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Intracranial Hypertension Secondary to Eosinophilic Meningitis Caused by *Angiostrongylus Cantonensis*

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***Angiostrongylus Cantonensis*, a nematode, is a well-known cause of eosinophilic meningitis in endemic areas such as Southeast Asia, the Pacific Islands, and Hawaii. Nevertheless, an increasing number of cases in the southeast of the U.S. have been documented recently, specifically in Louisiana, Texas, and Florida. Infection is acquired after ingesting undercooked fresh water snails, mollusks, or undercooked vegetables contaminated by the slime from infected snails or slugs. Typical signs and symptoms include fever, general malaise, meningeal signs, headaches, photophobia, nausea and vomiting. Here we present a 23 year-old woman who presented to our emergency department with signs and symptoms consistent with intracranial hypertension, malaise, mild photophobia, and without fever, or meningeal signs. We also provide a review of the most recent literature regarding eosinophilic meningitis secondary to *A. cantonensis*.**

CASE REPORT

A 23 year-old woman presented to the emergency department at University Medical Center in New Orleans, LA in July 2017 complaining of headaches and vision changes for one week. Our neurology service was emergently consulted. She has no prior significant past medical history other than recent uncomplicated vaginal delivery ten months prior to presentation. She is originally from Pahn Thiet City, Vietnam but has lived in New Orleans, LA since arriving to the U.S. in 2015 and has not traveled out of the state since her arrival. She is a stay-at-home mom and denies taking over the counter medications or supplements. She mentioned her daily diet was very rich in seafood, which she usually obtains directly from local fishermen. She denied, however, eating raw, or undercooked food to her knowledge. She shops at a local Asian food market for produce. She denied any outdoor activities or travel with the exception of visiting a Louisiana State Park and campsite where she picnicked 13 days prior to her presentation. At time of admission the patient mentioned having diffuse pounding headaches for about one week. She mentioned that the headaches were worse when lying flat and improved with standing or sitting up. The severity has worsened to a 10 out of 10 on the day of admission. She also mentioned new onset horizontal diplopia, blurry vision, and pulsatile tinnitus. Upon further questioning she reported mild sensitivity to light and new onset of mild neck pain. She initially was evaluated at another emergency department nine days prior to presentation to our medical center, at which time of nausea, vomiting, headaches, and general malaise with a subjective fever for one week. She was diagnosed with a viral illness and was discharged with supportive measures. She denied any diarrhea, abdominal pain, dysuria, or respiratory symptoms.

The patient's triage vitals were an initial blood pressure of 106/74 mm Hg and a heart rate of 62 beats per minute, and she was afebrile. The physical exam was significant for mild neck stiffness and photophobia; cranial nerve examination was significant for Frisen grade IV papilledema bilaterally with peripapillary hemorrhages on the left optic nerve located superior-nasally, 20/20 vision bilaterally, normal intraocular pressures of 16 and 15 mm Hg on right and left eye respectively, large angle esotropia in the left eye at primary gaze, and a right cranial nerve (CN) VI palsy. The rest of the neurological examination was unremarkable, with the exception of decreased sensation to touch on her left lateral thigh.

Magnetic resonance imaging (MRI) of the brain with and without gadolinium had no abnormalities, and the MRI venogram of the head showed an intact venous system without thrombosis or stenosis. A lumbar puncture (LP) was then performed at the bedside in the left lateral decubitus position. Opening pressure (OP) was documented at 35 cm H_20. After collecting 11 ml of

cerebrospinal fluid (CSF), the closing pressure was measured at 26 cm H20. All symptoms improved significantly after the procedure. On laboratory testing a complete blood count showed a mild leukocytosis at 11.8 × 109 cells/L (reference range 4.5–11.0 × 103/UL) with 11% eosinophils, an elevated absolute eosinophil count at 1.3 (reference range 0.0–0.6 × 103/UL). Sedimentation rate and C-reactive protein were both within normal limits. Human immunodeficiency virus (HIV), syphilis antibody, hepatitis panel, and interferon gamma release assay for tuberculosis were all non-reactive. Analysis of the CSF revealed elevation of leukocyte count at 383 UL (reference range 0-5 UL) with 62% eosinophils, elevated protein at 63.8 mg/dl (reference range 15.0 - 45.0 mg/dl), and normal glucose at 50 mg/dl. Cultures and gram stains of the CSF were negative for bacteria, acid-fast bacilli, and fungi. Malaria antigen was negative. Pathology review of the blood was negative for Plasmodium, Babesia, and other parasites. *A. cantonensis* polymerase chain reaction (PCR) on the CSF resulted positive indicating infection by *A. cantonensis*.

