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An outbreak of meningitis caused by *Angiostrongylus cantonensis* in Kaohsiung

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Eight Thai laborers developed meningitis after eating raw snails (*Ampullarium canaliculatus*) during the period from September 27 to October 6, 1998. The diagnosis of *Angiostrongylus cantonensis* infection was established in all patients by serologic studies of serum and cerebral spinal fluid (CSF). Clinical manifestations included meningitis, radiculitis and cranial nerve palsy. Symptoms included fever, headache, orbital pain, gastrointestinal upset, hyperesthesia, muscle weakness, skin rash and diplopia. Laboratory abnormalities included peripheral eosinophilia, CSF eosinophilia, transient elevation of liver enzymes and creatinine phosphokinase, elevation of IgE. No space occupying lesions were detected by magnetic resonance imaging of the brain. None of the patients developed severe sequelae during the 6-month follow-up except for occasional headache in one patient. This report also provides evidence that third stage larvae were present in the intermediate host, *A. canaliculatus*, which the laborers had eaten.

Key words: *Ampullarium canaliculatus, Angiostrongylus cantonensis*, meningitis

In 1933, Chen first reported a hitherto unknown nematode in the lungs of rats, in a study of parasites in wild rats in the vicinity of Canton, China [1]. He named the parasite *Pulmonema cantonensis*. In Taiwan, Matsumoto described the same nematode and named it *Haemostrongylus ratti* [2]. In 1946, the parasite received its taxonomic designation as *Angiostrongylus cantonensis* [3]. The first human case of *A. cantonensis* infection was reported in Taiwan by Nomura and Lin in 1945 [4]. It was a fatal case of eosinophilic meningitis in a 15-year-old boy, from whom 10 worms were recovered from the spinal fluid. However, it was not until the report of Rosen *et al* in 1962 that physicians in Taiwan became more aware of the importance of eosinophilic meningitis caused by *A. cantonensis* [5]. Since then, many cases of *A. cantonensis* infection have been reported in Taiwan [6-13]. In addition, the first case with adult worms recovered from the human lung was also reported in Taiwan [14]. In this study, we report eight cases of meningitis caused by *A. cantonensis* in Kaohsiung, Taiwan. We present the clinical manifestations and laboratory findings of these cases. In addition, we show evidence of the existence of third stage larvae in the intermediate host, *Ampullarium canaliculatus*, or so-called "golden apple snail" in the Kaohsiung vicinity.

Materials and Methods

Eight laborers from Thailand were admitted to Kaohsiung Veterans General Hospital in October, 1998. All eight patients presented with meningitis after eating raw golden apple snail (*A. canaliculatus*) and fresh water fish *Oreochromis niloticus*. Data collected included the type of food eaten before this outbreak, incubation period, and food preparation and consumption habits before this outbreak. After admission, each patient received a complete physical examination including a careful neurologic and ophthalmic examination. Each patient received serial examinations of the cerebrospinal fluid (CSF). CSF analysis included cell counts, biochemistry, and cultures for bacteria, virus, mycobacteria, and fungus. Gram stain, acid-fast stain, India ink and wet mount examination of the CSF were also done. Blood examination included blood smear and differential count, liver and renal function tests, creatinine phosphokinase (CPK) and immunoglobulin E (IgE) levels, and indirect hemagglutination test (IHA) for

