A Large Outbreak of Brainerd Diarrhea Associated with a Restaurant in the Red River Valley, Texas

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(See the brief report by Vugia et al. on pages 62–4)

Background. In June 1996, an outbreak of chronic diarrhea was reported to the Texas Department of Health (Austin).

Methods. We initiated active case finding, performed 2 case-control studies, and conducted an extensive laboratory and environmental investigation.

Results. We identified 114 persons with diarrhea that lasted ≥4 weeks. Symptoms among 102 patients who were studied included urgency (87%), fatigue (86%), fecal incontinence (74%), and weight loss (73%); the median maximum 24-h stool frequency was 15 stools. Diarrhea persisted for ≥6 months in 87% and for >1 year in 70% of patients who were observed. Fifty-one (89%) of 57 ill persons had eaten at a particular restaurant within 4 weeks before onset, compared with 8 (14%) of 59 matched control subjects (matched odds ratio [OR], undefined; 95% confidence interval [CI], 11.2–∞). At the restaurant, patients were more likely than their unaffected dining companions to have drunk tap water (OR, 2.8; 95% CI, 1.0–9.9) and to have eaten several specific food items, and they were less likely to have drunk iced tea made from boiled water and store-bought ice (OR, 0.3; 95% CI, 0.05–1.0). A multivariable model that included consumption of tap water and salad bar tomatoes best fit the data. The restaurant had multiple sanitary and plumbing deficiencies. Extensive laboratory and environmental testing for bacterial, parasitic, mycotic, and viral agents did not identify an etiologic agent.

Conclusions. The clinical, laboratory, and epidemiologic findings are consistent with those of previous outbreaks of Brainerd diarrhea. To our knowledge, this is the largest reported outbreak of Brainerd diarrhea associated with a restaurant.

Brainerd diarrhea is an idiopathic syndrome characterized by the acute onset of explosive, watery diarrhea that lasts many months and that is refractory to antimicrobial treatment. The syndrome is named for Brainerd, Minnesota, the site of the first recognized outbreak in 1983 [1]. Since then, 8 outbreaks have been documented [2–6]. Raw milk [1] and untreated water [2, 3, 6] have been implicated as vehicles of transmission; however, a causative agent has never been identified.

Fannin County, Texas, is a farming community of ~27,000 residents located in the Red River Valley, 70 miles northeast of Dallas. In June 1996, area gastroenterologists notified the Texas Department of Health (Austin) of an increase in the number of patients with chronic diarrhea. Illness was characterized by severe, watery diarrhea lasting ≥4 weeks; extensive evaluations of several patients had not identified an etiology. This report describes the investigation of this outbreak, which is, to our knowledge, the second largest reported outbreak of Brainerd diarrhea.

METHODS

Case finding. Potential cases were identified by direct patient reports and calls to area physicians, hospitals, and other patients. In addition, the Texas Department of Health...
of Health issued a press release to local media encouraging residents of Fannin County with diarrhea to contact the health department. For the purposes of our investigation, we defined Brainerd diarrhea as diarrhea ($\geq$3 loose stools in 24 h) of unknown etiology that lasted $\geq$4 weeks and that began after 31 March 1996 in a Fannin County resident or visitor. We reviewed all available medical records, laboratory results, and pathology and procedure reports pertaining to each case.

**Case-control studies.** To identify risk factors for illness, we conducted 2 case-control studies. We limited case-control study patients to those interviewed before 1 September 1996, to increase the likelihood that exposures would be accurately recalled. Both studies were conducted by telephone using written questionnaires. The first case-control study was limited to patients who met the case definition, were Fannin County residents, and were the index case in their household. One age- and telephone exchange–matched control subject was recruited for each patient. Eligible control subjects were within 15 years of the matched patient’s age and denied having diarrheal illness in the previous 3 months. Patients were asked about a variety of exposures within Fannin County, including water, food sources (e.g., groceries and restaurant food), contact with pets and livestock, and travel during the 4 weeks before illness onset; control subjects were asked about the same exposures during a standard referent period (the month of June 1996).

