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Eosinophilic Meningitis Attributable to *Angiostrongylus cantonensis* Infection in Hawaii: Clinical Characteristics and Potential Exposures

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Abstract. The most common infectious cause of eosinophilic meningitis is *Angiostrongylus cantonensis*, which is transmitted largely by consumption of snails/slugs. We previously identified cases of angiostrongyliasis that occurred in Hawaii from 2001 to 2005; the highest incidence was on the island of Hawaii. We now report symptoms, laboratory parameters, and exposures. Eighteen patients were evaluated; 94% had headache, and 65% had sensory symptoms (paresthesia, hyperesthesia, and/or numbness). These symptoms lasted a median of 17 and 55 days, respectively. Three persons recalled finding a slug in their food/drink. Case-patients on the island of Hawaii were more likely than case-patients on other islands to consume raw homegrown produce in a typical week (89% versus 0%, $P < 0.001$) and to see snails/slugs on produce (56% versus 0%, $P = 0.03$). Residents and travelers should be aware of the potential risks of eating uncooked produce in Hawaii, especially if it is from the island of Hawaii and locally grown.

INTRODUCTION

Eosinophilic meningitis is an uncommon clinical syndrome characterized by meningeal inflammation and an eosinophilic pleocytosis in the cerebrospinal fluid (CSF). Non-infectious etiologies include intracranial hardware, medications, and neoplasms.[1] Among the infectious causes, the rat lung worm *Angiostrongylus cantonensis* is the most common worldwide.[1,2] Individual cases and outbreaks of infection with this nematode have been reported for years in endemic areas of Southeast Asia and the Pacific Rim (e.g., China, Taiwan, Thailand, and the Pacific Islands) and travelers returning from endemic areas.[3–6] In the United States, angiostrongyliasis is endemic in Hawaii; one human case was reported in New Orleans, LA.[7] *A. cantonensis* is becoming more widespread in the world, in part because of ship-borne transport of rats and introduction of non-native snails/slugs.[3,4,8,9]

Humans become infected by ingesting third-stage larvae in intermediate hosts (slugs and snails) or transport hosts (e.g., freshwater crustaceans). Although intentional consumption of snails/slugs is common in certain cultures, in areas like Hawaii, such practices may be less customary. There have been few studies of potential sources of accidental or incidental exposure; presumptive transmission from food items contaminated with larvae (e.g., salad or juice containing snails, slugs, or larvae) has been reported.[5,10,11] After penetrating the gastrointestinal tract, the larvae spread hematogenously to the central nervous system.[12,13] Following an average incubation period of 1–3 weeks, symptomatic persons often develop headache, meningeal symptoms, and sensory abnormalities.[14–17] Uncommonly, infection results in severe neuropathic and motor symptoms, coma, and death.[14–17] Most studies have reported acute symptoms; to our knowledge, few descriptions of long-term outcomes have been published.[18–20] Treatment is primarily supportive; systemic corticosteroids may decrease symptom duration, but the use of antihelminthic therapy is controversial.[21,22]

We previously reported a laboratory- and hospital-based investigation in Hawaii that included case data from January 2001 to February 2005.[23] In that study, we found a cluster of angiostrongyliasis cases that occurred on the island of Hawaii from November 2004 to February 2005.[23] We subsequently performed a retrospective analysis of cases from January 2003 to April 2005 (including the cluster cases) to ascertain clinical and epidemiologic characteristics. We report our findings here, with an emphasis on long-term sequelae and possible exposures for persons in Hawaii.

MATERIALS AND METHODS

Ascertainment and classification of cases. Cases were ascertained using methodology described in detail previously.[23] In brief, we carried out a retrospective review of CSF data provided by clinical laboratories in Hawaii for all lumbar punctures (LPs) performed at 22 of Hawaii's 24 acute care hospitals from January 2001 to February 2005. Eosinophilic meningitis was defined as the presence of ≥ 6 white blood cells (WBC) per mm^3 and either an eosinophil percentage of ≥ 10% or an absolute eosinophil count of ≥ 10/mm^3 in the CSF.[2] For each of six persons with multiple LPs, the LP with the highest absolute eosinophil count was included in the analyses. Persons were excluded if they were not in Hawaii during the exposure period (the 45 days before symptom onset) or if their CSF WBC or eosinophil counts were below inclusion levels after adjusting for the presence of red blood cells (RBC).

