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Diagnosis of cryptococcal and tuberculous meningitis in a resource-limited African setting

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Summary

OBJECTIVES Cryptococcal meningitis (CM) and tuberculous meningitis (TBM) are common in HIV-infected adults in Africa and difficult to diagnose. Inaccurate diagnosis results in adverse outcomes. We describe patterns of meningitis in a Malawian hospital, focusing on features which differentiate CM and TBM with the aim to derive an algorithm using only clinical and basic laboratory data available in this resource-poor setting.

METHODS Consecutive patients admitted with meningitis were prospectively recruited, clinical features were recorded and cerebrospinal fluid (CSF) was examined.

RESULTS A total of 573 patients were recruited, and 263 (46%) had CSF consistent with meningitis. One hundred and twelve (43%) had CM and 46 (18%) had TBM. CM was associated with high CSF opening pressure and low CSF leukocyte count. Fever, neck stiffness and reduced conscious level were associated with TBM. A diagnostic index was constructed demonstrating sensitivity 83%and specificity 79% for the differentiation of CM and TBM. An algorithm was derived with 92% sensitivity for the diagnosis of CM, but only 58% specificity.

CONCLUSIONS Although we demonstrate features associated with CM and TBM, a sufficiently sensitive and specific diagnostic algorithm could not be derived, suggesting that the diagnosis of CM and TBM in resource-limited settings still requires better access to laboratory tools.

keywords cryptococcal, tuberculous, meningitis, malawi, resource-limited setting

Introduction

The HIV epidemic has dramatically affected the spectrum of central nervous system disease in sub-Saharan Africa. Cryptococcal meningitis (CM) and tuberculous meningitis (TBM) are strongly associated with HIV infection and are now both common causes of nonpyogenic meningitis (Schutte *et al.*; Hakim *et al.* 2000; Park *et al.* 2009). CM and TBM present with a similar clinical picture of chronic meningitis and differentiation between the two on clinical grounds is difficult. Also, basic cerebrospinal fluid (CSF) characteristics are frequently indistinguishable as both organisms classically produce a lymphocytic pleocytosis with high CSF protein levels (Heyderman *et al.* 1998; Karstaedt *et al.* 1998; Helbok *et al.* 2009). In resource-poor settings, laboratory tools are limited and confirmatory microbiological diagnosis is often not possible. Delay in appropriate treatment of meningitis is associated with adverse outcomes (Karstaedt *et al.* 1998; Sheu *et al.* 2009).

There have been several algorithms published which use clinical and laboratory features to differentiate various forms of meningitis in an attempt to improve the accuracy and timely diagnosis of meningitis (Thwaites *et al.* 2002; Chavanet *et al.* 2007; Trachtenberg *et al.* 2007). Although a number of descriptions of CM and TBM from sub-Saharan Africa have been published (Heyderman *et al.* 1998; Bogaerts *et al.* 1999; Mwaba *et al.* 2001; French *et al.* 2002), none has directly compared the two in order to derive an algorithm to be used by clinicians treating patients who present with chronic meningitis.

This article describes the pattern of meningitis in a central hospital in Malawi. We focus on the features of chronic meningitis which could potentially be used to derive an algorithm to differentiate CM and TBM, using

only clinical and basic laboratory tests which are widely available in this resource-limited setting.

Methods

This was a cross-sectional observational study of patients presenting with meningitis in a Sub-Saharan African country.

Setting and participants

Malawi is a small country in sub-Saharan Africa with a population of 14 million and an HIV prevalence of 11.9% in the adult population (UNAIDS 2008 http://www.unaids.org/en/CountryResponses/Countries/malawi.asp). Queen Elizabeth Central Hospital in Blantyre is a large teaching hospital associated with the Malawi College of Medicine. The Department of Medicine admits more than 8000 patients per year, serving an urban and semi-urban population and taking referrals from surrounding district hospitals. HIV seroprevalence on the medical wards exceeds 70% (Lewis *et al.*).

