

Neuroangiostrongyliasis: updated provisional guidelines for diagnosis and case definitions

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Abstract: *Angiostrongylus cantonensis* is the main causative agent for eosinophilic meningoencephalitis in humans. Larvae are rarely found in the cerebral spinal fluid (CSF). Consequently, serology and DNA detection represent important diagnostic tools. However, interpretation of the results obtained from these tools need more extensive accuracy studies to be conducted. The aim of the present study is to update guidelines for diagnosis and case definitions of neuroangiostrongyliasis (NA) as provided by a working group of a recently established International Network on Angiostrongyliasis. A literature review, discussion regarding criteria and diagnostic categories, official recommendations issued by health authorities in China, and Hawaii (USA), as well as the experience from Thailand, were considered. Classification of NA cases and corresponding criteria are proposed as follows: minor (exposure history, positive serology, and blood eosinophilia); major (headache or other neurological signs or symptoms, CSF eosinophilia); and confirmatory (parasite detection in tissues, ocular chambers or CSF, or DNA detection by PCR and sequencing). In addition, diagnostic categories are proposed as: suspected, probable, and confirmatory. Updated guidelines should improve clinical study design, epidemiological surveillance, and proper characterization of biological samples. Moreover, the latter will further facilitate accuracy studies of diagnostic tools for NA to provide better detection and treatment.

Keywords: angiostrongyliasis; neuroangiostrongyliasis; rat-lungworm disease; eosinophilic meningitis

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1. Introduction

Angiostrongylus cantonensis is an intra-arterial nematode that accidentally infects humans to cause eosinophilic meningitis [1]. Eosinophilic inflammatory responses in the

central nervous system (CNS) are mainly elicited by helminths. However, these inflammatory responses can also occur in association with cancer, intra-theal drugs, and intravesicular devices [2].

A. cantonensis are parasites that live inside the pulmonary arteries of rodents, and mollusks serve as intermediate hosts. Several other invertebrates, such as shrimp, frogs, and lizards, can also serve as paratenic hosts. Larvae of *A. cantonensis* develop in the fibromuscular tissues of mollusks, and subsequently infect humans when raw or undercooked food is ingested [1,3]. Larvae contaminated water may also be a source of human infection [4,5]. In accidental hosts, including humans, larvae migrate and are retained in the CNS. This retention prevents complete maturation of adult worms inside the pulmonary arteries [1,3].

Larvae are rarely detected at examination of cerebrospinal fluid (CSF), thereby preventing confirmation of a diagnosis by direct identification of parasites [6]. Therefore, immunological and DNA detection methods are important tools for evaluating patients with suspected neuroangiostrongyliasis (NA) [7,8,9]. While antibody and DNA-detection methods have been standardized, evaluations of these methods as reliable detection tools have been less than adequate due to the small number of well-characterized reference biological samples that are currently available from different geographical areas. More recently, a highly sensitive and specific quantitative PCR method has been developed to confirm diagnosis of NA [10].

A. cantonensis is native to southeastern Asia and the Pacific Islands [11], yet its presence has expanded to multiple continents. It is also a food-borne disease that has been linked to travelers. A rough estimate of the cumulative number of reported cases worldwide is 2,800 [3]. Despite the potential for severe CNS disease, a recent expansion of transmission areas, and a rising concern for travelers, NA is not a highly prevalent infection worldwide. To date, the Hawaiian Islands and southeastern Asia, especially Thailand, have been the most affected endemic areas. However, reduced rates of occurrences have been observed in recent years [12,13].

Disease caused by *A. cantonensis* includes isolated meningeal lesions and meningitis associated with brain tissue inflammation (meningoencephalitis) [14]. More rarely, ocular angiostrongyliasis can develop [15]. For severe cases of encephalitis, mortality may reach 80% [16]. The objective of the present work is to update and explore possible consensus regarding diagnostic criteria and case definitions for NA. It is anticipated that such effort will improve patient management worldwide, will promote comparable clinical and epidemiological studies, and will define conditions for establishing an international biobank of well characterized samples. The latter would represent a valuable resource for evaluations of diagnostic tests to achieve detection and control of NA.

