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Rat Lungworm Disease for the Veterinary Professional

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Introduction

Rat lungworm disease, also known as angiostrongyliasis or neuroangiostrongyliasis, affects the brain, spinal cord, and peripheral nerves of animals and humans. Infection may cause mild and transient symptoms in humans if the infectious dose is small, but in severe cases, in which the infectious dose is large, it can cause long-lasting neurological signs and symptoms, permanent neurological damage, and even death (Yii 1976). Worldwide, there have been over 2,800 documented human cases, mostly in southern China (Wang, Lai, Zhu, Chen, & Lun 2008). Cases in domestic animals and wildlife (mammals and birds) have been reported mainly in Australia and the southeastern United States (Spratt 2015; Dalton, Fenton, Cleveland, Elsmo, & Yabsley 2017). Rat lungworm disease is considered established in Hawai'i and is an important disease that both veterinarians and animal owners must be aware of.

Figure 1: Adult *Angiostrongylus cantonensis* (Photo: S.I. Jarvi)

Etiology

Rat lungworm disease is caused by *Angiostrongylus cantonensis* (Figure 1), a zoonotic nematode parasite in the family Angiostrongylidae. Other members of this genus include *A. costaricensis*, which causes primarily an intestinal disease of humans (Mota & Lenzi 2005), and *A. vasorum*, a parasite of the heart and pulmonary vessels of dogs and other canids such as wolves and coyotes (Morgan et al. 2010, De Liberato et al. 2017). These latter two species have not been reported in Hawai'i.

Life cycle of *A. cantonensis*

Adult worms are found in the pulmonary arteries and right ventricle of the heart of rats. Adult male worms are 20–25 mm long and females are 22–34 mm long (Graeff-Teixeira, da Silva, & Yoshimura 2009). They have an indirect life cycle involving snails and slugs, with humans and other vertebrates as incidental (or accidental) hosts.

Hosts

Definitive hosts: These are hosts in which the parasite can reproduce. *Rattus rattus* (black rat), *R. exulans* (Polynesian rat), and *R. norvegicus* (brown rat) are the main definitive hosts in Hawai'i, but other rat species (though not mice) can also serve in this role (Yong & Eamsobhana 2013). Definitive hosts become infected by ingesting infected intermediate or paratenic hosts.

Intermediate hosts: In intermediate hosts, first-stage (L1) larvae (shed in rat feces and eaten by snails and slugs) develop into infective third-stage (L3) larvae, but the parasite cannot reach its full adult form or reproduce.

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Figure 2: *Lissachatina fulica* (Photo: R.H. Cowie)

Figure 3: *Parmarion martensi* (Photo: J.R. Kim)

Important intermediate hosts in Hawai'i include the giant African land snail (*Lissachatina fulica*) (Figure 2) and a semi-slug (*Parmarion martensi*) (Figure 3), but many other molluscs can serve in this role.

Paratenic hosts: These are animals that become infected by ingesting gastropod intermediate hosts or other paratenic hosts containing L3 larvae. These L3 larvae become quiescent and do not develop in paratenic hosts. However, if a paratenic host containing infective L3 larvae is eaten by a definitive host (e.g., a rat) or an incidental host (e.g., a human or dog), the L3 larvae can continue their development. Freshwater prawns or shrimp, frogs, toads, lizards (including large monitor lizards), land crabs, centipedes, and planarians can serve as paratenic hosts.

Incidental (accidental) hosts: These hosts also become infected by eating intermediate or paratenic hosts containing L3 larvae. However, the larvae cannot mature to the full adult form and reproduce. Incidental hosts cannot pass the parasite on to any other organisms. These are the reasons they are also known as "dead-end" hosts. Humans, dogs, horses, birds, opossums, non-human primates, Australian marsupials including macropods, and fruit bats have all been recorded as incidental hosts; experimentally, calves, cats, guinea pigs, rabbits, and pigs have also been infected (Alicata 1964; Mason 1987; Gardiner et al. 1990; Wright, Kelly, Wadell, & Hamilton 1991; Reddacliff, Bellamy, & Hartley 1999; Yang et al. 1999; Costa, McClure, Snider, & Stewart 2000; Kim, Stewart, Bauer, & Mitchell 2002; Monks et al. 2004; Lunn et al. 2012; Burns et al. 2014; Spratt 2015).

