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A Prospective Study of Rotavirus Infection in Infants and Young Children

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Diarrhea in neonates, followed as a cohort, and their families was studied prospectively. The families were followed for an average of 16.3 months. Stool and serum specimens were obtained at least every three months. Stool specimens were examined for viruses by electron microscopy and cultured for enteropathogens, and serum specimens were tested for antibodies to rotavirus and Norwalk virus. During the study, 237 episodes of gastroenteritis were observed in 104 infants and their 62 siblings. Rotavirus, detected 82 times in 72 children, was by far the most common enteropathogen. It was associated with gastrointestinal symptoms in 72% (with diarrhea in 65%). Rotavirus diarrhea occurred mostly in winter months and was significantly more frequently associated with respiratory symptoms than were diarrheas with other etiologies. Rotavirus infection was uncommon in the first six months of life, but by two years of age, 62% of the infants had had at least one infection. Neither breast feeding nor the presence of antibody to rotavirus in cord blood appeared to be protective.

Although gastroenteritis is no longer a major cause of death in children in North America, this illness remains a major cause of morbidity in infants and young children. Pathogens such as rotavirus, Norwalk virus, enterotoxigenic *Escherichia coli*, and *Campylobacter fetus* subspecies *jejuni* have been recognized recently as etiologic agents in diarrhea. The relative role of these different enteropathogens has been investigated, for the most part, in children hospitalized with diarrhea [1–4]. The risk of diarrheal disease and the types of pathogens causing diarrhea have not been systematically investigated prospectively in nonhospitalized patients in North America.

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Informed consent was obtained from all of the families participating in this study, and the research was approved by the University of Manitoba Committee on Human Experimentation.

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We report clinical and epidemiologic data, prospectively acquired, concerning diarrheal disease in neonates, followed as a cohort, and their siblings, with specific emphasis on rotavirus, which was numerically the most important pathogen recognized. The clinical and epidemiologic features of diarrhea and of rotavirus infection in the parents of these young children have been reported [5].

Materials and Methods

Subjects. The children participating in this study were part of a prospective investigation of diarrhea in families with newborn children. We enrolled families by approaching mothers at the Health Sciences Centre, Winnipeg, Manitoba, Canada, during their early postpartum period. We attempted to find families who were likely to remain at the same residence for one to two years. Nonetheless, the families were not biased toward the high socioeconomic classes [5]. We enrolled approximately 10 new families a month until the goal of approximately 100 families was reached.

Specimen collection. Base-line stool and serum were obtained from each family member. Cord blood was used as a base-line specimen for the neonates. At each visit, serum and stool specimens were obtained, and family members were questioned concerning illnesses between visits. We also asked to be notified of acute gastrointestinal or respiratory illness in any family member. When

such an illness was reported, another home visit was made, and a stool specimen and throat swab were obtained. A gastrointestinal illness was defined as occurring if the parents noticed vomiting, loose stools representing a change in character of the stool, or a significant increase in number of stools. Gastroenteritis as thus defined was almost always accompanied by other signs of illness, such as irritability or anorexia, and lasted for at least a 24-hr period. Respiratory illnesses were similarly defined on the basis of the parents' perception of upper respiratory symptoms such as cough, runny nose, or conjunctivitis, lasting for at least 24 hr and usually accompanied by irritability, anorexia, or fever. Otitis media, bronchiolitis, or pneumonia was included when diagnosed by a physician.

Stool specimens. Each stool specimen collected in the study was examined by direct electron microscopy for rotavirus and other virus-like particles [2]. All stools were cultured for *E. coli* of the classical enteropathogenic serotypes, *Shigella*, *Salmonella*, *Aeromonas hydrophila*, *Aeromonas shigelloides*, and *Yersinia enterocolitica*, and stool specimens and throat swabs obtained during acute illnesses were cultured for viruses [5]. Stool specimens obtained at routine visits during a 12-month period (November 1976–November 1977) and obtained from patients at the time of diarrheal or respiratory illnesses were screened for *E. coli* producing heat-labile enterotoxin with a modification of the Y-1 mouse adrenal tumor cell assay [6] and for *E. coli* producing heat-stable enterotoxin with a modification of methods described by Brunton et al. [7]. The modification was that all *E. coli* isolates from routine fecal specimens were pooled before being tested in the infant mouse assay instead of being tested individually. *A. hydrophila* isolates from fecal specimens were tested for the production of a cytotoxin [8].