The second case-control study evaluated specific food and drink exposures at a local restaurant (restaurant X) implicated as the source of the outbreak in the first case-control study. All patients who met the case definition, were the index case in their household, and reported eating at restaurant X in the 4 weeks before becoming ill were recruited for the study. One matched control subject was selected from unaffected friends or family members who had shared a meal with the patient at restaurant X in the 4 weeks before illness onset. A questionnaire compiled from the restaurant X menu was administered to all patients and control subjects by telephone.

**Follow-up studies.** To determine the duration and long-term burden of illness, we attempted to reinterview all patients by telephone in December 1996, July 1997, and December 1997. Patients were asked about ongoing symptoms, medications, visits to health care providers, diagnostic procedures, and the number of days they had been unable to conduct usual activities because of illness.

**Laboratory investigation.** Laboratory results were abstracted from chart reviews for 71 patients. Gastrointestinal tissue biopsy specimens from 23 patients were examined at the Centers for Disease Control and Prevention (CDC; Atlanta, GA) for histopathological changes using routine histochemical stains. Various laboratory methods were used to detect and identify bacterial, parasitic, mycotic, and viral agents in stool, biopsy, and gastrointestinal aspirate specimens. These included culture, microscopic examination, special histochemical stains, cell culture, immunoassay, and molecular techniques, as indicated in table 1.

**Environmental investigation.** On 29 July 1996, water from a tap in the restaurant’s kitchen was analyzed for the presence of *Cryptosporidium* and *Giardia* species by Texas Department of Health laboratories [7]. Hot and cold water from the sink preparation room, the water dispenser tap from the drink station, and an in-line filter and water filtrate from the ice machine were collected and sent to the CDC for amoebic and fungal culture. A sample of the water filtrate from the ice machine filter was examined for protozoa by microscopy [8]. Water samples were collected for measurement of total dissolved solids and total and free chlorine. Total and fecal coliform bacteria counts were measured in water samples from restaurant X, the municipal water plant, and the Texas Department of Health Fannin County field office. The water treatment plant was inspected, water samples were tested, and water-quality reports were reviewed.

**Statistical analysis.** We used conditional logistic regression to calculate maximum likelihood estimates of matched ORs, exact 95% CIs, and $P$ values with use of SAS software, version 9.1 (SAS Institute). We used case exposure ($>50\%$) and significance of association (exact $P$ value of $<.1$) as initial screens for building the multivariable model, with forward selection, backwards selection, and sensitivity analysis used for missing values.

**RESULTS**

**Case finding.** We identified 117 patients who met the case definition. Eleven patients identified only after considerable local press coverage of the implicated restaurant and 4 patients who were unable to answer questions because of hearing loss or dementia were excluded from further study. Dates of illness onset for the remaining 102 patients ranged from 1 April through 1 August 1996, with a peak occurring in late May (figure 1). Sixty-nine patients were Fannin County residents, and 33 had visited Fannin County. The median age of patients was 63 years (range, 30–90 years), and 59% were female.

Ninety patients (88%) reported having watery diarrhea without visible blood (table 2). The median maximum number of stools per 24-h period was 15 (range, 5–35 stools). Frequently associated symptoms included urgency (87%), fatigue (86%), gas (85%), and fecal incontinence (74%). Weight loss was reported by 73% of patients, with a median loss of 4.5 kg (range, 1.35–22.5 kg). Few reported vomiting (15%) or fever (6%).

