RISK FACTORS FOR INTUSSUSCEPTION IN INFANTS IN VIETNAM AND AUSTRALIA: ADENOVIRUS IMPLICATED, BUT NOT ROTAVIRUS

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Objective This study aimed to investigate risk factors for the development of intussusception in infants in a developing country with a suspected high incidence and in a developed country with a low incidence.

Study design A prospective case-control study of infants <2 years of age with idiopathic intussusception confirmed by air enema or surgery was conducted at the National Hospital of Paediatrics (NHP), Vietnam (n = 533) and the Royal Children's Hospital (RCH), Australia (n = 51). Diagnosis was validated in a subset (84% NHP; 67% RCH) by an independent blinded radiologist. Risk factor assessment was performed using a standardized questionnaire. Stool specimens were assayed for bacterial, viral, and parasitic agents.

Results The incidence of intussusception in Vietnam was 302/100,000 in infants <1 year of age (95% CI: 258-352), substantially higher than in Australia (71/100,000). A strong association with adenovirus infection was observed at both sites (cases positive at NHP: 34%, OR 8.2; cases positive at RCH: 40%, OR 44). No association was identified between intussusception and rotavirus, other enteric pathogens, oral polio vaccine, feeding practices, or living conditions.

Conclusions The incidence of intussusception in infants was markedly higher in Vietnam than in Australia. A strong association between adenovirus infection and intussusception was identified at both sites suggesting that adenovirus may play a role in the etiology of intussusception. *(J Pediatr 2006;149:452-60)*

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The withdrawal of the first oral rotavirus vaccine licensed in the United States (Rotashield®, Wyeth Lederle Vaccines, USA) because of an association with intussusception was a major setback in efforts to reduce the global burden of rotavirus disease.[1] Although impacting on the development of alternative rotavirus vaccines, the withdrawal also highlighted the limited knowledge of the epidemiology of intussusception, the most common cause of bowel obstruction in infants worldwide.[2]

In young children, intussusception usually occurs in the ileocecal region and in more than 90% of cases no clear etiological factor is identified.[3] The invaginating bowel is propelled along by peristalsis, drawing with it its blood supply. Venous occlusion results in bowel edema, and if the obstruction is not relieved, ischemia and infarction of the bowel may occur.

The incidence of intussusception is <100 per 100,000 live births in children <1 year of age in developed countries.[4-6] However, substantially higher rates of intussusception have been reported from Vietnam and China.[2,3,7] Interpretation of these studies has been guarded because of their retrospective design and the use of ultrasonography to establish the diagnosis.[2,7,8]

Investigation of potential risk factors, including infectious agents, may provide clues to understanding the etiology in locations with both low and high incidence rates. The

NHP	National Hospital of Paediatrics	RCH	Royal Children's Hospital
OPV	Oral polio vaccine		

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rotavirus disease burden in children of Vietnam and China is high,[9] so both countries will benefit significantly from the introduction of a rotavirus vaccine. However, in regions with a high background incidence of intussusception, the choice of vaccine and timing of vaccine administration may need careful consideration before introduction.

In this prospective case-control study we investigated potential risk factors for intussusception in children <2 years of age in pediatric hospitals in Vietnam and Australia. The aim of this study was to define the incidence of intussusception in different locations and to compare risk factors for intussusception in a developing country with a suspected high incidence of intussusception (Vietnam) with those in a developed country with a low incidence of intussusception (Australia).

METHODS

A prospective case-control study was conducted at the National Hospital of Paediatrics (NHP), Hanoi, Vietnam, over a 14-month period (November 1, 2002 to December 31, 2003) and the Royal Children's Hospital (RCH), Melbourne, Australia, over a 24-month period (March 19, 2002 to March 18, 2004). The study was approved by the Ethics Committee of the Ministry of Health, Vietnam, and the Ethics in Human Research Committee of the RCH.

Cases

Infants <2 years of age with signs and symptoms suggestive of intussusception seeking care at the Departments of Emergency Medicine at NHP and RCH were considered for enrollment into the study. Only patients with a final diagnosis of primary idiopathic intussusception confirmed by air enema or at surgery were included in the data analysis. Validation of the diagnosis of intussusception on air enema was later assessed by an independent radiologist blinded to case assignment in a subset of patients from NHP and RCH.

Controls

At RCH, three healthy community control subjects were recruited and matched to each case by sex, age (within 1 month of index case), and region. Control subjects were identified through community Maternal and Child Health Centres in metropolitan Melbourne or regional Victoria depending on where the case patient resided. The nurse at each relevant center identified the first three infants from the center who fulfilled the age and sex criteria and obtained informed consent for the parents to be contacted by the investigator. At NHP, because of the higher expected recruitment of cases with intussusception, only one control subject was recruited for each case and was matched by sex and age (within 2 months of the index case). Control subjects were recruited from patients admitted for minor elective surgery, nongastrointestinal or infectious diseases, or from patients attending the Outpatient Department. All control subjects were recruited and interviewed within 1 month of the index case presentation and were clinically stable, without diarrhea or a respiratory tract infection.

Incidence

The incidence of acute intussusception was estimated from the number of cases of primary idiopathic intussusception, restricted to children <1 year of age, for comparability with previously published studies. Published data on the age-specific population at risk during the study period in the city of Hanoi (as defined by government census authorities) and the state of Victoria were used as denominators for this calculation.[10-12]

To verify study ascertainment of eligible cases we retrospectively matched all attendees to the Emergency Department who had a diagnosis of intussusception with patients in the study database. NHP and RCH both are the major pediatric hospitals in their respective regions, but it is possible that patients with intussusception also may have been treated at other healthcare centers. Only case patients who were residents in Hanoi were included in incidence calculations as some patients travel long distances from rural areas in North Vietnam to attend the pediatric facilities provided at NHP, whereas other rural case patients are treated at local healthcare facilities. A prospective survey of cases of intussusception in infants <2 years of age was conducted in other hospitals treating children in Hanoi during the period of the study (Viet Duc Hospital, Vietnam-France Hospital, St. Paul's Hospital, E Hospital, Thanh Nhan Hospital, Bach Mai Hospital). In Australia, the number of intussusception admissions to other hospitals in Victoria was identified based on a statewide computerized medical record database system (ICD-10-CM code K56.1). These data were used in the calculation of incidence to estimate the proportion of the total cohort of infants with intussusception in the state of Victoria who were admitted to RCH.

Risk Factor Assessment

Risk factor measurements were collected via an interview with the parents of intussusception case patients and controls using a standardized questionnaire (in Vietnamese or English). The questionnaire included information on the infant's general health, medications, feeding history, immunization history, family history, ethnic background, and data related to housing, sewerage, and water supply.

Assessment for Infectious Pathogens

Stools were collected from intussusception cases from RCH and from the first 25 to 30 cases presenting in each 3-month period to NHP to identify any seasonal variability. All samples were collected within 24 hours of admission and stored at 4°C. Stool specimens were collected from control subjects within 1 month of the date of the presentation of the index case. Specimens were examined for red and white blood cells and parasites by light microscopy using a wet preparation. Routine culture media was used to assay for common