Objective of the research

Angiostrongyliasis, a disease caused by *Angiostrongylus cantonensis*, has spread from the tropical endemic area to various regions throughout the world due to extensive international travel and eating habits. The route of infection is through ingestion of raw freshwater snails, shrimps or monitor lizards. *A. cantonensis* is a neurotropic parasite, which presents as three main clinical manifestations: eosinophilic meningitis, eosinophilic encephalitis, and ocular angiostrongyliasis.

The presenting symptom of meningitic angiostrongyliasis, the most common form, is acute severe headache. In contrast, encephalitic angiostrongyliasis is rare, but fatal. Limited information is currently available on the risk factors for encephalitic angiostrongyliasis. Here, we perform a hospital-based, comparison study to identify the clinical factors predictive of encephalitis caused by *A. cantonensis*. Knowing the risk factors for encephalitic angiostrongyliasis may be a helpful hint for clinicians as preventive strategies.

Method

We recruited adult patients hospitalized for angiostrongyliasis at Srinagarind Hospital, Khon Kaen University, Thailand. The clinical diagnostic criteria for angiostrongyliasis were as follows: i) CSF with a white blood cell count of more than 10 cells/mm³, ii) CSF eosinophils constituting more than 10% of the total CSF white blood cell count, iii) negative tests for CSF Gram-, acid-fast- and India ink staining, cryptococcal antigen testing and cultures, and iv) history of ingesting raw freshwater snails or other paratenic hosts, such as shrimps and monitor lizards.

Exclusion criteria aim to eliminate other possible causes of CSF eosinophils included history of raw fish consumption, history of migratory swelling, clinical diagnosis of subarachnoid hemorrhage or myeloencephalitis, positive serologic test for Gnathostomiasis or Cysticercosis, abnormal brain computed tomography or magnetic resonance findings, symptomatic or serology-positive HIV infection, and active or previous history of tuberculosis or malignancy.

The mentioned clinical criteria were applied to both encephalitis and meningitis groups. As previously reported, both conditions were differentiated by a...
complaining symptom, in that encephalitic angiostrongyliasis presented with acute coma.

We recorded the baseline characteristics, symptoms, physical signs and laboratory results of all participants. Baseline characteristics included gender, age, season of admission defined by the Thailand meteorological classification system (winter, summer or rainy), incubation period (number of days after the last exposure to snails or paratenic hosts to the first day of developing symptoms), duration of headache (days), history of paresthesia, and history of vomiting.

Physical signs included fever (oral temperature of greater than 38°C), cranial nerve abnormalities, papilledema, and stiff neck. Laboratory examinations comprised complete blood count (CBC), serologic test for *A. cantonensis*, and cerebrospinal fluid analyses.

Baseline and clinical characteristics of both groups were compared using descriptive statistics. Wilcoxon rank-sum and Fisher’s exact tests were applied to compare the differences in medians and proportions between the two groups, respectively.

Univariate logistic regression analyses were applied to calculate the crude odds ratios of individual variables for the development of encephalitis. All variables with p values < 0.20 in univariate analysis were included in subsequent multivariate logistic regression analyses. All variables with p > 0.15 in the multivariate model were excluded with the stepwise approach, while those with p < 0.15 were retained in the final model. To account for possible interaction, interaction terms were forced into the final model, and considered significant at p < 0.10. Analytical results were presented as crude odds ratios (OR), adjusted OR, and 95% confidence intervals (CI).

The goodness-of-fit of the final model was evaluated using Hosmer-Lemeshow statistics. Nagelkerke’s $R^2$ was calculated to estimate the proportion of explained variance in the model. To evaluate the discriminatory power or accuracy of the model, $c$ statistics or area under the receiver operating characteristic curve were examined. All data analyses were performed with SAS software version 8.2.

**Result**

We enrolled fourteen patients diagnosed with encephalitic angiostrongyliasis and 86 unmatched patients with meningitic angiostrongyliasis randomly selected from the hospital registration database (1996-2007). Six patients in meningitis group were excluded because of incomplete clinical information. The mortality rate in the encephalitic group was 79% (11 of 14 cases). On the other hand, no deaths were recorded in the meningitis group.

