OUTBREAK OF EOSINOPHILIC MENINGITIS ASSOCIATED WITH DRINKING RAW VEGETABLE JUICE IN SOUTHERN TAIWAN

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Abstract. The most common cause of eosinophilic meningitis is the rat lungworm Angiostrongylus cantonensis, a parasite that is endemic in the southeast Asian and Pacific regions. Outbreaks of eosinophilic meningitis associated with drinking raw vegetable juice are rarely reported, even in regions of endemic infection. We performed a cohort study among Taiwanese with eosinophilic meningitis who drank raw vegetable juice within three months of the onset of the outbreak. Clinical manifestations, laboratory examinations, and outcomes were prospectively followed. Five native Taiwanese met the case definition of eosinophilic meningitis. Specific antibodies to A. cantonensis were detected in the serum of five of the patients and in the cerebrospinal fluid (CSF) of four of the patients. Central nervous system manifestations included headache (n = 5 [100%]), Brudzinski’s sign/stiff neck (n = 5 [100%]), hyperesthesia/paresthesias (n = 5 [100%]), and cranial nerve palsy (n = 1 [20%]). Laboratory findings included peripheral (n = 5 [100%]) and CSF eosinophilia (n = 4 [80%]), transient increases in the white blood cell count (n = 1 [20%]), and in serum levels of creatine kinase (n = 1 [20%]). Meningeal enhancement, as well as high signal intensity, at the subcortical white matter on T2 weighted and fluid attenuated inversion recovery images were observed on magnetic resonance imaging in four patients. There were three episodes of relapse during treatment and all resolved with after a lumbar puncture and/or administration of steroids. At the 12-month follow up, all five patients had recovered without neurologic sequelae. Risk factors identification showed that consumption of raw vegetable juice was associated with illness (Pearson correlation test r = 0.867, P = 0.01). There was association between the presence of raw vegetable juice and CSF eosinophilia (Spearman’s correlation test r = 0.816, P = 0.004).

INTRODUCTION

Angiostrongylus cantonensis, also known as the rat lungworm, is the major cause of eosinophilic meningitis in the Pacific Islands and southeast Asia.1-4 Rats serve as the definitive host of the nematode. Humans are infected by ingestion of freshwater and terrestrial snails and slugs, or transport hosts, such as freshwater prawns, frogs, fish, and planarians.5-7 Infection can be acquired by the consumption of fresh produce, such as lettuce, contaminated with these intermediate or transport hosts.8,9 The major intermediate hosts in Taiwan are the African giant snail (Achatina fulica) and the golden apple snail (Ampullaria canaliculatus). Field studies in southern Taiwan have shown that 14–31% of Ampullaria canaliculatus contain third-stage larvae of A. cantonensis.10 To date, Taiwan has recorded hundreds of cases of eosinophilic meningitis with reports coming from nearly all parts of the island. In contrast to findings in other geographic areas,3,11 most of the cases occurred among children. There was usually a history of eating or playing with snails or slugs. However, most of the cases were recorded before the 1970s. Only scattered cases reports were found during the past three decades. In 1998 and 1999, we reported two outbreaks of eosinophilic meningitis caused by A. cantonensis infection among 17 adult male Thai laborers who had eaten raw golden apple snails.12,13 In this report, we describe an outbreak among family members associated with a health drink consisting of raw vegetable juice.

METHODS

Description of the outbreak. On August 6, 2001, a 30-year-old woman visited the emergency department of Kaohsiung Veterans General Hospital with a 14-day history of headache, nausea, vomiting, neck stiffness, facial palsy, and paraesthesias. Cerebrospinal fluid (CSF) analysis was consistent with a diagnosis of aseptic meningitis. However, her hemogram showed mild leukocytosis with 62% granulocytes, 13% lymphocytes, and 20% eosinophils. She was kept under observation at the emergency department. The next day, three of her family members visited the emergency department with complaints of headache, neck stiffness, nausea/vomiting and paresthesias for the past 2–3 weeks. Lumbar punctures were done and all family members had eosinophilic meningitis with peripheral eosinophilia. On August 8, another family member came to the emergency department with the similar symptoms. All five patients were hospitalized for further evaluation. All of her other family members not showing clinical symptoms were also included in this investigation.

