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นิพนธ์ต้นฉบับ **Original Article**

Central Nervous System Infections in HIV-Infected Patients in Nakhonpathom Hospital

ภาวะติดเชื้อทางระบบประสาทส่วนกลางในผู้ป่วยติดเชื้อไวรัสเอชไอวี ในโรงพยาบาลนครปฐม

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ABSTRACT

Objective: 1.To determine etiology, clinical presentations and outcomes of HIV-infected patients presented with central nervous system infection. 2.To establish clinical and laboratory parameters to differentiate between cryptococcal meningitis and tuberculous meningitis and to identify predictors for mortality among them.

Material and methods: Retrospective study of HIV-infected patients admitted with central nervous system infection was conducted during January 1, 2011 and December 31, 2012. Patients' characteristics, investigations and clinical outcomes were collected. Clinical and laboratory features were evaluated to identify factors to differentiate among patients diagnosed with cryptococcal meningitis and tuberculous meningitis. Predictive values for mortality of these two conditions were assessed.

Result: There were 98 patients with mean (S.D.) age of 38.5 (10.4) years and 53.1% were male. Median CD4+T-lymphocyte count was 42.5 (4-509) cells/mm^3. Median duration of illness was 7 (1-84) days. Of all, cryptococcal meningitis (60 cases, 61.2%) and tuberculous meningitis (21 cases, 21.4%) were the most common central nervous system infections. Alteration of consciousness (52.4% vs 26.7%, p 0.03), hydrocephalus (70% vs 30.2%, p 0.002), cerebral infarction (35% vs 9.4%, p 0.01), low CSF opening pressure (16.5 vs 28.5 cmH_2O, p 0.01), high CSF WBC count (62.5 vs 5 cells/mm^3, p 0.002), increased CSF protein level (189.5 vs 66 mg/dl, p 0.001) and hyponatremia (129 vs 132 mEq/L, p 0.03) were associated with tuberculous meningitis. Predictors influenced in-hospital mortality among cryptococcal meningitis included depressed level of consciousness (42.3% vs 14.7%, p 0.02), stiffness of neck (80.8% vs 52.9%, p 0.03), absence of headache (23.1% vs 0%, p 0.005) and low CSF WBC count (2 vs 10 cells/mm^3, p 0.01). Peripheral WBC count (9,200 vs 6,700 cells/mm^3, p 0.04) was the only factor associated with prognosis in

tuberculous meningitis.

Conclusions: Various parameters can be used to differentiate between cryptococcal and tuberculous meningitis including level of consciousness, serum sodium level, abnormalities of cranial imaging, CSF opening pressure, CSF WBC count and protein level. Alteration of consciousness, stiffness of neck, absence of headache and low CSF WBC count were associated with dead of cryptococcal meningitis. High peripheral WBC count was the only factor predicting mortality in tuberculous meningitis.

Keywords: cryptococcal meningitis, tuberculous meningitis, HIV-infected patients

บทคัดย่อ

วัตถุประสงค์ : เพื่อศึกษาสาเหตุ ข้อมูลทางคลินิก ผลการรักษา และปัจจัยเสี่ยงต่อการเสียชีวิตของภาวะติดเชื้อทางระบบประสาทส่วนกลางในผู้ป่วยติดเชื้อไวรัสเอชไอวี และศึกษาปัจจัยทางคลินิกที่ใช้แยกเยื่อหุ้มสมองอักเสบจากเชื้อราคริปโตคอกคัส จากเยื่อหุ้มสมองอักเสบจากเชื้อวัณโรค

วัสดุและวิธีการศึกษา : เป็นการศึกษาแบบย้อนหลัง โดยรวบรวมข้อมูลจากเวชระเบียนผู้ป่วยในของผู้ป่วยติดเชื้อไวรัสเอชไอวีที่มาด้วยภาวะติดเชื้อทางระบบประสาทส่วนกลาง ระหว่างวันที่ 1 มกราคม 2554 ถึง 31 ธันวาคม 2555 ศึกษาลักษณะทางคลินิก ผลการตรวจทางห้องปฏิบัติการ ผลการรักษา ปัจจัยเสี่ยงต่อการเสียชีวิต และปัจจัยที่ใช้แยกระหว่างเยื่อหุ้มสมองอักเสบจากเชื้อราคริปโตคอกคัส กับเชื้อวัณโรค

