3

A 26-Year-Old Woman from Malawi with Headache, Confusion and Unilateral Ptosis

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Clinical Presentation

History

A 26-year-old Malawian woman is brought to the emergency department of a local central hospital by two relatives. She has been unwell for at least 1 week. She complained of a headache of insidious onset and has been confused for 2 days. One day before presentation the relatives ('guardians') noticed an eyelid drooping on the left side.

The guardians say her past medical history is unremarkable. The patient lives in an urban high-density area. She works as a businesswoman, selling vegetables. She has three healthy children, but another four of her children have died as toddlers. Her husband died a year ago of 'high fever.'

Clinical Findings

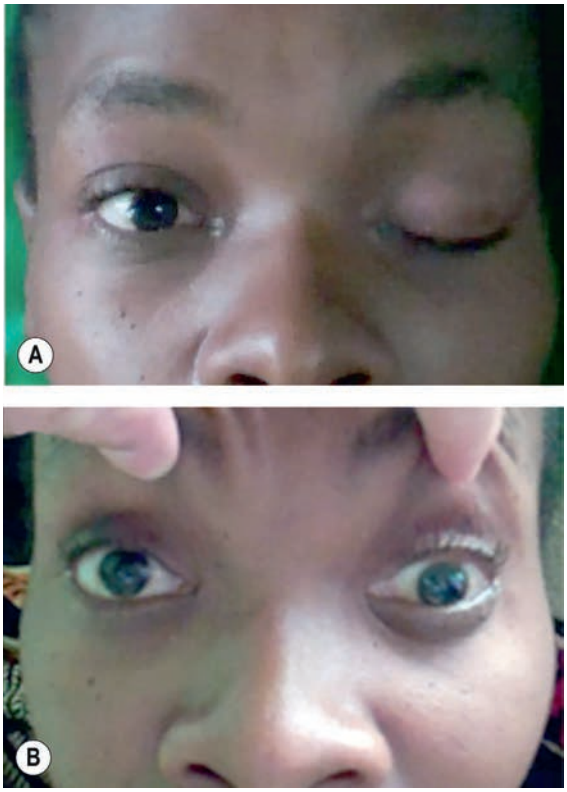
On examination she looks seriously unwell. Glasgow Coma Scale 14/15, temperature 38.4°C (101.1°F), blood pressure 115/75 mmHg, heart rate 86 bpm, respiratory rate 18 breath cycles per minute. There is no neck stiffness. The chest is clear. Figure 3.1 shows the examination of her eyes. The remainder of her neurological examination is normal.

Laboratory Results

Her blood results are shown in Table 3.1. A lumbar puncture is done. The opening pressure is markedly raised, at 32 cmH_2O (12–20 cmH_2O). The available CSF results are shown in Table 3.2.

Questions

1. What is the clinical syndrome and what is the differential diagnosis?
2. How would you manage this patient?



• **Fig. 3.1** (A) There is complete ptosis on the left. (B) On primary gaze, the left eye is in a 'down and out' position.

Discussion

A young Malawian widow presents with headache and confusion. She is febrile and has a unilateral third nerve palsy. The CSF examination reveals an inflammatory picture with low glucose.

TABLE 3.1 Blood Results on Admission

Parameter	Patient	Reference
WBC ($\times 10^9$/L)	3.2	4–10
Hb (g/dL)	10.2	12–14
Platelets ($\times 10^9$/L)	155	150–350
Serum glucose (mmol/L)	4.0	3.9–11.1
Thick film for malaria and trypanosomes	Negative	Negative

TABLE 3.2 CSF Results on Admission

Parameter	Patient	Reference
White cell count (/μL)	54	0–5
CSF protein (g/L)	3.0	0.25–0.55
CSF glucose (mmol/L)	1.3	2.0–2.64*

*½ to ⅔ of paired serum glucose sample.

Answer to Question 1

What Is the Clinical Syndrome and What Is the Differential Diagnosis?