For persons who met the inclusion criteria for eosinophilic meningitis, we systematically reviewed their medical record to identify documented signs and symptoms and to categorize cases by known or likely cause. We sought alternative explanations for eosinophilic meningitis (including medications, intracranial hardware, neoplastic disease, or recent exposure to neuroradiographic contrast medium) and analyzed the available laboratory data for any infectious cause of eosinophilic meningitis (including fungi, viruses, bacteria, and parasites).

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If no other potential etiology for eosinophilic meningitis was identified by the study neurologist (J.J.S.) and the case was clinically and epidemiologically compatible, we attributed it to *A. cantonensis* infection. In part on the basis of published descriptions of angiostrongyliasis, we defined a clinical case as a person with two or more of the following symptoms or signs: headache, neck stiffness or nuchal rigidity, visual disturbance, photophobia or hyperacusis, cranial nerve palsy, abnormal skin sensation (e.g., paresthesia or hyperesthesia), sensory deficit, nausea or vomiting, documented fever, irritability (if < 4 years of age), and bulging fontanelle (if < 18 months of age).[1,2,5,11,14–16,24,25] A parasitologically confirmed case was defined as having *A. cantonensis* larvae or young adult worms identified in the CSF.

Interviews of case-patients. From March to June 2005, two study personnel conducted in-depth telephone interviews of case-patients (or their surrogates) to assess clinical manifestations, long-term outcomes, and potential exposures. To reduce recall bias, we limited interviews to patients whose LP was performed from January 2003 to February 2005; we also included two case-patients whose LPs were in March and April of 2005 (i.e., shortly after completion of the retrospective incidence study).

Survey instrument. The interview addressed previously described clinical manifestations of angiostrongyliasis as well as duration, temporal pattern, character, severity, and distribution of symptoms associated with the initial presentation; case-patients rated their wellbeing and estimated the duration of their convalescence in days.[5,14,16,26] For persons with a history of headaches, we inquired whether their symptoms were compatible with their prior headaches. One infant case-patient was only included in the analysis of objective findings. The interview also addressed past medical history, medications taken before the LP, and treatment rendered.

A food history was obtained to identify possible ingestion of intermediate or transport hosts of *A. cantonensis* (specifically, snails, slugs, frogs, and freshwater shellfish) during the exposure period. We inquired about typical habits (during the exposure period and the year before symptom onset) for eating these foods and purchasing, growing, consuming, and handling raw produce that might have contained (or been exposed to) snails/slugs or their slime trails. Homegrown produce was defined as coming from one's own or a non-commercial garden. Produce consumption patterns were compared between the island of Hawaii (where the outbreak was centered) and Oahu and Maui combined.[23] We also assessed contact with *A. cantonensis* hosts through activities such as gardening.

Data analysis and human subjects protection. Data were entered into Epi Info, Version 2002 (Centers for Disease Control and Prevention [CDC], Atlanta, GA) and analyzed using SAS version 9.1 (SAS Institute, Cary, NC). Statistical testing was performed using the Fisher exact test and the Wilcoxon rank sum test. Spearman correlation coefficients and linear regression models were used to assess the association between laboratory values and illness duration. Informed consent was obtained from adult participants (or their surrogates) and the parents or legal guardians of minors. We followed CDC's human subjects policies.

RESULTS

Demographics. All 18 persons who met our case definition for angiostrongyliasis enrolled in the study. One case (in an infant) was parasitologically confirmed; 17 cases were clinically defined. The case-patients were interviewed a median of 4.5 months after symptom onset (range < 1–24.8 months). Eleven (61%) were male; the median age was 31.8 years (range = 11 months to 45.5 years) (Table 1), and only one case-patient was

Table 1

Demographic, laboratory, and symptom data for persons with eosinophilic meningitis attributable to infection with *Angiostrongylus cantonensis* in Hawaii from January 2003 to April 2005 ($N = 18$)

