

Rotavirus Gastroenteritis Associated with Afebrile Convulsion in Children: Clinical Analysis of 40 Cases

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Background: The purpose of this study was to evaluate the clinical manifestations and outcomes of hospitalized children with afebrile seizures following rotavirus gastroenteritis.

Methods: We conducted a retrospective study enrolling patients under 18 years old who were admitted to our hospital during a 10-year period with the diagnosis of rotavirus gastroenteritis. We identified and further analyzed patients who presented with afebrile seizures, without previous seizure disorders, electrolyte imbalances or hypoglycemia. The statistical methods used were the Chi-square test, the Kruskal-Wallis test and the Mann-Whitney test.

Results: Of 1937 patients, 40 patients (24 female and 16 male patients) met the inclusion criteria. The incidence of afebrile seizures following rotavirus gastroenteritis was 2.06%. The age of the patients ranged from 6 months old to 6 years old (mean, 1.9 years). The highest incidence of afebrile seizures was 4.67% in children 1 to 2 years of age ($p < 0.001$). Twenty-seven patients (67.5%) had two or more seizures, which usually were in clusters within a 24-hour period. No status epilepticus was observed. More than half of the patients (52.5%) suffered from seizures on the third day of diarrhea. Only five of 35 patients showed abnormal electroencephalogram (EEG) findings, which reverted to normal in four of the patients during the follow-up period. Most patients did not require long-term anticonvulsant treatment. During the follow-up period, all patients displayed normal psychomotor development without the recurrence of seizures, except in one patient who had a febrile convulsion.

Conclusion: We found that the course of afebrile seizures following rotavirus gastroenteritis was benign with satisfactory outcomes.
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Key words: Rotavirus gastroenteritis; afebrile seizure.

The rotavirus is a major pathogen of viral gastroenteritis in infancy and early childhood and is especially prevalent during the winter. The disease is usually self-limiting. However, afebrile seizures

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occur in a subgroup of children with rotavirus gastroenteritis even without severe electrolyte imbalance or hypoglycemia. Its etiology remains unclear. Benign convulsions with mild gastroenteritis were first reported in Japan in 1982.⁽¹⁾ Several reports have described the disease in recent years and some of the subjects were shown to have rotavirus infection.^(2,3) Some researchers suggested that the rotaviral infections may cause serious damage to the central nervous system (CNS) of affected children.⁽⁴⁻⁶⁾ Others described good outcomes in the majority of children who had recurrent episodes of afebrile seizures associated with rotavirus gastroenteritis.^(7,8) We conducted a retrospective study to evaluate the clinical manifestations and outcomes of hospitalized children with rotavirus gastroenteritis associated with afebrile seizures.

METHODS

This retrospective study included patients under the age of 18 years who were admitted to our hospital from September 1991 through August 2001 with the diagnosis of rotavirus gastroenteritis, as demonstrated by positive rotavirus antigens in their stools. Rotavirus antigens in fecal specimens were detected using latex agglutination (LA) from 1991 through 1995, while specimens from 1996 through 2001 were analyzed using enzyme-linked immunosorbent assay (ELISA). Patients who developed afebrile seizures associated with rotavirus gastroenteritis were identified and further analyzed.

If patients had at least one of the following, they were excluded from the study: 1) fever occurring 24 hours before, during or after seizures; 2) history of underlying epilepsy or other intracranial organic diseases; 3) remarkable electrolyte imbalance or hypoglycemia; or 4) bacteria growth in the stool culture. We reviewed and analyzed the clinical data, laboratory results, seasonal distribution, seizure type and frequency, electroencephalogram (EEG) features and prognosis of the patients who were enrolled. The incidence of afebrile seizures and seizure frequency among the different age groups were compared. The Chi-square test was used to compare the incidence of afebrile seizures in the different age groups and during different months. The frequency of seizure episodes in the different age groups was evaluated with the Kruskal-Wallis test and the Mann-Whitney

test. A *p*-value less than 0.05 was considered statistically significant.

RESULTS

A total of 1937 patients with rotavirus gastroenteritis were observed during a 10-year period, including 40 patients with afebrile seizures who were included for analysis. The incidence of afebrile seizures in children following rotavirus gastroenteritis was 2.06%. There were 24 girls and 16 boys (male:female=5:4) and the age distribution ranged from 6 months to 6 years (mean±standard deviation [SD], 1.9±0.8 years). The age-of-onset and incidence of afebrile seizures in the four different age groups are shown in Fig. 1. The highest incidence of afebrile seizures was 4.67% in the children 1 to 2 years of age and the incidence was significantly different among the four groups (*p*<0.001, Chi-square test).