The clinical syndrome is that of infectious meningitis. Infectious encephalitis should also be considered; however, the cranial nerve involvement makes this diagnosis less likely. Moreover, the main causes of infectious encephalitis are viral or – less commonly – protozoan (e.g. cerebral toxoplasmosis, human African trypanosomiasis), and the CSF findings of very high protein and very low glucose are not consistent with a viral or protozoan CNS infection. Cerebral malaria has to be considered in any patient with fever and impaired consciousness living in a malarious area. However, cerebral malaria would be an uncommonly severe manifestation in a most probably semi-immune adult residing in a holoendemic area. In addition, cranial nerve palsies are an unusual feature of cerebral malaria.

The differential diagnosis comprises bacterial, tuberculous and cryptococcal meningitis (Table 3.3). Neither the patient's clinical presentation nor her CSF results can help differentiate reliably between the three. Furthermore, onset, acuteness and duration of symptoms and signs may have to be interpreted with caution in many cultures, particularly when the history cannot be taken from the patients themselves.

Answer to Question 2

How Would You Manage This Patient?

The patient has a suspected CNS infection and is seriously ill with confusion, cranial nerve palsy and a high fever. Immediate action should be taken, and treatment should not be delayed whilst further test results are being awaited. Pragmatic treatment should cover bacterial, cryptococcal and tuberculous meningitis.

Gram-stain and bacterial culture should be done from the CSF. If available, an ultrasensitive PCR for *M. tuberculosis* (e.g. Xpert MTB/RIF Ultra) should be ordered. The sensitivity of Ziehl–Neelsen stain from the CSF is low in many settings. Cryptococcal antigen (CrAG) testing should be done from CSF and serum; additionally, India ink stain and fungal culture should be done for detection of *Cryptococcus neoformans.*

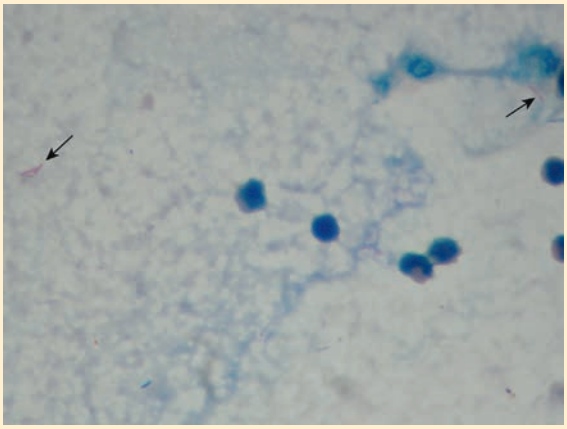
An HIV-serology study is crucial because cryptococcal meningitis is associated with immunosuppression. Tuberculous meningitis is also more common in HIV-positive than in uninfected persons.

The Case Continued. . .

The patient was started on ceftriaxone 2 g bid, fluconazole 1200 mg od (local protocol for cryptococcal meningitis in the absence of amphotericin B and flucytosin) and on treatment for presumptive TB-meningitis.

TABLE 3.3 Clinical and CSF Features of Acute Bacterial, Tuberculous and Cryptococcal Meningitis

	Bacterial Pathogen	Clinical Features	CSF Features
Acute Bacterial Meningitis	*Streptococcus pneumoniae, Neisseria meningitidis, Streptococcus suis* (Asia)	Often very rapid onset with high fever and meningism, cranial nerve involvement less common	Often cloudy, high leukocyte cell count, predominance of polymorphs, low glucose
Tuberculous Meningitis	*Mycobacterium tuberculosis*	Often a history of several days of illness, onset less abrupt, cranial nerve involvement common	Often clear, high CSF protein, low CSF glucose
Cryptococcal Meningitis	*Cryptococcus neoformans*	Often subacute onset, severe headache common, cranial nerve involvement common	CSF can be normal in at least 25% of cases



• **Fig. 3.2** Ziehl–Neelsen stain of CSF sample showing acid-fast bacilli *(arrows).* (Courtesy Prof. Jeremy Day).