The patient was discharged on acetazolamide 500 mg twice a day to manage intracranial hypertension and two weeks of prednisone 60 mg daily with an eight-day taper. She had full resolution of papilledema, right CN VI palsy, headaches, and nuchal rigidity at her one-month clinic follow-up. After discharge, serum Strongyloides Stercoralis immunoglobulin – G (IgG) by enzyme-linked immunosorbent assay (ELISA) resulted positive at 1.56 IV (Reference range <= 0.99). Per infectious disease recommendations, the patient was prescribed ivermectin at 200 mcg per kilogram daily for two days after *Strongyloides Stercoralis* IgG was found to be positive. It was thought that the S. stercoralis IgG positivity was indicative of a prior infection or exposure; however, initiation of steroid therapy warranted anitparasitic treatment for *S. stercoralis*.

LITERATURE REVIEW

Angiostrongylus Cantonensis (A. cantonensis), or "rat lungworm," is one of the most known infectious causes of eosinophilic meningitis. It is a parasitic nematode that is widely found in endemic areas such as Southeast Asia, the Pacific Islands, and the Caribbean.[1,2] Although, the area of distribution of *A. cantonensis* has drastically increased over time to areas including Africa and the U.S. due to global transport networking. To date, thousands of cases have been reported worldwide.[3,4,5]

The life cycle of this parasitic nematode includes an intermediate host of raw land and freshwater snails and a definitive host of rats or other rodents where the adult rat lungworms live and lays eggs in the pulmonary arteries of rodents.[2,6] After the eggs hatch, the larvae migrate into the pharynx of infected rats and are swallowed, subsequently passing in the rodent's feces. Snails and slugs then ingest the larvae becoming infected. When rats subsequently ingest infected snails and slugs, the larvae can then mature to adult worms in the rodents (Figure 1).

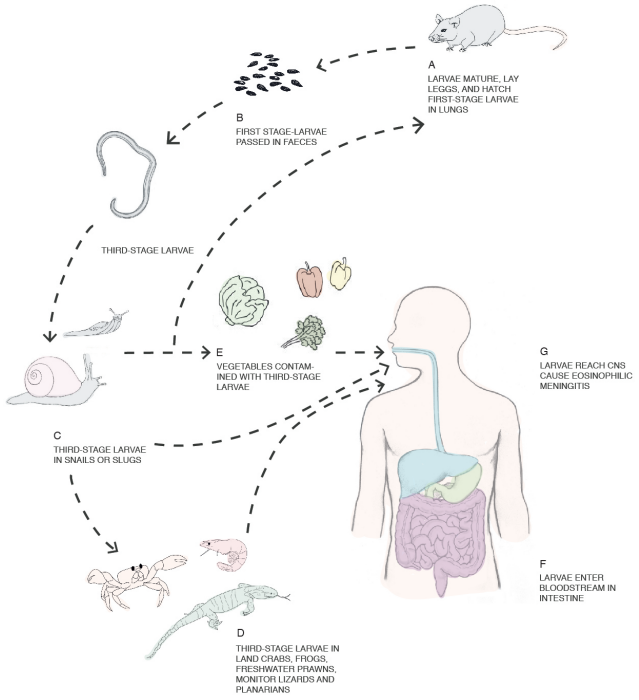

Figure 1: The life cycle of this parasitic nematode includes an intermediate host of raw land and freshwater snails and a definitive host of rats or other rodents where the adult rat lungworms live and lays eggs in the pulmonary arteries of rodents.[2,6] Humans occasionally serve as incidental hosts of the organism.

Humans occasionally serve as incidental hosts of the organism, in which eosinophilic meningitis can present. The transmission of *A. cantonensis* to humans is usually via consumption of the undercooked larvae-infected snails or mollusks (i.e. fresh-water shrimp, crabs), or via undercooked vegetables, prawns, crabs and frogs that become contaminated by the mucus of infected slugs, or snails.[5,7] The onset of clinical symptoms of infection due to *A. cantonensis* usually arises between 1-4 weeks from exposure.[8] Once ingested by a human host, the larvae of *A. cantonensis* cannot complete its life cycle, and it will typically die within the gastrointestinal system, which can cause eosinophilic gastroenteritis.[4] However, the larvae can invade the vasculature of the digestive tract, and migrate within the blood.[3,4] Usually, the larvae tend to migrate to the brain and spinal cord of human hosts, where they develop further only to be extinguished by the activation of cytokines and eosinophils of the human host. *A. cantonenensis* is unique in the human host as the eyes can also be involved. Once the human host has elicited an immune response to eliminate the CNS pathogen, inflammatory symptoms of eosinophilic meningitis may ensue due to direct physical larval damage and immune reaction.[3,9] Such symptoms include headache, visual disturbances, nuchal rigidity, fever, nausea, and vomiting. Death may occur in severe infections.[10] The symptoms most often resolve spontaneously after 7-14 days, however headaches and paresthesias can take longer to resolve, varying from weeks to months.[8,11,12] The most common presentations in a case series of 34 patients were: headache (90%), stiff necks and emesis (56%), paresthesias (54%) and fever (41%).[11] Infection has been found to involve the cranial nerves, although less common, as well as the eyes

with visual disturbances due to larval invasion of the ocular structures.[6,11]

