Clinical Aspects of Eosinophilic Meningitis and Meningoencephalitis caused by *Angiostrongylus cantonensis*, the Rat Lungworm

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Abstract

Angiostrongylus Eosinophilic Meningitis is caused by human infection with larvae of the rat lungworm, Angiostrongylus cantonensis. *The clinical presentation includes a spectrum of disease, from meningitis through radiculitis, cranial nerve abnormalities, ataxia, encephalitis, coma, and rarely death. The condition is diagnosed by recognizing the triad of: the clinical syndrome, eosinophils in the cerebrospinal fluid or blood, and exposure history. A history of eating raw or poorly cooked snails is classic, but ingestion of other intermediate hosts or unwashed produce (such as lettuce) harboring hosts is not uncommon. Several serologic tests exist but none has yet been fully validated. There is good evidence that a 2 week course of high dose corticosteroids shortens the duration and severity of symptoms. There is somewhat weaker evidence that albendazole reduces symptoms. The combination of prednisolone and albendazole is being used more commonly for treatment. Some suggestions for future research are given.*

Keywords

Albendazole, Angiostrongylus cantonensis, *Anthelmintic, Corticosteroid, Diagnosis, Eosinophilic meningitis, Eosinophilic meningoencephalitis, Eosinophilic radiculomeningoencephalomyelitis, Human, Nematode, Prednisolone, Rat lungworm, Slug, Snail, Treatment*

Introduction

Human disease from infection by the rat lungworm, *Angiostrongylus cantonensis*, is primarily seen in the Central Nervous System (CNS). Ingested third stage larvae (L3) migrate to the brain and spinal cord where they molt to L4 larvae (day 6-7 post ingestion, in the rat) and then to L5 young adult worms (day 11-13).[1] During this development they wander through the brain, sometimes emerging in the subarachnoid space. In the definitive host, the rat, young adult worms migrate to the pulmonary arteries via the cerebral venous system, but in humans most worms presumably die in the CNS before reaching the lungs.[2-8] Their presence, movement, and death in the CNS, and the immune response provoked, probably all contribute to the symptoms and signs.

There is a spectrum of disease produced when *A. cantonensis* invades the human CNS.[3] Most patients present with a meningitis characterized by eosinophils in the CSF. But, heavy infestations can produce an encephalitis characterized by severe neurological symptoms, coma, and even death. Spinal cord involvement can produce radiculitis. This range of presentations has led to several variations in nomenclature. Two species of *Angiostrongylus* produce human infection; the other being *A. costaricensis*, which produces a gastrointestinal syndrome. So the term "Angiostrongyliasis cantonensis" was proposed by Alicata to specify the neurological disease.[9] "Neuroangiostrongyliasis" also has been used infrequently. Although *A. cantonensis* is the most common cause of eosinophilic meningitis, there are many other etiologies. We favor the term "Angiostrongylus Eosinophilic Meningitis" (AEM) to describe the entire spectrum of human infection of the CNS by *A. cantonensis*. We will include encephalitis, encephalomyelitis, and radiculitis under this term for simplicity. AEM specifies both the neurologic syndrome and the etiology in a way that succinctly describes the disease. Additionally, an ocular form of the disease is recognized.[10] We briefly summarize the diagnosis and treatment of AEM from the clinical point of view, and offer some suggestions for future research.

Diagnosis

Diagnosis of infection due to *A. cantonensis* (AEM) is based primarily on clinical criteria. The worm is infrequently found in patient specimens, and antibody responses to the parasite are most commonly demonstrated during convalescence. Therefore, recognition of the main clinical syndromes, elicitation of a specific food consumption history, and travel to, or residence in, endemic regions are critical to establishing a presumptive diagnosis and initiating therapy.

The most common clinical syndrome encountered by residents of and travelers to endemic regions is uncomplicated meningitis.[11] One of the present authors reported an outbreak of AEM among a group of medical students and friends who traveled to Jamaica.[12] While this outbreak may not have represented the most severe presentation of AEM, it was possible to carefully define the timing of symptom onset, range of symptoms, and laboratory findings present at the time of evaluation at the hospital. Symptoms began a median of 11 days (range 1 week to 1 month) after consumption of the implicated meal, with a trend toward earlier onset among those that were hospitalized compared to those not hospitalized. The main symptoms reported and their relative frequency included headache (100%), photophobia or visual disturbance (92%), neck stiffness (83%), fatigue (83%), hyperesthesias (75%), vomiting (67%), and paresthesias (50%). The headaches were described as progressive and severe, and the cutaneous sensory findings were randomly present on the extremities and/or the trunk and did not have a single dermatomal pattern of distribution. The only other focal neurological finding was a subtle resting tremor in one of the more severely affected students. Fever was uncommon. Formal ophthalmologic evaluations of 2 patients showed only mild papilledema in one patient. Cerebral spinal fluid (CSF) was examined microscopically in 7 patients without demonstration of larvae. These symptoms and clinical findings are similar to other reports of meningitis due to *A. cantonensis*.[13] In contrast, researchers in Taiwan described high recovery rates of worms from the CSF of affected children in which large volumes of CSF were obtained with a "pumping" technique.[14]

