Review

Angiostrongylus cantonensis Eosinophilic Meningitis

Francis D. Pien, MD, MPH;* and Brian C. Pien, MS*

ABSTRACT

In the past 50 years, *Angiostrongylus cantonensis*, the most common cause of eosinophilic meningitis, has spread from Southeast Asia to the South Pacific, Africa, India, the Caribbean, and recently, to Australia and North America, mainly carried by cargo ship rats. Humans are accidental, "dead-end" hosts infected by eating larvae from snails, slugs, or contaminated, uncooked vegetables. These larvae migrate to the brain, spinal cord, and nerve roots, causing eosinophilia in both spinal fluid and peripheral blood. Infected patients present with severe headache, vomiting, paresthesias, weakness, and occasionally visual disturbances and extraocular muscular paralysis. Most patients have a full recovery; however, heavy infections can lead to chronic, disabling disease and even death. There is no proven treatment for this disease. In the authors' experience, corticosteroids have been helpful in severe cases to relieve intracranial pressure as well as neurologic symptoms due to inflammatory responses to migrating and eventually dying worms.

Key Words: Angiostrongylus cantonensis, *eosinophilic meningitis*

Int J Infect Dis 1999; 3:161–163.

Angiostrongylus cantonensis is the major cause of eosinophilic meningitis. This parasite was first described by Chen in 1935 in rat lungs, in Canton, China,[1] and reported to cause human disease in 1945 by Nomura and Lin, in Taiwan.[2] Since then, this parasite has been taken by shipboard rats throughout Southeast Asia, the South Pacific, Madagascar, Africa, the Caribbean, and most recently, to the continents of Australia and North America.[3-7] Over 2500 cases of *A. cantonensis* meningitis have been reported in approximately 30 countries.[5] The human case reports from Australia and North America occurred since publication of the authors' previous article 11 years ago,[3] and make *A. cantonensis* an emerging infectious disease, worthy of an updated review.

*Straub Clinic and Hospital, University of Hawaii John A. Burns School of Medicine, Honolulu, Hawaii.

Address correspondence to Dr. Francis D. Pien, 888 S. King Street, Honolulu, HI 96813. E-mail: pienb@jabsom.biomed.hawaii.edu.

PARASITOLOGY

Angiostrongylus is a genus of roundworms (nematodes) that infect mainly animals. The best known of these parasites is *Angiostrongylus costaricensis*, a rat lung worm that causes abdominal eosinophilic granulomas in Central and South America, although a case was recently reported from California.[8] Clinical symptoms are abdominal pain, vomiting, bowel obstruction, and rarely, gastrointestinal bleeding.[8,9]

Angiostrongylus cantonensis also normally resides in rat lungs where it lays eggs in pulmonary arteries. Larvae subsequently hatch and migrate via the trachea and gastrointestinal tract into rat feces. First stage larvae are consumed by snails and slugs, then develop eventually into infectious third stage larvae, often in extremely high numbers. Rats and humans become infected by eating infected snails or contaminated uncooked vegetables, such as lettuce and watercress. In man, many larvae migrate to the brain where they cause abscesses, brain swelling, and hemorrhage.[3] Additionally, worms can travel to the spinal cord where they also eventually die and degenerate.[10]

CLINICAL PRESENTATION

Clinical symptoms occur approximately 2 to 35 days after larvae ingestion. Patients present with severe headache, neck stiffness, and often, nausea and vomiting.[3,11,12] Most patients do not have high fever, but may have severe muscular weakness, paresthesias, and extremity pain, which in chronic cases can cause wheelchair dependence. If not diagnosed promptly, clinical symptoms can progress to diplopia, blindness, ataxia, and in very heavy infections, coma and death due to hydrocephalus.[12]

LABORATORY FINDINGS

The most important diagnostic finding is eosinophilia. Two-thirds of patients have peripheral blood eosinophilia. It is important that spinal fluid be stained with Wright's stain, which reveals cerebrospinal fluid (CSF) eosinophilia in 15 to 95% of infections. Eosinophilia recently has been shown to be related to interleukin-5 stimulation and Th2-cytokine production.[13]

