Original Article

Spectrum of Cryptococcal Meningoencephalitis in Tertiary Hospital in Nepal

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Abstract

Introduction: Cryptococcal meningoencephalitis is the most frequently encountered manifestation of cryptococcosis and prevalent throughout the globe**.** The majority of patient suffering from cryptococcosis is immunocompromised and AIDS account for most of the case. We aimed to determine the spectrum of cryptococcal meningoencephalitis at Tribhuvan University Teaching Hospital (TUTH), Kathmandu, Nepal.

Methods: A retrospective study was performed among all the patients (n=15) who were admitted with cryptococcal meningoencephalitis at TUTH over a period of one fiscal year July 2017 to June 2018. Data on patient's demography, history, complaints, clinical findings, neuroimaging, cerebrospinal fluid (CSF) investigation, hospital medication information, complications, mortality and Left Against Medical Advise (LAMA) were extracted from patient medication records of the hospital. Descriptive statistics was performed using IBM-SPSS 20.0.

Results: Of total 15 patients with Cryptococcal meningoencephalitis, majority (9, 60%) had HIV infection. The most common complaints were vomiting (12, 80%) and headache (11, 73%) and clinical findings showed meningeal irritation (8, 53%) and papilledema (4, 27%). Only two neuroimagings among all patients were abnormal. CSF investigation depicted high total cell count (>5cells/mm^3), high protein (>45 mg/dl) and positive cryptococcal antibody in all patients while lymphocytic predominance and lower sugar levels (<3 mmol/dl) in 93% along with ADA of <10 U/L in 67%. Amphotericin-B (mean duration 17 days) and fluconazole antifungals were used in all the patients. Twenty seven percent patients died during hospital stay. Pancytopenia, hydrocephalus and hospital acquired pneumonia were observed in 7 percent of patient from each group and 13 percent of cases left against medical advice.

Conclusion: Cryptococcal meningoencephalitis is common in People Living with HIV (PLHIV) and caused substantial mortality.

Keywords: Cryptococcal Meningoencephilitis, HIV, immunocompromised

Introduction

Cryptococcosis is an invasive fungal infection due to *Cryptococcus neoformans* or *Cryptococcus gattii. Cryptococcus neoformans* meningoencephalitis is the most frequently encountered manifestation of cryptococcosis and is prevalent worldwide. The majority of patient suffering from cryptococcosis is immunocomprised and AIDS account for most of the patient. Other conditions that are associated with cryptococcosis include prolonged steroid therapy, use of immunosuppressive medicine, malignancy, liver disease and sarcoidosis.[1-3]

Cryptococcal infection is the fourth most common opportunistic infection in patients with AIDS and is a relatively common AIDS-presenting illness. Cryptococcal meningoencephalitis has been estimated that there are approximately one million new cases of cryptococcosis worldwide each year, with over

600,000 deaths.[4] In Nepal, there are few studies about cryptococcal meningoencephalitis as opportunistic infection in patient with HIV AIDS and very few studies done in patient without HIV infection.[5-7] We try to evaluate burden of cryptococcal meningoencephalitis in tertiary hospital in one fiscal year.

Methods

This is a retrospective study including patients with Cryptococcol meningoencephalitis aged 16 years and above admitted at Tribhuvan University Teaching Hospital (TUTH) between July 2017 to June 2018. Ethical approval for this study was obtained from Institutional Review Committee of Institute of Medicine. Patient medical records with serologically confirmed Cryptococcal meningoencephalitis cases were reviewed for this study. Demographic information (age, gender occupation and area of residence), history of illness and medication use; complaints and clinical findings on presentation; findings of neuroimaging and cerebrospinal fluid (CSF) investigation; hospital medication information; and information on complications, mortality and LAMA were retrieved from patient medication records of the hospital. Descriptive statistics was used to analyze data using IBM SPSS version 20.0 (IBM Corporation, Armonk, NY, USA).

Results

Total numbers of laboratory confirmed cryptococcal meningoencephalitis were 15 with age ranging from 28 to 70 years (table 1). Among them majority of patients were male (13, 86.7%), migrant worker (7, 46.7%) and residing outside Kathmandu (11, 73.3%).

Table 1: Demographic information (n=15)

Characteristics		n(%) or mean±SD
Age (years)	28 to 70	45.7±12.8
Gender	Male	13(86.7)
	Female	2(13.3)
Occupation	Migrant Worker	7(46.7)
	Housewife	3(20.0)
	Teacher	1(6.7)
	Business	2(13.3)
	Farmer	2(13.3)
Residence	Inside Kathmandu	4(26.7)
	Outside Kathmandu	11(73.3)

Retro-positive status was predisposing factors in sixty percent (table 2). Few patients with HIV infection also had other co-infection which included Koch's abdomen, pulmonary infection and Hepatitis E positive status at the time of admission. Malignancy, chronic liver disease, Hepatitis B positive status, and immunosuppressant use for renal transplant each accounted one case (6.7%). Two cases did not manifest any acquired cause for reduced immunity (13.3%).

