

Adenovirus Types 40 and 41 and Rotaviruses Associated with Diarrhea in Children from Guatemala

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Received 27 December 1989/Accepted 30 April 1990

From March 1987 to February 1988, fecal excretion of adenovirus types 40 and 41 and rotavirus serotypes in 194 children (age, 0 to 3 years) from a rural community of Guatemala was monitored. In total, 458 samples taken during 385 episodes of diarrhea and 191 specimens obtained during symptom-free periods were examined by enzyme-linked immunosorbent assay. Fifty-seven children hospitalized because of diarrhea were also studied. Among the rural children, 43 (22.2%) excreted adenovirus types 40 and 41 and 20 (10.3%) shed rotaviruses. Adenovirus types 40 and 41 were associated with 54 (14.0%) illnesses, and rotaviruses were associated with 18 (4.7%) illnesses. Asymptomatic infections with adenovirus types 40 and 41 were documented in nine children and with rotaviruses in two children. Fifteen typeable rotaviruses were identified as serotype 2. In the hospital population, 36 (63.2%) children had viral infections. Rotaviruses were identified in 29 (50.9%) and adenovirus types 40 and 41 were identified in 15 (31.2%) of 48 subjects tested. Dual infections by these viruses were found in eight children. Of 22 typeable strains of rotaviruses, 9 (34.6%) were serotype 1, 12 (46.1%) were serotype 2, and 1 (3.8%) was serotype 3. All the children infected with serotype 2 rotavirus were coinfecting with other enteric pathogens, while only three (37.5%) of those infected with rotavirus serotype 1 excreted another pathogen. Adenovirus types 40 and 41 are an important cause of gastroenteritis in both ambulatory and hospitalized Guatemalan children. There seems to be a difference in the pathogenicity among rotavirus serotypes.

Adenovirus types 40 and 41 (Ad40 and Ad41) have recently been recognized as important etiologic agents of gastroenteritis in children, especially in temperate climates where they are second in importance only to rotaviruses as a cause of diarrhea (14, 18). Herrmann et al. (9) have reported that Ad40 and Ad41 are associated with a small proportion (2.0%) of gastroenteritis in Thai children attending an outpatient clinic in Bangkok; this rate is very similar to that reported in Rio de Janeiro, Brazil (1.9%) (13). Shinozaki et al. (16) presented data on antibodies to Ad40 and Ad41 in a Japanese population showing that neutralizing activity peaked in children ages 18 to 24 months, suggesting that this may be the time when most infections occur. Additionally, Kidd and collaborators (12) have reported that the prevalence of serum neutralizing antibodies in children aged less than 2 years from London, Hong Kong, New Zealand, and an isolated village in The Gambia was about half that of antibodies found in children ages 2 to 4 years.

To determine the relative importance of the most common viral agents of diarrhea in the Guatemalan population aged 0 to 36 months, we studied the prevalence of excretion of Ad40 and Ad41 and rotaviruses in healthy and sick children from a rural community in Guatemala and in a group of patients hospitalized because of gastroenteritis.

MATERIALS AND METHODS

Rural population and field procedures. The rural children who we studied lived in Santá María de Jesús, a community of approximately 10,000 inhabitants that is 50 km from our central laboratories in Guatemala City and 2,050 m above

sea level. In Guatemala, there are two markedly different seasons: the rainy season, which extends from May to October, and the dry season, which extends from November to the end of April. The coolest months are November, December, and January, when the minimum temperature may reach 2°C in Santá María de Jesús; during the warm part of the year, March and April, the maximum temperature may reach 30°C. In the remaining months of the year, the daily ambient temperature fluctuates between 12 and 22°C.

For the duration of the study, from March 1987 to February 1988, there was no piped water system in the households in the community, and therefore, the inhabitants of Santá María de Jesús collected running water from public spigots or, during the rainy season, rain water in metal barrels. Eighty-two percent of the male heads of household worked in subsistence agriculture; literacy rates among individuals aged 10 years or older were 77% for males and 39% for females. Civil records for the preceding 5 years showed that the most common causes of mortality in preschool children were diarrhea or dehydration (25%) and pneumonia or respiratory infections (22%). Breast-feeding is common in the community, with 99% of children aged 11 months, 95% of children aged 12 to 17 months, 63% of children aged 18 to 23 months, 54% of children aged 24 to 29 months old, and 14% of children in their third year of life being breast-fed. Introduction of semisolid or solid foods begins between 3 and 6 months after birth, although sporadic ingestion of liquids is very common from the time of birth.