The seasonal distribution of rotavirus gastroenteritis and associated afebrile seizures is shown in Fig. 2. Rotavirus gastroenteritis was the most prevalent from February to May, and the prevalence of cases with afebrile seizures was the highest from January to June. However, the incidences of afebrile seizures during different months were not significantly different from one another (*p*=0.142, Chi-square test).

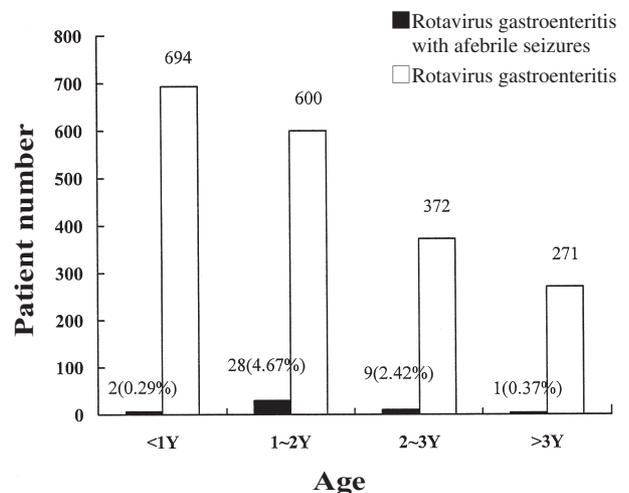


Fig. 1 The incidence of afebrile seizures following rotavirus gastroenteritis in four different age groups.

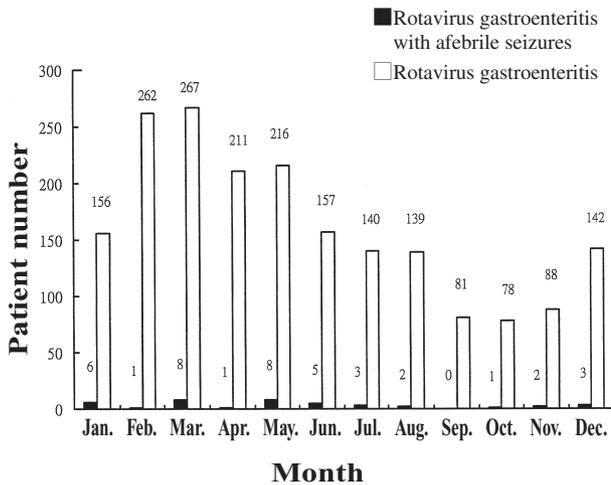


Fig. 2 The seasonal distribution of rotavirus gastroenteritis and afebrile seizures associated with rotavirus gastroenteritis

The laboratory results for the 40 patients, including range, mean values and standard deviations of leukocyte count, serum electrolytes, and blood sugar were: leukocyte count from 3800 to 15000/mm³ (mean ± SD: 8373 ± 2332/mm³); serum sodium concentration from 131 to 159 meq/L (138.3 ± 5.4 meq/L); serum potassium concentration from 3.2 to 5.4 meq/L (4.3 ± 0.5 meq/L) and serum calcium level from 8.1 to 10.0 mg/dL (9.2 ± 0.5 mg/dL.); serum sugar from 61 to 117 mg/dL (82.1 ± 16.2 mg/dL).

Cerebrospinal fluid (CSF) studies were performed in five patients, and we had no abnormal findings for cell counts, biochemistry and bacterial and viral cultures. A brain echo was performed in six patients and a brain computed tomography (CT) in two. The results of these image studies showed no abnormalities.

All patients experienced generalized seizures. The seizure episodes ranged from 1 to 7 times per day and 27 patients (67.5%) had two or more seizures. The seizures of these 27 patients were in clusters within a 24-hour period and no status epilepticus was observed. The mean numbers of seizure episodes in each age group were 1.5 in two patients younger than 1 year old, 2.0 in 28 patients 1 to 2 years old, 3.0 in nine patients 2 to 3 years old, and seven in one patient older than 3 years old. The frequencies of seizure episodes were significantly different among the different age groups ($p=0.036$, Kruskal-Wallis test). The frequency of seizure in patients older than 2 years was higher than that in patients younger than two years ($p=0.008$, Mann-Whitney test).

The timing of afebrile seizures associated with the onset of diarrhea was analyzed. Seizures occurred from the first to the seventh day after the onset of diarrhea and most occurred on the third day. Two (5%) of the 40 patients suffered from seizure episodes on the first day, six (15%) on the second day, 21 (52.5%) on the third day, eight (20%) on the fourth day, two (5%) on the fifth day, and one (2.5%) on the seventh day.

