Differential Diagnosis of CNS Angiostrongyliasis: A Short Review

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Abstract

The diagnostic criterion for eosinophilic meningitis (EOM) is the identification of an absolute count of 10 eosinophils per ml or more than 10% of the total white blood cells in the cerebrospinal fluid (CSF) in the proper clinical context. The most common cause of EOM is Angiostrongylus cantonensis *infection, termed meningitic angiostrongyliasis (MA). Neurognathostomiasis (NG) is the main parasitic disease in the differential diagnosis of meningitic angiostrongyliasis. This short review is based on articles published on Medline between 2000 and 2012 related to EOM. There are three main approaches that can be used to differentiate between MA and NG, involving clinical factors, history of larval exposure, and serological tests. MA patients presented with acute severe headache but without neurological deficit, combined with a history of eating uncooked snails or slugs. NG patients always presented with motor weakness, migratory swelling, radicular pain and had history of eating uncooked poultry or fish. Specific antigenic bands in immunoblot tests are helpful tools to differentiate the two diseases. Other causes of eosinophilic meningitis are neurocysticercosis, cerebral paragonimiasis,* Toxoplasma canis, Baylisascaris*, tuberculous meningitis, and cryptococcal meningitis.*

Keywords

Angiostrongyliasis, Differential diagnosis, Eosinophilic meningitis, Gnathostomiasis, Rat lungworm disease

Introduction

Angiostrongyliasis, caused by the nematode *Angiostrongylus cantonensis*, is an emerging disease and has been reported worldwide particularly in tropical countries.[1] There are three major forms of human angiostrongyliasis: meningitic, encephalitic, and ocular.[2] In addition, there are several case reports with gastrointestinal, spinal, or cochlear involvement.[3-5]

The majority of angiostrongyliasis patients exhibit the meningitic form that leads to eosinophilic meningitis. The presence of an absolute count of 10 eosinophils per ml or more than 10% of the total white blood cells in the cerebrospinal fluid (CSF) meets the definition of eosinophilic meningitis and is one of the clinical clues for meningitic angiostrongyliasis.[2]

Although the causes of eosinophils in the CSF need to be explored further, the most common cause of eosinophilic meningitis is infection by *A. cantonensis*. Other causes include other parasitic infections , tuberculosis, cryptococcal meningitis, use of nonsteroidal anti-inflammatory drugs (NSAIDs), or malignancy. *Gnathostoma spinigerum* is the most important other cause of meningitic angiostrongyliasis. Even though eosinophilic meningitis can be diagnosed clinically, there are some situations in which its causes cannot be identified. This short review aims to differentiate the causes of CNS eosinophilia, focusing primarily on meningitic angiostrongyliasis.

This short review is based on articles published on Medline between 2000 and 2012. There are three main factors that can be used to differentiate between meningitic angiostrongyliasis and CNS gnathostomiasis, including clinical factors, history of larval exposure, and serological tests (Table 1).

Clinical Factors

Acute severe headache is the most common presenting symptom of meningitic angiostrongyliasis,[6] while CNS gnathostomiasis causes intracerebral hemorrhage, subarachnoid hemorrhage, myelitis, or radiculitis.[7] Symptoms of CNS gnathostomiasis depend on the location to which the worm migrates. Hemiparesis or hemiplegia, acute severe headache with neck stiffness, paraparesis, or radicular pain are presenting symptoms of the syndromes mentioned above. CSF eosinophils may be found particularly associated with subarachnoid hemorrhage, myelitis, or radicultis.

In addition to the presenting symptoms, some clinical features are suggestive of CNS gnathostomiasis. These include migratory swelling and radicular pain. Migratory swelling is defined as swollen soft tissue along the extremities that lasts for a few days before moving to adjacent areas. The swollen area can be painful and exhibit redness. Acute severe pain or radicular pain usually along the distribution of the cervical nerve roots may be found before developing CNS lesions.[8] Radicular pain from gnathostomiasis is different clinically from the pain experienced by patients with angiostrongyliasis. In angiostrongyliasis, about 5% of patients may complain of severe pain similar to

Table 1. Clinical features to differentiate the two main causes of eosinophilic meningitis.

Factors	Angiostrongyliasis	Gnathostomiasis
Presenting symptom	Acute severe headache	Motor weakness
Migratory swelling	None	Yes
Pain	With focal numbness	Along nerve root
Peripheral eosinophilia	Yes	Yes
CSF[a] appearance	Coconut juice	Non-traumatic bloody
Brain imaging	No pathognomonic sign	SAH[a] or unusual site ICH[a]
History of larval exposure	Uncooked snails or slugs	Uncooked poultry, fish
Diagnostic immunoblot band	29 or 31 kDa	21 or 24 kDa

[a]CSF: cerebrospinal fluid; SAH: subarachnoid hemorrhage; ICH: intracerebral hemorrhage

that experienced by patients with gnathostomiasis. However, the pain in angiostrongyliasis will not be along the nerve root distribution, as it is in gnathostomiasis. Also, the pain is very sensitive to touch and is accompanied with focal numbness. If patients with eosinophilic meningitis have focal numbness, it is very likely that *A. cantonensis* is a causative agent.[6] Both symptoms (migratory swelling and radicular pain) may occur with or without CNS gnathostomiasis.