2. Materials and Methods

Several meetings of the International Symposium on Angiostrongyliasis (ISA), also named the International Symposium on Rat-Lungworm Disease, have been held in various countries over many years: Thailand, China, Hawaii (USA), and Australia. Canary Islands will host next ISA in September 2023. When a group of researchers and clinician attendees of the ISA met in an online discussion in October 2021, the need for more extensive studies, including multicenter accuracy studies, of diagnostic tests for NA was highlighted. Basic requirements for such studies are: (i) clear and well-defined diagnostic criteria and (ii) establishment of a collaborative international biobank with well-characterized biological samples. On November 23, 2021, the International Network on Angiostrongyliasis was established. Subsequently, several online meetings were hosted throughout 2022 to discuss many issues, including diagnostic criteria. Health authorities in both China and Hawaii (USA) have independently established recommendations for diagnosing and treating NA [17,18]. Diagnostic and patient management experience from Thailand, currently the most endemic country, are also available. In particular, the results from a systematic review published by Khamsai and collaborators (2020) were

examined [13]. Based on these considerations, the following revised guidelines were developed and are not to be definitive but a starting point for continuous improvement.

3. Results

The present updated guidelines were developed based on the following principles: (i) to provide clear definition and expression (“taxonomy”) of symptoms, signs, or laboratory results; (ii) to select the most relevant symptoms most closely related to NA (sensitivity) and classify them as minor, major, or confirmatory criteria. Meanwhile, excessive value for general, less specific symptoms and signs is avoided. (iii) to define categories of diagnosis according to the degree of certainty for etiological diagnosis, from lower (suspected) to highest (probable and confirmed) degrees, conforming to standard organization of diagnostic and treatment guidelines [19,20,21,22,23].

Criteria are classified as minor, major, or confirmatory (Table 1 and Figure). Diagnosis categories (suspected, probable, and confirmed) and recommended actions are also presented in Table 2 and Figure. Antibody detection (serology), blood eosinophilia, and history of exposure are considered minor criteria, since their isolated presence does not constitute strong evidence for NA. In addition, these criteria may be absent in patients. While serological studies are useful for epidemiological exposure studies [5,24], cross-reactivity and persistence of antibodies after cure are recognized as universal limitations of serology for detection of current infections. Elements of exposure history are summarized in Table 3.

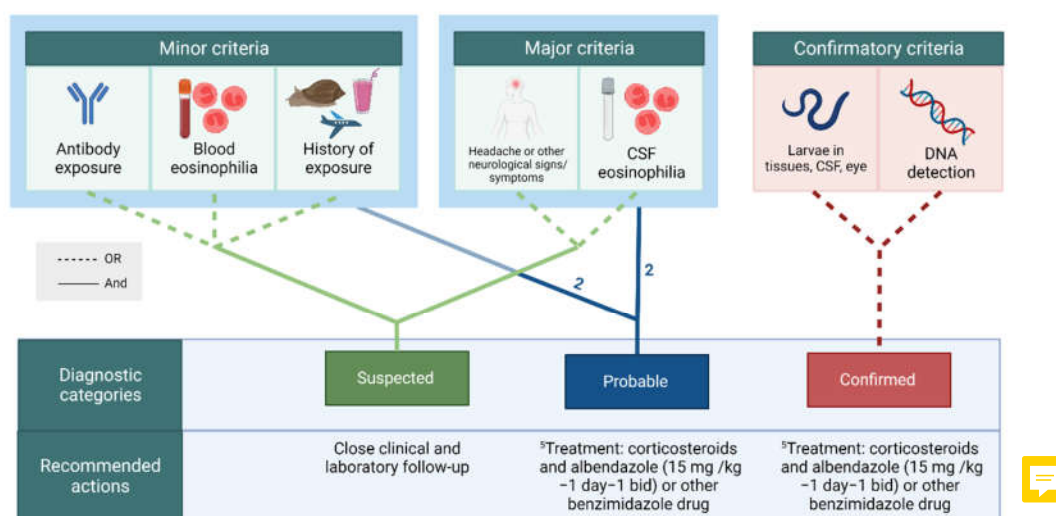


Figure 1.

Table 1. – Diagnostic criteria for neuroangiostrongyliasis and criteria classification according to the strength of evidence for the etiological diagnosis.

