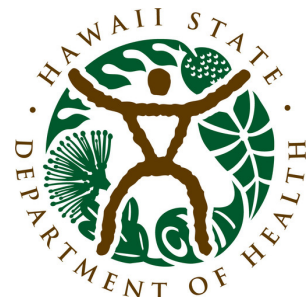


# Preliminary Guidelines for the Diagnosis and Treatment of Human Neuroangiostrongyliasis (Rat Lungworm Disease) in Hawaii

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Governor's Joint Task Force on Rat Lungworm  
Disease**

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# Table of Contents

Introduction.....	<a href="#">2</a>
Key Points.....	<a href="#">3</a>
Life Cycle of <i>Angiostrongylus cantonensis</i> .....	<a href="#">4</a>
Illustrative Case.....	<a href="#">5</a>
Diagnosis of Neuroangiostrongyliasis.....	<a href="#">6</a>
Characteristic Symptoms.....	<a href="#">6</a>
Signs on Physical Examination.....	<a href="#">7</a>
Exposure History.....	<a href="#">7</a>
The Importance of the Lumbar Puncture.....	<a href="#">8</a>
Real-Time Polymerase Chain Reaction Test for Confirming Cases.....	<a href="#">8</a>
Reporting Neuroangiostrongyliasis to DOH.....	<a href="#">9</a>
Submitting a CSF Sample for RTi-PCR.....	<a href="#">9</a>
Additional Laboratory Testing.....	<a href="#">9</a>
Radiologic Testing.....	<a href="#">9</a>
Differential Diagnosis.....	<a href="#">9</a>
Management of Neuroangiostrongyliasis.....	<a href="#">10</a>
Initial and Serial Lumbar Punctures.....	<a href="#">10</a>
Corticosteroids.....	<a href="#">10</a>
Anthelmintic Drugs.....	<a href="#">10</a>
Summary on the Use of Albendazole.....	<a href="#">11</a>
Acute Pain Management.....	<a href="#">11</a>
Patient Monitoring.....	<a href="#">11</a>
Long-Term Sequelae.....	<a href="#">11</a>
Ocular Angiostrongyliasis.....	<a href="#">11</a>
Bibliography.....	<a href="#">12</a>
Members of the Clinical Subcommittee.....	<a href="#">13</a>
Authors' Affiliations.....	<a href="#">14</a>

# Introduction

Human infection with the parasitic nematode *Angiostrongylus cantonensis* (*A. cantonensis*) causes neuroangiostrongyliasis. Increased awareness of this condition, also known as human angiostrongyliasis, angiostrongylus eosinophilic meningitis, or rat lungworm disease, in Hawaii has caused concern among the general population and among clinicians unfamiliar with managing cases.

To address these concerns, Governor David Ige, in 2016, appointed a Joint Task Force on Rat Lungworm Disease to advise him and Hawaii's medical professionals about how best to deal with this illness. The Clinical Subcommittee of this Task Force, comprising local tropical disease and infectious disease experts, has carefully reviewed the published literature and consulted with national and international experts in preparing these Preliminary Guidelines to assist clinicians faced with diagnosing and managing this unique parasitic disease.



