Norovirus Infection as a Cause of Diarrhea-Associated Benign Infantile Seizures

Shih-Yen Chen,[1,4,a] Chi-Neu Tsai,[4,a] Ming-Wei Lai,[1] Chih-Yen Chen,[5] Kuang-Lin Lin,[2] Tzou-Yien Lin,[3] and Cheng-Hsun Chiu[3]

Divisions of [1]Pediatric Gastroenterology, [2]Pediatric Neurology, and [3]Pediatric Infectious Diseases, Chang Gung Children's Hospital, and [4]Graduate Institute of Clinical Medical Sciences, Chang Gung University College of Medicine, Taoyuan, and [5]Department of Molecular Biotechnology, Da-Yeh University, Changhua, Taiwan

Background. Norovirus and rotavirus cause outbreaks of diarrheal disease worldwide. This prospective observational study was undertaken to investigate the clinical characteristics and complications, with a focus on convulsive disorders, of gastroenteritis caused by norovirus and rotavirus in hospitalized pediatric patients in northern Taiwan.

Methods. Children hospitalized with acute gastroenteritis in Chang Gung Children's Hospital from August 2004 through January 2007 were enrolled in the study. Rotavirus and norovirus were detected by reverse-transcriptase polymerase chain reaction with fecal specimens and were genotyped by sequence analysis. The symptoms and complications, in particular convulsions, of acute gastroenteritis caused by rotavirus and norovirus were reviewed and compared. The occurrence of convulsions associated with norovirus infection was specifically analyzed and discussed. The neurological outcomes for all norovirus-infected patients with or without convulsions were followed up for 1 year.

Results. Among the 353 patients with acute viral gastroenteritis without coinfection, rotavirus and norovirus isolates were detected in 101 patients (28.6%) and 64 patients (18.1%), respectively. We compared the symptoms between the 2 groups and found that rotavirus caused a higher frequency and longer duration of vomiting and a higher body temperature than did norovirus. Norovirus infection, on the other hand, caused significantly longer hospital stays (mean duration of stay [interquartile range], 6 [5–8] days vs. 5 [4–7] days; $P < .001$) and a significantly higher incidence of convulsions than did rotavirus infection (29.7% vs. 5%; $P < .001$). Three of the 19 patients with convulsions showed an abnormal record on electroencephalogram, but none had any neurological sequelae at the subsequent 1-year follow-up. The majority of norovirus strains (41 of the 56 genotypeable strains) belonged to genogroup GGII/4.

Conclusions. Norovirus is a major cause of acute gastroenteritis in children. This study identified norovirus as an emerging agent causing convulsive disorder in children, particularly in young infants. Long-term neurological sequelae are uncommon.

Viral acute gastroenteritis (AGE) is one of the most prevalent infectious diseases in the world, and rotavirus and norovirus are the 2 most common viral agents that cause infantile diarrhea. Rotavirus infection results in ~500,000–800,000 childhood deaths annually in underdeveloped countries [1]. Rotavirus infection generally causes vomiting, watery diarrhea, and occasionally fever. Complications such as dehydration, convulsions, and bowel obstruction have been reported [2, 3]. After 2006, 2 vaccines to prevent rotavirus gastroenteritis were launched in several countries [4, 5].

Norovirus is the second most common cause of diarrhea in children. This virus circulates in community environments, and evidence indicates that it is involved in sporadic cases of AGE in infants and adults [6, 7]. Norovirus can be genetically divided into 5 genogroups (GGI–GGV), of which GGI, GGII, and GGIV cause AGE in humans [8]. Norovirus GGII has caused a global AGE epidemic, and the emergence of the norovirus subgenogroup GGII/4 has been associated with large outbreaks of AGE in the United States, Australia,

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[a] S.-Y.C. and C.-N.T. contributed equally to this article.

Reprints or correspondence: Dr. Cheng-Hsun Chiu, Dept. of Pediatrics, Chang Gung Children's Hospital, 5 Fu-Hsin St., Kweishan 333, Taoyuan, Taiwan (chchiu@adm.cgmh.org.tw).