Ninety-three patients (91%) sought medical treatment within 5 months after onset, and 14 (14%) were hospitalized, mostly for dehydration. Forty-eight patients (48%) underwent endoscopic procedures, most frequently colonoscopy. Most patients (71%) were treated with antimicrobial medications, includ-
<table>
<thead>
<tr>
<th>Specimen, investigated etiologic agent</th>
<th>Assay</th>
<th>No. of samples tested</th>
<th>No. of samples with positive results</th>
<th>Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ova and parasites*</td>
<td>Microscopy</td>
<td>8</td>
<td>0</td>
<td>TDH, 1996</td>
</tr>
<tr>
<td>Listeria monocytogenes, Staphylococcus aureus, diarrheagenic E. coli, Aeromonas hydrophila, Plesiomonas shigellodes, and Bacillus cereus</td>
<td>Culture</td>
<td>16</td>
<td>0</td>
<td>[11, 14–17]</td>
</tr>
<tr>
<td>Campylobacter species, including non-jejuni/coli species</td>
<td>Culture</td>
<td>28</td>
<td>0</td>
<td>Campylobacter-like organisms (but not Campylobacter curvae), 2 [12]</td>
</tr>
<tr>
<td>CDC group DF-3</td>
<td>Culture</td>
<td>16</td>
<td>0</td>
<td>[18]</td>
</tr>
<tr>
<td>Anaerobic bacteria</td>
<td>Culture</td>
<td>9</td>
<td>0</td>
<td>Clostridium butyricum, 2; Clostridium bifermentans, 2; Clostridium coliiiforme, 1; Clostridium sorae, 2; Clostridium perfringens, 1; Clostridium species, 2; Bacteroides thetaiotaomicron, 2 [19–21]</td>
</tr>
<tr>
<td>Yeast</td>
<td>Culture</td>
<td>11</td>
<td>0</td>
<td>Candida albicans, 5; Candida parapsilosis, 1; Candida tropicalis, 1; Candida zeylanoides, 1; Rhodotorula glutinis, 1 [22, 23]</td>
</tr>
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<td>Caliciviruses</td>
<td>RT-PCR</td>
<td>11</td>
<td>0</td>
<td>Calicivirus particles, 11 [24]</td>
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<tr>
<td>Viral particles and other microbes</td>
<td>Negative stain electron microscopy</td>
<td>35</td>
<td>0</td>
<td>Small, round, virus-like particles, 9; small, round structured viruses (Norovirus-like), 4; Microsporidia-like or bacterium-like particles, 3 [25, 26]</td>
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<td>Protozoa</td>
<td>Trichrome stain</td>
<td>50</td>
<td>0</td>
<td>[8]</td>
</tr>
<tr>
<td>Amebae</td>
<td>Culture</td>
<td>49</td>
<td>0</td>
<td>Free-living amoebae, 4 [27]</td>
</tr>
<tr>
<td>Cryptosporidium and Cyclospora species</td>
<td>Kinyoun modified acid fast stain</td>
<td>52</td>
<td>0</td>
<td>[28]</td>
</tr>
<tr>
<td>Cryptosporidium and Giardia speciesb</td>
<td>IFA</td>
<td>51</td>
<td>0</td>
<td>...</td>
</tr>
<tr>
<td>Cryptosporidium speciesc</td>
<td>EIA</td>
<td>49</td>
<td>0</td>
<td>...</td>
</tr>
<tr>
<td>Giardia speciesc</td>
<td>EIA</td>
<td>49</td>
<td>0</td>
<td>...</td>
</tr>
<tr>
<td>Cyclospora species</td>
<td>Safranin stain</td>
<td>49</td>
<td>0</td>
<td>[29]</td>
</tr>
<tr>
<td>Stool and duodenal tissue and aspirate specimens: microsporidia</td>
<td>PCR</td>
<td>10 stool specimens, 3 duodenal tissue and aspirate specimens</td>
<td>0</td>
<td>[30–33]</td>
</tr>
<tr>
<td>Duodenal tissue and aspirate specimens: amoebae</td>
<td>Culture</td>
<td>3</td>
<td>0</td>
<td>[27]</td>
</tr>
<tr>
<td>Duodenal tissue, aspirate, and colon aspirate specimens: microsporidia</td>
<td>Gram-chromotrope stain</td>
<td>5 duodenal tissue and aspirate specimens, 2 colon aspirate specimens</td>
<td>0</td>
<td>[34]</td>
</tr>
<tr>
<td>Duodenum, ileum, cecum, and colon tissue specimens</td>
<td>Electron microscopy</td>
<td>9</td>
<td>Spore-like structures, 6</td>
<td>[35]</td>
</tr>
<tr>
<td>Duodenum and sigmoid-colon specimens: viral particles and other microbes</td>
<td>Negative stain electron microscopy of cell culture aspirates</td>
<td>3</td>
<td>Spore-like structures, 2</td>
<td>[35]</td>
</tr>
</tbody>
</table>