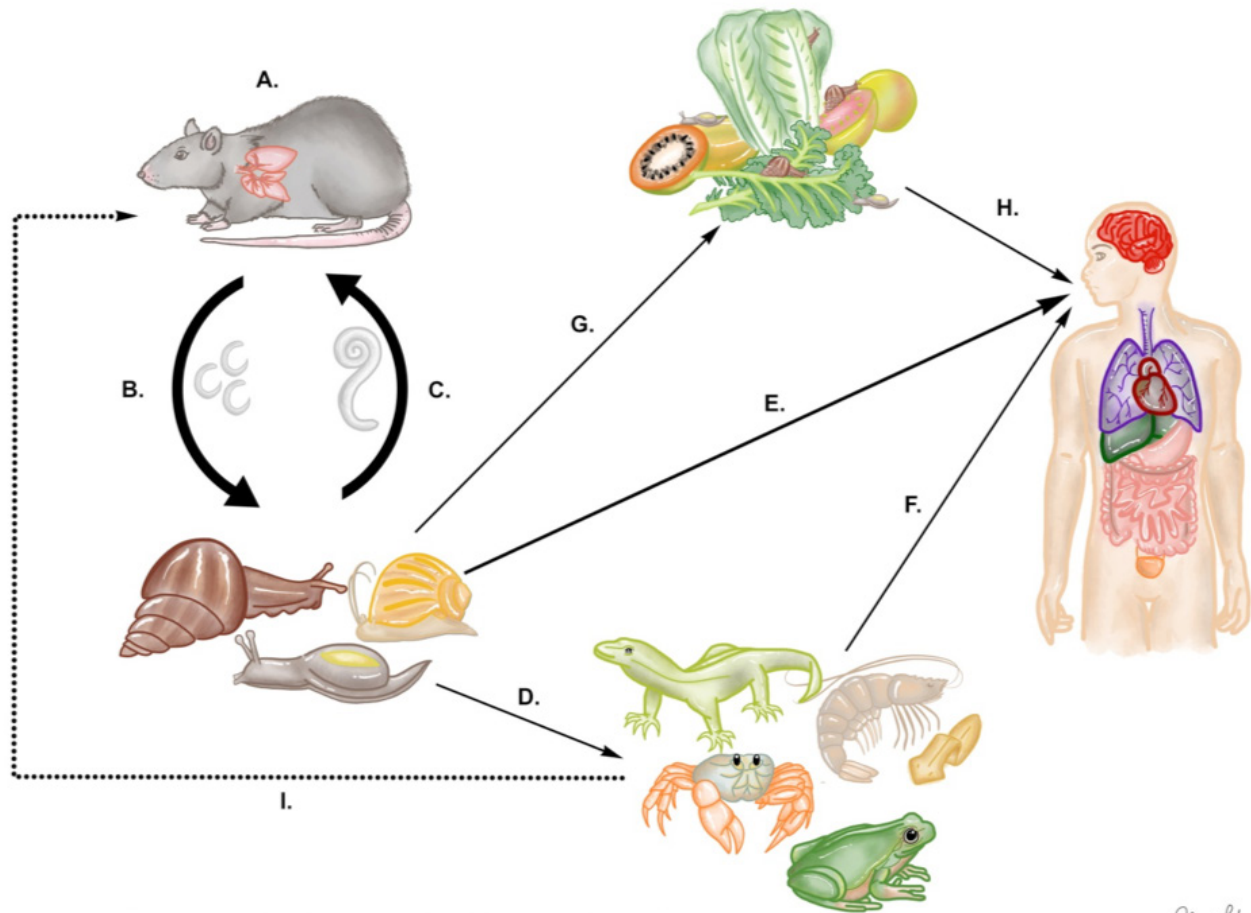
**Figure 1 (left).** *Parmarion martensi* or “semi-slug.” Photo courtesy L. Castro, Hawaii State Department of Agriculture. **Figure 2 (right).** Snail lodged in garden water hose. Photo courtesy Hawaii State Department of Health.

# Key Points

1. Clinicians in Hawaii should have a high index of suspicion for neuroangiostrongyliasis.
  - Suspect cases should be discussed with the Department of Health (DOH) Disease Investigation Branch (DIB) at the earliest opportunity to facilitate prompt, accurate diagnosis and appropriate patient management. Call (808) 586-4586 for the Disease Reporting Line.
2. Typical symptoms in adults include severe headaches, neck stiffness, nausea, paresthesias, and limb pains. Highly suggestive symptoms include migratory hyperesthesias, cranial nerve abnormalities, ataxia, and focal neurologic findings which are migratory or do not follow a dermatomal distribution.
3. Typical symptoms in children include fever, abdominal pain, vomiting, irritability, poor appetite, muscle weakness, fatigue, and lethargy.
4. Lumbar puncture (LP) is an essential part of the evaluation of suspected neuroangiostrongyliasis. It is a low-risk procedure and has therapeutic benefits, including relief of headaches, nausea, and vomiting.
5. A presumptive diagnosis of neuroangiostrongyliasis requires all three of the following:
  - a) A history of suggestive symptoms and signs,
  - b) Evidence of eosinophilic meningitis in the cerebrospinal fluid (CSF), and
  - c) An exposure history, which includes residence in or recent travel to an endemic area.
6. Eosinophilic meningitis is the hallmark of the disease and is defined as the presence of 10 or more eosinophils per  $\mu\text{L}$  of CSF and/or eosinophils accounting for more than 10% of CSF white blood cells when there are at least 6 total WBC per  $\mu\text{L}$  in CSF.
7. CSF eosinophil counts may be absent or low early in the course of the disease, requiring repeat LPs if neuroangiostrongyliasis is still suspected.
8. Real-time polymerase chain reaction (RTi-PCR) of CSF for *A. cantonensis* DNA is the best way to confirm the infection and is available in Hawaii through the DIB or from the Centers for Disease Control and Prevention (CDC) for the rest of the United States.
  - CSF RTi-PCR may be negative in the early stages of infection.
  - Repeat LP and testing is indicated if neuroangiostrongyliasis is still suspected.
9. Baseline studies should include a complete blood count (CBC) with differential, serum electrolytes, liver function tests, renal function tests, blood glucose, urinalysis, and chest x-ray.
10. Peripheral eosinophil counts of  $\geq 500$  cells/ $\mu\text{L}$  are often present during the course of the illness but may be absent.
11. Magnetic resonance imaging (MRI) of the brain, although not required, may be helpful in diagnosing suspected neuroangiostrongyliasis. Focused MRI of the spine may be appropriate if indicated by clinical presentation.
12. Serological tests for antibodies against *A. cantonensis* in the serum or CSF are not recommended for the diagnosis of neuroangiostrongyliasis.
13. High dose corticosteroids have been shown to improve clinical outcomes. Start corticosteroids as soon as a presumptive diagnosis of neuroangiostrongyliasis is made and assuming no contraindications.
  - Individuals with diabetes or glucose intolerance should be closely monitored.
  - Modifications to the patient's diabetes medications may be needed.
14. The addition of albendazole, an anthelmintic drug, may provide additional benefits, although there is limited evidence of this in humans.
  - If albendazole is used, combine with corticosteroids to blunt any possible increase in the inflammatory response to dying worms.
15. Careful clinical monitoring is recommended in all patients, and specialist consultation (e.g., infectious disease, neurology, etc.) may be advisable.
16. Pain management may require early consultation with a pain specialist.

