Diagnostic accuracy of Xpert MTB/RIF Ultra for tuberculous meningitis in HIV-infected adults: a prospective cohort study

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Summary

Background WHO recommends Xpert MTB/RIF as initial diagnostic testing for tuberculous meningitis. However, diagnosis remains difficult, with Xpert sensitivity of about 50–70% and culture sensitivity of about 60%. We evaluated the diagnostic performance of the new Xpert MTB/RIF Ultra (Xpert Ultra) for tuberculous meningitis.

Methods We prospectively obtained diagnostic cerebrospinal fluid (CSF) specimens during screening for a trial on the treatment of HIV-associated cryptococcal meningitis in Mbarara, Uganda. HIV-infected adults with suspected meningitis (eg, headache, nuchal rigidity, altered mental status) were screened consecutively at Mbarara Regional Referral Hospital. We centrifuged CSF, resuspended the pellet in 2 mL of CSF, and tested 0·5 mL with mycobacteria growth indicator tube culture, 1 mL with Xpert, and cryopreserved 0·5 mL, later tested with Xpert Ultra. We assessed diagnostic performance against uniform clinical case definition or a composite reference standard of any positive CSF tuberculous test.

Findings From Feb 27, 2015, to Nov 7, 2016, we prospectively evaluated 129 HIV-infected adults with suspected meningitis for tuberculosis. 23 participants were classified as probable or definite tuberculous meningitis by uniform case definition, excluding Xpert Ultra results. Xpert Ultra sensitivity was 70% (95% CI 47–87; 16 of 23 cases) for probable or definite tuberculous meningitis compared with 43% (23–66; 10/23) for Xpert and 43% (23–66; 10/23) for culture. With composite standard, we detected tuberculous meningitis in 22 (17%) of 129 participants. Xpert Ultra had 95% sensitivity (95% CI 77–99; 21 of 22 cases) for tuberculous meningitis, which was higher than either Xpert (45% [24–68]; 10/22; p=0·0010) or culture (45% [24–68]; 10/22; p=0·0034). Of 21 participants positive by Xpert Ultra, 13 were positive by culture, Xpert, or both, and eight were only positive by Xpert Ultra. Of those eight, three were categorised as probable tuberculous meningitis, three as possible tuberculous meningitis, and two as not tuberculous meningitis. Testing 6 mL or more of CSF was associated with more frequent detection of tuberculosis than with less than 6 mL (26% *vs* 7%; p=0·014).

Interpretation Xpert Ultra detected significantly more tuberculous meningitis than did either Xpert or culture. WHO now recommends the use of Xpert Ultra as the initial diagnostic test for suspected tuberculous meningitis.

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Introduction

Tuberculous meningitis is the second most common cause of adult meningitis in Africa.[1–4] Meningitis from tuberculosis leads to fatality in more than 50% of cases, in large part due to difficulty and delay in diagnosis.[5] Cerebrospinal fluid (CSF) smear microscopy for acid-fast bacilli has poor sensitivity (≤15%) in routine care.[5] Although mycobacterial culture has higher sensitivity (50–60%), culture is too slow to be clinically useful.[5]

In 2013, WHO endorsed the Xpert MTB/RIF assay (Cepheid, Sunnyvale, CA, USA) as the preferred initial test to investigate tuberculous meningitis after a systematic review of 13 studies.[6–8] The Xpert is cartridge-based fully-automated PCR test. Of three large cohorts, the first reported 67% sensitivity using Xpert in microbiologically proven tuberculous meningitis in HIV-infected South Africans.[9] This study initially tested 1 mL of CSF but later found higher sensitivity (82%; 22 of 27 positive cases) when centrifuging 3 mL of CSF.[9] Sensitivity compared with consensus clinical case definition was only 36%.[9,10] The second large cohort study, in Vietnam, measured Xpert against the same clinical case definition and found 59% sensitivity generally using 2 mL or less of centrifuged CSF.[11,12] A third Ugandan study reported 28% sensitivity with 2 mL of uncentrifuged CSF and 72% sensitivity when centrifuging a median volume of 6 mL (IQR 4–10) with Xpert.[12] Thus, the imperfect sensitivity has meant no test can exclude tuberculous meningitis.[13,14]

The Xpert MTB/RIF Ultra (Xpert Ultra) is a new, fully automated, nested real-time PCR assay for the GeneXpert

