Tuberculous meningitis; save time and dreadful fate by using GeneXpert MTB/RIF assay

Mohammad Yahya Abdulrazaq[1]

ABSTRACT

Tuberculous meningitis (TBM) is the most common form of central nervous system tuberculosis (TB), one of the most dangerous forms of tuberculosis that has very high morbidity and mortality. Early diagnosis and treatment of this condition is very important issue for a better prognosis. A 23-year-old female presented with headache, nausea and vomiting, with fever and sweating. On examination neck rigidity, and upward plantar reflexes were present. She has a history of splenectomy before 3 years. Spinal tap performed for her. Cerebrospinal fluid (CSF) was lymphocytic-predominant, with elevated protein, and low glucose. CSF acid-fast smear was negative. The diagnosis of TBM was confirmed by the GeneXpert MTB/RIF assay to cerebrospinal fluid (CSF). Antitubercular chemotherapy was started. The patient condition improved. GeneXpert MTB/RIF assay endorsed by WHO in December 2010 as diagnostic test for TB , this test is available in Iraq since 2011 , this test should be used immediately in CSF samples of patients suspected of TBM to increase the likelihood of early diagnosis and treatment.

Key words: tuberculosis, meningitis, GeneXpert MTB/RIF assay.

Iraqi New Medical Journal January 2019;4(9)

INTRODUCTION

Tuberculosis (TB) is a highly prevalent global human infection caused by Mycobacterium tuberculosis (MTB). One-third of the world's population is infected with latent TB. These individuals are not clinically affected but carry a lifetime risk of 10% for developing active disease.[1]

Tuberculous meningitis (TBM) is caused by MTB and is the most common form of central nervous system (CNS) tuberculosis.[2] TBM the most severe form of infection caused by Mycobacterium tuberculosis, causing death or disability in more than half of those affected.[3] Particularly among patients coinfected with HIV.[4-6]

Tuberculous meningitis can occur as the sole manifestation of TB or concurrent with pulmonary or other extrapulmonary sites of infection. [7,8] CNS disease accounts for only 5% of all cases of extra-pulmonary tuberculosis.[9]

TBM means the infection of the meninges; the system of membranes which envelop the central nervous system by MTB.[10] The disease occurs when subependymal or subpial tubercles, also known as "Rich foci" seeded during bacillemia of primary infection or disseminated disease, rupture into the subarachnoid space.[11,12] Mycobacterium tuberculosis of the meninges is the cardinal feature and the inflammation is concentrated towards the base of the brain.[13] When the inflammation is in the brain stem subarachnoid area, cranial nerve roots may be affected. The symptoms will mimic those of space-occupying lesions.[14] Blood-borne spread certainly occurs, presumably by crossing the blood–brain barrier; but a proportion of patients may get TB meningitis from rupture of a cortical focus in the brain; an even smaller proportion get it from rupture of a bony focus in the spine.[15]

Individuals with increased risk for TBM include young children with primary TB and patients with immunodeficiency caused by ag-

[1]CABM, FIBMS, FRCP; Consultant Internist & Pulmonologist at the National Specialized Centre for Chest and Respiratory Diseases. Baghdad.
E mail: ntp.mohammad@gmail.com

ing, malnutrition, or disorders such as HIV and cancer.[16] Most patients have no known history of TB, but evidence of extrameningeal disease (e.g., pulmonary) can be found in about half of patients.[17]

TBM is typically a subacute disease.[2] A prodromal phase of low-grade fever, malaise, headache, dizziness, vomiting, and/or personality changes may persist for a few weeks, after which patients can then develop more severe headache, altered mental status, stroke, hydrocephalus, and cranial neuropathies. Seizures are uncommon manifestations of TBM in adults and when present should prompt the clinician to consider alternate diagnoses such as bacterial or viral meningitis or cerebral tuberculoma; in contrast, seizures are commonly seen in children with TBM, occurring in up to 50% of paediatric cases.[18,19]