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New Zealand, Japan, and Taiwan since the late 1990s [9, 10].

Few studies have discussed and compared the clinical manifestations of rotavirus and norovirus infections in children. Uncommon complications, such as convulsion, of viral AGE in children were sporadically reported [11] but not prospectively documented. The purpose of this study was to comprehensively investigate the clinical features, especially infantile convulsions, associated with viral AGE in hospitalized pediatric patients in northern Taiwan.

PATIENTS AND METHODS

Patient selection and data collection. This study was approved by the Institutional Review Board of Chang Gung Memorial Hospital (CGMH 95-1058B), and either the participants or their guardians gave informed consent for both specimen and clinical data collection. Patients aged 3 months to 18 years who were hospitalized at Chang Gung Children's Hospital from August 2004 through January 2007, whose major clinical manifestation was acute nonbloody diarrhea, and who fulfilled the criteria for hospitalization were offered enrollment. Patients were not enrolled if they or their guardians declined to participate or if they were discharged before the study team could approach them. The medical records of the patients were reviewed. Demographic data, details of the disease course (under a prescribed list of clinical features provided by an interview of the child's caregivers or the child), and the results of physical examinations and laboratory testing were collected and analyzed.

Severity of AGE. The severity of AGE was evaluated by scoring the frequency and duration of diarrhea and vomiting, electrolyte and dehydration status, and fever, as described elsewhere [12]. A severity score >11 indicated severe AGE [12].

The level of dehydration was defined as mild if patients had a slightly decreased urine output and a normal or slightly increased pulse rate, moderate if patients had tachycardia at rest and dry mucous membranes, and severe if patients showed hypotension and cold, mottled skin [13]. Complications were defined as the occurrence of extraintestinal or unusual presentations of AGE, such as hypoglycemia (serum sugar level, <70 mg/dL), electrolyte imbalance (hyponatremia: serum sodium level, <135 mmol/L; hypokalemia: serum potassium level, <3.5 mmol/L; or hypochloremia: serum chloride level, <98 mmol/L), liver function impairment (serum alanine aminotransferase or aspartate aminotransferase level, >46 IU/L), hypotension (systolic blood pressure, <70 mmHg), or severe hyperthermia (body temperature, >41°C). Leukocytosis was defined as a blood leukocyte count $>10^4$ leukocytes/mm^3.

Sample collection and extraction of viral nucleic acid. All fecal samples collected from the patients were sent to the clinical microbiology laboratory for bacterial culture of *Salmonella, Shigella,* and *Campylobacter* species to exclude patients with bacterial AGE from the study, as described elsewhere [14]. All samples were stored at −70°C before extraction of viral nucleic acid with a kit (High Pure Viral Nucleic Acid Kit; Roche Diagnostics), which was performed according to the manufacturer's recommendations.

Detection of viruses by RT-PCR. The first-strand complementary DNA (cDNA) synthesis for viral nucleic acids was performed according to the manufacturer's recommendations (Transcriptor First Strand cDNA Synthesis Kit; Roche Diagnostics). The PCR primer sets used for detection of rotavirus and norovirus have been described elsewhere [15, 16]. The PCR products were separated on 2% agarose gel, were stained with ethidium bromide, and were visualized using VL PHOTO-print system (ITS Science & Medical).

Viral DNA sequencing analysis. Sequencing was used to genotype the rotavirus and norovirus strains that caused AGE in the patients. The PCR products were first purified with a PCR cleanup kit (Qiagen), according to the manufacturer's instructions, before undergoing direct sequencing with the ABI 3730 autosequencer (Applied Biosystems). The sequences obtained were aligned, genotyped, and compared with other sequences available in the GenBank and/or European Molecular Biology Laboratory databases.

Statistical analysis. Continuous data were analyzed using the Student's t test and were expressed as the mean ± SD, and binary data were analyzed using the χ^2 test. $P < .05$ was considered statistically significant. All tests were analyzed using SAS system software, version 8 for Windows (SAS Institute).