# Life Cycle of *Angiostrongylus cantonensis*

The adults of *A. cantonensis* are found in the pulmonary arteries of rats, the definitive host. In the rat, the parasite must complete a 4-week maturation phase in the central nervous system (CNS) before migrating to the lungs. Gastropods (slugs and snails) are the natural intermediate hosts for the parasite. Paratenic (transfer or transport) hosts (e.g., freshwater shrimp, prawns, planarians, land crabs, monitor lizards, centipedes, and frogs) are an additional source of infection for humans. Humans are accidental hosts, and human-to-human transmission does not occur.



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**Figure 3. Life cycle of *A. cantonensis***

Adult worms are found in the pulmonary arteries of rats (definitive hosts) [A]. Females produce eggs that are carried to the lungs and hatch into first stage (L1) larvae. The L1 larvae migrate to the trachea, are swallowed and excreted in rat feces [B]. L1 larvae are ingested by slugs and snails (intermediate hosts) and molt twice to become infectious third stage (L3) larvae. Rats become infected by eating slugs and snails containing L3 larvae [C]. In the rat, the L3 larvae migrate through the wall of the intestine and are carried in the blood to the central nervous system (CNS). In the brain, the L3 larvae molt twice to become fifth stage (L5), immature adults. The immature adults migrate to the pulmonary arteries where they become sexually mature adults. Infected slugs and snails may also be eaten by paratenic (transport or transfer) hosts such as freshwater shrimp and prawns, flatworms, land crabs, centipedes, monitor lizards, and frogs [D]. Theoretically rats may also become infected by eating paratenic hosts containing L3 larvae [I].

infected snails or slugs [E], raw or undercooked infected paratenic hosts [F], or unintentionally ingesting food products containing hidden slugs or snails [G, H], e.g., uncooked or inadequately washed green leafy vegetables, fruits, and blended vegetable or fruit juices.

In humans, L3 larvae migrate through the intestinal wall and may pass through various organs in their attempt to reach the CNS. The L3 larvae that enter the human brain and spinal cord molt twice over a 2 to 3 week period to become L5 immature adults. L4 larvae and L5 immature adults may cause eosinophilic meningitis, meningoencephalitis, myeloradiculitis, or (rarely) ocular angiostrongyliasis. Immature adults usually are unable to migrate to the pulmonary arteries and subsequently die in the CNS leading to inflammation.

In Hawaii, *A. cantonensis* was found in rats in 1960. The prevalence of the parasite in Hawaii has been recently described for the definitive host in the Hilo area and in the intermediate host statewide.

Humans are infected by intentionally ingesting raw or undercooked

# Illustrative Case

The following illustrative case is a composite of multiple patients who acquired neuroangiostrongyliasis in Hawaii and demonstrates common diagnostic delays resulting from the potentially confusing constellation of symptoms, protean physical findings, and lack of noninvasive diagnostic tests. Since 2007 (when neuroangiostrongyliasis became a reportable disease in Hawaii), less than 100 cases have been recorded. However, neuroangiostrongyliasis is an increasingly recognized emerging infection. An uncommon condition such as this, with protean manifestations, requires a high index of suspicion by medical practitioners.

*A 35-year-old teacher was admitted to the hospital with a three-week illness characterized by headache, numbness in the left leg, painful tingling sensations in the right upper arm and left hand, migratory muscle pains in the extremities, and insomnia. She had no prior history of headaches, and there was no family history of migraines. She moved to Hawaii from the U.S. mainland several years earlier. She denied any foreign travel within the preceding six months.*

*The patient had been in her usual state of health until three days before presentation to her primary care provider, when she felt generally unwell and had transient nausea and abdominal pain, followed by headache. During the next two to three days, the headache worsened, and she was unable to obtain relief with non-steroidal anti-inflammatory drugs (NSAIDs) or acetaminophen. She was diagnosed with sinusitis and was prescribed amoxicillin and hydrocodone.*

