Eosinophilic Meningitis Caused by *Angiostrongylus Cantonensis*: Report of 17 Cases

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PURPOSE: To describe two outbreaks of *Angiostrongylus cantonensis* infection that occurred in Kaohsiung, Taiwan, during 1998 and 1999, and to characterize the source of the outbreaks and the clinical manifestations of the disease.

SUBJECTS AND METHODS: We performed a retrospective cohort study among Thai laborers with eosinophilic meningitis who ate raw snails (*Ampullarium canaliculatus*), as well as an environmental surveillance of larvae in snails.

RESULTS: We enrolled 17 Thai laborers in whom severe headache and eosinophilia developed within 4 to 23 days after eating raw snails. Twelve (71%) developed eosinophilic meningitis. Third-stage larvae were found in the cerebrospinal fluids of 2 patients and in all 12 tested snails. Specific antibodies to *A. cantonensis* were detected in serum from 16 of the patients and in cerebrospinal fluid from 5 of the patients. Central nervous system manifestations included headache (n = 17 [100%]), fever (n = 11 [65%]), Brudzinski's sign/stiff neck (n = 11 [65%]), hyperesthesia (n = 3 [18%]), cranial nerve palsy (n = 2 [12%]), diplopia (n = 2 [12%]), and ataxia (n = 1 [6%]). Laboratory findings included peripheral eosinophilia (n = 15 [88%]) and cerebrospinal fluid eosinophilia (n = 12 [71%]); elevated immunoglobulin (Ig) E levels (n = 13 [100%]); and transient increases in white blood cell count (n = 7 [41%]) and in serum levels of creatine kinase (n = 7 [41%]), transaminase (n = 3 [18%]), and lactate dehydrogenase (n = 2 [12%]). The severity of illness and eosinophilia were correlated with the number of ingested snails. Meningeal and basal ganglion enhancement was noted on magnetic resonance imaging in several patients. Treatment with mebendazole combined with glucocorticosteroids appeared to shorten the course of the infection, but not the number of relapses. The eosinophil count fell to normal within 3 months, but IgE levels remained elevated for as long as 6 months. All patients recovered with minimal neurologic sequelae.

CONCLUSION: Eosinophilic meningitis caused by *A. cantonensis* should be considered in patients who have headache or central nervous system manifestations after eating raw snails. **Am J Med. 2001;111:109–114.** ©2001 by Excerpta Medica, Inc.

The major cause of eosinophilic meningitis in the Pacific Islands and Southeast Asia is *Angiostrongylus cantonensis*, also known as the rat lungworm (1–4). Humans are infected by ingesting freshwater and terrestrial snails and slugs (5–11). The major intermediate hosts in Taiwan are the African giant snail (*Achutina fulica*) and the golden apple snail (*Ampullarium canaliculatus*). *Ampullarium canaliculatus* was introduced to Taiwan in 1979 as a food source. It spread widely in paddy fields and drainage ditches and has become an important cause of outbreaks of eosinophilic meningitis (12).

Two outbreaks of eosinophilic meningitis caused by *A. cantonensis* occurred in Kaohsiung, Taiwan, in 1998 (13) and 1999. All of the 17 patients were adult male Thai laborers who had eaten raw golden apple snails approximately 1 to 3 weeks earlier. In this report we describe the epidemiologic, clinical, and laboratory features of the outbreaks, discuss the effect of therapy on the disease, and review the pertinent literature.

METHODS

Patients

All patients with headache who had eaten raw snails within 3 weeks of the outbreak's onset were included in the study. The incubation period was defined as the number of days between eating raw snails and onset of headache.

We recorded demographic information, the date snails were eaten and the amount ingested, symptoms, recent drug use, allergic reactions, and prior parasitic infections. Each patient underwent a physical, neurologic, and ophthalmic examination.

Laboratory Values

Laboratory tests were performed at the time of admission. Spinal taps were performed on all patients (14,15). Cerebrospinal fluid analysis included cell count, glucose and protein levels, gram and acid-fast stains, India ink preparation, wet mount preparations for larvae, and

measurement 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 (Ig) E (Radioimmune assay IgE kit; Daiichi Radioisotope Laboratories, Ltd., Tokyo, Japan). Serologic tests for amoeba and the human immunodeficiency virus (HIV) were obtained. Stools were examined for ova and amoebic trophozoites on 3 consecutive days. Each patient underwent chest radiography, electrocardiography, liver and spleen sonography, and brain magnetic resonance imaging.