Cerebrospinal fluid protein is elevated, but CSF glucose is usually normal.[14] In a small percentage of cases, worms can be recovered from spinal fluid.[12] Magnetic resonance imaging (MRI) of the brain shows evidence of cerebral edema and infarction, with areas of enhancement due to vasculitis and meningitis; ventricular dilatation can occur with hydrocephalus.[15] Recently, Shih et al reported that chest radiographs may show dense opacities with ill-defined margins and segmental distribution in the lower lung fields, presumably due to either vascular thrombosis or larval track reactions.[16]

Several serologic tests have been developed for the diagnosis of *A. cantonensis*, although none are commercially available. The most specific and sensitive test is the enzyme-linked immunosorbent assay (ELISA) method, which yields good results when testing either CSF or serum.[17,18] This method uses antigens prepared from *A. cantonensis* rat larvae, and is available, on a limited basis, from the Centers for Disease Control and Prevention (Atlanta, Georgia).

Several recent publications have studied specific purified worm antigens to improve the sensitivity and especially the specificity of the ELISA test. These include a 204 kD antigen,[19] 29 and 31 kD antigens,[20] AW-3C2 antigen,[21-23] and excretory products in a coagglutination assay.[24] With such experimental methods, cross-reaction with other nematodes can be greatly reduced.

DIFFERENTIAL DIAGNOSIS

Eosinophilic meningitis can be attributable by both allergic and infectious causes, as well as malignancies.[25,26] Reactions to drugs (e.g., ibuprofen and ciprofloxacin) and foreign material (e.g., ventricular shunt, contrast dye), as well as Hodgkin disease and multiple sclerosis are the most common noninfectious causes,[26-30] whereas nonparasitic infections include tuberculosis, coxsackie virus, rickettsial disease, coccidioidomycosis, and neurosyphilis.[25,26,31] The main parasitic causes of eosinophilic meningitis, besides *A. cantonensis*, include cysticercosis, paragonimiasis, gnathostomiasis, and schistosomiasis.[3,25,26] Neurocysticercosis produces characteristic lesions seen on computed tomography (CT) and MRI brain scan and can be diagnosed by commercially available serologic testing. Paragonimiasis is usually associated with cavitary lung disease and calcifications on brain scan. Gnathostomiasis is caused by subcutaneous larval migration of *Gnathostoma spinigerum* that usually appears first on extremities and later causes cerebral hemorrhages demonstrated by CT brain scan and by blood in the CSF. Similar to neurocysticercosis, schistosomiasis often presents with seizures, produces mass lesions on brain, and may have positive stool ova. Other nematodes, such as *Ascaris*, *Baylisascaris*, *Trichinella*, and *Toxocara* only rarely are associated with eosinophilic meningitis.[25]

CLINICAL COURSE AND TREATMENT

Most infections are mild and recover spontaneously without neurologic residua, usually within 1 week. However, paresthesias and muscular weakness may persist for months or even years, representing the "chronic form" of this disease. An 11-month-old Australian girl reportedly had residual blindness, profound mental retardation, spasticity, and epilepsy as the result of *A. cantonensis* meningitis.[32]

There is no specific treatment for this illness. Thiabendazole, albendazole, mebendazole, and ivermectin are effective in rats, but have not yet been shown to be clinically efficacious in humans.[33-36] Japanese researchers recently have reported two new compounds, VD-99-11 and PF1022A, which demonstrate activity against *A. cantonensis*.[37-39] Some uncontrolled clinical studies suggest that patients may worsen with chemotherapy, because of an inflammatory reaction to toxic substances released by dying worms.[30] In the authors' experience, as well as that of others,[32] the best treatment is the use of high-dose prednisone, 40 to 60 mg daily, tapered after a few weeks, or in cases of chronic infection, after several months. In cases of increased intracranial pressure, patients also may benefit from mannitol or repeated lumbar fluid aspirations.[32,40]