RESULTS

During the 2.5-year study period, 387 children were admitted to the Department of Pediatric Gastroenterology, Chang Gung Children's Hospital, because of AGE symptoms. Of those children, 15 who had bacterial gastroenteritis and 19 who had viral and bacterial coinfection were excluded from the study. The study included a total of 353 patients with nonbacterial AGE, consisting of 194 boys and 159 girls (male-to-female ratio, 1.22:1). The mean age of the patients was 28.2 ± 23.5 months, and the age range was 3 months to 15.6 years. Most (298 [84.4%]) of the children were <5 years of age, and the mean duration of hospital stay was 5.6 ± 2.9 days (range, 2–20 days).

RT-PCR was used to detect rotavirus and norovirus in the fecal samples. Rotavirus and norovirus isolates were found in 101 patients (28.6%) and 64 patients (18.1%), respectively. Figure 1 shows the seasonal distribution and rates of cases of rotavirus infection and norovirus infection among all patients admitted for treatment during the study period. The number of AGE cases caused by rotavirus and norovirus peaked from late winter to early spring, and the increase in the rate of norovirus infection preceded the increase in the rate of rotavirus infection. The majority of cases of norovirus infection occurred

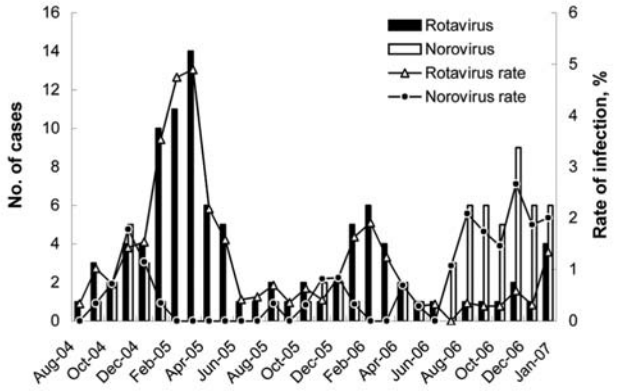

Figure 1. Seasonal distribution of the number of cases and the rates of rotavirus and norovirus gastroenteritis among all patients admitted to the Department of Pediatric Gastroenterology, Chang Gung Children's Hospital, Taiwan, from August 2004 through January 2007.

in late 2006, with a higher infection rate that lasted for 6 months, from August 2006 through January 2007.

Rotavirus cDNA derived from the fecal samples was further sequenced. The obtained VP7 sequences (G type) were aligned and pairwise compared with sequences in the NCBI database. Among the 101 specimens that tested positive for rotavirus, G typing of 89 of those specimens showed that 18 (20.2%) were G1, 15 (16.9%) were G2, 24 (27.0%) were G3, 1 (1.1%) was G4, 17 (19.1%) were G9, 4 (4.5%) were mixed types, and 10 (11.2%) were nontypeable. Among the 64 samples that tested positive for norovirus, 56 were successfully genogrouped by sequence analysis. Seven (12.5%) were classified as GGI and 49 (87.5%) as GGII, including 41 (73.2%) that were further subgenogrouped as GGII/4. The genogroups of norovirus could not be determined in the remaining 8 samples.

The symptoms of AGE caused by rotavirus and norovirus are shown in table 1. Statistical analysis showed a significant difference in the symptoms between the 101 children with rotavirus infection and the 64 children with norovirus infection. Rotavirus infection caused a higher frequency of vomiting ($P = .002$) with longer duration ($P = .01$), a higher body temperature (i.e., fever severity; $P = .005$), and more frequent abdominal pain ($P < .001$). These children also showed a higher summarized disease score ($P < .001$). Compared with rotavirus infection, norovirus infection resulted in a significantly longer hospital stay ($P < .001$), and the incidence of convulsion was significantly higher ($P < .001$). No difference between the 2 groups was observed in terms of the occurrence of electrolyte imbalance.

