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Original Article

Predictive models for *Angiostrongylus cantonensis* and *Gnathostoma spinigerum* infection in pathologically or serologically proved eosinophilic meningitis

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Abstract: Objective: The two most common causes of eosinophilic meningitis (EOM) are the parasites: *Angiostrongylus cantonensis* and *Gnathostoma spinigerum*. This study aimed to evaluate whether clinical factors can predict either neuroangiostrongyliasis or gnathostomiasis in EOM patients. Materials and methods: We included reports of patients with eosinophils in the CSF and either serological or pathological diagnosis of neuroangiostrongyliasis or gnathostomiasis published in 2014 or earlier and available on PubMed. Predictive clinical models were generated for neuroangiostrongyliasis and gnathostomiasis. Results: In total, 155 patients were included in the study, 24 in the gnathostomiasis group and 131 in the neuroangiostrongyliasis group. According to the separate models, factors associated with neuroangiostrongyliais were gender of male, *Pila/Pomacea* snail exposure, and headache, and independent factors for gnathostomiasis were weakness (adjusted odds ratio 50.8) and radicular pain (adjusted odds ratio 35.3). The combined model identified two independent factors for neuroangiostrongyliasis: weakness and radicular pain. The laboratory models revealed that xanthochromic CSF perfectly predicted both neuroangiostrongyliasis and gnathostomiasis. Two other predictive factors were blood eosinophilia and CSF eosinophils, which positively predicted gnathostomiasis (adjusted odds ratios of 1.13 and 1.08, respectively). Conclusion: Clinical factors may be predictive of neuroangiostrongyliasis and gnathostomiasis in EOM.

Keywords: Weakness, migratory swelling, headache, snails, fish

Introduction

There are numerous causes of eosinophilic meningitis (EOM) including parasitic infection, tuberculous meningitis, medications such as ibuprofen, and others [1]. However, the two most common causes are the nematode parasites *Angiostrongylus cantonensis* and *Gnathostoma spinigerum*. Definitive diagnosis of both diseases can be made pathologically or by observation of the parasite larvae in human tissue. Although the opportunities for such diagnoses are rare, serological laboratory tests provide an alternative.

One of several available serological tests is immunoblotting. The 29-kDa antigenic diagnostic band of *A. cantonensis* has a sensitivity of only 56% but 100% specificity for neuroangiostrongyliasis when compared with serum of gnathostomiasis patients [2, 3], while the 21- or 24-kDa antigenic diagnostic bands of *G. spinigerum* have a specificity of 96%. Although these methods exhibit good diagnostic properties for both diseases, they are not widely available. A previous study showed that a cerebrospinal fluid (CSF) eosinophil count of over 40% of total leukocytes was correlated with a positive serological test for angiostrongyliasis [4], with an adjusted odds ratio of 5.0 (95% confidence interval 1.3, 18.5). The present study aimed to evaluate whether any clinical factors could predict either neuroangiostrongyliasis or gnathostomiasis in EOM patients.

Materials and methods

This was a retrospective, analytical study. The inclusion criteria were presence of eosinophils in the CSF and either serological or pathologi-

cal diagnosis of neuroangiostrongyliasis or gnathostomiasis. The study criteria were that articles were published in 2014 or before and available on PubMed [5-49]. The serological tests used to detect *A. cantonensis* were 29- or 31-kDA antigenic immunoblot tests, while those for *G. spinigerum* were 21- or 24-kDa antigenic immunoblot tests [3].

Data on baseline characteristics, physical signs, and laboratory tests of eligible patients were retrieved. Clinical features were compared between the gnathostomiasis and neuroangiostrongyliasis groups using descriptive statistics. Numerical data were shown as median (1^{st}-3^{rd} interquartile range), while categorical data were shown as number (percentage). Differences between the two groups were compared by using Wilcoxon rank sum test for numerical data and Fisher exact test for categorical data. Multivariate logistic regression analysis was used to identify independent factors associated with disease diagnosis, which were divided into two main categories: history/physical signs and laboratory tests. Three models were used to analyze history/physical signs. Models 1 and 2 were computed separately for neuroangiostrongyliasis and gnathostomiasis based on potential diagnostic factors for each, while model 3 was computed for neuroangiostrongyliasis by combining potential factors for both diseases. Only models 1 and 2 were used to analyze laboratory test results, as they examined similar factors. The Hosmer-Lemeshow method was used to assess the goodness of fit of the models. Statistical analyses were performed using STATA version 10.1 (College Station, Texas, USA).