*Over the following three days, there was no improvement in the headache, which had become unremitting. She began to experience diffuse pruritus, which she described as “skin itching all over like sunburn” and “electric shock sensations.” She returned to her physician who found no dermatologic abnormalities. The amoxicillin was discontinued, and antihistamines were prescribed for a presumed allergic reaction.*

*Four days later, she returned to the clinic and reported increased fatigue, loss of appetite, and frustration about not getting well. She also noted new onset of migratory “muscle” pains affecting her right shoulder, left upper neck and left thigh. The unremitting headache persisted. She denied fever or night sweats. A complete blood count (CBC) and basic metabolic panel returned as normal. Her vital signs and physical exam were also normal. She was prescribed a muscle relaxer and advised to continue NSAIDs and acetaminophen for pain.*

*Five days later, she presented to the emergency department (ED) with persistent, poorly localized headaches unresponsive to NSAIDs, acetaminophen, and hydrocodone. She reported neck stiffness as well as a strange sensation: the touch of her clothing or a breeze from a fan elicited pain. She declined antidepressants and gabapentin but was given oxycodone.*

*Two days prior to admission, she returned to the ED complaining of persistent headaches, constipation, and difficulty walking. The pain on light touch had worsened to the point that even loose-fitting clothing caused discomfort. She also described episodic blurring of vision and difficulty urinating. Physical exam remained unremarkable. Urinalysis was normal, and a CBC was notable for a white blood cell count of 10,200 /  $\mu$ L with 6% eosinophilia. She was given an optometry referral and encouraged to drink fluids.*

*In the ED on the day of admission, she noted no change in the headache. Her skin hypersensitivity and limb and trunk pains continued, and she now described numbness over the lateral aspect of the left leg. She also noted increased difficulty walking. She was frustrated that she was not improving and no one had been able to give her a diagnosis. A friend had suggested she might have “rat lungworm,” and she inquired if this was possible.*

*Further workup included an LP. Results showed slightly turbid CSF, with an opening pressure of 230 mm water (normal 60-200 mm water). CSF leucocyte count was 350 cells/ $\mu$ L with 31% eosinophils. CSF protein concentration was 62 mg/dL (normal in adults 28-38 mg/dL); CSF glucose concentration was normal relative to the serum glucose. CSF was examined for the presence of nematode worms, and none were seen. The patient’s clinical history was discussed with DIB, who approved the submission of a CSF sample for testing at Hawaii State Laboratories Division (HSLD).*

*Prednisone (60 mg daily) was started empirically, while waiting for the results of the A. cantonensis RTi-PCR results. Results from the RTi-PCR for A. cantonensis DNA was received two days later and was positive.*

*Corticosteroids were given for two weeks with a slow taper over the following two weeks.*

*Her symptoms showed significant improvement over the next six months, but she had residual headaches, limb pain, and fatigue, and has not been able to return to work.*

The purpose of this illustrative case is to highlight the challenge of evaluating patients who may initially present with nonspecific complaints that evolve into more suggestive symptoms of neuroangiostrongyliasis. This type of scenario should prompt the clinician to perform a lumbar puncture to evaluate the cause of the patient's neurological symptoms and signs.

The following are important symptoms and signs, which when occurring together, should alert physicians to neuroangiostrongyliasis:

- Severe, new onset, headaches with poor response to analgesics (present in 80-90% of case series);
- Hypersensitivity to touch and burning dysesthesia (if present is highly suggestive);
- Migratory trunk and limb pains;
- Cranial nerve palsy, e.g., abducens (6th nerve) palsy causing diplopia or facial (7th nerve) palsy resulting in facial weakness; and
- Urinary hesitancy and difficulty urinating, which may progress to urinary retention.

Once neuroangiostrongyliasis is suspected, the physician should immediately contact DIB to discuss the case, CSF should be obtained to evaluate for eosinophilic meningitis, the hallmark of this infection. Confirmation of neuroangiostrongyliasis is made by RTi-PCR testing of CSF performed at the HSLD after approval is received from DIB or at CDC for other areas of the United States. For details, please see below.

## Diagnosis of Neuroangiostrongyliasis

A presumptive diagnosis of neuroangiostrongyliasis is made on clinical grounds, based upon this triad of findings:

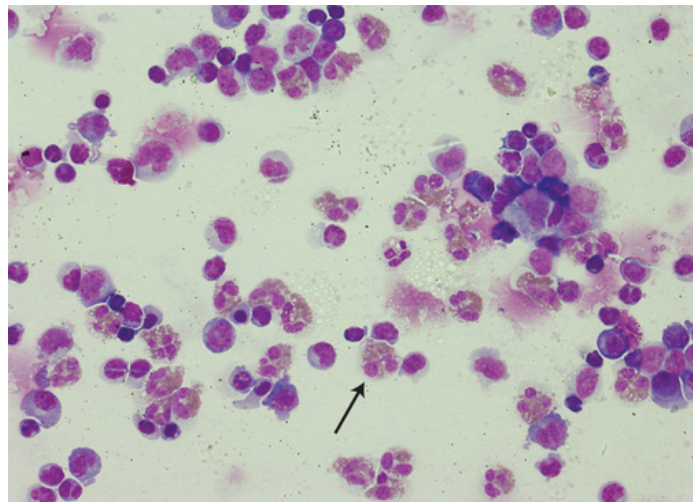
- a) Characteristic symptoms and signs;
- b) Eosinophilic meningitis upon LP; and
- c) Exposure history, including residence in or travel to an endemic area.