Consecutive patients admitted to the Queen Elizabeth Central Hospital between April and December 2007 were prospectively recruited. Patients who were thought to have possible meningitis by the admitting medical officer underwent lumbar puncture as part of the routine clinical assessment. Local departmental guidelines are followed by admitting medical officers when deciding to perform lumbar puncture. Features such as meningism, headache, reduced conscious level and fever prompt consideration of lumbar puncture. The opening pressure was recorded, and 10 ml of CSF was obtained for analysis. Patients who had undergone lumbar puncture were identified by reviewing the laboratory log book of CSF samples received each morning and recruited by the study team within one working day. After a weekend, all patients who had had lumber puncture performed over the weekend were recruited on the Monday morning. Patients were included if the diagnosis was suspected CNS infection. Patients were excluded from the study if they had had a previous diagnosis of CM or TBM and symptoms had not completely resolved prior to presentation, if lumbar puncture had been performed for therapeutic reasons or if lumbar puncture had been performed for evaluation of paraplegia. All cases were reviewed by a study nurse and clinician following a standard protocol for recording demographic details, history and full clinical examination.

Informed consent was obtained from all patients or from their relatives if the patient was unable to provide consent. A preliminary consent to obtain CSF for research purposes was obtained by the admitting officer performing the lumbar puncture. Formal consent to enter the study was then obtained by a member of the study team at recruitment. The study was approved by the Malawi College of Medicine Research and Ethics Committee.

Laboratory methods

The HIV status of all study participants was confirmed using two standard rapid immunoassays (Uni-Gold™ Recombigen® HIV and Determine® HIV-1/2). Those who were HIV positive had CD4 cell count measurements using a Becton Dickinson FACSCount analyser. All patients had peripheral blood analysed for full blood count (Beckman Coulter HmX analyser).

Cerebrospinal fluid from the lumbar puncture at the time of admission was analysed. Standard hospital procedure for CSF analysis included immediate processing for cell count and differential, gram stain, india ink stain and culture for pyogenic organisms and fungi. An additional 5 ml of CSF was refrigerated for mycobacterial culture and cryptococcal antigen testing which were performed on the day of recruitment. CSF was processed using standard laboratory techniques for cell count, differential white cell count if there were >20 cells/mm^3 present in the CSF, and gram stain. All samples were cultured onto sheep blood and chocolate agar for 48 h, and cystine-lactose-electrolyte-deficient medium or brain heart infusion liquid medium as appropriate. *Cryptococcus neoformans* was identified using India ink stain, culture on Sabouraud dextrose agar or cryptococcal antigen agglutination Test (Pastorex Crypto Plus Biorad performed according to manufacturer's guidelines). All CSF samples were cultured on Ogawa's medium for up to 8 weeks to detect mycobacteria, and positive cultures were confirmed with Ziehl–Neelsen stain.

Case definitions

Based on laboratory findings, each study participant was given a diagnosis using the definitions shown in Table 1. The diagnostic category of each patient was allocated by a panel of two independent clinician investigators according to these definitions. If investigators assigned different diagnoses, cases were re-examined and consensus was reached.

Statistical analysis

Data recorded manually was entered in duplicate into secure databases created in Microsoft Access and analysed using Stata version 8 and SPSS version 15 (for CART analysis). Univariate analyses were performed to identify

Table 1 Summary of case definitions for laboratory results

Meningitis type	Case definition
Cryptococcal meningitis	CSF positive for India ink stain or fungal culture or cryptococcal antigen
TB meningitis	CSF positive for mycobacterial culture
Bacterial meningitis	CSF positive for pyogenic organisms on microscopy or culture
Pyogenic meningitis	CSF WBC >20 cells/mm^2 with >50% polymorphs, not fulfilling any other criteria
Lymphocytic meningitis	CSF WBC >20 cells/mm^2 with >50% lymphocytes, not fulfilling any other criteria
Unspecified meningitis	Other abnormal CSF (CSF WBC 5–19 cells/mm^2) not fulfilling any other criteria