A total of 19 patients with norovirus infection (11 boys and 8 girls) had convulsions associated with AGE. The detailed symptoms in these patients are described in tables 2 and 3. The median age was 18 months (range, 15–21 months). Diarrhea was observed in all these patients, and vomiting occurred in 12 (63.2%). The majority (15 [78.9%]) of the patients experienced convulsions within 3 days after the onset of AGE symptoms, and 14 patients (73.7%) experienced >1 convulsive episode within 24 h after the first convulsion (5 patients had 2 episodes, 5 had 3, 1 had 4, 1 had 5, and 2 had >5; mean number of episodes, 2.8). Two patients presented with status epilepticus during the first episode of convulsion. All convulsions were general tonic-clonic type except for 3 with focal neurological signs (focal seizure with secondary generalization). None of the patients who had convulsions had parents with epilepsy, according to their family history. Mild dehydration was found in 8 patients (42.1%), moderate dehydration was found in 10 patients (52.6%), and severe dehydration was found in 1 patient (5.3%). Five of the 19 patients had electrolyte imbalance (hyponatremia in 4 and hypokalemia in 1), and 4 had hypoglycemia. More than half (10 [52.6%]) of the patients had a fever, but only 2 experienced a body temperature >39°C. Lumbar puncture was performed in 3 patients with focal neurological signs. Results of cellular and biochemical analysis were negative for norovirus, and RT-PCR showed no norovirus in the CSF. Brain ultrasonography performed for 15 patients showed no abnormalities, except for 1 child who had brain edema. An electroencephalogram (EEG) examination was performed for 10 patients in the acute stage of the infection, and 6 were found to have abnormal EEG records: 3 had cortical dysfunction, 2 had focal spikes, and 1 had epileptiform waves. These patients received anticonvulsant therapy (phenobarbital) for 3 months to 1 year (2 patients received it for 3 months, 1 patient for 9 months, and 3 patients for 1 year), until the EEG results appeared normal in the follow-up examination. None of these patients showed neurological sequelae in the 1-year follow-up period.

We compared the clinical symptoms of patients who experienced convulsions with those of patients who did not (table 3). Convulsions occurred in young children at a median age of 18 months ($P = .033$). Statistical analysis of other clinical and laboratory findings showed no differences between the 2 groups of patients. Patients with convulsions tended to stay in the hospital longer; however, the difference was not statistically significant (mean duration ± SD, 6.5 ± 1.8 days vs. 5.9 ± 2.3 days; $P = .83$). Sequence analysis of the 19 norovirus isolates responsible for the convulsions showed that 16 (84.2%) were genogroup GGII/4.

DISCUSSION

The results of our study showed that AGE caused by rotavirus was more severe than AGE caused by norovirus in terms of the frequency and duration of vomiting, fever, abdominal pain, and overall disease severity score. In our study, the duration of diarrhea was not significantly longer and the frequency of

Table 1. Demographic and clinical characteristics of pediatric patients with acute gastroenteritis caused by rotavirus and norovirus.

Characteristic	Rotavirus (n = 101)	Norovirus (n = 64)	P
Demographic			
Age, months	20 (12–31)	22 (13–35)	.47
Male-to-female ratio	60:41	39:25	.85
Clinical			
Frequency of diarrhea, times per day	5 (3–7)	4 (3–6)	.28
Duration of diarrhea, days	4 (3–6)	4 (3–5)	.81
Frequency of vomiting, times per day	3 (1–4)	2 (1–3)	.002
Duration of vomiting, days	2 (1–3)	1 (0–2)	.01
Fever severity score	1 (0–2)	0 (0–1)	.005
Disease severity score	10 (8–12)	8 (6–10)	<.001
Abdominal pain	48 (47.5)	13 (20.3)	<.001
Occult blood in stool	26 (25.7)	9 (14.1)	.07
Length of hospital stay, days	5 (4–7)	6 (5–8)	<.001
Associated symptoms or complications			
Hypoglycemia	21 (20.8)	13 (20.3)	.94
Electrolyte imbalance	24 (19.8)	9 (14.1)	.13
Convulsion	5 (5)	19 (29.7)	<.001
Laboratory findings			
Leukocytosis	48 (47.5)	26 (40.6)	.39
C-reactive protein, mg/L	11 (4–28)	6 (2–15)	.13

NOTE. Data are median value (interquartile range) or no. (%) of patients, unless otherwise specified.

diarrhea was not significantly higher among children who had norovirus infection than among children who had rotavirus infection. On the other hand, norovirus infection resulted in longer hospital stays and a significantly higher incidence of convulsions, compared with rotavirus infection. Such a high rate of convulsions in hospitalized patients with norovirus infection might be the reason for the prolonged hospital stays, but confirmation of this inference requires further studies.