Cohort study. A case of eosinophilic meningitis was clinically defined as an acute onset of headache, eosinophil pleocytosis in the blood/CSF, accompanied by at least one of the following: fever, ataxia, visual disturbances, photophobia, nuchal rigidity, neck pain, hyperesthesia, or paresthesias. All patients with headache who had drank health drinks consisting of raw vegetable juice (clover, leaf of sweet potatoes, and apples) within three months of the onset of the outbreak were included to the study. To identify risk factors and severity of eosinophilic meningitis, we used a structured questionnaire that provided information pertaining to the amount of health drink ingested, duration of intake, source of vegetables, and juice production procedures.

Laboratory values. Laboratory tests were performed at the time of admission. Spinal taps were performed in all patients. The patient was placed in an upright or sitting position for one hour prior to the procedure. A 20-gauge spinal needle was inserted and 1–2 mL of CSF was allowed to flow spontaneously. One milliliter of CSF was then slowly withdrawn and 0.8 mL was returned. The procedure was repeated until 5–10 mL of CSF had been withdrawn.14
Cerebrospinal fluid analysis included cell counts, glucose and protein levels, gram and acid-fast stains, India ink preparation, wet mount preparations for larvae, and detection of cryptococcal antigen. Cultures were obtained for bacteria, mycobacteria, fungi, and viruses. Blood tests included complete blood and differential cell counts, total eosinophil count, and serum levels of creatinine, aminotransferases, creatine kinase, and immunoglobulin E (radioimmune assay IgE kit; Daiichi Radioisotope Laboratories, Ltd., Tokyo, Japan). Serologic tests for amoeba and the human immunodeficiency virus were performed. Stools were examined for ova and amoebic trophozoites on three consecutive days. A chest radiograph, electrocardiogram, sonogram of the liver and spleen, and a magnetic resonance image of the brain was obtained for each patient. Antibodies to *A. cantonensis* were detected in serum and CSF by a micro–enzyme linked immunosorbent assay using young-adult worm antigen (molecular mass = 204 kD) purified with a monoclonal antibody.  

Blood routine examination and serologic tests for antibodies to *A. cantonensis* were also carried out in family members without any clinical symptoms.

**Detection of *A. cantonensis* in vegetables.** Clover, leaf of *A. fulica* to *H11505* 204 kD) purified with a monoclonal antibody.  

**Statistical analysis.** The relationship between the amount of health drink and clinical abnormalities was analyzed with Spearman’s correlation coefficient test. The relationship between risk factors of acquisition and disease were analyzed with Fisher’s exact test or Pearson’s correlation test. A *P* value < 0.05 was considered statistically significant.

**RESULTS**

Five of the 10 family members met the case definition for eosinophilic meningitis. Two of the patients were males. All of them were hospitalized. They drank raw vegetable juice daily for health and constipation. The mean ± SD age of the patients was 37 ± 11 years (range = 30–57 years). They had lived in Kaohsiung for decades. None of them had previous habits of eating raw vegetables, fish, pork, beef, prawns, *Achatina fulica*, and *Ampullarius canaliculatus*. The mean ± SD incubation period was 54 ± 30 days. We examined the larvae of *A. cantonensis* in the vegetables obtained from the same market from which the patients did, and third-stage larvae of *A. cantonensis* was not found.

**Clinical features.** All five patients had headache, fever, neck stiffness, paresthesias/pain, and nausea/vomiting. One patient had ataxia and abdominal pain. The amount of raw vegetable juice ingested and the duration of intake of each patient are summarized in Table 1. None had altered consciousness. One patient had left, peripheral type, facial palsy and recovered completely. Results of an ophthalmic examination were unremarkable. None of the patients had papilledema.

**Laboratory findings and image studies.** Among the five patients, all had peripheral-blood eosinophilia and four (80%) had CSF eosinophilia on initial evaluation. Cerebrospinal fluid leukocyte counts and protein levels were elevated in all patients (Table 1). Larva of *A cantonensis* were not identified in the CSF specimens after 13 lumbar punctures. Antibodies to *A. cantonensis* were detected at the time of admission in the serum in five (100%) patients and CSF in four (80%) patients. All other family members who were not infected showed no clinical symptoms and had negative serologic test results for *A. cantonensis*. One patient had increased serum levels of creatine kinase. Indirect hemagglutination for *Entamoeba histolytica* and stool examination for amoeba, ova, and parasites were negative. Additional diagnostic tests included magnetic resonance imaging of the brain in all five patients. Meningeal enhancement and high signal intensity at the subcortical white matter on T2 weighted and fluid attenuated inversion recovery (FLAIR) images were observed in four patients.

