Comparison of the Demographics and Ratio of Rotavirus-Associated Benign Convulsions with Mild Gastroenteritis to Rotavirus Gastroenteritis before and after Rotavirus Vaccination over a Period of 20 Years

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Purpose: Through a study of rotavirus gastroenteritis (RVGE) cases experienced over 20 years at our center, we aimed to investigate changes in the ratio of rotavirus-associated benign convulsions with mild gastroenteritis (RaCwG) to RVGE and in patients' demographics after rotavirus vaccination.

Methods: We analyzed the data of patients aged ≤ 6 years who visited Inha University Hospital between January 1999 and December 2019 and were confirmed to have RVGE. Patients were divided according to whether they had convulsions with mild gastroenteritis, and their demographics were compared. The yearly and monthly ratios of RaCwG to RVGE were evaluated. To investigate the effects of rotavirus vaccination, data regarding demographics and prevalence were divided into periods I (pre-vaccination, 1999–2009) and II (post-vaccination, 2010–2019) and compared.

Results: Altogether, 2,100 children had RVGE, and 50 (2.4%) had RaCwG. RaCwG occurred frequently every 4 to 6 years. Although the total number of RVGE and RaCwG cases significantly decreased in period II versus period I, the ratio of RaCwG to RVGE did not differ between the two groups ($P=0.921$). The age distribution shifted upwards in period II versus period I ($P=0.001$), but the sex ratio and seasonal distribution showed no significant difference.

Conclusion: Considering that the ratio of RaCwG to RVGE is dynamic, an increase in the ratio of RaCwG may be possible in the future. Although there was no change in the ratio of RaCwG to RVGE, the number of RVGE and RaCwG patients decreased simultaneously, suggesting that rotavirus vaccination was effective in preventing RaCwG.

Keywords: Rotavirus vaccines; Rotavirus infections; Seizures

Introduction

Rotavirus gastroenteritis (RVGE) is a major form of acute gastro-

enteritis that is associated with a high hospitalization rate, resulting in 215,000 deaths in children under 5 years of age each year [1]. Children infected with rotavirus may have watery diarrhea, vomit-

ing, and fever but symptoms are less severe in infants because of the protective effect of the maternal antibodies that are transferred through the placenta or through breast milk [2]. Prevention is important, as rotavirus infection is associated not only with enteric symptoms, but also with neurologic disorders such as seizures, leukoencephalopathy, meningoencephalitis and cerebellitis [3,4].

The most common neurologic complication of rotavirus infection is benign convulsions with mild gastroenteritis (CwG). CwG was reported for the first time by Morooka [5] in 1982 as mild gastroenteritis that causes afebrile convulsions without severe dehydration, electrolyte imbalance, or hypoglycemia. Rotavirus-associated benign convulsions with mild gastroenteritis (RaCwG) is characterized by a short duration, and all episodes of clustered seizures usually stop within 24 hours of seizure onset [6-9]. The underlying pathological mechanisms remain unclear. Some researchers have attempted to detect neurologic disorders based on the presence of rotavirus RNA and antigens in the cerebrospinal fluid of infected patients [10-12]. Although CwG is frequently reported in East Asian countries, including Japan, South Korea, and Taiwan, it has also been recently reported in the United States and Europe [3,13-15]. Such convulsions are often associated with RVGE [5,16].

The prevalence of RVGE has decreased since the introduction of rotavirus vaccines [17,18]. In South Korea, RotaTeq (Merck & Co. Inc., West Point, PA, USA), a pentavalent vaccine, and Rotarix (GlaxoSmithKline Biologicals, Rixensart, Belgium), a monovalent vaccine, became available in June 2007 and March 2008, respectively. However, rotavirus vaccines have not yet been incorporated into a national immunization program. Since then, the rotavirus vaccination rate exceeded 50% in 2009 and reached 84.5% in 2016 [19,20].

Emerging data suggest that vaccines may not protect all population equally. Females, in particular, typically develop higher antibody responses after vaccination [21]. Moreover, after rotavirus vaccination, changes in the age and the seasonal distribution were founded and a decreased prevalence of RVGE was observed [22,23]. However, studies investigating the demographic changes and ratio of RaCwG to RVGE have been scantily conducted.