**NOTE.** CDC, Centers for Disease Control and Prevention; DF-3, dysgonic fermenter 3; IFA, immunofluorescent antibody; TDH, Texas Department of Health.

*a* Tested at TDH Laboratory, Clinical Bacteriological Section (Austin, TX).

*b* Tested with use of Merifluor Crypto & Giardia direct IFA kit (Meridian Bioscience).

*c* Tested with use of ProSpecT Giardia/Cryptosporidium-EIA kits (Alexon).

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ing metronidazole, fluoroquinolones, paromomycin, and fluconazole, without self-reported improvement. Fifty-six patients (57%) reported partial relief of symptoms with opiate antimitotility agents.

The median incubation period for 32 patients who had visited the restaurant only once was 11 days (range, 1–37 days). Seven patients were household contacts of other patients; however, all 7 had eaten at restaurant X before becoming ill. Therefore, no cases of secondary transmission were documented. No restaurant employees were ill.

**Case-control studies.** Eighty-five (83%) of the 102 patients were interviewed before September 1996 and were potentially eligible for inclusion in the case-control studies. The first case-control study included 59 patients and matched control subjects who resided in Fannin County. Illness was strongly associated with eating at restaurant X during the 4 weeks before onset (OR, undefined; 95% CI, 11.2–∞). Overall, 51 (89%) of 57 patients but only 8 (14%) of 59 control subjects reported eating at restaurant X. In contrast, patients were no more likely than control subjects to eat at any of 16 other local restaurants, including 5 on the same city block as restaurant X. Sixteen (80%) of 20 patients who were not Fannin County residents also reported eating at restaurant X before becoming ill. Included in this group were travelers whose only stop in Fannin County was to eat at restaurant X. There was no association between illness and other exposures, such as the consumption of raw milk, food or water source, contact with animals, or travel.

Fifty (81%) of 62 patients who ate at restaurant X and who had index cases in their households were included in the second case-control study. The remaining 11 eligible patients were excluded, because no unaffected control subjects who ate at restaurant X with these case patients were available. In univariate analysis, patients were more likely than control subjects to have drunk tap water and to have eaten tomatoes and chicken at restaurant X (table 3). Conversely, patients were less likely to report drinking iced tea. Thirty-three patients (67%), compared with 23 control subjects (47%), ate tomatoes from the salad bar (OR, 2.7; 95% CI, 1.0–8.3), and 38 patients (81%), compared with 39 control subjects (63%), ate chicken (OR, 2.6; 95% CI, 0.9–9.3). Among the 2 beverages, tap water was reportedly consumed by 32 (65%) of 49 patients and by 22 (45%) of 49 control subjects (OR, 2.8; 95% CI, 1.0–9.9), whereas 30 (60%) of 50 patients and 38 (76%) of 50 unaffected meal companions reported drinking iced tea (OR, 0.3; 95% CI, 0.05–1.0). The iced tea was made from restaurant X tap water that was boiled and, because the restaurant’s ice machine had been broken since February 1996, from ice purchased from an outside supplier.

