Tropical Medicine and Health Vol. 41 No. 3, 2013, pp. 121-127
doi:10.2149/tmh.2013-09
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Original article

A High Incidence of Intussusception Revealed by a Retrospective Hospital-Based Study in Nha Trang, Vietnam between 2009 and 2011

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Received 12 April, 2013 Accepted 3 May, 2013 Published online 20 August, 2013

Abstract: Rotavirus is a leading cause of severe diarrhea among children worldwide. Thus, the World Health Organization recommended including rotavirus vaccines in national immunization programs. One concern about rotavirus vaccine, however, is a possible association with intussusception. Thus, it is crucial to know the baseline incidence of intussusception in the first year of life. A study conducted in Hanoi, Vietnam showed that the incidence of intussusception was the highest in the world. This retrospective cross-sectional study was undertaken to determine the incidence of intussusception among children <5 years of age in Nha Trang, Vietnam. Hospital charts between 2009 and 2011 were reviewed in Khanh Hoa Provincial General Hospital where virtually all cases of intussusception occurring in the city were assumed to have been encountered. The incidence of intussusception among children <1 year of age was 296 per 100,000 person-years (95% confidence interval [CI]: 225–382), and that among children <5 years of age was 196 per 100,000 person-years (95% CI: 169–226), confirming the high incidence of intussusception in Vietnam. Nevertheless, there was no intussusception in the first three months of life. We therefore recommend that the first dose of any rotavirus vaccine be administered to infants between 6 and 12 weeks of age.

Key words: intussusception, incidence, rotavirus vaccine, Vietnam

INTRODUCTION

Rotavirus, a leading cause of diarrheal illness among children in both industrialized and developing countries, claims the lives of an estimated 453,000 children less than 5 years of age worldwide each year [1]. Five countries accounted for more than half of all deaths attributable to rotavirus infection: Democratic Republic of the Congo, Ethiopia, India, Nigeria, and Pakistan [1]. The high mortality associated with rotavirus disease underscores the need for rotavirus vaccines.

The first rhesus-human reassortant rotavirus tetravalent vaccine, RotaShield, licensed in the USA in 1998, proved highly effective against severe rotavirus gastroenteritis and raised hopes for the control of the disease by mass vaccination [2]. However, within a year after licensure, RotaShield was withdrawn from the market because it was suspected to increase the risk of intussusception in recipients, with an attributable risk of ~1 per 10,000 administered (range 1/5,000 to 12,000) [3]. Thus, intussusception became an issue of great concern for any rotavirus vaccine that followed in the wake of RotaShield. Intussusception is rare in children with an estimated baseline incidence between 0.5 and 4.3 cases per 1,000 live births among children less than 1 year of age in developed countries or 0.66 and 1.2 cases per 1,000 children less than 1 year of age [4]. Variability in the incidence of intussusception exists in different populations by ethnic groups, geographical areas, and different study periods even in the same country. The incidence of intussusception peaks between 4 and 9 months of age. Previous studies showed that a greater number of cases occurred in males than in females with a ratio of 1.5 to 9 [4].

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The seasonality of the illness is not consistent among studies.

The monovalent human rotavirus vaccine (Rotarix; GlaxoSmithKline Biologicals, Rixensart, Belgium), and the pentavalent human-bovine reassortant vaccine (RotaTeq; Merck and Co., Whitehouse Station, NJ., USA) were introduced into the private market in Vietnam a few years ago. Currently, the coverage of the two vaccines remains low in Vietnam, where both are used mostly in a few big cities like Hanoi and Ho Chi Minh. Additionally, another monovalent human rotavirus vaccine, Rotavin-M1, was manufactured in Vietnam and licensed in 2012. Rotavin-M1 promises to be effective in reducing the number of rotavirus diarrhea in Vietnam that accounted for more than 50% of diarrheal hospitalizations and 5,300–6,800 deaths in children less than 5 years of age annually [5]. However, recent studies conducted in Mexico and Brazil showed that there was an increased risk of intussusception associated with the use of rotavirus vaccines [6]. In this regard, it is noteworthy that the incidence of intussusception among infants in Hanoi, Vietnam was previously reported to be very high: 302 per 100,000 children less than one year of age [7]. Since the introduction of rotavirus vaccines into the national immunization program can be expected to bring about a much larger volume of administration in Vietnam, it is crucial to confirm the high incidence of intussusception in settings other than Hanoi.