Classic features of bacterial meningitis, such as stiff neck and fever, may be absent. When allowed to progress without treatment, coma and death almost always ensue. In survivors of TBM, neurologic sequelae may occur that include mental retardation in children, sensorineural hearing loss, hydrocephalus, cranial nerve palsies, stroke-associated lateralizing neurological deficits, seizures, and coma.[20]

The diagnosis of TBM remains difficult as its presentation is non-specific and may mimic other causes of chronic meningoencephalitis. Rapid recognition of TBM is crucial as delays in initiating treatment are associated with poor outcome. The laboratory diagnosis of TBM is hampered by the low sensitivity of cerebrospinal fluid microscopy and the slow growth of M. tuberculosis in conventional culture systems.[3]

A recent diagnostic advance is Xpert MTB/RIF, an automated rapid nucleic acid amplification test for MTB endorsed by the WHO in December 2010. Xpert technology employs sealed disposable cartridges that avoid contamination of testing equipment and requires minimal technical training to operate.[21]

Contrast-enhanced brain CT or MRI can help support a diagnosis of TBM because of the high frequency of abnormalities on initial presentation the most common findings in descending order are meningeal enhancement, hydrocephalus, basal exudates, infarcts, and tuberculomas.[22]

The treatment of TB meningitis is isoniazid, rifampicin, pyrazinamide and ethambutol for two months, followed by isoniazid and rifampicin for a further ten months.[3] HIV-infected patients receiving treatment for TBM are at risk for clinical deterioration after initiation of antiretroviral therapy (ART) due to immune reconstitution inflammatory syndrome (TBM-IRIS). It is recommended to defer ART to 4–6 weeks after beginning anti-TB Medication.[23]

CASE PRESENTATION

A 23-year-old female not married from rural area, east of Baghdad presented to Al-Kindy Teaching Hospital in Baghdad complaining from headache, nausea, vomiting, fever, and sweating of 2 weeks duration. On examination neck rigidity, and upward plantar reflexes were present. She diagnosed as a case of meningitis. The patient level of consciousness started to deteriorate quickly for which the patient is transferred to the neurological department of Baghdad Teaching Hospital at Medical City Directorate. A full medical history was taken and a comprehensive physical examination was done. Her past medical history was notified by a history of splenectomy before 3 years.

On investigation erythrocyte sedimentation rate (ESR) and total white blood cells (WBC) count were elevated. Spinal tap has been done for her. Cerebrospinal fluid (CSF) examination was done, the result showed total leukocytes count was high 320 cells/mm^3 with ,a lymphocytic cell predominance 70 cells/mm^3, with elevated protein (180 mg/100 ml), and low glucose(40 mg/100 ml). Part of the CSF sample was send to tuberculosis referral laboratory at the National Specialized Centre for Chest and Respiratory Diseases, CSF acid-fast smear was negative by direct smear microscopic examination. But the diagnosis of TBM was confirmed by the GeneXpert MTB/RIF assay to cerebrospinal fluid (CSF). The detected tubercle bacilli was sensitive to rifampicin. The patient was registered at the National Specialized Centre for Chest and Respiratory Disease outpatient clinic as a case of extrapulmonary TB (TB meningitis).

Antitubercular chemotherapy was started with 2 months as initial phase with 4 tablets of combined fixed dose 4 drugs formula anti-TB medication (INH, rifampicin, pyrazinmaide,

and ethambutol) HREZ followed by 10 months continuation phase with 4 tablets of combined fixed dose 2 drugs formula anti- TB medication (INH and rifampicin) HR, steroid was used and tapered during the initial phase antitubercular chemotherapy. The patient condition started to improve gradually and discharged from the hospital within 2 weeks. The patient was doing well with her medication after continuous follow up, and showed a full improvement in her general condition.

DISCUSSION

Fever and headache are the cardinal features of tuberculous meningitis; confusion is a late feature while coma bears a poor prognosis. Meningism is absent in a fifth of patients with TB meningitis so high index of suspicion is always needed even in absence of neck stiffness. Patients may also have focal neurological deficits.[24,25] The classical triad of meningitis; fever, headache, and neck rigidity may not be present in all patient with TBM,[26] Our patient has presented with these classical symptoms, in addition to sweating. Later on, her level of consciousness has deteriorated suddenly.

