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Clinical features of eosinophilic meningitis caused by *Angiostrongylus cantonensis* in Thailand: a systematic review

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Abstract

Angiostrongylus Eosinophilic Meningitis (AEM) is an emerging disease worldwide. The majority of reported cases are from Thailand. This study aimed to evaluate whether clinical features of AEM in Thailand. We conducted a systematic review using PubMed and Scopus databases. Search terms included "eosinophilic meningitis," "parasites," "*Angiostrongylus cantonensis*," and "humans." There were 1,688 potential articles from the two databases after duplication removal. Of those, 15 were fully reviewed and eight were included in the analysis. The eight articles that were analyzed were all reports of studies in northeastern Thailand. There were a total of 527 patients, and the majority were male (with the highest proportion being 84.3%). The most common clinical feature was headache, while fever and neck stiffness were found in 80 (15.2%) and 215 patients (40.8%), respectively. Paresthesia was found in 51 patients (9.7%). This study raises awareness of physicians and healthcare personnel on this emerging zoonotic infection with a bulk of characteristic clinical presentation.

Keywords: Angiostrongyliasis, Headache, Snails

1. Introduction

Angiostrongylus Eosinophilic Meningitis (AEM) is an emerging disease worldwide [1,2]. Acute headache is a common presenting symptom [3], which if left untreated, may last for up to two months and is an independent factor for development of severe disease. Patients with AEM may present with only headache and have normal neurological examinations. These may result in misdiagnosis particularly in non-endemic areas or travelers returning from the endemic areas which may cause more severe conditions or morbidity.

A previous review showed that approximately 50% of reported AEM patients were from Thailand [1]. Previous reports have found the prevalence of AEM to be associated with weather factors (coefficient: -0.204; $p = 0.014$), particularly wind velocity [4,5], meaning that the number of patients may differ by region. Because clinical features may also exhibit geographic variation with limitation of clinical review in Thailand, we conducted a systematic search to determine the clinical features of AEM in Thailand.

2. Materials and methods

This systematic review was performed using the PubMed and Scopus databases. The search terms used were "eosinophilic meningitis," "parasites," "*Angiostrongylus cantonensis*," and "humans" (Table 1). The last search was conducted on March 21, 2020. We reviewed randomized controlled trials, controlled trials, cohort/ retrospective cohort studies, case- control studies, and descriptive studies (either prospective or retrospective) with only fix treatment regimens. Those studies with ecological designs, case series, or for which the full text was not in English were excluded. After duplication removal, the eligible articles were reviewed for relevance, and those deemed relevant were subsequently fully reviewed. The included articles were those reported on clinical manifestations of AEM. There were 354 eligible articles from PubMed database (Table 1) and 1,688

articles from Scopus database. The search terms for Scopus database were as follows: TITLE-ABS-KEY (meningit*) AND TITLE-ABS-KEY (eosinophil* OR parasitic* OR helminth* OR nematod* OR "Angiostrongylus cantonensis" OR A. cantonenesis") AND ALL (human*) AND SRCTYPE (j).

Details regarding baseline characteristics, symptoms, risk factors, physical signs, and laboratory results were summarized and reported. The diagnostic criteria for AEM caused by *A. cantonensis* were presence of cerebrospinal fluid (CSF) of eosinophils of 10% or over without other identified causes of CSF eosinophils [3]. Serological testing for *A. cantonensis* by either 29- or 31-kDa antigenic tests can be used to confirm the diagnosis of AEM [3]. Those studies using clinical diagnosis for AEM were also included. No treatment or outcomes were reported in this review. Descriptive statistics were used to calculate mean (SD) and proportions of studied variables.

3. Results

We retrieved a total of 1,688 potentially relevant articles after duplication removal (Figure 1). Of those, 15 were fully reviewed and eight were included in the analysis [6-13], all of which were reports from northeastern Thailand (Table 2). There were a total of 527 patients, and the majority were male (with the highest proportion being 84.3%) [7,8]. In most of the studies, the mean age of the patients was between 30-40 years (the highest was 70). In two reports, over 95% of patients reported consuming raw freshwater snails (97.1% and 96.9%). The longest incubation period was 365 days, reported in two articles [7,8]. Headache was a presenting symptom in all eight articles, with a mean duration of two weeks and a longest duration of 60 days [7,11]. Three articles reported severe headache in 77.4%-92.7% of cases. Fever, neck stiffness, and paresthesia were reported in 80 (15.2%) and 215 patients (40.8%), and 51 patients (9.7%), respectively. In one study, papilledema was found over 50% of patients [9].