Natural life cycle in the rat

- Adult worms live in the pulmonary arteries and right ventricle of the heart of rats (the definitive host). The worms lay eggs, which travel to and subsequently develop in pulmonary capillaries.
- L1 larvae emerge from the eggs, penetrate the alveolar epithelium, and are carried to the pharynx in respiratory secretions (via the mucociliary escalator), and are then swallowed.
- L1 larvae pass through the digestive tract and are excreted in the rat's feces.
- Intermediate hosts (snails or slugs) ingest rat feces and are infected by the L1 larvae.
- Within these molluscs, L1 larvae develop into the L2 stage, and then into infective L3 larvae.
- The life cycle is completed when a rat ingests infective L3 larvae in a snail/slug. L3 larvae penetrate the rat's intestinal walls to enter the bloodstream (portal circulation) and variably migrate through the liver, heart, lungs, and kidneys before entering the central nervous system (CNS). In the brain and spinal cord, L3 larvae migrate extensively, grow in length and diameter, then eventually mature into subadults, which penetrate the meningeal veins, and finally situate themselves in the pulmonary arteries, where they mature and reproduce. The prepatent period is 42–46 days in the rat.

Mode of human/animal infection

Incidental hosts, including humans and numerous other animals such as dogs, horses, and birds, become infected by ingesting L3 larvae in snails, slugs, or infected paratenic hosts (Figure 4). In these hosts, the parasite life cycle progresses in the same way as in definitive hosts, but only to the subadult stage. These subadults are in general unable to leave the CNS, where they die; they do not reach the pulmonary arteries and reproduce.

Geographic Distribution

The first reported human case of eosinophilic meningitis caused by *Angiostrongylus cantonensis* was in Taiwan in 1944 (Beaver & Rosen 1964). The parasite has been detected in Hawai'i, the southeastern United States, American Samoa, Australia, Brazil, Canary Islands, China, Chuuk, Cook Islands, Cuba, Dominican Republic, Ecuador, Egypt, Fiji, Guam, Haiti, India, Indonesia, Ivory Coast, Jamaica, Japan, Madagascar, Malaysia, Marshall Islands, Mauritius, New Caledonia, Okinawa, Papua New Guinea, Philippines, Pohnpei, Puerto Rico, Réunion, Saipan, South Africa, Sri Lanka, Tahiti, Taiwan, Thailand, and Vanuatu (reviewed by Cowie 2013a), and more recently in Guadeloupe, Lesser Antilles (Dard et al. 2017) and Colombia (Giraldo, Garzón, Castillo, Córdoba-Rojas et al. 2019).

In the Hawaiian Islands, the disease was first reported in a human in 1961 and sporadically thereafter (Cowie 2017). *Angiostrongylus cantonensis* has been documented on Hawai'i Island, Maui, Moloka'i, O'ahu, and Kaua'i (Kim et al. 2019). It is also likely to be on Lāna'i. There has been an increase in reported cases over the last decade, which may be attributable in part to the spread of invasive semi-slugs (*Parmarion martensi*), which are frequently heavily infected (Hollingsworth, Howe, & Jarvi 2013; Kim et al. 2014, 2019; Cowie, Hayes, Kim, Bustamente, & Yeung 2018), as are rats (Jarvi et al. 2017). However, this increase is probably not statistically significant (Johnston et al. 2019).

Transmission

Animals and humans become infected with *A. cantonensis* by eating raw or undercooked food or drinking liquids containing the infective larvae. Methods of transmission include the following:

- Intermediate or paratenic hosts parasitized by infective larvae (L3). This might be deliberate (e.g., eating raw or undercooked snails) or inadvertent (e.g., accidentally eating slugs in salad vegetables) (Cowie 2013b).