Specific history of contact with or ingestion of a snail, slug, or paratenic host, although helpful, is not necessary to make the diagnosis and initiate treatment.

As soon as neuroangiostrongyliasis is suspected, contact DIB to discuss diagnosis, testing, and/or treatment.

**Neuroangiostrongyliasis is a reportable disease in Hawaii and must be reported by physicians to DOH. Call the Disease Reporting Line at (808) 586-4586 for assistance.**

A presumptive diagnosis is clinically valid and sufficient to begin treatment. The diagnosis is confirmed when parasites are seen in the CSF, but this is uncommon. RTi-PCR for *A. cantonensis* DNA in the CSF is a valuable new test for confirmation of neuroangiostrongyliasis. However, it is not necessary to have RTi-PCR confirmation to begin treatment, provided eosinophilic meningitis has been diagnosed with exposure in an endemic area, and there are no other obvious causes of the illness.



**Figure 4.** Cerebrospinal fluid histopathology using Romanowsky stain (azure B and eosin Y) showing eosinophilia (arrow). Nicholas F Blair, et al. *Med J Aust* 2013; 198 (8): 440-442. doi: 10.5694/mja12.11085.

## Characteristic Symptoms

There is a broad spectrum of clinical presentation, and patients may only present with a few non-specific symptoms and signs. Often, the clinical presentation will evolve over a week or more, with more specific signs becoming apparent during follow up. In mild cases the picture may be less clear; however, in severe cases, the neurologic findings can be quite suggestive.

Early in the clinical course, there may be a gastrointestinal prodrome of nausea, abdominal pain, and vomiting within hours to a few days of ingestion of an infected intermediate host. There may also be malaise, low-grade fever, cough, pruritus, and rash. This prodrome is usually self-limited and likely results from penetration of the intestinal wall by L3 larvae that gain access to the circulation and migrate to other organs en route to the central nervous system. There may be an asymptomatic period of days to weeks, followed by the appearance of headache and other neurologic signs and symptoms.

General but nonspecific symptoms: headache, feeling feverish, nausea, vomiting, photophobia, insomnia, anxiety, myalgias, fatigue, and lethargy.

More suggestive symptoms: severe, new-onset, unremitting headache; paresthesias, including itching, pain, tingling, crawling or burning feelings; hyperesthesia; diplopia; bowel or bladder difficulties; and seizures.

Children tend to have less paresthesias but more fever, irritability, somnolence, lethargy, gastrointestinal symptoms (e.g., vomiting, poor appetite, nonspecific abdominal pain), muscle twitching, convulsions, and weakness of the extremities.

## Signs on Physical Examination

A complete neurologic examination, including an ophthalmological examination for extraocular muscle function and papilledema, should be performed in all patients.

Possible general nonspecific signs: fever (often low grade if present).

More suggestive signs on physical examination: Neck stiffness; motor weakness or sensory abnormalities, especially if migratory or involving multiple dermatomes; cranial nerve abnormalities, especially palsies of the abducens nerve (CN VI) causing diplopia, facial nerve (CN VII) causing a facial droop or Bell's Palsy, or auditory nerve (CN VIII) resulting in tinnitus or hearing loss; tremors or inability to coordinate fine motor movements; ataxia; and altered consciousness.

## Exposure History

An exposure history should be carefully sought.

Experience in Hawaii has shown that a definitive exposure may not always be found. Nonetheless, a careful and thorough food history is important. This should include:

- a) A history of possible contact with or ingestion of snails or slugs (intermediate hosts), either intentional or unintentional;
- b) A history of eating uncooked, unwashed, or inadequately washed vegetables or fruits;
- c) A history of eating uncooked or undercooked paratenic hosts such as freshwater shrimp or prawns, centipedes, land crabs, flatworms, frogs or lizards; and
- d) A history of consuming potentially contaminated beverages (e.g., raw, blended vegetable juices; non-potable water).

Children under age five years or with developmental disabilities may be at higher risk for infection because of an

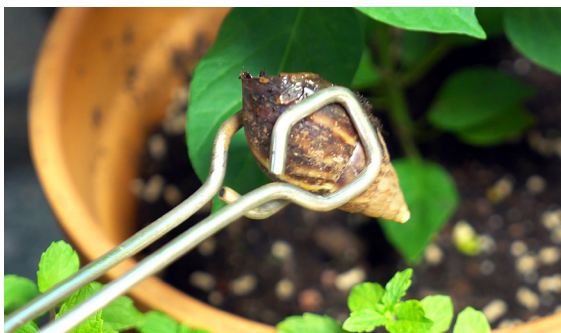
increased tendency to ingest or play with slugs or snails.

