CONCISE COMMUNICATION

Outbreaks of Adult Gastroenteritis Traced to a Single Genotype of Rotavirus

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Between November 1998 and December 2000, the Centers for Disease Control and Prevention screened samples from 263 outbreaks of gastroenteritis in the United States and identified 3 that were associated with rotavirus among adults. Rotaviruses from each outbreak were further characterized by reverse-transcription polymerase chain reaction. Surprisingly, all specimens were of serotype G2, a strain that is, as determined by high-stringency hybridization analysis, genetically distinct in all 11 gene segments from the other common rotavirus strains in circulation. The unusual coincidence of identification of only G2 strains in these 3 outbreaks of rotavirus gastroenteritis among adults is similar to results from other studies, in which G2 strains were found in association with more-severe disease in children than other rotavirus serotypes and in association with outbreaks of diarrhea among adults in Japan. Although rotavirus infections in adults are relatively uncommon, which indicates that good overall protective immunity exists, the predominance of G2 strains in outbreaks that have occurred in adults suggests that natural immunity to more common strains does not always provide adequate heterotypic immunity to G2 strains. For the rotavirus vaccines under development, special attention may need to be paid to protection against G2 strains.

Rotavirus is the most common cause of severe diarrhea in children worldwide. More than 90% of children are infected with rotavirus by 3 years of age [1]. Whereas first infections in infants > 3 months of age are associated with diarrhea, subsequent infections are generally milder or asymptomatic [2]. In fact, subclinical rotavirus infections are very common among adults. Rotavirus diarrhea has been reported in parents and caretakers of children with rotavirus diarrhea, in elderly residents of hospital wards and long-term care institutions, in travelers, and in persons of all ages who live in isolated communities [3]. Unfortunately, the circulating rotavirus strain(s) have not been characterized where these outbreaks have been reported. We know little about why adults developed rotavirus diarrhea when they should have had immunity from multiple previous natural exposures in childhood.

Rotavirus is a triple-layered virus that has 11 gene segments in its inner core that code for either a structural or a nonstructural protein. Strains are commonly characterized by the 2 outer capsid proteins VP4 (protease activated or P type) and VP7 (glycoprotein or G type), and each of these types elicits a serotype-specific and cross-reactive neutralizing immune response [4]. Serotypes G1–G4 and, most recently, G9 are the 5 most prevalent strains in the world [5, 6]. The mechanism of natural protection to rotavirus is not known, but immunity may involve multiple gene targets. Infection with strains that share most or all gene products and are of a single genogroup [7] may provide better protection against other strains belonging to the same genogroup (even when the serotype is different) than against strains of another genogroup and serotype. For example, strains of the Wa genogroup may provide little protection against G2 strains, which have been found to have 11 genetically distinct gene segments on analysis by high-stringency hybridization.

Each year, the Viral Gastroenteritis Section at the Centers for Disease Control and Prevention (CDC) tests fecal specimens from individuals involved in outbreaks of gastroenteritis in the United States to assist in the identification of a causative agent. In many of these cases, no bacterial or parasitic pathogen is identified, and the most prevalent agent identified by reverse-transcription polymerase chain reaction (RT-PCR) in these outbreaks has been “Norwalk-like viruses” (NLVs) [8]. From January 1998 through December 2000, we screened specimens from 263 gastroenteritis outbreaks for NLVs, and specimens from only 32 (12.2%) of these outbreaks tested negative for NLVs [9]. In this study, we
further examined these 32 outbreaks of unknown cause for rotavirus, using antigen EIA, RT-PCR, and nucleotide sequencing.

Materials and Methods

In 1998, 1999, and 2000, we screened specimens from 73, 94, and 96 outbreaks, respectively, for NLVs by RT-PCR. Specimens from outbreaks in which all samples tested negative for NLVs were further screened by EIA for astrovirus (IDEIA Astrovirus; Dako) and for adenovirus and rotavirus (Adenoclone and Rotaclone; Meridian Diagnostics) [8]. In each year, specimens from a single NLV-negative outbreak contained rotavirus particles, as determined by electron microscopic examination; these findings were subsequently confirmed by EIA, and strains were characterized for G and P type by RT-PCR as described elsewhere [10, 11]. Specimens from each of these outbreaks had tested negative for bacterial and parasitic pathogens at the respective source state’s health department, which also performed epidemiologic investigations of the outbreaks.

Results

Outbreak 1: Hawaii nursing home. Between 26 November and 6 December 1998, 7 (28%) of 25 elderly residents in a privately owned skilled-nursing facility in Hawaii experienced at least 1 episode of diarrhea, with or without fever and vomiting; these episodes lasted 24–48 h (mean duration, 34 h; table 1). All 7 patients received medical care, and 1 patient was hospitalized for dehydration. No nursing staff or food handlers reported gastrointestinal symptoms during the outbreak, and the incubation period was estimated to be 48 h. A stool specimen was obtained from each patient. Neither contaminated food nor water could be implicated in the spread of infection, and investigators from the Hawaii Department of Health concluded that transmission was from person to person.