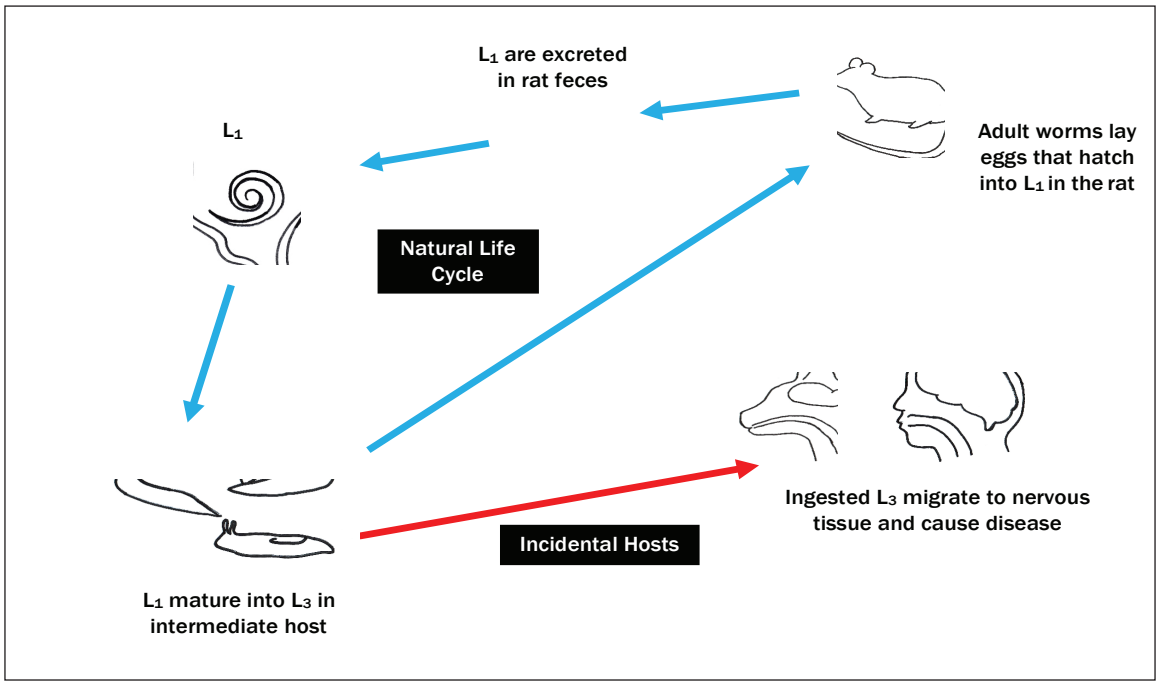

Figure 4: Life cycle of *A. cantonensis* and mode of incidental host infection

- Water contaminated with larvae released from molluscs (reviewed by Jarvi, Howe, & Macomber 2018, Howe et al. 2019).
- Vegetation, food, or liquids that are contaminated with snail/slug slime containing infective larvae (L3). These have been suggested as being involved in transmission, but only few or no L3 have been found in the slime (reviewed by Kramer, Posner, & Gosnell 2018).

Consumption of contaminated slime in food or liquids seems less likely to be an important pathway of infection resulting in serious disease than direct consumption of an infected snail/slug (Cowie 2013b). It is also important to note that the disease is not transmitted animal-to-animal or person-to-person, nor is it transmitted by eating *fully* cooked food.

Infections in Animals

Species Affected

Many species of mammals and birds have been infected naturally or experimentally (see above), although some hosts are naturally more resistant than others.

Incubation Period

In dogs, neurological signs most often occur approximately 11 days after ingesting L3 larvae (Jindrak & Alicata 1970). Vomiting and diarrhea can be seen shortly after ingestion (Mason, Prescott, Kelly, & Waddell 1976; Lunn et al. 2012), probably because of L3 larvae penetrating the stomach and intestinal wall.

Clinical Signs

These are caused by migration of L3 larvae out of the gut and into the peripheral nerves, spinal cord, and brain (causing neurologic signs and symptoms) and by the granulomatous/eosinophilic inflammation that occurs in response to the parasite.

- **Dogs**: The disease is described classically as an ascending paralysis (especially in puppies), with variable (often severe) lumbar or cervical hyperesthesia (excessive sensitivity). Hindlimb gait abnormalities (including proprioceptive ataxia), tail paralysis, muscle wasting, and urinary incontinence are commonly seen. Cranial nerve deficits, altered mentation, vomiting, and diarrhea may also be present (Mason et al. 1976, Mason 1987, Lunn et al. 2012). The clinical syndrome is well recognized in dogs from Hawai'i Island, and two cases were diagnosed in dogs on O'ahu in 2018, based on eosinophilic pleocytosis in cerebrospinal fluid (CSF) and confirmed by real-time polymerase chain reaction testing (PCR) on CSF (J. Odani, unpublished).
- **Horses**: The disease has been reported in horses from Hawai'i Island, Louisiana, and Australia. Cases typically present with tetraparesis, i.e., leg weakness (worse in the hindlimbs), urinary incontinence, and decreased tail tone and perineal reflex. Muscle wasting may be present in some cases (Wright et al. 1991, Costa et al. 2000). The recent cases from Hawai'i Island were confirmed by real-time PCR on brain, other tissues, and blood (S. Jarvi unpublished).
- Animals can be repeatedly infected; no long-term protective immunity has been reported.

