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Angiostrongylus cantonensis Meningoencephalitis in Three Pediatric Patients in Florida, USA

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Abstract

Eosinophilic meningoencephalitis caused by *Angiostrongylus cantonensis* has been reported in several southern U.S. states and Hawai'i. We present the first locally acquired human cases of *A. cantonensis* meningoencephalitis in three children in Florida, occurring between June 2021 and January 2022. Clinicians should be attuned to this possible diagnosis in this region.

Keywords

Angiostrongylus cantonensis ; angiostrongyliasis; eosinophilia; eosinophilic meningitis; rat lung worm

DESCRIPTION OF CASES

Case 1

A previously healthy 19-month-old, fully immunized male presented in summer 2021 to a hospital in Orlando, Florida, with a fever of 103°F, 11 days of malaise, and refusal to walk. He had no significant exposure other than the geophagia of sand at the beach. He had a positive Kernig sign and a lack of spontaneous lower extremity movement. An ophthalmologic evaluation was unremarkable. Admission blood culture had no growth.

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Cerebrospinal fluid (CSF) on hospital day 2 showed pleocytosis with a white blood cell count of 143 cells/μL with 8% eosinophils; opening pressure (OP) was not obtained. CSF bacterial culture was negative for bacterial growth; CSF was not assessed for the larva. Multiplex polymerase chain reaction (PCR) panel result was positive for human herpesvirus 6 (HHV6); SARS-CoV2-PCR was negative. Fevers reached 105.1°F, and blood absolute eosinophil count (AEC) fluctuated between 90 and 1,980 cells/μL. A commercial microbial cell-free DNA next-generation sequencing (mcfDNA NGS) test (Karius®, Redwood City, CA) detected *A. cantonensis* DNA at 186 molecules/μL in plasma. CSF sample obtained on hospital day 15 revealed pleocytosis and 27% eosinophils. Testing of CSF at Centers for Disease Control and Prevention (CDC) was positive for *A. cantonensis* DNA by PCR and negative for *Baylisascaris procyonis* antibodies. The patient received intravenous methylprednisolone 1 mg/kg every 12 hours (2 mg/kg/day) for 7 days with rapid resolution of symptoms including fever. Given rapid improvement with steroids, albendazole was not prescribed. He recovered without sequelae and was discharged home on hospital day 21. By 3 months after discharge, he was well-appearing and at his neurological baseline.

Case 2

A previously healthy 10-year-old boy was admitted to a hospital in Tampa, Florida in October 2021 with 3 weeks of progressive headache and vomiting concerning for meningitis. The patient reported eating a raw snail 1 month prior to admission “on a dare by a friend.” He had no history of travel and no other exposures of concern. OP was not obtained during the initial LP. No larvae were visualized on the exam. Treatment with ceftriaxone was started. The patient was admitted to the intensive care unit (ICU) and on hospital day 2 he required intubation and mechanical ventilation for altered mental status and central apnea. He developed intracranial hypertension initially treated with mannitol, 3% saline, and mild hyperventilation. OP was 45 mmHg during intracranial pressure (ICP) monitor placement on hospital day 2. Brain CT revealed mildly enlarged ventricles likely related to obstructive hydrocephalus, and an external ventricular drain (EVD) was placed on hospital day 6. The brain MRI was abnormal. Antimicrobial coverage was broadened to cefepime, vancomycin, and fluconazole given worsening clinical status and unknown diagnosis. CSF analysis was notable for pleocytosis; eosinophils in the CSF ranged from 18% to 40%. Blood AEC ranged from 250 to 2,100 cells/μL. CSF cultures were negative for bacterial growth. CSF studies were negative for enterovirus, herpes simplex viruses 1 and 2, *Bartonella* spp., and Epstein Barr virus. The result of *Toxocara spp.* antibody testing was negative. Due to concern for *A. cantonensis* meningoencephalitis, the patient received intravenous methylprednisolone 10 mg/kg for 5 days starting on hospital day 7, followed by a taper, and albendazole 400 mg twice daily starting on hospital day 9. Commercial microbial cell-free DNA next-generation sequencing (mcfDNA NGS) test (Karius®, Redwood City, CA) was positive for *A. cantonensis* at 27 molecules/μL. The patient was extubated on hospital day 12, EVD was removed on hospital day 18, and he was discharged to inpatient rehabilitation on hospital day 22. The patient completed inpatient rehabilitation and returned to his normal activities without gross neurological deficits several months after hospitalization.

Case 3

A previously healthy 8-month-old, fully immunized female infant presented to a hospital in St. Petersburg, Florida, in January of 2022 with six days of vomiting, lethargy, fever up to 103°F and intermittent left-sided esotropia. SARS-CoV-2 test was negative. She had no significant travel and no known history of unusual ingestions. On admission, she was irritable but consolable. CSF obtained on hospital day 1 had pleocytosis with 41% eosinophils; OP was not obtained. CSF bacterial culture and multiplex PCR panel results were negative; CSF was not assessed for larva. Blood AEC ranged from 700 to 2,360 cells/μL. Commercial microbial cell-free DNA next-generation sequencing (mcfDNA NGS) test (Karius®, Redwood City, CA) of plasma returned positive for *A. cantonensis* at 127 molecules/μL. Fevers and emesis resolved after starting parenteral methylprednisolone 2 mg/kg/day. On hospital day 6, she developed hypotonia and ataxia, requiring ICU monitoring. She received acetazolamide and increased methylprednisolone dosing to 5 mg/kg/day; albendazole was not prescribed. No seizure activity was detected on the electroencephalogram (EEG). The patient was discharged home on hospital day 14 to complete a 4-week taper of oral steroids. She required physical therapy for motor development. By 16 months of age, she was meeting all developmental milestones and had improvement in left eye esotropia without gross neurologic sequelae.

