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-
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).

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).
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 Taiwan, 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            | 0.273*  |
| Sex           |              |               |         |
| Boys          | 13 (41.9)    | 11 (57.9)     |         |
| Girls         | 18 (58.1)    | 8 (42.1)      |         |
| Age (mo)      | 21 (16–23.5) | 31 (23.5–34)  | 0.001b  |
| Prevalence    | 2.4          | 2.4           | 0.921a  |
| Season        |              |               | 0.052c  |
| 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).

*Chi-square test; *Mann-Whitney U test; *Linear by linear association.

![Figure 3](https://doi.org/10.26815/acn.2020.00297)
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 electronic 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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Conceptualization: YSK. Methodology: YSL. Data curation: YSL and DJH. Formal analysis: DHK. Validation: DHK. Writing-original draft: YSL and DHK. Writing-review & editing: YSK.

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**References**

1. Clark A, Black R, Tate J, Roose A, Kotloff K, Lam D, et al. Estimating global, regional and national rotavirus deaths in children aged < 5 years: current approaches, new analyses and proposed improvements. PLoS One 2017;12:e0183392.
2. Bishop RF, Barnes GL, Cipriani E, Lund JS. Clinical immunity after neonatal rotavirus infection: a prospective longitudinal study in young children. N Engl J Med 1983;309:72-6.
3. Kang B, Kwon YS. Benign convulsion with mild gastroenteritis. Korean J Pediatr 2014;57:304-9.
4. Lee KY, Weon YC, Choi SH, Oh KW, Park H. Neurodevelop-
mental outcomes in newborns with neonatal seizures caused by rotavirus-associated leukoencephalopathy. Seizure 2018;56:14-9.
5. Morooka K. Convulsions and mild diarrhea. Shonika 1982;23:131-7.
6. Uemura N, Okumura A, Negoro T, Watanabe K. Clinical features of benign convulsions with mild gastroenteritis. Brain Dev 2002;24:745-9.
7. Okumura A, Tanabe T, Kato T, Hayakawa F, Watanabe K. A pilot study on lidocaine tape therapy for convulsions with mild gastroenteritis. Brain Dev 2004;26:525-9.
8. Kawano G, Oshige K, Syotou S, Koteda Y, Yokoyama T, Kim BG, et al. Benign infantile convulsions associated with mild gastroenteritis: a retrospective study of 39 cases including virological tests and efficacy of anticonvulsants. Brain Dev 2007;29:617-22.
9. Tanabe T, Okumura A, Komatsu M, Kubota T, Nakajima M, Shimakawa S. Clinical trial of minimal treatment for clustering seizures in cases of convulsions with mild gastroenteritis. Brain Dev 2011;33:120-4.
10. Ushijima H, Xin KQ, Nishimura S, Morikawa S, Abe T. Detection and sequencing of rotavirus VP7 gene from human materials (stools, sera, cerebrospinal fluids, and throat swabs) by reverse transcription and PCR. J Clin Microbiol 1994;32:2893-7.
11. Weclewicz K, Svensson L, Kristensson K. Targeting of endoplasmic reticulum-associated proteins to axons and dendrites in rotavirus-infected neurons. Brain Res Bull 1998;46:353-60.
12. Yeom JS, Kim YS, Jun JS, Do HJ, Park JS, Seo JH, et al. NSP4 antibody levels in rotavirus gastroenteritis patients with seizures. Eur J Paediatr Neurol 2017;21:367-73.
13. Dura-Trave T, Yoldi-Petri ME, Gallinas-Victoriano F, Molins-Castiella T. Infantile convulsions with mild gastroenteritis: a retrospective study of 25 patients. Eur J Neurol 2011;18:273-8.
14. Lloyd MB, Lloyd JC, Gesteland PH, Bale JF Jr. Rotavirus gastroenteritis and seizures in young children. Pediatr Neurol 2010;42:404-8.
15. Junquera CG, de Baranda CS, Mialdea OG, Serrano EB, Sanchez-Fauquier A. Prevalence and clinical characteristics of norovirus gastroenteritis among hospitalized children in Spain. Pediatr Infect Dis J 2009;28:604-7.
16. Komori H, Wada M, Eto M, Oki H, Aida K, Fujimoto T. Benign convulsions with mild gastroenteritis: a report of 10 recent cases detailing clinical varieties. Brain Dev 1995;17:334-7.