DEMOGRAPHICS

Angiostrongylus cantonensis was first described as a human pathogen in China in 1945.[9] Today, numerous countries have experienced severe outbreaks including China, Taiwan, Jamaica, and Thailand.[5,8] While *A. cantonensis* is prevalent in Southeast Asia and the Pacific Islands, there have been increasing numbers of documented cases in the continental U.S.

The current theory of introduction into the continental U.S. begins in the 1980s from rats aboard ships arriving into New Orleans, Louisiana. Since then, a few numbers of cases have presented in the southeastern U.S. including Louisiana, Texas, and Florida.[9,10] One study conducted by Walden, et al., sought PCR positivity in vectors such as snails and *Rattus* rats in multiple Florida counties to confirm the roundworm's migration to the continental U.S. They established that *A. cantonensis* was found in 5 of the 18 counties tested.[10] Walden, et al., necropsied 171 *Rattus Rattus* and found 22.8% (n=39) showed PCR positivity while only 1.9% (n=27, of 1,437) of gastropods were positive for *A. cantonensis*. Other mammalian hosts have been documented in the southeastern U.S. including a horse in Picayune, Mississippi, a captive howler monkey, wild wood rat, and four wild opossums in New Orleans, Louisiana, and a captive white-handed gibbon in Miami, Florida.[9]

With readily available global transportation, other cases of eosinophilic meningitis caused by *A. cantonensis* have been noted in other regions of the U.S. as well. One case documented in 2002 by Slom, et al., documented a large outbreak among a group of U.S. citizens that traveled from Jamaica to the U.S. and presumably occurred after eating salads in Jamaica.[8] Of the 12 patients that demonstrated illness in this study, 75% (n=12) were male with a median age of 22. Conversely, another larger study conducted in Vietnam by McBride, et al., also demonstrated a slight male predominance with an infected population of 59.4% male (n=51) and a median age of 31.21-44

PRESENTATION AND CLINICAL FEATURES

The most common symptoms of meningitis are headache, fever, and nuchal rigidity that develop within a few days of the infection. In cases of typical bacterial meningitis, roughly 44-46% of patients present with all three classical features.[13] However, eosinophilic meningitis caused by *A. cantonensis* can demonstrate an atypical presentation as in this case. One infectious disease report published in 2017 of 69 adults in southern Vietnam has shown that patients who meet diagnostic criteria for eosinophilic meningitis present with headache (n=63, 96.9%), fever (n=58, 84.1%), and vomiting (n=39, 62.9%).[2] Their observations have also shown that 72.5% (n=50) of patients initially presented with nuchal rigidity, 37.7% (n=20) initially presented with a fever of 38°C or above, and 12.1% (n=9) initially presented with cranial nerve palsy – most commonly CN VI.[2]

These percentages of the signs and symptoms of eosinophilic meningitis caused by *A. cantonensis* found by McBride, et al., are consistent among many other research articles in similar regards.[1,2,8,14] However, other associated signs and symptoms were noted elsewhere. One case report followed an outbreak of eosinophilic meningitis first noted on April 29, 2000 of 23 travelers.[8] Twelve of the 23 travelers met diagnostic criteria for eosinophilic meningitis – headache beginning 35 days after the trip plus: nuchal rigidity, or visual disturbances, or altered cutaneous sensations.[8] Of these 12 individuals, 100% (n=12) presented with a headache, 92% (n= 11) presented with visual disturbance or photophobia, 83% (n=10) presented with fatigue and nuchal rigidity, 67% (n=8) presented vomiting, and other associated symptoms included muscle pain (50%, n=6), fever (42%, n=5), muscle weakness (33%, n=4), and diarrhea (17%, n=2).[8]

Although, some isolated case reports exhibit atypical presentations to the aforementioned similarly to the patient in this case. A case report on eosinophilic meningitis caused by *A.cantonensis* in 2011 found a 24-year-old male with later confirmed eosinophilic meningitis to have presented with merely a persistent headache for three days with associated episodes of nausea without vomiting.[14] This patient did not experience or exhibit signs of myotonia, speech difficulty, weakness, abnormal cutaneous sensations, or focal neurologic deficit.[14]