EEG examinations performed 1 to 28 days after seizures in 35 of the patients displayed abnormal epileptiform discharge in five patients, which is shown in Table 1. Follow-up EEG examinations performed from 1 to 25 months after the onset of seizures revealed normal results in four patients, and only one had persistent abnormal epileptiform discharges at 1 year after the onset of illness. Intravenous phenobarbital infusion was administered to 10 patients during hospitalization. No long-term anticonvulsants were administered, except for two patients who received oral phenobarbital therapy for

Table 1. Abnormal EEG Findings and Anti-convulsant Treatment in 5 Patients

Case	Age	EEG Features (days after seizure)	EEG follow-up (months after seizure)	Anti-convulsant treatment
1	1Y10M	Focal epileptiform activity over left parietal and middle temporal area (1)	Normal (1)	No
2	1Y2M	Focal epileptiform activity over left parieto-temporal area (5)	Normal (2)	No
3	1Y10M	Focal epileptiform activity over right temporal area (3)	Normal (5)	Yes
4	10M	Focal epileptiform activity over left temporal area (18)	Normal (25)	Yes
5	1Y11M	Focal epileptiform activity over left middle temporal-frontal area (2)	Focal epileptiform activity over left temporal-frontal area (12)	No

Abbreviation: Y: year; M: month.

5 months and 28 months, respectively, due to abnormal EEGs after discharge. The periods of follow-up for patients with afebrile seizures ranged from 5 to 94 months (mean, 39.1 months). The psychomotor development was normal in all 40 patients during the follow-up. None developed epilepsy. Only one patient with normal EEG experienced febrile convulsions 2 months after discharge.

DISCUSSION

The Rotavirus is an important agent of viral gastroenteritis in children.⁽⁹⁾ Rapid diagnosis can be made by detecting the rotavirus antigen in fecal specimens. LA or ELISA confirmed the diagnosis of rotavirus gastroenteritis in this study. Both methods are reliable. LA is a highly specific and rapid method for detecting the rotavirus antigen in fecal specimens.⁽¹⁰⁾ However, indeterminate results were found in 9.5% of the samples by LA in one series that needed to be confirmed using other methods, such as ELISA or electron microscopy.⁽¹⁰⁾ Therefore, the ELISA is the more sensitive method and has been in our hospital since 1996. Because LA and ELISA are highly specific for detecting the rotavirus antigen, we assumed that the diagnosis of rotavirus gastroenteritis in this study was reliable.

Rotavirus gastroenteritis is usually self-limited and complications such as severe dehydration, shock and death are rare. However, afebrile seizures have been observed in some patients with rotavirus infections. Whether such seizures are related to mild encephalitis from direct viral invasion or enterotoxin is not clear.⁽¹¹⁾ Our retrospective study was limited in determining the pathogenesis of afebrile seizure, but some studies have shown that the rotavirus might directly invade the CNS.⁽¹²⁻¹⁷⁾ Rotavirus particles were detected in the CSF and stool specimens using immunoelectron microscopy in 1984.⁽¹²⁾ In recent years, several studies have detected rotavirus genomic RNA in the CSF or blood of patients with convulsions and gastroenteritis by means of reverse transcription polymerase chain reaction (RT-PCR).⁽¹³⁻¹⁷⁾ These reports provided evidence that the rotavirus might directly invade the CNS through the blood stream. More studies are needed to further confirm this hypothesis and to exclude other possible underlying mechanisms.

The incidence of afebrile seizures following

rotavirus gastroenteritis was 2.06% and most occurred between 1 and 2 years of age in this study. Other researchers in Taiwan reported that 6.4% of 125 patients with rotavirus gastroenteritis had seizure episodes.⁽¹⁸⁾ The difference from our results may be because febrile seizures were not excluded in the latter study.⁽¹⁸⁾ In Hong Kong, Wong reported that the incidence of convulsions in patients with rotavirus gastroenteritis was 5.7%.⁽¹⁹⁾ In Japan, seizures occurred in 2.6% of patients with rotavirus infection.⁽²⁰⁾ The incidence found in our study is similar to that reported in Japan.

With regard to the timing of the seizure episodes, two previous reports described the seizures usually occurred within the first three days of the onset of diarrhea.^(3,8) The authors did not discuss or explain this interesting phenomena. In this study, we found that most seizure episodes occurred on the third day after the onset of diarrhea, but not on the first day. It is postulated that the virus may invade and replicate in the intestine initially, afterwards transient viremia might occur. Finally, the virus migrates from the original infectious focus to the CNS through the blood stream. This process might take several days to occur, such that seizures would not appear until 3 days after the onset of diarrhea.