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ameba. Stool samples were examined for parasites and amebic trophozoites. Four patients received magnetic resonance (MR) imaging of the brain due to severe and persistent cerebral symptoms. All eight patients were treated with mebendazole and steroids for a variable duration, depending on the severity of the disease. The duration of disease was defined as the time from symptom-onset until the patient was symptom-free. Patients were followed up for 6 months after starting treatment for possible sequelae. Serum and CSF antibody levels of eight patients were assayed by microenzyme-linked immunosorbent assay using antigen from young-adult worms purified by monoclonal antibody with a 204 kD molecular weight as described elsewhere [32]. Briefly, antigen was diluted to a concentration of 10 μg/mL and coated onto the wells of an enzyme immunoassay (EIA) plate (Sigma chemicals, MO, USA) and incubated overnight at 4 °C. After blocking with 1% bovine serum albumin and washing with phosphate-buffered saline containing 0.05% Tween 20, serum or CSF with a dilution of 100 was added and incubated for 1 h. Horseradish peroxidase conjugated goat antihuman immunoglobulins (Nordic, Tilburg, Netherlands) was added after removal of unbound components by washing. Excess enzyme was washed off after 1-h incubation and then the substrate o-phenylenediamine solution was added and incubated for 15 min. Optical density (O. D.) was read at 490 nm using an EIA reader (Dynatech Lab., MR 5000, VA, USA). The cut-off levels for consideration of positive results were 0.3 for serum and 0.25 for CSF. Positive control for serum was 1.949 and negative control was 0.108. Positive control for CSF was 1.139 and negative control was 0.108. Wilcoxon rank-sum test was used to compare the antibody level of CSF and serum. Snails were collected from the same pond from which the laborers caught the snails they ate. The shells were crushed and the body was then homogenized and digested in pepsin-hydrochloride solution at 37 °C for 1 h, according to the method described by Chao [15]. The solution was then carefully examined under the microscope for the presence of third stage larvae.

Results

Environment

The eight patients worked in a factory surrounded by cane-fields. Just beyond their factory was a lotus pond with an abundance of golden apple snails. Many wild rats were seen in the cane-fields. This environment provided all the components required in the life cycle of *A. cantonensis*. Seven snails (Fig. 1) were examined. A total of 33 live, third stage larva were found in two snails (Fig. 2). The worm burden seemed low and not every snail was found to be infected with *A. cantonensis*.

Fig. 1. *Ampullarium canaliculatus* (golden apple snail) from the lotus pond.

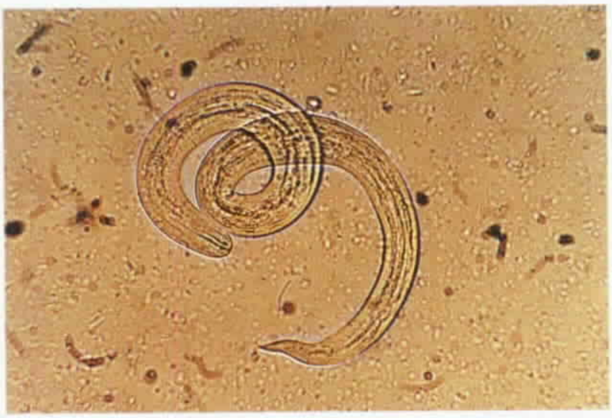

Fig. 2. Third stage larvae of *A. cantonensis* isolated from *A. canaliculatus* (x 400).

Patients

All patients were male Thai laborers. Their ages ranged from 25 to 39 years (32 ±5 years). They had been living in Taiwan for over 6 months. All eight patients had the habit of eating raw fish, snails, pork, beef and mutton in Thailand. The types of snails most commonly consumed were *Achatina fulica* and golden apple snails. Poultry was never eaten uncooked. Before this admission, they had eaten uncooked fish and snails (Table 1). The snails were crushed and the foot was eaten raw. Since raw snails were the only food they had all eaten it was considered the most probable vehicle of infection.

Table 1. Summary of clinical presentation and therapy

Case no.	Age	Food	Incubation period (day)	Illness duration (day)	Treatment	Laboratory abnormality
1	30	Snail, fish	Not sure	12	Mebendazole x 7d Dexamethasone x 12d	IgE: 3918 U/mL (< 200 U/mL)[b]
2	25	Snail, fish	5	21	Mebendazole x 6d Dexamethasone x 17d Prednisolone x 5d	CPK: 540 U/L (0-140 U/L) IgE: 1534 U/mL
3	37	Snail, fish	11	17[a]	Mebendazole x 11d Dexamethasone x 9d Prednisolone x 16d	AST: 131 U/L (5-45 U/L) ALT: 348 U/L (0-40U/L)
4	30	Snail, fish	Not sure	27	Mebendazole x 7d Dexamethasone x 12d	ALT: 81 U/L
5	32	Snail, fish	Not sure	3	Mebendazole x 7d Dexamethasone x 10d	AST: 50 U/L, GPT: 48 U/L CPK: 311 U/L, IgE:6154 U/mL
6	34	Snail, fish	5	8	Mebendazole x 6d Dexamethasone x 10d	
7	27	Snail	12	11	Mebendazole x 6d Dexamethasone x 7d	CPK: 168 U/L
8	39	Snail, fish	5	4	Mebendazole x 4d	IgE: 507 U/mL

Abbreviations: AST= aspartate aminotransferase; ALT = alanine aminotransferase; CPK = creatinine phosphokinase; IgE = immunoglobulin E
[a]Irregular treatment.
[b]IgE value unavailable in four patients.