FOLLOW UP

CDC and Florida Department of Health conducted a public health investigation into the three cases, including discussions with patient families to elicit travel history, symptoms, duration of illness, risk factors, ingestions, and review of medical records. Testing of anonymized CSF specimens performed at CDC confirmed the presence of *A. cantonensis* in two of three patients based on positive PCR results (Table 1). One of three samples had DNA below the limit of PCR detection but had a known exposure risk and positive microbial cell-free DNA next-generation sequencing (mcfDNA NGS) test (Karius®, Redwood City, CA). Therefore, all three patients were considered confirmed cases of *A. cantonensis* for the purposes of the public health investigation.

DISCUSSION

A. cantonensis is a parasitic nematode known as rat lungworm. The larvae progress through freshwater and terrestrial mollusks to the definitive hosts, rats, where they achieve maturation in the pulmonary arteries over an approximately 45-day life cycle. Humans become accidental hosts when they accidentally or deliberately ingest the infected mollusks [1].

Angiostrongylus cantonensis is the leading cause of infectious eosinophilic meningitis worldwide, especially in tropical regions where the parasite is endemic [2]. Over the last few decades, *A. cantonensis* has been identified in increasingly broad geographic regions and is considered an emerging infectious disease. It is endemic in many parts of Asia, the Pacific Islands, Australia, South America, and the Caribbean [1]. Angiostrongyliasis has been endemic in Hawai'i since the late 1950s [3]. While human infections are still rare, there is evidence from animal infections that the parasite is spreading. In Florida, the

first published report of *A. cantonensis* infection occurred in a primate at a Miami zoo in 2003 [4]. Since then, *A. cantonensis* has been identified in definitive and intermediate hosts throughout the state [5]. Since 1995, human cases have been periodically diagnosed in the southern U.S., many of them locally acquired [6] (Table 2). The three cases reported above represent the first known locally acquired human cases of angiostrongyliasis in Florida.

Clinical presentations of angiostrongyliasis vary widely. The typical presentation may include fever, headache, generalized weakness, hyperesthesias, and meningismus [2, 6–8]. The severity of illness and prognosis depends on the parasite burden; spontaneous resolution without long-term sequelae is common but severe sequelae, including coma and death, can occur [8]. While most patients with neuroangiostrongyliasis meet the criteria of eosinophilic meningitis with 10 eosinophils/mm^3 or 10% eosinophils present in the CSF, blood and CSF eosinophil counts can fluctuate. One retrospective cohort study of adults with eosinophilic meningitis due to angiostrongyliasis showed that only 44% of patients had eosinophilia in peripheral blood and only 56% had increased eosinophils in CSF on presentation [9]. Repeat CSF analysis may aid in diagnosis.

The definitive diagnosis requires visualization of the larvae in the CSF or detection of *A. cantonensis* DNA through real-time PCR of CSF samples [10]. Serologic testing is not available. Currently, *A. cantonensis* PCR diagnostic testing is only available through the Hawai'i State Public Health Laboratory for patients in Hawai'i and CDC's Parasitic Diseases Laboratory. In all three cases described above, a commercial microbial cell-free DNA next-generation sequencing (mcfDNA NGS) test (Karius®, Redwood City, CA) identified *A. cantonensis* DNA using peripheral blood samples. The judicious use of novel diagnostic tools may expedite the diagnosis and appropriate management of patients with neuroangiostrongyliasis.

Treatment of angiostrongyliasis includes primarily supportive care and symptomatic management. Lumbar puncture often provides relief of headache symptoms by decreasing intracranial pressure [2]. Treatment with steroid monotherapy or steroids combined with antihelminth therapy are also options, although the literature is mixed regarding patient outcomes with these treatments [8, 11]. In one randomized control study of clinical outcomes in patients treated with prednisone alone versus prednisone and albendazole, all patients recovered, and there was no significant difference in outcome between the two groups [12]. Subject matter experts are available for consultation through CDC's Parasitic Diseases Branch (parasites@cdc.gov or 404-718-4745).

CONCLUSIONS

These patients represent the first known locally acquired human cases of *A. cantonensis* infection in Florida. While parasitic meningoencephalitis due to angiostrongyliasis in the continental U.S. is rare, it should be considered in the differential diagnosis in areas where the parasite is known to be present, even in the absence of previous human cases. CSF pleocytosis with any eosinophils should prompt testing for angiostrongyliasis in these regions. Prompt molecular testing with directed CSF PCR tests or plasma-based mcfDNA NGS test can aid in diagnosis.

