Diagnostic Accuracy of GeneXpert MTB/RIF assay for Tuberculous Meningitis keeping CSF culture as gold standard

Nauman Idrees[1], Rabeeka Bakhtiar[2], Kashif Kamal[2], Fawad Rahim[1], Muhammad Asif Khan[3], Raza Ullah[3]

ABSTRACT

Background: Tuberculous meningitis (TBM) is a very severe type of tuberculosis with high mortality and severe complications. The early diagnosis and management has a great role in better outcome and prognosis. Pakistan is ranked 5th in the world in 2010 with a prevalence of 364/100000. Tuberculous Meningitis with Mycobacterium tuberculosis as a causative agent is a leading cause of morbidity and mortality globally . This study has been carried out to evaluate GeneXpert MTB/RIF assay diagnostic accuracy on CSF for Tuberculous meningitis keeping CSF AFB culture as gold standard.

Methods: This cross sectional study has been conducted at a tertiary care hospital Hayatabad Medical Complex Peshawar. A total number of 125 patients were included in this study.

Results: Out of 125 patients 56% were male and 44% patients were female. Mean age was 43±1.26 years. Sensitivity was 91%, Specificity was 82%, Positive predictive value was 90%, Negative predictive value was 84% and the overall accuracy was 88%,taking CSF culture as gold standard.

Conclusion: Compared with culture-based methods of CSF testing, GeneXpert in CSF is a reliable, rapid and affordable test for the diagnosis of TBM cases based on its sensitivity and specificity.

Key words: GeneXpert MTB/RIF, Tuberculous meningitis, CSF

INTRODUCTION

Mycobacterium tuberculosis is a leading cause of morbidity and mortality around the globe. Killing 2-3 million people every year. 1 More than 90% of these deaths occur in the developing world that includes Pakistan.2, 3 About 8–9 million cases and 1–1.5 million deaths were estimated in 2010, which was almost equal to 15 deaths per 100 000 lives. It also includes deaths from TB among people having HIV. Pakistan is ranked 5th worldwide in 2010 with more number of incident cases, with incidence rate 231/100000 population and prevalence rate of 364/100000. Mortality rate was 22-49/100000 population. 4 TB can manifest as pulmonary and extra pulmonary TB. Although pulmonary TB is more common but there is significant incidence of extra pulmonary TB in Pakistan. Tuberculous meningitis (TBM) is the most lethal type of tuberculosis with increase mortality and morbidity worldwide. 5

Nonspecific sign and symptoms similar to other neoplastic and inflammatory diseases is a major difficulty in the diagnosis of extra-Pulmonary TB which results in a delay of treatment. Therefore, a high index of suspicion is important for early diagnosis. 6 Another reason for difficulty in diagnosis is that collection of extra pulmonary material mostly needs invasive procedures, and it is usually not convenient to obtain additional samples.7

Culture is gold standard confirmatory test for diagnosis of TBM. It takes 4-6 weeks and can result in delay in treatment that can be disastrous for TBM and thus limits its value. 4, 8 Commercial serological tests sensitivity and specificity is highly variable and provides inconsistent and imprecise results with high proportions of false-negative and false-positive results.

New diagnostic techniques with nucleic acid amplification are buying attention because of their rapidity, sensitivity, and specificity. GeneXpert MTB/RIF is a TB-specific automated nucleic acid amplification assay which detects Mycobacterium tuberculosis DNA along with mutations conferring resistance to rifampicin directly from clinical specimen, e.g. sputum, cerebrospinal fluid (CSF), tissue etc., and provides results within 100 minutes. 9

GeneXpert is therefore a potentially attractive tool for rapid diagnosis of tuberculous meningitis. Studies have found varying and conflicting results when GeneXpert done on CSF. Sensitivity ranged from 36% to over 85% in various studies conducted in different countries.10, 11, 12, 13 A Meta-analysis study showed the overall pooled sensitivity 80.4% and specificity 86.1% for extra pulmonary TB. 14 WHO has also recommended conducting studies at domestic levels to generate data for this new

1. Department of Medicine
Hayatabad Medical Complex (HMC), Peshawar KP
2. Department of Dermatology
Hayatabad Medical Complex (HMC), Peshawar KP
3. Department of Pulmonology
Hayatabad Medical Complex (HMC), Peshawar KP

Address for Correspondence:
Dr Nauman Idrees
Department of Medicine, HMC Peshawar KP
drnaumanidrees@yahoo.com
Cell # 03329914410

test.