The aim of this study, therefore, was to estimate the incidence of intussusception in children less than 1 year and less than 5 years of age in Nha Trang city in the central region of Vietnam. This will help fill the gap in the baseline information regarding the incidence of intussusception in Vietnam before rotavirus vaccines become more widely used in the country.

MATERIALS AND METHODS

Study design and study area

A retrospective, cross-sectional study was conducted in Khanh Hoa Provincial General Hospital by abstracting data from hospital charts during the period from January 1, 2009 to December 31, 2011. Located in Nha Trang city, Khanh Hoa province Khanh Hoa Provincial General Hospital is one of the two largest hospitals in the central region of Vietnam. It is the only hospital in Nha Trang city with facilities for the treatment of intussusception. Moreover, severe cases from all district hospitals of Khanh Hoa province were transferred to Khanh Hoa Provincial General Hospital.

Given the location of the hospital, the nature of the disease, and the fact that a surgical emergency in children requires a definite diagnosis and prompt treatment, we assumed that all children with intussusception living in Nha Trang city between 2009 and 2011 were presented and treated at Khanh Hoa Provincial General Hospital.

Patients and enrollment criteria

Hospital discharge records were screened for the keyword of intussusception (K56.1 under the ICD-10-CM coding system) between January 2009 and December 2011. A data collection form for each patient was then filled out by the first author of the paper (Lan Anh T. Tran) after carefully going through hospital charts. The data collection form was used to collect information on demography, clinical signs, ultrasound findings, radiological findings, method of treatment, medical history and treatment outcome. Based on the information collected from hospital charts, each case was ascertained according to the definitive diagnosis defined by the Japanese Society of Emergency Pediatrics [8]. Patients coded under K56.1 and matched with the definitive diagnosis of the Japanese Society of Emergency Pediatrics, less than 5 years of age and living in Nha Trang city were included in the final analysis.

Statistical analysis

To calculate the incidence of intussusception in Nha Trang city each year during the study period, the number of intussusception cases was divided by person-years. The demographic data used to calculate the person-years were obtained from Khanh Hoa Provincial Health Service without any adjustment. The Poisson model was employed to calculate the 95% CI of incidence. Data were entered and organized then analyzed using using Epidata 3.1 and Stata.12 (StataCorp, College Station, TX, USA), repectively.

RESULTS

A total of 293 hospital charts were extracted with the keyword of intussusception (K56.1 under the ICD-10-CM coding system) between January 2009 and December 2011. We excluded 101 charts because 1) the patients were outside the study area or beyond the study age group, 2) the records were for recurrent events for the same patients, or 3) the diagnosis was incorrectly coded (Fig. 1). The cases recorded in the remaining 192 hospital charts were subjected to the diagnostic criteria proposed by the Japanese Society of Emergency Pediatrics, and 187 cases satisfied the criteria of definitive intususception (Fig. 1). The distribution of these 187 cases skewed toward a younger age, with a broad peak forming between 5 and 22 months of age (Fig. 2). However, there was no case of intussusception among infants less than 3 months of age (Fig. 2). Predominance of

