ETIOLOGY DIAGNOSIS, MANAGEMENT AND TREATMENT OUTCOMES OF CHILDREN WITH EOSINOPHILIC MENINGITIS: 5 YEARS EXPERIENCE IN A MEDICAL CENTER IN SOUTH VIETNAM

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Background: Eosinophilic meningitis (EOM), which is related to parasitic infections in medical literature, can also lead to permanent neurological disability among survivors. Data about the etiology of EOM in Vietnam, as a tropical country, especially on children is still limited. In addition, these patients' management and treatment outcomes are poorly understood.

Objectives: This study was designed to investigate the etiology of common causes, management, and outcomes in children with EOM in Children's Hospital 2, Vietnam.

Subjects and methods: A retrospective case series was conducted at the Infectious Diseases Department of Children's Hospital 2, involving children diagnosed with EOM between March 2018 and March 2023.

Results: A total of 53 patients (2.1% among the cases of meningitis) meeting the diagnostic criteria were enrolled in the study. Using cerebrospinal fluid (CSF) PCR assay, 7 out of 53 (13.2%) identified the causative agents. These included 4/7 (57.1%) parasites and 3/7 (42.9%) *M. tuberculosis*. The treatment rate with corticosteroids was 66.04%, while the rate with albendazole was 60.37%. Post-discharge neurological disability was observed in 11.3% of the cases.

Conclusions: EOM is a rare condition, comprising 2.1% of all cases of meningitis in Children's Hospital 2. The causative agents mainly consist of parasites, with special emphasis on *Mycobacterium tuberculosis*. The mortality rate is low, yet the prevalence of long-term complications remains significant.

Keywords: Eosinophilic meningitis, children, parasite, corticosteroid.

INTRODUCTION

Eosinophilic Meningitis (EOM) is diagnosed based on clinical features and cerebrospinal fluid (CSF) presence of ≥ 10 eosinophils/mm or ≥ 10% of the total CSF leukocytes count. The statistic of Wang and his colleague's research show the two countries with the highest prevalence of disease are Thailand (comprising about 47.33% of all EOM cases over the world) and China (27.22%)[8]. The cause of EOM is classified into communicable and non-communicable groups[3]. According to medical documents, EOM is most related to parasitic infections, especially by Angiostrongylus cantonensis, in addition, Gnathostoma spiniform, Baylisascaris procyonis also associated with EOM, this explain why EOM is more popular in tropical countries[3,8]. Evidence-based medicine has not yet issued general practice guidelines for this group of diseases, access to corticosteroids and antiparasitics is based primarily on single studies conducted in Thailand[3,5,7,8]. EOM usually resolves on its own, rarely fatal, about 4.9% - 9% according to studies in Taiwan and Korea[2,6]. However, the rate of sequelae can be up to 20%, especially in children1. In tropical and middle-income countries such as Vietnam, statistical data on the causative agent is very limited, and there are not

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many studies evaluating the treatment and outcomes of EOM. Therefore, we carry out the research topic "Etiology diagnosis,maneagement and treatment outcomes of children with eosinophilic meningitis from March 2018 to March 2023 in Children's Hospital 2" in order to investigate the etiology of common causes, management, and outcomes in children with EOM in Children's Hospital 2, Vietnam.

SUBJECTS AND METHODS

Subjects: Children who were diagnosed with EOM in Children's Hospital 2 from March 2018 to March 2023.

Research design: Retrospective case series.

Sample selection criteria: Children with suspected meningitis such as headaches, fever, neck stiffness, nausea and vomiting. The cerebrospinal fluid present of ≥ 10 leukocytes/μL and:

- Eosinophils present in CSF ≥ 10 cell/μL, or

- Eosinophils present in CSF ≥ 10% of the total CSF leukocyte count.

Exclusion criteria

Medical records did not reach 80% or more of the research data for medical records between March 2018 and March 2023.