Norovirus is a more common cause of AGE in children than was previously recognized [17–21]. Norovirus outbreaks have placed a great burden on economic and health resources and have called attention from around the world to the threat that the virus poses [17–21]. Humans of any age can be infected by norovirus, but seroepidemiological surveys demonstrated that antibody (65% against recombinant Norwalk virus and 70% against Mexican virus) was acquired at an early age, indicating that first exposure to the virus occurred early in life [22]. In accord with previous studies, we found that GGII was the most frequently detected genogroup of norovirus strains in this study [23]. The majority of the viruses were further subclassified as GGII/4 group, which has been documented to cause a global epidemic of AGE [24].

The seasonal distribution revealed that rotavirus peaked in the winter, and norovirus was predominant in early winter, although this trend was subtle. Over the 3 consecutive winter seasons investigated in this study, norovirus peaked ahead of rotavirus and decreased before the rotavirus infection started to increase. A similar situation was reported in a previous study [25]. The reasons for the different seasonal distribution should be studied further. The 4 major rotavirus genotypes (G1, G2, G3, and G9) found in this study are either included in or cross-protected by the reassortant pentavalent rotavirus vaccine containing human serotypes G1, G2, G3, G4, and P[8] [5]. Therefore, most of the rotavirus infections in Taiwan could be prevented by the current rotavirus vaccine. The interplay of rotavirus and norovirus, which cause similar diseases in humans, especially in infants and young children, is a concern, given that effective prevention of rotavirus-associated gastroenteritis by rotavirus vaccine has resulted in an overall reduction of 85%–95% in the number of cases of severe AGE of any cause [5]. There is no vaccine available yet to prevent norovirus infection, but the epidemiology of norovirus infection after universal use of rotavirus vaccine should be carefully monitored.

In 1982, Morooka [26] first described an entity of benign infantile seizures associated with AGE in Japan. It is characterized by nonfebrile generalized seizures associated with symptoms of gastroenteritis in previously healthy patients aged 6 months to 3 years. Rotavirus has been reported to cause benign infantile seizures [27, 28]. Our study showed a significantly

Table 2. Demographic and clinical characteristics of 19 children with convulsions caused by norovirus infection.

Age in months, sex	Fever	Symptom(s)	Onset, days after AGE	Electrolyte imbalance	Hypoglycemia	EEG findings	Recurrence within 24 h
18, M	No	Mild dehydration	4	No	No	No abnormalities	Yes
18, M	Yes	Vomiting and mild dehydration	4	No	No	ND	No
18, M	Yes	Mild dehydration	3	No	No	ND	No
18, F	Yes	Vomiting and moderate dehydration	2	No	Yes	Cortical dysfunction	Yes
21, M	No	Vomiting and moderate dehydration	2	No	No	ND	Yes
22, F	Yes	Mild dehydration	3	Hypokalemia	No	Focal spikes	Yes
9, F	Yes	Vomiting and moderate dehydration	5	No	ND	Focal spikes	Yes
18, F	Yes	Moderate dehydration	3	No	No	Epileptiform waves	No
17, M	Yes	Vomiting and moderate dehydration	1	No	No	ND	Yes
22, F	Yes	Vomiting and moderate dehydration	3	No	Yes	ND	No
12, M	No	Vomiting and mild dehydration	2	No	Yes	ND	Yes
15, F	Yes	Vomiting and moderate dehydration	6	Hyponatremia	No	ND	Yes
3, M	No	Vomiting and moderate dehydration	2	No	ND	Cortical dysfunction	Yes
24, M	No	Vomiting and mild dehydration	2	Hyponatremia	No	ND	Yes
15, M	No	Vomiting and severe dehydration	3	Hyponatremia	Yes	No abnormalities	Yes
13, F	Yes	Moderate dehydration	3	Hyponatremia	No	Cortical dysfunction	Yes
23, M	No	Vomiting and moderate dehydration	3	No	No	No abnormalities	Yes
17, M	No	Mild dehydration	2	No	ND	ND	No
24, F	No	Mild dehydration	1	No	ND	No abnormalities	Yes