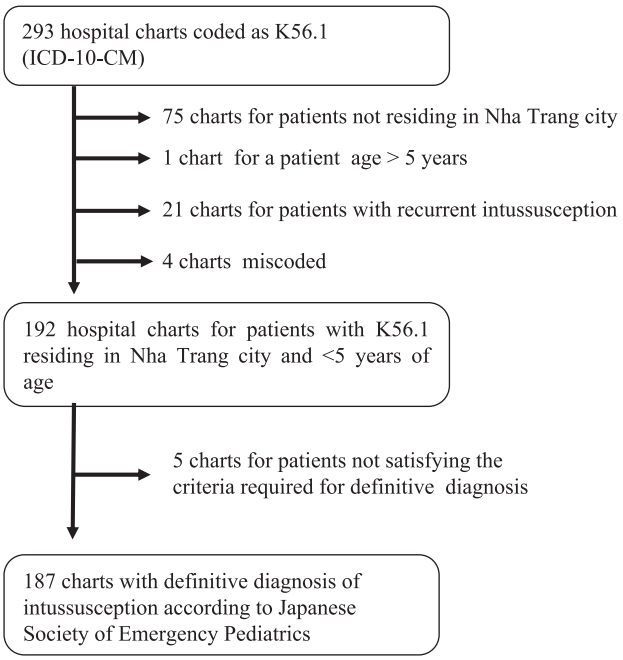

Fig. 1. Flow chart illustrating the selection process of definitive cases of intussusception as defined by the Japanese Society of Emergency Pediatrics starting from the screening of hospital discharge records with the ICD-10-CM code for intussusception.

males was observed with a male/female ratio of 1.8. While the monthly occurrence of intussusception varied during the study period, there was no clear seasonality (Fig. 3).

The incidence of intussusception was an average of 296 per 100,000 person-years (95% CI: 225–382) and 196 per 100,000 person-years (95% CI: 169–226) among children less than 1 year of age and less than 5 years of age, respectively, during the 3-year study period (Table 1).

Table 2 shows the incidence of intussusception for three different age-in-week-specific groups in consideration of the first dose and full dose schedules recommended separately for the three different brands of rotavirus vaccines currently licensed in Vietnam. Intussusception was not observed in infants less than 14 weeks of age, although this fact is not shown in Table 2. The incidence rate was estimated at 53 per 100,000 person-years during the period for the first dose recommended for Rotarix (6–20 weeks of age).

Symptoms and signs observed at presentation of the 187 patients were abdominal pain, vomiting, and palpable abdominal mass in the order of frequency (Table 3). The classical triad of intussusception (i.e., vomiting, abdominal pain, bloody stools) was present only in 26 patients (13.9%) as compared to 122 patients (65.2%) who showed a combination of vomiting, abdominal pain and abdominal mass. For those patients whose records were available for calculation of the time that elapsed from the onset to presentation

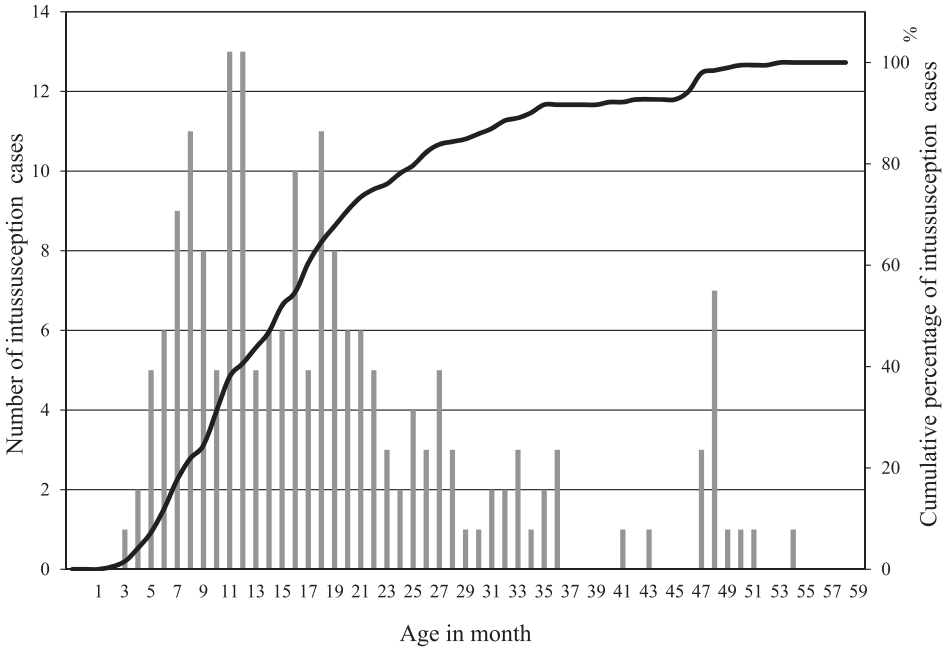

Fig. 2. Age distribution and cumulative percentage of patients with intussusception less than 60 months of age (5 years of age), Nha Trang city, Vietnam, 2009–2011.