17. Park DK, Chung JY. The changes in the outbreak of rotavirus gastroenteritis in children after introduction of rotavirus vaccines: a retrospective study at a tertiary hospital. Korean J Pediatr Infect Dis 2014;21:167-73.
18. Payne DC, Boom JA, Staat MA, Edwards KM, Szilagyi PG, Klein EJ, et al. Effectiveness of pentavalent and monovalent rotavirus vaccines in concurrent use among US children < 5 years of age, 2009-2011. Clin Infect Dis 2013;57:13-20.
19. Choe YJ, Yang JH, Park SK, Choi EH, Lee HJ. Comparative estimation of coverage between national immunization program vaccines and non-NIP vaccines in Korea. J Korean Med Sci 2013;28:1283-8.
20. Lee H, Park SY, Clark A, Debellut F, Pecenka C, Kim DS, et al. Cost-effectiveness analysis of the implementation of a National Immunization Program for rotavirus vaccination in a country with a low rotavirus gastroenteritis-related mortality: a South Korean study. Vaccine 2019;37:4987-95.
21. Fischinger S, Boudreau CM, Butler AL, Streeck H, Alter G. Sex differences in vaccine-induced humoral immunity. Semin Immunopathol 2019;41:239-49.
22. Alibadi N, Antoni S, Mwenda JM, Weldegebril G, Biye JN, Cheikh D, et al. Global impact of rotavirus vaccine introduction on rotavirus hospitalisations among children under 5 years of age, 2008-16: findings from the Global Rotavirus Surveillance Network. Lancet Glob Health 2019;7:e893-903.
23. Choi UY, Lee SY, Ma SH, Jang YT, Kim JY, Kim HM, et al. Epidemiological changes in rotavirus gastroenteritis in children under 5 years of age after the introduction of rotavirus vaccines in Korea. Eur J Pediatr 2013;172:947-52.
24. Hung JJ, Wen HY, Yen MH, Chen HW, Yan DC, Lin KL, et al. Rotavirus gastroenteritis associated with afebrile convulsion in children: clinical analysis of 40 cases. Chang Gung Med J 2003;26:654-9.
25. Kang B, Kim DH, Hong YJ, Son BK, Kim DW, Kwon YS. Comparison between febrile and afebrile seizures associated with mild rotavirus gastroenteritis. Seizure 2013;22:560-4.
26. Chen SY, Tsai CN, Lai MW, Chen CY, Lin KL, Lin TY, et al. Norovirus infection as a cause of diarrhea-associated benign infantile seizures. Clin Infect Dis 2009;48:849-55.
27. Chen B, Cheng M, Hong S, Liao S, Ma J, Li T, et al. Clinical outcome of recurrent afebrile seizures in children with benign convulsions associated with mild gastroenteritis. Seizure 2018;60:110-4.
28. Kim DH, Lee YS, Ha DJ, Chun MJ, Kwon YS. Epidemiology of rotavirus gastroenteritis and rotavirus-associated benign convulsions with mild gastroenteritis after the introduction of rotavirus vaccines in South Korea: nationwide data from the Health Insurance Review and Assessment Service. Int J Environ Res Public Health 2020;17:8374.
29. Yang HR, Jee YM, Ko JS, Seo JK. Detection and genotyping of viruses detected in children with benign afebrile seizures associ-
ated with acute gastroenteritis. Korean J Pediatr Gastroenterol Nutr 2009;12:183-93.
30. Choi JH, Kim YJ, Oh JW, Kim CL, Yum MK, Sul IJ, et al. Genotype of rotavirus isolated from patients with rotaviral enteritis and neurological complications. Korean J Pediatr 2006;49:513-8.
31. Markkula J, Hemming-Harlo M, Salminen MT, Savolainen-Kopra C, Pirhonen J, Al-Hello H, et al. Rotavirus epidemiology 5-6 years after universal rotavirus vaccination: persistent rotavirus activity in older children and elderly. Infect Dis (Lond) 2017;49:388-95.
32. Aliabadi N, Tate JE, Haynes AK, Parashar UD; Centers for Disease Control and Prevention (CDC). Sustained decrease in laboratory detection of rotavirus after implementation of routine vaccination: United States, 2000-2014. MMWR Morb Mortal Wkly Rep 2015;64:337-42.
33. Han TH, Kim CH, Chung JY, Park SH, Hwang ES. Genetic characterization of rotavirus in children in South Korea from 2007 to 2009. Arch Virol 2010;155:1663-73.
34. Lee SY, Hong SK, Lee SG, Suh CI, Park SW, Lee JH, et al. Human rotavirus genotypes in hospitalized children, South Korea, April 2005 to March 2007. Vaccine 2009;27 Suppl 5:F97-101.