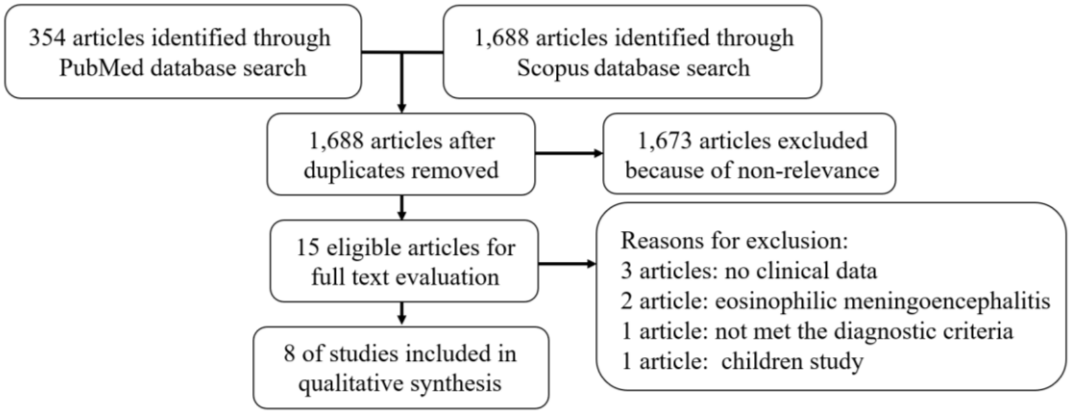

Figure 1 Systematic review flow diagram for clinical features of eosinophilic meningitis caused by *Angiostrongylus cantonensis.*

Table 1 Search terms and eligible articles for clinical manifestations of *Angiostrongylus* eosinophilic meningitis.

No.	Search term	Results
1	Meningit*[Title/Abstrct]	59,929
2	Eosinophil*[Title/Abstract]	75,653
3	parasites	362,018
4	((parasitic disease) OR helminthiasis OR (nematode infections))	376,726
5	(parasite* OR helminth* OR nematod*)	426,765
6	Angiostrongylus cantonensis	1,122
7	((angiostrongylus cantonensis) OR (A. cantonensis))	1,122
8	(angiostrongylus cantonensis) OR (a. cantonensis)	1,155
9	(#3 OR #4 OR #5 OR #6 OR #7 OR #8)	582,075
10	(#1 AND #2)	708
11	(#9 AND #10)	501
12	“Humans”[Mesh]	18,356,388
13	(#11 AND #12)	354

Table 2 Baseline characteristics and physical signs of eosinophilic meningitis patients in Thailand.

