CLINICAL AND PARACLINICAL CHARACTERISTICS OF CRYPTOCOCCAL MENINGITIS IN NON HIV INFECTED PATIENTS

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Summary

Objectives: Describe clinical features and paraclinical characteristics in 45 patients of Cryptococcal meningitis who were not HIV infected at National Hospital of Tropical Diseases - Giaiphong and Center for Tropical Diseases - Bachmai Hospital. *Subjects and methods:* including patients aged 16 years or older diagnosed with Cryptococcal meningitis who were not HIV - infected treated at National Hospital of Tropical Diseases - Giaiphong and Center for Tropical Diseases - Bachmai Hospital from 1/2015 to 06/2020. Descriptive and retrospective and prospective cross - sectional study. *Results:* 53.3 % (24/45) were males, the mean age of the study patients was 48.9 ± 14.6 years, ranging from 21 to 79 years. The patients have comorbidities, the most common underlying disease was hepatitis and hematologic diseases 11.1%, renal diseases 8.9%, hypertension 8.9%, duration from the onset of symptoms to diagnosis 19.0 ± 15.8 days. The headache was the most common 95.6%, followed by fever 84.4%, stiff neck 80%, nausea/vomiting 62.2%, visual disturbance 13.3%, focal paralysis 8.9%. The mean protein in CSF was 1.22g/l, the mean cell count in CSF was 342/mm^3. 67.4% patients had a positive culture result and 65.1% had a positive ink stainin for C. *neoformans* in CSF. 5.1% patients had a positive blood culture result for C. *neoformans.* The mean CD4 was 316.4 ± 196.0 cells/μL.

Key words: Cryptococcal meningitis, *Cryptococcus neoformans.*

INTRODUCTION

Cryptococcus neoformans are responsible on a worldwide basis, for most cases of fungal meningitis, especially in HIV patients. The incidence of HIV - associated Cryptococcal meningitis has been decreasing in recent years owning to the advent of highly active antiretroviral therapy (HAART). However there are few data on the clinical and paraclinical characteristics of Cryptococcal meningitis in non - HIV - infected patients in the world and in Vietnam. Understanding the epidemiological characteristics, clinical features and paraclinical characteristics of Cryptococcal meningitis in non - HIV - infected patients is essential for the development of efficient diagnosis and treatment strategy. Therefore, in this study we study the clinical features and paraclinical characteristics in 45 patients of Cryptococcal meningitis who were not HIV - infected at National Hospital of Tropical Diseases, Giaiphong and Center for Tropical diseases - Bachmai Hospital, 1/2015 - 6/2020.

SUBJECTS AND METHODS

Participants: 45 patients aged over 16 years old with a diagnosis of Cryptococcal meningitis and anti HIV(-) were eligible for inclusion.

- *Inclusion criteria:* The patient agrees to join the research. The patient aged over 16 years old. The patient was diagnosed with Cryptococcal meningitis: all were cultured positive for *Cryptococcus neoformans* from cere-

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brospinal fluid (CSF) or patient blood.

- *Exclusion criteria:* The patient has a positive HIV test. The patient refuse to join the research.

Methods: Study design: descriptive and cross - sectional study. Study time: from 1/2015 to 6/2020. Retrospective research: from 1/2015 to 6/2019. Prospective research: from 7/2019 to 6/2020. Location: at National Hospital of Tropical Diseases - Giaiphong and Center for Tropical Diseases - Bachmai Hospital.

Statistical analysis: Statistical analyses were performed by SPSS version 22.0. Data were presented as either mean ± SD or median (range) for continuous variables and the number (%) for categorical variables.

Ethical issues: We protected the confidential information of participants. The study did not harm patients. We fully informed patients about all aspects of the study and participants had the right to refuse to participate in the study at any time. All patients gave informed consent and they could withdraw from the study at any time without giving reasons.

RESULTS

From 1/2015 to 06/2020, there were 45 patients diagnosed with Cryptococcal meningitis and treated at National Hospital of Tropical Diseases - Giaiphong and Center for Tropical Diseases - Bachmai Hospital: 33 patients in the retrospective stage and 12 patients in the prospective stage.