ผลการศึกษา : ผู้ป่วยทั้งสิ้น 98 ราย เป็นชายร้อยละ 53.1 อายุเฉลี่ย (ส่วนเบี่ยงเบนมาตรฐาน) 38.5 (10.4) ปี CD4 T-lymphocyte count เฉลี่ย 42.5 (พิสัย 4-509) cells/mm^3 ระยะเวลาป่วยโดยเฉลี่ย 7 วัน (พิสัย 1-84 วัน) สาเหตุสำคัญ 2 อันดับแรกคือ เยื่อหุ้มสมองอักเสบจากเชื้อราคริปโตคอกคัส (60 ราย, ร้อยละ 61.2) และเยื่อหุ้มสมองอักเสบจากเชื้อวัณโรค (21 ราย, ร้อยละ 21.4) ปัจจัยที่สัมพันธ์กับเยื่อหุ้มสมองอักเสบจากเชื้อวัณโรคเปรียบเทียบกับเชื้อราคริปโตคอกคัส ได้แก่ ความรู้สติที่เปลี่ยนแปลง (ร้อยละ 52.4 และร้อยละ 26.7, p 0.03) hydrocephalus (ร้อยละ 70 และร้อยละ 30.2, p 0.002) เส้นเลือดสมองอุดตัน (ร้อยละ 35 และร้อยละ 9.4, p 0.01) ความดันเปิดในน้ำไขสันหลังที่ต่ำ (16.5 vs 28.5 cmH_2O, p 0.01) การพบเม็ดเลือดขาว (62.5 vs 5 cells/mm^3, p 0.002) และโปรตีนปริมาณมากในน้ำไขสันหลัง (189.5 vs 66 mg/dl., p 0.001) และโซเดียมในเลือดต่ำ (129 vs 132 mEq/L, p 0.03) ปัจจัยที่สัมพันธ์กับอัตราตายในเยื่อหุ้มสมองอักเสบจากเชื้อราคริปโตคอกคัสระหว่างนอนโรงพยาบาล ได้แก่ ระดับความรู้สติที่เปลี่ยนแปลง (ร้อยละ 42.3 และร้อยละ 14.7, p 0.02) การตรวจพบคอแข็ง (ร้อยละ 80.8 และร้อยละ 52.9, p 0.03) การไม่ปวดศีรษะ (ร้อยละ 23.1 และร้อยละ 0, p 0.005) การตรวจพบเม็ดเลือดขาวปริมาณน้อยในน้ำไขสันหลัง (2 vs 10 cells/mm^3, p 0.01) ปัจจัยที่สัมพันธ์กับอัตราตายในภาวะเยื่อหุ้มสมองอักเสบจากเชื้อวัณโรค ได้แก่ ปริมาณเม็ดเลือดขาวในเลือด (9,200 vs 6,700 cells/mm^3, p 0.04)

สรุป : ปัจจัยทางคลินิกที่ใช้แยกภาวะเยื่อหุ้มสมองอักเสบจากเชื้อราคริปโตคอกคัสกับเยื่อหุ้มสมองอักเสบจากเชื้อวัณโรค ได้แก่ ระดับความรู้สติ ความผิดปกติของเอกซเรย์คอมพิวเตอร์สมอง ระดับความดันเปิดในน้ำไขสันหลัง ปริมาณเม็ดเลือดขาวและโปรตีนในน้ำไขสันหลัง ระดับโซเดียมในเลือด ปัจจัยที่สัมพันธ์กับอัตราตายในผู้ป่วยเยื่อหุ้มสมองอักเสบจากเชื้อราคริปโตคอกคัส ได้แก่ ระดับความรู้สติการตรวจพบคอแข็ง การไม่มีอาการปวดศีรษะ และปริมาณเม็ดเลือดขาวในน้ำไขสันหลังที่ต่ำ ปริมาณเม็ดเลือดขาวในเลือดเป็นปัจจัยเดียวที่สัมพันธ์กับอัตราตายในผู้ป่วยเยื่อหุ้มสมองอักเสบจากเชื้อวัณโรค