The patients were observed daily during their hospital course. Cerebrospinal fluid was examined weekly. Complete blood and differential cell counts, eosinophil count, and serum IgE levels were obtained weekly for the first 2 months, every other week for the next 2 months, and monthly thereafter for as long as 6 months.

Antibodies to *A. cantonensis* were detected in serum and cerebrospinal fluids by a microenzyme-linked immunosorbent assay (ELISA) using young-adult worm antigen, molecular weight 204kD, purified by monoclonal antibody (16).

For the detection of *A. cantonensis* in snails, golden apple snails were collected from the same pond as used by the laborers in the 1999 epidemic. The shells were crushed; the bodies were homogenized and digested in pepsin-hydrochloride solution at 37°C for 1 hour (17). The solution was examined for third-stage larvae by light microscopy.

Statistical Analysis

The relation between the number of snails ingested and incubation time, laboratory abnormalities, and clinical severity and duration of disease were analyzed with Spearman's correlation coefficient or with Fisher's exact test (for consumption of 6 or more snails). Student's *t* test was used to compare mean durations of illness. A *P* value <0.05 was considered statistically significant.

RESULTS

Two outbreaks of eosinophilic meningitis occurred in Kaohsiung County among 17 young adult Thai laborers who had eaten raw golden apple snails. There were 8 cases in 1998 and 9 at a different site in 1999. The 1998 outbreak was reported in the Taiwanese literature (13). During the 1999 outbreak, 39 Thai laborers worked in a factory surrounded by cane fields and fishponds. On October 31, 1999, they were given a day off from work. They attempted to fish in one of the ponds, but were unsuccessful. Some resorted to harvesting golden apple snails. The shells were crushed, and the feet were mixed with lemon juice and red pepper and eaten. On November 25,

Table 1. Frequency of Clinical Symptoms and Signs among 17 Patients with *Angiostrongylus cantonensis* Infection*

	Number (Percent)
Symptoms	
Headache	17 (100)
Neck stiffness	8 (47)
Fever	11 (65)
Paresthesia	2 (12)
Muscle weakness	8 (47)
Orbital/retro-orbital pain	7 (41)
Diplopia	2 (12)
Ataxia	1 (6)
Nausea	4 (24)
Vomiting	4 (24)
Abdominal pain	3 (18)
Skin rash	4 (24)
Signs	
Stiff neck	11 (65)
Brudzinski's sign	11 (65)
Hyperesthesia (pain)	3 (18)
Abducen nerve palsy	1 (6)
Facial palsy	1 (6)
Transient labyrinth insufficiency	1 (6)

* Includes cases reported by Tsai et al. (13) from the 1998 outbreak: headache (n = 8 patients), fever (n = 8), muscle weakness (n = 2), orbital/retro-orbital pain (n = 4), diplopia (n = 1), nausea (n = 2), vomiting (n = 2), abdominal pain (n = 2), skin rash (n = 2), stiff neck (n = 8), Brudzinski's sign (n = 8), hyperesthesia (n = 2), and abducen nerve palsy (n = 1).

1999, 2 of the Thai laborers were admitted to Kaohsiung Veterans General Hospital complaining of headache and neck stiffness for several days. They were noted to have eosinophilia, and they acknowledged eating several raw snails. Seven more laborers were admitted over the next few days with the same complaints and history of eating raw snails.

The mean (± SD) age of the patients was 31 ± (4) years (range, 23 to 39). They had lived in Kaohsiung for 5 to 18 months. All ate raw fish, pork, and beef in Thailand. Twelve had previously eaten the African giant snail, *A. fulica*, in Thailand. Fourteen had never eaten raw golden apple snails before the outings. The mean incubation period was 13 ± 7 days. The attack rate could not be determined because we were unable to obtain a food history from the 30 Thai laborers who did not become ill. We examined 12 golden apple snails from the same area; all had numerous third-stage larvae.