**Clinical course and therapy.** At 12-month follow-up, all five patients had recovered without neurologic sequelae. Patients were treated with dexamethasone at a dose of 5 mg every eight hours for one week, and then given oral prednisone at a dose of 60 mg/day for another one week. There were three relapses of meningitis in this outbreak and all resolved after a lumbar puncture and/or administration of steroids. Two patients showed side effects due to the steroid treatment. One had oral candidiasis and the other had facial folliculitis. All recovered without treatment in approximately three weeks.

**Relationship between the amount of health drink and severity of illness.** The amount of health drink ingested and duration of intake was estimated in this outbreak. There was association between presence of health drink and CSF eosinophilia (Spearman’s correlation test *r* = 0.816, *P* = 0.004).

<table>
<thead>
<tr>
<th>Patient</th>
<th>Amount (mL) of drink and duration (months) of use</th>
<th>Blood</th>
<th>Cerebrospinal fluid</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>WBC</td>
<td>Eosinophils (%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(x10^3/μL)</td>
<td>(%)</td>
</tr>
<tr>
<td>1</td>
<td>360, 0.5</td>
<td>9,440</td>
<td>20</td>
</tr>
<tr>
<td>2</td>
<td>600, 2</td>
<td>8,750</td>
<td>21</td>
</tr>
<tr>
<td>3</td>
<td>360, 3</td>
<td>12,670</td>
<td>20</td>
</tr>
<tr>
<td>4</td>
<td>500, 3</td>
<td>6,020</td>
<td>14</td>
</tr>
<tr>
<td>5</td>
<td>360, 3</td>
<td>5,650</td>
<td>5</td>
</tr>
</tbody>
</table>

Table 1
Blood/cerebrospinal fluid (CSF) findings and amount of health drink consisting of raw vegetable juice among five patients with *Angiostrongylus cantonensis* infection in southern Taiwan.
<table>
<thead>
<tr>
<th>Authors</th>
<th>Location</th>
<th>Outbreak (years)</th>
<th>No. of cases</th>
<th>Source</th>
<th>Diagnosis</th>
<th>Treatment</th>
<th>Outcome</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosen and others</td>
<td>Tahiti</td>
<td>1958–1960</td>
<td>Hundreds of adults, 202 cases with typical CSF changes</td>
<td>Raw pelagic fish, skipjack tuna, oceanic bonito</td>
<td>Clinica, not serology proven</td>
<td>Antibiotics, anti-histamine, anti-parasitic drugs, analgesic drugs, some relief by lumbar puncture removing CSF</td>
<td>All recovery</td>
<td>18</td>
</tr>
<tr>
<td>Bowden</td>
<td>New Hebrides</td>
<td>July 1976–Nov 1976</td>
<td>8 males, 9 females</td>
<td>Lettuce</td>
<td>L4 larvae in the brain at autopsy (2), Clinical (17)</td>
<td>Thia bendazole (2)</td>
<td>Death (2), left sixth cranial nerve palsy (1), right leg anesthetics patches (1)</td>
<td>9</td>
</tr>
<tr>
<td>Kliks and others</td>
<td>American Samoa</td>
<td>1980</td>
<td>16 Korean fishman</td>
<td>Achatina fulica</td>
<td>L4 larvae in spinal cord (1), serology (10)</td>
<td>Thia bendazole (9)</td>
<td>Death (1), persistent paresthesia of the foot (1)</td>
<td>11</td>
</tr>
<tr>
<td>Tsai and others</td>
<td>Kaohsiung, Taiwan</td>
<td>1998</td>
<td>8 male Thai laborers</td>
<td>A. canaliculatus, fish</td>
<td>Serology (8)</td>
<td>Me bendazole (8), Steroid (7)</td>
<td>Full recovery</td>
<td>19</td>
</tr>
<tr>
<td>Tsai and others</td>
<td>Kaohsiung, Taiwan</td>
<td>1999</td>
<td>9 male Thai laborers</td>
<td>A. canaliculatus</td>
<td>Serology (8), CSF larvae (2)</td>
<td>Acetaminophen and naproxen (9)</td>
<td>Full recovery</td>
<td>12</td>
</tr>
<tr>
<td>Slom and others</td>
<td>Jamaica</td>
<td>2000</td>
<td>12 American young adults (9 men, 3 women)</td>
<td>Caesar salad (lettuce)</td>
<td>Western blot, antibody against 31-kD antigen (11)</td>
<td>Opioid (7) plus NSAID, NSAID alone (5), repeat lumbar puncture plus steroid (3)</td>
<td>Full recovery</td>
<td>8</td>
</tr>
</tbody>
</table>

* Values in parentheses are numbers of patients. CSF = cerebrospinal fluid; NSAID = nonsteroidal anti-inflammatory drug.
Risk factors identification showed that consumption of raw vegetable juice was associated with illness (Pearson correlation test $r = 0.867, P = 0.01$).

