

SPECIAL FEATURE

Diagnosis and Treatment of Neuroangiostrongyliasis in Hawai‘i

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Abstract

Angiostrongylus cantonensis is a metastrongylid lungworm of rats with a global distribution and the cause of neuroangiostrongyliasis in humans. In Hawai‘i, neuroangiostrongyliasis cases have occurred sporadically since 1960; however, in 2001, the number of cases on Maui and Hawai‘i Island began to increase significantly. Since most human treatment trials have been conducted in Thailand, where the disease is usually mild, there is a need to develop treatment protocols for Hawai‘i, where there is a broader disease spectrum. In 2018, preliminary guidelines for the diagnosis and treatment of neuroangiostrongyliasis were developed for Hawai‘i’s physicians. This article summarizes those guidelines and provides additional recommendations for individuals who recently ingested an infected intermediate host.

Keywords

Angiostrongylus cantonensis, eosinophilic meningitis

Acronyms and Abbreviations

CDC = Centers for Disease Control and Prevention

CNS = central nervous system

CSF = cerebral spinal fluid

HIDOH = Hawai‘i State Department of Health

NAS = Neuroangiostrongyliasis

RTI-PCR = real-time polymerase chain reaction

Hawai‘i played a significant role in defining the etiology, epidemiology, pathology, and prevention of neuroangiostrongyliasis (NAS) in Hawai‘i and the Pacific.^{1,2} Since its recognition in 1945, this painful disease continues to expand its geographical range and evoke a lifelong malady for small percentage of cases.³⁻⁵ Other countries look to Hawai‘i for guidance in the diagnosis and treatment of NAS due to our consistent but sporadic number of annual cases.⁶

Angiostrongylus cantonensis (*A. cantonensis*) is a parasitic nematode of rats. This neurotropic organism has an obligatory but transient developmental phase in the rat’s central nervous system (CNS) before migrating to and maturing in the pulmonary arteries.⁷ Gastropods (slug and snails) are the intermediate host, but various vertebrates and invertebrates serve as transport hosts.⁸

Humans are accidental dead-end hosts. The infectious larval stage, encapsulated within the intermediate host, enters the CNS and molts twice to form young adults. Migrating and disintegrating larvae and young adults induce an inflammatory response leading to eosinophilic meningitis, the hallmark of NAS. The disease in humans is commonly known as Rat Lungworm Disease. The infection results in various neurologic manifestations with the possibility of long-term disabilities.^{9,10} Death may occur with heavy infections, although the rate is considered low.^{9,11,12} Infants and young children, however, are at greater risk for severe neurological damage and mortality.^{13,14}

A. cantonensis was introduced into Hawai‘i from Asia, although the exact date of the parasite’s establishment is unknown. The first cases of eosinophilic meningitis in Hawai‘i were reported in the 1960s.^{15,16} In both case reports, the parasite was found on autopsy and was noted to be present in the geographic locations frequented by the patients.

In 2016, Governor David Ige established a Joint Task Force to assess the threat of NAS in Hawai‘i.¹⁷ The clinical subcommittee of the Task Force, in 2018, released preliminary clinical guidelines to facilitate the diagnosis and treatment of this erratically occurring infection.¹⁸ Since the release of the guidelines, awareness has led to patients being diagnosed and treated promptly; however, there are individuals in which the disease is not considered upon presentation of symptoms. This delay in the initiation of treatment may lead to neurological deterioration.¹³

The key recommendations of the guidelines are summarized here, followed by additional recommendations for individuals with a recent history of gastropod ingestion.

Diagnosis

1. Physicians should have a high index of suspicion for NAS, especially in residents or recent visitors to Hawai‘i, especially Hawai‘i Island, also known as the Big Island.¹²

2. Typical symptoms in adults include severe headaches, neck stiffness, nausea, abnormal sensations of the skin, and muscle pains. The majority of patients present with headache, but the lack of headache should not exclude the consideration of NAS.

3. Highly suggestive symptoms and signs include papilledema, migratory hyperesthesia, cranial nerve abnormalities, ataxia, and focal neurologic findings that are migratory or do not follow a dermatomal distribution.

4. Typical symptoms in infants, toddlers, and young children include fever, abdominal pain, vomiting, irritability, inconsolability, poor appetite, muscle weakness, fatigue, and lethargy.¹⁹

5. Lumbar puncture is an essential procedure in the evaluation of suspected NAS. It is a low-risk procedure with diagnostic and therapeutic benefits.