NOTE. All patients exhibited diarrhea. AGE, acute gastroenteritis; EEG, electroencephalogram; ND, not done.

higher incidence of convulsions associated with norovirus infection, compared with the incidence of convulsions associated with rotavirus infection (29.7% vs. 5%). The incidence of rotavirus-associated convulsions (5%) was similar to that previously reported (~5.7%) by Wong [29]. The detection of a small, round virus similar to norovirus in stool samples from patients with symptoms of infantile benign convulsions has been previously reported [25, 30]. The extremely high rate of convulsive disorder among hospitalized children with norovirus infection in our study is impressive, although norovirus has been described as an important agent causing gastroenteritis and convulsions in children during winter [11]. We identified the following features of norovirus infection–associated seizures in this study: seizures often occurred in a cluster but without focal signs, and recurrence within 24 h was very common. Furthermore, fever frequently accompanied the convulsions,

Table 3. Comparison of clinical presentations of norovirus-infected children with convulsions and those without convulsions.

Characteristic	Convulsion (n = 19)	No convulsion (n = 45)	P
Demographic			
Age, months	18 (15–21)	33 (12–50)	.03
Male-to-female ratio	11:8	28:17	.75
Clinical			
Frequency of diarrhea, times per day	4 (3–6)	5 (3–8)	.08
Duration of diarrhea, days	4 (3–7)	4 (3–8)	.94
Frequency of vomiting, times per day	2 (0–4)	2 (0–5)	.76
Duration of vomiting, days	1 (0–3)	1 (0–3)	.93
Fever	10 (52.6)	23 (51.1)	.91
Disease severity score	8 (7–9)	9 (7–10)	.29
C-reactive protein value, mg/L	12 (2–30)	10 (2–23)	.83
Occult blood in stool	2 (10.5)	7 (15.6)	.58
Length of hospital stay, days	6 (4–8)	6 (4–9)	.83
Hypoglycemia	2 (10.5)	11 (24.4)	.08
Electrolyte imbalance	5 (26.3)	4 (8.9)	.07

NOTE. Data are median value (interquartile range) or no. (%) of patients, unless otherwise specified.

but a severe fever (body temperature, >39°C) was uncommon. All these features are unusual in benign convulsions with mild gastroenteritis (defined as seizures accompanying symptoms of mild diarrhea without signs of dehydration or electrolyte derangement and with a temperature <38°C). On the other hand, the time from the onset of gastroenteritis symptoms to convulsion in norovirus infection (mean, 2.8 days; range, 1–6 days) is similar to the time from the onset of gastroenteritis symptoms to convulsion reported for benign afebrile seizures [31]. The age distribution of our patients with convulsion is similar to that of patients with rotavirus-associated seizures [32–34]. However, a recent report described a significantly younger age for norovirus-associated seizures, compared with the age for rotavirus-associated seizures [11]. Young age may be a risk factor for convulsion in children with norovirus infection; our data showed that patients who experienced convulsions were significantly younger than those who did not. Most of the convulsions were benign; only 6 patients received short-course anticonvulsant therapy. None of these patients had any neurological sequelae.

In conclusion, rotavirus and norovirus are both responsible for severe symptoms in infants. Our study highlights the clinical importance of norovirus and the need for future studies of the interplay between rotavirus and norovirus as causes of gastrointestinal infections. Norovirus infection was associated with a higher rate of convulsion in young children than was previously recognized. In view of the high extraintestinal morbidity, the development of a norovirus vaccine is of paramount importance.

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Potential conflicts of interest. All authors: no conflicts.

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