คำสำคัญ: เยื่อหุ้มสมองอักเสบจากเชื้อราคริปโตคอกคัส เยื่อหุ้มสมองอักเสบจากเชื้อรา ผู้ป่วยติดเชื้อไวรัสเอชไอวี

Introduction

Central nervous systems (CNS) are common sites of opportunistic infections (OIs) among individuals living with HIV. Although the incidence of such conditions has decreased as a consequence of the introduction of highly active antiretroviral therapy (HAART), they remain a major cause of morbidity and mortality, particularly in Thailand.[1-3]

Cryptococcal meningitis (CM) and tuberculous meningitis (TM) are the common etiology of HIV associated CNS OIs.[4-6] Clinical and initial laboratory findings cannot exclusively differentiated among them. Cerebrospinal fluid (CSF), lymphocytic pleocytosis with decreased glucose and increased protein levels can be found in both conditions.[7-11] Definite diagnosis by culture detection of *M.tuberculosis* using conventional method is time consuming. Although there has been increasingly used of PCR detection of *M.tuberculosis,* low sensitivity and false positivity of test is problematic.[12,13]

The aim of this study was to determine the prevalence, etiology, clinical presentations and outcomes of CNS OIs in all HIV-infected patients hospitalized at Nakhonpathom Hospital. Clinical and laboratory findings were compared to differentiate among patients with CM and TM. In addition, predictors of mortality among these two conditions were identified.

Material and methods

This retrospective study was conducted during January 1, 2011 and December 31, 2012. Eligible patients were adults, aged 12 years, who were HIV-positive and hospitalized due to CNS infection. Medical records were retrospectively identified by searching the disease codes based on International Classification of Diseases-10 (ICD-10). Baseline data were collected including demographic data, prior opportunistic infections, CD4+T-lymphocyte count, clinical manifestations, duration of illness, CSF profiles (WBC count and differential, protein and glucose level), CSF microbiology and computed tomography (CT) brain. Clinical outcomes of the patients were recorded at hospital discharge. Clinical and laboratory features were assessed to identify factors to differentiate among CM and TM. Predictive values for mortality of these two conditions were assessed.

Definition

CM was diagnosed when CSF India ink stain was seen, cryptococcal antigen and/or *Cryptococcal neoformans* culture were detected.

Definite TM was diagnosed when acid fast bacilli (AFB) was seen, M.tuberculosis culture was positive or *M.tuberculosis* DNA was detected by PCR in CSF.

Probable TM was defined as clinical meningitis and 1 of the followings: suspected active pulmonary TB on the basis of chest radiography, AFB found in any sample other than from CSF and clinical evidence of other extrapulmonary TB.

Possible TM was defined as clinical meningitis and 4 of the followings: history of TB, predominance of lymphocytes in CSF, illness of > 5 days in duration, CSF: blood glucose ratio < 0.5, altered consciousness, focal neurological signs and evidence of TBM in CT brain (1 of the followings): basal meningeal enhancement, hydrocephalus or infarctions.[13]

Toxoplasma encephalitis (TE) was diagnosed when: 1) CT scan showing single or multiple lesions with mass effect and/or enhancing with contrast plus 2) positive result on serological testing of serum for Toxoplasma species and 3) resolution of finding after antitoxoplasmic therapy.[4]

Bacterial meningitis was diagnosed when: 1) bacteria were isolated from CSF or 2) a patient presented with clinical features of meningitis and i) a CSF neutrophil predominance and showed a good response to antibacterial treatment in the absence of other treatment, or ii) a CSF polymorphonuclear cell count >1,000 cells/mm^3, regardless of outcomes.

Statistic analysis

All statistical analyses were performed using SPSS software (version 16; SPSS, Inc., Chicago, IL, USA). Bivariate analyses were performed separately for each of the variables. The p-values were calculated by Fisher's exact test for categorical variables and by Student's t test for continuous variables and p- values of < 0.05 was considered statistical significant.