6. Eosinophilic meningitis is a distinctive feature of NAS. It has been traditionally defined as the presence of 10 or more eosinophils per μL of cerebral spinal fluid (CSF) or eosinophils accounting for more than 10% of the white blood cells when there are at least six total white blood cells per μL of CSF.²⁰

- a. CSF eosinophil counts may be absent or low early in the course of the disease, requiring repeat lumbar punctures if NAS is still suspected.
- b. The diagnostic laboratory should specifically stain the CSF smear for the presence of eosinophils.

7. A presumptive diagnosis of NAS requires all three of the following:

- a. A history of suggestive symptoms and signs,
- b. Evidence of eosinophilic meningitis, and
- c. A history of intermediate host exposure or residence in or recent travel to an endemic area.

8. Confirmation of infection is determined by finding larvae in the CSF, although this is rare, or by detecting *A. cantonensis* DNA by real-time polymerase chain reaction (RTi-PCR) in CSF.²¹ This test is available in Hawai‘i through the Hawai‘i State Department of Health (HIDOH).²² RTi-PCR may be negative in the early stages of the infection, necessitating repeating the lumbar puncture and RTi-PCR assay.¹²

9. Baseline studies should include a complete blood count with differential, serum electrolytes, liver function tests, renal function tests, blood glucose, urinalysis, ophthalmologic exam, and chest x-ray. Peripheral eosinophil counts of ≥ 500 cells/ μL are often present during the illness but may be absent.²³

10. Occasionally, larvae can migrate into the eye. Infection can be mildly symptomatic or cause an inflammatory reaction leading to pain, iritis, vitreous haziness, ophthalmitis, or retinal detachment. Diplopia and strabismus have been reported.

11. Magnetic resonance imaging (MRI) of the brain, although not required, may help rule out other causes of meningitis. Focused MRI of the spine may be appropriate if indicated by clinical presentation.

12. Other diagnostic tests for NAS are not approved by the US Food and Drug Administration.

Treatment

1. Start corticosteroids as soon as a presumptive diagnosis of NAS is made and assuming there are no contraindications. High-dose corticosteroids for 14 days have been shown to improve clinical outcomes.²⁴

2. For ocular angiostrongyliasis, several treatment options are available to remove the parasite from the eye.²⁵ Anthelmintic drugs are contraindicated for ocular angiostrongyliasis.

3. The addition of albendazole, an anthelmintic drug, may provide additional benefits, though there is limited evidence of this in the literature.^{26,27}

- a. Dosage (adults): 15 mg/kg/day twice daily for 14 days with meals.
- b. If albendazole is used, combine with corticosteroids to blunt any possible increase in the inflammatory response to dying larvae.

4. Careful clinical monitoring is recommended in all patients, and specialist consultation (eg, infectious disease, neurology, pain management, etc) may be advisable.

- a. Patients should be monitored until all symptoms have resolved, which may range from weeks to months.
- b. Psychosocial issues may arise and should be identified and addressed as needed.

Post-Exposure Prophylaxis

The infectious dose and the probability of infection following the ingestion of a gastropod are unknown. We postulate that prophylactic treatment with albendazole should be effective if given within 2 weeks post-ingestion. There is no human evidence for the use of albendazole to prevent infection. Therefore, these recommendations are expert opinion extrapolated from animal studies and 1 human treatment trial.^{26,28}

1. Individuals who have ingested a gastropod or transport host (eg, flatworms, centipedes, freshwater shrimp, frogs, etc.) within the past 14 days should be considered for post-exposure prophylaxis with albendazole.

2. Individuals who suspect they ingested a gastropod or transport host should be evaluated on a case-by-case basis.

3. Albendazole should be given at 15 mg/kg/day twice a day with meals for 14 days (adults).

4. Patients should be closely monitored for the development of neurological signs and symptoms for 30 days or more and for the possible adverse effects of the long-term use of albendazole.