Demographics

Table 1. Demographic features of 45 Cryptococcal Meningitis Patients

Demographic (n = 45)		n	%
Gendar	Male	24	53.3 %
	Female	21	46.7 %
Ages (years)	< 30	4	8.9 %
	30 - 59	26	57.8 %
	≥ 60	15	33.3 %
	X ± SD (min - max)	48.9 ± 14.6 (21 - 79)	
Duration from the onset of symptoms to diagnosis	≤ 1w	9	20 %
	1w - 1m	31	68.9 %
	> 1 m	5	11.1 %
	X ± SD (min - max) (days)	19.0 ± 15.8 (1 - 60)	
Comorbidity	Hypertension	4	8.9 %
	Diabetes mellitus	2	4.4 %
	Renal diseases	4	8.9 %
	Cardiovascular diseases	1	2.2 %
	Hematologic diseases	5	11.1%
	Hepatitis	5	11.1 %

Comment: The mean age of the study patients was 48.9 ± 14.6 years, ranging from 21 to 79 years. 53.3 % (24/45) patients were males, and 33.3 % (15/45) patients were classified as being elderly (≥ 60 years). Duration from the onset of symptoms to diagnosis 19.0 ± 15.8 days, ranging from 1 to 60 days. Hepatitis and hematologic diseases were the most common 11.1%, followed by renal diseases 8.9 %, hypertension 8.9%.

Clinical characteristics

Table 2. Initial clinical manifestations of 45 patients with Cryptococcal meningitis

Symptoms	n	%
Headache	43	95.6 %
Fever	38	84.4 %
Stiff neck	36	80.0 %
Kernig	31	68.9 %
Nausea/vomiting	28	62.2 %
Visual disturbance	6	13.3 %
Focal paralysis	4	8.9 %
Seizures	3	6.7 %

Comment: The headache was the most common 95.6%, followed by fever 84.4%, stiff neck 80.0%, nausea/vomiting 62.2%, visual disturbance 13.3%, focal paralysis 8.9%.

Paraclinical characteristics

Table 3. Cerebrospinal fluid characteristics at the time of admission

Variable (n = 43)		n	%
Protein (g/l)	≤ 0.45	6	13.9 %
	0.45 < Protein ≤ 1	19	44.2 %
	> 1	18	41.9 %
	X ± SD	1.22 ± 1.20	
Glucose (mmol/l)	X ± SD	2.04 ± 1.84	
Clo (mmol/l)	X ± SD	112.7 ± 6.47	
Cell count/mm^3	≤ 5	1	2.3 %
	5 < Cell ≤ 200	18	41.9 %
	> 200	24	55.8 %
	X ± SD	342.1 ± 305.5	
Lympho (%)	≥ 50%	15	34.9 %
	< 50%	28	65.1 %

Comment: Lumbar puncture was performed in 43 patients at the time of admission. 19 of 43 (44.2 %) patients had a protein in CSF: 0.45g/l < protein ≤ 1g/l. 18 of 43 (41.9 %) patients had a protein in CSF > 1g/l. The protein mean in CSF was 1.22g/l.

The cell count mean in CSF was 342/mm^3.

Table 4. Culture results for C. *neoformans* in cerebrospinal fluid (CSF)

Varialble	Culture	At the time of admission (n = 43)	After 48 hours (n = 37)	After 1 week (n = 39)	After discharge (n = 31)
Ink stainin	Positive	28 (65.1%)	27 (73%)	30 (76.9%)	13 (41.9%)
	Negative	15 (34.9%)	10 (27%)	9 (23.1%)	18 (58.1%)
Culture for C. *neoformans*	Positive	29 (67.4%)	24 (64.9%)	21(53.8%)	6 (19.4%)
	Negative	14 (32.6%)	13 (35.1%)	18(46.2%)	25 (81.6%)

Comment: Lumbar puncture was performed in 43 patients at the time of admission. 29 of these patients (67.4%) had a positive culture result for C. neoformans in CSF. 28 of these patients (65,1%) had a positive ink stainin.

Table 5. Culture results for C. neoformans in blood

Culture (n = 39)	n	%
Positive	2	5.1%
Negative	37	94.9%

Comment: There were 39 patients receiving blood culture at the time of admission. 2 of these patients (5.1%) had a positive culture result for *C. neoformans*

Table 6. Brain CT scan MRI

Brain CT scan or MRI (n = 41)	n	%
Intracerebral haemorrhage	1	2.4%
Cerebral infarction	2	4.9%
Cerebral edema	4	9.8%
Ventricular dilation	7	17.1%
Other	4	9.8%

Comment: Brain CT scan (MRI) was performed in only 41 patients. The most common findings were ventricular dilation 17.1%; cerebral edema 9.8%; cerebral infarction (4.9%), intracerebral haemorrhage 2.4%.

Table 7. CD4 cell count in patient blood

CD4 cell count/µL (n = 35)	n	%
< 50	3	8.6
51 - 200	9	25.7
201 - 500	17	48.6
> 501	6	17.1
X ± SD (min - max)	316.4 ± 196.0 (14 - 902)	

Comment: CD4 tests are performed in 35 out of 45 patients. 3 of 35 (8.6 %) patients had a CD4 < 50cells/µL. 9 of 35 (25.7 %) patients had a CD4: 51 - 200cells/µL. 17 of 35 (48.6 %) patients had a CD4: 210 - 500cells/µL. 6 of 35 (17.1%) patients had a CD4 > 500cells/µL. The CD4 mean was 316.4 ± 196.0cells/µL.