DISCUSSION

Angiostrongylus cantonensis, the rat lung worm, is the most common infectious cause of eosinophilic meningitis in southern Asia and the Pacific Basin. The etiologic agent of the outbreak. Slom and others reported an outbreak of infections and serologic data provides strong evidence that all five cases of infection that we describe were not parasitologically confirmed, the combination of the clinical manifestations and serologic data provides strong evidence that A. cantonensis was the etiologic agent of the outbreak. Slom and others reported an outbreak of A. cantonensis meningitis among travelers from the United States returning from the Caribbean. Although the exact vehicle of transmission was unclear, they found that the meal eaten the night before departure for the United States was associated with a strong risk of illness. The lettuce of the Caesar salad at that meal was most likely contaminated. In this outbreak, although the possible vehicle cannot be identified in the vegetable juice, the infection may have resulted from accidental ingestion of small intermediate or paratenic hosts, or infective larvae in their mucus deposited on the vegetables. However, it must be noted that infective larvae of A. cantonensis have not yet been identified in snail mucus trails. Results of experiments to detect A. cantonensis larvae in infected slug secretions were negative. Ash found that most cases of eosinophilic meningitis in New Caledonia occurred not in direct association with small snails of a size easily overlooked on raw vegetable, but with the influx of infected planarians in local produce gardens, and their subsequent accidental ingestion on lettuce or other raw vegetable products. Further study is necessary to clarify this phenomenon in Taiwan.

Several clinical and laboratory features of this outbreak are noteworthy. Eosinophilia in CSF was not always present on initial laboratory examination. One of our patients had typical aseptic meningitis without CSF eosinophilia. He would have been incorrectly diagnosed if a detailed history was not obtained. Three presentations were noted in the present outbreak: meningitis, radiculitis, and cranial nerve involvement. All of our patients were adults and had prominent meningeal signs and radiculitis. All of them complained of sharp, shooting pains, numbness, and hyperesthesias involving the trunk and limbs. This manifestation was different from those cases reported in Taiwan. The cases reported in Taiwan were more likely to involve children, to be associated with encephalitis, papilledema and peripheral leukocytosis, and to have A. cantonensis larvae recovered from the CSF specimens. This discrepancy may due to a higher load of worms relative to body size, different host susceptibilities between adult and children, or the strains of A. cantonensis involved. Similar to the patients described in the case reports from Thailand, the patients in our series were adults with a predominance of radiculitis.

Four of our patients had unusual magnetic resonance imaging manifestations. This involved meningeal enhancement, as well as high signal intensities, at the subcortical white matter on T2 weighted and FLAIR images. Nye and others reported a pathologic change of the brain in eosinophilic meningitis, and they showed that the lesions included meningitis with eosinophils and plasma cells infiltrations, tortuous tracks with neurons degenerations, granulomatous reaction to dead A. cantonensis, and vascular thrombosis with arteritis. It was postulated that a granulomatous reaction to dead worm and meningitis were present in our patients, similar to the findings described by Hwang and Chen.

Our patients were not treated with anthelminthic agents because of the theoretical possibility of exacerbating neurologic symptoms as a result of the death of larvae in the central nervous system. Punyagupta and others found no difference in the duration or severity of illness in patients treated with analgesics alone, analgesics and glucocorticosteroids, or analgesics and antibiotics. Most of the patients showed a good response to conservative treatment alone. Corticosteroid therapy was recently shown to provide symptomatic relief of headache caused by eosinophilic meningitis in a well-designed clinical study in Thailand. However, three of our patients showed relapsing symptoms during treatment with corticosteroid and two patients developed oral candidiasis and folliculitis. All three of these patients recovered after lumbar puncture and/or the administration of corticosteroids. Therefore, repeated lumbar puncture and the use of corticosteroid therapy should be reserved for patients with more severe symptoms.

In conclusion, clinical manifestations of headache, CSF pleocytosis, paresthesias, or hyperesthesias accompanied by a history of drinking raw vegetable juice should suggest the possibility of A. cantonensis infection. Travelers and residents of endemic areas should avoid eating raw foods, such as vegetables and snails.

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