The HIV test came back reactive. India Ink stain, cryptococcal and bacterial culture were reported negative, but acid-fast bacilli were detected in the CSF (Fig. 3.2).

TABLE 3.4 The Four Pillars of Clinical Diagnosis of Tuberculous Meningitis

Clinical Criteria	Symptom duration >5 days Systemic symptoms suggestive of tuberculosis (one or more of the following): weight loss (or poor weight gain in children), night sweats, or persistent cough for more than 2 weeks History of close contact with an individual with pulmonary tuberculosis or a positive tuberculin skin test within the past year Focal neurological deficit Cranial nerve palsy Altered consciousness
CSF Criteria	Clear appearance Leukocytes: 10–500/μL Lymphocytic predominance (>50%) Protein concentration >1 g/L CSF to plasma-glucose ratio <50% or absolute CSF glucose concentration <2.2 mmol/L
Neuroimaging Criteria	Hydrocephalus Basal meningeal enhancement Tuberculoma Infarct Pre-contrast basal hyperdensity
Evidence of TB Elsewhere	Chest radiography suggestive of active TB Evidence for TB outside the CNS on CT, MRI or ultrasound AFB identified or *M. tuberculosis* cultured from another source (sputum, lymph node, gastric washing, urine, blood culture) Positive commercial *M. tuberculosis*-PCR from extraneural specimen

Footnote: Marais, S., Thwaites, G., Schoeman, J.F., et al., 2010. Tuberculous meningitis: a uniform case definition for use in clinical research. Lancet Infect Dis. 10, 803–812.

The diagnosis of tuberculous meningitis was established. A few days into treatment the patient slipped into a coma. An MRI scan of her brain revealed bilateral basal ganglia infarctions. She died in the hospital.

SUMMARY BOX

Tuberculous Meningitis

Tuberculous (TB) meningitis is the most dramatic form of tuberculosis. After the release of bacilli and granulomatous material into the subarachnoid space, a florid gelatinous exudate forms, which may impair CSF circulation and cause hydrocephalus, cranial nerve palsies and vasculitis. Vasculitis is the most serious complication of tuberculous meningitis and may lead to cerebrovascular accidents.

A definitive diagnosis of TB-meningitis is established when acid-fast bacilli are seen in the CSF or detected by a reliable molecular method such as PCR, or if *Mycobacterium tuberculosis* is cultured from the CSF. It is crucial to maintain a high index of suspicion in settings with high TB prevalence (Table 3.4). The WHO now recommends the use of Xpert MTB/RIF Ultra as the initial diagnostic test for suspected tuberculous meningitis. The Xpert is a cartridge-based fully automated PCR test that can easily be used, even in resource-limited settings.

TB-meningitis is an emergency. Treatment should be started without delay once the diagnosis is considered. The WHO recommends treatment with the same regimen as any form of tuberculosis starting with isoniazid, rifampicin, ethambutol and pyrazinamide. Usually, treatment is for 9 to 12 months. Corticosteroids seem to improve clinical outcomes and are currently recommended; however, their effects may vary in different clinical settings.

Further Reading

1. Thwaites G. Tuberculosis. In: Farrar J, editor. Manson's Tropical Diseases. 23rd ed. London: Elsevier; 2014 [chapter 40].
2. Bahr NC, Nuwagira E, Evans EE, et al. Diagnostic accuracy of Xpert MTB/RIF Ultra for tuberculous meningitis in HIV-infected adults: a prospective cohort study. Lancet Infect Dis 2018;18:68–75.
3. Marais S, Thwaites G, Schoeman JF, et al. Tuberculous meningitis: a uniform case definition for use in clinical research. Lancet Infect Dis 2010;10:803–12.
4. Thwaites G. Advances in the diagnosis and treatment of tuberculous meningitis. Curr Opin Neurol 2013;26:295–300.
5. Davis A, Mentjes G, Wilkinson RJ. Treatment of Tuberculous Meningitis and Its Complications in Adults. Curr Treat Options Neurol 2018;20:5–15.