The hallmark of AEM is the presence of eosinophilia, either in the CSF or in the peripheral blood. While all patients in the outbreak discussed above had eosinophilia at some point in their clinical course, only half had CSF eosinophils at the time of their first lumbar puncture, and fewer than half had peripheral blood eosinophils on their initial blood draw.[12] The median CSF white blood cell count (375/mm^3), percent eosinophils (33%), protein (54 mg/dL) and glucose concentrations (59 mg/dL), and opening pressure (24 cm H_20) were similar to other reports.[13] The peripheral blood eosinophilia peaked 2 weeks after their acute presentation and resolved 1 month later.

Other clinical syndromes associated with *A. cantonensis* infection include encephalitis/encephalomyelitis and ocular angiostrongyliasis. Kliks, et al, gave a very detailed clinical description of an outbreak of radiculomyeloencephalitis among a group of Korean fisherman who shared a large meal of giant African snails (*Achatina fulica*) while in American Samoa.[5] The most prominent symptoms and findings in this outbreak involved sensory and motor disturbances of the legs with pain, weakness, absent reflexes, bowel/bladder dysfunction, and labile hypertension. In this outbreak and in other reports of severe infection, the neurologic symptoms were often preceded by a transient abdominal pain syndrome.[5,15] Three patients in this outbreak had particularly severe courses complicated by coma and quadriparesis. Although one patient died, the other patients recovered completely after several months. In contrast to the incubation period in our experience with uncomplicated meningitis (several weeks), the incubation in this outbreak was 1-6 days and suggested that severe disease due to *A. cantonensis* may be associated with ingestion of a large worm inoculum; potentially thousands of infected larvae are present in highly permissive intermediate hosts such as *A. fulica*.[16] Others have correlated the severity of AEM with the number of ingested snails.[17] An important consideration in the differential diagnosis of severe eosinophilic encephalitis with radicular symptoms is infection with *Gnathostoma* spp.[18] Other infectious (parasitic and occasionally non-parasitic) and non-infectious etiologies (eg, drugs, malignancies) may also occasionally manifest as eosinophilic meningitis (see Graeff-Teixeira, et al,[13] for a more complete differential diagnosis). Encephalitis and severe disease may also be more common in specific settings and age groups. A high percentage of cases reported from southern Taiwan involved children, where one third of the cases present with encephalitis, fever is common, and the overall mortality (4.9%) is considerably higher than is typically seen with uncomplicated meningitis in adults.[14] Finally, reports of ocular angiostrongyliasis describe patients who primarily complain of unilateral visual disturbance, sometimes with minimal systemic symptoms to suggest AEM.[10] A single worm is usually identified on fundoscopic exam of the affected eye.

A careful food intake and a travel history are also important in the diagnosis of AEM. One usually finds a history of ingestion of a raw or poorly cooked food source known to be an intermediate host (eg, snail, slug) or a paratenic host (eg, freshwater prawns, frogs, planaria, monitor lizards) for *A. cantonensis*. In other cases consumption of fresh produce is commonly noted, as with the romaine lettuce in the Caesar salad eaten by the travelers to Jamaica in the outbreak discussed above.[12] Sometimes mere contact with a snail during food preparation is all that is required for infection.[19] While most cases occur in Southeast Asia, the Pacific Basin, and nearby regions, cases have occurred in the Caribbean[12,20] and elsewhere,[13] and at least one autochthonous case has been reported in the continental US.[21] AEM continues to be seen at a low incidence in the Hawaiian Islands,[22] and one of the authors recently treated a patient there who had severe neurologic sequelae.[23]

Because of the severe symptoms present in AEM, brain imaging is often undertaken, but CT and MRI findings are relatively nonspecific and are supportive rather than diagnostic. CT abnormalities were noted in 6/19 (32%) of cases in one study and included leptomeningeal enhancement with contrast, mild ventricular dilation, and diffuse brain swelling.[24] There are no blinded studies of MRI findings, but several retrospective reviews have recently been published.[24-27] MRI appears to be abnormal in about 45%-69% of cases. Findings include leptomeningeal enhancement and increased signal intensity in the subcortical white matter of the cerebrum and cerebellum on T2 weighted and fluid attenuated inversion recovery (FLAIR) images. With gadolinium contrast, enhancing round, oval, or stick shaped lesions may be seen in the white matter measuring 3-14 mm in diameter on T1 weighted images. Lesions of the spinal cord, optic nerve, and lungs have been found infrequently. In one report a microcavity suggestive of a migratory tract was noted in the deep white matter.[24] In the report on the outbreak in travelers to Jamaica, head CT (n = 4) and MRI (n = 3) showed only non-specific leptomeningeal enhancement in one patient.