				CSF indices					Peripheral blood indices				
Patient no.	Age (years)	Sex	Days between symptom onset and LP	WBC (cells/mm³)	RBC (cells/mm³)	% Eo	Glu (mg/dL)	Prot (mg/dL)	WBC (cells/mm³) × 1,000	% Eo	Initial symptom(s)	Duration of headache (days)	Duration of sensory symptoms (days)
Median	32	–	7	637	7	33	46.5	110	10.3	10	–	–	–
1	0.9	F	6	442	1,629	67	52	–	16	16	Fever	UNK	UNK
2	17	M	7	1,583	0	74	37	94	7.8	19	Headache	21	NA
3	18	M	23	910	9	54	35	76	11.8	10	Myalgia and fatigue	42	28
4	21	F	2	419	5	6	63	54	–	–	Headache	310*	NA
5	22	M	3	424	56	7	67	108	11.6	0	Headache and fever	10	10
6	25	M	7	690	735	42	54	43	5.9	4	Myalgia	7	NA
7	29	M	15	513	1	51	–	–	9.5†	7	Chest pain	18	50*
8	31	M	8	344	1	52	51	60	8.2	16	Paresthesia	21	14
9	31	F	12	129	4	16	32	227	7.2	9	Hyperesthesia	7	90
10	32	M	1	684	46	11	51	119	8.3	3	Headache	44*	NA
11	34	F	1	703	–	4	70	56	10.3‡	16	Headache	70*	5
12	35	F	14	8,168	1	60	39	165	8.8	3	Headache	14	NA
13	35	M	3	843	6	14	26	110	8	7	Headache	3	NA
14	35	F	11	860	2	23	26	110	16.7‡	4	Lethargy	7	82*
15	35	M	7	330	–	20	–	–	20.3	24	Abdominal pain	2	18*
16	42	M	48	1,425	203	12	28	215	12.1‡	20	Paresthesia	NA	129*
17	43	M	1	373	14	47	36	186	15.9	8	Headache	UNK	UNK
18	46	F	12	590	8	43	48	153	14	27	Paresthesia	14	150*

WBC = white blood cell count; RBC = red blood cell count; Eo = eosinophil; Glu = glucose; Prot = protein; NA = not applicable; UNK = unknown.
* Symptom still present at time of interview.
† Peripheral blood WBC and eosinophil percent were not available on the same day: WBC was from day 3, and eosinophil percent was from day 2.
‡ Peripheral blood results were not from the same day as CSF results. Reported results were from closest day to LP.

less than 17 years old. Seven case-patients were Caucasian, six were Asian, and five had mixed ethnicities. Four case-patients (22%) went only to an emergency department, and the other 14 (78%) were hospitalized (median duration = 5 days, range = 2–68 days).

Symptoms. Headache, the most frequently reported symptom (94%), was the initial manifestation in 8 (44%) case-patients, one of whom also had fever (Tables 1 and 2). The headaches were severe in 94%, and the distribution was primarily occipital (38%) or generalized (31%). Headaches lasted a median of 17 days; the two individuals whose headaches had persisted more than 2 months (310 and 70 days) had had intermittent symptoms. Other initial symptoms included hyperesthesia/paresthesia (22%), myalgia (11%) or chest/abdominal discomfort (11%), fever (a total of 11%) and lethargy (6%).

Although not usually the initial manifestations, meningeal symptoms often developed during the clinical course; 71% of case-patients reported neck pain or stiffness, and 65% reported photophobia. Sensory symptoms (paresthesia [59%], hyperesthesia [59%], and numbness [47%]) were usually symmetric and present in the limbs (Table 2). Six (35%) patients reported migratory sensory symptoms. Descriptions of sensory symptoms included "pain under the surface (of the skin)" and "like a sunburn" as well as discomfort with wearing clothing. Paresthesia, hyperesthesia, and numbness lasted a median of 21, 28, and 47 days, respectively (Table 2). Fever, focal weakness, cranial nerve dysfunction, and vision changes were also common (Table 2). There were no significant associations between age or sex and the presence of any particular symptom (data not shown).