Symptoms and signs

Five patients (cases 2, 3, 6, 7, 8) had eaten raw snails only once and had a definite incubation time ranging from 5 to 12 days (Table 1). The other three patients had eaten the snails at least twice. Since not every snail contained *A. cantonensis*, we could not be sure the actual time of infection in these three patients. All eight patients had throbbing headaches on admission (Table 2). No fever was noted initially, yet each patient sustained a low-grade fever of 37 °C to 38 °C after lumbar puncture was done. None of the patients complained of neck stiffness, but Brudzinski's sign was elicited in all patients on physical examination. Sensory impairment with hyperesthesia occurred in two patients. Case 1 complained of a painful sensation over the right L2 through L3 and right T5 through T6 dermatomes. Case 8 had a painful sensation over the bilateral thoracic 9 dermatomes. Neither of these patients had paresthesia or other sensory loss to light touch, temperature or pain. Two patients had decreased muscle power. One (case 2) had weakness of bilateral upper limbs (muscle power grade 4) and another (case 7) experienced weakness of all four limbs (muscle power grade 4). Four patients (cases 1, 3, 7, 8) had orbital or retro-orbital pain on admission. Ophthalmic examination of all eight patients disclosed no abnormalities except for bilateral abducens nerve palsy in case 4. No larvae were found in the anterior chamber. Papilledema was not found in any of the eight patients throughout the course of the illness. Two patients (cases 2, 3) had initial symptoms of nausea, vomiting and abdominal pain. Mild epigastric tenderness was noted in these patients, but no hepatosplenomegaly was detected. Two patients (cases 4, 5) developed a transient maculopapular skin rash over the trunk during treatment. Case 4 became severely ill

Table 2. Characteristics of eight patients with meningitis caused by *A. cantonensis*

Symptom and sign	No. of patients
Fever	8
Headache	8
Orbital/retro-orbital pain	4
Hyperesthesia	2
Muscle weakness	2
Nausea	2
Vomiting	2
Abdominal pain	2
Skin rash	2
Diplopia	1
Objective neck stiffness	8
Brudzinski's sign	8
Hyperesthesia (pain)	2
Paralysis of extremity	2
Cranial nerve palsy	1

Table 3. Summary of blood and CSF data in eight patients

Case no.	Blood		CSF					
	WBC (/mm^3)	Eosinophil (%)	Appearance	Protein (mg/dL)	Sugar (mg/dL)	CSF/blood sugar	WBC (/mm^3)	Eosinophil (%)
1	14030	25	Clear	70	57	0.44	540	2
2	12130	27	Clear	52	89	0.48	350	13
3	12180	34	Cloudy	135	62	0.44	650	25
4	10700	24	Clear	70	86	0.84	650	18
5	7560	4	Cloudy	54	55	0.63	477	50
6	8650	26	Clear	92	77	0.60	240	4
7	11220	33	Clear	72	45	0.55	727	22
8	5140	10	Clear	50	88	0.66	330	46

Table 4. Levels of serum and CSF antibodies to surface antigen of fifth stage larvae of *A. cantonensis* with molecular weight of 204 kD

Case no.	Days after onset	CSF O.D.[a]	Serum O.D.[b]
1	4	0.435	2.224
2	2	0.375	2.262
3	8	0.383	2.163
4	2	0.263	2.228
5	2	0.242	2.278
6	2	0.237	1.973
7	8	0.212	1.993
8	2	0.828	2.147
Mean antibody level		0.372	2.159

Abbreviations: CSF = cerebrospinal fluid; O.D. = optical density
[a]CSF positive control: 1.139, negative control: 0.108, cut-off level: 0.25 .
[b]Serum positive control: 1.949, negative control: 0.108, cut-off level: 0.3.

after the second lumbar puncture and experienced diplopia during treatment. None of the patients suffered from any changes of consciousness during the course of the illness.