Thus, in this study, we focused on changes in the ratio of RaCwG to RVGE and the demographics after rotavirus vaccination through the examination of cases of RVGE that we have experienced over the past 20 years at a single center.

Materials and Methods

1. Participants and sample collection

We assessed the medical records of patients with RVGE aged ≤ 6

years who visited Inha University Hospital, which is a tertiary hospital in Incheon with a population of 2.9 million people, between January 1999 and December 2019. RVGE was confirmed using immunochromatography, enzyme immunoassay, or reverse transcription-polymerase chain reaction (RT-PCR). Patients infected with norovirus, enteric adenovirus or astrovirus were excluded. With reference to the diagnostic criteria suggested by Komori et al. [16], CwG was defined as follows: (1) afebrile seizure occurring within 5 days of acute viral gastroenteritis in previously healthy infants and children; (2) absence of moderate or severe dehydration; (3) absence of abnormal findings in cerebrospinal fluid analyses, serum electrolytes, and blood glucose; and (4) cases with good prognosis. Being afebrile was defined as a body temperature below 38.0°C when measured on the tympanic membrane or axilla. Findings of seizure were confirmed through the statement of caregivers or others that observed the seizure, and neurological imaging and electroencephalography results were confirmed through consultation with the Radiology and Pediatric Neurology Departments.

To compare the demographics and ratio of RaCwG to RVGE before and after rotavirus vaccination, data were divided into period I (January 1999 to December 2009) and period II (January 2010 to December 2019), because prescription of rotavirus vaccines was started in 2009 in our hospital and the rotavirus vaccination rate reached 50% in South Korea [19].

The rotavirus antigen detection test for stool samples was conducted using immunochromatography assay kits (SD BIOLINE Rotavirus, Standard Diagnostics Inc., Yongin, Korea) until 2010 and using enzyme immunoassay (RIDASCREEN Rotavirus, R-Biopharm Aktiengesellschaft, Darmstadt, Germany) between 2011 and 2019. Rotavirus RT-PCR has been conducted using Allplex GI-Virus Assay (Seegene, Seoul, Korea) since June 2014.

This study was approved by the Institutional Review Board of Inha University Hospital (IRB No. 2020-04-012). Written informed consent by the patients was waived due to a retrospective nature of our study.

2. Statistical analyses

Statistical analyses were performed using SPSS version 19.0 (IBM Corp., Armonk, NY, USA). Changes in the ratio of RaCwG to RVGE and the sex ratio were compared between periods I and II using chi-square tests, and the changes in season were compared using linear by linear association test. The age at onset was compared between the periods using the Mann-Whitney U tests. *P* values < 0.05 were considered statistically significant.

Results

1. Demographics of patients with RVGE and RaCwG

Overall, 2,100 children were confirmed to have RVGE between 1999 and 2019. Of these, 50 had RaCwG while 2,050 did not. The male-to-female ratio in children with CwG was 1:1.1 and of RVGE without CwG was 1:0.8. The median age was 23.0 and 10.0 months in children with CwG and RVGE without CwG, respectively. The age at onset was significantly lower in children without CwG than in those with CwG ($P < 0.01$). Seasonally, RaCwG was most common in winter ($n = 28$, 56.0%), followed by spring ($n = 17$, 34.0%) but RVGE without CwG was most common in spring ($n = 772$, 37.7%), followed by winter ($n = 755$, 36.8%) (Table 1).

2. Yearly and monthly prevalence of RaCwG

The ratio of RaCwG to RVGE was 2.43 per 100 RVGE cases. The ratio of RaCwG to RVGE increased most noticeably in 2011, reaching 6.19 per 100 RVGE patients and RaCwG occurred periodically, almost every 4 to 6 years (Fig. 1). Regarding the monthly number of patients, RaCwG was common between December and April and was most common in January ($n = 11$, 22%). In contrast, no cases were noted in June, August, and October. RVGE without CwG was most common in March ($n = 343$, 16.7%) and least common in September ($n = 58$, 2.8%) (Fig. 2).