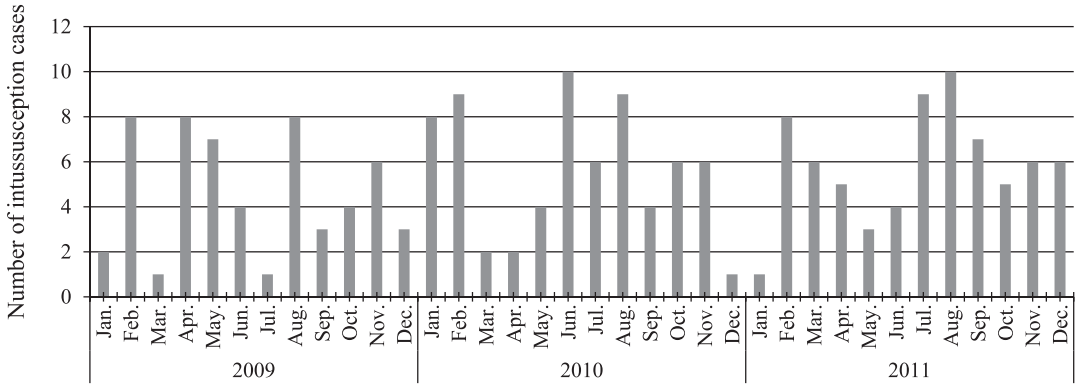

Fig. 3. Monthly distribution of patients with intussusception less than 5 years of age, Nha Trang city, Vietnam, 2009–2011.

Table 1. Incidence rate of intussusception in children <1 year of age and <5 years of age in Nha Trang city, Vietnam, 2009–2011

Year	< 1 year of age				< 5 years of age			
	No. of cases	No. of children	Incidence rate*	95% CI**	No. of cases	No. of children	Incidence rate*	95% CI**
2009	18	6,891	261.2	154.8–412.8	53	31,908	116.1	124.4–217.3
2010	21	6,643	316.1	195.7–483.2	66	31,886	207	160.1–263.3
2011	19	6,080	312.5	188.2–488.0	68	31,567	215.4	167.3–273.1
Total	58	19,614	295.7	224.5–382.3	187	95,361	196.1	169–226.3

* Per 100,000 person-years
** Confidence interval

Table 2. Number of cases and incidence rate of intussusception among infants during different age-in-week periods, Nha Trang city, Vietnam 2009–2011in consideration of different administration schedules of the first and the full doses of the rotavirus vaccines licensed in Vietnam.

For the first dose					For completion of all doses				
Age (week)	No. of cases	Person-years	Incidence*	95% CI**	Age (week)	No. of cases	Person-year	Incidence*	95% CI**
7–12[(1)]	0	2,263	0	0–163.0	6–32[(1)]	21	10,184	206.2	127.6–315.2
6–12[(2)]	0	2,640	0	0–139.7	6–24[(2)]	8	7,166	111.6	48.2–220.0
6–20[(3)]	3	5,658	53	11–155.0	6–24[(3)]	8	7,166	111.6	48.2–220.0

[(1)] The age period for the first dose of Rotateq is recommended by the manufacturer
[(2)] The age period for the first dose of Rotavin-M1 is recommended by the manufacturer
[(3)] The age period for the first dose of Rotarix is recommended by the manufacturer
* Per 100,000 person-years
** Confidence interval

Table 3. Major clinical symptoms and signs observed at presentation in 187 patients with intussusception age less than 5 years, Nha Trang city, Vietnam, 2009–2011

Clinical symptoms and signs at presentation	Frequency (%)
Abdominal pain (intermittent)	185 (98.9)
Vomiting	158 (84.5)
Abdominal mass	143 (76.5)
Bloody stool	32 (17.1)
Abdominal distention	16 (8.6)

at the hospital, the median was 5 hours (IQR n = 77; 3, 10). Air enema was successfully used for the treatment of 185 patients with intussusception; only two patients required surgery. The median length of hospital stay was 2 days (IQR n = 187; 1, 3).