Steps of research

All pediatric patients who met the sampling criteria would have their medical records reviewed. Research data were entered into Microsoft Excel 2016 software, processed, and analyzed by JASP software. Quantitative variables are presented as the median (interquartile range). Qualitative variables are presented as frequency (percentage).

Ethics in research

The research topic was approved from the scientific and ethical aspects by the Ethics Committee in Biomedical Research at Children's Hospital 2. Research code: 15/23-BVND2. No: 116/GCN-BVND2. Issue date: 08/3/2023.

RESULTS

This study from March 2018 to March 2023 at Children's Hospital 2 recorded 53 cases of EOM with the following characteristics:

Main clinical features

Fever is the most common complaint, accounting for 86.8%. The second most common complaint is nausea and/ or vomiting comprising about 66%. Headache accounted for 62.3% of cases. However, when considering the group of patients from 4 years of age and older (capable of accurately exploiting headache symptoms), we recorded a headache rate of up to 97% (Table 1).

Table 1. Rate of clinical symptoms in the study

Clinical symptoms	Frequency	Ratio (%)
Fever	46	86.8
Nause, vomiting	35	66
Headache	33	62.3
Headache in children ≥ 4 years old	32/33	97
Neck stiffness	19	35.8
Kernig sign	4	7.5
Brudzinski sign	2	3.7
Visual effects	7	13.2
Paralysis of the 6th nerve	6	11.3
Convulsion	6	11.3
Limbs weakness	3	6
Paralysis of the 7th nerve	1	1.9
Papilledema	1	1.9
Cerebellum signs	1	1.9
Paresthesia	0	0

Subclinical

Biochemical characteristics of CSF in patients with EOM are usually mildly increased CSF protein, and slightly decreased CSF glucose (Table 2). Suggests that the most common agent is the parasite.

Table 2. Characteristics of CSF in EOM

CSF characteristics	Results
Neutrophil count (cell/mm^3)	84 (30 - 178)
Neutrophil percentage	13 (5 - 25)
Eosinophil count (Cell/mm^3)	215 (140 - 451)
Eosinophil percentage	37 (22 - 45)
Protein (g/L)	0.64 (0.44 - 0.8)
Glucose (mmol/L)	2.16 ± 0.78
CSF Glucose/blood	0.41 (0.32 - 0.51)
CSF Chlor (mmol/L)	122 (119 - 124)
CSF Lactate (mmol/L)	2.9 (2.0 - 3.5)

Imaging: Anormal brain CT scan, accounting for 31.7%. Common abnormalities are ventricular dilatation (35%) and mega cisterna magna (17%). Brain MRI with abnormalities comprise about 57.1%. Common abnormalities are white matter lesions (20%) and encephalitis (17%).

Cause

Only 11 cases (21%) are directly detected in the CSF. Five types of tests were performed to identify the causative agent in the CSF with the performance rate and the positive rate for each type of test, respectively: CSF culture for bacteria (52.8% and 3.6%); Diagnostic sera (9.4% and 80%); PCR tuberculosis/CSF (56.6% and 8%); PCR 32 agents/CSF (7.5% and 75%); PCR Angiostrongylus cantonensis (1.9% and 100%) (Table 3).

Table 3. Rate of agents detected in CSF (n = 11)

Agents	Rate (%)
Angiostrongylus cantonensis	7
Escherichia coli	14
Toxoplasma gondii	14
Measles virus	7
Epstein - Barr virus	7
Elizabethkingia meningoseptica	7
Echinococcus granulosus	22
Mycobacterium tuberculosis	22

In 18 cases (34%) the indirect agent was detected through four types of blood tests: Gram stain and blood culture, serology for parasite diagnosis, and PCR for parasites. The results recorded that the most common agent was *Toxocara* sp. (20%) (Table 4).

