Xpert MTB/RIF® assay for the diagnosis of HIV-related tuberculous meningitis in São Paulo, Brazil

Human immunodeficiency virus (HIV) associated tuberculous meningitis (TBM) remains a public health problem in resource-limited settings. Our group recently found high sensitivity (100% for 'definite TBM') and high specificity (100%) of a nested real-time polymerase chain reaction (RT-PCR) assay among HIV-infected patients.[1] Here we present our experience after the first year of using the Xpert MTB/RIF® assay (Cepheid, Sunnyvale, CA, USA). The objectives of this study were 1) to identify the sensitivity and specificity of the Xpert assay on cerebrospinal fluid (CSF) for TBM diagnosis, and 2) to estimate the prevalence of positive Xpert results in routine practice.

This retrospective observational study was conducted at the Instituto de Infectologia Emílio Ribas, São Paulo, SP State, Brazil. The inclusion criteria were: 1) HIV-infected adults (aged ⩾16 years) hospitalised with suspected meningitis, and 2) CSF samples with simultaneous analysis using acid-fast bacilli (AFB) smear, *Mycobacterium tuberculosis* culture and Xpert. The CSF volume typically used to perform the Xpert assay was 1–2 ml, and samples were not centrifuged.

Patients were categorised using a uniform TBM case definition, as follows: 1) 'definite TBM': the gold standard category, with positive AFB smear or CSF culture for *M. tuberculosis*; 2) 'probable TBM': those with a score of 7–12, indicating a higher risk of a TBM diagnosis; 3) 'possible TBM': those with a score of 6–11, indicating a lower risk of a TBM diagnosis; and 4) 'not TBM': those with a confirmed alternative diagnosis.[2] Xpert results were not included in assigning case status. 'Definite TBM' and 'not TBM' cases were used to determine the sensitivity and specificity of Xpert, respectively.

The Research Ethics Committee of the Instituto de Infectologia Emílio Ribas approved the protocol.

We analyzed CSF specimens from 101 participants collected over a 12-month period. Six (5.9%) CSF samples were positive for tuberculosis on at least one test. Two participants had positive AFB smears, five participants had positive cultures and three participants were positive on Xpert. Three participants only had positive CSF cultures. No cases had only positive Xpert assay or AFB smear. Xpert sensitivity for 'definite TBM' ($n = 6$) was 50% (95% confidence interval [CI] 12–88), and for the 'not TBM' category ($n = 86$) the specificity was 100% (95%CI 96–100). Xpert was not positive for any 'probable TBM' ($n = 7$) or 'possible TBM' ($n = 2$) cases. Only 3% (3/101) of the Xpert assays were positive.

We identified a sensitivity for Xpert of 50%, similar to the values described in other studies (28–55%) when low CSF volume without centrifugation was used.[3–5] When centrifugation was performed with[3,4,6] or without[7] higher CSF volumes, Xpert sensitivity was 72–82% and 55%, respectively. Specificity was usually ⩾95%,[3–5,7] with 'false positives' typically representing disease missed by the reference standard.

The low prevalence (3%) of positive Xpert results identified in this study is similar to that reported in a retrospective study in London (4.5% [33/740]).[7] These findings revealed the low pretest probability of disease using Xpert in routine practice, and highlight the need to implement algorithms to optimise the test request. This is particularly important in scenarios with limited resources where shortages are a constant concern. A better strategy would be to perform a second lumbar puncture where 6–10 ml CSF could be collected and centrifuged for Xpert testing.

In conclusion, we found that the Xpert assay had moderate sensitivity in the diagnosis of TBM diagnosis, but a very low prevalence of positive tests. The optimisation of laboratory procedures and implementation of clinical algorithms are key in the diagnosis of TBM.

Renata Guise Azevedo*
Fernanda Suyama Dinallo*
Laryssa Sanches de Laurentis*
David R. Boulware†
José Ernesto Vidal*‡§
*Instituto de Infectologia Emilio Ribas, São Paulo SP, Brazil
†University of Minnesota, Minneapolis MN, USA
‡Universidade de São Paulo, Faculdade de Medicina, Hospital das Clínicas
§Universidade de São Paulo, Instituto de Medicina Tropical
São Paulo
SP, Brazil
e-mail: josevibe@gmail.com
http://dx.doi.org/10.5588/ijtld.18.0191

Conflicts of interest: none declared.

References

1 Gualberto F A S, Gonçalves M G, Fukasawa L O, et al. Performance of nested RT-PCR on CSF for tuberculous meningitis diagnosis in HIV-infected patients. Int J Tuberc Lung Dis 2017; 21: 1139–1144.
2 Marais S, Thwaites G, Schoeman J F, et al. Tuberculous meningitis: a uniform case definition for use in clinical research. Lancet Infect Dis 2010; 11: 803–812.
3 Patel VB, Theron G, Lenders L, et al. Diagnostic accuracy of quantitative PCR (Xpert MTB/RIF) for tuberculous meningitis in a high-burden setting: a prospective study. PLoS Med 2013; 10: e1001536.
4 Bahr N C, Tugume L, Rajasingham R, et al. Improved diagnostic

sensitivity for tuberculous meningitis with Xpert® MTB/RIF of centrifuged CSF. Int J Tuberc Lung Dis 2015; 19: 1209–1215.
5 Rufai S B, Singh A, Singh J, et al. Diagnostic usefulness of Xpert MTB/RIF assay for detection of tuberculous meningitis using cerebrospinal fluid. J Infect 2017; 75: 125–131.
6 Nhu N T, Heemskerk D, Thu D D, et al. Evaluation of GeneXpert MTB/RIF for diagnosis of tuberculous meningitis. J Clin Microbiol 2014: 52: 226–233.
7 Pink F, Brown T J, Kranzer K, Drobniewski F. Evaluation of Xpert MTB/RIF for detection of *Mycobacterium tuberculosi*s in cerebrospinal fluid. J Clin Microbiol 2016; 54: 809–811.

ERRATA

IN THE CORRESPONDENCE entitled 'No evidence of *Mycobacterium tuberculosis* in breast milk of 18 women with confirmed TB disease in Kisumu, Kenya', by E. S. Click, G. Ouma, K. DeGruy, et al. (Int J Tuberc Lung Dis 2018; 22(4): 464–465, http://dx.doi.org/10.5588/ijtld.17.0375), the author list should have read as follows:

Eleanor S. Click*
Gregory S. Ouma †
Kyle DeGruy*
Wilfred Murithi†
July A. Okonji†
Kimberly D. McCarthy*
Susan Musau†
Albert Okumu†
Heather Alexander*
James Posey*
Kevin P. Cain ‡
**Centers for Disease Control and Prevention*
Atlanta, GA, USA
†*Kenya Medical Research Institute*
Kisumu
‡*Centers for Disease Control and Prevention*
Kisumu, Kenya
e-mail: eoc9@cdc.gov
[http://dx.doi.org/10.5588/ijtld.17.0375-e]