Human Parasitic Meningitis Caused by *Angiostrongylus cantonensis* Infection in Taiwan

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Abstract

The major cause of eosinophilic meningitis in Taiwan is Angiostrongylus cantonensis. *Humans are infected by ingesting terrestrial and freshwater snails and slugs. In 1998 and 1999, two outbreaks of eosinophilic meningitis caused by* A. cantonensis *infection were reported among 17 adult male immigrant Thai laborers who had eaten raw golden apple snails (*Pomacea canaliculata*). Another outbreak associated with consuming a health drink consisting of raw vegetable juice was reported in 2001. These adult cases differed from reports in the 1970s and 1980s, in which most of the cases were in children. With improvements in public health and education of foreign laborers, there have since been only sporadic cases in Taiwan. Review of clinical research indicates inconsistent association of Magnetic Resonance Imaging (MRI) results with clinical features of eosinophilic meningitis. MRI features were nonspecific but there was an association between the presence of high brain MRI signal intensities and severity of peripheral and cerebrospinal fluid (CSF) eosinophilia. Inflammatory markers have been identified in the CSF of patients with eosinophlic meningitis caused by* A. cantonensis *infection, and vascular endothelial growth factor (VEGF), hepatocyte growth factor (HGF), and the matrix metalloproteinase system may be associated with blood-brain barrier disruption. Eosinophilic meningitis caused by* A. cantonensis *infection is not a reportable disease in Taiwan. It is important that a public advisory and education program be developed to reduce future accidental infection.*

Keywords

Angiostrongylus cantonensis, *Eosinophilic meningitis, Taiwan*

Epidemiology

The major cause of eosinophilic meningitis in the Pacific Islands and Taiwan is *Angiostrongylus cantonensis*, the rat lungworm.[1-4] Humans are infected with *A. cantonensis* by ingesting terrestrial and freshwater snails and slugs.[5-8] The major intermediate hosts for *A. cantonensis* in Taiwan are the giant African snail (*Achatina fulica*) and the golden apple snail (*Pomacea canaliculata*).[5-8] *Pomacea canaliculata* was introduced to Taiwan in 1979 as a food source. It spread widely in paddy fields and drainage ditches and has become an important cause of outbreaks of eosinophilic meningitis. Since the first human infection was reported in Taiwan in 1945,[1] many cases have been reported, mainly in children and most of them in the 1970s and 1980s.[9,10] A study of the epidemiologic characteristics of 125 cases of eosinophilic meningitis or meningoencephalitis that occurred in southern Taiwan in 1968 and 1969 revealed a close association of the disease with the rainy season.[4] Most of these cases were in children; most were among native Taiwanese people; and most patients had eaten a giant African snail prior to their illness. As Taiwanese people habitually do not eat snails uncooked, it was suspected that infection resulted from inadvertently ingesting *A. cantonensis* larvae liberated when the snails were prepared for cooking prior to consumption. In another study on the clinical characteristics of *A. cantonensis* infection among 82 children in Taiwan, 38 (46%) were male and 44 (54%) female, and 87% could be traced to a history of contact with the giant African snail.[10] The most common clinical symptom was fever (92%), followed by vomiting and headache. The sixth and seventh cranial nerves exhibited neuropathy in 20% and 11% of cases, respectively. Worms were recovered from cerebrospinal fluid (CSF) by lumbar puncture in 34 (42%) of the 82 cases. Albendazole and levamisole were used for clinical treatment and with good results.

The epidemiology of eosinophilic meningitis in Taiwan has changed since the 1990s, largely due to improvement in water quality and sanitation. Most of these more recent cases were in adults, especially foreign laborers.[11,12] Between 1991 and 2009, 37 cases were reported.[13] The median age in these cases was 32 years (range 2-80 years), with 35 (95%) being ≥18 years old. The median incubation period was 10.5 days. Most of the patients presented with headache (29, 78%), fever (25, 68%), and hyperesthesia (11, 30%). Among these patients, 22 (60%) were infected after eating raw snails, seven (19%) after drinking raw vegetable juice (probably contaminated with snails), and one after eating raw frog (paratenic host). Eight patients suffered from recurrence of headache after treatment and two patients died. Eosinophilic meningitis caused by *A. cantonensis* infection is not a reportable disease in Taiwan so the actual number of cases is probably underestimated. There have been only sporadic cases reported in recent years, mainly in foreign laborers.