Specific evidence for AEM can be obtained serologically and several different ELISA and immunoblot assays have been studied.[28,29] The 31 and 29 kDa antigens prepared from adult female worms appear to have particular utility in assays for antibody detection,[30] but none of these assays is commercially available, standardized, and available for use outside of specific laboratories. Another limitation with serodiagnosis is that antibodies are not predictably present in the acute stage of infection. In the experience of the present authors, strong reactions to the 31 kDa antigen were present by Western blot in the convalescent sera of 11 of the 12 student travelers to Jamaica, but in the acute serum of only 1 patient.[12] Others have developed assays to detect circulating antigen.[31] A recently developed, species-specific, real-time PCR holds promise for the timely diagnosis of acute *A. cantonenis* infection that, if validated, may be more readily available to clinicians.[32]

Treatment

Treatment of Angiostrongylus eosinophilic meningitis (AEM) and meningoencephalitis is not well defined and remains controversial.[11,13,33-36] Mild cases resolve spontaneously without specific therapy. More serious cases can be improved with serial lumbar punctures and symptoms shortened with corticosteroid therapy. Severe cases can develop permanent, neurologic sequelae or

progress to coma and death, so specific treatments to reduce morbidity and mortality would be welcome. Yet, there are very few convincing studies of therapy for AEM, in part because it is a rare disease and tends to occur in more rural areas. Studies from different populations demonstrate different severities of illness, possibly related to the size of the inoculum of *A. cantonensis* L3 larvae ingested.[3] For example, adult Thais who consume *Pila* or *Pomacea* snails, with a relatively low larval burden, tend to have milder disease,[3,17,37] whereas ingestion of the giant African snail (*Achatina fulica*) with its high inoculum,[16] such as happened with adults in Samoa[5] and among children in Taiwan,[3,14] can lead to severe or fatal disease. Children also tend to have more severe disease than adults.[3,17]

In discussing treatment, we are confronted by the lack of knowledge regarding the pathophysiology of the disease. Part of the pathology of AEM appears related to increased intracranial pressure, and many reports have noted the immediate, although usually temporary, relief of headache afforded by a spinal tap.[3,11,12,37] This increased intracranial pressure (ICP) may be related to vasodilation of both arteries and veins seen in the subarachnoid space and brain parenchyma, decreased absorption of CSF, or brain edema.[2,5] One autopsy study suggested death may result from tentorial herniation due to increased ICP.[5] Autopsies of fatal cases of AEM have shown that numerous live worms (L4 larvae and L5 young adult worms) are present at the time of death, and they leave migration tracks with visible, axonal damage in both grey and white matter.[2,5,6] In addition, a robust, Th2 type inflammatory response, characterized by eosinophils, develops in the CNS and subarachnoid space.[2,38] The timing of this response may be most pronounced as the larvae molt from L4 to young adult stage and begin to emerge from the brain parenchyma into the meningeal vessels.[1,2,38] It is not clear which of these processes is most responsible for the pathology. To complicate matters further, anthelmintic drugs appear to be more effective at killing larval forms than adult worms,[39,40] yet patients generally seek medical care about the time when the L4 to young adult molt is just taking place.[1]

Most experts recommend high volume spinal taps to relieve headache and prevent the pathology associated with increased intracranial pressure.[3,11,14,37] The frequency is dictated by the patient's clinical course, with worsening headache and neurological status suggesting the need for a repeat tap. Acetaminophen and non-steroidal anti-inflammatory agents (NSAIDs) do not seem to offer much relief.[11,37]