Results

In total, there were 155 patients included in the study, 24 (15.5%) in the gnathostomiasis group and 131 (84.5%) in the neuroangiostrongyliasis group. There were eight significant baseline characteristics across the two groups: exposure to *Pila/Pomacea* spp. snails, exposure to fish, incubation period, headache, weakness, radicular pain, paresthesia, and migratory swelling (**Table 1**). The neuroangiostrongyliasis group had higher proportions of *Pila/Pomacea* snail exposure and headache, while the gnathostomiasis group had higher proportions of the other six significant factors. In terms of physical signs, the gnathostomiasis group had significantly higher proportions of patients with cranial nerve palsies (21.74% vs. 5.38%), weakness (78.26% vs. 2.29%), and urinary incontinence (43.48% vs. 1.53%) than the neuroangiostrongyliasis group (**Table 2**). The gnathostomiasis group also had a significantly higher proportion of patients with xanthochromic CSF (17.39% vs. 0%; P<0.001; **Table 3**).

There were three independent factors associated with neuroangiostrongyliasis in model 1 (**Table 4**): male sex, *Pila/Pomacea* snail exposure, and headache, with adjusted odds ratios of 21.52, 33.67, and 16.44, respectively. Model 2 showed two independent factors for gnathostomiasis: weakness (adjusted odds ratio of 50.8) and radicular pain (adjusted odds ratio of 35.29), and two perfect predictors: fish exposure and migratory swelling. The combined model (model 3) showed three perfect predictors for gnathostomiasis: fish exposure, migratory swelling, and paresthesia, and two independent factors for angiostrongyliasis: weakness and radicular pain (both with adjusted odds ratios below 1 [0.02]). The Hosmer-Lemeshow Chi square values (*P* values) for models 1, 2, and 3 were 3.04 (0.93), 10.16 (0.25), and 4.26 (0.51), respectively. The laboratory models revealed that xanthochromic CSF perfectly predicted both neuroangiostrongyliasis and gnathostomiasis. Two other predictive factors were blood eosinophilia and CSF eosinophils, which positively predicted gnathostomiasis (adjusted odds ratios of 1.13 and 1.08, respectively) but negatively predicted neuroangiostrongyliasis (**Table 5**). The Hosmer-Lemeshow Chi square values (*P* values) for these two models were equal at 6.61 (*P* value: 0.57).

Discussion

Although both *A. cantonensis* and *G. spinigerum* are neurotropic parasites that can cause EOM, there are clinical differences, with some clinical factors being highly suggestive of one and not the other. These differences may be due to size differences between the two parasites. *G. spinigerum* larvae are larger (2.65 mm long and 0.32 mm wide), causing more damage to neurological systems, and migrate randomly, while *A. cantonensis* larvae are smaller (L3 stage length 0.46-0.51 mm and width 0.026 mm) and mainly migrate to the meninges or

Table 1. Baseline characteristics of patients with eosinophilic meningitis caused by *Gnathostoma spinigerum* and *Angiostrongylus cantonensis*

Factors	Gnathostoma group n=24	Neuroangiostrongylus group n=131	*P* value
Age, year	35 (23-47)	32 (23-42)	0.362
Male sex, n	16 (66.67)	80 (73.39)	0.615
Exposure			
Pila/Pomacea snails, n	1 (10.00)	63 (70.79)	<0.001
African snails, n	0	11 (12.36)	0.597
Fish, n	10 (100.00)	12 (13.48)	<0.001
Shrimp, n	2 (20.00)	10 (11.24)	0.348
Lizard, n	0	8 (8.99)	0.999
Frog, n	0	3 (3.33)	0.999
Incubation period, days	70 (28-4745)	14 (7-30)	0.025
Presentations			
Headache, n	6 (26.09)	109 (83.21)	<0.001
Weakness, n	3 (13.04)	1 (0.76)	0.011
Pain, n	2 (8.70)	13 (9.92)	0.999
Radicular pain, n	9 (39.13)	0	<0.001
Fever, n	2 (8.70)	1 (0.76)	0.059
Duration of presenting symptom, n	10 (5-14)	7 (5-14)	0.355
Nausea, n	3 (12.50)	44 (34.11)	0.052
Paresthesia, n	11 (47.83)	19 (14.73)	0.001
Burning sensation, n	0	9 (6.92)	0.193
Migratory swelling, n	9 (39.13)	0	<0.001
Vision disturbance	0	6 (4.58)	0.592

Note: Totals may not be equal to the number of patients in each group due to missing data; data presented as median (1st and 3rd quartile) unless indicated otherwise.