Some cases in adults and older children have resulted from swallowing snails or slugs after a dare or wager, and these patients may be initially embarrassed to divulge how they were exposed.

A definite exposure is often not identified despite a careful food history. Therefore, living in an endemic area should be considered a sufficient exposure.

A history of travel to other areas should also be sought. Neuroangiostrongyliasis has been reported from tropical and subtropical regions of Southeast Asia, China, Taiwan, Australia, the Islands of the North and South Pacific, India, Sri Lanka, the Caribbean, South America, southern portions of the United States, and parts of Africa. There is evidence that this parasite's geographical range may be increasing.

The date of exposure should be identified whenever possible. The incubation period of neuroangiostrongyliasis can range from a few days to more than six weeks. However, the median time from exposure to presentation is usually between one and three weeks.



**Figure 5 (left).** *Achatina fulica* or "giant African snail." Photo courtesy Hawaii State Department of Health.

**Figure 6 (right).** *Parmarion martensi* or "semi-slug." Photo courtesy L. Castro, Hawaii State Department of Agriculture.



## The Importance of the Lumbar Puncture



**Figure 7 (left).** Performing a lumbar puncture. Blausen.com staff, “Blausen gallery 2014”, Wikiversity Journal of Medicine, via Wikimedia Commons.  
**Figure 8 (right).** Using a manometer while performing a lumbar puncture. Image courtesy of Simon Fraser, RVI, Newcastle upon Tyne, Science Source.

Lumbar puncture (LP) is essential to diagnosing eosinophilic meningitis—the hallmark of neuroangiostrongyliasis—and is both diagnostic and therapeutic.

Once there is a suspicion of neuroangiostrongyliasis, an LP and examination of the CSF should be performed unless there is a specific contraindication. Typical LP and CSF findings in neuroangiostrongyliasis include an elevated opening pressure and increased white blood cells, particularly eosinophils.

It is important to record the opening CSF pressure, because elevated intracranial pressure (ICP) likely contributes to some of the neurologic damage of neuroangiostrongyliasis. The finding of increased ICP should prompt removal of a large volume of CSF (e.g., 20–40 mL in adults), which often results in dramatic, if temporary, relief of headache. Elevated ICP during the initial LP may suggest subsequent LPs may be beneficial if severe headache returns or if the neurologic condition worsens.

Eosinophilic meningitis is the hallmark of the disease and is defined as the presence of 10 or more eosinophils per  $\mu\text{L}$  of CSF and/or eosinophils accounting for more than 10% of CSF white blood cells when there are at least 6 total WBC per microliter in the CSF. However, eosinophils may be few or even absent early in the disease. Repeat LP at least several days later may be indicated if symptoms or exposure history are highly suggestive.

Nearly all patients will have a CSF eosinophilic pleocytosis

at some point during their illness. Clinicians should verify that the laboratory looks explicitly for eosinophils in the CSF using appropriate stains, such as Giemsa or Wright.

The LP also helps to exclude other causes of meningitis. Routine studies to exclude other causes of meningitis should always be ordered.

### Real-Time Polymerase Chain Reaction (RTi-PCR) Test for Confirming Cases

RTi-PCR for *A. cantonensis* DNA in CSF is available in Hawaii through HSLD.

In some cases, the test may be negative early in the disease but will become positive later. Therefore, if clinical suspicion is high and the first RTi-PCR is negative, the LP should be repeated about 5 to 10 days later. If repeat LP demonstrates eosinophilic meningitis, DIB should be contacted before submitting additional CSF samples to HSLD.

It is not necessary to wait for the RTi-PCR results (which may take 2 to 3 business days to become available) to begin treatment. Standard tests to evaluate for other causes of meningitis should be performed.

Consultation and approval from DIB is required before HSLD will perform the RTi-PCR test.

## Reporting Neuroangiostrongyliasis to DOH

Neuroangiostrongyliasis is a reportable disease in Hawaii. Clinicians should call DIB as soon as a patient is suspected of having neuroangiostrongyliasis. DIB can facilitate testing and provide guidance on management.

- Oahu (Disease Reporting Line): (808) 586-4586
- Hawaii District Health Office: (808) 933-0912
- Maui District Health Office: (808) 984-8213
- Kauai District Health Office: (808) 241-3563
- After Hours: (808) 600-3625 or call Toll Free 1 (800) 360-2575

## Submitting a CSF Sample for RTi-PCR for Neuroangiostrongyliasis:

- Collect 500 µL of CSF (200 µL minimum)
- Make sure the sample is labeled with two (2) patient identifiers
- Ship on ice or, if > 24 hours delay, on dry ice
- Complete Clinical Specimen Form – SLD Form 81.3, available at: <http://health.hawaii.gov/statelab/forms/>
- After discussion with DIB (see above), Contact HSLD at (808) 453-5399 regarding sample submission.