Results

During the study period, there were 98 patients. Among these, 52 (53.1%) cases were male and mean (S.D.) age was 38.5 (10.4) (range 13-66) years. Sixty-two patients (63.3%) were known to have HIV infection (table 1). The absolute number and percentage of CD4+T-lymphocyte count during hospitalization were 42.5 and 5% (range 4-509 cells/ mm^3 and 1-25%). One-third had history of prior opportunistic infections, 80% of these were caused by TB. Median duration of illness before presentation was 7 days (range 1-84 days). Headache and fever were the major clinical presentations, whereas stiffness of neck, nausea and vomiting were found in half of cases. Altered consciousness, weakness and seizure had been less frequently observed. CM was the most common CNS OIs found in this study (60 cases, 61.2%), followed by TM (21 cases, 21.4%), TE (6 cases, 6.1%), meningitis of unknown etiology (4 cases), bacterial meningitis and brain abscess (3 cases each) and herpes simplex virus encephalitis (1 case). Forty-one patients died, accounting for 41.8% of mortality.

Patients with cryptococcal meningitis

Headache and fever occurred in most patients (90% and 83.3%, respectively) (Table 2). Nearly two-third presented with stiffness of neck, nausea and vomiting. Less common findings included altered consciousness (26.7%), seizure (15%) and weakness (13.3%). Median duration of symptom was 7 (range 1-84) days. Forty patients had available CD4+T-lymphocyte counts. Twenty-five (62.5%), 12 (30%) and 3 (7.5%) patients had CD4+T-lymphocyte counts ≤ 50, ≤ 100 and ≤ 200 cells/mm^3, respectively. Neuroimaging of 54 patients revealed 1 or more abnormalities in 26 patients (48.1%) including hydrocephalus (16 of 26 patients, 61.5%), meningeal enhancement (12 patients, 46.2%), brain atrophy (8 patients, 30.7%) and cerebral infarction (5 patients, 19.2%). Lumbar puncture was performed in all, however only 46 patients had a recorded opening pressure. CSF opening pressure was elevated (> 20 cmH_2O) in 65.2% of patients. Median CSF cell

Table 1 Study population characteristics (98 patients)

Variable	Number (%)
Gender (men)	52 (53.1)
Age, year, mean ± S.D. (range)	38.5 ± 10.4 (13-66)
Diagnosis of HIV infection	
Known HIV infection	62 (63.3)
CD4+ T-lymphocyte count, cell/mm^3, n, median (range)	68, 42.5 (4-509)
Previous OIs	34 (34.7)
TB lung	20 (20.4)
TB Meningitis	7 (7.1)
PCP	5 (5.1)
Symptoms & Signs	
Headache	84 (88.8)
Fever	82 (83.7)
Stiffness of neck	57 (58.2)
Nausea/vomiting	54 (55.1)
Alteration of consciousness	33 (33.7)
Neurological deficit	22 (22.4)
Seizure	18 (18.4)
Duration of illness, days, median (range)	7 (1-84)
Duration of hospitalization, days, median (range)	14 (2-125)
Clinical outcome	
Survivors	57 (58.2)
Deaths	41 (41.8)

count was 5 (range 0-610) cells/mm^3 and the predominant type of cell seen was lymphocyte. Median CSF protein was 66 (range 1-469) and glucose was 39 (range 4-93) mg/dl. India ink and cryptococcal antigen testing were positive in 85% and 97.7% of cases, respectively.

Patients with TB meningitis

Five, 11, 5 patients had definite, probable and possible TM, respectively. The median duration of symptoms was 14 (range 2-28) days (Table 2). The most common manifestations were fever (95.2%) and headache (81%). Other presentations

included stiffness of neck (57.1%), altered consciousness (52.4%), nausea and vomiting (42.9%), seizure (23.8%) and weakness (19%). Median CD4+T-lymphocyte count was 46.5 (range 9-259) cells/mm^3. An abnormality on cranial imaging was noted in most patients (90%). The most frequent findings were hydrocephalus (70%) and meningeal enhancement (45%), while cerebral infarction and brain atrophy were found in only one-third of cases. Lumbar puncture was performed in all but one patient. Among 16 patients who had available opening pressure data, 10 patients (62.5%) had pressure below 20 cmH_2O. Median CSF WBC, protein and glucose level were 62.5 (range 0-540) cells/mm^3, 189.5 (range 5-2,813) and 30.5 (4-197) mg/dl, respectively. Normal CSF profiles (CSF WBC < 5 cells/mm^3, protein < 45 and glucose > 45 mg/dl) were presented in 10% of patients (data not shown).