Table 2. Physical signs of eosinophilic meningitis caused by *Gnathostoma spinigerum* and *Angiostrongylus cantonensis*

Factors	Gnathostoma group n=24	Neuroangiostrongylus group n=131	*P* value
Fever, n	4 (17.39)	36 (27.48)	0.441
Deterioration of consciousness, n	4 (17.39)	11 (8.40)	0.243
Neck stiffness, n	4 (17.39)	45 (34.62)	0.145
Papilledema, n	0	6 (4.58)	0.592
6th cranial nerve palsy, n	1 (4.35)	4 (3.05)	0.560
Other cranial nerve palsy, n	5 (21.74)	7 (5.38)	0.019
Motor weakness, n	18 (78.26)	3 (2.29)	<0.001
Paraparesis, n	13	2	
Hemiparesis, n	4	1	
Monoparesis, n	1	0	
Urinary incontinence, n	10 (43.48)	2 (1.53)	<0.001

Note: Totals may not be equal to the number of patients in each group due to missing data; data presented as number (percentage).

brain parenchyma [50, 51]. Additionally, the *G. spinigerum* head has rows of spines that may cause more damage than that by *A. cantonensis* larvae.

As previously reported, neuroangiostrongyliasis is more likely to cause EOM without significant motor weakness, which was reported in only 2.3% of neuroangiostrongyliasis patients

Table 3. Laboratory results of patients with eosinophilic meningitis caused by *Gnathostoma spinigerum* and *Angiostrongylus cantonensis*

Factors	Gnathostoma group n=24	Neuroangiostrongylus group n=131	*P* value
Blood count			
White blood cell, cells/mm^3	9950 (8850-16105)	10100 (7800-13800)	0.460
Eosinophils, %	21 (9-33)	15 (7-22)	0.140
Cerebrospinal fluid (CSF)			
Xanthochromic, n	4 (17.39)	0	<0.001
Opening pressure, mmH_2O	210 (115-250)	250 (200-320)	0.170
White blood cell, cells/mm^3	470 (94-660)	550 (330-910)	0.079
Eosinophils, %	39 (23-70)	39 (21-54)	0.382
PMN, %	6 (2-20)	3 (1-9)	0.488
Lymphocyte, %	50 (36-98)	50 (29-69)	0.987
Protein, mg/dL	81 (37-108)	91 (57-133)	0.284
Sugar, mg/dL	51 (42-56)	49 (43-59)	0.749
CSF/plasm glucose ratio, %	43 (9-51)	48 (37-56)	0.361

Note: Totals may not be equal to the number of patients in each group due to missing data; data presented as median (1st and 3rd quartile) unless indicated otherwise.

Table 4. Adjusted odds ratios for the angiostrongyliasis, gnathostomiasis, and combined models by multivariate logistic regression analysis: history and physical signs

Factors	Model 1: Neuroangiostrongyliasis	Model 2: gnathostomiasis	Model 3: combine model
Age	1.01 (0.92, 1.11)	0.97 (0.91, 1.03)	
Male sex	**21.52 (1.28, 363.17)**	0.53 (0.07, 3.60)	
Pila snails	**33.67 (1.39, 812.83)**		
Headache	**16.44 (1.22, 221.63)**		3.89 (0.43, 34.90)
Fever	0.70 (0.08, 5.73)		
Neck stiffness	1.48 (0.19, 11.89)		0.29 (0.03, 2.38)
Paresthesia	0.19 (0.02, 1.91)		
Weakness		**50.78 (7.56, 241.17)**	**0.02 (0.01, 0.14)**
Radicular pain		**35.29 (4.29, 290.00)**	**0.02 (0.01, 0.21)**
Urinary retention		4.22 (0.12, 152.09)	0.22 (0.01, 10.69)
Nausea			0.45 (0.05, 4.23)

Note: Bold type indicates independent factors; model 2 found fish exposure and migratory swelling to be perfect predictors; model 3 found fish exposure, migratory swelling, and paresthesia to be perfect predictors.

in our study (**Table 2**). Such weakness may indicate spinal cord involvement, as reported by Kliks et al. [9] in Korean fishermen who became infected after consuming giant African snails (*Lissachatina fulica*). We found that headache was the only clinical sign of meningism that was an independent factor for angiostrongyliasis (**Table 4**), along with male sex and exposure to *Pila/Pomacea* spp. snails. A clinical report on angiostrongyliasis found that clinical signs for meningism are only found in 10% of cases [52], with fever and neck stiffness present in 15.2% and 40.8% of patients, respectively. Therefore, clinicians should consider neuroangiostrongyliasis in adult patients presenting with acute headache but without fever or neck stiffness. History of travel to endemic areas and/or exposure to *A. cantonensis* larvae such as by consumption of snails, contaminated vegetables, or shrimp should be evaluated [52].