## Additional Laboratory Testing

A CBC with differential should be performed, and the absolute eosinophil count (AEC) should be calculated to distinguish clinically significant eosinophilia. Peripheral eosinophil counts of  $\geq 500$  cells/ $\mu$ L are often present during the course of the illness but may be absent. A peripheral blood eosinophilia is suggestive but not diagnostic of neuroangiostrongyliasis.

Serologic testing for antibodies against *A. cantonensis* is not recommended. Current *A. cantonensis* antibody tests are difficult to interpret and should not be relied upon to diagnose neuroangiostrongyliasis. Seroconversion would

not be expected until several weeks after exposure. In addition, serological tests have a high likelihood of false positives because of the low prevalence of the disease in Hawaii, have problems with cross-reactivity, and cannot distinguish between current and past infection.

The CSF RTi-PCR test has superseded immunologic tests for the diagnosis of neuroangiostrongyliasis.

## Radiologic Testing

Although not required for diagnosis or treatment, brain MRI may demonstrate the following findings: non-specific signs of leptomeningeal enhancement in post-contrast studies; increased signal intensity in the subcortical white matter on T2 weighted and FLAIR images; and sometimes nodular, linear, or hockey stick-like small lesions in white matter on gadolinium-enhanced T1 images. New modalities in MRI imaging may offer more specific and helpful findings, but those modalities still require further study. In patients with radicular symptoms, MRI of the spine may be considered.

Reports have not shown head CT to be useful in diagnosing neuroangiostrongyliasis.

Some researchers have shown that small, nodular lesions can be seen in the lungs of some patients with neuroangiostrongyliasis, presumably caused by larvae or adult worms. Therefore, if respiratory symptoms are present, a chest CT should be considered.

## Differential Diagnosis

In Hawaii, *A. cantonensis* is the leading parasitic cause of eosinophilic meningitis. However, the differential diagnosis includes several other infectious diseases, many of which are geographically restricted and should be considered when there is an appropriate exposure history. These include:

- Neurognathostomiasis
- Neurococcidioidomycosis
- Neurocysticercosis
- Neuroschistosomiasis
- Baylisascariasis (neural larva migrans)
- Visceral toxocarosis
- Cerebral paragonimiasis
- Neurotrichinosis
- Noninfectious causes include ventriculoperitoneal shunts, lymphomas, drugs (e.g., ibuprofen, ciprofloxacin), and intrathecal contrast material.

# Management of Neuroangiostrongyliasis

## Initial and Serial Lumbar Punctures

As described above, the first LP can be therapeutic as well as diagnostic. Repeat LPs should be performed as often as necessary to relieve headache, as dictated by the patient's symptoms and signs. Serial LPs may be the best treatment option for patients in whom high dose corticosteroids are relatively contraindicated.

## Corticosteroids

High dose corticosteroid therapy for at least 14 days has been shown to improve outcomes in non-comatose patients in limited studies and is becoming accepted as standard therapy. Prednisolone significantly reduced days of headache and number of repeat LPs required in Thailand.

Prednisone at a dose of 60 mg/day in adults or dexamethasone 10 to 20 mg/day in divided doses, in the absence of contraindications is recommended. For children, the prednisone dose is 2 mg/kg/day with a maximum of 60 mg/day.

Fourteen days of corticosteroid therapy may be a minimum duration of treatment. Experience in Hawaii suggests a benefit from a prolonged steroid taper in severe cases to reduce recurrence of symptoms. There are no data to define an ideal regimen for tapering steroids, so it seems reasonable to adjust the taper based on the patient's clinical course. Tapering of steroids is generally recommended for courses longer than 14 days and for children to prevent complications such as adrenal insufficiency.

Corticosteroids are known to induce hyperglycemia in patients with diabetes mellitus and may reveal undiagnosed diabetes. Therefore, patients should be closely monitored.

## Anthelmintic Drugs

Limited studies suggest there may be benefits to using albendazole in treating human infection. One randomized, blinded, placebo-controlled trial of albendazole versus placebo (without steroids) in Thai adults showed a decrease in days of headache that just reached statistical significance.

When anthelmintic drugs are used, albendazole is preferred over mebendazole, because it achieves higher concentrations in the CNS. Thiabendazole has not shown benefit in neuroangiostrongyliasis.

Theoretical benefits in killing the worms early in the course of the illness include (a) limiting damage caused by worm migration and (b) preventing smaller worms from maturing into larger worms that can potentially induce a greater inflammatory reaction when they die.

Anthelmintic drugs such as albendazole are controversial because of theoretical concerns that rapid worm death might exaggerate the inflammatory response in the brain and spinal cord. However, studies in mice suggest inflammation is reduced when albendazole alone is used for treatment. Despite this evidence, until better safety data are available, we recommend albendazole be given concurrently with corticosteroids when used to treat neuroangiostrongyliasis.