Compared factors between cryptococcal meningitis and TB meningitis

Patients with TM were more likely to had a more depressed level of consciousness (52.4% vs 26.7%, p 0.03). Although there was no different in duration of illness, patients with CM tend to have a more acute onset of symptom developing over 1-7 days (63.8% vs 38.1%, p 0.07). Leukopenia (5,800 vs 7,200 cells/mm^3, p 0.04) and thrombocytopenia (225,000 vs 321,000 cells/mm^3, p 0.001) were associated with CM. CM was more frequently to occur at CD4+T-lymphocyte count ≤ 100 cells/mm^3 (92.5% vs 81.3%). Abnormalities on cranial imaging were found more commonly in TM including hydrocephalus (70% vs 30.2%, p 0.002) and cerebral infarction (35% vs 9.4%, p 0.01). In addition, lower CSF opening pressure (16.5 vs 28.5 cmH_2O, p 0.01), high CSF WBC (62.5 vs 5 cells/mm^3, p 0.002), elevated CSF protein level (189.5 vs 66 mg/dl, p 0.001) and low serum sodium level (129 vs 132 mEq/L, p 0.03) were significant associated with TM. The mortality rate (43.3% vs 38.1%, p 0.675) and median time to dead (22.5 vs 22 days, p 0.975) did not differ significantly between these two conditions (Table 2).

Clinical outcomes of cryptococcal meningitis

Clinical outcomes were assessed at hospital discharge. Overall mortality was 43.3%. Patients who were dead were more likely to have stiffness of neck (80.8% vs 52.9%, p 0.03), depressed level of consciousness (42.3% vs 14.7%, p 0.02), however they were less likely to have headache (76.9% vs 100%, p 0.005) (Table 3). Lower CSF WBC was associated with death during hospitalization (2 vs 10 cells/mm^3, p 0.01). In addition, there was a trend towards higher fatality in those with decreased CSF protein and glucose level (50 vs 70, p 0.056 and 27 vs 43 mg/dl, p 0.075, respectively). Nevertheless, duration of illness, patients' immune status, abnormalities of CT brain as well as presentation of india ink or cryptococcal antigen did not influence patients' outcomes.

Clinical outcomes of TB meningitis

Overall mortality was 38.1%. The median time to death was 22 (range 4-137) days. High median peripheral WBC count was the only variable contributing to mortality (6,700 vs 9,200 cells/mm^3,

Table 2 Comparison factors between Cryptococcal meningitis and TB meningitis.