Clinical presentations of gnathostomiasis are distinct from those of neauroangiostrongyliasis due to the larger size of the larvae, as mentioned above. Migratory swelling, xanthochromic cerebrospinal fluid, and weakness and radicular pain are clinically suggestive of gnathostomiasis. A large case series of 162 patients in Thailand found that gnathostomiasis predo-

Table 5. Adjusted odds ratios for the angiostrongyliasis and gnathostomiasis models by multivariate logistic regression analysis: laboratory tests

Factors	Model 1: Neuroangiostrongyliasis	Model 2: gnathostomiasis
White blood cells	1.00 (0.99, 1.00)	0.99 (0.99, 1.00)
Eosinophilia	**0.87 (0.74, 0.98)**	**1.13 (1.01, 1.27)**
CSF opening pressure	0.99 (0.989, 1.00)	1.00 (0.99, 1.01)
CSF white blood cells	1.00 (0.99, 1.00)	0.99 (0.99, 1.00)
CSF eosinophils	**0.91 (0.84, 0.99)**	**1.08 (1.01, 1.18)**
CSF protein	0.98 (0.97, 1.00)	1.01 (0.99, 1.02)
CSF glucose	1.00 (0.90, 1.10)	0.99 (0.90, 1.09)

Note: Bold type indicates independent factors; xanthochromic cerebrospinal fluid was a perfect predictor of both neuroangiostrongyliasis and gnathostomiasis.

minantly involves the spinal cord and brain parenchyma, which causes weakness and both paraparesis and hemiparesis [53]. Additionally, migratory swelling and radicular pain are highly suggestive. Bleeding in the CSF may also occur because of large spinal larvae, resulting in xanthochromic CSF. If the patient has not undergone traumatic lumbar puncture and there are no other causes of bleeding in the CSF, gnathostomiasis should be considered, particularly if there is also evidence of CSF eosinophils. Raw fish consumption is a strong predictor for gnathostomiasis. Note that duration since larvae exposure in cases of gnathostomiasis may be around 4,745 days (or 13 years), longer than the 10 years previously reported by Katchanov et al. [54]. According to our third model, which combined the potential factors for both diseases, the clinical factors for gnathostomiasis were stronger predictors than those for neuroangiostrongyliasis, with the exception of exposure to *Pila/Pomacea* snails (**Table 4**). This indicates that the clinical presentations of gnathostomiasis are more obvious than those of angiostrongyliasis [43]. A radiological study confirmed that patients with gnathostomiasis exhibited more intracerebral and spinal abnormalities than those with angiostrongyliasis [55].

In addition to xanthochromic CSF, we found that blood eosinophils and CSF eosinophils were also independently associated with gnathostomiasis (**Table 5**). Previous reports have found both blood eosinophilia and CSF eosinophils to be lower in neuroangiostrongyliasis than those in gnathostomiasis (median blood eosinophilia of 19% in neuroangiostrongyliasis patients compared to 54% in those with gnathostomiasis) [6, 56]. Although CSF eosinophils in both diseases were comparable in our study (**Table 3**), it was positively associated with gnathostomiasis after adjustment with other laboratory tests (**Table 5**). This may indicate stronger eosinophilic responses in gnathostomiasis due to the larger larval size.

The strength of this study is that it included only cases that were confirmed either serologically or pathologically. However, there are some limitations. First, some information may be missing because of the retrospective data collection. Bioinformatics analysis of web-based datasets was not performed. Second, the small sample size led to wide 95% confidence intervals. Finally, the record of larval exposure may not be complete, as is also the case in clinical practice.

Conclusions

Clinical factors may be predictive for the two main causes of EOM and may aid in distinguishing between them under certain circumstances. Male, *Pila/Pomacea* snail exposure, and headache were suggestive for neuroangiostrongyliasis, while fish exposure, migratory swelling, weakness, and radicular pain were predictors for gnathostomiasis. Our combined model found that weakness and radicular pain were negatively associated with neuroangiostrongyliasis. Regarding laboratory tests, xanthochromic CSF, blood eosinophilia, and CSF eosinophils may be factors that can help differentiate between the two diseases.

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Disclosure of conflict of interest

None.

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