After informed consent was given by the parents, 194 children (96 males, 98 females; ages, 0 to 35 months) were kept under surveillance for diarrheal illnesses by twice-weekly home visits by field personnel. Whenever a case of

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TABLE 1. Distribution of infections caused by Ad40 and Ad41 and rotaviruses, by age

Age (mo)	No. with the following infections:				No. of specimens examined
	Ad40 and Ad41		Rotavirus		
	Diarrhea present	Asymptomatic	Diarrhea present	Asymptomatic	
0-5	4	6	1	2	111
6-11	14	1	3	0	125
12-17	15	1	6	0	136
18-23	14	1	6	0	120
≥24	7	0	2	0	149
Total	54	9	18	2	649 ^a

^a In eight instances, the exact age of the child was not recorded.

diarrhea was detected, the date of onset was recorded and a fecal sample was collected for microbiological studies, which included detection of bacteria, protozoa, rotaviruses, and Ad40 and Ad41. Sick children were visited every other day until the episode subsided (symptoms absent for 72 h). Routine treatments, which were given free of charge, included oral rehydration therapy and, when bloody diarrhea occurred in association with shigellae, trimethoprim-sulfamethoxazole.

A total of 458 fecal samples obtained from 143 children during 385 episodes of diarrhea were studied microbiologically during the 12-month period; additionally, we examined 191 stool samples taken from 128 of those same children when they were healthy (≥3 weeks without gastroenteritis) and from 51 individuals who participated for less than 2 months in the study and among whom diarrhea was not reported.

Hospital population. Fifty-seven children (males; ages, 8 to 31 months) who were admitted to the Pediatric Ward of the Roosevelt Hospital in Guatemala City between August 1986 and November 1988 as part of a study on dietary management of diarrhea were included in the microbiological studies; 10 children lived in rural areas, while the remaining 47 children came from urban areas and families with low socioeconomic status. Stool samples were collected on 2 consecutive days after admission.

Sample collection and laboratory procedures. Suspensions of fecal material were prepared in buffered Formalin, polyvinyl alcohol, selenite broth, phosphate-buffered saline, Cary-Blair medium, and veal infusion broth with 0.5% albumin and were handled as described previously (3). The

identification of Ad40 and Ad41 and rotaviruses was done in the material in veal infusion broth by an enzyme-linked immunosorbent assay (21) with commercially available kits (Adenoclone, type 40/41, and Rotaclone; Cambridge Bioscience, Worcester, Mass.) according to the specifications of the manufacturer. A sample was considered positive when the A_{450} exceeded 0.14 and was three times higher than those of the negative controls (veal infusion broth with 0.5% albumin). Determination of rotavirus serotypes was also done by enzyme-linked immunosorbent assay in the fecal suspension by using monoclonal antibodies (17). Other enteric pathogens were studied as described elsewhere (3).

RESULTS

Rural population. Of the 194 children from Santá María de Jesús studied, 43 (22.2%) excreted Ad40 and Ad41 and 20 (10.3%) shed rotaviruses. Four infections were documented in 3 children, and two different infections were documented in 11 children. In total, 63 infections by Ad40 and Ad41 were detected. Shedding of enteric adenovirus tended to be more common among males (26 of 96; 27.0%) than among females (17 of 98, 17.3%), although this tendency did not attain statistical significance ($\chi^2 = 2.668$; $P = 0.103$). Of the 26 infections documented among males, 21 (80.8%) resulted in diarrhea, while 13 (81.2%) of those among females were symptomatic. In regard to rotaviruses, 9 (9.4%) males and 11 (11.2%) females were positive. Two of these infections, one in each gender group, were asymptomatic. The age distribution of the infections and their outcomes are summarized in Table 1. Ad40 and Ad41 were found in the fecal samples taken during every month of the year; rotaviruses were not detected in August, September, or December (Fig. 1).