	Cryptococcal meningitis (n = 60)	TB meningitis (n = 21)	P-value
Clinical features			
Headache	54/60 (90.0)	17/21 (81.0)	0.26
Fever	50/60 (83.3)	20/21 (95.2)	0.27
Stiffness of neck	39/60 (65.0)	12/21 (57.1)	0.52
Nausea/vomiting	35/60 (58.3)	9/21 (42.9)	0.22
Alteration of consciousness	16/60 (26.7)	11/21 (52.4)	0.03
Neurological deficit	8/60 (13.3)	4/21 (19.0)	0.50
Seizure	9/60 (15.0)	5/21 (23.8)	0.50
Duration of illness, days**	58, 7 (1-84)	21, 14 (2-28)	0.16
≤ 7 days	37 (63.8)	8 (38.1)	0.07
≤ 14 days	11 (19)	5 (23.8)	-
≤ 28 days	8 (13.8)	8 (38.1)	-
> 28 days	2 (3.4)	0 (0)	-
Investigations			
Peripheral blood WBC, cells/mm^3**	60, 5,800 (2,200-22,700)	21, 7,200 (3,100-11,500)	0.04
Platelet count, cells/mm^3**	60, 225,000 (3,000-485,000)	21, 321,000 (77,000-498,000)	0.001
CD4 count, cells/mm^3**	40, 38 (4-132)	16, 46.5 (9-259)	0.38
CD4 ≤ 50 cells/mm^3	25 (62.5%)	9 (56.3%)	0.44
CD4 ≤ 100 cells/mm^3	12 (30%)	4 (25%)	-
CD4 ≤ 200 cells/mm^3	3 (7.5%)	2 (12.5%)	-
CD4 > 200 cells/mm^3	0	1 (6.25%)	-
CT brain			
Normal	28 (51.9)	2 (10.0)	-
Abnormal	26 (48.1)	18 (90.0)	0.001
Hydrocephalus	16/53 (30.2)	14/20 (70.0)	0.002
Meningeal enhancement	12/53 (22.6)	9/20 (45.0)	0.06
Infarction	5/53 (9.4)	7/20 (35.0)	0.01
Space occupying lesions	0/53 (0)	0/20 (0)	-
Atrophy	8/53 (15.1)	6/20 (30.0)	0.19
CSF opening pressure (cmH_2O)**	46, 28.5(9-60)	16, 16.5 (6-46)	0.01
Opening pressure ≤ 20 cmH_2O	16 (34.8)	10 (62.5)	0.05
Opening pressure > 20 cmH_2O	30 (65.2)	6 (37.5)	-
CSF WBC	60, 5 (0-610)	20, 62.5 (0-540)	0.002
% CSF PMN**	58, 0 (0-100)	18, 1 (0-93)	0.27
% CSF lymphocytes**	58, 99 (0-100)	18, 95 (0-100)	0.80
CSF Protein, mg/dl**	52, 66 (1-469)	20, 189.5 (5-2,813)	0.001
CSF Glucose, mg/dl**	52, 39(4-93)	20, 30.5 (4-197)	0.22
CSF/Serum glucose**	52, 0.37 (0.04-0.67)	20, 0.30 (0.04-0.64)	0.33
CSF India ink	51/60 (85.0)	0/20 (0)	-
CSF Cryptococcal Ag	43/44 (97.7)	0/15 (0)	-
CSF PCR TB	0/15 (0)	5/12 (41.7)	-
CSF *M.tuberculosis culture*	0/2 (0)	0/1 (0)	-
Serum sodium, mEq/L, n (mean ± S.D.)	60 (132.6 ± 5.7)	21 (129.2 ± 6.9)	0.03
Median time to death, days**	54, 22.5 (6-153)	19, 22 (4-137)	0.98

Notes: Data are number (%) of patients, unless otherwise noted.

** n, median (rang).

p 0.04) (Table 4). There was no significant difference between clinical presentations, immune status, abnormality on cranial imaging and profile of CSF studies among patient who survivors and deaths.

Discussion

CNS OIs were the initial AIDS-defining illness in a significant percentage of patients in this case series. The most common etiologies were CM and TM which is similar to that described in earlier studies.[4-5,14] The majority of patients occurred in the setting of advanced immunosuppression.

CM and TM had similar clinical characteristics and CSF parameters. Accurate diagnosis and early treatment may provide the opportunity of reduced morbidity and mortality. There has been only one recent study demonstrated clinical parameters to differentiate CM and TM.[14] High CSF opening pressure and low CSF WBC were associated with CM while fever, neck stiffness and depressed level of consciousness were associated with TM.

In this study, there was no difference in duration of illness between CM and TM, nevertheless patients with CM tended to present in acute to subacute onset compared to the other. Both conditions generally demonstrated similar clinical and laboratory features. However, alteration of consciousness, leukocytosis, thrombocytopenia and hyponatremia were more consistent with TM.

Abnormal CT findings were exclusively observed among TM (90%). These included hydrocephalus (70%), meningeal enhancement (45%), cerebral infarction (35%) and cerebral atrophy (30%). Conversely, cranial abnormalities were detected only one half of patients with CM. Of these, hydrocephalus and meningeal enhancement were found in 30% and 22.6% of patients. This is different from other studies. The majority of patients with TM had neuroimaging abnormalities (55-100%), including hydrocephalus (20-72%), meningeal enhancemen t(16-63%), cerebral infarction (13-50%) and cerebral atrophy (5-57%)[11]. Whereas patients with CM demonstrated normal CT finding of 8-80%, hydrocephalus of 4-20% and meningeal enhancement of 4-78%.[15-16]

Increased CSF opening pressure was observed more commonly in CM. Two-third were found to have opening pressure more than 20 cmH_2O, while there were reported only one-third of patients with TM. Patients with TM had significantly higher CSF WBC count and protein levels than those with CM. Low CSF glucose and low CSF:plasma glucose ratio were observed but did not differ significantly between both conditions.