Peripheral eosinophilia is common in both angiostrongyliasis and CNS gnathostomiasis, exhibited by up to 80% of patients.[6,7] However, it cannot be used to differentiate between angiostrongyliasis and gnathostomiasis. Nonetheless, it can be helpful in conjunction with a known history of larval exposure. For example, peripheral eosinophilia with a history of eating raw snails, combined with CSF eosinophils, may indicate angiostrongyliasis. The number of CSF white blood cells and percent of CSF eosinophils cannot be used to differentiate between the two diseases. However, gross appearance of the CSF may be different. In meningitic angiostrongyliasis, the CSF may appear like coconut juice. *Gnathostoma spinigerum* larvae may commonly cause hemorrhage in the CNS. As a result, in gnathostomiasis the CSF may have non-traumatic bleeding or contain unclotted blood.

Brain imaging may be helpful to differentiate the two diseases. Even though most meningitic angiostrongyliasis cases do not exhibit pathognomonic brain imaging signs, certain abnormal signs that are not specific for angiostrongyliasis may be found, such as periventricular linear hypersignal lesions, small nodules, or small hemorrhagic tracts.[9,10] In CNS gnathostomiasis, abnormal brain lesions are quite pathognomonic and specific. Unusual intracerebral hemorrhage, tract-like intracerebral hemorrhage, non-traumatic subdural hematoma, or unexplained subarachnoid hemorrhage are reported.[8,11,12] Common sites for intracerebral or hypertensive hemorrhages include basal ganglia, pons, thalamus, and cerebellum. For spinal gnathostomiasis, there is no specific lesion. The increased signal in the spinal cord was the only common finding in myelitis caused by *G. spinigerum*.

History of Larval Exposure

History of larval exposure as a risk factor for parasitic infection is the crucial factor for differentiating causative parasites. Many species of snails, including the giant African snail (*Achatina fulica*) and apple snails (*Pila* and *Pomacea* species), and slugs act as intermediate hosts of *A. cantonensis*, and paratenic hosts include freshwater shrimp, frogs, and monitor lizards.[13] Eating these hosts uncooked is a risk for developing meningitic angiostrongyliasis and the incubation period ranges from 1-90 days.[6,14-17] Freshwater fish and shrimp, poultry, snakes, and frogs are risk factors for gnathostomiasis. Note that freshwater shrimp and frogs can carry both parasites. Unlike angiostrongyliasis, gnathostomiasis can be silent in humans for years.

Serological Tests

Definitive diagnosis of any parasitic disease can be made based on the presence of young or mature parasites. In angiostrongyliasis or gnathostomiasis, it is rare to find the larvae in human cases.[1,18] Serological diagnosis is a helpful diagnostic tool. The problem with serological tests, however, is that they are not readily available. Polymerase chain reaction and immunoblot technique have high sensitivity and specificity. Regarding immunoblot techniques, the antigenic bands for angiostrongyliasis are 29and 31 kDa bands,[19,20] while for gnathostomiasis they are 21 and 24 kDa bands.[7] The specificity of the 29 kDa band for eosinophilic meningitis caused by *A. cantonensis* is 100%, while that of the 21 and 24 kDa bands for CNS gnathostomiasis is 95.5%.[21] The sensitivity of the diagnostic immunoblot band method is 50-100% for angiostrongyliasis and 80-90% for gnathostomiasis.[7]

Other Causes of Eosinophilic Meningitis

Other causes of eosinophilic meningitis are neurocysticercosis, cerebral paragonimiasis, *Toxicaria canis*, *Baylisascaris*, tuberculous meningitis, and cryptococcal meningitis.[22] There are several forms of neurocysticercosis. Not all forms cause eosinophilic meningitis. Subarachnoid cysticercosis is the major form of neurocysticercosis that results in raised levels of CSF eosinophils. Patients usually present with subacute to chronic headache. Intramuscular cysticercus may be a supportive evidence for cysticercosis. Magnetic resonance imaging of the brain showing multiple cystic lesions, and serological tests for neurocysticercosis are helpful.

Two less common parasitic causes of encephalitis in children with CSF eosinophils are toxocariasis and baylisascariasis.[22] Exposure to dog or raccoon feces is a risk factor for toxocariasis and baylisascarisis, respectively. A history of ingestion of freshwater crabs in patients with cavitary lung lesions or characteristic brain calicifications is suggestive of paragonimiasis. The clinical setting is an important clue for tuberculous or cryptococcal meningitis. Most patients have lymphocytic CSF, but only few have eosinophilic meningitis. An Indian ink exam of the CSF is a worthwhile test for cryptococcal infection.

Conflict of Interest

None of the authors identifies any conflict of interest.