Clinical Features

All 17 patients had a throbbing headache combined with a variety of other symptoms and signs (Table 1). None had altered consciousness. Glycerol was given intravenously to 2 patients who had signs of increased intracranial pressure. Transient focal neurologic deficits were

Table 2. Blood and Cerebrospinal Fluid Findings in 17 Patients with *Angiostrongylus cantonensis* Infection*

	Blood		Cerebrospinal Fluid					
Patient No.	White Blood Cell Count ($\times10^3/\mu$L)	Eosinophils (%)	Appearance	Protein (mg/dL)	Glucose (mg/dL)	Ratio†	White Blood Cell Count ($\times10^3/\mu$L)	Eosinophils (%)
1	14,030	25	Clear	70	57	0.44	540	2
2	12,130	27	Clear	52	89	0.48	350	13
3	12,180	34	Cloudy	135	62	0.44	650	25
4	10,700	24	Clear	70	86	0.84	650	18
5	7,560	4	Cloudy	54	55	0.63	477	50
6	8,650	26	Clear	92	77	0.60	240	4
7	11,220	33	Clear	72	45	0.55	727	22
8	5,140	10	Clear	50	88	0.66	330	46
9	10,500	36	Cloudy	154	36	0.38	1,270	36
10	9,480	16	Cloudy	347	45	0.37	1,660	6
11	13,270	29	Cloudy	201	59	0.63	1,390	17
12	8,510	2	Clear	27	70	0.60	0	0
13	7,570	10	Clear	49	60	0.52	0	0
14	5,920	7	Clear	95	72	0.79	9	0
15	6,490	20	Clear	50	71	0.82	1	0
16	6,990	16	Cloudy	36	66	0.78	139	6
17	8,210	8	Clear	67	75	0.65	1	0

* Cases 1 to 8 were described in the 1998 outbreak (13).
† Cerebrospinal fluid glucose level divided by serum glucose level.

common. Three patients had hyperesthesia in various dermatomes (right-sided L2/L3 and T5/T6, bilateral T9, and bilateral L2/L3). Two patients had paresthesias with impaired sensation to pain and light touch (right-sided L2/L3 and L4/L5). One patient had bilateral abducens nerve palsy, and another had transient right central facial palsies; both recovered completely. Ophthalmic examination was unremarkable except for corneal maculas (spots) in 2 patients. No larvae were seen in the anterior chamber. None of the patients had papilledema.

Laboratory Findings

Most of the patients had a normal or slightly elevated white blood cell count (Table 2), and most had eosinophilia ($\geq$5%). The cerebrospinal fluid was cloudy and had a rice-water appearance in 6 patients (35%). Cerebrospinal fluid leukocyte counts were elevated in all but 4 patients. Cerebrospinal fluid eosinophilia was common, and ranged as high as 50%. Cerebrospinal fluid glucose was >40 mg/dL in all but 1 patient. Cerebrospinal fluid protein was elevated (>100 mg/dL) in only 4 patients. Third-stage larvae were found in the cerebrospinal fluid of 2 patients. Results of stains and cultures of the cerebrospinal fluid were negative.

Antibodies to *A. cantonensis* were detected at the time of admission in the serum of 16 (94%) patients and in the cerebrospinal fluid of 5 (29%) patients. Serum IgE levels were elevated in all 13 patients tested; increased serum levels of creatine kinase (n = 7 patients), alanine amino transferase (n = 3), and lactate dehydrogenase (n = 2)

were also seen. Results of indirect hemagglutination for *Entamoeba histolytica* and stool examination for amoeba, ova, and parasites were negative.

Imaging Studies

Chest roentgenography was normal except for bilateral upper lobe pleural thickening in 1 patient. Sonography of the liver and spleen revealed no parenchymal lesions except for mild fatty liver in 2 patients and splenomegaly in 1 patient. Magnetic resonance imaging of the brain was performed in 13 patients and disclosed varying degrees of meningeal enhancement and abnormal globus pallidus enhancement in 9 patients (Figure 1). There were no localized lesions suggesting the presence of young adult worms.