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Data availability.

Additional data are available for specific cases with author approval.

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Table 1.

Summary of Cases

	Case 1	Case 2	Case 3
Age and sex	19-month-old male	10-year-old male	8-month-old female
Location	Orlando, Florida	Tampa, Florida	St. Petersburg, Florida
Exposure	No known exposure but had a history of pica including geophagia of beach sand	Ate a raw snail on a dare	No known exposure
Clinical signs	Fever to 103°F, malaise, vomiting, refusal to walk, positive Kernig sign, lack of spontaneous lower extremity movement	Headache, vomiting	Fever to 103°F, vomiting, lethargy, left-sided intermittent esotropia, decreased smile
Imaging	**Hospital day 2** MRI brain and spine were normal	**ED presentation** CT brain showed enhancement of dural and leptomeningeal areas **Day 1 hospitalization** MRI brain had FLAIR sulcal hyperintensity, leptomeningeal enhancement, cerebellar tonsillar ectopia	MRI brain had nonspecific findings of enlarged ventricles, dural enhancement and signal change to right temporal region and right basal ganglia.
Laboratory results: Blood absolute eosinophil count	0.09–1.98 × 10^3 cells/μL	0.25–2.1 × 10^3 cells/μL	0.7–2.36 × 10^3 cells/μL
First CSF results	**Hospital day 2** WBC 143 cells/μL 44% lymphocytes 38% monocytes 4% neutrophils 6% atypical lymphocytes 8% eosinophils	**ED presentation** WBC 239 cells/μL 70% lymphocytes 9% monocytes 2% neutrophils 18% eosinophils	**Hospital day 1** WBC 174 cells/μL 38% lymphocytes 13% monocytes 2% neutrophils 41% eosinophils
Second CSF results	**Hospital day 15** WBC 124 cells/μL 14% lymphocytes 25% monocytes 1% neutrophils 28% atypical lymphocytes 27% eosinophils Glucose 55 mg/dL Protein 52 mg/dL	**Hospital day 4** WBC 244 cells/μL 54% lymphocytes 3% monocytes 2% neutrophils 40% eosinophils	
***A. cantonensis* CSF PCR Result**	Reactive	Non-reactive	Reactive
Karius	**Hospital day 10** Positive at 186 molecules/μL	**Hospital day 8** Positive at 27 molecules/μL	**Hospital day 5** Positive 127 molecules/μL
Treatment	Methylprednisolone 2 mg/kg/day IV × 7 days Oral prednisone taper × 3 weeks	Methylprednisolone 10mg/kg IV twice daily × 3 days followed by 20-day taper with transition from IV to PO prednisolone at day 12 of taper Albendazole 400 mg twice daily × 14 days	Methylprednisolone 2 mg/kg/day, increased to 5 mg/kg/day for total of 7 days then oral prednisone taper × 4 weeks

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	Case 1	Case 2	Case 3
Outcome	Recovered without sequelae	Required inpatient rehabilitation and returned to normal activities without gross neurological deficits	Required physical therapy and continued meeting developmental milestones without gross neurologic sequelae

Table 2.

Representative Pediatric *A. cantonensis* Meningoencephalitis Cases in the Continental United States

Reference, Year	Age[a], Sex[b]	Location	Symptoms/Signs	Presumed Exposure	Diagnostic Methods	Treatment (Duration)	Outcome	Locally Acquired
New, 1995 [13]	11 y M	New Orleans, LA	Low grade fevers, myalgia, headache, stiff neck, vomiting	Raw snail ingestion	Serology enzyme immunoassay (Taiwan)	None	Recovered	Yes
Foster, 2016 [14]	19 m F	Houston, TX	Prolonged high fever (*T*max: 40°C), irritability, ataxia, refusal to ambulate	Unknown	CSF PCR (CDC)	Albendazole (400 mg daily × 10 days) Methylprednisolone 2 mg/kg/day × 7 days, tapered over 14 days	Recovered	Yes
Foster, 2016 [14]	13 m M	Houston, TX	Prolonged high fever, irritability, malaise, bulging fontanelle, nuchal rigidity	Lettuce leaf ingestion	CSF PCR (CDC)	Prednisone 2mg/kg/day x 14 days followed by taper	Recovered; speech delay	Yes
Al Hammoud, 2017 [15]	12 m F	Houston, TX	High fevers, irritability, refusal to bear weight	Unknown	CSF PCR (CDC)	Albendazole (14 days), Prednisone (3 months including taper)	Recovered	Yes
Tucker, 2017 [16]	2 y M	Mobile, AL	Fevers, irritability, ataxic gait, strabismus, papilledema	Geophagia	CSF PCR (CDC)	Albendazole (20 days), Methylprednisolone (10 days)	Recovered	Yes
Flerlage, 2017 [17]	12 m M	Memphis, TN	Fevers, irritability, decreased oral intake, emesis	Unknown	CSF PCR (CDC)	Albendazole (3 weeks), Dexamethasone (3-week taper)	Recovered	Yes

[a]Age as documented in months (m) or years (y).

[b]Sex is documented as male (M) or female (F).

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