Animal studies suggest there is decreased efficacy of albendazole when started after two weeks post-exposure, presumably because mature worms become less susceptible to the drug. Therefore, if albendazole is used for treatment, it should be given as soon as a presumptive diagnosis is made.

The most studied dose of albendazole in the treatment of neuroangiostrongyliasis is 15 mg/kg/day in two divided doses for 14 days. It is usually well tolerated, and absorption is increased when taken with a high-fat meal.

Because of rare, idiosyncratic, severe reactions, including liver failure and pancytopenia, baseline CBC with differential and liver function tests are recommended before treatment. Additional monitoring every 1 to 2 weeks may be prudent.

Albendazole is teratogenic in some animals and is listed as Pregnancy Category C. Therefore, albendazole should be used with caution in women who are pregnant if the benefits clearly outweigh the risks and with informed consent. The safety of albendazole in breastfeeding infants is unknown.

Until further evidence is available, the Clinical Subcommittee believes the potential benefits of albendazole may outweigh theoretical risks in the treatment of neuroangiostrongyliasis. The decision to use anthelmintics, however, should be made on a case-by-case basis.

## Summary on the use of Albendazole:

1. The decision to use albendazole for treatment should be made on a case-by-case basis.
2. Limited evidence suggests albendazole may be beneficial.
3. Early treatment (within the first two weeks after ingestion of the parasite) may provide the most benefit. However, the specific time of ingestion of the parasite is often not known.
4. If albendazole is used, it should be combined with corticosteroids.
5. There is very little, if any, evidence of harm when albendazole combined with corticosteroids is used for the treatment of neuroangiostrongyliasis.

## Acute Pain Management

Large volume LP (e.g., 20-40 mL in adults) is effective in controlling acute headache with neuroangiostrongyliasis. High dose corticosteroids may also reduce the number of lumbar punctures required. NSAIDs may be relatively contraindicated because of the increased risk of gastrointestinal bleeding when used with high dose steroids and the theoretical risk of intracranial bleeding. Opioids should be used judiciously (if at all) because they may cause confusion, increase the risk of falls, and have a high potential for abuse or dependence.

## Patient Monitoring

Patients with neuroangiostrongyliasis should be followed closely, and serial neurologic exams should be routinely performed. Worsening symptoms or signs should prompt neuroimaging (e.g., brain or spinal cord MRI) and repeat LP. If the ICP is high, removal of large volumes of CSF (e.g., 20-40 mL) may be indicated. Elevated blood pressure may give warning of increased ICP. If neuroangiostrongyliasis has not yet been confirmed and eosinophilic meningitis is present, after consultation with DIB, a repeat CSF specimen should be submitted to the HSLD for RTi-PCR.

If steroids are used for more than 14 days or used in children, the steroid dose should be carefully tapered under medical supervision. Patients with diabetes should have their glycemic control monitored while on steroids.

## Long-term Sequelae

To our knowledge, there are no studies regarding long-term follow up of neuroangiostrongyliasis patients. However, anecdotal experience in Hawaii has shown several patients develop chronic neurologic sequelae that adversely affect their activities of daily living. Symptoms include severe limb weakness and pain, difficulties with executive function, dysesthesias, difficulty walking, insomnia, and recurrent headache. These patients may benefit from multidisciplinary support, including occupational or physical therapy, social work support, and alternative/complementary medical care. (e.g., acupuncture).

Some clinicians have used gabapentin or pregabalin with variable success for chronic pain.

Long-term opioid use should be discouraged.

Neurology and pain management consultation may be appropriate.

Patient support groups have been formed to enable patients, caregivers, and healthcare workers to share stories, information, and suggestions.

## Ocular Angiostrongyliasis

Direct involvement of the eye is a rare manifestation of *A. cantonensis* infection, only occurring in about 1% of cases reported in the literature. Larvae may be found in the anterior chamber, vitreous cavity, or sub-retinal space. Usually, only a single larva is present. The presence of a larva may or may not be associated with inflammation. It is not clear how larvae access the eye—they may enter via the retinal artery or along the surface and base of the brain, traveling between the sheath and the optic nerve. Concomitant eosinophilic meningitis occurs in about 50% of cases.

Visual symptoms may include blurred vision, partial or complete blindness, loss of color vision, eye redness or pain, and the sensation of a worm crawling in the eye.

Treatment may include surgical removal of the worm and local or systemic corticosteroids. Live larvae are usually killed with laser therapy prior to surgical removal. Anthelmintics such as albendazole should not be used alone as they may kill larvae and trigger an acute inflammatory response. Patients with suspected or proven neuroangiostrongyliasis who have visual symptoms should be referred to an ophthalmologist for careful fundoscopic examination and additional procedures such as a slit lamp examination.

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