DISCUSSION

This retrospective study showed a high incidence of intussusception-associated hospitalization in children less than 12 months of age in the Central region of Vietnam with an estimated 296 per 100,000 person-years (95% CI: 225–

382). This high incidence of intussusception was closely consistent with the previous study conducted in Hanoi, Northern Vietnam between November 2002 and December 2003 [7]. On the other hand, the incidence of intussusception was reported to be substantially different among different ethnic groups [9, 10], geographic regions even within the same country [4, 11], and study periods [9, 10, 12]. A hospital-based study carried out between 1995 and 1999 in Hanoi, Hue, Ho Chi Minh city suggested a frequent occurrence of intussusception in children less than 12 months of age in Vietnam, with cases occurring in the range of 472 to 722 each year [13]. The incidence in Vietnam was considerably higher than in any neighboring country, including Japan with 185 per 100,000 person-years (95% CI: 133–251) [14] or 158 per 100,000 person-years (95% CI: 131–188) [15], Hong Kong with 108 per 100,000 person-years (95% CI: 95.3–119.7) [16], Taiwan with 77 per 100,000 person-years (range 64.2–86.5) [17], Singapore with 22.8–100.8 per 100,000 [18], Thailand with 19.7–47.8 per 100,000 person-years [11] and Malaysia with 17.8 per 100,000 person-years [19].

Rotavirus vaccines are recommended for administration early in infancy when the incidence of intussusception is low [20]. Indeed, there was no case of intussusception in infants less than 3 months of age. More specifically, we examined the incidence of intussusception during different age-in-week periods that were recommended for the first dose and completion of all doses of each of the rotavirus vaccines currently licensed in Vietnam (Table 2). The incidence of intussusception was low in the age-in-week group that received the first dose of RotaTeq, Rotavin-M1 and Rotarix, and this age group was outside the time period when the incidence of intussusception sharply increased (Fig. 2). However, the incidence increased sharply toward the completion of the full doses of rotavirus vaccine (Table 2). Therefore, early completion of vaccination is recommended to minimize the occurrence by chance alone of intussusception immediately after rotavirus vaccination.

As to the age distribution of intussusception, an interesting observation was that the proportion of cases of intussusception was larger in the second year of life (43%) than in the first year of life (31%). This was similar to the trend previously reported in Taiwan [17] but different from that in other neighboring countries where the largest proportion of intussusception cases occurred in the first year of life (a median of 65%) [11, 14, 16, 19]. The trend resulted from the continuation of a high incidence of intussusception observed for children from 5 to 22 months of age (Fig. 2).

Like other studies, the present study also showed a predominance of intussusception among males. The sex ratio in the present study was similar to that reported in neighboring countries, and there was no significant variation between different age groups. Intussusception occurred year-round with no apparent seasonality.

In the present study, the most common clinical manifestation of intussusception included abdominal pain, vomiting, and palpable abdominal mass, a combination of which was observed in 65% of patients, whereas the triad of classical symptoms with bloody stools along with vomiting and abdominal pain was present in only 26 cases (13.9%). A very high proportion of symptoms such as abdominal pain, vomiting and abdominal mass was also reported in the previous study [7]. The concurrent occurrence of abdominal pain, vomiting, palpable mass in children less than 5 years of age strongly suggests the presence of intussusception in Vietnam. A high proportion of abdominal pain (99%) and vomiting (84%) in this study was closely consistent with other studies.