Serum specimens. All serum specimens were examined for antibodies to rotavirus by an indirect fluorescent antibody assay, using SA-11 simian rotavirus (supplied by Dr. L. Spence, University of Toronto, Ontario, Canada) as a cross-reacting antigen [5]. The final serum specimen from each patient in the study was screened for antibody to Norwalk virus by radioimmunoassay [9]. If antibody to Norwalk virus was present in this final serum in a titer of ≥1:100, the first serum specimen from the patient was tested; if there had been a fourfold increase in antibody titer, all serum specimens from the patient were tested for antibody to Norwalk virus. For the cohort of neonates, from whom the initial specimen was cord blood, all serum specimens were tested for antibody to Norwalk virus if the titer in the final specimen was ≥1:100. Serologic evidence of infection with rotavirus or Norwalk virus was defined as a fourfold or greater increase in antibody titer.

The study period covered 34 months, from April 1976 through January 1979. Ninety-eight families, comprising 98 women, 90 men, and 166 children, were enrolled. The duration of follow-up observation ranged from three to 29 months (mean, 16.3 months; median, 13 months). There were 48 families with one child, 36 with two children, and 14 with three or more children. In six families a second newborn infant was included in the study. Thus, the 166 children comprised 104 infants (the newborn cohort) followed from birth and 62 older siblings.

Results

Clinical syndromes. There were 167 episodes of gastrointestinal illness in the 104 infants, with diarrhea occurring with or without other symptoms in 153 of these episodes (table 1). In the 62 siblings there were 70 episodes of gastroenteritis, including 52 diarrheal episodes, a rate of about 0.8 per child per year. In the newborn cohort, age-specific attack rates were calculated for each six-month interval through 23 months of age (table 2); both gastroenteritis and rotavirus infection were relatively uncommon in the first six months of life compared with later six-month intervals. The gastroenteritis rate for infants younger than six months of age was 0.047 per infant per month, but in later six-month intervals the rate was almost three times higher. The rotavirus infection rate for the first six months of life was 0.003 per month but increased >10-fold, ranging from 0.037 to 0.054, for the later age intervals. In the winter months (defined as October through April in Manitoba [5]), the rate was as high as 0.079 per child per month. Although in the first six months of life gastroenteritis was common during summer months, it was less common in summer months in older infants. The increase in gastroenteritis during winter in older infants appeared to be due mainly to rotavirus because the gastroenteritis rates in summer and winter months would have been similar if gastroenteritis associated with rotavirus was excluded.

Table 1. Relationship of episodes of acute illness and specific infections in 104 infants and their 62 siblings.

Group, infection	Symptoms				
	Gastrointestinal alone*	Gastrointestinal and respiratory	Respiratory alone	Other†	No symptoms
Infants	90	77	152	20	. . .
No pathogens	63	39	136	20	. . .
Rotavirus	15	24	8	0	3
Other‡	14	16	9	0	10
Siblings	47	23	103	8	. . .
No pathogens	32	12	87	7	. . .
Rotavirus	9	11	10	1	1
Other‡	6	0	6	0	6

NOTE. Data are given as no. of episodes of illness or asymptomatic infection.

* Diarrhea and/or vomiting without respiratory symptoms.

† Includes fever, acute exanthems, and cellulitis.

‡ Includes dual infections.

Etiology. The most common gastrointestinal pathogen was rotavirus, although most episodes of gastroenteritis were not associated with any recognized pathogen (table 1). Rotavirus was associated with 39 (23%) of 167 episodes of gastroenteritis in the neonates and 20 (28%) of 70 episodes in their siblings, but 102 (61%) of episodes of gastroenteritis in the neonates and 44 (63%) in their siblings could not be associated with a recognized pathogen. However, if we consider only episodes of gastroenteritis in which both diarrhea and vomiting occurred, 36 (72%) of 50 episodes in infants and seven (33%) of 21 in their siblings were associated with rotavirus. Other etiologic agents accounted for a relatively small number of episodes of gastroenteritis. Enteropathogenic *E. coli,* the second most common pathogen, was present in 10 episodes of gastroenteritis in the newborn cohort (although three of these episodes were dual infections with rotavirus and one was a dual infection with adenovirus); this pathogen was found in two episodes in the siblings. Adenovirus was associated with six episodes of gastroenteritis in the newborn cohort and one in their siblings. Other pathogens associated with gastroenteritis included coronavirus in three episodes, toxigenic *A.*

Table 2. Age- and season-specific rates of gastroenteritis and rotavirus infection for 104 infants.