CM, cryptococcal meningitis; CSF, cerebrospinal fluid; WBC, white blood count.

variables associated with CM and TBM. Two independent sample *t*-tests were used to compare means while Mann–Whitney-*U* tests were used to compare medians. For binary variables, Fisher's exact test was used to assess an association between the type of meningitis and the variable. Significance tests were performed using the 5% significance level. To identify features which may be used to discriminate CM from TBM, two statistical approaches were used. First, multiple logistic regression modelling was performed and used to construct a diagnostic index. A stepwise variable selection procedure was used to find independent predictors of CM with p-to-enter of 0.05 or less and p-to-remove of 0.055 or more. Receiver Operating Characteristic (ROC) Curves were derived and used to find optimum cut-off points (equal sensitivity and specificity). Sensitivity, specificity, positive predictive value and negative predictive value of the diagnostic index derived from the multiple logistic regression model are reported. Secondly, a classification and regression tree (CART) model was used to develop a clinical decision rule for the initial diagnosis of CM and TBM.

Results

Population characteristics

A total of 573 patients were recruited between April and December 2007. The median age was 33 (IQR 27–40 years), and 52% were male. HIV prevalence was 77%. CSF findings consistent with a diagnosis of meningitis were found in 46% (263/573) of patients who underwent lumbar puncture. CM and TBM were the most common diagnoses (Figure 1).

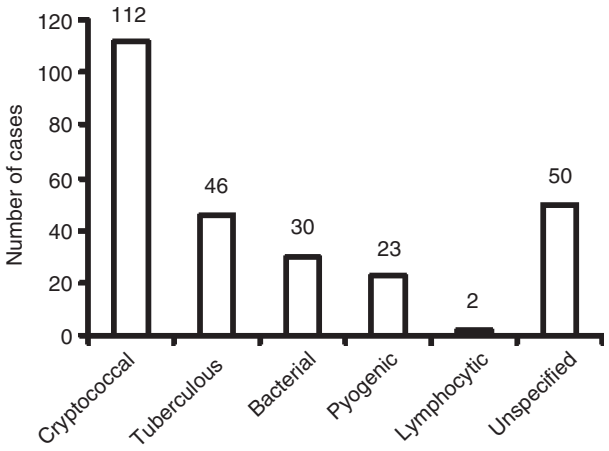

Figure 1 Frequency of types of meningitis.

Clinical features of patients with meningitis

The commonest presenting symptoms in patients with meningitis were headache (88%), fever (67%), vomiting (46%) and confusion (38%). The overall HIV prevalence amongst patients with meningitis was 89%, and 103/263 patients with meningitis were on antiretroviral therapy. Clinical features of patients with meningitis according to type of meningitis are shown in Table 2.

Comparison between patients with cryptococcal and TBM

Univariate analysis of only those patients who had a diagnosis of either CM or TBM demonstrated low Glasgow Coma Score (GCS); higher temperature and neck stiffness were significantly associated with TBM; high CSF opening pressure, low CSF white blood count, low CSF polymorphonulcear percentage and low peripheral white blood count were significantly associated with CM (Table 3). Multivariate analysis of patients who are HIV-positive confirmed the associations of high CSF opening pressure and low CSF white blood cell count with CM; and the association of fever, neck stiffness and reduced GCS with TBM (Table 4). Duration of symptoms did not differ between patients with CM and patients with TBM.

The diagnostic index derived was:
$-0.007 \times$ OP + $1.60 \times$ neck stiffness + $0.002 \times$ CSF WBC$-0.25 \times$ GCS total + $3.34 \times$ fever (fever and neck stiffness were coded 1 if present and 0 if absent). Using the same sample, the diagnostic test and Receiver Operator Characteristic curves demonstrated a sensitivity and specificity of 78% for the differentiation of CM and TBM. Excluding patients who are HIV-negative, the score improved to a sensitivity of 83% and a specificity of 79%.