Three foods associated with illness—seafood salad, fish, and pineapple—were consumed by, at most, 40% of case patients and were excluded from further analysis. When multivariable models were constructed including tomatoes, chicken, water, and iced tea as candidates, a final model containing only water and tomatoes best fit the data, with an exact joint significance level of .02 and adjusted parameter estimates of 2.9 for water (95% CI, 0.9–11.2) and of 2.6 for tomatoes (95% CI, 0.9–9.0).

**Follow-up studies.** Six months after the initial investigation, 82 (87%) of 94 patients contacted reported persistent diarrhea. At 13 and 19 months after illness onset, 54 (70%) and 32 (42%) of 77 patients contacted, respectively, reported...
uniformly negative. Only 2 of 28 specimens tested yielded biopsy specimens was largely unrewarding (table 1). Results of interference with daily activities lasted a median of 26 weeks, and attendance at social functions, and 21 (66%) of 32 em-

ability to perform daily activities, including household chores stated that the illness had significantly interfered with their procedure, and 1 patient reported undergoing 6 colonoscopies.

Forty-eight patients (62%) had undergone at least 1 endoscopic movement had decreased to a median of 5 per day (range, 1–19 months). Among those who reported persistent tion of symptoms, the median duration of illness was 15 months continued diarrhea. For those who reported complete resolution of symptoms, the median duration of illness was 15 months (range, 1–19 months). Among those who reported persistent symptoms at 19 months, the maximum number of bowel movements had decreased to a median of 5 per day (range, 1–12 bowel movements per day).

By 19 months after illness onset, 71 (92%) of 77 patients had visited a physician, for a median of 8 visits per patient. Forty-eight patients (62%) had undergone at least 1 endoscopic procedure, and 1 patient reported undergoing 6 colonoscopies and 6 upper endoscopies. Sixty-seven (87%) of 77 patients stated that the illness had significantly interfered with their ability to perform daily activities, including household chores and attendance at social functions, and 21 (66%) of 32 employed patients reported missing work because of illness. Interference with daily activities lasted a median of 26 weeks, and employed patients missed a median of 23 days of work.

Laboratory investigation. The results of biochemical, hematologic, and imaging studies from 71 patients’ medical records were largely unremarkable. Small numbers of fecal leukocytes were reported in 10 (48%) of 21 patients. Four (57%) of 7 patients had a positive qualitative fecal fat test result; however, the result of a subsequent quantitative fecal fat study in 1 patient was negative. Hypokalemia was documented in 18 (38%) of 48 patients, and 7 (44%) of 16 patients had mildly increased erythrocyte sedimentation rates. No other laboratory abnormalities were consistently reported.

Culture and examination of stool, gastrointestinal aspirate, and biopsy specimens was largely unrewarding (table 1). Results of tests for bacterial, viral, and parasitic pathogens were almost all uniformly negative. Only 2 of 28 specimens tested yielded Campylobacter-like organisms. Neither isolate was Campylobacter jejuni or Campylobacter coli; both most closely resembled C. concisus. Several species of anaerobic bacteria were identified, with no predominant strain. Candida albicans was recovered from 5 of 11 specimens; however, the isolates had distinct PFGE patterns. Free-living amoebae were cultured from 4 of 49 specimens. Electron microscopy revealed particles resembling small round viruses, small round structured viruses, and spore-like structures suggestive of microsporidia in gastrointestinal tissue biopsy and cell culture aspirate samples. However, RT-PCR for caliciviruses in stool specimens and microscopic examination, culture, and PCR tests for microsporidia in stool, tissue biopsy, and aspirate specimens yielded negative results.

