



Comparison between febrile and afebrile seizures associated with mild rotavirus gastroenteritis

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ABSTRACT

Purpose: We aimed on identifying the differences of febrile and afebrile seizures associated with mild rotavirus gastroenteritis (RVGE) in the pediatric population.

Method: Medical charts of pediatric patients who had been admitted between July 1999 and June 2011 due to RVGE were retrospectively reviewed. Subjects were ultimately divided into three groups; 'no seizure' (NS: patients without seizure), 'febrile seizure' (FS: patients with fever during seizure), 'afebrile seizure' (AFS: patients without fever during seizure). Comparisons between groups were carried out on demographic and clinical characteristics, laboratory test results, electroencephalogram findings, brain magnetic resonance imaging findings, antiepileptic treatment, and prognosis.

Results: Among the 755 subjects who had been admitted due to mild rotavirus enteritis, 696 (90.3%) did not have any seizures, 17 (2.2%) had febrile seizures, 42 (5.5%) had afebrile seizures. The duration of gastrointestinal symptoms before the onset of seizures were significantly shorter in the FS group compared to the AFS group (1.3 ± 0.8 vs. 2.8 ± 1.0 days; $p < 0.0001$). A single seizure attack was significantly higher in the AFS group (3.0 ± 1.6 vs. 1.7 ± 1.0 episodes; $p = 0.0003$), and the frequency of seizures that were of focal type with or without secondary generalization were significantly higher in the AFS group (33.3% vs. 6.0%; $p = 0.0139$). All patients among the FS and AFS group had not received further antiepileptic treatment after discharge, and none developed epilepsy during follow up period.

Conclusion: Despite some differences in seizure characteristics, both febrile and afebrile seizures associated with mild RVGE were mostly benign with a favorable prognosis.

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1. Introduction

Rotavirus is the most common cause of gastroenteritis and the leading cause of severe diarrhea due to dehydration in infants and young children worldwide. It is responsible for over 2 million hospitalizations and up to 600,000 deaths per year,¹ and its proportion among diarrhea hospitalizations is increasing worldwide.² Although, rotavirus replicates mainly in epithelial cells that line the small intestine causing gastroenteritis, mild forms of rotavirus gastroenteritis (RVGE) are known to be capable of inducing benign afebrile convulsions in infants and young children.

The clinical condition in which mild viral gastroenteritis without severe dehydration, electrolyte imbalance, or hypoglycemia could trigger afebrile convulsions was first reported in Japan.³ Thereafter, several reports and studies have described the

association of benign afebrile seizures with mild gastroenteritis mainly from East Asian countries, such as Japan, Korea, and Taiwan,^{4–10} and some from Europe,^{11–13} the United States,^{14–16} and South America,¹⁷ indicating the possibility of predominant occurrence in East Asian ethnicity. This distinct clinical entity is now widely recognized as 'benign convulsion with mild gastroenteritis (CwG)'.⁴ CwG is defined as convulsions accompanying symptoms of mild diarrhea without moderate to severe dehydration, electrolyte imbalance, and fever (defined as a body temperature $\geq 38^\circ\text{C}$) before and after the seizures in previously healthy infants and children without meningitis, encephalitis or encephalopathy.^{4,18}

Until now studies on seizures associated with rotavirus have mainly focused on determining the characteristics of CwG. Data on the comparison of characteristics between patients with seizures and without seizures among mild RVGE is scarce.^{8,19} Moreover, despite the fact that RVGE is known to be associated with fever and that febrile seizures are known to occur during the illness, data on the comparison of characteristics of febrile and afebrile seizures associated with RVGE is insufficient. Therefore our aim in this

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study was to identify the characteristics of both febrile and afebrile seizures in infants and children with mild RVGE, and to clarify the clinical differences of febrile and afebrile seizures associated with mild RVGE and reveal the differences between the two distinct clinical entities of seizure in a common infection by rotavirus, which is distinguished until now mainly by the presence of fever during seizure.

2. Material and methods

Electronic databases were queried to identify patients who had been admitted to the pediatric department of Inha University Hospital and diagnosed as RVGE between July 1999 and June 2011. Laboratory tests of these patients were additionally checked in order to confirm positive stool rotavirus antigen test results during admission. Electronic medical records and laboratory tests were initially reviewed in order to exclude patients who had been initially admitted due to other diseases and later obtained nosocomial rotavirus infections or had co-infections identified by other positive antimicrobial tests or stool culture during admission.

We limited 'mild gastroenteritis' to the extent of a medical condition of gastroenteritis without moderate to severe dehydration, electrolyte derangement or hypoglycemia during the illness. Therefore, children that were under such condition were excluded from the study. As other abnormal medical conditions are capable of inducing seizures, we also excluded patients who had abnormal neurological development, previous histories of meningitis, encephalitis, encephalopathy, cerebral trauma, brain tumor, hypoxia or epilepsy, and other underlying diseases of the central nervous system.