IMAGING AND LABORATORY INVESTIGATION

Investigatory laboratory studies and diagnostic imaging are crucial in the diagnosis of eosinophilic meningitis. Beyond basic hematologic laboratory investigations, a CT, MRI, and lumbar puncture should be considered in patients with meningeal irritation symptoms. In theory, a hallmark eosinophilic meningitis presentation should presumably show evidence of increased opening pressure on lumbar puncture, PCR positivity for *A. cantonensis*, and eosinophilia in the blood or CSF.[2,8]

McBride, et al., in a very large retrospective studies of eosinophilic meningitis, conducted a study of 69 individuals with eosinophilic meningitis and found an elevated CSF leukocyte count/mm^3 median of 564 (347-1015) with a CSF eosinophilia differential median of 39% (27-52%), and an elevated opening pressure median of 23 cm H_20 (17-33 cm H_20). Additionally, they also found an elevated CSF protein median of 0.8 g/dL (0.5-1.2), an elevated CSF glucose median of 2.5 g/dL (1.9-2.8), and an elevated CSF lactate median of 2.8 mmol/L (2.2-3.9).[2] They also noted that PCR positivity correlated with an increased duration of illness at presentation (median of 14; 10-20 vs. nine days, P=0.027). Severity, however, was unrelated to PCR positivity. Some of the findings they found on MRI and CT imaging include cerebral edema (45%), meningeal inflammation (36.4%), and focal parenchymal hyper-intense lesions on T2-weighted FLAIR MRI (45%).[2]

Another larger study after an outbreak in Jamaica found to have a median opening pressure of 24 cm H20 (12-55 cmH_20), an

increased WBC count in the CSF with a median of 333 cells/mm^3 (18-765), and a median eosinophil differential count of 13% (0-54).[8] This study also found a CSF glucose median of 55 mg/dL (51-81), and an elevated CSF protein median of 52 mg/dL (36-82). Of note, this study found that a significant hematologic eosinophilia was not seen until the midpoint of the clinical course. The mean eosinophil count at initial presentation was 443 +/- 90 cells/mm^3 and the eosinophil count at the midpoint of the clinical course was 957 +/- 203 cells/mm^3. However, a significant varying leukocytosis on a complete blood count was not noted over the clinical course.[8]

TREATMENTS

Eosinophilic meningitis caused by *A. cantonensis* is traditionally self-limiting. Mild infections do not require any medical treatment, though increased severity of infection may warrant treatment. Certain anti-helminthic medications (i.e. mebendazole, albendazole) have been used in treatments for eosinophilic meningitis, but recent studies have shown a lack of efficacy of these medications for this condition.[3] It is theorized that swiftly killing the CNS larvae may promote a larger immune response, which could exacerbate meningeal irritation symptoms. However, corticosteroids have been shown to reduce meningeal inflammation and lessen the severity of the associated headache. Repeated lumbar punctures have also shown some benefit in reducing headache duration.[2,3,8,14]

During one study, McBride, et al., treated 86.7% (n=50) with dexamethasone and albendazole. Of all the patients, one died, though he had multiple comorbidities including disseminated salmonellosis at the age of 78. Additionally, they noted that 69.4% (n=43) of patients had some residual symptoms at discharge that were not evaluated further. PCR positivity was irrelevant in treatment outcomes.[2]

CASE DISCUSSION

The initial presentation of right CN VI palsy, pulsatile, tinnitus, positional headaches, and papilledema were consistent with intracranial hypertension. She initially did not endorse, either light sensitivity or neck stiffness; however, upon review of symptoms, she admitted to having mild symptoms. The patient was also afebrile and meningeal signs were not elicited on physical examination; therefore, she was admitted to rule out idiopathic intracranial hypertension, and meningitis was lower in the differential. Infectious disease was consulted after LP showed a high WBC with 60% eosinophilia, it was thought that the presence of *Strongyloides S*. IgG was an incidental finding and unrelated to patient's symptomatology; nevertheless, it was decided to treat with ivermectin in the setting of starting steroid therapy for *A. Cantonensis* to avoid a possible *Strongyloides S*. super infection. Headaches and papilledema responded immediately after the LP and initiation of acetazolamide. The CN VI palsy persisted until steroid therapy was initiated.

This case was proven challenging due to its atypical presentation, and no known exposure history of eating raw fresh water snails, or mollusks. Patient did endorse eating raw vegetables from local food market, which could also have been the potential source of infection due to contamination from snails or slugs, also another potential exposure to rats or intermediate hosts could have been when she went picnicking at the state campground on the lake, particularly given the incubation period which is usually two weeks. It is important to increase awareness to practitioners about *A. cantonensis* in patients with eosinophilia in serum or in CSF specially if patients have exposure history, or have recently travel to endemic areas now including Louisiana, Texas, or Florida.

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