Discussion

Eosinophilic meningitis caused by *A. cantonensis* is a migratory, multifocal CNS inflammatory condition. The extent and severity of the illness are determined by the number of larvae reaching the CNS, the movement of those larvae within the CNS, the host's inflammatory response to the larvae, as well as the location of the dying larvae within the CNS.²⁹ The average incubation period ranges from 1 to 3 weeks; however, it can vary from 1 day to 6 weeks.³⁰

A. cantonensis has been an enzootic parasite in Hawai'i since the 1960s, with human cases reported in most years since then.³¹ In humans, the disease ranges from mildly symptomatic to a severe illness requiring hospitalization. The most widely reported symptom is headache, which prompts patients to seek medical help. We are aware of symptomatic patients visiting multiple physicians or clinics before an appropriate workup was conducted. Although there is limited human evidence, animal studies suggest that early treatment may improve patient outcomes.²⁸

Physicians should consider NAS in the differential diagnosis of patients presenting with dysesthetic neuropathic symptoms, especially with a history of recent gastropod exposure. The initial presentation of NAS might be misinterpreted as functional disease, Guillain-Barré syndrome, acute encephalopathic, or myelopathic syndromes.¹⁴

The administration of high-dose corticosteroids can significantly reduce the duration of headache.²⁴ Severe muscle pain, which may be refractory to standard analgesics, is a common complaint by patients with acute illness.³² Recently, intravenous lidocaine and ketamine have been shown to help with intractable neuropathic pain associated with severe NAS.^{10,32,33}

There are conflicting opinions on the use of albendazole in managing NAS patients. However, it may be the timing of administration that influences outcomes.³⁴ A study in rabbits, using albendazole without steroid coverage, indicated that albendazole was unsuitable for the treatment of NAS.³⁵ Conversely, studies in mice have shown that albendazole can arrest parasite development in the CNS if given within 10 days of ingestion.^{28,36} Human studies indicate that albendazole is safe in the treatment of NAS, although its effectiveness cannot be determined.^{27,37} Since most patients do not know when they were infected, the consensus of this group is that the benefits of using albendazole under steroid coverage in symptomatic patients outweigh the potential for increased inflammatory response.

Rare adverse effects have been reported with the long-term use of albendazole. Patients should be monitored for hematological, liver, and renal changes.³⁸ In the United States, albendazole is expensive and sometimes difficult to obtain, necessitating the need to develop a statewide plan to ensure its affordability and availability.³⁹

Eosinophilic meningitis became a reportable disease in Hawai'i in 2007. Since then, the majority of cases have been reported from Hawai'i Island (Figure 1). The RTi-PCR assay for NAS was developed in 2016 by the Centers for Disease Control and Prevention (CDC) and the HODOH's Laboratory Division and has been used to confirm the presence of *A. cantonensis* DNA in the CSF of patients with eosinophilic meningitis.²¹ A study conducted by the HODOH revealed 82 probable NAS cases between 2007 and 2017. Fifty-one of these cases were confirmed by parasite isolation (n=1) or a positive RTi-PCR.¹²

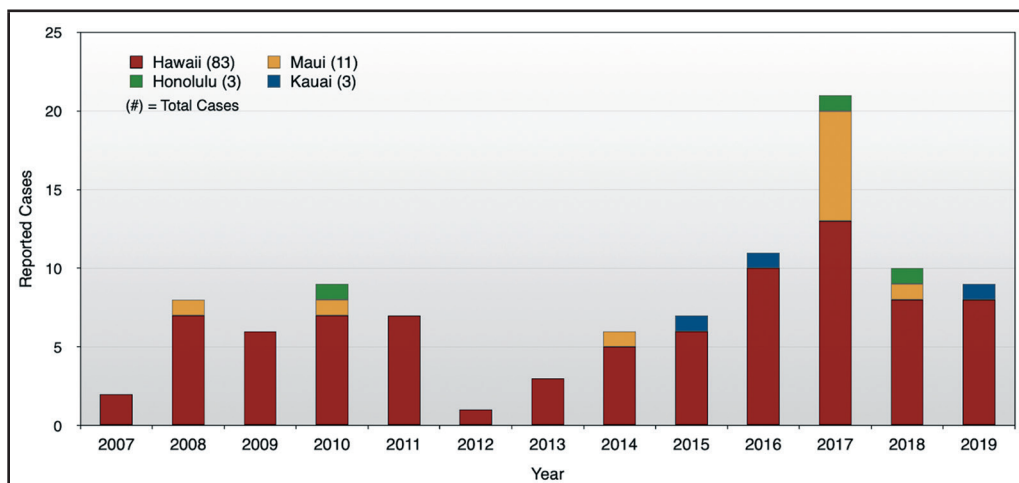


Figure 1. Number of Neuroangiostrongyliasis Cases Reported in the Hawaiian Islands by County and Year.⁴⁶

