

Original Article

Regional Variations in the Incidence of Rotavirus Hospitalization in Children Living in Defined Regions of Akita and Kyoto Prefectures, Japan

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SUMMARY: Variable incidence rates of rotavirus gastroenteritis hospitalizations have been reported in Japan. However, it is not known whether the observed regional differences were due to the real difference in the occurrence of severe disease or other causes. This study aimed to determine the incidence rates of rotavirus hospitalization among children aged <5 years in the Yuri district in Akita prefecture and the Nantan district in Kyoto prefecture between March 2012 and February 2013. During this period, rotavirus vaccine uptake rates were equally low in both regions. All specimens were evaluated using the standardized case definition, severity scores, and the same assays. There were 44 rotavirus cases (44%) among 101 acute gastroenteritis-related hospitalizations in the Yuri district with a catchment population of 3,853, and 18 rotavirus cases (47%) among 38 acute gastroenteritis-related hospitalizations in the Nantan district with a catchment population of 5,128. While the severity score at the time of the hospitalizations was 11 in both hospitals, the incidence rates in Akita and Kyoto were 11.7 (95% confidence interval [CI]: 8.5–15.6) and 3.9 (95% CI: 2.1–5.5) per 1,000 child-years, respectively. Thus, there was a real difference in the occurrence rate of severe rotavirus infections between the 2 regions.

INTRODUCTION

Rotavirus, the most common cause of severe acute gastroenteritis in infants and young children worldwide, imposes a large health and economic burden on the healthcare systems and societies in high-income countries (1–4). In Japan, a retrospective, multicenter epidemiological study conducted in 8 hospitals revealed that 11.9%, 4.8%, and 0.6% of hospitalizations of children <6 years of age were due to acute gastroenteritis, rotavirus gastroenteritis, and hospital-acquired rotavirus gastroenteritis, respectively (5). Since the introduction in the private sector of the monovalent human rotavirus vaccine in 2011 and the pentavalent human-bovine reassortant vaccine in 2012, a few studies have suggested that the burden of rotavirus disease in Japan has decreased (6,7).

The incidence rate of rotavirus hospitalization is a fundamental parameter in measuring the burden of rotavirus disease; hence, accurate national estimates are required to inform policy and decision-making regarding the incorporation of rotavirus vaccines into the in-

fant immunization program. Previous studies in Japan consistently showed substantial variations in the incidence rates of rotavirus hospitalizations according to study region and time period. Regarding the higher incidence rates of rotavirus hospitalizations reported previously in Akita (8–10), a 10-year, retrospective hospital-based cross-sectional study conducted by Kinoshita et al. (11) confirmed that the incidence rate of rotavirus hospitalization in Akita prefecture was substantially higher than those in Kyoto (12) and Mie prefectures (13,14). However, it remained unclear whether this represented a real difference in the occurrence rate of severe rotavirus disease or if it was due to other social factors, such as the discretion of the pediatrician in admitting patients to hospital for the treatment of acute gastroenteritis. The aim of this study, therefore, was to conduct a head-to-head comparison study using the same standardized protocol, including the same rotavirus-detection method, and to determine whether the incidence rate of rotavirus hospitalizations differed between 2 geographically remote regions in Japan, namely the Yuri district in Akita prefecture and the Nantan district in Kyoto prefecture.

MATERIALS AND METHODS

The study period was one year, from March 2012 to February 2013 inclusive. The incidence of rotavirus hospitalizations during this period was calculated. Each hospital (Yuri-Kumiai General Hospital and Nantan General Hospital) was virtually the sole pediatric facili-

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ty that provided beds to children <5 years of age who lived in the respective administrative regions. Therefore, we used data from these hospitals for the numerator, and the <5-year-old population from the 2010 census data (3,853 and 5,128, for the Yuri and Nantan districts, respectively) for the denominator, to calculate the incidence of rotavirus hospitalizations. These hospitalizations were defined as test-positive cases. In addition, we examined the residence of each of the rotavirus-positive patients to confirm that they were from the catchment area of each hospital, the denominator administrative region. The study protocol was reviewed and approved by the ethical committee of each of the participating institutions.