Of the 385 selected episodes of diarrhea studied, 301 (78.2%) lasted 1 to 13 days (short episodes), while 84 (21.8%) lasted 2 weeks or more (prolonged episodes). Overall, Ad40 and Ad41 were associated with 54 (14.0%) of the illnesses and rotaviruses were associated with 18 (4.7%) of the illnesses. Ad40 and Ad41 were found in 33 (11%) of the short episodes of diarrhea and 21 (25.0%) of the prolonged episodes of diarrhea, while rotaviruses were documented in 13 (4.3%) of the short episodes and 5 (5.9%) of the prolonged episodes of diarrhea (Table 2). In the 54 illnesses associated with Ad40 and Ad41, they were the only pathogens identified in 27 (50.0%) of the episodes, and the duration of the episodes ranged between 2 and 115 days. Infections by rotaviruses alone were documented in 11 (61.1%) of the 18 episodes, with durations ranging from 2 to 19 days.

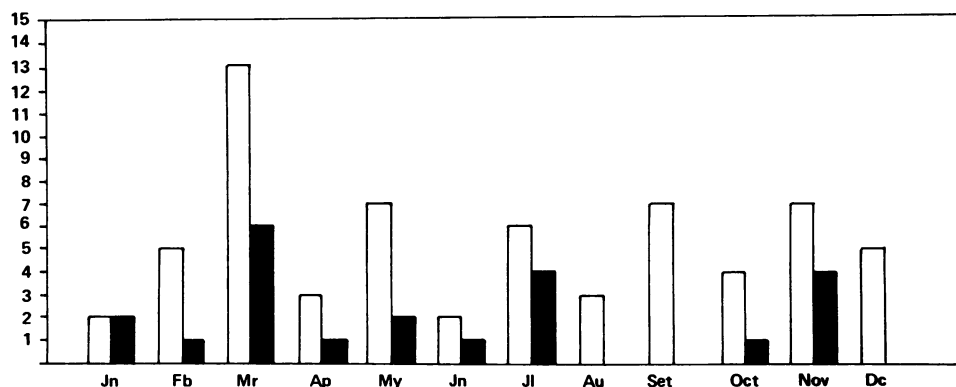


FIG. 1. Monthly distribution of infections by Ad40 and Ad41 (□) and rotavirus (■) in Santá María de Jesús.

TABLE 2. Characteristics of infections caused by Ad40 and Ad41 and rotaviruses

Type of infection	Infections caused by Ad40 and Ad41					Infections caused by rotaviruses				
	No.	Median duration (days)	Age (mo)		No. with coinfection	No.	Median duration (days)	Age (mo)		No. with coinfection
			Median	Range				Median	Range	
Symptomatic										
Total	54	10	17	0-34	27	17	8	17	4-26	6
Duration <14 days	33	6	14	0-33	11	12	4	17	4-26	2
Duration >14 days	21	20	18	6-34	16	5	26	15	8-21	4
Asymptomatic	9		3	1-22	1 ^a	2			0, 3	1 ^a

^a Ad40 and Ad41 and rotavirus.

Seventeen strains of rotaviruses, including the two strains from asymptomatic patients, were serotyped by enzyme-linked immunosorbent assay. In two assays, the background readings were too high to permit adequate interpretation of the results. In all of the 15 cases in which absorbance readings were appropriate, rotavirus serotype 2 was identified.

Hospital population. Of the 57 hospitalized patients, 36 (63.2%) of the children had viral infections. Rotaviruses were identified in 29 (50.9%) of the children, and Ad40 and Ad41 were detected in 15 (31.2%) of 48 children tested. Dual infections by Ad40 and Ad41 and rotaviruses were documented in eight children. The other pathogens identified are presented in Table 3. A total of 26 strains of rotaviruses were serotyped: 9 (34.6%) were identified as serotype 1, 12

(46.1%) were identified as serotype 2, 1 (3.8%) was identified as serotype 3, and 4 (15.4%) could not be differentiated as either serotype 2 or serotype 4.

Of the eight individuals with infections caused by rotavirus serotype 1, three (37.5%) were coinfecting with other potential pathogens (Table 4), while all nine children in whom rotavirus serotype 2 was detected were also infected with other diarrhea-inducing agents. In the eight children with infections caused by rotavirus serotype 1, vomiting occurred in seven (87.5%), dehydration occurred in five (62.5%), and fever occurred in six (75.0%). Although vomiting occurred in all nine children with infections caused by rotavirus serotype 2, dehydration was seen in only two (22.2%) children (one coinfecting with rotavirus serotype 1) and fever occurred in six (66.6%) children.