TABLE 2

Presence and duration of symptoms among persons with eosinophilic meningitis attributable to infection with *Angiostrongylus cantonensis* in Hawaii from January 2003 to April 2005 ($N = 18$)

Symptom	N (%)*	Median duration in days (range)	Number of persons with symptom still present at time of interview†
Headache	16 (94)	17 (2–310)	3
Fatigue	14 (82)	28 (2–180)	6
Arthralgia/myalgia	14 (82)	10 (2–740)	6
Neck pain/stiffness	12 (71)	7 (5–56)	1
Fever‡	12 (67)	7 (2–73)	1
Sensory symptoms	11 (65)	55 (5–150)	5
Hyperesthesia	10 (59)	28 (10–150)	5
Paresthesia	10 (59)	21 (5–129)	3
Numbness	8 (47)	47 (10–150)	5
Photophobia	11 (65)	10 (2–35)	2
Cranial nerve abnormality	11 (65)	11 (1–52)	2
Dizziness	10 (59)	11 (1–180)	1
Vision changes§	9 (53)	16 (2–49)	1
Vomiting	9 (50)	3 (2–14)	0
Tremors or muscle jerking	8 (47)	30 (1–60)	4
Focal limb weakness	7 (41)	18 (1–150)	2
Hyperacusis	7 (41)	10 (2–135)	2
Confusion	7 (41)	10 (4–74)	3
Diarrhea	5 (28)	3 (1–8)	0
Rash	4 (22)	2 (2–28)	0
Bowel or bladder problems	1 (6)	45	0

* Denominator is 18 for objective findings (fever, rash, vomiting, and diarrhea) that could be assessed for the 11-month-old infant; otherwise, the denominator is 17.

† Interviews occurred between March and June 2005, which was a median of 4.5 months after symptom onset (range < 1–24.8 months).

‡ For the 9 of 12 persons with fever who recalled a maximum temperature, the median was 102°F (range = 100–105°F).

§ Vision changes included blurred vision ($N = 3$), double vision ($N = 1$), and both blurred and double vision ($N = 5$).

Laboratory results, radiographic findings, and treatment. LPs were performed a median of 7 days after symptom onset. In the CSF, the median WBC was 637 cells/mm^3, the median eosinophil percentage was 33% (Table 1), and the median absolute eosinophil count was 177 cells/mm^3. For case-patients with available data, the median glucose level was 46.5 mg/dL, and 8 of 16 (50%) case-patients had hypoglycorrhachia; the median protein level was 110 mg/dL, and the value was elevated for 14 of 15 (93%) case-patients.

In the peripheral blood, the median WBC was 10,300 cells/mm^3, and 9 of 17 (53%) case-patients had leukocytosis (> 10,000 cells/mm^3). The median eosinophil percentage was 10%, and 13 of 17 (76%) case-patients had eosinophilia (> 5% or > 500 cells/mm^3). There was no correlation between degree of eosinophilia in the CSF and periphery. Higher peripheral eosinophil counts were noted among case-patients who had skin numbness compared with those who did not (median = 1,369 versus 428 cells/mm^3, $P = 0.03$). A higher CSF eosinophil percentage correlated with a longer duration of photophobia ($r = 0.74$, $P < 0.01$), and a higher CSF WBC correlated with a longer duration of numbness ($r = 0.78$, $P = 0.04$).

Six case-patients underwent brain and/or spine magnetic resonance imaging, and four (66%) scans were abnormal. Observed abnormalities included subarachnoid hyperintensities and meningomyelitis, abnormal signal intensity in the pons and corona radiata, leptomingeal and facial nerve enhancement, and lacunar infarcts.

Thirteen case-patients (72%) received pain medications, including narcotics ($N = 9$) for a median of 30 days (range = 5–120 days) or gabapentin ($N = 4$) for a median of 9 days (range = 7–63 days). At the time of the interview, four (24%) persons reported having fully recovered after a 14-day median duration of illness (range = 10–14 days); of the 13 who reportedly were still ill, 3 (23%) continued to require narcotics. Overall, nine (50%) case-patients had received corticosteroids, and one person had received mebendazole. Neither treatment was associated with shorter illness duration.