Investigators previously reported that seizures tended to occur repetitively.^(2,3) In our experience, 67.5% of our patients had two or more seizures, which all occurred in clusters within a 24-hour period. The seizure types were generalized and symmetric in our study, as well as other studies.^(3,7,8)

We found that most of the patients had normal EEGs. Although five patients initially had abnormal EEGs, the EEGs became normal in four (80%) of them during the follow-up period. Furthermore, three of them had no recurrent seizures even without protective anticonvulsant therapy during the follow-up period. This suggests that abnormal EEGs in patients with rotavirus gastroenteritis are transient and are not absolute indicators for initiating long-term anticonvulsant therapy. A report by Lin et al.⁽⁸⁾ showed that EEGs were abnormal in six of eight patients. These EEGs returned to normal 4 to 11 months after the onset of seizures. Clinically, these patients did not have any recurrent seizures. It has been suggested, therefore, that the administration of long-term anticonvulsant therapy in such patients is not needed.

Image studies of the CNS and CSF tests seemed to be unnecessary when patients presented with only afebrile seizures without other signs of encephalitis or meningitis. Two patients in this study received brain CT examinations with normal results. Other researchers had similar findings.^(4,6,7,13) The CSF examinations, performed in five patients in this study and 10 patients in other studies, showed no abnormal findings for cell counts, biochemistry and bacterial cultures.^(7,8)

The prognoses for our patients are excellent. The majority did not need long-term anticonvulsant treatment. During the follow-up period, all 40 patients had normal psychomotor development without recurrence of seizures, except for one patient that had a febrile convulsion. Other studies also showed that the course of afebrile seizures following rotavirus gastroenteritis is usually benign and patients exhibit favorable outcomes.^(3,7,8)

We concluded that good outcomes were observed in the majority of the children with afebrile seizures associated with rotavirus gastroenteritis. When the patients do not have signs of meningitis or encephalitis after seizures, CSF and image studies are unnecessary. When patients present with severe encephalitis, more aggressive treatment should be initiated. Further studies are needed to clarify the underlying pathogenesis of afebrile seizures in patients with rotavirus gastroenteritis.

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兒童期輪狀病毒胃腸炎合併無熱性痙攣：40病例的臨床分析

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背景：本研究之目的在於評估因感染輪狀病毒胃腸炎且合併無熱性痙攣而住院之病童，探討有關其臨床表現以及預後之研究。

方法：本研究以回溯性的方法收集在10年期間，因輪狀病毒胃腸炎住院且未滿18歲的病人中，合併有無熱性痙攣，且排除掉有抽筋病史或有電解質異常或低血糖之病童後，進一步分析感染輪狀病毒胃腸炎且合併無熱性痙攣病童之臨床表現及預後，統計方法是採用Chi-square test, Kruskal-Wallis test及Mann-Whitney test。

結果：在1937個病人當中有40個合併非熱性痙攣的病人符合研究條件，其中24人是女性，16人是男性。感染輪狀病毒胃腸炎後發生非熱性痙攣的比例約2.06%。這40人的年齡分布由6個月至6歲(平均1.9歲)，非熱性痙攣發生率最高的是一至兩歲間的兒童(4.67%, $p < 0.001$, Chi-square test)。27個病人(67.5%)痙攣次數超過兩次而且都是在24小時內反覆發生，以兩歲以上小孩容易有較多痙攣次數($p = 0.008$, Mann-Whitney test)，但並沒有病人產生癲癇重積狀態。超過半數(52.5%)的病人在腹瀉後第三天發生痙攣。部分病人做了腦脊髓液，腦部超音波及電腦斷層檢查，結果都是正常。在35個接受腦波檢查的病人中有5個人腦波呈現異常，其中4人在往後的追蹤轉為正常。大多數病人都不需要長期的抗癲癇藥物治療，經過平均39.1個月的追蹤，他們的生長發育及神經學發展都是正常的。除了一個病人在這之後曾發生一次熱性痙攣，其餘的病人日後都不再有痙攣發生。

結論：兒童期輪狀病毒胃腸炎合併無熱性痙攣為一良性病程，預後都很好。大多都不會再有痙攣復發，也不需要長期使用抗痙攣藥物。
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關鍵字：輪狀病毒胃腸炎，無熱性痙攣。

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