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References

1. Wang QP, Lai DH, Zhu XQ, Chen XG, Lun ZR. Human angiostrongyliasis. *Lancet Infect Dis*. 2008;8(10):621-630.
2. Sawanyawisuth K, Sawanyawisuth K. Treatment of angiostrongyliasis. *Trans R Soc Trop Med Hyg*. 2008;102(10):990-996.
3. Sawanyawisuth K, Pugkhem A, Mitchai J, et al. Abdominal angiostrongyliasis caused by *Angiostrongylus cantonensis*: a possible cause of eosinophilic infiltration in human digestive tract. *Pathol Res Pract*. 2010;206(2):102-104.
4. Diao Z, Yin C, Jin E. Images in clinical tropical medicine. Myelitis caused by infection of *Angiostrongylus cantonensis*. *Am J Trop Med Hyg*. 2010;83(6):1176-1177.
5. Chotmongkol V, Yimtae K, Intapan PM. Angiostrongylus eosinophilic meningitis associated with sensorineural hearing loss. *J Laryngol Otol*. 2004;118(1):57-58.
6. Chotmongkol V, Sawanyawisuth K, Thavornpitak Y. Corticosteroid treatment of eosinophilic meningitis. *Clin Infect Dis*. 2000;31(3):660-662.
7. Intapan PM, Khotsri P, Kanpittaya J, Chotmongkol V, Sawanyawisuth K, Maleewong W. Immunoblot diagnostic test for neurognathostomiasis. *Am J Trop Med Hyg*. 2010;83(4):927-929.
8. Sawanyawisuth K, Chlebicki MP, Pratt E, Kanpittaya J, Intapan PM. Sequential imaging studies of cerebral gnathostomiasis with subdural hemorrhage as its complication. *Trans R Soc Trop Med Hyg*. 2009;103(1):102-104.
9. Kanpittaya J, Sawanyawisuth K, Intapan PM, Khotsri P, Chotmongkol V, Maleewong W. A comparative study of neuroimaging features between human neuro-gnathostomiasis and angiostrongyliasis. *Neurol Sci*. 2012;33(4):893-898.
10. Kanpittaya J, Jitpimolmard S, Tiamkao S, Mairiang E. MR findings of eosinophilic meningoencephalitis attributed to *Angiostrongylus cantonensis*. *Am J Neuroradiol*. 2000;21(6):1090-1094.
11. Sawanyawisuth K, Tiamkao S, Nitinavakarn B, Dekumyoy P, Jitpimolmard S. MR imaging findings in cauda equina gnathostomiasis. *Am J Neuroradiol*. 2005;26(1):39-42.
12. Sawanyawisuth K, Tiamkao S, Kanpittaya J, Dekumyoy P, Jitpimolmard S. MR imaging findings in cerebrospinal gnathostomiasis. *Am J Neuroradiol*. 2004;25(3):446-449.
13. Ramirez-Avila L, Slome S, Schuster FL, et al. Eosinophilic meningitis due to *Angiostrongylus* and *Gnathostoma* species. *Clin Infect Dis*. 2009;48(3):322-327.
14. Sawanyawisuth K, Takahashi K, Hoshuyama T, et al. Clinical factors predictive of encephalitis caused by *Angiostrongylus cantonensis*. *Am J Trop Med Hyg*. 2009;81(4):698-701.
15. Chotmongkol V, Wongjitrat C, Sawadpanit K, Sawanyawisuth K. Treatment of eosinophilic meningitis with a combination of albendazole and corticosteroid. *Southeast Asian J Trop Med Public Health*. 2004;35(1):172-174.
16. Chotmongkol V, Sawadpanitch K, Sawanyawisuth K, Louhawilai S, Limpawattana P. Treatment of eosinophilic meningitis with a combination of prednisolone and mebendazole. *Am J Trop Med Hyg*. 2006;74(6):1122-1124.
17. Jitpimolmard S, Sawanyawisuth K, Morakote N, et al. Albendazole therapy for eosinophilic meningitis caused by Angiostrongylus cantonensis. *Parasitol Res*. 2007;100(6):1293-1296.
18. Sangchan A, Sawanyawisuth K, Intapan PM, Mahakkanukrauh A. Outward migration of *Gnathostoma spinigerum* in interferon alpha treated hepatitis C patient. *Parasitol Int*. 2006;55(1):31-32.
19. Maleewong W, Sombatsawat P, Intapan PM, Wongkham C, Chotmongkol V. Immunoblot evaluation of the specificity of the 29-kDa antigen from young adult female worms *Angiostrongylus cantonensis* for immunodiagnosis of human angiostrongyliasis. *Asian Pac J Allergy Immunol*. 2001;19(4):267-273.
20. Eamsobhana P, Yoolek A, Punthuprapasa P, Suvouttho S. A dot-blot ELISA comparable to immunoblot for the specific diagnosis of human parastrongyliasis. *J Helminthol*. 2004;78(4):287-291.
21. Sawanyawisuth K, Sawanyawisuth K, Intapan PM, et al. Specificity of immunoblotting analyses in eosinophilic meningitis. *Mem Inst Oswaldo Cruz*. 2011;106(5):570-572.
22. Solomon T, Danesi M, Bia FJ, Plekc TP. Neurologic disease. In: Guerrant RK, Walker DH, Weller PF, eds. *Tropical Infectious Diseases: Principles, Pathogens and Practice*. Philadelphia: Churchill Livingstone; 2006:1601-1608.