In the case of Ad40 and Ad41, 3 (20.0%) of the 15 children infected did not have any other enteric pathogen in their stools; only one reported vomiting in association with diarrhea and none presented either temperature above normal limits or dehydration. Of the 12 children with coinfections, 10 (83.3%) suffered vomiting, 7 (58.3%) were dehydrated, and 7 (58.3%) had a maximum rectal temperature above 37.9°C.

DISCUSSION

Infections caused by Ad40 and Ad41 are very common among Guatemalan children. This study is the first to deal with ambulatory rural children, and results showed that Ad40 and Ad41 are associated with 14% of all episodes of diarrhea tested, a rate three times higher than that of rotaviruses (4.7%). It is possible that the active surveillance of diarrhea cases by our field personnel detected mild illnesses among children in the community who otherwise would not have sought medical attention. Ad40 and Ad41, however, were found in association with 25% of prolonged episodes of diarrhea, which are known to have a strong negative effect on nutritional status and mortality (20). Furthermore, Ad40 and Ad41 were documented in every month of the year and every age category studied, suggesting that they may be easily transmitted in a small community where hygienic conditions are poor; their pathogenicity, however, was reduced in infants under 6 months of age, among whom only 40% of the infections were symptomatic; in older children, however, 94.3% of the infections were symptomatic. Breast-feeding, which is a common practice in Santá María de Jesús, may be an important factor in this regard, either because it reduces the infectious burden for the child or because of the antiinfectious properties of breast milk (4). Actually, breast-feeding may contribute to the elevated rate of asymptomatic infections caused by Ad40

TABLE 3. Enteropathogens identified in 57 inpatients

Pathogen	Positive cases	
	No.	%
Rotaviruses	29	50.9
Ad40 and Ad41	15 ^a	31.2
Adherent <i>Escherichia coli</i>		
Diffuse pattern	7	12.3
Localized pattern	1	1.8
Autoaggregative	1	1.8
Shigellae	6	10.5
<i>Giardia lamblia</i>	6	10.5
Toxigenic <i>Escherichia coli</i>		
Heat-stable toxin	4	7.0
Heat-labile toxin	1	1.8
Heat-stable and -labile toxins	1	1.8
<i>Salmonella enteritidis</i>	4	7.0
<i>Campylobacter jejuni</i>	4	7.0
<i>Cryptosporidium</i> spp.	4	7.0
Enteropathogenic <i>Escherichia coli</i>	3	5.3
<i>Aeromonas hydrophila</i>	1	1.8
<i>Entamoeba histolytica</i>	2	3.5
Negative	6	10.5

^a Only 48 children were tested.

TABLE 4. Characteristics of inpatients infected with Ad40 and Ad41 and rotaviruses

Infection	Age (mo)	Vomiting	Dehydration	Maximum rectal temp (°C)	Illness duration (days)
Ad40 and Ad41					
No coinfection					
	16	+	-	37.8	14
	16	-	-	37.6	3
	31	-	-	37.8	5
Coinfection					
Rotavirus (SND ^a)	14	-	-	37.2	8
Rotavirus (SND)	13	+	+	39.0	7
Rotavirus (SND)	14	+	+	39.0	10
Rotavirus (SND), adherent <i>Escherichia coli</i>	15	+	-	37.5	5
Rotavirus (SND), <i>Shigella</i> and <i>Campylobacter</i> spp.	25	+	+	37.8	8
Rotavirus serotype 1, adherent <i>Escherichia coli</i>	15	+	+	39.8	6
Rotavirus serotype 2, <i>Giardia</i> spp.	27	+	+	38.8	2
Rotavirus serotype 2, <i>Shigella</i> spp.	22	+	-	37.8	7
Adherent <i>Escherichia coli</i>	13	+	-	39.0	9
Toxigenic <i>Escherichia coli</i> (heat-stable toxin)	24	-	-	39.0	10
<i>Cryptosporidium</i> spp.	15	+	+	38.3	7
<i>Giardia lamblia</i>	18	+	+	37.4	2
Rotavirus serotype 1					
No coinfection					
	10	+	+	38.8	5
	13	+	-	38.0	11
	12	+	-	37.0	6
	23	-	-	37.4	3
	09	+	+	38.5	5
Coinfection					
Adherent <i>Escherichia coli</i> , Ad40 and Ad41	15	+	+	39.8	6
<i>Cryptosporidium</i> spp.	21	+	+	39.0	21
Rotavirus serotype 2	12	+	+	39.5	8
Rotavirus serotype 2					
Coinfection					
Ad40 and Ad41, <i>Giardia</i> spp.	27	+	+	38.8	2
Ad40 and Ad41, <i>Shigella</i> spp.	22	+	-	37.8	5
Enteropathogenic <i>Escherichia coli</i> O126	05	+	-	37.8	5
Toxigenic <i>Escherichia coli</i> (heat-labile toxin)	17	+	-	38.9	6
<i>Salmonella enteritidis</i>	08	+	-	37.5	7
Adherent <i>Escherichia coli</i>	08	+	-	38.5	7
<i>Campylobacter jejuni</i>	15	+	-	38.6	9
<i>Plesiomonas shigelloides</i> , enteropathogenic	08	+	-	38.7	11
<i>Escherichia coli</i> O20					
Rotavirus serotype 1	12	+	+	39.5	8
Rotavirus type 3, no coinfection					
	12	+	+	38.8	10