## Relation between Amount of Snails Eaten and Severity of Illness

The number of snails eaten was determined in the 1999 outbreak. This correlated with severity of headache ($r = 0.80$, $P = 0.01$), muscle weakness ($r = 0.75$, $P = 0.02$), orbital pain ($r = 0.79$, $P = 0.01$), cerebrospinal fluid white cell count ($r = 0.79$, $P = 0.01$), cerebrospinal fluid eosinophil count ($r = 0.81$, $P = 0.008$), and serum IgE level ($r = 0.79$, $P = 0.01$). Subjects who remembered eating 6 or more snails were more likely to develop orbital and retro-orbital pain ($P = 0.05$), a Brudzinski sign ($P = 0.05$), cerebrospinal fluid pleocytosis ($P = 0.05$), cloudy cerebrospinal fluid ($P = 0.007$), and eosinophilia ($P = 0.008$).
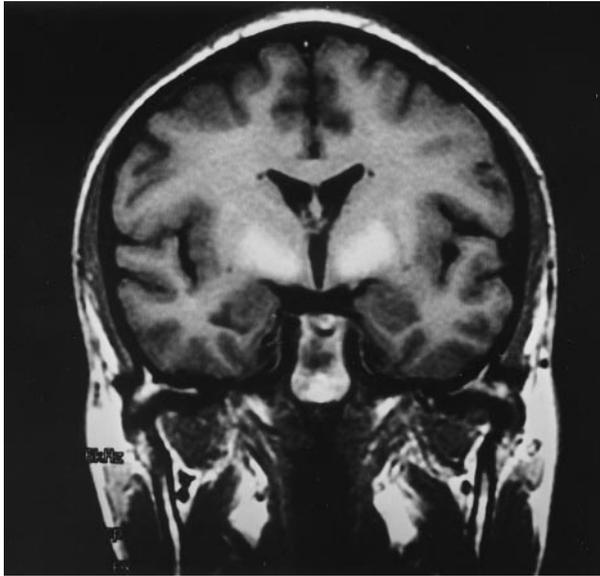
Figure 1. Coronal T1-weighted magnetic resonance imaging (600/20, TR/TE) shows increased signal intensity within the globus pallidus.

Clinical Course and Response to Therapy

At 6-month follow-up, all 17 patients had recovered with minimal neurologic sequelae. The white blood cell count and eosinophil count (Figure 2), and the serum creatine kinase and lactic dehydrogenase levels gradually returned to normal, but IgE levels remained elevated (Figure 3). The mean duration of illness for all patients was 20 ± 14 days. Patients treated with mebendazole and dexamethasone in the 1998 outbreak had a shorter duration of illness than those treated with acetaminophen and naproxen in the 1999 outbreak (13 ± 8 days compared
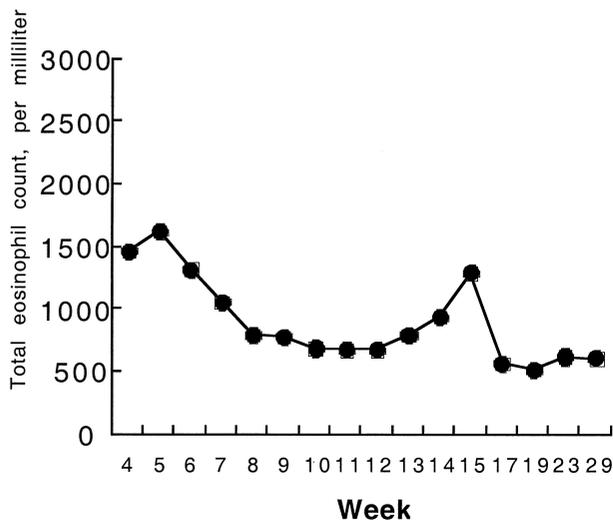
Figure 2. Changes in mean total eosinophil count during the 6-month follow-up after the 1999 epidemic.
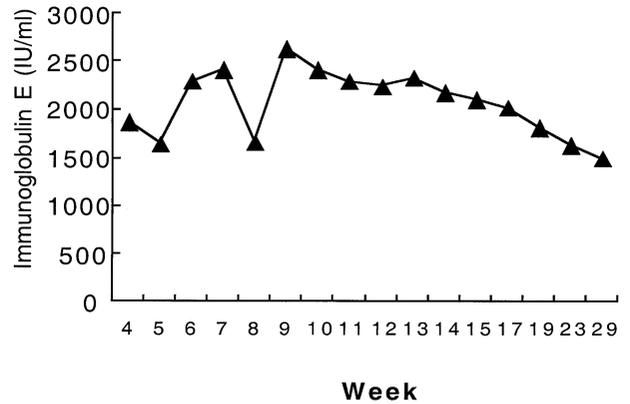
Figure 3. Changes in mean serum immunoglobulin E levels during the 6-month follow-up after the 1999 epidemic.

with 27 ± 15 days; mean difference, 14; 95% confidence interval: 1 to 27; $P = 0.04$). There were 2 relapses of meningitis in each outbreak. During the 1999 outbreak, headache, stiff neck, transient right facial palsy, ataxia, and diplopia recurred in 1 patient 55 days after eating the snails; he was treated with intravenous glycerol for 7 days and recovered in a week. Vomiting and headache developed in a second patient 29 days after he first became ill. A spinal tap revealed an elevated opening pressure of 240 mm H_2O, a white cell count of 1110×10^3 cells per μL with 74% eosinophils, a protein level of 107 mg/dL, and a glucose level of 46 mg/dL (serum glucose 79 mg/dL). He recovered without treatment in about a week.