Exposures. Of the 18 case-patients, 10 lived on the island of Hawaii, 9 of whom lived within a 20-mile radius in a small, agrarian community (including 7 persons who used catchment water). Five case-patients lived on Oahu, two persons lived on Maui, and one person was visiting Oahu from out of state. One person recalled eating a cooked snail at a restaurant during the exposure period. Three other case-patients discovered slugs in their food/drink; one person found a slug in her cup of tea, and two persons saw a slug in a shared salad. The infant was presumed to have ingested snails/slugs or contaminated grass; snails and slugs had been seen on the property, and she was found with grass in her mouth.

Excluding the infant, the other 17 case-patients consumed raw produce or fruit at home or in restaurants. Case-patients on the island of Hawaii were more likely than case-patients on Maui or Oahu to consume raw home grown produce during a typical week (89% versus 0%, $P < 0.001$) and to see either snails/slugs or their slime trails on produce (56% versus 0%, $P = 0.02$). Case-patients on the island of Hawaii also consumed raw green, leafy vegetables more frequently (median of 7 versus 2.5 times per week, $P = 0.05$) and washed their produce less consistently than case-patients on Maui or Oahu (22% versus 75% of the time, $P = 0.04$). Comparing adult case-patients on the island of Hawaii with case-patients on Oahu and Maui, nine of nine (100%) versus three of eight (38%)

persons gardened or had bare-handed soil contact ($P = 0.009$), and seven of nine (78%) versus zero of eight persons had touched snails/slugs ($P = 0.002$).

DISCUSSION

A. cantonensis infection is the most common infectious cause of eosinophilic meningitis worldwide.[1,2] To our knowledge, ours is the first epidemiologic study to use a systematic evaluation of laboratory data to identify and evaluate persons in an endemic area with eosinophilic meningitis that was likely caused by *A. cantonensis*.[27–29] We found that, in our cohort of patients in Hawaii, headache and sensory symptoms may be prolonged and require long-term analgesia. Affected persons in Hawaii often did not report the classic exposure of snail or slug ingestion; it is possible that accidental ingestion of intermediate hosts (directly or through fresh produce) caused infection.

Our study shows that symptoms can be protracted. Previous reports suggest that headaches last up to 8 weeks,[5,16] but we found that they may recur intermittently over 10 months. Paresthesia, hyperesthesia, and numbness also may persist for months.[30,31] Sensory symptoms were notable for their migratory nature and the association between numbness and higher peripheral eosinophil counts. Vision changes (including blurred or double vision) were more frequently reported by case-patients in our cohort than in previous studies; these symptoms could be caused by larval invasion or an inflammatory response.[13,15,16,18,32,33]

Potential exposures within this cohort differ from exposures reported for point source outbreaks, particularly in Asia. With some exceptions, infected persons identified in outbreaks in Taiwan, Thailand, and elsewhere knowingly or intentionally consumed slugs or snails (e.g., during a meal or for medicinal purposes).[14,15,18,27] In our study in Hawaii, only one person knowingly ate a snail (which was cooked and thus, unlikely to have caused infection), and three persons discovered a slug in their food/drink. Other studies have reported infection from consuming undetected small slugs, snails, or planaria on produce (e.g., in a Caesar salad and raw vegetable juice).[5,10,11,28,34] Although we did not identify a point source for this outbreak, unintentional consumption of snails/slugs or larvae in homegrown produce likely occurred on the island of Hawaii; almost all case-patients there described consuming produce from their own (or a non-commercial) garden, usually unwashed. Environmental studies found *A. cantonensis* larvae in slugs in the yards of the infant with a parasitologically confirmed case and two case-patients who shared a household.[35,36]

The possibility of transmission through snail/slug slime trails on produce requires further investigation. Studies have detected *A. cantonensis* larvae and larval DNA in the slime trails of 12% of infected snails/slugs, but it is unclear whether the parasite can be transmitted in this mucus.[9,37,38] Effective, practical strategies for removing *A. cantonensis* larvae from potentially contaminated produce have not been identified. Although larvae can be killed by bleach, they may survive in vinegar and saturated cooking salt solutions.[39] To our knowledge, detailed studies have not been done of larval removal after washing with water, but reports suggest cross-contamination of vegetables can occur in common wash buckets.[40–43]