Laboratory findings

The gross appearance of CSF was cloudy in two patients (cases 3, 5) and appeared somewhat like rice water. CSF leukocyte count ranged from 210/mm^3 to 930/mm^3, with 2% to 50% eosinophils (Table 3). Peripheral leukocyte counts ranged from 5140/mm^3 to 14030/mm^3, and eosinophil counts from 4% to 33%. Data on acute stage IgE was available in four patients and ranged from 507 U/mL to 6154 U/mL with the mean value of 3028 U/mL (normal range < 200 U/mL). Liver function tests were abnormal in four patients (cases 2, 3, 4, 5) and CPK elevation was found in three patients (cases 2, 5, 7). Microbiologic examinations were all negative. No bacterial, viral, mycobacterial or fungal organism was isolated. Test for CSF cryptococcal antigen was negative in all patients. IHA tests for ameba on admission and 1 month later were negative. Gram stain and acid-fast stain did not reveal any pathogen. A careful search for third stage larvae of *A. cantonensis* under direct examination of centrifuged CSF was negative. Examination of stool samples did not disclose any parasite ova or protozoa. Chest roentgenography (CXR) of all eight patients revealed no evidence of focal infiltration or parenchymal lesions. MR imaging of four patients with severe cerebral symptoms showed diffuse meningeal enhancement. There was no evidence of localized lesions attributable to the presence of young adult worms. CSF antibody on admission was positive in five out of eight patients (Table 4). Serum antibody on admission was positive in all eight patients. Antibody level of CSF on admission was significantly lower than that of serum on admission ($p < 0.01$).

Clinical course

After admission, all patients received oral mebendazole at a dose of 100 mg twice daily for variable durations (4-11 days) and steroid therapy was given with intravenous dexamethasone initially, followed by oral prednisolone, until all symptoms subsided (Table 1). Two cases relapsed after one course of treatment. Case 3 received irregular treatment and case 2 relapsed after he had been free of symptoms for 10 days. Symptoms became more severe during treatment in one patient (case 4). This patient had general weakness, malaise, and diplopia after a second lumbar puncture during treatment with mebendazole and dexamethasone. He had the longest hospital stay but eventually recovered fully. The other patients had an uneventful hospital course with gradual resolution of symptoms after treatment. All eight patients recovered from meningitis without severe neurologic sequelae. Case 1 had occasional headache requiring analgesic for pain control. Peripheral eosinophil count and liver function returned to normal range on follow-up in all patients.

Discussion

In Taiwan, many cases of meningitis due to *A. cantonensis* infection have been reported. Most cases were children who were infected incidentally after contact with intermediate hosts, most commonly, *A. fulica* or the so-called African giant snail. The largest reported series were from Kaohsiung Medical College by Yii [6] and Hwang [12,13]. In the present outbreak, all eight patients were adults who became infected by eating uncooked golden apple snails (*A. canaliculatus*). Most cases of *A. cantonensis* infection reported in Thailand were in adults between 20 to 40 years old who ate raw snails [16]. In Tahiti, most reported cases acquired infection due to consumption of fresh water shrimp or their products [18].

Five of our eight patients had a definite incubation time from 5 to 12 days. The mean incubation time in reports from Thailand [16] and Tahiti [17] were 16 and 16.5 days respectively. The incubation time was shorter in the cases of Hwang *et al*'s series, ranging from 2 to 45 days with a mean incubation time of 13 days [13]. However, an incubation time as short as one day has been reported in adult cases [19].

According to the classification of Hung and Chen, clinical manifestations of *A. cantonensis* infection can be categorized into five groups as follows: meningitis, meningoencephalitis, ocular lesions, radiculomyelitis and cranial nerve involvement [20]. Three presentations were noted in the present outbreak: meningitis, radiculitis and cranial nerve involvement. All eight patients had fever during admission. Yii [6] and Hwang reported that most cases had fever on admission [13]. In a report from Thailand [16], fever occurred in only 33% of patients. In the present series, all eight patients presented with intractable headache, similar to the previous report from Thailand [16], in which 99% of the patients complained of headache. In contrast, only 48.3% of the cases of Hwang *et al* complained of headache [13]. One of our patients was found to have bilateral abducens nerve palsy. As in the previous report by Punyagupta *et al* from Thailand [16] and Hwang *et al* from Taiwan [13], the most common cranial nerves involved were the sixth and seventh. Hepatomegaly and splenomegaly did not occur in any of our patients, and was also rare in the report from Thailand [16]. However, in Yii and Hwang's series from Taiwan [6,13], hepatomegaly was noted in 46% and 29.9%, respectively. The symptoms and signs of our patients were similar to those in the cases reported from Thailand [16] and Tahiti [18] but different from those previously reported in Taiwan.