^a SND, Serotype not determined.

and Ad41 in Santá María de Jesús (4.7%; 9 of 191 infections), which is much higher than those reported for hospitalized controls in Thailand (0.6%) (9) and the United States (0.3 and 0.8% [1] and 1.4% [22]). In the hospital setting, Ad40 and Ad41 were associated with 31.2% of the illnesses studied. This value, although from only 48 individuals, was much higher than the rates reported for inpatients by Brandt et al. (1) in Washington, D.C., by Cevenini et al. (2) in Italy, and by Uhnoo and colleagues (18) in Sweden. In our study, Ad40 and Ad41 were second in importance only to rotaviruses, which were detected in 50.9% of the patients, as a cause of diarrhea. In general, the illness observed in the patients with infections caused solely by Ad40 and Ad41 tended to be milder than those seen when other microorganisms coinfect the patients.

The rates of rotavirus detection, both in the community and the hospital, did not differ from those reported from

other parts of the world (5, 11). Mata and colleagues (15), however, reported that the rate of rotavirus-associated diarrhea in children aged 0 to 3 years in another rural Guatemalan community was 10%, with outbreaks occurring from September to December of 2 consecutive years. The monthly rates fluctuated with no apparent trend in the 4 years of that study. The contrasts between those data and ours could be due to year-to-year variations in the epidemiology of rotavirus in rural communities of Guatemala. Nevertheless, the facts that all of the strains detected in the ambulatory children were serotype 2 and that those infections caused by serotype 2 seen in hospitalized children were always associated with other pathogens raise the possibility that serotype 2 has lower virulence compared with those of rotaviruses serotypes 1 and 3, which belong to subgroup II (10). Previous studies among Guatemalan infants (23) have also demonstrated that diarrhea and dehydration are more

commonly associated with subgroup II rotaviruses. Additionally, fever has been found to be more frequent among South African children who shed subgroup II rotaviruses (6). Observations in hospitalized children in Venezuela (7, 19) have shown that the duration of illnesses associated with subgroup II rotaviruses tends to be longer than those episodes of gastroenteritis caused by subgroup I rotaviruses. Other studies (8) suggesting that there is no apparent difference in pathogenicity among specific rotavirus serotypes have not taken into consideration either the severity of illness or coinfection with other enteric pathogens in analyses of the serotype-associated degree of pathogenicity and have only reported the proportions of symptomatic and asymptomatic infections.

In conclusion, Ad40 and Ad41 and rotaviruses are associated with at least 18% of diarrheal illnesses tested in children in a rural community and with 63% of illnesses tested in hospitalized patients admitted for gastroenteritis. More detailed studies, however, are necessary in order to determine the risk factors for infection by each viral serotype and the determinants of the outcomes once infections occur.

ACKNOWLEDGMENTS

This work was supported by project 596-0115 of the Regional Office of Central America and Panama of the U.S. Agency for International Development.

The technical assistance of Milagro de Castillo, Clara Luz de Celada, Mayra de Sánchez, Nora Lucrecia Coj, Laura de Mendez, Esperanza Perea, Delfina Curup, Toribia Lorenzo, Thelma de Juárez, Elia Yolanda Castillo, María Antonieta de Ruiz, Cristina de Campos, María Teresa Véliz, María Antonieta Monterroso, Aura Estela Díaz, Berta Lidia Veliz, Luis A. Rodríguez, and Magalí Marroquín is highly appreciated.

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