Table 4. Percentage of agents detected by serological tests (n = 18)

Agents	Ratio (%)
Toxocara sp.	20
Ascaris lumbricoides	19
Echinococcus granulosus	18
Taenia solium	16
Strongyloides stercoralis	14

Agents	Ratio (%)
Angiostrongylus cantonensis	3
Chlamydia pneumoniae	2
Cytomegalovirus	1
Epstein-Barr Virus	1
Escherichia coli	1
Gnathostoma spinigerum	1
Legionella pneumoniae	1
Mycoplasma pneumoniae	1
Methicillin-Resistant Coagulase-Negative Staphylococci	1
Gram-negative Rods	1

According to different etiology of EOM in discharge documentation, we recorded 8 bacterial meningitis, 20 tuberculous meningitis, 23 parasitic meningitis, and 2 cases of unknown causative agents. Table 5 described laboratory data and treatment characteristics of patients with EOM grouped by 3 major different etiologies in our study.

Table 5. Characteristics of patients with EOM according to different etiology in discharge documentation

	Bacteria (n = 8)	M. tuberculosis (n = 20)	Parasite (n = 23)
Time (days) from the presence of symptoms to the first post-hospital lumbar puncture	7 (5 - 18)	14 (11 - 15)	7 (6 - 13)
Percent CSF eosinophils (%)	37.5 (25 - 47.5)	25 (20 - 45)	40 (33.75 - 46.25)
CSF eosinophils count (cells/mm^3)	183 (35 - 299)	215 (130 - 600)	314 (163 - 519)
Percent CSF neutrophils (%)	15 (9.25 - 19.75)	17 (10 - 35)	13 (5.75 - 18.5)
CSF neutrophils count (cells/mm^3)	55 (12 - 103)	157 (84 - 345)	105 (44 - 154)
CSF protein (g/L)	0.875 (0.675 - 1.867)	0.64 (0.49 - 0.77)	0.6 (0.417 - 0.735)
CSF glucose (mmol/L)	2.25 (1.625 - 2.575)	1.9 (1.8 - 2.5)	2,3 (2.15 - 2.75)
CSF/plasma glucose ratio	0.446 (0.356 - 0.821)	0.32 (0.298 - 0.421)	0.449 (0.402 - 0.517)
CSF lactate (mmol/L)	2.3 (1.7 - 3.25)	3.1 (2.6 - 3.9)	2.65 (1.875 - 3.025)
Day of the highest CSF eosinophilia (Nth)	7 (5 - 19)	15 (13 - 24)	10 (8 - 14)
Antibiotic treatment (cases)	7 (87.5%)	20 (100%)	20 (87%)
Corticoid treatment (cases)	0	14 (70%)	20 (87%)
Prednisolone dosage (mg/kg/day)	0	0.42 (0.335 - 1.000)	1.000 (0.847 - 1.075)
Course of Prednisone treatment (days)	0	17 (12 - 18)	13 (10 - 15)
Dexamethasone dosage (mg/kg/day)	0	0.412 (0.237 - 0.500)	0.400 (0.387 - 0.400)
Course of Dexamethasone (days)	0	12 (8 - 21)	9 (6 - 11)
Time (days) from presence of symptoms to initial treatment	0	23 (18 - 29)	15 (11 - 22)
Albendazole treatment (cases)	0	8 (40%)	23 (100%)

	Bacteria (n = 8)	M. tuberculosis (n = 20)	Parasite (n = 23)
Albendazole dosage (mg/kg/day)		21.811 (15.000 - 24.150)	20 (14.250 - 22.100)
Course of Albendazole (days)	0	7 (4 - 16)	15 (11 - 17)
Anti-tuberculosis treatment (case)	0	12 (60%)	0
Length of stay (days)	20 (17 - 25)	22 (16 - 32)	20 (15 - 24)

Treatment

Corticoids: 35 (66.04%) patients received corticoids. Two drugs commonly used in Children Hospital 2 were prednisolone, with a median of 1.28 mg/kg/day (0.17 - 13.3), and dexamethasone, with a median of 0.37 mg/kg/day (0.14 - 0.52). The average course of corticoid usage was 14 days.

Anthelmintics: 32 (60.38%) patients received anthelmintic drugs, specifically albendazole, with a median of 21.28 mg/kg/day (8.16 - 50) and the average course was 14 days.

