Viewpoint

## Diagnosing and Understanding Angiostrongyliasis, A Zoonotic Cause of Meningitis

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**ABSTRACT:** Eosinophilic meningitis caused by *Angiostrongylus cantonensis* is spreading worldwide, and it can manifest as a severe neurological disease. Angiostrongyliasis is a food- and water-borne parasitosis that usually exhibits a seasonal and circumscribed geographical distribution. To improve control and treatment of these infections, further studies of transmission dynamics under natural conditions and the development of better diagnostic tools and treatment options are needed.

KEYWORDS: Angiostrongylus, rat lungworm, eosinophilic meningitis

Angiostrongylus cantonensis (Aca) is an intra-arterial nematode (Figure 1) that infects rodents, and mollusks serve as its



Figure 1. Angiostrongylus cantonensis, etiological agent of eosinophilic meningitis. Female worm is bigger (approximately 3 cm long) and clearly shows a dark red spiraling digestive organ and two white reproductive organs.

intermediate host. Eosinophilic meningoencephalitis (EoM), or cerebral angiostrongyliasis (CA), can develop in humans if infective third stage nematode larvae (L3) are accidentally ingested with the consumption of raw mollusks, vegetables or water that are contaminated with the mucus secretions of mollusks. CA has mainly been diagnosed in southeastern Asia, although an increasing number of cases have been reported in several countries worldwide. The biology, epidemiology, and clinical aspects of CA have been extensively reviewed.<sup>1</sup> Another angiostrongylid of medical importance is *Angiostrongylus costaricensis* (Aco). These worms inhabit mesenteric arterial branches and cause eosinophilic gastroenteritis. Here, peculiar biological aspects of both angiostrongylid nematodes will be reviewed, as well as the implications of these aspects in relation to risk assessment, diagnosis, and treatment.

Both species display low specificity for their intermediate hosts, and this may facilitate their spread in new transmission foci.<sup>2</sup> In addition, a given mollusk species may be susceptible to infection, but not necessarily have an important role in natural transmission of the parasite. For example, the role of *Cornu aspersum* (syn *Helix adspersa*) in the transmission of Aca in Australia remains controversial. Aca has been detected in approximately 4.5% of *Cornu aspersum* that have been sampled in Sydney, and has been detected in snails in Brisbane, Australia. However, elsewhere, this snail has not been found to be a suitable host for Aca.

Evaluating the adaptation and consequent contribution of a given host species to the survival of a parasite species demands more than prevalence studies in naturally infected populations and infectiveness studies in experimental models. The same consideration is valid for rodent hosts. A survey of Aca and the closely related "species", *Angiostrongylus mackerrasae*, in native and feral rats in forests of southern Australia has revealed spatial separation of the two forms. Surveys of genus *Rattus* populations in Queensland Australia have also revealed that focal populations of the parasite exhibit seasonal variations in incidence.

The territory and size of a host population usually characterize the focality of zoonoses. Transmission may also be seasonal depending on climate variability and the effects of this variability on the biological aspects of a host. Different focal areas may also be associated with differences in transmission intensity. For example, hot spots of human autochthonous infections have been described in Brazil and Hawaii.<sup>2,3</sup> Focality is good for control since public health services may face the prospect that spread of a disease will decrease with time due to complex interactions and self-containment within the biological

Received: January 15, 2018 Accepted: January 24, 2018 Published: February 7, 2018 cycle of Aca. Furthermore, invading exotic species have the potential to cause a dangerous imbalance in local fauna and increase risk for transmission.

Similarly, climatic variation may also significantly impact the transmission of angiostrongylids. For example, during clinical case studies of canines with EoM in Sydney, Australia, an increasing trend in the number of cases reported during the autumn (fall) months of the year was observed, and this period is typically characterized by higher than average rainfall and cooler weather. The implication of these observations is that terrestrial slugs in Australia are more active during cooler and wetter weather conditions, and this can lead to an increase in the incidence of accidental infections.

Aco L3 has been shown to penetrate severed skin in a murine experimental model, although there is no evidence to indicate that these larvae fully develop following penetration. It is known that passage through the stomach is important for activation of L3. It is also possible that penetration through the mucosal surface can occur in the upper digestive tract, although penetration is probably more efficient after the gastric-duodenal transition.

Experimentally infected mollusks have been found to shed low numbers of Aco larvae over time. When Aco L3 were exposed to various commonly used chemicals for food sanitization, only bleach was found to be effective in preventing their survival, with 95% of L3 eliminated at a 1% bleach concentration. However, much less information is available regarding L3 survival in soil and in slime trails. Under experimental conditions, Aco L3 that were kept in water were inactive after 3 days, although mathematical modeling has suggested that a few infective larvae may remain after 83 days.

While many infections are asymptomatic, a few will "emerge" as diseases with varying severity. When a 1 year AA serological follow-up study was conducted for 200 inhabitants of a rural area in southern Brazil, the rate of seroconversion was found to be 52%, yet there was no evidence for abdominal disease (data not published). Similarly, it is predicted that serological surveys and systematic reporting in Hawaii for CA would identify a greater number of less clinically severe cases.

It is important to recognize that detection of antibodies does not lead to a confirmed diagnosis. First, because antibodies may remain after a parasitic infection is eliminated. Second, crossreacting antibodies can exist, as demonstrated for the 31 kDa antigenic component of Aca.<sup>4</sup> In addition, despite the large number of investigations of immunological methods, there are currently no abundant sources of recombinant peptides or monoclonal antibodies available for the detection of parasitic infections. Crude worm antigen is used in enzyme-linked immunosorbent assays (ELISAs) and subsequent immunoblot for 31 kDa detection. See refs 1 and 5 for detailed epidemiological-clinical-laboratory protocols for angiostrongyliasis diagnosis.

Tissue dwelling parasites, especially those that dwell in the central nervous system, remain a significant challenge to treat. Angiostrongylid parasites are particularly dangerous due to their intravascular habitat. There is also no clear evidence to support the use of anthelminthic killing drugs for the treatment of angiostrongylid parasites, thereby leaving corticosteroids as a treatment option for the relief of clinical manifestations. For Aco, the most classical, yet controversial, recommendation is to avoid anthelminthics and lesion aggravation in order to prevent a massive release of antigenic molecules that can increase the risk of arterial thrombosis. Thus, the need remains for welldesigned clinical trials to improve treatment options.

Public education regarding known population dynamics of parasites and hosts is an important and ongoing effort. The education model proposed for Hawaiian schools is useful, although it requires ongoing awareness by educational and health authorities. In Australia, it is observed that dogs, as well as native birds and mammals, can act as sentinels of parasite transmission in certain regions, while animals in zoos are at risk of infection in endemic foci. Thus, interactions between medical and veterinary authorities are important for expanding the body of knowledge regarding parasites and their hosts, with veterinary standards being at a high level.

Eosinophilic meningitis caused by Aca is an emerging infectious disease spreading worldwide. This zoonosis is associated with unsafe food habits and the consumption of contaminated water. Beyond the severe neurological disease that can manifest, complex interactions exist among metastrongylid worms, between their vertebrate and mollusk hosts, in response to climate and environmental changes, and in relation to cultural factors. Understanding these complex interactions is key for the design of effective control measures, diagnostic tools, and new treatment options. Increased awareness and knowledge of angiostrongyliasis among health personnel is also critical for improving patient outcome.

## AUTHOR INFORMATION

## Notes

The authors declare no competing financial interest.

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