Table 2 Characteristics of patients with meningitis at presentation

	Cryptococcal *n* = 112	Tuberculous *n* = 46	Bacterial *n* = 30	Pyogenic *n* = 23	Lymphocytic *n* = 2	Unspecified *n* = 50
History						
Headache*	109 (98)	42 (91)	27 (90)	21 (91)	2 (100)	38 (76)
Headache duration (days)†	7 (3–14)	7 (3–14)	4 (3–7)	4.5 (2–7)	4 (2–14)	4 (2–7)
Fever*	68 (62)	41 (89)	22 (73)	18 (78)	(2) 100	34 (68)
Fever duration (days)†	7 (3–14)	7 (4–14)	4 (2–14)	3.5 (2–5)	7 (3–14)	7 (4–14)
Nightsweats*	29 (26)	17 (37)	9 (30)	8 (35)	1 (50)	11 (2)3
Weight loss*	27 (25)	15 (33)	7 (25)	2 (9)	0 (0)	10 (20)
Fit*	44 (40)	14 (30)	14 (47)	8 (35)	0 (0)	15 (31)
Confusion*	38 (34)	23 (50)	15 (50)	7 (32)	1 (50)	14 (29)
Cough*	22 (20)	10 (22)	5 (17)	2 (9)	0 (0)	13 (27)
History of TB*	43 (40)	8 (18)	2 (7)	0 (0)	0 (0)	9 (18)
Current anti TB treatment*	11 (9.8)	2 (4.2)	0 (0)	0 (0)	(0)	2 (4)
Examination						
Pulse (bpm)†	84 (80–99)	91.5 (80–116)	103 (84–120)	88.5 (73–104)	90 (80–100)	88 (80–101.5)
Glasgow coma score (/15)†	15 (14–15)	12 (8–15)	10 (6–14)	9 (315)	15 (12–15)	15 (10–15)
Temperature†	37 (36.5–37.9)	38 (36.85–38.55)	38.2 (37.25–38.9)	38 (37.2–39.3)	36.85 (35–38.7)	37.5 (36.8–38.2)
Neck stiffness*	60 (55)	36 (78)	23 (767)	15 (65)	1 (50)	17 (34.0)
Photophobia*	19 (16.8)	4 (9.1)	2 (6.7)	1 (4.4)	0 (0)	5 (10)
Cranial nerve defect*	8 (7)	2 (4)	1 (3)	2 (9)	0 (0)	3 (6)
Hemiparesis*	4 (2.9)	1 (2.2)	1 (3.3)	1 (4.4)	0 (0)	5 (10)
Lymphadenopathy*	13 (3.7)	7 (15.6)	0 (0)	0 (0)	0 (0)	2 (4.0)
Splenomegaly*	9 (8.4)	6 (13.3)	1 (3.3)	1 (4.4)	0 (0)	6 (12)
Herpes simplex*	29 (26.4)	7 (15.6)	8 (26.7)	6 (27.3)	0 (0)	10 (20)
Oral Candida*	43 (40.0)	8 (55.6)	11 (36.7)	4 (17.4)	0 (0)	13 (26.5)
Kaposi's sarcoma*	10 (9.4)	2 (4.4)	0 (0)	0 (0)	0 (0)	4 (8.2)
Investigations						
HIV positive*	110 (98.2)	41 (89.1)	28 (93.3)	18 (81.8)	2 (100)	34 (70.8)
CD4 count ($\times 10^6$ cells)†	56.5 (25–97)	60 (33–130)	119 (56–457)	595 (426–764)	121 (66–248)	135 (80–200)
CSF opening pressure (mm H_2O)†	280 (160–340)	200 (150–280)	250 (120–340)	135 (9135–135)	182 (150–320)	140 (100–240)
CSF WBC (cells/μl)†	0 (0–18)	40 (0–240)	260 (32–960)	872 (65–1680)	255 (120–1120)	10 (515)
CSF lymphocytes (%)†	0 (0–45)	26 (13–46)	10 (2–23)	81 (68–95)	30 (8–38)	0 (0–0)
CSF polymorphs (%)†	1 (0–54)	60 (36–77)	90 (72–97)	18 (5–32)	70 (62–92)	0 (0–0)
Peripheral blood WBC ($\times 10^9$ cells)	4.45 (3.3–6.5)	5.75 (3.65–8.65)	9.6 (4.9–14)	8.35 (4.6–11.2)	13.15 (11.1–15.2)	5.1 (4–7.1)
Hemoglobin (g/dl)‡	10.4 (2.2)	9.9 (2.7)	10.0 (2.0)	13.2 (1.1)	10.7 (1.9)	10.2 (2.9)