Analgesics: 27 (82%) patients received acetaminophen, 5 (15.2%) took ibuprofen, and 1 (3%) was prescribed morphine. There was 1 case diagnosed with tuberculous meningitis and used mannitol 20% intravenous infusion at a dose of 140 mL/30 minutes x 3 times for 3 days, of which 1 day was given NaCl 10% intravenous infusion at a dose of 1 mL/kg/hour.

Treatment outcomes

No deaths were recorded. 47 (88.7%) cases recovered entirely at the time of hospital discharge. 6 cases (11.3%) had neurologic sequelae remaining at discharge: 1 case of left lower limb weakness, 3 cases of VI nerve palsy, 4 had visual acuity affected (1 had worsened on the right eye compared to admission). No recurrent bouts were observed during the study. The median length of stay was 24 days.

DISCUSSION

Etiology diagnosis in children with EOM

We did not record any CSF samples that directly detect parasites. According to author Jill Weatherhead, the rate of direct detection of *A. cantonensis*, *G. spinigerum*, and *Toxocara* sp. in CSF was rare[8]. Out of the 11 (21%) cases the causative agents were directly detected in CSF (Table 2), most of which were thanks to CSF PCR results (7 cases); the positive rate of TB PCR was only about 10%, PCR for 32 parasitic agents was about 75%, and PCR for Angiostrongylus cantonensis DNA raised to 100%. Besides, the CSF testing for causative agents' antibodies (4 cases) had a quite high positive rate, around 80%. Bacterial CSF culture had almost no role in the etiology diagnosis, with a minimal positive rate of 3.6%. Studies in Vietnam such as that of Pham Thi Hai Men et al.[1] focused on a specific group of *A. cantonensis*-caused EOM, thus they did not assess the effectiveness of laboratory tests in the diagnosis of this disease. Hence, we would like to emphasize the role of immunological and molecular biology techniques in etiology diagnosis in children with EOM.

In addition to the etiology diagnosis based on the CSF tests, we also further evaluated the role of blood tests. The study of Pham Thi Hai Men et al. used the diagnostic criteria for EOM caused by *A. cantonensis* based on blood antigen-antibody reaction tests[1]. Through serologic diagnosis tests, we found that *Toxocara* sp. was the most frequent agent (Table 3). One notable point is that it was not a neurotropic pathogen, yet mainly caused damage to the liver and lungs, and rarely caused an increase in CSF eosinophils[3,8]. Blood antibody testing was of indirect value in diagnosing CNS pathogens, in contrast to the direct value of CSF PCR of another rare agent that would be discussed presently. In brief, positive testings for *Toxocara* sp. antibodies

did not help us confirm whether these cases were truly related to *Toxocara* sp. or not. There were 2 cases enrolled in our study that had positive testings for *A. cantonensis* antibodies, and it was fairly certain that this agent was involved since *A. cantonensis* was well-documented as the leading neurotropic pathogen in EOM. Thus, we believe that clinicians had best to understand and be aware of which parasitic agents should be screened in EOM, which not only helps reduce the cost burden but also avoids difficulties in interpreting the results.