Laboratory abnormalities were similar to previous reports including increased peripheral blood and CSF eosinophil counts, transient liver function impairment, elevated CPK and IgE levels. The appearance of CSF in two of our patients had the characteristic cloudy appearance of ricewater, as previously reported by Punyagupta [16]. Two of our patients had CSF eosinophil level of less than 10% in contrast to the previous report from Thailand, and that from Yii and Hwang in Taiwan in which most patients had significant CSF eosinophilia more than 10%. These findings suggest that a CSF eosinophilia of less than 10% cannot rule out the diagnosis of *A. cantonensis* infection.

The diagnosis of *A. cantonensis* infection can be made based on clinical evidence and microbiologic studies including microscopic examination of CSF and detection of antibody or antigen in CSF and serum [24, 25,32,33]. Many other etiologies may cause eosinophilic meningitis including infectious and noninfectious causes, among which *Gnathostoma spinigerum* is the most important [21]. However, *G. spinigerum* infection has never been reported in Taiwan. The clinical manifestations of *G. spinigerum* infection are usually more severe than that in *A. cantonensis* infection. In general, *A. cantonensis* infection is neurotrophic while *G. spinigerum* infection can cause central nervous system (CNS), cutaneous or visceral lesions [22,23]. Our patient did not exhibit the migrating signs characteristic of *Gnathostoma* infection. Although skin rash was found in two of our patients, the lesions were not typical of larvae migrans. Despite the likelihood that manifestations between these two diseases may overlap, serology should allow differentiation between them.

In this series no larvae was recovered from CSF from a total of 22 spinal taps in eight patients. In contrast, Hwang *et al* had an exceedingly high worm recovery rate from CSF of about 43.7% [13]. The use of a modified spinal tapping technique with a pumping method was considered to contribute to this high recovery rate. However we did not use the same technique. The lower level of CSF antibody to 204 kD antigen of larvae in the fifth stage makes it a less sensitive test than serum antibody for detection of *A. cantonensis* infection.

Many anthelminthic agents have been used to treat *Angiostrongylus* infection. Thiabendazole, albendazole, mebendazole, levamisole and ivermectin have all been shown to be effective in treating infected rodents [26-30]. The role of steroid therapy in the treatment of meningitis caused by *A. cantonensis* is still controversial. Punyagupta *et al* [16] concluded that no difference was found among patients who received analgesics alone, analgesics and steroids, or analgesics and antibiotics (penicillin or tetracycline). Although we treated our patients with mebendazole and steroid according to previous recommendations [31], no control group was available for comparison with other anthelminthic agents. Hwang *et al* [12, 13] treated their patients with albendazole or levamisole with good results. Compared with albendazole and levamisole, mebendazole is poorly absorbed from the gastrointestinal tract and has a lower tissue concentration. Albendazole or levamisole thus seem to be better agents for this treatment.

None of our eight patients had severe neurologic sequelae similar to that in the series of Punyagupta [16], in which only one death occurred in a total of 484 patients, and no severe sequelae were found. In contrast to our patients, the cases of Hwang *et al* [12,13] had more sequelae, with four deaths and six patients having permanent neurologic sequelae among 87 cases.

In conclusion, our patients had clinical manifestations and prognosis of *Angiostrongylus* infection which were similar to the cases previously reported from Thailand and different from those previously reported in Taiwan. This discrepancy may be explained by the difference in worm burden and age of patients. A difference in the worm burden of snails and loose tissue density in childhood lead to severe symptoms of children. In addition, children cannot clearly describe their symptoms such as headache and sensory impairment. Whether steroid or anthelminthic chemotherapy aids in the treatment of *A. cantonensis* infection is worth further study.

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