REFERENCES

1. Chen HT. Un nouveau nematode pulmonaire: *Pulmonema cantonensis* n.g., n. sp. des rats de Canton. Ann Parasitol Hum Comp 1935; 13:312-317.
2. Beaver PC, Rosen L. Memorandum on the first report of *Angiostrongylus* in man, by Nomura and Lin, 1945. Am J Trop Med Hyg 1964; 13:589-590.
3. Koo J, Pien F, Kliks MM. *Angiostrongylus (Parastrongylus)* eosinophilic meningitis. Rev Infect Dis 1988; 10:1155-1162.
4. Alicata JE. The discovery of *Angiostrongylus cantonensis* as a cause of human eosinophilic meningitis. Parasitol Today 1991; 7:151-153.
5. Kliks MM, Palumbo NE. Eosinophilic meningitis beyond the Pacific basin: the global dispersal of a peridomestic zoonosis caused by *Angiostrongylus cantonensis*, the nematode lungworm of rats. Soc Sci Med 1992; 34:199-212.
6. Prociv P, Tiernan JR. Eosinophilic meningoencephalitis with permanent sequelae. Med J Aust 1987; 147:294-295.
7. New D, Little MD, Cross J. *Angiostrongylus cantonensis* infection from eating raw snails. N Engl J Med 1995; 332: 1105-1106.
8. Hulbert TV, Larson RA, Chandrasoma PT. Abdominal angiostrongyliasis mimicking acute appendicitis and Meckel's diverticulum: report of a case in the United States and review. Clin Infect Dis 1992; 14:836-840.
9. Silvera CT, Ghali VS, Roven S, et al. Angiostrongyliasis: a rare case of gastrointestinal hemorrhage. Am J Gastroenterol 1989; 84:329-332.
10. Kliks MM, Kroenke K, Hardman JM. Eosinophilic radiculomyeloencephalitis: an angiostrongyliasis outbreak in