According to the authors Sawanyawisuth & Chotmongkol[3], and Jill[8], tuberculosis or *Mycobacteria tuberculosis* is a rare agent causing elevation in CSF eosinophils. In the study period, we recorded 3 cases with PCR evidence of TB in CSF, and a total of 20 cases (37.7%) were diagnosed with tuberculous meningitis based on clinical features and consultation with pulmonary tuberculosis doctors. In Korea, an Asian country, the author Park et al. reported that 4/22 cases (18.2%) of adults with EOM had *M. tuberculosis* isolated[6]. We believe that our research results are fairly consistent in the context of Vietnam, which is a country with a high tuberculosis burden. While analyzing patients' CSF results (Table 1), we discovered group 1 including patients that "failed with initial treatment", as shown as symptoms remained persistent despite using anthelmintics therapy, the biochemical characteristics of this group were similar to tuberculous meningitis rather than parasitic meningitis (protein increased higher, glucose dropped lower). The most common abnormalities noted on cranial CT-scan were ventriculomegaly (35%) and enlarged cisterna magna (17%). A retrospective cohort by Ozates et al. of 214 children diagnosed with tuberculous meningitis reported the most frequent abnormalities on cranial CT-scans were hydrocephalus (80%)[4]. Though it is not rational to diagnose tuberculous meningitis based on imaging tools alone, combined with the CSF biochemical characteristics, we believe that the abnormalities on CT-scans that we have recorded were related to the causative agent - *M. tuberculosis*. The diagnostic PCR tests for *A. cantonensis*, a widely known typical agent of EOM, were not conventionally used in low-middle-income countries, including Vietnam. Therefore, on the one hand, we agree with the literature that parasites are remained the leading causes of EOM in Vietnamese children, besides, we think that, in the condition of inadequate means of diagnosis or when failing with anthelmintics initial therapy, tuberculosis would be considered for being diagnosed or excluded.

Treatment characteristics

To date, there is a lack of data about corticosteroids or anthelmintics therapy for EOM patients in general, and for children, in particular. First of all, currently, several randomized, controlled trials were conducted, with treatment knowledge base came primarily from expert opinions[3,8]. Secondly, these studies mainly examined adults[5,7]. Finally, these studies focused on the group of EOM patients who had *A. cantonensis* isolated[5]. The evidence-based treatment dosage is albendazole 15mg/kg/day for 14 days5 and prednisolone 60 mg/day divided into three doses for 14 days[7]. The regimen at Children's Hospital 2 (Table 4) has a slight difference in the treatment dosage but ensures a duration of treatment of 14 days. We assume that this regimen is appropriate for children based on practical experience in Vietnam. Nevertheless, large clinical trials are crucial to evaluate the safety and effectiveness of this intervention. One thing worth noting was that 40% of patients definitively diagnosed with tuberculosis received initial treatment with albendazole. These cases were at first claimed to be caused by parasites. This once again affirms the role of TB agents in children EOM in an endemic region like Vietnam.

Treatment outcomes

No deaths were recorded in our study, consistent with Pham Thi Hai Men et al.'s study).

We also recorded no recurrent bouts throughout the treatment period. In Hwang and Chen's study in Taiwan, and Park et al.'s in Korea, the mortality rates were estimated at 4,9 - 9%[2],). Predictors of mortality propounded by Park were coma at admission, fungal *Cryptococcus* neoformans, *Exophiala dermatitidis, Prototheca wickerhamii* as causative pathogens[6]. Almost all patients recovered completely before discharge. Out of the 6 cases (11.3%) with neurologic sequelae at discharge, 2 (33%) improved, 3 (50%) remained unchanged after the treatment period, and 1 (17%) had worsened visual acuity on right eye. Research by Pham Thi Hai Men et al. showed that 20% had neurologic sequelae after discharge but did not specify the proportion of each group of children and adults[1]. Hwang and Chen noted that 7,3% of patients still had sequelae remaining after discharge, but the authors of this study did not name what type of sequelae[2]. Although EOM was rarely fatal, it could leave permanent neurologic sequelae for patients, especially in such vulnerable one like children, and affect their quality of life. Therefore, early detection, prompt diagnosis and post-discharge management are the messages that our research team would like to convey.

CONCLUSIONS

Eosinophilic meningitis is rare condition, comprising 2.1% of all cases of meningitis in Children's Hospital 2. The causative agents are mainly parasites; besides that, *Mycobacterium tuberculosis* is an agent that should not be neglected in a tuberculosis-endemic region like Vietnam. Treatment options depend on the causative organism and may include corticosteroids, anthelmintic drugs, antibiotics, or anti-tuberculosis drugs. Although no deaths were recorded, the prevalence of post-discharge sequelae was 11.3%; therefore, it appeared to be requisite to diagnose and treat EOM promptly and properly.

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