CSF, cerebrospinal fluid; WBC, white blood count.
*Percentage.
†Median and interquartile range.
‡Mean and standard deviation.

Table 3 Summary statistics and univariate comparisons of the features of CM and TBM in HIV positive patients

	Cryptococcal	Tuberculous	*P* value
Clinical features			
Glasgow coma score (/15)*	15 (14–15)	12.5 (8–15)	0.0001
Headache duration (days)*	7 (3–14)	7 (3–14)	0.33
Fever duration (days)*	7 (3–14)	7 (4–14)	0.55
Temperature (°C)†	37.2 (1.0)	39.8 (13.3)	0.06
Neck stiffness (%)‡	54.6	78.3	0.007
Laboratory investigations			
CD4 count ($\times 10^6$ cells)*	56.6 (25–97)	60 (33–30)	0.14
Haemoglobin (g/dl)†	10.4 (2.1)	9.9 (2.7)	0.28
Opening pressure (mm H_2O)*	270 (160–340)	200 (145–275)	0.03
Peripheral WBC ($\times 10^9$ cells)*	4.4 (3.3–6.5)	5.8 (3.7–8.7)	0.03
CSF investigations			
CSF WBC (cells/μl)*	0 (0–18)	45 (0–280)	0.0001
% CSF lymphocytes*	0 (0–47)	11 (0–25)	0.13
% CSF polymorphs*	2 (0–53)	60 (40–80)	0.0001

CM, cryptococcal meningitis; TBM, tuberculous meningitis.
*Median and interquartile range.
†Mean and standard deviation.
‡Percentage.

Table 4 Multivariable logistic regression model to discriminate between CM and TBM

	β Coefficient	Odds ratio (95% confidence interval) for diagnosis of TBM	*P* value
Opening pressure (mm H_2O)	−0.007	0.993 (0.988, 0.998)	0.009
Neck stiffness (%)	1.60	3.11 (1.13, 8.56)	0.008
CSF WBC (cells/μl)	0.002	1.0024 (1.00021, 1.0047)	0.032
Glasgow coma score (/15)	−0.25	0.78 (0.67, 0.91)	0.002
Temperature (°C)	3.34	28.01 (3.1, 251.69)	0.003

CM, cryptococcal meningitis; TBM, tuberculous meningitis.

The positive predictive and negative predictive values were 60% and 90% (Figure 2).

A classification and regression tree model was derived utilising the following variables and cut-off points: CSF white blood cell count (more or less than 13 cells/μl), neck stiffness (presence or absence) and CSF opening pressure (more or less than 310 mm H_2O) (Figure 3). This model had 92% sensitivity for the diagnosis of CM, but only 58% specificity. The positive and negative predictive values for CM were 86% and 72%, respectively, for the population sampled.

Discussion

Cryptococcal meningitis was the most common microbiological diagnosis in this large cohort of adults with meningitis in Malawi, accounting for 43% of all meningitis. This result is in keeping with previous studies from the region and reflects the high prevalence of HIV in this group (McCarthy *et al.* 2006; Bisson *et al.* 2008). Mycobacterial culture of adult CSF samples had not previously been performed in Malawi. Our finding that TBM accounts for 18% of all cases of meningitis is consistent with other reports from similar settings in Sub-Saharan Africa which report rates of 12–36% among adult patients with meningitis (Schutte *et al.*; Bergemann & Karstaedt 1996; Hakim *et al.* 2000).