One stool sample was collected from each patient at the earliest possible time point following hospital admission. Subsequently, the samples were stored at -20°C in a freezer in each study hospital. At various intervals, the samples were sent to the laboratory at the National Institute of Infectious Diseases (Murayama branch laboratory, Tokyo, Japan) for rotavirus detection. The presence of rotavirus gastroenteritis was confirmed by the detection of rotavirus antigen using an enzyme-linked immunosorbent assay (ELISA) (RotacloneR; Premier Bioscience, Cincinnati, OH, USA) or by the detection of rotavirus-specific genomic RNA bands by polyacrylamide gel electrophoresis (PAGE), as described previously (15). Severity of illness was scored at the time of hospitalization according to the Vesikari 20-point scoring system.

RESULTS

During the study period, there were 44 rotavirus gastroenteritis cases (44%) among 101 patients with acute gastroenteritis in Akita, and 18 rotavirus gastroenteritis cases (47%) among 38 patients with acute gastroenteritis in Kyoto (Table 1). The incidence rates of rotavirus hospitalizations in Akita and Kyoto were 11.7 cases (95% confidence interval [CI]: 8.5–15.6) and 3.9 cases (95% CI: 2.1–5.5) per 1,000 child-years, respectively (Table 1). Thus, there was a statistically significant difference in hospitalization rate between the 2 hospitals (Chi-square test, $P < 0.01$).

As the survey was performed using a standardized protocol and rotavirus detection was carried out in the reference laboratory in the National Institute of Infectious Diseases, the observed difference was not due to variations in case definition or detection assay. Moreover, while rotavirus cases were defined as a positive test result using either ELISA or PAGE, all positive samples were confirmed by nucleotide sequencing (data not shown). Thus, there was no false-positive case that might otherwise increase the rotavirus hospitalization rates.

We next examined potential differences in patient characteristics between the study hospitals, paying special attention to whether one of the hospitals systematically admitted less severe or more severe cases compared to the other. We concluded that such systematic biases were unlikely to exist based on a number of observations. First, the proportions of rotavirus-positive patients were similar between the 2 hospitals (44% vs 47%), and were within the commonly observed range

Table 1. Comparison of the features of rotavirus gastroenteritis in Yuri and Nantan districts, Japan

	Yuri	Nantan
Period	2012/3–2013/2	
Method of detection	ELISA or PAGE positive	
Under-5-yr-population in catchment	3,853	5,128
Total number of AGE hospitalizations	101	38
Number of RVGE hospitalizations	44	18
Proportion of RVGE hospitalizations (%)	44	47
Hospitalization incidence rate (per 1,000 child-years; 95%CI)	11.7; 8.6–15.6	3.5; 2.1–5.5
Vesikari score (SD)	11 (2.8)	11 (2.8)
Average age and range of rotavirus-positive patients (mo)	18 (4–54)	20 (9–44)
The rotavirus vaccine uptake rates in the rotavirus test-negative patients (%) (95%CI)	5.2 (1.1–14)	0 (0–16.8)
Predominant genotypes in circulation	G1P[8] 73%	G1P[8] 72%

ELISA, enzyme-linked immunosorbent assay; PAGE, polyacrylamide gel electrophoresis; AGE, acute gastroenteritis; RVGE, rotavirus gastroenteritis; CI, confidence interval; SD, standard deviation.

(1). Second, the mean Vesikari scores for patients who were hospitalized due to acute gastroenteritis were the same in both hospitals: a mean score of 11 with a standard deviation of 2.8 in both Yuri-Kumiai General Hospital and Nantan General Hospital. The mean score of 11 represents the borderline score for severe cases, which is usually defined as 11 or greater. However, it should be noted that the severity was scored at the time of admission (and not at the time of discharge) in order to examine whether there was a marked difference in the decision to admit patients between the 2 hospitals. Third, the average ages of rotavirus-positive patients in Yuri-Kumiai General Hospital and Nantan General Hospital were 18 months and 20 months, respectively, with no significant statistical difference (Mann-Whitney U test, $P = 0.25$). Fourth, the rotavirus vaccine uptake rates in rotavirus test-negative patients were equally low in the 2 districts: 5.2% (3/57; 95% CI: 1.1–14%) in the Yuri district and (0/20; 95% CI: 0–16.8%) in the Nantan district.