Outbreak 2: Maryland nursing home. Between 31 March and 13 April 1999, 26 (27%) of 96 elderly residents of a long-term care facility in Maryland experienced at least 1 episode of diarrhea, with or without fever and vomiting; these episodes lasted 2–168 h (mean duration, 29 h; table 1). None of the patients was hospitalized or received medical attention, and several employees were ill with gastroenteritis before the outbreak. Ten stool specimens were obtained from 9 patients, but none were obtained from employees. In the absence of an obvious food or water source, investigators from the Maryland Department of Health and Mental Hygiene concluded that the disease was transmitted from person to person.

Outbreak 3: Washington, DC, university. Between 27 March and 11 April 2000, 85 (1.6%) of 5453 students at a Washington, DC, university experienced >3 episodes of diarrhea and/or >2 episodes of vomiting within a 24-h period (table 1). Some patients reported fever and nausea. The illness had a mean duration of 96 h (range, 24–192 h). Of the 85 students affected, 53 (62%) sought medical attention, and 9 of those received intravenous fluids. All but 8 of the affected students resided on campus. Because food was the suspected vehicle of infection, 23 of the 29 employees of the university dining hall were interviewed, and several reported having gastroenteritis during the outbreak. Six stool specimens from students and 21 from employees were received for testing. The investigators from the Washington, DC, Department of Health identified contaminated dining-hall food as the source of infection [12].

Analysis of outbreaks. Outbreaks of rotavirus gastroenteritis in adults are not common. These 3 outbreaks represent 1% of 263 outbreaks for which samples were submitted to the CDC for testing and 9.4% of the 32 outbreaks for which NLVs were not detected. The 3 outbreaks occurred in different states and among young adults and elderly individuals, and the infection was believed to have been transmitted by food and by person-to-person contact (table 1). Of note, all occurred from November through April, timing which is consistent with the temporal patterns of the rotavirus season in the areas involved [1]. The outbreaks ranged in duration from 11 to 16 days.

The symptoms of acute gastroenteritis, including diarrhea, fever, and vomiting, were common among patients in all 3 outbreaks (table 1). Attack rates in the nursing homes were relatively high.

Table 1. Characteristics of 3 outbreaks of rotavirus diarrhea in adults in the United States, by location and type of institution.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Hawaii nursing home</th>
<th>Maryland nursing home</th>
<th>Washington, DC, university</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration, days</td>
<td>11</td>
<td>14</td>
<td>16</td>
</tr>
<tr>
<td>Suspected mode of transmission</td>
<td>Person to person</td>
<td>Person to person</td>
<td>Foodborne</td>
</tr>
<tr>
<td>Age range for patients, years</td>
<td>72–91</td>
<td>74–94</td>
<td>18–22</td>
</tr>
<tr>
<td>No. of persons ill/no. at risk</td>
<td>7/25</td>
<td>26/96</td>
<td>77/1641*</td>
</tr>
<tr>
<td>Attack rate, %</td>
<td>28</td>
<td>27</td>
<td>5</td>
</tr>
<tr>
<td>No. of persons who sought medical care</td>
<td>7</td>
<td>0</td>
<td>53</td>
</tr>
<tr>
<td>Duration of illness, h (mean)</td>
<td>24–48 (34)</td>
<td>2–168 (29)</td>
<td>24–192 (96)</td>
</tr>
<tr>
<td>Symptoms</td>
<td>D, F, V</td>
<td>D, F, V</td>
<td>D, F, N, V</td>
</tr>
</tbody>
</table>

NOTE. D, diarrhea; F, fever; N, nausea; V, vomiting.

*For students residing on campus.
(27%–28%), whereas the attack rate for the university outbreak was 5% (77/1641) for students residing on campus and 0.2% (8/3812) for students living off campus. The severity of the illness ranged from mild, in outbreak 2, in which no patients received medical attention, to more severe, in outbreak 1, in which all ill patients were treated for symptoms and 1 resident was hospitalized, and in outbreak 3, in which 53 of 85 ill students sought medical care and 9 received intravenous fluids.

A total of 22 fecal specimens from these outbreaks were submitted to the CDC for viral testing (table 2). Rotavirus-like particles were detected by electron microscopy in 5 of 6, 4 of 5, and 1 of 3 stool specimens from outbreaks 1, 2, and 3, respectively. Group A rotavirus was confirmed by EIA in 2 of 7, 5 of 9, and 3 of 6 samples and by RT-PCR in 3 of 7, 8 of 9, and 4 of 6 specimens from outbreaks 1, 2, and 3, respectively. In total, 5 (71%) of 7 specimens from outbreak 1, 8 (89%) of 9 specimens from outbreak 2, and 4 (67%) of 6 specimens from outbreak 3 tested positive for group A rotavirus.

Selected rotavirus strains from each outbreak were P- and G-typed, and, to our surprise, each outbreak was caused by rotavirus strain P[4],G2. To determine whether these G2 strains from adults were unusual variants or just typical G2 strains, we sequenced the VP4, VP7, and NSP4 genes of strains from outbreak 2 and compared the sequences to those of other G2 strains isolated from children in the United States who had been hospitalized with rotavirus gastroenteritis during the same time period as outbreak 2. No marked differences were observed (data not shown). Furthermore, in outbreak 3, 3 of 21 specimens from the dining-hall employees tested positive for rotavirus, and strains from all 3 specimens were P[4],G2 (data not shown). One of the rotavirus-positive employees was asymptomatic and assisted in preparation of the delicatessen sandwiches that were implicated as the suspected vehicle of the outbreak.

