CASE REPORT

GeneXpert MTB/RIF assay as initial test for diagnosis of tuberculous meningitis

Poojan Shrestha,¹ Buddhi Paudyal,² Buddha Basnyat³¹Clinical Research Unit, Oxford University, Patan Hospital, Kathmandu, Nepal²Department of Internal Medicine, Patan Academy of Health Sciences, Kathmandu, Nepal³Clinical Research Unit, Oxford University, Kathmandu, Nepal**Correspondence to**

Professor Buddha Basnyat, buddhabasnyat@gmail.com

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SUMMARY

Tuberculous meningitis (TBM) remains the most dangerous form of tuberculosis with high mortality and potential complications. The prompt diagnosis and treatment of this condition remains a key for better prognosis. A 39-year-old woman presented with severe headache, fever, nausea and vomiting, with a history of headache for a month. On examination, confusion, neck rigidity, ptosis and upward plantar reflexes were present. After 7 days of empiric treatment without resolution of her symptoms, she had another spinal tap performed. The diagnosis of TBM was performed by the GeneXpert MTB/RIF assay from her cerebrospinal fluid (CSF). Antitubercular chemotherapy was started. The patient subsequently improved. Where available, the GeneXpert assay should be used immediately in CSF samples of patients suspected of TBM as an adjunct to clinical algorithms to increase the chance of a prompt diagnosis and treatment.

BACKGROUND

There are 0.8 million patients diagnosed with extrapulmonary tuberculosis (TB) all over the world,¹ with the most dangerous form being tuberculous meningitis (TBM). It kills almost a third of patients presenting to the hospital and many are left with debilitating neurological consequences.²⁻³ It is difficult to diagnose and effectively treat this disease, and, unfortunately, a delay in treatment leads to a poorer outcome.⁴⁻⁵ A prompt microbiological diagnosis of TBM is hard to make because the Ziehl-Neelsen (ZN) smear of cerebrospinal fluid (CSF) has low sensitivity and the time taken by CSF culture is not practical for starting treatment. Rapid diagnostic tests giving a confirmatory diagnosis would aid in starting the treatment promptly and thus improving the outcome of patients when used in conjunction with clinical algorithms. Hence, the usage of the GeneXpert MTB/RIF assay (hereafter referred to as Xpert), approved by the WHO, may be a game changer in the prompt diagnosis and treatment of TBM.

CASE PRESENTATION

In late October 2013, a 39-year-old woman presented to the emergency department of Patan Hospital, Nepal, with severe headache, fever, nausea and vomiting for 6 days. She had visited the psychiatry outpatient clinic 2 days earlier for sudden onset of hearing loss and uncontrolled laughter. She had also visited the hospital with a complaint of headache a month ago, for which she was treated with paracetamol. She worked in the

kitchen of a general hospital with limited direct contact with patients.

On examination, mental confusion, neck rigidity, ptosis of the left eye and bilateral up going plantar reflexes were noted. Her cardiovascular and pulmonary examination was normal. There was no history of TB in the patient or her family members and close contacts. No abnormalities were detected on fundoscopic examination. No previous testing for TB had been carried out for the patient.

INVESTIGATIONS

A CT scan prior to a lumbar puncture (LP) revealed only a calcific granuloma in the left frontal lobe and no other abnormalities. The initial LP showed red cell count 20/mm³, white cell count 195/mm³, neutrophils 8%, lymphocytes 92%, protein 162 mg% and glucose 46 mg% blood sugar 117 mg%). The ZN staining of the LPs did not show any acid fast bacilli on either. No abnormalities were detected on the chest X-ray (figure 1). The other laboratory tests were normal and the patient was HIV negative.

Owing to persistence of symptoms, a repeat LP was performed on the seventh day, revealing similar CSF findings (lymphocytic pleocytosis and high protein) as the first time. This time, the diagnosis of TBM was considered and CSF was tested with

Figure 1 Chest X-ray showing no abnormalities at the initial presentation.

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the Xpert for *Mycobacterium tuberculosis*. *M. tuberculosis* was detected (figure 2) in the CSF, which was not resistant to rifampicin. Solid culture of the CSF after 6 weeks grew out *M. tuberculosis* susceptible to first line drugs.

DIFFERENTIAL DIAGNOSIS

The CSF picture along with the longer duration of symptoms helped narrow the diagnosis of meningitis in our setting. Besides TBM, the other differential diagnoses were cryptococcal meningitis, herpes encephalitis and rabies, in an endemic setting such as ours. Our patient was immunocompetent and the rarity of this cause in our setup put the diagnosis lower in the list.⁶ Herpetic encephalitis was considered but there were no characteristic changes in the temporal lobe in the initial CT scan, and we also did not have facilities to check for the virus in CSF. The absence of a history of dog bite ruled out rabies in this adult patient.