Steroids have been postulated to work by reducing intracranial pressure and by blunting the inflammatory reaction to dying worms.[11,12,41] There is one double blind, placebo controlled, randomized trial to test corticosteroids in the treatment of AEM.[42] Chotmongkol, et al, enrolled 129 Thai adults with AEM but without altered consciousness; 63 subjects received prednisolone 20 mg orally, thrice daily, for 2 weeks; 66 received placebo. Patients received acetaminophen for headaches but no anthelmintics. The number of subjects who still had headache after 14 days was 5/55 (9.1%) in the prednisolone group versus 25/55 (45%) in the placebo group ($P < .001$). The median days to resolution of symptoms was 5 versus 13 in the treatment and control groups, respectively ($P < .001$). No relapses or serious side effects were noted. Despite the rather high drop out rate (8 in the treatment and 11 in the control group), this well designed study provided the first convincing evidence that high dose steroids could be beneficial in treating AEM. These researchers conducted an uncontrolled study using the same dose of prednisolone for only 1 week and found that 47/52 (90%) had recovered by day 7, but 8 (15%) relapsed, suggesting that a 1 week course was too short.[43] They also reported 11 comatose cases separately, seven of whom received high dose corticosteroids for variable periods of 2-15 days and 4 of whom did not.[44] None of the patients in either group improved and 10/11 died, suggesting that steroids alone may not be helpful once the patient is in coma. An earlier study had seen no benefit from a 5 day course of 30-60 mg/d prednisone, but the report compared results from several hospitals and details were not given.[37] A more recent report described a small outbreak in which 5 patients were given dexamethasone for 1 week followed by prednisone for 1 week.[45] All 5 initially improved; 3 relapsed, but then responded to repeat spinal tap and more steroids.

The use of anthelmintics to kill worms in the CNS is controversial, because it was postulated that an immune reaction to rapidly dying worms would be worse than allowing them to die or migrate out of the CNS naturally.[37,46] Animal studies with a mouse model of AEM have not demonstrated this, but rather have shown that treatment with flubendazole, mebendazole, or albendazole reduces both worm burden and inflammatory response.[39,47-50] Thiabendazole was not effective in mice.[47] Only a study using a rabbit model has shown an decrease in inflammation due to albendazole therapy.[51] There is only one published double blind, placebo controlled, randomized anthelmintic trial without corticosteroids in human AEM.[52] Jitpimolmard, et al, enrolled 71 Thai adults with AEM but without altered consciousness; 36 randomized to albendazole 7.5 mg/kg, orally, twice daily, after meals, for 2 weeks, and 35 to placebo. Patients received acetaminophen for headaches but no corticosteroids. The number of patients who still had headache after 14 days was 7/34 (21%) in the treatment group versus 13/32 (41%) in the placebo group ($P = .08$). The mean days to resolution of symptoms was 8.9 in the albendazole group versus 16.2 in the controls ($P = .05$). Acetaminophen use was 24.2 doses in the albendazole group versus 38.1 in the controls ($P < .01$). No serious side effects were noted. Thus albendazole alone may be effective in decreasing duration and severity of symptoms, but this has not been definitely proven. There is a report of two patients with AEM in the New Hebrides (now Vanuatu) who were thought to have gotten markedly worse during treatment with thiabendazole.[4] During a particularly severe outbreak in American Samoa, thiabendazole was used in 9 of 16 patients, and no appreciable salutary or deleterious clinical responses were noted.[5] Anecdotal reports of mebendazole, albendazole, and ivermectin have shown mixed results, but it is difficult from these uncontrolled reports to infer cause and effect.[15,53-55] Flubendazole has also been tested in animal studies, but is not

licensed for human use in most locales.[47-49] Of the benzimidazoles, albendazole has the highest bioavailability in the central nervous system, and may be the anthelmintic of choice.[56] Absorption of albendazole is better after a fatty meal, and CSF levels are increased when steroids are given concomitantly.[57]

Recently, a combination of corticosteroids and anthelmintics has been tested, but there are no blinded, placebo controlled trials. Chotmongkol, et al, conducted an open labeled trial of albendazole in combination with prednisolone versus prednisolone alone, at the previously reported doses, in 110 Thai adults with uncomplicated meningitis.[58] No significant differences were noted between the study groups, but the study did not have a sufficient number of subjects to prove no difference statistically. However, no harmful effects were seen in adding albendazole to prednisolone. These researchers also conducted an uncontrolled study demonstrating that combination therapy with mebendazole 5 mg/kg orally, twice daily, plus prednisolone 20 mg orally, thrice daily, for 2 weeks, produced a similar cure rate to that seen previously with the albendazole plus prednisolone combination.[59] Tsai et al compared two outbreaks a year apart in Taiwan.[17,60] In the first outbreak, 8 patients received mebendazole 100 mg twice daily for 4-11 days, and 7 of these patients also received dexamethasone alone or dexamethazone followed by prednisolone for 7-25 days. During the subsequent outbreak, 9 patients treated only with acetaminophen and naproxen served as historical controls. Median duration of illness was 13 days in the mebendazole plus prednisolone group versus 27 days in the controls. Animal studies in mice treated with the combination of albendazole and prednisolone have shown that the mice treated with albendazole alone or the combination tend to have a milder immune response than untreated controls or those treated with prednisolone alone, suggesting that the decreased worm burden resulting from anthelmintic therapy led to a less inflammatory immune response while also reducing worm migration.[40,61]

Suggestions for Further Research

Further research into the pathophysiology of this disease is needed, including autopsies of fatal human cases and experiments using animal models. The relative contribution of the several possible causes of neurological injury should be determined to help direct therapy.