Age group (no. of infants studied)*	Total months at risk	All gastroenteritis	Rotavirus gastroenteritis	All rotavirus
0–5 months (104)				
Summer	279	15 (0.054)	0 (0)	0 (0)
Winter	339	11 (0.032)	0 (0)	2 (0.006)
Total	618	26 (0.047)	0 (0)	2 (0.003)
6–11 months (94)				
Summer	197	21 (0.106)	1 (0.005)	2 (0.010)
Winter	340	54 (0.159)	24 (0.071)	27 (0.079)
Total	537	75 (0.140)	25 (0.047)	29 (0.054)
12–17 months (83)				
Summer	163	11 (0.067)	0 (0)	1 (0.006)
Winter	160	26 (0.163)	10 (0.063)	11 (0.069)
Total	323	37 (0.115)	10 (0.031)	12 (0.037)
18–23 months (37)				
Summer	65	8 (0.123)	0 (0)	1 (0.015)
Winter	125	19 (0.152)	5 (0.040)	6 (0.048)
Total	190	27 (0.142)	5 (0.026)	7 (0.037)

NOTE. Data are no. of episodes (no. of episodes per month per child). Episodes occurring after infants were 23 months of age were excluded.

* Summer and winter were defined as May–September and October–April, respectively.

Table 3. Method of diagnosis for rotavirus infection in infants and older siblings.

Rotavirus infections	Seroconversion	Electron microscopy	Seroconversion and electron microscopy
Gastroenteritis	32	4	23
Respiratory symptoms only	16	1	1
Neither gastrointestinal nor respiratory symptoms	5	0	0
Total	53	5	24

NOTE. Data are given as no. of infections.

hydrophila in five, coxsackievirus B2 in two, parainfluenza virus in two, *Salmonella infantis* in one, enterotoxigenic *E. coli* in one, poliovirus in three, and Norwalk virus in one. The poliovirus isolates were found in infants only, were vaccine strains, and were not associated with paralytic disease or aseptic meningitis. During the study, methods adequate to detect *C. fetus* subspecies *jejuni* were not routinely used.

Rotavirus was also the most frequently recognized enteric pathogen overall; when asymptomatic infections were included, rotavirus was identified 82 times. Twenty-three (28%) of the infections were not associated with any gastrointestinal symptoms, but only four (5%) were entirely asymptomatic.

In the majority of rotavirus infections, the method of diagnosis was seroconversion with or without visualization of the organism in the stool by electron microscopy (table 3). In contrast to the parents of these children, in whom 10 (23%) of 43 infections were diagnosed by electron microscopy without seroconversion [5], in only five of the 82 rotavirus infections in the children was there no seroconversion. Rotavirus detectable in fecal specimens by electron microscopy appeared to be related to the presence of diarrhea; rotavirus was seen by electron microscopy in 26 of 53 rotavirus infections associated with diarrhea compared with three of 29 without diarrhea ($P < 0.001$; $\chi^2 = 12.29$).

Clinical features. Diarrhea, present in 53 (65%) rotavirus infections, was the most common symptom in these infections. Vomiting was present in 39 (48%) rotavirus infections and was the most common first symptom, occurring in 21 (34%) patients (table 4). The character of the diarrhea associated with rotavirus was generally not remarkable; bloody stools were not seen in association with these 82 rotavirus infections and in general were uncommon during the study. The mean duration of the diarrheal episode associated with rotavirus was 5.2 days, whereas the mean duration of diarrhea not associated with rotavirus was 4.3 days. These figures exclude rotavirus infections without diarrhea and any diarrheal episode lasting for >10 days.

Within the cohort of neonates (zero to 23 months of age), in which the relationship of age to type of symptoms could be studied most accurately, there seemed to be no relation of age to type or severity of symptoms during rotavirus infection. Twenty-one of the children with rotavirus infection required some type of medical attention; only three were hospitalized. One child was hospitalized because of rotavirus-associated diarrhea and dehydration. One child, hospitalized because of cellulitis, developed diarrhea, and rotavirus was diagnosed by seroconversion. One child was hospitalized with pneumonia and never had gastrointestinal symptoms; rotavirus infection was later diagnosed by seroconversion. Of the 82 rotavirus infections, 10 were the second rotavirus infection in an individual child during the study period. Seven of these second infections were associated with gastrointestinal symptoms, a rate essentially identical with

Table 4. Clinical manifestations of 82 rotavirus infections in 72 children.