Despite extensive investigation, 29% of patients with elevated CSF white blood cell counts still had no microbiologically confirmed meningitis diagnosis. This may be in part due to insensitivity of laboratory tests, but it may also suggest that alternative diagnoses such as viral infections or malignancies play a role in central nervous system pathology in this group of patients. There are no prevalence data for these conditions in sub-Saharan Africa; this is an area which requires further investigation.

A total of 15 patients with meningitis were taking anti-tuberculous treatment (ATT) at the time of recruitment to the study. History of TB and current ATT were both more

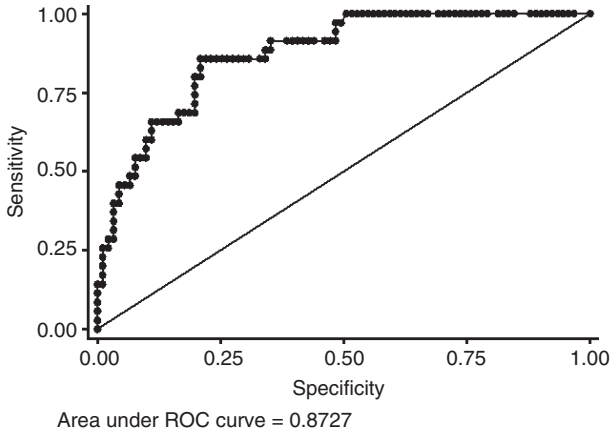

Figure 2 Covariate adjusted ROC curve using multiple logistic regression for HIV positive patients with cryptococcal or tuberculous meningitis.

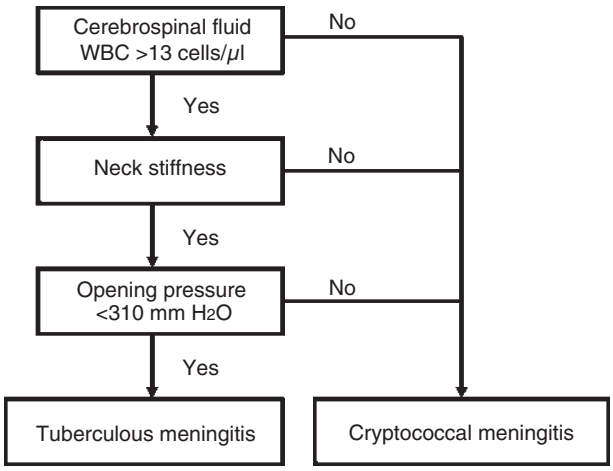

Figure 3 Classification tree for the diagnosis of cryptococcal and tuberculous meningitis.

common in patients with CM than patients with TBM. Current chemotherapy may have affected our ability to culture mycobacteria. Of the two patients who were diagnosed with TBM whilst on ATT, one had been started on treatment only 7 days prior to recruitment. The other had been on treatment for 2 months and so this may represent treatment failure, but unfortunately, sensitivity testing was not available.

We found features significantly associated with CM and TBM using multiple regression modelling. The features use information which would be available in health care facilities with even the most basic of resources: CM is associated with the presence of high CSF opening pressure and low CSF white blood cell count. TB meningitis is associated with the presence of fever, neck stiffness and reduced Glasgow Coma Score. Using this analysis in conjunction with a CART model, a diagnostic index using clinical and basic laboratory tests could not be derived which was both sensitive and specific for diagnoses of CM and TBM. Although we identified clear differences between the presentation of CM and TBM, these were not robust enough to construct a clinical decision rule which would allow clinicians to confidently treat only one condition.