Clinical Pathology

In dogs, eosinophilia (increased numbers of white blood cells known as eosinophils) in peripheral blood is commonly seen, but this may also be caused by intestinal parasites (e.g., hookworms) or other non-neurotropic parasites. Demonstration of eosinophilic pleocytosis in CSF (Figure 5) can be helpful in making a presumptive diagnosis, although eosinophils may not be present if CSF is collected too early or too late in the disease course.

Depending on the case and clinical findings, it may be prudent to test for other causes of neurologic disease (e.g., *Neospora caninum* or canine distemper virus in dogs). No diagnostically useful biochemical changes

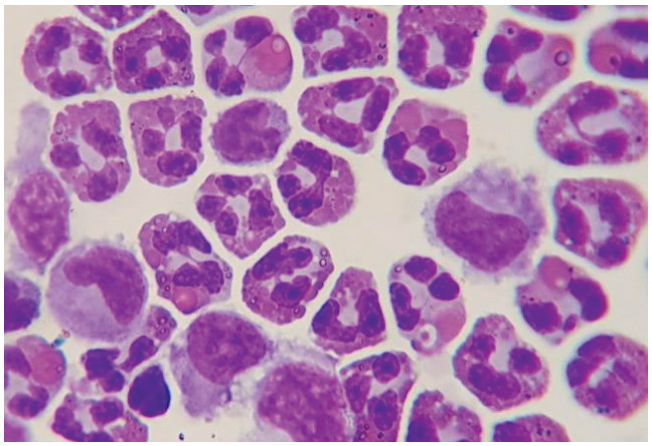

Figure 5: Eosinophilic pleocytosis in canine CSF (Photo: P. Smith).

have been reported in the literature (Mason 1987; Collins, Rothwell, Malik, Church, & Dowden 1992; Lunn et al. 2012).

In horses, neutrophilia and hyperfibrinogenemia (increased levels of neutrophils and fibrinogen in the blood) have been seen. Peripheral eosinophilia was absent, but eosinophilic pleocytosis of the CSF was present in the reported cases (Wright et al. 1991, Costa et al. 2000).

Post-Mortem Lesions

Larvae are variably present in the CNS (brain, spinal cord, and meninges) in dogs at necropsy. Granulomatous encephalitis with a variable eosinophilic component may be observed (Mason et al. 1976, Collins et al. 1992, Lunn et al. 2012).

In horses, only a few cases have been reported in the literature. Gross lesions in reported cases vary and include subdural parasitic larvae (approx. 8–10 mm long) in the subarachnoid space and spinal cord, eosinophilic meningitis, spinal cord malacia (softening) with verminous tracts multi-focally in the brain and spinal cord, or simply a meningeal reaction. Microscopically, these malacic areas were well-demarcated with gitter cells, mononuclear cells, and eosinophils, with or without intralesional nematode larvae.

In one equine case, the parasite larvae were seen but there was no remarkable malacia, hemorrhage, or inflammation, yet extensive diffuse eosinophilic meningitis of the cauda equina was present (Wright et al. 1991, Costa et al. 2000).

Infections in Humans (brief)

In humans, rat lungworm disease will manifest as an eosinophilic meningitis (less commonly, encephalitis) with clinical signs and symptoms including headache, neck stiffness, hyperesthesia (physical hypersensitivity), low-grade fever, nausea, vomiting, and, less commonly, temporary facial paralysis, abducens palsy, and light sensitivity. In some patients, clinical features can be more severe, with signs of encephalitis and increased intracranial pressure eclipsing signs of meningitis; in some patients, this encephalitic form results in coma and even death. Severe cases typically are left with some residual neurological impairment (e.g., blindness) even after successful therapy. The incubation period is typically 1–3 weeks but can range from 1 day to 6 weeks. Symptoms and signs are usually observed for 2–8 weeks, although they can last longer in some cases, and in the more severely affected patients there can be permanent neurologic deficits (Murphy & Johnson 2013). Humans who have been exposed to rat lungworm or are exhibiting clinical signs suspicious for rat lungworm disease should consult their health care provider for more information.

Diagnostic Tests

Evidence of eosinophilic pleocytosis (reflecting meningitis) on CSF analysis, coupled with the appropriate history, strongly supports a diagnosis of rat lungworm disease (Lunn et al. 2012).