Among symptoms, the frequency of fever in TBM has been reported to vary between 60% and 95%.[27] Seizures have been reported to occur in TBM with variable incidence ranging from 17% to 93%.[28] On studying the CSF profile of patients with TBM in 2013, Sarkar et al have found that CSF sugar (mmol/L) was low 2.6 ± 1.2 (0.8–6.5), protein (mg/dL) was high 212.3 ± 275 (137–1440), total leukocytes count /mm^3 was high 484.7 ± 1317 (5–6400), and lymphocytic pleocytosis 72.08 ± 31.2/ mm^3 (10–100).[29] Similar findings were also detected in our patient; lymphocytic cell predominant CSF infiltration, elevated protein, and low glucose.

CSF acid-fast smear was negative in our patient by direct smear microscopic examination. However, the diagnosis of TBM was confirmed by the GeneXpert MTB/RIF assay to cerebrospinal fluid. TB is one of the most challenging causes of meningitis to diagnose because of the difficulties in rapidly identifying MTB in CSF samples. TBM should be strongly considered in any patient presenting with symptoms and signs of meningitis in regions with a high burden of TB and in high-risk individuals in regions with lower burdens of TB. Clinical, microbiologic, and radiologic findings should be used conjunctively to support a diagnosis of TBM. The Xpert MTB/RIF assay provides the ability to rapidly diagnose infection with MTB, although additional studies are needed to define the sensitivity and specificity for the diagnosis of TBM.[22] When 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.[30] GeneXpert is highly specific diagnostic test for diagnosis of TBM, but negative test does not rule out TBM. The diagnosis is still made in combination clinical findings and other biochemical and radiological investigations.[31] The World Health Organization recommends the use of GeneXpert Mycobacterium tuberculosis (MTB)/rifampin (RIF) as initial test for diagnosis of TBM in comparison to microscopy and culture.[32]

Poor sensitivity and a low positive predictive value limit the use of smear microscopy for acid-fast bacilli (AFB). Nucleic acid amplification techniques have emerged as an effective diagnostic tool for rapid identification, early treatment, and it associated with improved patient outcomes. The GeneXpert MTB/RIF test is a cartridge bases test which performs processing of sample with real-time polymerase chain reaction (PCR) not only for TB diagnosis but also it detects of RIF resistance.[33,34]

We started anti TB medication immediately after reaching the diagnosis, that even in presumptive cases with negative Ziehl–Neelsen (ZN) staining of CSF for acid-fast bacilli empirical treatment with anti-TB drugs is the standard of care.[22] TBM is the most devastating consequence of infection with Mycobacterium tuberculosis. Approximately a third of patients die soon after presenting to hospital, and many of those surviving are left with severe neurological sequelae.[35,36] Early diagnosis and treatment for TBM have been shown in numerous studies to be the best predictor of survival.[6, 37-40]

A microbiologically confirmed TBM diagnosis is rare in most laboratories, as in our case. Ziehl-Neelsen microscopy staining of cerebrospinal fluid (CSF) is the most widely applied rapid diagnostic technique; however, sensitivity for TBM rarely exceeds 20%.[41] Liquid culture techniques, including the mycobacterial growth

indicator tube (MGIT; Bactec) and the mycobacterial observation drug susceptibility assay (MODS) culture offer improved sensitivity over solid culture, to a sensitivity of almost 60%.[42]

Several studies have reported successful use of the Xpert MTB/ RIF test on extrapulmonary samples, with overall sensitivities of over 80% and specificity reaching 100%.[43-45] Xpert MTB/ RIF test is able to rapidly confirm a diagnosis of TBM with 59% sensitivity and 99% specificity.[46] Because CSF samples tend to be paucibacillary compared to sputum.[47,48]

With the introduction of geneXpert assay, there has been a huge change in the detection time and more accuracy. It is proved to be highly effective not only in the detection of tuberculosis but also in identifying rifampicin resistant strains.[49] Introduction of GeneXpert in the initial testing of tuberculosis is a game changer in the detection of tuberculosis and in its management since it can delineate rifampicin resistant strains.[50]

CONCLUSION

GeneXpert assay should be used immediately in CSF samples of patients suspected of TBM to increase the likelihood of early diagnosis and treatment; however, negative test does not rule out TBM.