Endoscopic and histopathologic findings were consistent with Brainerd diarrhea [9]. Endoscopic procedure reports described abnormal features in 22 (79%) of 28 colonoscopies, primarily in the ascending colon (13 [46%]). Colitis was the most commonly reported lesion, noted in 17 colonoscopy reports (61%). Twelve esophagoduodenoscopy reports describe atrophic gastritis (9 reports) and/or duodenitis (6 reports). At the CDC, examination of 14 (82%) of 17 colon biopsy specimens revealed intraepithelial lymphocytosis typical of Brainerd diarrhea [9]. One ileal biopsy specimen had predominant lymphocytosis; 3 were normal. Two small bowel biopsy specimens and all 5 duodenal biopsy specimens showed lymphocytic infiltrates. One gastric biopsy specimen had increased lymphocyte and plasma cell infiltrates and organisms compatible with Helicobacter pylori, as determined by Giemsa stain. Two other gastric biopsy specimens had no significant histopathologic changes.

Environmental investigation. The restaurant was inspected on 29 July, 12 days after closing because of declining patronage and after all food items had been removed. Among other sanitary deficiencies, the inspection identified a large quantity of dark material in a water filter in the line serving the ice machine. Immediate examination of this material by light microscopy revealed numerous freshwater organisms, including rotifers, diatoms, and algae. Although it was reported that the ice machine had not been in use since March, it was still connected to a water dispenser that was the primary source of water for customers. There was no device to prevent backflow of water from the ice machine filter into the water dispenser line. Cultures of water specimens from the dispenser tap and from the ice machine filter both yielded Pseudallescheria boydii, a fungal marker of organic contamination. Cultures of water samples collected from 5 other taps at restaurant X did not yield P. boydii. Free-living amoebae were cultured from the ice machine filter water sample but not from tap water samples.

The restaurant was served by the chlorinated municipal system. There were no known interruptions in service to the restaurant before the outbreak, and no secondary water sources were identified. The filtration test yielded no Giardia or Cryptosporidium cysts. Coliform bacteria were not detected in restaurant water samples. Free chlorine levels in water samples collected on 21 August were 2.8 mg/L at the treatment plant, 0.5 mg/L at the health department, and 0.15 mg/L at the restaurant.

Table 3. Frequency of selected food exposures among restaurant X patrons with Brainerd diarrhea and their unaffected meal companions, Fannin County, Texas, 1996.

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Case patients</th>
<th>Control subjects</th>
<th>Matched OR (95% CI)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iced tea</td>
<td>30/50 (60)</td>
<td>38/50 (76)</td>
<td>0.3 (0.05–1.0)</td>
<td>.06</td>
</tr>
<tr>
<td>Water</td>
<td>32/49 (65)</td>
<td>22/49 (45)</td>
<td>2.8 (1.0–9.9)</td>
<td>.06</td>
</tr>
<tr>
<td>Tomato</td>
<td>33/49 (67)</td>
<td>23/49 (47)</td>
<td>2.7 (1.0–8.3)</td>
<td>.05</td>
</tr>
<tr>
<td>Chicken</td>
<td>38/47 (81)</td>
<td>31/49 (63)</td>
<td>2.6 (0.9–9.3)</td>
<td>.1</td>
</tr>
<tr>
<td>Seafood salad</td>
<td>20/50 (40)</td>
<td>8/50 (16)</td>
<td>5.0 (1.4–26.9)</td>
<td>.008</td>
</tr>
<tr>
<td>Fish</td>
<td>17/49 (35)</td>
<td>7/49 (14)</td>
<td>4.3 (1.2–23.7)</td>
<td>.02</td>
</tr>
<tr>
<td>Pineapple</td>
<td>17/50 (34)</td>
<td>7/49 (14)</td>
<td>3.5 (1.1–14.6)</td>
<td>.03</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Exposure</th>
<th>No. of subjects with exposure/no. with available data (%</th>
<th>Matched OR (95% CI)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iced tea</td>
<td>30/50 (60)</td>
<td>0.3 (0.05–1.0)</td>
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<td>Water</td>
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<td>.03</td>
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</tbody>
</table>
DISCUSSION

Since 1983, eight outbreaks of Brainerd diarrhea have been reported, 7 of which have been in the United States [1–4, 6]. Although the causative agent remains unidentified, the epidemiologic and clinical findings are remarkably similar, strongly suggesting a common etiologic process [6].