Real-time PCR testing performed on CSF is the most accurate way to diagnose the disease in incidental host animals with neurologic disease, but *A. cantonensis* DNA can also be detected in the blood of rats (Jarvi et al. 2015). The testing can be performed on blood, CSF, and tissues at Dr. Susan Jarvi's laboratory at UH-Hilo. The link to the veterinary sample submission forms at UH Hilo is http://pharmacy.uhh.hawaii.edu/rat-lungworm/veterinary-sample-submission-form. Alternatively, the UC Davis Real-Time PCR Research and Diagnostics Core Facility can run the real-time PCR test on CSF as a stand-alone assay or as an add-on to their Canine Neurologic Panel I or II, which is useful in cases that might be caused also by other neuropathogens. The link to their website is https://www2.vetmed.ucdavis.edu/taqmanservice/forms.html. Instructions for collection and submission of different types of samples are described in the forms.

Serologic assays to test for the presence of antibodies against *A. cantonensis* in serum may be useful for initial screening, but there are concerns because of the potential for cross-reactivity with non-neurotropic helminths and their uncertain correlation with active infection. ELISA or Western blot testing of CSF can be useful if the real-time PCR is negative and can be arranged by sending CSF and/or serum to Rogan Lee at Level 3, ICPMR, Westmead Hospital, Sydney, Australia (Lunn et al. 2012), or the Jarvi lab (http://pharmacy.uhh.hawaii.edu/rat-lungworm/veterinary-sample-submission-form).

Fecal assays are not useful in animal species other than rats, as the definitive hosts are generally the only animals that shed larvae in the feces.

Treatment

The treatment of animals with neuroangiostrongyliasis generally consists of symptomatic and supportive care, with high doses of glucocorticoids to reduce inflammation, analgesics to control pain, and anthelmintics (e.g., fenbendazole and/or moxidectin) to kill migrating larval stages. Antibiotics to treat translocated bacteremia should be considered (Lunn et al. 2012).

Glucocorticoids are used to decrease inflammation associated with dead and/or molting larvae. However, in some cases, the resulting immunosuppression can lead to an extended period of larval migration and progression of the disease (Lunn et al. 2012).

Anthelmintics may increase the inflammatory response and worsen clinical disease if there is a large, sudden release of antigen from the dead and dying worms, although this can be largely mitigated by prior treatment with high doses of corticosteroids. Anthelmintics may be useful if the animal's clinical signs are attributable to larval migration through tissues. Fenbendazole (orally once a day for 4–5 days) and macrocyclic lactones (moxidectin, milbemycin) have been used with success to treat dogs when given in concert with high doses of corticosteroids (usually prednisolone) (R. Malik, J. Braddock, M. Linton, & A. Mina, unpublished).

It has been suggested that providing a gradually increasing dosage regimen for anthelmintics to allow a more gradual release of nematode antigens and administering it along with glucocorticoids may theoretically be a successful treatment combination (Lunn et al. 2012).

Control/Prevention

Controlling snails, slugs, and rats in the environment, if feasible, can reduce exposure to *A. cantonensis* (Hollingsworth et al. 2013).

Routine anthelmintics (e.g., many heartworm preventatives, dewormers) may control development of the disease in animals, depending on the product used and timing of administration. Duration of action is an important consideration, if there is ongoing/repeated exposure to infective larvae. Moxidectin has a much longer half-life than many other anthelmintics and therefore may be beneficial as a prophylaxis against *A. cantonensis* infection.

For dogs, a 6-month depot formulation of moxidectin (Proheart® 6; Zoetis) is available that provides a sustained release of the drug, and this may be useful for prevention, although drug levels in the last few months may be insufficient to kill migrating larvae. Alternatively, topical (transdermal) products containing moxidectin (Coraxis®, Advantage Multi®; Bayer) result in high and enduring blood concentrations of moxidectin for up to 28 days and probably affords more reliable, longer-lived protection (Lunn et al. 2012).

A feline preparation of Advantage Multi® is available, although cats are thought to be protected to some extent from rat lungworm disease because of their predisposition to vomit soon after ingesting infective larvae.

Moxidectin is also available for use in horses (Quest®, Quest Plus®; Zoetis) and cattle (Cydectin®; Bayer). Should a dog or other animal be seen to ingest potentially infected molluscs, administration of any macrocytic lactone within 2 days of ingestion should kill larvae before they reach the central nervous system.

Owners should consult with their veterinarians before giving any medication to their animals.

Disclaimer

This information is intended for veterinary professionals and is based on a review of the scientific literature. It is not intended to be a substitute for medical evaluation by a veterinary professional. Usage of trade names does not imply endorsement by the University of Hawai'i and is for informational purposes only. This publication may be updated as new knowledge becomes available.

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