The relatively low proportion of bloody stools observed in this study (17%) was probably related to the short duration of time before presentation at the hospital (a median of 5 hours). In contrast, the average time before presentation at hospital was 12 hours in Hanoi where the percentage of bloody stools was higher (47%). A study conducted in Saudi Arabia reported a high incidence of bloody stools (91%), and the average duration of the symptoms was 38 hours [21]. In another study in Pakistan that analyzed 50 patients up to 12 years of age with surgically diagnosed intussusception, all cases presented after 24 hours with a mean duration of 3 days from onset to presentation and red current jelly stools was reported in 60% [22]. Studies from Thailand [11], and India [23] also reported a high percentage of bloody stools with a long duration of symptoms. Bloody stools as a clinical manifestation of intussusception is time dependent, a fact proven in studies from the USA [24] and the United Kingdom [25].

Previous studies reported that surgical intervention was required in 2.5%–95% of patients with intussusception (Table 4). The low frequency of surgical intervention (1%) in the present study may be explained by the easy access to hospital enjoyed by the residents in Nha Trang as demonstrated by the fact that the median time from the onset to presentation to the hospital was only 5 hours and that Khanh Hoa Provincial Genneral Hospital was within 20 km of the city's boundary. Studies conducted in Thailand, Australia and Saudi Arabia [11, 27, 28] indicated that the proportion of surgical intervention cases increased with the length of time that elapsed between the onset and presentation at the hospital. Alternatively, the fact that only cases coded under K56.1 were included in this study may be a contributing factor. That is, the slection procedure might have excluded cases that were coded under other gastrointestinal diseases

Table 4. Proportion of surgical intervention for intussusception

Country	Study period	Surgery (%)	Reference
Switzerland	2003–2006	23	[26]
Japan	1978–2002	13	[14]
Thailand	2001–2006	49	[11]
Malaysia	2000–2003	56.5	[19]
Vietnam (Hanoi)	2002–2003	12.2	[7]
Hong Kong	1997–1999	2.5	[16]
Bahrain	1999–2003	29.6	[29]
India	2001–2004	65	[23]
Israel	1990–2004	8.7–21.3	[30]
Saudi Arabia	1993–2000	76	[21]
USA	1993–2004	51–59	[9]
Mexico	2008–2010	87	[6]
Brazil	2008–2010	95	[6]
Australia	2001–2009	19	[7]

rarely associated with intussusception or possible complication of intussusception like bowel obstruction.

Other limitations to this study should be mentioned. First, by reviewing hospital charts we noticed that the K56.1 code was incorrectly entered into the discharge records of 4 patients. Likewise, there might be cases in which patients with genuine intussusception were coded under different ICD-10-CM codes. Such cases were irretrievable and might have been missed in this study. Second, like any other retrospective hospital chart review, the completeness and accuracy of the data depend on the quality of the medical records reflecting the clinical practice of local doctors. In addition, hospital charts are not necessarily designed for epidemiological investigations. Of 192 cases of intussusception diagnosed by local doctors, 5 were excluded because these cases did not meet with the case definition employed in this study (that of the Japanese Society of Emergency Pediatrics [8]). In at least one case, however, there was a very detailed description of the patient that strongly suggested the presence of intussusception. On the other hand, there may be cases in which doctors made an overdiagnosis of intussusception. Thus, the number of cases is sensitive to the case definition applied.

In conclusion, this study showed that the incidence of intussusception was very high in children less than 1 year of age in Nha Trang, Vietnam. Nevertheless, there was no case of intussusception among infants less than 3 months of age. We therefore recommend that the first dose of any rotavirus vaccine should be administered to infants between 6 and 12 weeks of age.

ACKNOWLEDGMENTS

The authors sincerely thank Dr. Le Huu Tho, Dr. Phu Quoc Viet and Mr. Luu Trung Hieu, Khanh Hoa Provincial Health Service Office, for their assistance in conducting this study.

Tran Thi Lan Anh is a graduate student in the Master Course in Tropical Medicine, Nagasaki University, supported by a scholarship from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

This study was supported in part by the Cooperative Research Grant (2012-A-14) of the Institute of Tropical Medicine, Nagasaki University, and by the Collaborative Study on Emerging and Re-emerging Infectious Diseases in Vietnam, Enhancement of Research Capacity Phase II, funded by the Ministry of Education, Culture, Sports, Science and Technology, Japan.

CONFLICTS OF INTEREST

There is no conflict of interest for any author to declare regarding this study.

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