REFERENCES

1. Zumla A, Raviglione M, Hafner R, von Reyn CF. Current concepts: tuberculosis. *N Engl J Med* 2013;368:745–755.
2. Marx GE, Chan ED. Tuberculous Meningitis: Diagnosis and Treatment Overview. *Tuberculosis Research and Treatment*.Volume 2011, Article ID 798764, 9 pages .doi:10.1155/2011/798764
3. Török ME. Tuberculous meningitis: advances in diagnosis and treatment. *British medical bulletin*. 2015 Feb 18;113(1):117-31.
4. Katrak SM, Shembalkara PK, Bijwe SR, Bhandarkar LD. The clinical, radiological and pathological profile of tuberculous meningitis in patients with and without human immunodeficiency virus infection. *J Neurol Sci* 2000;181:118–126.
5. Cecchinia D, Ambrosioni J, Brezzo C, et al. Tuberculous meningitis in HIV-infected patients: drug susceptibility and clinical outcome. AIDS 2007;21:373–374
6. Marais S, Pepper DJ, Schutz C, Wilkinson RJ, Meintjes G. Presentation and outcome of tuberculous meningitis in a high HIV prevalence setting. *PLoS ONE* 2011;6:e20077.
7. Thwaites G, Fisher M, Hemingway C, Scott G, Solomon T, Innes J. British Infection Society guidelines for the diagnosis and treatment of tuberculosis of the central nervous system in adults and children. *J Infect* 2009;59:167–187.
8. Cherian A, Thomas SV. Central nervous system tuberculosis. *Afr Health Sci* 2011;11:116–127.
9. Farer LS, Lowell AM, Meador MP. Extrapulmonary tuberculosis in the United States. *Am J Epidemiol*. 1979;109:205–17.
10. "Tuberculous Meningitis Medical Definition" (http://www.medilexicon.com/medicaldictionary.php?t=54120). Retrieved 2015-06-02.
11. Rich AR and McCordock HA. The pathogenesis of tuberculous meningitis. *Bulletin of the Johns Hopkins Hospital* 1933;52:5–37.
12. "Tuberculous Meningitis : Background , Pathophysiology , Etiology " (http://emedicine.medscape.com/article/1166190-overview#a3).
13. Christodoulides, Myron (2013). Meningitis: Cellular and Molecular Basis ABI. p. 154. ISBN 9781780641621.
14. Robbins and Cotran, Pathologic Basis of Disease, 8th edition, p1301
15. Nicoll, J. A. R.; Bone, Ian; Graham, David (2006-11-24). A. dams & Graham's Introduction to Neuropathology 3E d. CRC Press. p. 127. ISBN 9780340811979.
16. Berenguer J, Moreno S, Laguna F, Vicente T, Adrados M, Ortega A, González-LaHoz J, Bouza E. Tuberculous meningitis in patients infected with the human immunodeficiency virus. *New England Journal of Medicine*. 1992 Mar 5;326(10):668-72.
17. Verdon R, Chevret S, Laissy JP, and Wolff M. Tuberculous meningitis in adults: review of 48 cases. *Clinical Infectious Diseases*, 1996;22(6):982–988.
18. Farinha NJ, Razali KA, Holzel H, Morgan G, and Novelli VM. Tuberculosis of the central nervous system in children: a 20-year survey. *Journal of Infection* 2000;41(1):61–68.
19. Alzeer AH and FitzGerald JM. Corticosteroids and tuberculosis: risks and use as adjunct therapy. *Tubercle and Lung Disease* 1993;74(1):6–11.
20. Henry M and Hlzman RS. Tuberculosis of the brain, meninges, and spinal cord. In Tuberculosis, W. N. Rom, S. M. Garay et al., Eds., pp. 445–464, Lippincott Williams & Wilkins, Philadelphia, Pa, USA, 2nd edition, 2004.
21. Steingart KR, Sohn H, Schiller I, et al. Xpert® MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults (review). Cochrane Database Syst Rev 2013;1:CD009593
22. Neurology® Clinical Practice Tuberculous meningitis Diagnostic and therapeutic challenges .Jerome H. Chin, MD, PhD, MPH) Neurology: Clinical Practice | June 2014 ;199-205
23. Bahr N, Boulware DR, Marais S, et al. Central nervous system immune reconstitution inflammatory syndrome. Curr Infect Dis Rep 2013;15:583–593. Marais S, Meintjes G, Pepper DJ, et al. Frequency, severity, and prediction of tuberculous meningitis immune reconstitution inflammatory syndrome. Clin Infect Dis 2013;56:450–460. (**This reference is two in one !!!!???**)
24. Harman, Robin J.; Mason, Pamela (2002-01-01).Handbook of Pharmacy Healthcare: Diseases and Patient Advice. Pharmaceutical Press. p. 93. ISBN 9780853695073. Leach, Richard M. (2010-06-11).
25. Acute and Critical Care Medicine at a Glance. John Wiley & Sons. p. 101. ISBN 9781444327229.
26. Udani PM, Parekh UC, Dastur DK. Neurological and related syndromes in CNS tuberculous meningitis: Clinical features and pathogenesis. *J Neurol Sci* 1971;14:341-57.
27. Thwaites GE, Hein TT. Tuberculous meningitis: Many questions, too few answers. *Lancet Neurol* 2005;4:160-70.
28. Patwari AK, Aneja S, Ravi RN, Singhal PK, Arora SK. Convulsions in tuberculous meningitis. *J Trop Pediatr* 1996;42:91-7.
29. Sarkar DN, Hossain MI, Shoab AK, Quraishi FA. Presentation of