Factors/reference no.	6	6	7	8	9	10	10	11	11	12	13	13
Year	2001	2001	2004	2006	2207	2007	2007	2009	2009	2009	2012	2012
N	55[a]	55[b]	26	41	15	34[a]	32[b]	53[a]	51[b]	80	26[a]	49[b]
Age, year*	33.69 (15-70)	33.54 (16-63)	36.5 (15-64)	37.3 (11.90)	27.3 (8.4)	30.7 (9.1)	30.2 (9.6)	34 (15-70)	32 (17-65)	33.5 (15-70)	34 (15-51)	32 (16-60)
Male, n (%)	37 (67.3)	39 (70.9)	16 (61.5)	31 (75.6)	11 (73.3)	22 (64.7)	19 (59.4)	39 (73.6)	43 (84.3)	60 (75)	17 (65.4)	33 (67.4)
Snail ingestion, n (%)						33 (97.1)	31 (96.9)					
Incubation, days	15 (1-90)	21 (1-90)	30 (3-365)	30 (1-365)		13.4 (10.5)	14.2 (9.8)	13.5 (1-90)	7 (1-60)	20 (1-90)	19 (1-60)	21 (1-60)
Headache												
Duration, days	7 (1-30)	7 (1-30)	7 (2-60)			11.6 (8.0)	14.9 (12.1)	6 (1-60)	7 (1-14)	7 (1-30)	7 (2-21)	7 (1-30)
Degree, n (%)						9.5 (1.1)**	8.7 (1.7)**					
Mild			0	7 (17.2)								
Moderate	6 (10.9)	4 (7.3)	3 (11.5)	33 (80.5)				12 (22.6)	9 (17.6)			
Severe	49 (89.1)	51 (92.7)	23 (88.5)	12 (29.3)				41 (77.4)	42 (82.4)			
Nausea/vomiting, n (%)	21 (38.2)	31 (56.4)	12 (46.2)	12 (29.3)	13 (87)	22 (64.7)	22 (68.8)	16 (30.2)	17 (33.3)	31 (39)	14 (53.9)	21 (42.9)
Fever, n (%)	2 (3.6)	6 (10.9)	3 (11.5)	0	6 (40)	2 (5.9)	1 (3.1)	6 (11.3)	4 (7.8)	8 (10)	4 (15.4)	11 (22.5)
Stiff neck, n (%)	32 (58.2)	27 (49.1)	11 (42.3)	12 (29.3)	3 (20)	18 (52.9)	19 (59.4)	8 (15.1)	10 (19.6)	38 (48)	15 (57.7)	22 (44.9)
Cranial nerve palsy, n (%)	5 (9.1)	2 (3.6)	0	0		1 (2.9)	1 (3.1)	1 (1.9)	0	5 (6.3)	0	3 (6.1)
Paresthesia, n (%)	4 (7.3)	4 (7.3)			1 (7)	9 (26.5)	11 (34.4)	3 (5.7)	4 (7.8)	9 (11)	0	6 (12.2)

Factors/reference no.	6	6	7	8	9	10	10	11	11	12	13	13
Papilledema, n (%)						20 (58.8)	17 (53.1)			2 (3)	0	2 (5.4)
Ataxia						0	1 (3.1)					
Numbness								8 (15.1)	10 (19.6)			

Note. *mean (SD or range); **mean visual analogue scale; a: group A; b: group B; blanks indicate missing data.

Table 3 Laboratory results of eosinophilic meningitis patients in Thailand.

Factors/reference no.	6	6	7	8	9	10	10	11	11	12	13	13
Year	2001	2001	2004	2006	2007	2007	2007	2009	2009	2009	2012	2012
N	55[a]	55[b]	26	41	15	34[a]	32[b]	53[a]	51[b]	80	26[a]	49[b]
Blood eosinophilia, n (%)	40 (72.7)	46 (83.6)	20 (76.9)	31 (75.6)	7 (46.7)	15.0 (9.3)*	18.0 (12.6)*	36 (67.9)	39 (76.5)	15 (1-45)*	13 (50.0)	33 (67.4)
CSF profiles												
High pressure, n (%)	21 (38.2)	21 (38.2)	7 (26.9)	4 (9.8)		275.6 (129.2)*	269.6 (118.0)*	5 (9.4)	2 (3.9)	280 (50-600)*	6 (23.1)	18 (28.6)
WBC/mm^3	760 (50-5700)	782 (85-2390)	1,401 (100-5,100)	850 (12-3,520)	670 (90-3,244)	982.4 (705.9)	902.7 (567.2)	780 (70-8,000)	822 (52-9,800)	765 (12-5,100)		
Eosinophils, %	46 (10-81)	45 (12-84)	53 (18-86)	57 (12-84)	36 (10-81)	46.5 (18.8)	48.5 (19.6)	33 (10-88)	32 (10-88)	49 (10-84)		
Protein, mg/dL	113 (31-574)	110 (27-470)	75 (17-207)	71 (17-320)	106 (30-228)	87.2 (45.0)	95.5 (48.9)	91 (28-297)	99 (29-263)	94 (17-470)		
Glucose ratio, %	42 (18-71)	46 (17-100)	42 (13-94)	53 (27-100)	47 (23-68)	47 (10)	50 (10)	26 (26-100)	44 (7-72)	45 (15-113)		
Serum positive, n (%)**				2 (4.9)	8 (53%)	28 (82.4)	27 (84.4)			33 (62)		65.3%
CSF positive, n (%)**						20 (58.8)	25 (78.1)					
Larva recovery, n (%)	0	0	0	0	0	0	0	0	0	0	0	0

Note. Data presented as mean (SD) or median (range); CSF: cerebrospinal fluid; WBC: white blood cell; *mean (SD) or median (range); ** enzyme-linked immunosorbent assay; a: group A; b: group B; blanks indicate missing data.