**Discussion**

In the United States, most outbreaks of gastroenteritis are associated with NLVs; such outbreaks occur more often during the winter and spring and are seen commonly among adults and often in nursing-home populations [8]. From 1998 to 2000, group A rotavirus was the causative agent in 3 (1%) of the 263 outbreaks of gastroenteritis for which the CDC examined samples for NLVs and from which only 32 (12.2%) were NLV negative. In the United States, rotavirus infection has a winter seasonality and is most frequently identified from November through April [1]. All 3 of the outbreaks we studied occurred during the rotavirus season. Two of the 3 outbreaks were identified in nursing homes among elderly patients and some nursing staff, and the third outbreak occurred among university students (18–22 years old) and staff at the university dining hall. The symptoms in these patients were similar, and ill persons reported diarrhea, fever, and/or nausea and vomiting. Transmission of rotavirus in the 2 nursing-home outbreaks was suspected to be from person to person, and transmission in the university outbreak was suspected to be by food prepared in the university dining hall. The most unusual finding in the present study is that rotavirus P[4],G2 strains were identified in all 3 outbreaks. Furthermore, a recent Japanese review identified 4 geographically and temporally distinct outbreaks of gastroenteritis among school-aged children (1 of 4 outbreaks) and adults 30–80 years old (3 of 4 outbreaks) in Japan during 2000, and, remarkably, all were associated with G2 strains [13–16]. The attack rates for the Japanese outbreaks (~11%–70%) were similar to those found here (5%–28%).

The mechanism(s) responsible for the apparent predominance of G2 outbreaks in adults is unknown, but it can be speculated that virulence and/or antigenic differences between strains could be involved. For example, G2 strains, which make up a relatively small proportion overall of the 5 common rotavirus serotypes, belong to a genetically distinct genogroup (DS-1), compared with the other 4 common strains, which belong in the Wa genogroup, as defined by a lack of cross-hybridization under stringent assay conditions [7]. These genetic differences also reflect antigenic differences between the strains, including the presence of unique G and P serotype antigens in G2 strains. Thus, infection with common strains of the Wa genogroup may provide better homotypic immunity against other Wa-like strains than it would against the G2 strains, resulting in more outbreaks of G2 in adults. Although we know of no direct evidence for genotype-specific immunity, serotype-specific immunity has been documented [4]. In addition, a report showing a relative lack of G2-specific neutralizing antibodies in adults supports the hypothesis that adults could be more susceptible to G2 infections [17].

Several studies have found also that G2 strains cause more-severe dehydrating diarrhea and, thus, may be more virulent [18,
19]. If this is true, the disproportionate number of G2 infections that occur in adults may reflect a combination of reduced heterotypic protection against the antigenically distinct G2 strains induced by infection with common strains of the Wa genogroup and intrinsic differences in the virulence of the strains themselves.

Our study has several limitations. Although we found that rotavirus was implicated in only 1% of the outbreaks for which samples were submitted, we only searched for the virus in those outbreaks in which no NLVs were identified. Therefore, we would have missed any outbreak caused by a mixed infection and underestimated the prevalence of infections associated with rotaviruses. In addition, not all of the specimens from each outbreak were positive for rotavirus. Serologic testing could have helped in confirming these results, but serum samples were not available for cases from these outbreaks. Furthermore, measurement of neutralizing antibodies in serum samples obtained during the acute phase of infection might have provided a clue as to whether titers of serotype-specific antibody to G2 strains were relatively low, compared with the titers associated with other strains, which could have helped to explain our results. The mode of transmission of rotavirus in each of these outbreaks was investigated, but the conclusions could not be proven, so we remain uncertain of how to prevent the spread of these outbreaks in the future. However, our report, along with others from the United States and Japan, suggests that rotavirus can be transmitted by contaminated food [11, 16]. Finally, no attempt to analyze possible differences in the severity of symptoms within individual outbreaks was made; thus, we cannot exclude the possibility that some outbreaks were characterized by milder symptoms.

In this study, we demonstrate that group A rotavirus can cause epidemic gastroenteritis in adults and in elderly individuals and that, when it does, genotype G2 strains are likely to be involved. Therefore, reference laboratories should consider rotavirus as a possible causative agent for outbreaks of diarrhea in adults. Once rotavirus is identified, the strains should be characterized for G and P types. From our results, we would suspect that adults and elderly individuals might have lower levels of G2-specific neutralizing antibody to rotavirus, compared with levels of antibody to the other common strains, a hypothesis that could be tested easily. Furthermore, when future vaccines are designed, antigens from the G2 genogroup may need to be included to ensure protection against these distinct strains. Use of vaccines that do not provide specific protection against G2 strains might lead to a risk of some vaccine failures in rotavirus seasons in which G2 strains are prevalent.

References