Criteria Category	Criteria
Minor	a. Exposure history
	b. Serology (antibody detection)
	c. Blood eosinophilia
Major	a. CSF ¹ eosinophilia
	b. Headache, other neurological signs or symptoms, and other obvious etiologies ruled out.

Confirmatory	a. Larvae in tissues, CSF, or eye	
	b. DNA detection ²	
¹ CSF: cerebrospinal fluid; ² Antigen detection in CSF (no test currently available) may be an additional criterion for confirmed diagnosis in the future, see Sears <i>et al.</i> for novel highly sensitive PCR [10].		

Table 2. Classification of diagnostic categories for neuroangiostrongyliasis and recommended actions: follow-up and treatment.

Diagnosis Categories	Criteria	Recommended actions
Suspected		
	- Headache, OR other neurological signs/symptoms, OR - CSF eosinophilia¹ AND - Any minor criteria²	Close clinical and laboratory follow-up
Probable		
	- Headache, OR other neurological signs/symptoms AND - CSF eosinophilia¹ AND - At least two minor criteria²	³ Treatment: corticosteroids and albendazole (15 mg /kg–1 day–1 bid, 14 days) or other benzimidazole drug
Confirmed		
	- Larvae in tissues, CSF, or eye chambers OR - DNA detection⁴	³ Treatment: corticosteroids and albendazole (15 mg /kg–1 day–1 bid, 14 days) or other benzimidazole drug

If serology is positive¹ and CSF eosinophilia² is higher than 40% consider NA as highly probable/suspected; ³For details and treatment alternatives, see Sawanyawisuth, K., & Sawanyawisuth [14]; and Jacob *et al.* [25]. ⁴Antigen detection in CSF (no test currently available) may be an additional criterion for confirmed diagnosis in the future, see Sears *et al.* for novel highly sensitive PCR [10].

Major criteria, headache, or other neurological signs or symptoms associated with CSF eosinophilia are proposed as defining criteria for eosinophilic meningitis or meningoencephalitis. Importantly, these major criteria are labeled as such to be highly suggestive for NA, since *A. cantonensis* is their main causative agent. Clinical manifestations' strength of evidence for NA depends on the absence of other obvious causes for eosinophilic meningoencephalitis [18].

Finding parasitic structures in cerebrospinal fluid or brain tissues is extremely rare, yet represents undisputed criteria for confirming a diagnosis. Ocular examination, including anterior and posterior chambers, may also disclose larvae or even adult worms since the eye is an area of localization second to meningeal vessels for *A. cantonensis* [15]. Worms may rarely be found inside pulmonary arteries in fatal cases [26,27,28].

4. Discussion

In 2006, the Chinese Ministry of Health published recommendations on diagnostic criteria for angiostrongyliasis and proposed three case definitions: (i) suspected; (ii) clinical, and (iii) parasitologically diagnosed [17]. Eating history (C1), clinical manifestations (C2), blood eosinophilia (C3), CSF eosinophilia (C4), seropositivity (C5), and presence of parasites in CSF or other sites (C6) were the suggested criteria. Suspected NA is considered whenever a combination of two criteria of C1 to C5 are observed. A clinical diagnosis is considered when C1, C2, C3, and C4 are present. NA is confirmed with demonstration of parasites (C6).

In 2018, a State Task Force in Hawaii (USA) prepared guidelines for diagnosis and treatment of NA. An update was subsequently published in 2020 [18]. The latter guidelines consider two diagnostic categories: presumptive and definitive, or confirmed by identification of parasites or DNA detection with PCR. A presumptive diagnosis is

established by: (i) characteristic symptoms and signs, (ii) exposure history, and (iii) CSF eosinophilia.

Headache is the most common clinical manifestation and can occur in the absence of other neurological signs or symptoms. Neck stiffness and fever are also present in 15% and 40% of cases, respectively, and occur more often in children [29, 30]. Among less common manifestations, dysesthesias (paresthesias and hyperesthesias) and migratory myalgia may be valuable to indicate neuroangiostrongyliasis, to be properly investigated in prospective clinical studies [3,6]. Other early symptoms can be prodromal symptoms, that is, due to the physiological and neurological damages due to the larval migration from the gastrointestinal tract into the CNS [31,32]. It is likely that the severity of prodromal symptoms is directly associated with the number of parasites involved in the infection. Larvae attempting to penetrate the gastrointestinal walls may cause symptoms such as nausea, vomiting, abdominal pain, or diarrhea. Larval migration through the liver, kidneys, and lungs may cause malaise, low-grade fever, coughs, jaundice-like symptoms, and hematuria. Larvae stranded beneath the skin may produce rashes or pruritis-like symptoms. Prodromal symptoms are nonspecific, thus, unless there is a great degree of suspicion of infection, it is unlikely to alert the medical practitioner [32,33].