Intermediate Hosts in Taiwan

The major intermediate hosts of *A. cantonensis* in Taiwan are the giant African snail (*Achatina fulica*) and the golden apple snail (*Pomacea canaliculata*),[5,8] both introduced species. In southern Taiwan one study found 14-31% of *P. canaliculata* with third stage larvae of *A. cantonensis*,[8] while a more recent study found infection rates in this species of 12-29% with an average of 36-65 motile larvae per infected snail.[14] The high infection rate of *P. canaliculata* emphasizes the risk of infection via eating raw snails. Regular surveillance of the infection rate of these intermediate hosts is recommended.

Magnetic Resonance Imaging (MRI)

MRI scans of the brains of 13 patients from the 1998 and 1999 outbreaks showed normal, high signal intensities over the globus pallidus and cerebral peduncle on T1-weighted imaging, leptomeningeal enhancement, ventriculomegaly, and punctate areas of abnormal enhancement within the cerebral and cerebellar hemisphere on gadolinium-enhancing T1 imaging, and a hyperintense signal on T2-weighted images.[15] There was a significant ($P < .05$) correlation of MRI signal intensity

in T1-weighted imaging with severity of headache, CSF pleocytosis, and CSF and blood eosinophilia.[15] However, in other cases, there was no association between intensities over the globus pallidus on T1-weighted imaging and *A. cantonensis* infection.[16] In another retrospective study,[17] the brain MRI findings were nonspecific, ie, normal (n = 1), leptomeningeal enhancement (n = 21), hyperintense signal lesions (n = 11) on T2-weighted MRI, and nodular enhancing lesions in gadolinium-enhanced T1-weighted imaging (n = 1). There were significant associations between high brain MRI signal intensities and peripheral eosinophilia ($P < .02$), CSF eosinophil count ≥ 10% ($P = .01$), and the presence of antibodies to *A. cantonensis* in the CSF ($P < .01$). The time from onset of symptoms to spinal tapping or brain MRI did not have an effect on the presence of MRI abnormalities. These brain MRI findings thus did not add any additional rigorous diagnostic evidence to the clinical evaluation of patients with eosinophilic meningitis. Brain MRI should therefore be used as a follow up modality rather than a diagnostic tool.

Inflammatory Markers in CSF of Patients with Eosinophilic Meningitis

Studies in Taiwan have shown that vascular endothelial growth factor (VEGF),[18] hepatocyte growth factor (HGF),[19] and the matrix metalloproteinase system may be associated with blood-brain barrier (BBB) disruption in patients with eosinophilic meningitis caused by *A. cantonensis* infection.[20] There was an association between CSF levels of VEGF, CSF protein, white cell counts, and eosinophil counts. However, the serum levels of VEGF fluctuated during the follow-up period.[18] The CSF/blood ratio of HGF, another neurotropic factor, was higher at presentation when compared with uninfected individuals, but the levels of HGF in CSF were not correlated with the amount of CSF cells or proteins.[19] In another study of 40 patients with eosinophilic meningitis caused by *A. cantonensis*, possible BBB dysfunction caused by matrix metalloproteinase-9 (MMP-9) and its regulation by tissue inhibitors of metalloproteinase (TIMPs) was evaluated.[20] The concentrations of MMP-2, MMP-9, TIMP-1, and CSF/serum albumin ratios (QAlb values) were significantly increased in patients compared with controls, but concentrations of TIMP-4 were significantly lower in patients. Gradual decreases in levels of QAlb, MMP-9, and TIMP-1, and increases in levels of TIMP-4 were observed in six of the patients during recovery.[20] These results suggest that the source of MMP-9 in the CSF of patients with eosinophilic meningitis is probably associated with leukocytes migrating from peripheral blood to the CSF.[20]

Conclusion

The epidemiology of eosinophilic meningitis in Taiwan has changed since the 1990s and now occurs mainly in adults, and in sporadic outbreaks. It is important that a public advisory describing the dangers of eating raw snails and drinking raw vegetable juices be developed to reduce future accidental infection.

Conflict of Interest

None of the authors identifies any conflict of interest.

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