3. Comparison of period I and period II

There were 31 cases of RaCwG in period I compared with 19 cases in period II. The male-to-female ratio was 1:1.4 in period I, with more female patients affected by RaCwG. Although there were more male patients in period II (male-to-female ratio, 1:0.7), the difference was not statistically significant ($P = 0.273$). The median age of the patient in period I and period II were 21 and 31 months, respectively. The age at onset was significantly higher in period II than in period I ($P = 0.001$). The ratio of RaCwG to RVGE was 2.4% in period I as well as in period II, without any significant difference ($P = 0.921$). Regarding seasonality, RaCwG was common in winter during period I ($n = 20$, 64.5%) and in the spring during period II ($n = 10$, 52.6%), but there was no statistical significance ($P = 0.052$) (Table 2). Regarding monthly prevalence, in period I, the numbers of patients with RVGE with and without CwG were highest in January. In period II, the numbers of patients with RVGE with and without CwG were highest in March and April, respectively (Fig. 3).

Table 1. Demographic characteristics of patients with RaCwG and RVGE without CwG

Characteristic	RaCwG	RVGE without CwG
No. of subjects	50	2,050
Sex		
Boys	24 (48)	1,160 (56.6)
Girls	26 (52)	890 (43.4)
Age (mo)	23 (17–27.8)	10.0 (0–21)
Year		
1999	1 (2)	137 (6.7)
2000	1 (2)	43 (2.1)
2001	4 (8)	81 (4.0)
2002	3 (6)	181 (8.8)
2003	0	131 (6.4)
2004	5 (10)	125 (6.1)
2005	6 (12)	111 (5.4)
2006	4 (8)	89 (4.3)
2007	3 (6)	76 (3.7)
2008	3 (6)	94 (4.6)
2009	1 (2)	217 (10.6)
2010	3 (6)	161 (7.9)
2011	6 (12)	91 (4.4)
2012	5 (10)	115 (5.6)
2013	1 (2)	91 (4.4)
2014	1 (2)	71 (3.5)
2015	2 (4)	42 (2)
2016	0	31 (1.5)
2017	0	50 (2.4)
2018	0	60 (2.9)
2019	1 (2)	53 (2.6)
Season		
Spring	17 (34)	772 (37.7)
Summer	1 (2)	269 (13.1)
Autumn	4 (8)	254 (12.4)
Winter	28 (56)	755 (36.8)

Values are presented as number (%) or median (interquartile range).

RaCwG, rotavirus-associated benign convulsions with mild gastroenteritis; RVGE, rotavirus gastroenteritis; CwG, convulsions with mild gastroenteritis.

Discussion

This retrospective study included patients with RaCwG patients from a single center over an examined period of 20 years to determine changes in demographics and ratio of RaCwG to RVGE since the introduction of rotavirus vaccination. As a result, we found that RaCwG caused cyclic epidemics. After vaccination, the total number of patients with RaCwG decreased but there was no change in prevalence. In addition, change in demographics was found.

RaCwG commonly occurs in winter and early spring in temper-

Fig. 1. The ratio of rotavirus-associated benign convulsions with mild gastroenteritis (RaCwG) to rotavirus gastroenteritis (RVGE).

Fig. 2. Monthly distributions of rotavirus-associated benign convulsions with mild gastroenteritis (RaCwG) and rotavirus gastroenteritis (RVGE) without convulsions with mild gastroenteritis (CwG).

ate countries [6,24,25]. The ratio of RaCwG to RVGE differs by country: 2.6% to 2.9% in Japan, 3.7% in India, 2.1% to 5.0% in Tai-

wan, and 1.29% in Hong Kong [10,16,24,26]. In Korea, the reported incidence was 5.6% [25]. In this study, the ratio of RaCwG to RVGE was 2.4%, similar to those reported by previous studies.

RaCwG occurs between age 1 month and 6 years and peaks at age 1 to 2 years, [13,14,16,24,27]. Similar to previous study, RaCwG was most common in 1-year-old patients, and the median age at onset was 23 months in this study. In addition, patients with RVGE without CwG were significantly younger than those with RaCwG. This result is different from the recent study using nationwide data in South Korea that reported the age of RaCwG was younger than RVGE. We suspected that this is due to this research being conducted at a single center and the total number of patients being small. Further studies on the age of RaCwG patients compared to RVGE patients will be needed [28].