Because of high organism load in HIV associated cryptococcal infection, high sensitivities and specificities of cryptococcal antigen testing was reported from various studies.[17-18] It was notable that 85% and 98% of patients in this study have positive results of india ink and cryptococcal antigen. Conversely, only five patients in this study had a definite diagnosis of TM. Uncertainty about the diagnosis since not all CSF samples of patients suspected TM were sent for DNA detection and mycobacterial culture. Moreover, 10% of patients with TM in this study demonstrated normal CSF findings which can result in delayed treatment and

Table 3 Comparison factors between Survivors and Deaths in Cryptococcal meningitis.

Cryptococcal meningitis	Survivors (n = 34)	Death (n = 26)	P-value
Clinical factors			
Headache	34/34 (100)	20/26 (76.9)	0.005
Fever	27/34 (79.4)	23/26 (88.5)	0.49
Stiffness of neck	18/34 (52.9)	21/26 (80.8)	0.03
Nausea/vomiting	20/34 (58.8)	15/26 (57.7)	0.93
Alteration of consciousness	5/34 (14.7)	11/26 (42.3)	0.02
Neurological deficit	4/34 (11.8)	4/26 (15.4)	0.72
Seizure	5/34 (14.7)	4/26 (15.4)	1.0
Duration of illness, days**	32, 7 (1-84)	26, 7 (1-28)	0.37
Investigations			
Peripheral blood WBC, cells/mm^3**	34, 4,900 (2,200-19,800)	26, 6,300 (2,700-22,700)	0.14
Platelet count, cells/mm^3**	34, 235,000 (3,000-485,000)	26, 190,000 (37,000-400,000)	0.16
CD4 count, cells/mm^3**	31, 39 (4-132)	9, 34(5-85)	0.96
CT brain			
Normal	18 (58.1)	10 (43.5)	0.29
Abnormal	13 (41.9)	13 (56.5)	
Hydrocephalus	7/31 (22.6)	9/22 (40.9)	0.15
Meningeal enhancement	0/31 (0)	0/22 (0)	-
Infarction	3/31 (9.7)	2/22 (9.1)	1.0
Space occupying lesion	0/31 (0)	0/22 (0)	-
Atrophy	6/31 (19.4)	2/22 (9.1)	0.45
CSF opening pressure (cmH_2O) **	25, 25 (13-60)	21, 30 (9-60)	0.21
CSF WBC**	34, 10 (0-610)	26, 2 (0-128)	0.01
%CSF PMN**	34, 0 (0-90)	24, 0 (0-100)	0.03
%CSF lymphocytes**	34, 90 (0-100)	24, 100 (0-100)	0.88
CSF Protein, mg/dl**	27, 79 (15-469)	25, 50 (1-230)	0.06
CSF Glucose, mg/dl**	27, 43 (11-93)	25, 27 (4-61)	0.08
CSF/Serum glucose**	17, 0.37 (0.07-0.60)	17, 0.38 (0.04-0.67)	0.99
CSF India ink	27/34 (79.4)	24/26 (92.3)	0.28
CSF Cryptococcal Ag	24/25 (96.0)	19/19 (100)	1.0
Serum cryptococcal Ag	21/24 (87.5)	12/12 (100)	0.54
Positive H/C for cryptococcus	15/26 (57.7)	8/16 (50.0)	0.63
Positive CSF C/S for cryptoccocus	8/30 (26.7)	9/21 (42.9)	0.23
Serum sodium, mEq/L, n (mean ± S.D.)	34 (133.1 ± 6.2)	26 (132 ± 4.9)	0.47

Notes: Data are number (%) of patients, unless otherwise noted.