Approximately three-fourths of the subjects in each group were male. The encephalitis and meningitis groups displayed distinct clinical features in terms of...
age, season of presentation, duration of headache, history of vomiting, presence of fever, seventh cranial nerve palsy, papilledema and stiff neck, percentage of blood eosinophils, CSF white blood cell count, CSF eosinophil count, CSF protein level, and CSF/plasma glucose ratios. The sensitivity of the serologic test was 50% and 62% in the encephalitis and meningitis groups, respectively.

Univariate analyses disclosed that factors significantly associated with encephalitis were older age, summer season, longer duration of headache, fever, papilledema, neck stiffness, low percentage of eosinophils on CBC and low CSF/plasma glucose.

There were three factors remaining in the final model predictive of encephalitis by stepwise multiple logistic regression analysis, which include older age (adjusted OR, 1.22; 95% CI, 1.05-1.42), prolonged duration of headache (adjusted OR, 1.26; 95% CI, 1.03-1.55), and fever (adjusted OR, 37.05, 95% CI 1.59-862.35). Interaction terms for combinations of headache duration, age and fever were forced into the model, but were not statistically significant. For the final model, the Hosmer-Lemeshow value, Nagelkerke’s $R^2$, and the c value were 6.30 (p value 0.50), 0.78, and 0.97, respectively.

**Discussion**

Our results show that older age, prolonged headache duration and fever at presentation are predictive factors for encephalitis. After adjustment for other factors, the risk of encephalitis in infected patients increased by 22% for every additional year of age and by 26% for every additional day of headache, while fever at presentation was associated with a 37-fold higher risk of encephalitis.

Older age has not been identified as a risk factor for encephalitis angiostrongyliasis until now, but is a known risk factor for encephalitis induced by other agents, such as West Nile virus. This may relate to compromised immunity in older individuals.

The *A. cantonensis* larvae usually localized in the subarachnoid spaces and meninges in humans, leading to nonfatal headaches or meningitic forms. However, if a headache is disregarded by patients or diagnosis is missed or delayed, the larvae may attempt to migrate to the pulmonary arteries, as observed in rats, their definitive hosts. During migration, larvae may damage brain tissues, resulting in severe inflammatory processes, production of pyrogenic cytokines, and development of the encephalitic form. The presence of CSF eosinophils in the encephalitic group supports this theory.

Unlike in bacterial meningitis, only 10% of meningitic angiostrongyliasis experienced fever, compared to 71% in the encephalitic group. We propose that direct invasion of brain tissue by larvae may activate inflammatory processes and produce pyrogenic cytokines. Generation of pyrogenic cytokines may additionally contribute to fever, although the underlying mechanism of action in encephalitic
Angiostrongyliasis remains unknown.

Overall, the clinical manifestations of encephalitis and meningitis angiostrongyliasis are relatively dissimilar. Clear differences are evident in the duration of headache between the groups, with median of 7 days for the meningitis group and 18.5 days for the encephalitis group (p = 0.002). Thus, in clinical practice, if meningitic angiostrongyliasis patients have triad of elderly, febrile, and headache more than 7 days, they should be considered at high risk of encephalitis. Such patients may benefit from combination therapy, such as corticosteroids and albendazole.

The primary limitation of this study was the small number of patients in the encephalitis group. This led to wide confidence limits of ORs for the fever variable. Due to the retrospective design of the study, some information may be missing or unavailable. Finally, despite strict clinical criteria, a minor proportion of cases may be attributed to other causes such as gnathostomiasis. Clinically, the serologic test for angiostrongyliasis is not routinely utilized, and its sensitivity is only about 50-60%. However, the neurological manifestations of gnathostomiasis are rare, unique, and distinct from those of angiostrongyliasis. History of ingestion of uncooked fish, migratory swelling, subarachnoid hemorrhage, myeloencephalitis or unusual intracerebral hemorrhage are suggestive of gnathostomiasis.

**Conclusion**

Elderly patients with angiostrongyliasis experiencing fever and prolonged headaches are at the highest risk of developing encephalitis. Awareness, prompt diagnosis, and aggressive treatment are important factors in preventing the development of encephalitic angiostrongyliasis.