The study was performed to determine sensitivity,specificity,positive predictive value,nagative predictive value and accuracy of GeneXpert MTB/RIF assay for TBM keeping CSF culture as gold standard. There is no local data available for GeneXpert MTB/RIF assay in diagnosis of TBM, Therefore the need for study on CSF using GeneXpert in local setting cannot be ignored.

MATERIAL AND METHODS

This cross sectional study was conducted at Hayatabad Medical Complex Peshawar from 1st October 2015 to 31 March 2017. A total of 125 patients aged 18-60 were included through consecutive, non-probability sampling technique.

All patients admitted in medical A ward with clinical features of meningitis like fever,confusion,headache and neck stiffness were subjected to detailed history and clinical examination. Lumbar puncture was performed on every patients according to standard procedure guidelines under strict aseptic conditions. Three samples of 1 ml CSF were taken from each patient. Two samples were stored at 4°C in refrigerator at Tuberculosis control program laboratory, which has both the facilities of GeneXpert MTB/RIF assay and CSF culture by fully automated Bactec MGIT 960 system. The other sample was sent to hospital laboratory for routine analysis. When the routine analysis of CSF was suggestive of TBM, then the stored samples at TB control program laboratory were processed for Culture and GeneXpert and patients were started on anti tuberculous treatment as per national guidelines. Statistical analyses were carried out with SPSS-20. Frequency and percentage were calculated for categorical variables like GeneXpert result and CSF culture result while Mean ± SD was calculated for variables like age, sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy were calculated using standard formula as shown in table 3.

RESULTS

Out of 125, 70(56%) patients were male and 55(44%) patients were female (Table 1).GeneXpert was positive in 81 out of 125 patients and 73 out of these 81 patients were having positive CSF culture. GeneXpert was negative in 44 out of 125 patients and 37 out of these 44 patients were having negative CSF culture (table 2). sensitivity was 91%,Specificity was 82%, Positive predictive value was 90%, Negative predictive value

Table 1: Gender wise distribution of patients

Gender		
	Frequency	**Percentage**
Male	70	56%
Female	55	44%
Total	125	100%

Table 2: Comparison of GeneXpert MTB with CSF Culture Test for Diagnosis of Tuberculous Meningitis

		CSF Culture Test		
		Yes	**No**	**Total**
GeneXpert MTB	**Yes**	73	8	81
	No	7	37	44
	Total	80	45	119

Table 3: Sensitivity, specificity, positive and negative predictive value and accuracy of the GeneXpert MTB/RIF assay cpmoared with the CSF culture technique as reference

Sensitivity = TP/TP+FN	73/(73+7) X 100 = 91%
Specificity = TN/TN+FP	37/(37+8) X 100 = 82%
Positive Predictive Value = TP/TP+FP	73/(73+8) X 100 = 90%
Negative predictive value = TN/TN+FN	37/(37+7) X 100 = 84%
Accuracy	(73+37)/125 =88%

was 84% and the overall accuracy was 88% shown in Table 3.

DISCUSSION

Tuberculosis (TB) is a second most leading cause of death after HIV by an Infectious agent. It is a major cause of morbidity and mortality throughout the world, killing 2-3 million people every year. Most of these deaths occur in the developing world that includes Pakistan. Although extra pulmonary TB is less common than pulmonary TB but increasing incidence in Pakistan is observed. These include TB meningitis, pericarditis, peritonitis etc. TB meningitis is associated with high morbidity and mortality. Out of 125 patients 56% were male and 44% patients were female, mean age was 43±1.26 years. This study showed that the sensitivity of Gene Xpert was 91% for TBM, which is consistent with Ioannidis et al, where sensitivity of GeneXpert for smear positive extra pulmonary TB was 100%. Specificity in the study 82%, which was again comparable to Ioannidis et al. 14 Positive predictive value in the study was 90%, with Negative predictive value of 84% with the overall accuracy was 88%. This was comparable with Panday et al where Positive predictive value and Negative Predictive value for Gene Xpert were 100% and 93.8%, respectively. 15

A study designed in India by bhatia R to assess the diagnostic ability of GeneXpert in detecting MTB in CSF showed 38.24% sensitivity of GeneXpert in comparison to Bactec culture which was only 14.71%,and shows more diagnostic accuracy of GeneXpert with higher sensitivity as compared to conventional methods and liquid culture.16

Another study conducted by metcalf in spain showed diagnostic sensitivity of 88% for GeneXpert in diagnosis of TBM and 75% for MGIT culture. which is also comparable to our study which shows diagnostic sensitivity of 91%.17

WHO 2013 meta analysis also showed GeneXpert sensitivity of 79.5% for TBM with culture as a reference gold standard.18

CONCLUSION

The diagnostic accuracy of GeneXpert MTB assay is equivalent to CSF culture /sensitivity. Since the reports of GeneXpert MTb assay become available earlier as compared to CSF culture reports, the rapid accuracy of the test will reduce time between diagnosis and treatment of suspected cases of Tuberculous meningitis patients. More over the cost effectiveness of GeneXpert will also reduce the financial burden in the community and on the government.