** n, median (rang).

Table 4 Comparison factors between Survivors and Deaths in TB meningitis

TB meningitis	Survivors (n = 13)	Deaths (n = 8)	P- value
Clinical factors			
Headache	12/13 (92.3)	5/8 (62.5)	0.25
Fever	12/13 (92.3)	8/8 (100)	1.0
Stiffness of neck	9/13 (69.2)	3/8 (37.5)	0.20
Nausea/vomiting	6/13 (46.2)	3/8 (37.5)	1.0
Alteration of consciousness	6/13 (46.2)	5/8 (62.5)	0.66
Neurological deficit	3/13 (23.1)	1/8 (12.5)	1.0
Seizure	3/13 (23.1)	2/8 (25.0)	1.0
Duration of illness, days**	13, 14 (2-28)	8, 15 (2-28)	0.83
Investigations			
Peripheral blood WBC, cells/mm^3**	13, 6,700 (3,100-9,300)	8, 9,200(5,500-11,500)	0.04
Platelet count, cells/mm^3**	13, 321,000 (93,000-498,000)	8, 349,000 (77,000-493,000)	0.56
CD4 count, cell/mm^3**	12, 46.5 (9-259)	4, 45 (10-192)	0.90
CT brain			
Normal	2 (15.4)	0 (0)	0.52
Abnormal	11 (84.6)	7 (100)	
Hydrocephalus	9/13 (69.2)	5/7 (71.4)	1.0
Meningeal enhancement	1/13 (7.7)	0/7 (0)	1.0
Infarction	5/13 (38.5)	2/7 (28.6)	1.0
Space occupying lesion	0/13 (0)	0/7 (0)	-
Atrophy	4/13 (30.8)	2/7 (28.6)	1.0
CSF opening pressure (cmH_2O) , n (mean ± S.D.)	11 (22.4 ± 11.4)	5 (15.8 ± 7.1)	0.26
CSF WBC**	12, 47 (0-540)	72.5 (3-370)	0.44
%CSF PMN**	12, 2.5 (0-93)	6, 8, 1 (0-30)	0.65
%CSF lymphocytes**	12, 93 (0-100)	6, 99 (70-100)	0.19
CSF Protein, mg/dl**	12, 174.5 (41-301)	8, 232 (5-2,813)	0.64
CSF Glucose, mg/dl**	12, 26.5 (10-56)	8, 30.5 (4-197)	0.94
CSF/Serum glucose**	7, 0.31 (0.11-0.64)	8, 0.27 (0.04-0.44)	0.91
Serum sodium, mEq/L, n (mean ± S.D.)	13 (131.1 ± 7.0)	8 (126.1 ± 6.1)	0.12

Notes: Data are number (%) of patients, unless otherwise noted.

** n, median(rang)

subsequently associated with increased mortality.

There are a number of factors predicting an adverse outcome in CM included the absence of headache, abnormal mental status, elevated CSF opening pressure, low CSF WBC (< 20 cells/mm^3), low CSF glucose and high organism burden (positivity of india ink or high cryptococcal antigen titer).[16,19-20] In this study, patients who had no headache, presented with alteration of consciousness, had stiffness of neck and have low CSF WBC were associated with death.

Previous studies reported variables predicting in-hospital mortality of TM including a CD4+T lymphocyte count less than 50 cells/mm^3, reduced Glascow Coma Scale and presence of neurological signs on admission.[11,21] There was no clinical feature, CSF findings or cranial imagings found to be associated with mortality in this study.

The limitations of this study are mainly from the retrospective nature and incomplete clinical data from unavailable medical records. Only 3 CSF specimens were tested for mycobacterial culture. Moreover, we demonstrate only in hospital mortality, but not long-term outcomes.

In conclusion, this study demonstrates clinical and laboratory features to differentiate CM and TM. Atered consciousness, hyponatremia, hydrocephalus, cerebral infarction, CSF opening pressure below 20 cmH_2O, elevated CSF WBC and protein level were associated with TM. Alteration of consciousness, stiffness of neck, absence of headache and low CSF WBC were associated with in-hospital mortality among patients with CM. High peripheral WBC count was the only factor associated with dead in TM.

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