tuberculous meningitis patients: Study of 30 cases. *Med Today* 2013;25:32-5.

30. PShrestha P, Paudyal B, Basnyat B. GeneXpert MTB/RIF assay as initial test for diagnosis of tuberculous meningitis; BMJ Case Reports 2015; doi:10.1136/bcr-2014-207502
31. Kumari D, Anupurbha S, Gupta M, Kumari S, Singh A. Correlation of GeneXpert and cerebrospinal fluid culture in patients of tubercular meningitis. *Asian Pacific Journal of Health Sciences* 2018;5(2):148-151.
32. World Health Organization. Automated real-time nucleic acid amplification technology for rapid and simultaneous detection of tuberculosis and rifampicin resistance: Xpert MTB/RIF assay for the for the diagnosis of pulmonary and extrapulmonary TB in adults and children. Geneva, WHO, 2013.
33. Blakemore R, Story E, Helb D, Kop J, Banada P, Owens MR, et al. Evaluation of the analytical performance of the Xpert MTB/RIF assay. *J Clin Microbiol* 2010;48:2495-501.
34. Helb D, Jones M, Story E, Boehme C, Wallace E, Ho K, et al. Rapid detection of Mycobacterium tuberculosis and rifampin resistance by use of on-demand, near-patient technology. *J Clin Microbiol* 2010;48:229-37.
35. Brancusi F, Farrar J, Heemskerk D. Tuberculous meningitis in adults: a review of a decade of developments focusing on prognostic factors for outcome. *Future Microbiol* 2012;7(9):1101–1116. Available from: http://dx.doi.org/10.2217/fmb.12.86.
36. Thwaites GE. Advances in the diagnosis and treatment of tuberculous meningitis. *Curr Opin Neurol* 2013; 26:295–300.
37. Hosoglu S, Geyik MF, Balik I, Aygen B, Erol S, Aygencel TG, Mert A, Saltoglu N, Dokmetas I, Felek S, Sunbul M, Irmak H, Aydin K, Kokoglu OF, Ucmak H, Altindis M, Loeb M. Predictors of outcome in patients with tuberculous meningitis. *Int. J. Tuberc. Lung Dis* 2002;6:64–70.
38. Hsu PC, Yang CC, Ye JJ, Huang PY, Chiang PC, Lee MH. Prognostic factors of tuberculous meningitis in adults: a 6-year retrospective study at a tertiary hospital in northern Taiwan. *J. Microbiol. Immunol. Infect.* 2010;43:111– 118.
39. Misra UK, Kalita J, Roy AK, Mandal SK, Srivastava M. Role of clinical, radiological, and neurophysiological changes in predicting the outcome of tuberculous meningitis: a multivariable analysis. *J Neurol Neurosurg Psychiatry* 2000; 68:300–303.
40. Sheu JJ, Yuan RY, Yang CC. Predictors for outcome and treatment delay in patients with tuberculous meningitis. *Am J Med Sci* 2009;338:134–139.
41. Garg RK. Tuberculosis of the central nervous system. *Postgrad Med J* 1999;75:133–140.
