safe for children exhibiting signs of encephalopathy. Parents are counseled that a short course of oral anticonvulsant therapy, typically 2 to 4 weeks, will facilitate discharge home and decrease the likelihood of subsequent convulsions as the viral insult resolves. There are no clinical data to support oral anticonvulsant treatment of rotavirus-induced seizures, although it appears that they respond to conventional treatments such as phenytoin. We have recently chosen levetiracetam as the agent for seizure prophylaxis in this circumstance, given the recent data supporting its use for a multitude of seizure types in children, as well as the fairly innocuous nature and attractive side-effect profile.²⁶ However, it is unclear at present if this treatment is necessary, or if alternative medications might offer better outcomes.

We believe that such children should undergo standard testing for a first-time seizure, given the possible co-occurrence of a fairly common viral illness, such as rotavirus, and first-time seizures that are in fact due to epilepsy. However, further research may reveal a mechanism for clearly identifying rotavirus-induced seizures, and observation only may be necessary. Additionally, children who are experiencing a diarrheal illness that may affect fluid homeostasis should undergo simple laboratory screening for electrolyte abnormalities. Children who present with more fulminant encephalopathic symptoms consistent with encephalitis should also undergo a spinal tap.

In short, a diagnostic and therapeutic plan for a child who presented with ongoing or clusters of seizures, in association with a rotavirus-induced gastrointestinal illness, would consist of admission to the hospital for stabilization and diagnostic testing. EEG, and electrolyte screening would be reasonable in this circumstance. Once stable and seizure-free, discharge home with or without oral anticonvulsants would depend on EEG findings, parental anxiety, and clinical history. Single seizures, if short and the patient stable, might not necessitate admission if the gastrointestinal illness was well tolerated, and no fluid or electrolyte

abnormalities were noted. Rectal diazepam might be considered for such patients if they are discharged home, given the risk of recurrence early in the course of the illness, although none of our patients experienced status epilepticus. (Our patient 2 was discharged after her first seizure, but experienced 2 more in the next 12 hours.)

Further study on the possible association of rotavirus and seizures should include attempts to refine the population, to minimize the possibility of inclusion of other relatively benign seizure syndromes, such as febrile seizures. Serotype and genotype analysis may provide additional epidemiological clues to neurotropic strains.²⁷ The possibility that rotavirus may be inciting seizures remotely, without direct central nervous system involvement, is intriguing and should prompt further study in conjunction with research on the development of epilepsy in children.

Although justification for the use of a vaccine for rotavirus has been based on the occurrence of gastrointestinal and metabolic complications, a third justification would seem to be the occurrence of encephalopathy and seizures. The overall incidence of this association remains unclear. However, the combined cost and stress of hospitalization, diagnostic testing, and potential classification as epilepsy prompting prolonged medical therapy appears to justify attempts at prevention.

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