DISCUSSION

Cryptococcus usually acquired by inhalation, causes pneumonia and Cryptococcemia and exhibits a propensity to disseminate to the brain and presents as meningitis. Cryptococcal meningitis is the most severe and common form of cryptococcosis. Of 204 cases of cryptococcosis in a US hospital from 1996 to 2009, 62% (126/204) were Cryptococcal meningitis. In this study we analyzed the clinical features and paraclinical characteristics of Cryptococcal meningitis in non - HIV - infected patients with culture-confirmed meningitis.

A sex bias is observed in Cryptococcal studies. The prevalence of cryptococcosis is consistently common in males in both HIV - positive and negative patients. In our study male patients accounted for 53.3% (24/45). Similarly, male predominance was also shown in Wuhan - China (75.6%, 68/90 Cryptococcal meningitis cases). The reasonable explanation of male predominance remained elusive. In our study the median age of patient was 48.9 years old (Table 1). Furthermore, in this study 33.3% (15/45) were elderly patients (≥ 60 years). In a study in Taiwan, elderly patients were more vulnerable to Cryptococcal meningitis than those aged < 65 years and fewer males were affected in the elderly group (57.9%, 22/38) than in non - elderly group (78.7%, 48/61) (Tsai et al 2019).

Cryptococcosis is a rare opportunistic infection that occurs with an increased incidence in immunocompromised patients. However, it can also present in immunocompetent hosts (Lahiri et al 2019). The common risk factors for cryptococcosis generally involve HIV/AIDS, organ transplant, corticosteroid use and malignancy (Ellis et al 2019). In our study, the patients with apparent risk factors and the underlying status included hepatitis and

hematologic diseases were the most common 11.1%, followed by renal diseases 8.9 %, hypertension 8.9% (Table 1). Comparatively in Taiwan during 1997 - 2010, HIV infection was the most common underlying condition (54/219, 24.6%) and among HIV - negative patients, liver diseases (HBV carrier or cirrhosis) were common (30.2%) and 15.4% did not have any underlying condition (Tseng et al 2013).

Cryptococcal central nervous system infections may present as subacute or chronic meningitis, meningoencephalitis or a mass lesion. The prodromal phase is variable and ranges from a very subtle form to a fulminant course with seizures, rapidly progressive coma and death. Overall headache (95.6%), fever (84.4%) and nausea/vomiting (62.2%) seem to be the most common presenting symptoms, followed by mental status changes and visual disturbances (13.3%) (Table 2). The frequent involvement of cranial nerves in infected patients reflects the usual distribution of CNS lesions, where the inflammatory reaction is more pronounced at the base of the brain and in the dorsal area of the cerebellum. Both the distribution of the inflammatory process and the associated increased intracranial pressure explain the permanent blindness in reported by others.

Lumbar puncture is the diagnostic modality of choice for Cryptococcal meningitis. Our CSF findings are similar to those found in AIDS patients with Cryptococcal meningitis and consisted of elevated opening pressure, high protein value (mean 1.22g/l), low sugar level (mean 2.04mmol/l) and mildly elevated white blood cell count (mean 342.1 cell count/mm^3) (Table 3). The growth of Cryptococcus in CSF culture remains the definitive criteria for the diagnosis of Cryptococcal meningitis. In our study at the time of admission, Cryptococcal culture were positive in 29 of 43 (67.4%) patients (Table 4). However, cultures may take weeks to grow and the diagnosis is made initially by the CSF India ink stain which was positive in 28 of 43 (65.1%) patients (Table 4). Thus, in our study both of these tests were found to be positive in more than 65% of non - HIV - infected with Cryptococcal meningitis. Since Cryptococcus can gain access to the CNS from other sites. It is not surprising to have a positive culture from other organs as seen in 2 of our patients with positive culture results for C. neoformans in blood (Table 5).

In our study, brain CT scan (MRI) was performed in only 41 patients. The most common findings were ventricular dilation 17.1%; cerebral edema 9.8%; cerebral infarction (4.9%); intracerebral haemorrhage 2.4% (Table 6). Brain imaging by CT scan and/or magnetic resonance imaging is a useful modality as it may reveal the presence of a mass lesion (cryptococcoma) or hydrocephalus. A positive scan may reflect a more serious infection which would require prolonged suppressive treatment and/or intrathecal therapy.

CONCLUSION

In conclusion, Cryptococcal meningitis is a rare opportunistic infection especially non - HIV - infected patients. Clinical presentation is variable and nonspecific, diagnosis is based on CSF analysis and confirmed by culture.

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