42. Caws M, Dang TM, Torok E, Campbell J, Do DA, Tran TH, Nguyen VC, Nguyen TC, Farrar J. Evaluation of the MODS culture technique for the diagnosis of tuberculous meningitis. *PLoS One* 2007;2:e1173.
43. Lawn SD, Zumla AI. Diagnosis of extrapulmonary tuberculosis using the Xpert((R)) MTB/RIF assay. Expert Rev. *Anti Infect Ther* 2012;10:631–635.
44. Tortoli E, Russo C, Piersimoni C, Mazzola E, Dal MP, Pascarella M, Borroni E, Mondo A, Piana F, Scarparo C, Coltella L, Lombardi G, Cirillo DM. Clinical validation of Xpert MTB/RIF for the diagnosis of extrapulmonary tuberculosis. *Eur Respir J* 2012; 40:442–447. http://dx.doi .org/10.1183/09031936.00176311.
45. Hillemann D, Rusch-Gerdes S, Boehme C, Richter E. Rapid molecular detection of extrapulmonary tuberculosis by the automated GeneXpert MTB/RIF system. *J Clin Microbiol* 2011 49:1202–1205.
46. Nhu NTQ, Heemskerk D, Thu DDN, Chau TTH, Mai NTH, NghiaHDT, et al. Evaluation of GeneXpert MTB/RIF for Diagnosis of Tuberculous Meningitis. *Journal of Clinical Microbiology* 2014;52(1);226–233.
47. Using cerebrospinal fluid for the diagnosis of tuberculous meningitis with GeneXpert. *Eur Respir J* 2014; 44: 1094–1095. DOI: 10.1183/09031936.00066214
48. Ho J, Marais BJ, Gilbert GL, Ralph AP. Diagnosing tuberculous meningitis – have we made any progress? *Trop Med Int Health* 2013; 18:783–93.
49. Ioannidis P, Papaventsis D, Karabela S, Nikolaou S, Panagi M, Raftopoulou E, et al. Cepheid GeneXpert MTB/RIF Assay for Mycobacterium tuberculosis Detection and Rifampin Resistance Identification in Patients with Substantial Clinical Indications of Tuberculosis and Smear-Negative Microscopy Results. *J Clin Microb.* 2011;49:3068-70.
50. Nayantara Rao Gandra , Jayasri Helen Gali ;GeneXpert: a game changer in the detection and diagnosis of childhood tuberculosis. *International Journal of Contemporary Pediatrics* January-February 2018;5(1):35-41.

Abbreviation list: Acid-fast bacilli (AFB), Antiretroviral therapy (ART), Central nervous system (CNS), Cerebrospinal fluid (CSF), Cubic millilitre (mm^3), Erythrocyte sedimentation rate (ESR), Human Immunodeficincy Virus (HIV), Isoniazid (INH), Milligrams per decilitre (mg/dL), Millimoles per litre (mmol/L), Mycobacterial growth indicator tube (MGIT), Mycobacterial observation drug susceptibility assay (MODS), Polymerase chain reaction (PCR), Tuberculous meningitis (TBM), Tuberculosis (TB), Tuberculous meningitis/ Rifampicin (MTB/RIF), White blood cells (WBC), Ziehl–Neelsen (ZN)

Conflict of interest: Authors have nothing to declare.

Funding: Authors received no funds to complete this case presentation a part from self funding.