Regarding laboratory results (Table 3), blood eosinophilia was reported over 50% of patients in most studies. Cerebrospinal fluid pressure was high in approximately 30-50% of patients, with CSF white blood cell counts between 500-1,000 cells/mm^3 (the highest was 8,000 cells/mm^3). Cerebrospinal fluid eosinophils was found in an average of 40-60% of CSF white blood cells, with the highest being 88%. Average CSF protein levels were 100 mg/dL, and the highest was 574 mg/dL. Cerebrospinal fluid glucose per plasma glucose ratio ranged from 26-50%, with the lowest being 13%. No findings of *A. cantonensis* larva were reported. Serological testing was performed and reported in four of the studies, with positive results ranging from 4.9%-84.4%.

4. Discussion

We systematically reviewed clinical and laboratory findings in patients from northeastern Thailand, the main endemic area for AEM. There are indications that these findings may vary according to geographical location. In a report from China, fever, neck stiffness, and paresthesia were more common than in our study (56%, 100%, and 77% of cases, respectively, versus 15.2%, 40.8%, and 9.7%, respectively, in our study; Table 2) [14]. One study from Leoi province [8] reported fever in 40% of cases, but the sample in that study consisted of only 15 patients. The high percentage of patients with neck stiffness in the Chinese study may be explained by awareness of physicians during the outbreak. In Thailand, fever and neck stiffness were common in children diagnosed with AEM (78.9% and 68.4% of cases, respectively) [15]. A study from Europe found that paresthesia was more common (50% of cases), while fever and neck stiffness were found in only 29.4% and 20% of cases [16]. An observational study of 37 patients in Taiwan found fever and paresthesia to be present in 68% and 32% of cases, respectively (note that two were children) [17]. These data suggest that the clinical features of AEM vary by region. Physicians in all areas should be aware of these variations.

As raw freshwater snails are the most common vector for AEM in Thailand (97.1%), it may be important to ascertain the history of freshwater snail consumption over the previous three months in patients presenting with acute severe headache, even if they do not exhibit signs of fever or meningism as discussed above. However, two of the studies we reviewed found that the incubation period may be as long as one year [7,8]. A study from China found that AEM may have developed due to the consumption of raw freshwater snails or other vectors in 44.8%-56.3% of cases [18,19]. Other vectors include contaminated juice or salad, freshwater shrimp, frogs, or household pets [16,20,21].

Based on laboratory results, blood eosinophilia may be a useful clue for diagnosing AEM, as approximately 50%-80% of AEM patients in the studies examined had eosinophilia (Table 3). A previous study found that an absolute blood eosinophil count of 798 cells or greater with history of consumption of raw freshwater snails or other contaminated vectors yielded a sensitivity of 76.6% for AEM [22]. One possible explanation for the acute severe headaches associated with AEM is high CSF pressure, which has been found in up to 38.2% of patients [6]. In addition, CSF protein has been found to be as high as 500 mg/dL in AEM patients, and the CSF/plasma glucose ratio can be as low as in bacterial or tuberculous meningitis [23,24]. A crucial clue in diagnosing AEM is CSF eosinophils greater than 10%, regardless of lymphocyte or neutrophis ratio. Cerebrospinal fluid eosinophils measurement could possibly be used as an alternative to serological testing for *A. cantonensis* if the ratio is over 40% and the patient has a history of exposure [13], which could prove useful in healthcare facilities in which such tests are not available. As larva discovery in the CSF of AEM patients is rare, clinical criteria may be useful as alternative diagnostic indicators [3].

In conclusion, this study raises awareness of physicians and healthcare personnel (nurses and other healthcare personnel) on this emerging zoonotic infection with a bulk of characteristic clinical presentation, but also with variability in morbidity and epidemiological characteristics. AEM awareness will help to better clinical management of the disease as well as more efficient control efforts. Abnormal physical signs in AEM are not obvious. History of *A. cantonensis* exposure with peripheral eosinophilia are helpful hints.

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