DISCUSSION

In high-income countries where the incidence of rotavirus gastroenteritis-related death is minimal, the burden of rotavirus gastroenteritis is most significantly affected by the number of hospitalizations. This is because the health-care expenditure for a hospitalized case is approximately 10 times that of an outpatient case (16). The estimated numbers of national rotavirus hospitalizations range from 26,000 to 78,000 (10,12–14). This wide range of variation is due to methodological limitations; the national estimates were extrapolated from data obtained in epidemiologic studies in defined geographic regions. The studies performed in Akita prefecture consistently reported higher incidence rates, irrespective of the study periods or the design of the studies (8–11): 9–14 cases per 1,000 child-years among children aged <5 years. On the other hand, studies performed in Mie (13,14) and Kyoto pre-

fectures (12) consistently reported much lower incidence rates: 3–5 cases per 1,000 child-years among children aged <5 years.

Rotavirus infection is one of the most common infections in early childhood and it is believed that all children experience at least one episode of infection by the age of 5 years. The severity of rotavirus infection ranges from very mild, even asymptomatic, to very severe with fatal outcome. The primary purpose of hospitalization is to provide adequate and timely intravenous fluid replacement to patients with moderate to severe dehydration. The lack of a guideline for treating this very commonly-occurring disease may be the source of suspicion that some pediatricians allowed hospitalization of less severe patients with acute gastroenteritis, leading to a potential cause of variations in the incidence rates for rotavirus hospitalizations.

It is, therefore, necessary to perform an observational study in more than one defined area using the same study protocol, in which stool specimens are examined in a single, independent, reference laboratory. The most well-known study in this regard was the REVEAL (Rotavirus gastroenteritis Epidemiology & Viral types in Europe Accounting for Losses in Public Health & Society) study (1). This was a one-year, prospective, multicenter, observational study of acute gastroenteritis in children age <5 years in selected areas of 7 European countries: Belgium, France, Germany, Italy, Spain, Sweden, and the United Kingdom. In these European countries, the incidence rate of rotavirus hospitalizations ranged from the minimum of 2.9 cases (95% CI: 2.4–3.5) per 1,000 child-years in the United Kingdom to the maximum of 9.9 cases (95% CI: 7.9–11.8) per 1,000 child-years in Belgium, with a median of 6.5 cases (95% CI: 5.2–7.7) per 1,000 child-years in Spain. It should also be noted that the 95% CI rate in the United Kingdom did not overlap with that of Belgium; however, the cause of this statistically significant difference in the incidence of rotavirus hospitalizations was not discussed in detail. The difference could be attributable to the difference in the health-care seeking behavior of the different populations arising from differences in their respective health-care systems.

This head-to-head comparison study was conducted in defined regions of Akita and Kyoto prefectures. Therefore, the results obtained clearly excluded the possibility of systematic biases, including differences in the health-care systems, as the cause of the higher incidence rate of rotavirus hospitalizations in Akita or the lower incidence in Kyoto; the clinical features of the patients, such as average age or severity of illness, were very similar in both hospitals. Different methods of rotavirus detection show different sensitivity and specificity, potentially resulting in different incidence rates. In this regard, it should be noted that the clinical specimens from both hospitals were examined in the same laboratory using more than one method and that all test-positive cases were confirmed using nucleotide sequencing; hence, no false-positives were obtained in this study.

The magnitude of rotavirus cases can vary yearly. In a 10-year retrospective study, Kinoshita et al. (11) reported that the lowest incidence rate was 6.8 cases per 1,000 child-years, while the highest was 20.7 cases per

1,000 child-years. While the cause of such yearly variation is not known, different circulating strains are often suspected. Thus, the predominant genotype in this study (G1P[8]) was the same as that reported by Fujii et al. (17). G1P[8] was detected in both regions with a nearly identical frequency: 32 (73%) of 44 rotavirus-positive specimens collected in the Yuri district and 13 (72%) of 18 rotavirus-positive specimens in the Nantan district.

This head-to-head comparison study spanned only one year. However, this was the last period during which the effect of the rotavirus vaccine could be excluded from consideration; the vaccine uptake rate in both districts was minimal, with no statistical difference.

The incidence rates obtained in this study for the 2 districts were within the 95% CI of preceding studies in the same districts. Thus, despite the short study period (one year), the incidence rates obtained in this study likely represent that of the individual districts, for which there was a statistically significant difference.

In conclusion, the results of this head-to-head comparison study were in line with those of previous studies performed previously in Akita and Kyoto prefectures. The results confirmed the existence of regional differences in the incidence rates of rotavirus hospitalizations, that were unlikely to be influenced by the subjective decision-making procedures of the respective pediatricians regarding hospitalization or the difference in rotavirus detection procedures. Thus, estimating the national burden of rotavirus disease by extrapolating from a single, local dataset requires cautious interpretation. Multicenter studies are required for more robust estimates.