A number of individuals diagnosed with NAS in Hawai‘i have developed long-term debilitating conditions. Little is known about the percentage of patients who develop long-term sequelae, why it occurs, or how best to treat the residual disabilities. The Hilo Medical Center has organized a very successful support group for these patients.⁴⁰ We enthusiastically support this endeavor and encourage future studies on the long-term effects and care of NAS patients.

A debated issue is the use of anthelmintic drugs for individuals who recently ingested a slug or snail. There are currently no *in-vivo* or *in-vitro* studies on the post-exposure use of anti-parasitic medications to prevent NAS. The medical community in Australia has hypothetically addressed this issue by recommending the prophylactic use of albendazole in children.^{41,42} Although clinical evidence is lacking, we feel in such cases, prescribing albendazole, as recommended for treatment, is appropriate if given within 14 days of ingestion. These individuals should be closely monitored for the development of meningitis and drug side effects. Asymptomatic patients who ingested a gastropod greater than 14 days earlier should be evaluated on a case-by-case basis.

The Hilo Medical Center recently released a protocol for post-exposure prophylaxis using an over-the-counter medication commonly used for pinworms, pyrantel pamoate.⁴³ There are no published human trials supporting the use of pyrantel pamoate or shortening the course of albendazole mentioned in the protocol, but the regimen should not be detrimental if followed as directed. For these individuals, follow-up with their primary care physician is crucial since pyrantel pamoate is not a substitute for the urgent administration of albendazole.

Globally, the primary source of human infection is the ingestion of raw or undercooked intermediate or transport hosts for dietary or cultural reasons.⁴⁴ However, in Hawai‘i, terrestrial or freshwater gastropods are not part of the local diet. A survey of gastropods revealed high rates of infection across the state, with many different taxa being infected and some species harboring substantial parasite burdens.⁴⁵ Therefore, all gastropods encountered in Hawai‘i should be considered infected and capable of causing serious illness.

Many NAS patients cannot recall how they were infected. A 2011 study by the HODOH and the CDC showed that NAS patients from Hawai‘i Island were more likely to consume uncooked homegrown produce and see gastropods on their produce than patients from other islands.⁴⁶ These results suggest that not following safe food practices by not properly washing homegrown vegetables and leaving consumables unprotected from gastropods pose a potential risk for human infection. In addition, outdoor pet food can attract gastropods near homes and increase the potential for human exposure, especially for toddlers, pets, and other animals.⁴⁷

Visitors to Hawai‘i are also at risk of infection if they are unaware of the parasite’s presence. Between 2015 and 2018, 7 visitors acquired NAS while visiting the state of Hawai‘i.⁴⁸ HODOH, in collaboration with the State Tourism Authority, has developed messages directed at visitors, such as video warnings at baggage claim areas.⁴⁹

In theory, NAS is a preventable disease.⁵⁰ The decrease in the number of cases in Taiwanese children is believed, in part, to be due to public health measures.⁵¹ Public health messaging can be effective, but it requires a sustained societal commitment. With two years of funding, the HODOH developed announcements for radio, television, and movie theaters.^{49,52} In addition, informational posters were placed in shopping malls throughout the state. Privately, a few supermarkets and farmers markets post fliers promoting the washing of fruits and vegetables before consumption. Preventive messaging in schools can educate children about this illness, which may translate into parents becoming more aware of the risk of acquiring the disease.⁵³

Preventive messages should recommend the following actions: (1) cooking of intermediate and transport hosts in boiling water for 3–5 minutes, (2) the need to eradicate gastropods and rodents near homes and vegetable gardens, (3) the importance of handwashing after gardening or handling gastropods, and (4) the importance of not eating unwashed fruits and vegetables, where small gastropods may be hiding.^{54, 55}

Additional information about *Angiostrongylus cantonensis* for consumers and health care providers can be found on the HODOH’s webpage.⁵⁶

The clinical guideline posted on the HODOH website has recently been published.^{18,57}

Conflict of Interest

None of the authors identify a conflict of interest.

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