In this study, the ratio of RaCwG occurred frequently every 4 to 6 years. Mycoplasma infection, which causes outbreaks every 3 to 5 years, is known to contribute by gene divergences within the P1

Table 2. Comparison between periods I and II

Variable	Period I (%)	Period II (%)	P value
No. of subjects	31	19	
Sex			0.273 ^a
Boys	13 (41.9)	11 (57.9)	
Girls	18 (58.1)	8 (42.1)	
Age (mo)	21 (16–23.5)	31 (23.5–34)	0.001 ^b
Prevalence	2.4	2.4	0.921 ^a
Season			0.052 ^c
Spring	7 (22.6)	10 (52.6)	
Summer	1 (3.2)	0 (0.0)	
Autumn	3 (9.7)	1 (5.3)	
Winter	20 (64.5)	8 (42.1)	

Values are presented as number (%) or median (interquartile range).

^aChi-square test; ^bMann-Whitney U test; ^cLinear by linear association.

Fig. 3. Comparison of the monthly distributions between periods I and II. RaCwG, rotavirus-associated benign convulsions with mild gastroenteritis; CwG, convulsions with mild gastroenteritis.

adhesin. Thus, we suspected that this was because of the increased prevalence in the local community of a certain genotype such as CwG. Previously, Yang et al. [29] found no significant difference between RaCwG and genotype in an analysis of 13 patients with RaCwG. However, Choi et al. [30] compared the genotype of 82 rotavirus positive patients, of which 11 had neurologic complications, and G2P [4] was found to be significantly associated with neurologic complication. Considering the periodic outbreaks of RaCwG, an outbreak is possible in the future. Therefore, continuous monitoring of RaCwG and genotypes is required.

In this study, we observed cases for longer than 20 years and found that the ratio of RaCwG to RVGE, at 2.4%, was identical in periods I and II. However, the numbers of patients with RVGE and RaCwG decreased simultaneously. Moreover, patients with RaCwG were poorly observed after 2016. These results appear to be due to an increase in the vaccination rate in Korea. Therefore, we expect that the number of patients with RaCwG will decrease significantly as the use of rotavirus vaccines increases.

After vaccination, previous studies reported changes in the demographics of rotavirus. In Finland, rotavirus infection was most common in children aged < 5 years, but after the introduction of the vaccine, it became most common in children between the ages of 6 and 16 years and individuals over 70 years of age [31]. In addition, the start of the rotavirus season was delayed and the duration of the season was shortened after the rotavirus vaccination [32]. In this study, the age at onset of RaCwG was greater in period II than in period I. This may have been influenced by the higher prevalence in older children who have not received rotavirus vaccination in period II. In terms of seasons, RaCwG was more common in winter in period I and in spring in period II. This may be associated with the shift in peak in all RVGE cases from January in period I to March in period II.

In RaCwG, previous studies reported female-dominant prevalence, with male-to-female ratios of 1:1.5 to 1.8 [24,25]. However, data in these studies were mostly from pre-rotavirus vaccination days. Similar to previous studies, the male-to-female ratio was 1:1.4 in period I in this study, but RaCwG more commonly occurred in male patients in period II at a ratio of 1:0.7. Although this difference was not statistically significant, post-vaccination changes in the sex ratio should be monitored continuously.

This study had some limitations. Data were collected only from a single center. Although G1P is the most common genotype in South Korea [33,34], common genotypes of rotavirus change depending on season and geography [25,29]. Our study used data collected over 20 years, but an analysis of genotypes of RaCwG in various areas of South Korea is necessary. Furthermore, whether patients received vaccination could not be confirmed in their elec-

tronic chart data. If vaccination data were available, we would have been able to compare vaccinated and unvaccinated patients to investigate the effects of rotavirus vaccination, but we had to set different periods as the data were unavailable.

Considering the ratio of RaCwG to RVGE over the past 20 years and its fluctuation, it may be possible in the future to increase the ratio of RaCwG. Therefore, continuous monitoring of RaCwG and its genotyping will be required. Although there was no change in the prevalence of RaCwG, both RVGE, and RaCwG decreased simultaneously. Thus, rotavirus vaccination was effective in preventing RaCwG. As demographics such as patient sex, age, and season of RaCwG changed after rotavirus vaccination, further research is required on this aspect.

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

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