Electronic medical records of the subjects were reviewed to obtain data regarding demographic characteristics, clinical symptoms, and laboratory test results at the time of admission. Additional investigation was done in seizure patients on clinical features regarding seizure, electroencephalogram (EEG) findings, brain magnetic resonance imaging (MRI) findings, anticonvulsant therapy received during admission, and prognosis. According to the presence or absence of seizure, patients were initially divided into two groups; the 'seizure' group and the 'no seizure' (NS) group. Thereafter, the 'seizure' group was additionally divided into the 'febrile seizure' (FS) group and the 'afebrile seizure' (AFS) group, according to the presence or absence of fever, defined as a body temperature $\geq 38^\circ\text{C}$, at the time of their seizures. As fever is a common symptom of RVGE, and as fever is capable of occurring during interictal periods of seizures during the natural course of the disease, febrile seizures were limited to seizures that were associated with fever at the time of seizures. Consequently, patients that had fever only at the time of seizures were included in the FS group. Patients who had fever during interictal periods but who were afebrile at the time of seizures were included in the AFS group, even though fever may have occurred within 24 h before or after the seizures in these cases. Patients that had both febrile and afebrile seizures were also included in the FS group.

Rotavirus antigen detection tests in stool samples had been conducted by an immunochromatography assay kit (SD BIOLINE[®] Rotavirus, Standard Diagnostics, Inc., Yongin, Korea) until December 2010, and by enzyme immunoassay (RIDASCREEN[®] Rotavirus, R-Biopharm Aktiengesellschaft, Darmstadt, Germany) starting from January 2011.

Antiepileptic treatment had been initiated with single doses of intravenous benzodiazepines, such as midazolam, diazepam, or lorazepam as the primary drug for patients who had additional seizures after admission. In Korea, it is usual to perform intravenous catheterization in patients who visit a tertiary hospital due to seizures, and therefore antiepileptics are usually

administered intravenously in order to rapidly control seizures, rather than per oral or transrectal administration. A secondary drug of phenobarbital or phenytoin had been administered intravenously to patients that showed no response to maximum three doses of intravenous benzodiazepines.

Statistical analysis was carried out on the SAS 9.1.3 service pack 4 program (SAS Institute Inc., Cary, North Carolina, USA.). Chi-square test was used for the comparison of categorical data between groups. For the comparison of dimensional variables, Student *t* test was used for analysis between two groups, and one-way analysis of variance (ANOVA) test was carried out for analysis between three groups. The *p* value for statistical significance was defined as $p < 0.05$. Post hoc analyses with Bonferroni *t* test was carried out when the *p* value for the ANOVA test reached less than $p < 0.05$.

This study was approved by the Institutional Review Board of Inha University Hospital.

3. Results

During the study period between July 1999 and June 2011, 1185 pediatric inpatients had been diagnosed as RVGE with positive rotavirus antigen in stool samples. Among these patients, 430 patients were excluded from the study leaving 755 patients for inclusion into the study.

Among the 755 subjects who were included in the study, 696 (92.2%) did not have seizures, while 59 (7.8%) had seizures. Among the seizure patients, that were ultimately included for comparison, 17 patients had (2.2%) febrile seizures and 42 patients (5.6%) had afebrile seizures. Among the 17 patients in the FS group, six patients had both febrile and afebrile seizures. In these six patients, all cases of febrile seizures preceded afebrile seizures, and afebrile seizures occurred within 24 h of the development of febrile seizures. Seasonal distribution of incidences showed that there were 527 among 696 patients (75.7%) of the NS group, 13 among 17 patients (76.5%) of the FS group, and 37 among 42 patients (88.1%) of the AFS group that had been admitted between December and April. Comparisons of demographic characteristics and clinical symptoms between the three groups are summarized in Table 1.

Comparison of seizure characteristics among the FS group and the AFS group revealed significant differences in past history, family history, frequency, types of seizure attacks, the duration between GI symptoms and seizures, and the presence of diarrhea before seizures (Table 2). There were five patients (29.4%) in the FS group, and two patients (4.8%) in the AFS group who had a past history of febrile seizures, showing statistical significance between the two groups ($p = 0.0080$). There were three patients (17.6%) in the FS group, and five patients (11.9%) in the AFS group who had a family history of febrile seizure or epilepsy, showing no statistical significance between the two groups ($p = 0.5596$). All three patients in the FS group had a first degree family history of febrile seizures. Among the AFS group, one patient had a first degree family history of epilepsy, three patients had a first degree family history of febrile seizures, and one patient had a second degree family history of febrile seizure. There were 37 patients (88.1%) in the AFS group who had two or more seizures, ranging from one to eight episodes. Meanwhile, there were six patients (35.3%) in the FS group who had multiple seizures ranging from one to four episodes. The duration of the seizure attack (duration from the first to last seizure) ranged from 1 to 21 h in the six patients of the FS group and 1–32 h in the 37 patients of the AFS group. Seizure ceased within 24 h in all six patients in the FS group, while there were two patients among the AFS group whose seizures persisted for more than 24 h. The duration from the first to last seizure in these patients were 27 h and 32 h, respectively. The duration of

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