American Samoa related to ingestion of *Achatina fulica* snails. Am J Trop Med Hyg 1982; 31:1114-1122.
11. Kuberski T, Wallace GD. Clinical manifestations of eosinophilic meningitis due to *Angiostrongylus cantonensis*. Neurology 1979; 29:1566-1570.
12. Punyagupta S, Juttijudata P, Bunnag T. Eosinophilic meningitis in Thailand: clinical studies of 484 typical cases probably caused by *Angiostrongylus cantonensis*. Am J Trop Med Hyg 1975; 24:921-931.
13. Sugaya H, Aoki M, Abe T, et al. Cytokine responses in mice infected with *Angiostrongylus cantonensis*. Parasitol Res 1997; 83:10-15.
14. Yii CY. Clinical observations on eosinophilic meningitis and meningoencephalitis caused by *Angiostrongylus cantonensis* on Taiwan. Am J Trop Med Hyg 1976; 25:233-249.
15. Hsu WY, Chen JY, Chien CT, Han NT. Eosinophilic meningitis caused by *Angiostrongylus cantonensis*. Pediatr Infect Dis J 1990; 9:443-445.
16. Shih SL, Hsu CH, Huang FY, et al. *Angiostrongylus cantonensis* infection in infants and young children. Pediatr Infect Dis J 1992; 11:1064-1066.
17. Kliks MM, Lau WKK, Palumbo NE. Neurologic angiostrongyliasis: parasitic eosinophilic meningoencephalitis. In: Balows A, ed. Laboratory diagnosis of infectious diseases. Vol. I. Bacterial, mycotic, and parasitic diseases. New York: Springer-Verlag, 1988:754-767.
18. Bhopale MK, Limaye LS, Pradhan VR, et al. Studies on suspected clinical and experimental angiostrongyliasis: serological responses. J Hyg Epidemiol Microbiol Immunol 1985; 29:283-288.
19. Chye SM, Yen CM, Chen ER. Detection of circulating antigen by monoclonal antibodies for immunodiagnosis of angiostrongyliasis. Am J Trop Med Hyg 1997; 56:408-412.
20. Nuamtanong S. The evaluation of the 29 and 31 kDa antigens in female *Angiostrongylus cantonensis* for serodiagnosis of human angiostrongyliasis. Southeast Asian J Trop Med Public Health 1996; 27:291-296.
21. Eamsobhana P, Mak JW, Yong HS. Detection of circulating antigens of *Parastrongylus cantonensis* in human sera by sandwich ELISA with specific monoclonal antibody. Southeast Asian J Trop Med Public Health 1997; 28(Suppl 1): 139-142.
22. Eamsobhana P, Mak JW, Yong HS. Detection of circulating antigens of *Parastrongylus cantonensis* in human sera by sandwich ELISA with specific monoclonal antibody. Southeast Asian J Trop Med Public Health 1995; 26:712-715.
23. Eamsobhana P, Yong HS, Mak JW, Wattanakulpanich D. Detection of circulating antigens of *Parastrongylus cantonensis* in human sera by dot-blot ELISA and sandwich ELISA using monoclonal antibody. Southeast Asian J Trop Med Public Health 1997; 28:624-628.
24. Rivero LR, Fonte GL, Finlay VC. Identification of *Angiostrongylus cantonensis* in infected rats with a coagglutination assay. Southeast Asian J Trop Med Public Health 1995; 26:716-718.
25. Weller PF. Eosinophilic meningitis. Am J Med 1993; 95: 250-253.
26. Kuberski T. Eosinophils in the cerebrospinal fluid. Ann Intern Med 1979; 91:70-75.
27. Quinn JP, Weinstein RA, Caplan LR. Eosinophilic meningitis and ibuprofen therapy. Neurology 1984; 34:108-109.
28. Asperilla MO, Smego RA Jr. Eosinophilic meningitis associated with ciprofloxacin. Am J Med 1989; 87:589-590.
29. Tung H, Raffel C, McComb JG. Ventricular cerebrospinal fluid eosinophilia in children with ventriculoperitoneal shunts. J Neurosurg 1991; 75:541-544.
30. Mulligan MJ, Vasu R, Grossi CE, et al. Case report: neoplastic meningitis with eosinophilic pleocytosis in Hodgkin's disease: a case with cerebellar dysfunction and a review of the literature. Am J Med Sci 1988; 296:322-326.
31. Ragland AS, Arsura E, Ismail Y, Johnson R. Eosinophilic pleocytosis in coccidioidal meningitis. Am J Med 1993; 95: 254-257.
32. Reid IR, Wallis WE. The chronic and severe forms of eosinophilic meningitis. Aust N Z J Med 1984; 14:163-165.
33. Cuckler AC, Egerton JR, Alicata JE. Therapeutic effect of thiabendazole on *Angiostrongylus cantonensis* infections in rats. J Parasitol 1965; 51:392-396.
34. Hayashi M, Terada M, Ishii AI, et al. Studies on chemotherapy of parasitic helminths (XIV). Anthelminthic effect of mebendazole on *Angiostrongylus cantonensis* in rats. Jpn J Parasitol 1982; 31:575-580.
35. Ishii AI, Terada M, Sano M. Studies on chemotherapy of parasitic helminths (XXIII). Effects of ivermectin on *Angiostrongylus cantonensis* in rats. Jpn J Parasitol 1985; 34: 411-417.
36. Hwang KP, Chen ER. Larvicidal effect of albendazole against *Angiostrongylus cantonensis* in mice. Am J Trop Med Hyg 1988; 39:191-195.
37. Lee HH, Shyu LY, Terada M. In vitro effects of VD-99-11 on *Angiostrongylus cantonensis* and isolated frog rectus. Parasitol Res 1995; 81:615-621.
38. Kachi S, Terada M, Hashimoto H. Influence of PF1022A on the motility of *Angiostrongylus cantonensis* in vitro. Parasitol Res 1997; 83:578-582.
39. Kachi S, Ishih A, Terada M. Effects of PF1022A on adult *Angiostrongylus cantonensis* in the pulmonary arteries and larvae migrating into the central nervous system of rats. Parasitol Res 1995; 81:631-637.
40. Bowden DK. Eosinophilic meningitis in the New Hebrides: two outbreaks and two deaths. Am J Trop Med Hyg 1981; 30:1141-1143.