Infection from consumption of unwashed, homegrown produce may have been compounded by changes in the snail/slug host populations around the time of the outbreak.[23,36] In 2008, of 31 snail/slug species at selected nurseries in Hawaii, 29 (94%) species were alien to Hawaii, and 5 (16%) species had not previously been documented in the state.[44] In particular, the introduction of *Parmarion martensi* may have been a factor in the clustering of suspected angiostrongyliasis cases, especially on the island of Hawaii.[23,36] This semi-slug was first documented on Oahu in 1996 and on the island of Hawaii in 2004.[36,44] Data from a study in 2005 suggest that there were increasing numbers of *P. martensi* in home gardens, particularly on the island of Hawaii;[36] some of our case-patients reported similar anecdotal evidence. Juvenile forms of *P. martensi* tend to be smaller than other slugs/snails and therefore, might be even less readily noticed on produce.[36] Furthermore, they reportedly are efficient at transmitting *A. cantonensis*, because a higher proportion are infected (compared with *Veronicella cubensis*, the dominant large mollusk species in the area), they have greater parasite burdens, and they tend to enter human habitats (including houses and water tanks).[36]

Our understanding of transmission and the potential role of *P. martensi* is limited, in part because we were unable to identify a common source for this geographically and temporally dispersed cluster of suspected cases. Indeed, although we included a detailed food history, unrecognized exposures may have caused infection. Furthermore, the lack of a control group made it impossible to compare the frequencies of potential exposures and symptoms among case-patients with frequencies among uninfected persons; however, identification of an appropriate control group could be difficult, in part because of the possibility of asymptomatic or mild infection and the lack of a reliable serologic or diagnostic test.

Our study had other limitations. Only one case was confirmed parasitologically; the other 17 cases had compatible clinical and epidemiologic features.[23] Misclassification of the cause of the patients' meningitis was possible, but in most angiostrongyliasis-endemic areas, parasitologic confirmation is unusual. Presumptive diagnosis is typical; recovery of larvae and adult worms from the CSF is rare, except among Taiwanese children.[15] Although we sought to exclude all other known infectious and non-infectious etiologies of eosinophilic meningitis using data available in the medical records, we were unable to perform additional laboratory testing, because the study was retrospective. It is unlikely that a different, undiagnosed parasitic infection accounted for the cases of eosinophilic meningitis, because Hawaii is known to be hyperenzootic for *A. cantonensis* but not for *Gnathostoma spinigerum* or *Baylisascaris procyonis*, the two other parasites commonly associated with eosinophilic meningitis.

Because of our case detection methods, we did not include persons who were asymptomatic, did not undergo an LP, or had CSF data that did not meet criteria for eosinophilic meningitis (e.g., fewer eosinophils might have been present if the LP was done early or late in the clinical course).[5,16] Our case criteria might have biased our results by including more severe cases, but they increased the specificity of the case definition. As with all retrospective studies, physical examination data were limited by reliance on potentially incomplete medical records, and symptom and exposure recall bias was possible. Although we attempted to limit recall bias by including only the most recently diagnosed cases (see Materials and Methods), the fact that a median time of 4.5 months elapsed from symptom onset

to the interview suggests that erroneous recall was possible.[23] The persistence of symptoms at the time of the interview suggests that reporting was generally accurate but did impair our ability to determine the duration of some symptoms. Finally, asking about typical food consumption patterns is a common approach in investigations of prolonged outbreaks.

In conclusion, we described the clinical and laboratory features as well as possible exposures associated with suspected *A. cantonensis* infection in a cohort of persons in Hawaii from January 2003 to April 2005. We found that symptoms can be protracted; only a minority of patients reported complete recovery even months later. Clinicians should consider the diagnosis in persons with eosinophilic meningitis who live in (or have traveled to) Hawaii, even if a history of snail/slug ingestion is not elicited. Persons in endemic areas should be aware of the potential risk for infection through consumption of contaminated produce and may benefit from careful examination of raw food, especially leafy greens. Much remains unclear regarding the risk factors for transmission in Hawaii. Additional studies are needed to facilitate targeted public health interventions.

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