TREATMENT

Initially, the patient was started on ceftriaxone and vancomycin along with dexamethasone intravenously as empiric treatment for meningitis. However, the symptoms of headache and nausea did not subside, and thus the LP was repeated and this time tested for *M. tuberculosis* by the Xpert. After the Xpert detected *M. tuberculosis* in the sample, category 1 antituberculosis treatment along with 8 mg dexamethasone thrice daily was started immediately.

OUTCOME AND FOLLOW-UP

On the eighth day of admission, the patient had an episode of seizure followed by a period of confusion with the development of weakness involving the right half of her body. The MRI of the head revealed infarction in the left basal ganglia. Hyperintensity was also noted in the right temporofrontoparietal lobe (figure 3). However, she did gradually improve with regain of mental and motor function of the extremities. When last seen in June 2014, she was recovering, in a wheel chair and undergoing physiotherapy.

DISCUSSION

TBM is the deadliest form of TB. As in our patient, there may be unhelpful varied symptoms⁷ such as hearing loss and uncontrolled laughter. The neurological signs of TBM are non-specific, making it more confusing and thus delaying the

Figure 3 MRI showing high signal intensity area in posteromedial aspect of the left basal ganglia partly involving posterior limb of internal capsule. Patchy and confluent hyperintensity in right temporofrontoparietal lobe involving cortex and subcortical white matter.

decision to administer prompt antitubercular chemotherapy. The patient probably had a third nerve palsy to explain the ptosis and the seizures and right-sided hemiparesis were probably due to the infarction noted in the left basal ganglia area. The uncontrolled laughter could be due to a seizure, but TBM also presents in non-specific fashion.⁸ The delay in initiating the treatment may well have led to further complications.

A prompt microbiological diagnosis of TBM is hard to make with the ZN smear, as the sensitivity is generally low, ranging from 10% to 60%.² Although sensitivity has been shown to improve with meticulous examination of large volumes, this is very time consuming and impractical in a busy general public hospital.^{9 10} TB cultures too are less sensitive and where available take 6–8 weeks to grow.¹¹

A recent, rapid and specific test for the detection of *M. tuberculosis* through CSF has been the GeneXpert MTB/RIF assay, which is a fully automated real time PCR. It requires no special skills or laboratory and detects *M. tuberculosis* and rifampicin resistance in 2 h. According to a recent review, the pooled sensitivity and specificity of the Xpert was 80.5% (95% CI 59.0 to 92.2%) and 97.8% (95% CI 95.2 to 99.0%), respectively, against culture. Also, the pooled sensitivity and specificity relative to a composite reference standard was found to be 62.8% (95% CI 47.7 to 75.8%) and 98.8 (95% CI 95.7 to 100%), respectively.¹² This shows that it can be used effectively to rule-in TBM.^{13 14} Physicians should, however, be aware that a negative result does not rule-out the diagnosis of TBM, and need to give emphasis to the clinical picture.

In our patient, a confirmatory diagnosis of TBM was finally performed with the help of the Xpert, and suitable treatment was carried out immediately. Had the Xpert come into use earlier in the diagnostic chain, there might have been a possibility of averting some of these complications.

The use of adjunctive corticosteroids has shown to reduce death and disability for TBM in previous trials, although the mechanism remains unclear.¹⁵ We used dexamethasone in our patient, which has been found to improve the survival in patients >14 years of age diagnosed with TBM.¹⁶ The use of rapid diagnostics to assist in getting prompt results could help in

Figure 2 The GeneXpert MTB/RIF machine with the report of detection of *Mycobacterium tuberculosis* in the cerebrospinal fluid sample.

reducing the morbidity associated with delay in starting the treatment, although this will certainly not replace an accurate history and physical examination. In a relatively low HIV setting such as South Asia, where the greatest numbers of patients with TB in the world reside, this diagnostic tool could actually be a 'game changer' in improving the diagnosis of TBM, if used appropriately and efficiently, in addition to the clinical criteria.^{17 18} Furthermore, it has huge implications in diagnosing multidrug resistant TBM rapidly, given the 100% mortality in this group without institution of the second-line treatment.¹⁹

Furthermore, the WHO has strongly recommended the use of the Xpert as an initial diagnostic test for CSF specimens in patients suspected of having TBM.²⁰ Perhaps, with the recent WHO Xpert 'roll-out' programme in highly endemic regions, it may be prudent to consider using the Xpert as a first line diagnostic in conjunction with the clinical algorithms, where services permit.

Learning points

- ▶ Tuberculous meningitis (TBM) is a devastating form of tuberculosis with high rates of mortality and long-term neurological consequences.
- ▶ Although prompt diagnosis and treatment means better prognosis, the lack of sensitive and rapid tests have so far made diagnosis difficult, leading to delay in making decisions regarding treatment with antituberculosis drugs.
- ▶ The Xpert MTB/RIF assay could be used as a 'rule-in' test for TBM in conjunction with other clinical data to have a definite diagnosis and institute treatment early.
- ▶ Physicians should bear in mind that the Xpert MTB/RIF cannot be used to rule-out a diagnosis of TBM.

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Competing interests None declared.

Patient consent Obtained.

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