Although this is a large prospective cohort, we recognise the limitations of our study, such as small numbers in some diagnostic groups. In particular, the low specificity of the CART analysis is likely to be due to the small sample size (48) of patients with TBM. Due to practical constraints, the study team was not able to recruit patients to the study outside of normal working hours, and those who presented outside these hours were recruited the following day. This meant that the decision to perform lumbar puncture was made by the admitting medical officer. Although this may have affected the selection of patients, all patients were assessed for eligibility by a member of the study team prior to recruitment. The short delay in recruiting may also have been a potential source of bias as a small number of patients died or absconded prior to recruitment.

Although every effort was made to obtain quantitative protein and glucose measurements from CSF samples, these tests were not available consistently throughout the study due to technical difficulties with laboratory equipment, which meant that analysis could not be performed for these variables. Routine assessment of CSF biochemistry in Malawi depends on 'dipstix' testing of samples (Molyneux *et al.*), which is not a widely accepted tool. Although accurate measurement of CSF protein and glucose levels is essential to the investigation of patients with meningitis in well-resourced facilities, the difficulty in sustainably sourcing tests even in a study setting demonstrates that these tests are not easily available in Malawi. It would therefore not be helpful to include CSF protein and glucose measurements in a diagnostic pathway for use in government hospitals in Malawi, even if this information had been available for the period of the study.

In western settings, diagnosis of chronic meningitis depends heavily on confirmatory microbiological techniques that are not accessible in most African situations. Whilst cryptococcal antigen testing and fungal culture of CSF play a crucial role where available, diagnosis in many African countries relies solely on the use of India ink stain of CSF samples. Although it may provide a rapid diagnosis of CM, this technique has variable sensitivity and is highly operator dependent (McGinnis 1983; Sato *et al.* 1998). Microbiological diagnosis of TBM is notoriously difficult

even where culture and molecular amplification techniques are available (Pai *et al.* 2003; Thwaites *et al.* 2004; Thwaites & Tran 2005); as these are not accessible in most facilities in sub-Saharan Africa, diagnosis remains largely based on clinical suspicion.

The difficulty in distinguishing CM and TBM can result in adverse outcomes for patients. Diagnostic inaccuracy may lead to inadequate or delayed treatment, which is associated with increased mortality (Sheu *et al.* 2009). Lack of confirmatory tests can mean overtreatment for some patients because clinicians feel the need to prescribe empiric treatment for both CM and TBM for those who have undifferentiated lymphocytic meningitis (Moreira *et al.* 2008). This is particularly problematic where both antifungal and antituberculous therapies are prescribed. Drug interactions put patients at risk of both increased drug toxicity and reduced drug levels and therefore the potential for developing antimicrobial resistance (Bicanic *et al.* 2006). In countries where nevirapine constitutes part of the first-line antiretroviral therapy regime, starting patients on fluconazole and/or rifampicin also has implications for HIV treatment and so needs careful consideration (McIlleron *et al.* 2007; Manosuthi *et al.* 2009).

Thwaites *et al.* (2002) have produced a successful algorithm for the assessment of TBM and bacterial meningitis, whilst other authors have found the performance of predictive rules to distinguish bacterial and viral meningitis less helpful (Chavanet *et al.* 2007). More recently, Trachtenberg *et al.* (2007) have produced an algorithm for the management of patients with meningitis in Uganda in order to improve the time to diagnosis of CM. Although useful, this study analysed an even smaller number of patients, notably only four with TBM. Our difficulty in deriving a predictive tool may be due to the fact that the two conditions which we attempted to differentiate do present with very similar features.

Accurate diagnosis and prompt treatment of meningitis in African hospitals remains a challenge. We attempted to produce a simple diagnostic rule using only clinical features and basic laboratory tests that are available in most health care facilities in Malawi. Although differences in the presentation of chronic meningitis were identified, it seems increasingly likely that accurate diagnosis of lymphocytic meningitis in resource-limited African hospitals will only be achieved by improved access to better laboratory investigations.

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