CSF eosinophilia is another main indicator for NA and occurs in approximately 50% of patients [30]. To date, the definition of “CSF eosinophilia” remains controversial. Some authors consider any number of eosinophils as abnormal, while other authors have selected 10% or absolute number of 10 eosinophils as a threshold [18,30]. The degree of eosinophilia present may be a stronger indicator for NA, and patients with 40% are more likely to have NA [34]. In some cases, only a follow-up lumbar puncture can reveal CSF eosinophilia [3]. However, lack of appropriate staining and differential counting of CSF cells can prevent demonstration of an eosinophilic inflammatory response in meningeal tissues and fluids. Physicians are urged to check with their laboratory to determine if a proper examination was performed.

Different transmission areas may present predominant intentional or unintentional exposure behavior. For example, in Thailand, intentional food habits favor transmission; while in Hawaii, ingestion of infected mollusks is usually unintentional. More severe cases in Hawaii may be due to higher intake of larvae because of the high burden of infection of terrestrial gastropods. A definite exposure history may be absent [18]. The precise date of exposure is important to consider since the incubation period (IP) for NA is usually between 1 and 3 weeks, although a 1-year IP has been reported [3,16,32]. In addition to the well-known role of several foods as a source for infection, there are indications that larvae can be ingested in drinking water (Table 3) [4]. Thus, knowledge of active transmission areas may help increase and sustain awareness regarding NA and help identify cases for early treatment and prevention of more severe disease. In endemic areas, knowledge and attention to non-specific clinical manifestations (e.g., fever, nausea, vomiting, agitation, lethargy) can facilitate early diagnosis and treatment. There is need for continued research to decrease the time to diagnosis. Perhaps, antigen capture assays for blood, stool or urine will be helpful. Post-exposure treatment with pyrantel has been shown to be promising, especially in known endemic areas [35].

While several serological tests have been developed, limitations involving cross-reactivity [36,37], late seroconversion [38], and less than adequate accuracy evaluations have prevented these results from being confirmatory. Correspondingly, in the present classification proposed, positive serological examination is recognized as a minor criterion. Seroconversion will be helpful to confirm the diagnosis when CSF cannot be collected and an accurate diagnostic test is available.

The proposed guidelines advocate for early treatment of “probable” cases (without other obvious cause), as well as confirmed NA cases (Table 1). Possible exception for early treatment recommendation is prompt recovery (less than 24 hours) from headache and other neurological deficits without any clinical manifestations suggestive of encephalitic compromise. Prospective studies are needed to confirm and optimize diagnostic

workflow and case definitions. Corticosteroids are a cornerstone of NA management since they can potentially reduce both the intensity and duration of headaches, the main cause of distress in patients [39,40,41]. Non-steroid anti-inflammatory drugs should not be administered along with corticosteroids because of increased risk for upper gastrointestinal bleeding [39]. Measures to reduce intracranial pressure, such as therapeutic repeated CSF removal, have been shown to be effective, and are a choice symptomatic treatment for alleviating severe headaches in patients affected by NA [39]. Benzimidazole anthelmintic drugs, especially albendazole, are also recommended despite of multiple controversies regarding their safety and efficacy [42]. For detailed discussion and recommendations for angiostrongyliasis treatment, see specific reports and reviews [14,25,41].

5. Conclusion

In conclusion, it is anticipated that the present global revision and updated recommendations for diagnosis and treatment of NA will facilitate much needed clinical studies, with use of standardized diagnostic criteria leading to better comparative studies of patients from different geographic areas. The present revisions and updates, meant to support further discussions and developments, may also help provide well-defined diagnostic categories for public health surveillance and a strategy to better characterize biological samples for accuracy studies of diagnostic tools. The latter is especially relevant for evaluations of new methods developed for early and specific detection and treatment of NA.

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