Table 2: History of illness and medication use (n=15)

Characteristics		n(%)
Retro positive status		9(60.0)
Chronic illness	Hepatitis-E	1(6.7)
	Hepatitis-B	1(6.7)
	TB abdomen	1(6.7)
	PTB	1(6.7)
Malignancy (Hodgkin Lymphoma)		1(6.7)
Liver disease (Chronic liver disease)		1(6.7)
Immunosuppressant use (renal transplant)		1(6.7)

Main presenting complains were vomiting (12, 80%) and headache (11, 73.3%) however some also had altered sensorium (8, 53.3%) and fever (5, 33.3%). (Table 4)

Table 4: Complaints on presentation (n=15)

Complaints	n(%)
Vomiting	12(80.0)
Headache	11(73.3)
Altered sensorium	7(46.7)
Fever	5(33.3)

Sign of meningeal irritation was present in eight cases (53.3%) and Glassgow Coma Scale (GCS) at presentation ranged from 8 to 15. Papilledema was present only in four cases (28.6%) (Table 5).

Table 5: Clinical findings on presentation (n=15)

Clinical findings	n(%)
GCS	8-15 (53.3-100)
Meningeal irritation	8(53.3)
Papilledema	4(28.6)

Either CT scan or MRI scan was done in all cases which revealed abnormality only in two cases (13.3%) in MRI. The laboratory investigation of CSF has been provided

in table 7. It can be observed that all the patient had high total WBC count ranging from 10 to 190cells/mm^3). Similarly, differential count of WBC showed that lymphocytic cell was predominant (14, 93.3%). Protein and sugar ranged from 47.6 to 277 mg/dl and 0.3 to 3.9 mmol/dl respectively. All of them had high level of protein in their CSF; however, one but all of them had low sugar level (14, 93.3%). Furthermore, the investigation showed that about two third of the patients (10, 66.7%) had ADA less than 10 U/L. Additionally, all the patients had Cryptococcal antibody positive and bacterial culture negative while most (9, 60%) had India ink staining positive.

Table 7: Findings of CSF investigation (n=15)

CSF examination		n(%)
Total cell count (cells/mm3)	High (>5)	15(100)
Predominant cell	Neutrophilic	1(1.7)
	Lymphocytic	14(93.3)
Protein (mg/dl)	High (>45.0)	15(100.0)
Sugar (mmol/dl)	Low (<3)	14(93.3)
	Normal (>3)	1(6.7)
ADA (U/L)	<10	10(66.7)
	>10	5(33.3)
Cryptococcal antibody	Positive	15(100.0)
India Ink Staining	Positive	9(60.0)

Table 8: Hospital medical treatment information (n=15)

Medication information		n(%) or mean±SD
Antifungal used	Amphotericin-B	15(100.0)
	Fluconazole	15(100.0)
Duration of Amphotericin B (days)	2 to 42	16.9±11.0

Table 8 depicts that all the patients received amphotericin-B and fluconazole. The average duration of amphotericin-B was about 17 days though the duration ranges as high as 42 days. As 2 cases left against medical advice so they receive for amphotericin for less 14 days.

Table 9: Complication during hospital stay (n=15)

Complications, mortality and LAMA		n(%)
Complications	Pancytopenia	1(6.7)
	Hydrocephalus	1(6.7)
	Hospital Acquired Pneumonia	1(6.7)
Mortality		4(26.7)
LAMA		2(13.3)

Table 9 shows that four patients (26.7%) died while a single case of pancytopenia, hydrocephalus and pneumonia was observed. The patient with hydrocephalus underwent ventriculoperitoneal shunting. There were also two cases of LAMA.

Discussion

Cryptococcus neoformans meningoencephalitis is the most frequently encountered manifestation of cryptococcosis and is prevalent worldwide. The majority of patient suffering from cryptococcosis is immunocomprised and AIDS account for most of the patient. In Nepal, majority of cryptococcal meningoencephalitis reported in literature are HIV positive cases.[5-6] There are few studies mentioning non-HIV cases however the authors have described case as seropositive and seronegative without mentioning other associated condition with cryptococcal infection.[7] Other conditions that are associated with cryptococcosis include prolonged steroid therapy, use of immunosuppressive medicine, malignancy, liver disease and sarcoidosis.[1-3] Our study revealed HIV infection as the most common factor for cryptococcal meningoencephalitis. In the same way use of immunosuppressant, chronic liver disease, and malignancy was also seen in association in cryptococcal meningoencephalitis in our study. One multicenter retrospective study did not revealed any associated cause in 30 percent of cases.[8] Likewise in our study we could not find any associated cause in 2 cases (13.3%) . Though Hepatitis B positive status is not considered as risk factor for cryptococcal infection however mortality is higher in hepatitis B positive status.[9] Our case with hepatitis B positive had mortality during hospital stay.