Corticosteroids, which ameliorate intracranial pressure and blunt the immune response, are unlikely to prevent direct axonal damage from migrating worms, so there is a theoretical benefit to therapy with anthelmintics to kill the worms. Albendazole therapy has not proven harmful, despite expectations of some earlier researchers, although the question of anthelmintic treatment is still in some doubt because there was borderline significant efficacy seen with albendazole alone in the only double blind, placebo controlled trial.[52] Because earlier treatment with albendazole was more effective in animal studies,[39] additional human trials could be envisioned, with subjects stratified by duration from ingestion of intermediate host, or onset of symptoms, until initiation of therapy. Patients with higher worm burdens may respond differently to therapy, so studies could also be stratified by severity of illness. Other anthelmintics could be explored. Ivermectin reaches low concentrations in the mouse brain[62] and human CSF,[63] but it is effective against some other tissue nematodes at very low concentrations.[64] The effectiveness of ivermectin against *A. cantonensis* could be tested in the mouse model.

Anthelmintic and corticosteroid combinations have been used successfully in several studies, but this combination therapy has not been tested in a double blind, placebo controlled trial. In the studies to date, both groups had resolution of symptoms on day 3 or 4 of therapy,[58,59] suggesting that either the disease was relatively mild or the effect of steroid therapy was so potent that no benefit from anthelmintic could be seen. The possible benefit of anthelmintic treatment may be easier to demonstrate in patients with more severe disease. The challenge is to design a trial that enrolls subjects with sufficient disease severity and measures sensitive enough outcome variables to convincingly assess the presence or absence of differences between treatment groups.

Studies of severe cases of AEM with encephalitis, manifested as neurological signs and altered consciousness, are needed. A standard method for quantitating the severity of illness would facilitate comparison of studies from different regions. Measurements of intracranial pressure should be recorded, when practical. A standardized method of laboratory confirmation of infection with *A. cantonensis* is needed. Where practical, studies should include both adults and children. Because most areas have relatively low rates of infection and see small, sporadic outbreaks, multicenter trials with standardized, pre-approved protocols could be considered.

Conclusions

A presumptive clinical diagnosis of AEM can usually be made in a patient with consistent clinical symptoms and findings along with appropriate travel or residence and food consumption history. Severe headache with cutaneous paresthesias or hyperesthesias and evidence of eosinophilia on CSF or peripheral blood analysis are the usual symptoms and laboratory findings obtained, although eosinophilia may not be present on initial evaluation. Ingestion of a snail or fresh produce in an endemic region is the most frequent history given, but a history of ingestion of other intermediate or paratenic hosts may also be elicited. In addition, the endemic regions appear to be expanding. Serology is helpful in establishing the specific diagnosis, but is often not helpful with the initial clinical management of AEM. Serial lumbar punctures are effective in reducing headache, probably by temporarily relieving increased intracranial pressure. There is one pivotal study showing that a two week course of high dose corticosteroids is beneficial and safe in AEM without altered consciousness.[42] Based on this study, prednisolone 20 mg orally thrice daily or prednisone 60 mg orally daily may be considered. Prednisolone can be tapered after the two week course, as symptoms allow, but should be given for at least 2 weeks. Acetaminophen may be used as adjunctive therapy, but NSAIDs should be avoided if corticosteroids are employed,

because of increased risk of gastrointestinal bleeding. Although current evidence in support of anthelmintics is not as strong, there is modest evidence of improvement with albendazole alone in one well designed human trial,[52] and several studies have found no major evidence of harm, particularly if given with corticosteroids. Earlier concerns of worsened symptoms using anthelmintics have not been demonstrated in trials with albendazole, and until better data are available, it would seem prudent to consider albendazole treatment in combination with steroids for AEM, and in severe AEM in particular. Available animal data suggest that albendazole should be given for 2 weeks, and that it is more effective when given earlier in the course of illness.[39,40]

Conflict of Interest

Neither author identifies any conflict of interest.

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