REFERENCES

1. Anuradha B, Aparna S, VijyaLakshmi V, Akbar Y. Prevalence of drug resistance under the DOTS strategy in Hyderabad South India. Int J Tuberc Lung Dis 2006; 10:58-62.

2. Ducati RG, Santos DS. The resumption of consumption: a review on tuberculosis. Mem Inst Oswaldo Cruz 2006; 1017:697-14.

3. Dewan P, Cicenaite J, Laseron K, Johansen L. High prevalence of drug resistance tuberculosis. Int J Tuberc Lung dis 2005; 92:170-4.

4. Javaid A. Tuberculosis control; Where do we stand today in Pakistan. J Postgrad Med Inst 2011; 25(4):291-7.

5. Glaziou P, Floyd K, Rauiglione M. Global burden and epidemiology of tuberculosis. Clin Chest Med. 2009 Dec; 30(4):621-36.

6. World Health Organization. Global tuberculosis control 2009: surveillance, planning, and financing. Geneva: WHO; 2009.p.1-303.

7. World Health Organization. Global tuberculosis control. Geneva: WHO: 2010.

8. Young D, Perkins M, Duncan K, Barry C. Confronting the scientific obstacles to global control of tuberculosis. J Clin Invest 2008; 118:1255-65.

9. Ling DI, Flores LL, Riley LW, Pai M. Commercial nucleic-acid amplification tests for diagnosis of pulmonary tuberculosis
in respiratory specimens: meta-analysis and meta-re-

gression. PLoS ONE. 2008; 3:e1536.

10. Boehme CC, Nicol MP, Nabeta P, Michael JS, Gotuzzo E, Tahirli R, et al. Feasibility, diagnostic accuracy, and effectiveness of decentralised use of the Xpert MTB/RIF test for diagnosis of tuberculosis and multidrug resistance: a multicentre implementation study. Lancet. 2011 April 30; 377(9776):1495-505.

11. Pai M, Minion J, Sohn H, Zwerling A, Perkins MD. Novel and Improved Technologies for Tuberculosis Diagnosis: Progress and Challenges. Clin Chest Med. 2009 Dec; 30(4):701-16. Bowles EC, Freyée B, Ingen JV, Mulder B, Boeree MJ, Soolingen DV. Xpert MTB/RIF®, a novel automated polymerase chain reaction–based tool for the diagnosis of tuberculosis. Int J Tuberc Lung Dis. t; 15(7):988-9.

13. Harries AD, Zachariah R, Corbett EL, Lawn SD, Santos-Filho ET,et al. The HIV-associated tuberculosis epidemic when will we act? Lancet.2010; 375:1906-919.

14. Ioannidis P, Papaventsis D, Karabela S, Nikolaou S, Panagi M, Raftopoulou E, et al. Cepheid Gene Xpert MTB/RIF Assay for Mycobacterium tuberculosis Detection and Rifampicin Resistance Identification in Patients with Substantial Clinical ndications of Tuberculosis and Smear-Negative Microscopy Results. J Clin Microbiol. 2011 Aug; 49(8):3068-70.

15. Pandey P, Pant ND, Rijal KR, Shrestha B, Kattel S, Banjara MR, et al. Diagnostic Accuracy of GeneXpert MTB/RIF Assay
in Comparison to Conventional Drug Susceptibility Testing Method for the Diagnosis of Multidrug-Resistant Tuberculosis. PLoS One. 2017;12(1):e0169798.

16. Bhatia R, Dayal R, Jindal S, Agarwal D, Goyal A, et al. GeneXpert for diagnosis og tuberculous meningitis. J Ind pediatr.2016 Nov;83(11):1353-1355.

17. Metcalf T, Soria J, Montano SM, Ticona E, Evans CA, Huaroto L, Kasper M, et al.Evaluation of the GeneXpert MTB/RIF in patients with presumptive tuberculous meningitis.PloS One.2018 Jun;18;13(6):e0198695.

18. Nathan C, Suzaan M, Maxine C, Reinout V, Robert J, Jaya S, et al. GeneXpert MTB/RIF to diagnose tuberculous meningitis: perhaps the first test but not the last. J Clin Infect.2016 May;62(9):1133-1135.