Symptom	No. of infections (%) in which the symptom	
	Was present	Occurred first*
Diarrhea	53 (65)	18 (29)
Vomiting	39 (48)	21 (34)
Fever	28 (34)	8 (13)
Respiratory†	43 (52)	15 (24)

* Based on 62 infections in which it was possible to determine a first symptom.

† Respiratory symptoms were mostly those of upper respiratory tract infection, cough, rhinitis, otitis media; pneumonia occurred in one child.

the overall rate of gastrointestinal symptoms. Of the 10 children having two rotavirus infections during the study, all seven with gastrointestinal symptoms during their second infection had had gastrointestinal symptoms during the first infection, whereas the three asymptomatic in the second infection had also been asymptomatic in their first infection ($P = 0.017$ by Fisher's exact test).

Respiratory symptoms were associated with 53 (65%) of 82 rotavirus infections (table 4). In 18 (22%), respiratory symptoms were the only symptoms noted. Likewise, when all episodes of diarrhea were considered, respiratory symptoms were most frequently associated with rotavirus. Respiratory symptoms occurred in 32 (60%) of 53 diarrheal episodes associated with rotavirus, compared with 42 (34%) of 123 diarrheal episodes without a pathogen and 11 (35%) of 31 diarrheal episodes associated with other enteropathogens ($\chi^2 = 11.00$ with two degrees of freedom; $P < 0.01$).

Epidemiology. Factors predisposing to rotavirus infection, other than season or age, were difficult to identify. Seventy-seven (94%) of the rotavirus infections occurred during the seven months from October to April, a period that may be considered "winter" in Manitoba. In the neonatal cohort, only two cases of rotavirus occurred before six months of age, but by two years of age, by a life-table type of analysis, only 38% had not experienced a rotavirus infection. Although infection was uncommon before six months of age, neither breast-feeding nor the presence of maternal (cord blood) antibody to rotavirus correlated with protection from infection. Rotavirus infection occurred in 16 (55%) of 29 infants not breast-fed, compared with 29 (39%) of 75 infants who were breast-fed ($\chi^2 = 2.32$; $P < 0.20$). In addition, the presence of a titer of antibody to rotavirus of $\geq$1:10 in cord blood did not seem protective. Thirty-seven (42%) of 88 newborn infants with a titer of antibody of $\geq$1:10 developed rotavirus infection, a rate similar to the 50% rate (eight of 16) in those born with less than this level of antibody. Likewise, in the siblings, a preinfection antibody titer of $\geq$1:10 did not appear protective. The rate of rotavirus infection in siblings with this level of antibody throughout the study or immediately before rotavirus infection was 16 (42%) of 38, a rate similar to the 10 (46%) of 22 with less than this level of serum antibody. Finally, in children with documented rotavirus infection, gastrointestinal symptoms occurred in 36 (73%) of 49 with a preinfection antibody titer of <1:10, a proportion not significantly different from 12 (55%) of 22 with a preinfection titer of $\geq$1:10 ($\chi^2 = 2.48$; $P < 0.20$).

The male:female ratio among children with rotavirus infection (41:31) was slightly greater than the ratio among those children not developing rotavirus infection (49:45). It was difficult to determine the sequence of infection in families in which there was more than one rotavirus infection. The neonates appeared to be affected first in many cases, but this observation may have been biased by the greater severity of vomiting and diarrhea in the infants than in their older siblings. The older siblings did not appear to play an essential role in transmission of rotavirus infection in our study. In fact, the infection rate among infants without siblings (51% of 53) was higher than the infection rate among infants with siblings (45% of 51). In families with only one child, there may have been other sources of exposure to rotavirus, such as attendance at a day-care center, having parents who brought other children into the home for babysitting, or having one or both parents whose jobs required contact with children.

Discussion

Although we attempted to identify the cause of all episodes of gastroenteritis, in the majority of episodes of diarrhea no etiologic agent was identified. This finding is similar to that of our studies of children hospitalized with diarrhea in Winnipeg [2].