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Conflict of interest None to declare.

REFERENCES

1. Van Damme P, Giaquinto C, Huet F, et al. Multicenter prospective study of the burden of rotavirus acute gastroenteritis in Europe, 2004–2005: the REVEAL study. *J Infect Dis.* 2007;195:S4–S16.
2. Jit M, Edmunds WJ. Evaluating rotavirus vaccination in England and Wales. Part II. The potential cost-effectiveness of vaccination. *Vaccine.* 2007;25:3971–9.
3. Payne DC, Staat MA, Edwards KM, et al. Active, population based surveillance for severe rotavirus gastroenteritis in children in the United States. *Pediatrics.* 2008;122:1235–43.
4. Matson DO, Staat MA, Azimi P, et al. Burden of rotavirus hospitalisations in young children in three paediatric hospitals in the United States determined by active surveillance compared to standard indirect methods. *J Paediatr Child Health.* 2012;48:698–704.
5. Tajiri H, Takeuchi Y, Takano T, et al. The burden of rotavirus gastroenteritis and hospital-acquired rotavirus gastroenteritis among children aged less than 6 years in Japan: a retrospective, multicenter epidemiological survey. *BMC Pediatr.* 2013;13:83.
6. Oishi T, Taguchi T, Nakano T, et al. The occurrence of severe rotavirus gastroenteritis in children under 3 years of age before and after the introduction of rotavirus vaccine: a prospective observational study in three pediatric clinics in Shibata city, Niigata prefecture, Japan. *Jpn J Infect Dis.* 2014;67:304–6.

7. Hashizume M, Nakagomi T, Nakagomi O. An early detection of decline in rotavirus cases during the 2013/2014 season in Japan as revealed by time-series analysis of national surveillance data. *Trop Med Health*. 2015;43:177-81.
8. Nakagomi T, Nakagomi O, Takahashi Y, et al. Incidence and burden of rotavirus gastroenteritis in Japan, as estimated from a prospective sentinel hospital study. *J Infect Dis*. 2005;192: S106-10.
9. Hiramoto I, Nakagomi T, Nakagomi O. Population-based estimates of the cumulative risk of hospitalization potentially associated with rotavirus diarrhea among children living in two cities in Akita prefecture, Japan. *Jpn J Infect Dis*. 2005;58:73-7.
10. Nakagomi T, Chang BR, Nakagomi O. Rotavirus hospitalization and molecular epidemiology in northern Japan, 1987–1996. *Vaccine*. 2009;27:F93-6.
11. Kinoshita S, Noguchi A, Miura S, et al. A retrospective, hospital-based study to determine the incidence of rotavirus hospitalizations among children less than 5 years of age over a 10-year period (2001–2011) in Akita prefecture, Japan. *Jpn J Infect Dis*. 2014;67:464-8.
12. Ito H, Otabe O, Katsumi Y, et al. The incidence and direct medical cost of hospitalization due to rotavirus gastroenteritis in Kyoto, Japan, as estimated from a retrospective hospital study. *Vaccine*. 2011;29:7807-10.
13. Kamiya H, Nakano T, Inoue M, et al. A retrospective evaluation of hospitalizations for acute gastroenteritis at 2 sentinel hospitals in central Japan to estimate the health burden of rotavirus. *J Infect Dis*. 2009;200:S140-6.
14. Kamiya H, Nakano T, Kamiya H, et al. Rotavirus-associated acute gastroenteritis hospitalizations among Japanese children aged <5 years: active rotavirus surveillance in Mie prefecture, Japan. *Jpn J Infect Dis*. 2011;64:482-7.
15. Gauchan P, Nakagomi T, Sherchand JB, et al. Continued circulation of G12P[6] rotaviruses over 28 months in Nepal: successive replacement of predominant strains. *Trop Med Health*. 2013;41: 7-12.
16. Sato T, Nakagomi T, Nakagomi O. Cost-effectiveness analysis of a universal rotavirus immunization program in Japan. *Jpn J Infect Dis*. 2011;64:277-83.
17. Fujii Y, Nakagomi T, Nishimura N, et al. Spread and predominance in Japan of novel G1P[8] double-reassortant rotavirus strains possessing a DS-1-like genotype constellation typical of G2P[4] strains. *Infect Genet Evol*. 2014;28:426-33.