DISCUSSION

Eosinophilic meningitis is rare in Western countries, but is sometimes seen in association with tuberculosis, syphilis, and coccidioidomycosis (18). The disease is more common in South East Asia and Pacific regions. *Angiostrongyloides cantonensis* is the most frequent etiologic agent in these regions. Other helminthic infections that can cause eosinophilic meningitis include cysticercosis, schistosomiasis, paragonimiasis, and echinococcosis. *Gnanthostoma spinigerum* causes a particularly severe form of eosinophilic myeloencephalitis that may result in nerve root pain, paralysis of an extremity, and subarachnoid hemorrhage associated with visceral and cutaneous larvae migrans (19). It can be distinguished from *A. cantonensis* infections by serologic tests (20,21).

Most cases of *A. cantonensis* eosinophilic meningitis in Taiwan have been reported in children exposed to the African giant snail (*A. fulica*) (4,14,15). There is usually a history of eating or playing with snails or slugs. More recently there have been several outbreaks among adults, particularly Thai laborers who have eaten golden apple snails (*A. canaliculatus*). Field studies in southern Taiwan

revealed that 14% to 31% of these snails contain third-stage larvae of *A. cantonensis* (12). Because of the high level of infestation, it is not surprising that the disease can be produced after eating just a few snails. We found that more severe illness developed in patients who reported eating 6 or more snails; a previous study (22) did not find a significant correlation between the number of snails consumed and disease severity.

The disease appears to be the result of a vigorous host response to larvae in the central nervous system. It spontaneously resolves presumably because the larvae do not survive in human hosts. The acute illness is characterized by headache, fever, meningitis, focal neurologic deficits, ocular lesions, radiculomyelitis, and palsies of the sixth and seventh cranial nerves. It is rarely fatal in adults. None of our patients had severe neurologic sequelae. Punyagupta et al. (3) reported only 1 death and no severe sequelae in a series of 484 adult Thai patients.

The disease is much more serious in children. In a series of 87 cases (4,15), about 50% had fever and 30% had hepatomegaly. There were 4 deaths, and 6 patients had permanent neurologic sequelae (14,15). It is possible that the increased severity in children is due to a higher worm load relative to body size. We did not detect hepatomegaly in our patients.

Eosinophilia has been reported to disappear within 3 to 4 weeks after onset (4). In the our study, the eosinophil count fell more gradually, perhaps because corticosteroid drugs were not used during the second outbreak. Serum IgE levels are commonly elevated in helminthic infections (23–25). It is not known whether IgE is protective or is simply a response to foreign antigens. The elevated IgE level may persist for very long periods after an infection is resolved. For example, in infection caused by the roundworm *Capillaria philippinesis*, extremely high levels were noted in severely ill patients and did not fall to baseline levels until 18 months after elimination of the worms (25). In the current outbreaks with *A. cantonensis*, IgE level was not associated with illness severity, and elevated levels persisted for at least 6 months.

We found larvae in the cerebrospinal fluid in 2 of 17 patients, who underwent a total of 50 spinal taps. Cerebrospinal fluid larvae were not found in adults studied in Thailand (3). Placing a patient in sitting position for 1 hour before lumbar puncture has been shown to increase the yield of larvae in the cerebrospinal fluid.

The role of treatment with anthelminthic agents (26) and corticosteroids (3,27) remains controversial. Punyagupta et al. (3) found no difference in the duration or severity of illness in patients treated with analgesics alone, analgesics and glucocorticosteroids, or analgesics and antibiotics. Hwang et al. (14,15) reported good results with albendazole or levamisole in uncontrolled studies of children. Chotmongkol et al. (28) found that a 2-week course

of prednisolone helped relieve the headache, shortened the median time until resolution of headache, and reduced the need for repeated lumber puncture. In our study, glucocorticosteroids and mebendazole were used during the first outbreak, and appeared to shorten illness duration, as compared with the supportive care provided during the second outbreak, although the number of relapses was similar.

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