The most common symptoms in cryptococcal central nervous infection are fever, malaise, and headache.[10] Vomiting and headache was the most common presenting symptoms which is followed by alteration in sensorium and fever in our study. Fever accounted

for only one third of patients. Fever may not present in all patients and fever is observed in approximately 50 percent of cases.[10]

One study had shown that 24 percent of patients with cryptococcal meningoencephalitis had altered mentation on presentation, and 6 percent presented with focal neurologic deficits.[10] In our study 46.7 percent patients were in altered sensorium with GCS ranging from 8-15. One case had mild weakness due to central nervous system lesion. Study had shown that patients with typical symptoms of the meningeal irritation are less than 20%.[11] Sign of meningeal irritation was present in 53.3% of the cases. Disc edema and visual involvement in cryptomeningoencephalitis occurs in 40 percent of the patients.[12] Papilledema occurred in 28.6 percent of cases in our study.

The CSF examination in cryptococcal meningoencephalitis classically shows a low white blood cell count (eg: <50 cells/mm^3) with level up to 200 cells/mm^3 with a mononuclear predominance.[13] The CSF protein may be slightly elevated, while the glucose levels are usually low.[14] Approximately 25 to 30 percent of patients with culture-proven cryptococcal meningoencephalitis have a normal CSF profile.[15,16] CSF profile in our patients revealed CSF cells ranging from 10 to 190 cells/mm^3. In the same way differential count of WBC showed that lymphocytic cell was predominant (14, 93.3%). Protein and sugar ranged from 47.6 to 277 mg/dl and 0.3 to 3.9 mmol/dl respectively. All of them had high level of protein in their CSF; however, one but all of them had low sugar level (14, 93.3%). Few studies had shown increased Adenosine Deaminase (ADA) level in cryptococcal meningoencephalitis.[17-19] CSF examination of majority of patient showed high CSF ADA level (10, 66.7%) in our study. An India ink preparation of the CSF will usually demonstrate typical round encapsulated yeast organisms consistent with cryptococcus in approximately 75 percent of HIV-infected patients and in 50 percent of non–HIV-infected patients.[20,21] In our study, all patients had positive cryptococcal antibody while only 60 percent had positive India ink staining.

Amphotericin B, flucytocine or fluconazole are used for treatment of cryptococcal meningoencephalitis. Treatment includes three phases: Induction, consolidation and maintenance phases. Induction phase include parental amphotericin preferably liposomal at dose of 3-4 mg/kg once daily with flucytocine at dose of 100mg/kg/day in four divided doses. In resource limited setting amphotericin B deoxycholate at dose of 0.7 mg/kg once daily with fluconazole 400 mg twice can be given.[22,23] We used amphotericin B deoxycholate and fluconazole in all patient. Most patients received one cycle (14 days) of amphotericin however one patient left hospital early against medical advice and three patient died before completing complete 14 days cycle. One patient received 3 cycles (42 days) and 3 patients received 2 cycles (28 days) of amphotericin for sterilization of CSF in culture. Flucytocine was not given to any patient.

In hospital mortality in cryptococcal meningoencephalitis was found to be 17-19 percents. [24,25] Mortality in our study was higher than in other studies (4, 26.7%). Hydrocephalus can be complication of increased intracranial pressure not improved by serial spinal tapping. One study showed 26 percent of patient with cryptococcalcental nervous system illness required ventriculoperitoneal shunting.[26] However only one case (6.7%) required shunting in our study. Leucopenia, thrombocytopenia and anemia are common side effect of amphotericin therapy.[27] One of our patient developed pancytopenia and required blood transfusion during amphotericin therapy. Hospital acquired pneumonia occurred in one patient requiring antibiotics. Two patients went on LAMA (left against medical advice) during treatment.

This study tried to elaborate burden of cryptococcal meningoencephalitis in a tertiary hospital in resource limited setting. Number of patient in this study is less as probably diagnosis was not confirmed and patient had mortality before arriving to us. Also there is an infectious disease hospital which receives more cases of cryptococcal meningoencephalitis associated with HIV infection which in the most common associated condition. It is one of the descriptive study done in Nepal to look through all patients even without HIV infection with limitation of lesser number of study population.

Conclusion

Cryptococcal meningoencephalitis is common in HIV infection and male migrant patients. Besides retro positive status, chronic liver disease, malignancy, use of immunosuppressant use and tuberculosis are also associated with cryptococcal meningoencephalitis. Vomiting and headache are main presenting complaint and meningeal irritation sign may not be present in all patients. CSF examination shows high cells counts,

high protein content, low sugar with lymphocytic predominant cells. CSF India ink may still be negative in some cases. In hospital mortality and complications are not less even in tertiary hospital with antifungal treatment. Cryptococcal meningoencephalitis should be suspected in any immunocompromised patient with fever, headache, and signs or symptoms referable to the central nervous system. The disease should also be considered in immunocompetent individuals presenting with feature of subacute to chronic meningitis.

Conflict of interest: None declared

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