Research in context

Evidence before this study

The Xpert MTB/RIF (Xpert) Ultra is a new assay without prior publications. We searched PubMed with the terms ((tuberculous meningitis) or TB meningitis) AND (Xpert MTB/RIF Ultra) for articles published in English up to June 19, 2017, which yielded no results. We also searched Google Scholar for articles related to Xpert Ultra, which yielded one conference abstract, which had been cited by 13 publications relating to the future of tuberculosis diagnostics but without including any data on Xpert Ultra. When we searched PubMed with the terms (Tuberculous meningitis) or TB meningitis) AND (Xpert MTB/RIF), we found and reviewed 21 publications. These publications reported imperfect sensitivity of cerebrospinal fluid Xpert, ranging from 50% to 72% against cerebrospinal fluid *Mycobacterium tuberculosis* culture. A meta-analysis reported that Xpert has a pooled sensitivity of 80·5% against culture and 62·8% against a clinical reference standard. Three opinion pieces point out that with imperfect sensitivity, the Xpert assay cannot be used as a rule-out test for tuberculous meningitis and an assay with improved diagnostic performance is urgently needed.

Added value of this study

To our knowledge, we present the first evaluation of the diagnostic performance of Xpert Ultra in the diagnosis of tuberculous meningitis. Xpert Ultra has been re-engineered to improve diagnostic performance with a lower analytic limit of detection, comparable to mycobacterial culture. We assessed diagnostic performance in two ways. First, against any positive cerebrospinal fluid tuberculosis test being defined as definite tuberculosis, and second, against a consensus clinical case definition not including the Xpert Ultra result. Xpert Ultra had higher sensitivity of 95% than either Xpert (45%) or culture (45%) for definite tuberculous meningitis. Based on the consensus clinical case definition, Xpert Ultra found 70% sensitivity for probable or definite tuberculous meningitis. Xpert or culture each had 43% sensitivity for probable or definite tuberculosis based on the clinical case definition (which excluded Xpert Ultra results).

Implications of all the available evidence

A diagnostic test exhibiting more than 90% sensitivity for tuberculous meningitis with results available in fewer than 90 min holds great potential to improve patient outcomes, particularly to detect those with the lowest bacillary load. The negative predictive value of 99% against definite tuberculous meningitis is a major step forward in tuberculous meningitis diagnostics. However, negative predictive value was only 93% against probable or definite tuberculous meningitis, and thus clinical judgment remains paramount. Xpert Ultra's combination of lower analytic limit of detection and ability to detect dead bacilli after starting tuberculosis therapy vastly improves sensitivity compared with either culture or Xpert. On the basis of our findings, we believe Xpert Ultra should be a first-line test for tuberculous meningitis after excluding cryptococcal infection. The assay must now be evaluated prospectively in a larger study including in HIV-negative individuals and children, and in which post-mortem evidence of tuberculosis can be included in a reference standard.

platform. The re-engineered Xpert Ultra has sought to improve the analytical sensitivity for *Mycobacterium tuberculosis* detection and to improve rifampin resistance detection.[15] We analysed the diagnostic performance of Xpert Ultra for detection of *M tuberculosis* in CSF as compared with Xpert or culture. We hypothesised that Xpert Ultra would have improved sensitivity. Preliminary results of Xpert Ultra performance were summarised in a WHO report in March, 2017.[16]

See Online for appendix

Methods

Study design and participants

We prospectively obtained diagnostic CSF specimens during screening for the Adjunctive Sertraline for the Treatment of HIV-associated Cryptococcal Meningitis trial (NCT01802385). HIV-infected adults with suspected meningitis (eg, headache, nuchal rigidity, altered mental status) were screened consecutively at Mbarara Regional Referral Hospital in Mbarara, Uganda. Clinical history, general examination, and detailed neurological findings were prospectively recorded, in agreement with the data considered important by Marais and colleagues[17] for tuberculous meningitis studies. Further investigations, including chest radiography, abdominal ultrasonography, and sputum Xpert MTB/RIF, were undertaken as clinically indicated. Brain imaging was unavailable. Processing of CSF samples is described in the appendix (p 7). Eligible participants were at least 18 years of age with suspected meningitis. All participants or their surrogates provided written informed consent, including for additional future diagnostic testing. Institutional review board approvals occurred.

Procedures

After lumbar puncture, physicians did cryptococcal antigen lateral flow assay (IMMY, Norman, OK, USA) testing at the bedside. All participants without cryptococcosis were then evaluated for tuberculous and bacterial meningitis; this stepwise diagnostic approach was a deliberate cost-efficient approach.[1] Participants with cryptococcal meningitis with concern of tuberculous meningitis co-infection were included at physician discretion.

The algorithm for CSF diagnostic testing is fully described in the appendix (p 7). After bedside testing, approximately 1 mL of CSF was removed for routine testing (eg, white cell count, protein, glucose, Gram stain, Ziehl-Neelsen stain), and we centrifuged the