Although it would seem reasonable to expect breast-feeding, maternally transmitted antibody to rotavirus, or both to explain the relative infrequency of rotavirus infection during the first six months of life, we could find no evidence to support these hypotheses. Rotavirus infection was as common in infants who were breast-fed as in those who were not and as common in those infants with maternally acquired antibody as in those without. Because <20% of the infants were not breast-fed, a larger study might have shown a protective effect of breast-feeding against rotavirus infection. However, the results of our parallel studies of diarrhea in an isolated native Indian settlement and in an Inuit (Eskimo) settlement do not support a protective role for breast-feeding. In the Inuit settlement, where breast-feeding was nearly

universal, the rate of rotavirus infection was higher than in Winnipeg and higher than in the native Indian settlement, where <5% of the infants were breast-fed at any time (authors' unpublished observations). It is possible that other forms of gastrointestinal immunity in infants younger than six months of age account for the lower incidence of rotavirus infection in this age group and that most of the infants are no longer being breast-fed after six months of age, when they are at greater risk from rotavirus infection. However, several nosocomial rotavirus epidemics involving neonatal nurseries have been described [10, 11]. In one of these outbreaks, it was shown that neither maternally acquired serum antibodies to rotavirus nor antibody to rotavirus in breast milk correlated with protection against rotavirus infection [10]. Although it has been postulated that rotavirus infection occurs in young infants because the virus is brought into the home by older siblings, we were unable to find a difference in rate of rotavirus infection among infants with or without siblings. It is likely that rotavirus infection is so prevalent that only brief exposure to other children is required or that there is enough asymptomatic infection of parents to account for transmission to infants.

Reinfection or second infection with rotavirus occurred 10 times. At least two serotypes of rotavirus have been described [12, 13], and sequential infection by different serotypes may be a plausible explanation for these reinfections. However, it now appears that these previously identified serotypes are based on antigenic specificities not reacting with neutralizing antibody and are more properly termed subgroups or subtypes rather than serotypes [14].

We were not able to demonstrate a protective effect of serum antibody to rotavirus. The presence of antibody to rotavirus, in cord blood or immediately before infection, did not seem to correlate with protection either against infection or against clinical disease in those acquiring infection. One possible explanation is that preexisting antibody was specific for a serotype other than the one causing the infection. Another possibility is that even if serum antibody does contain neutralizing antibody to the infecting serotype, local gastrointestinal antibody may be required. Because in our present study and in other studies [1, 10–12] the antibody responses detected were not necessarily those of neutralizing antibody, we cannot evaluate these two possibilities on the basis of available data. It is interesting that children who were symptomatic with their initial rotavirus infection were also symptomatic during a second rotavirus infection. This finding parallels the observations that volunteers who had antibody to Norwalk virus before infection were, if anything, more likely to be symptomatic than volunteers without antibody and that those volunteers symptomatic during their first infection were symptomatic during their second infection [15].

Although there was not any absolutely characteristic clinical presentation for rotavirus infection, several features were highly suggestive of this infection [3, 16]. Vomiting, especially 1–24 hr before the onset of diarrhea, was uncommon in diarrheal episodes with other etiologies, including those without a diagnosis. Vomiting almost always occurred in the infants, although it was seen less frequently in older siblings and parents. Some young children and infants either complained of abdominal pain or gas or gave the appearance of suffering from abdominal pain by pulling up their legs. This nonspecific abdominal pain was also noted in parents symptomatic with rotavirus infection [5]. Thus, diarrheal illness associated with vomiting and/or abdominal pain and occurring during the winter months was likely to be caused by rotavirus. Although Norwalk virus and related viruses have been described as "winter vomiting disease," these viruses are not particularly associated with the winter season [17], are uncommon in young children [18], and were uncommon in our study. In the parents of these children respiratory symptoms occurred commonly; in 18 children the only symptoms associated with rotavirus infection were in the upper respiratory tract. The significance of the increased respiratory symptomatology in children with rotavirus infection is unclear. Although the winter predominance of rotavirus and the increased occurrence of respiratory symptoms [3, 16] in rotavirus infection suggest a possible respiratory mode of spread for this virus, to our knowledge respiratory spread has not yet been documented. When looked for specifically, rotavirus was not shown to be present in the upper airway or its secretions [3, 19]. However, the coincidence of increased frequency of rotavirus infection and increased frequency of some respiratory viral infections, due to agents such as influenza virus or respiratory syncytial virus, during winter months seems inadequate to explain the statistical association of respiratory symptoms with rota-

virus infection in our study. Possibly a respiratory mode of spread for rotavirus infection will be documented, or perhaps a synergistic effect between rotavirus and respiratory viruses will be found.

In summary, we found rotavirus to be the most commonly identified pathogen in diarrhea in infants, especially during the winter. The results of our study and those of Brandt et al. [12] suggest that prevention of rotavirus infection will require better understanding of the biology and epidemiology of the virus and of host factors and that the development of rotavirus vaccines will require even better understanding of these features.

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