The clinical and epidemiologic features of this outbreak are consistent with previous reports of Brainerd diarrhea [1–6]. Like other Brainerd diarrhea outbreaks, this one occurred in a rural setting and affected primarily elderly persons. The majority of patients had symptoms that lasted >1 year, none reported significant improvement with antimicrobial therapy, and extensive evaluation failed to identify known causes of chronic diarrhea. Biopsies of colonic tissue from many patients revealed intraepithelial lymphocytosis, a finding typical of Brainerd diarrhea [9].

In our investigation, illness was strongly associated with a single restaurant. This exposure was highly statistically significant in a case-control study of county residents and accounted for 80% of cases among county visitors. A specific vehicle at the restaurant was not definitively identified; however, the epidemiologic and environmental evidence suggests it may have been contaminated tap water. Water has been implicated in 3 previous outbreaks of Brainerd diarrhea [2, 3, 6]. Nearly two-thirds of ill patrons recalled drinking tap water at the restaurant, an exposure reported by fewer than one-half of their meal companions who remained healthy. Conversely, unaffected meal companions were significantly more likely to have drunk iced tea, which was made from boiled water and store-bought ice. The environmental investigation revealed a cross-connection between a broken ice machine and the drinking water dispenser line, which contained a diverse collection of fresh water organisms.

Illness among restaurant patrons was also associated with 4 food items. One food item, salad bar tomatoes (consumed by 67% of patients), was also implicated in a previous outbreak of Brainerd diarrhea [3]. As in that outbreak, the tomatoes may have been contaminated with water when washed before slicing or when moistened while on the salad bar. No more than 40% of all study cases recalled exposure to any of the 3 other food items, which are, therefore, less likely to have been the source of illness.

As in previous investigations of Brainerd diarrhea, we failed to identify the etiologic agent. The relative absence of secondary transmission in this and previous reports suggests it is not readily transmitted from person to person. In our study and in 2 previous waterborne outbreaks ([2] and Oklahoma State Health Department, unpublished data), drinking beverages made from boiled water was protective, indicating that boiling may inactivate the Brainerd agent.

A wide range of bacterial, viral, and parasitic pathogens cause chronic diarrhea [6]. Although particles resembling viruses were seen in approximately one-third of stool specimens examined by electron microscopy, their identity could not be established by PCR testing. Electron microscopy also revealed spore-like particles that resembled microsporidia in stool and tissue biopsy specimens; however, no microsporidia were identified by PCR, conventional microscopy, or culture.

Our investigation had several limitations. Because there is no diagnostic test for Brainerd diarrhea, some patients with chronic diarrhea due to other causes or with Brainerd diarrhea from another source might have been included in the study. However, the effect of this misclassification would be to bias our study against finding an association between illness and any one exposure, such as eating at restaurant X. Because the diagnosis of chronic diarrhea requires at least 4 weeks of symptoms, patients were generally identified and interviewed at least 1 month, and sometimes several months, after their potential exposure. To reduce the effects of recall bias associated with such long recall periods, we restricted the case-control study to patients who were interviewed by 1 September, excluded patients who were identified after considerable press coverage of the implicated restaurant, and asked control subjects about exposures during the month before the investigation.

The costs of Brainerd diarrhea in terms of direct medical expenses and lost productivity are considerable. Yet, despite much effort, the etiologic agent remains unknown, and other outbreaks are likely to occur. Our hope of identifying the Brainerd agent lies ultimately in enhancing surveillance for early detection and prompt investigations of clusters of chronic diarrhea and in continuing the development and application of more-sophisticated laboratory techniques, such as molecular methods for pathogen discovery [10, 36].

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Potential conflicts of interest. All authors: no conflicts.

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