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Xpert MTB/RIF in Pediatric Tuberculosis

ABSTRACT

Objective: The objective of the study was to study the usefulness of Xpert TB/Rif in diagnosis of childhood tuberculosis (TB) in India. **Methods:** Prospective study was including children from 1 month to 18 years of age with clinical suspicion of TB. All cases were classified as pulmonary and extrapulmonary TB based on symptoms. All children under 5 years of age underwent Mantoux test. Imaging was done based on symptoms. Appropriate specimens were tested for smear microscopy, Xpert MTB/RIF, and liquid culture. **Results:** In cases with a clinical diagnosis, microscopy had a sensitivity of 37.3% (confidence interval [CI] – 17.2–59.3%) and specificity of 100% (71.5–100%), Xpert MTB/RIF had a sensitivity of 75% (CI – 55.1–89.3%) and a specificity of 100% (CI – 75.2–100%) while mycobacterium growth inhibitor tube had a sensitivity of 68.2% (CI – 51.9–81.8%) and specificity of 100% (CI – 75.2–100%). In culture-positive cases of pulmonary TB, microscopy had a sensitivity of 42.2% (CI – 17.6–71.1%) and specificity of 75.0% (CI – 34.8–96.8%) while Xpert MTB/RIF had a sensitivity and specificity of 78.5% (CI – 49.2–95.3%) and 47.6% (CI – 21.2–73.4%), respectively. Xpert MTB/RIF had 100% sensitivity for the detection of rifampicin resistance. Resistance to moxifloxacin was noted in 78% (11/14) while ofloxacin was resistant in 50% of the isolates (7/14). **Conclusions:** With the availability of sensitive tests like Xpert MTB/RIF, paucibacillary disease in children can no longer be an excuse to start empiric antitubercular drugs. With high levels of resistance for the first- and second-line drugs, Xpert MTB/RIF may not yet replace traditional cultures and drug sensitivity.

Key words: Extrapulmonary tuberculosis, GeneXpert, Multidrug-resistant tuberculosis, Pediatric tuberculosis, Xpert MTB/RIF

INTRODUCTION

The global burden of tuberculosis (TB) worldwide is estimated to be 9 million of which India contributes to 2.7 million cases. The incidence of TB in Indian children under 14 years of age was 224,000 in 2017.[1] This high burden of disease is compounded by difficulty in reliably establishing a microbiological diagnosis. Conventionally, microbiological confirmation was done by the identification of acid-fast bacilli on smears and culture on solid or liquid medium. Recently, the World Health Organization (WHO) approved of a new diagnostic modality called Xpert MTB/RIF, which is a cartridge-based nucleic acid amplification test for rapid and reliable diagnosis of TB.[2] In this study, we compare the diagnostic usefulness of this new test with the more traditional methods of diagnosis.

METHODS

This prospective study was conducted, after ethical clearance from the Institutional Review Board, in Bombay Hospital Institute of Medical Sciences and Research between January 2014 and January 2016. All children from 1 month to 18 years of age with clinical suspicion of TB were included in the study. Informed consent was taken from the parents of all children under 16 years of age and from the patient if over 16 years of age. Children who had received antitubercular treatment in the past 2 years were excluded from the study. TB was clinically suspected in children who had unexplained significant weight loss or poor weight gain, unexplained documented fever (temperature >38°C).[3]

All cases were classified as pulmonary and extrapulmonary TB based on additional symptoms such as cough or findings in the respiratory system examination, seizures, altered sensorium, lymphadenopathy, and abdominal pain and all children underwent Mantoux test. Cases with clinical features suggestive of TB were classified as clinical TB while children who were finally given an alternative diagnosis or responded without antitubercular medications were classified as non-TB. Imaging was done based on symptoms (computed tomography [CT]/magnetic resonance imaging for TB meningitis, chest X-ray for

Suba Guruprasad[1], Mukesh Sanklecha[1], Rama Yelikar[1], Nupur Sanklecha[2]

[1]Department of Pediatrics, Bombay Hospital, Mumbai, Maharashtra, India, [2]Department of Pediatrics, Seth Gordhandas Sunderdas Medical College, Mumbai, Maharashtra, India

Corresponding Author:
Suba Guruprasad, Department of Pediatrics, Bombay Hospital, Mumbai, Maharashtra, India. E-mail: mail.suba.s@gmail.com

pulmonary TB, and ultrasound/CT abdomen for suspected abdominal TB). Sputum/gastric lavage/tissue/body fluid samples were tested for acid-fast bacilli by smear, Xpert MTB/RIF, and mycobacterium growth inhibitor tube (MGIT) with drug sensitivity. Ethics committee and Institutional Review Board approval for the study were obtained (Ref no. BHIMS/6468).

RESULTS

Demography of the study population

Fifty-four children were recruited for the study. The mean age of the study population was 10 years (IQR – 4 years–16 years). Twenty-nine children were suspected and investigated for pulmonary TB while 25 children were investigated for extrapulmonary TB. Of the total children investigated for either pulmonary or extrapulmonary TB, 13 were eventually found to have an alternative diagnosis and improved without antitubercular medications. TB lymphadenitis (8/25, 32%) was the most common form of extrapulmonary Tb followed by CNS TB (7/25, 28%).

Clinical profile

Out of the 41 children with microbiologically proven TB, all presented with fever (100%). Significant weight loss was seen in 24% (10/41) of the children with pulmonary TB and in 9% (4/41) of children with extrapulmonary TB. A history of significant contact with a case of TB was seen in 19% (8/41) of pulmonary and 14% (6/41) of the extrapulmonary cases. Mantoux was positive in 20% (5/25) children with proven TB who were tested for it.

Microbiological results

Acid-fast bacilli were observed using fluorescence microscopy in 27% (8/29) children with suspected pulmonary TB while 20% (5/25) extrapulmonary samples were positive for acid-fast bacilli. Xpert MTB/RIF was positive in 65% (19/29) pulmonary and 52% (13/25) extrapulmonary samples. MGIT was positive in 48.2% (14/29) pulmonary samples and 56% (14/25) extrapulmonary samples.

In cases with a clinical diagnosis of TB, AFB smear had a sensitivity of 37.3% (CI – 17.2–59.3%) and specificity of 100% (71.5–100%); Xpert MTB/RIF had a sensitivity of 75% (CI – 55.1–89.3%) and a specificity of 100% (CI – 75.2–100%) while MGIT had a sensitivity of 68.2% (CI – 51.9–81.8%) and specificity of 100% (CI – 75.2–100%).

In culture-positive cases of pulmonary TB, AFB smear had a sensitivity of 42.2% (CI – 17.6–71.1%) and specificity of 75.0% (CI – 34.8–96.8%) while Xpert MTB/RIF had a sensitivity and specificity of 78.5% (CI – 49.2–95.3%) and 47.6% (CI – 21.2–73.4%), respectively. In extrapulmonary TB, AFB had a sensitivity of 35.5% (CI – 12.7–64.8%) and 100% (CI – 47.8–100%) while Xpert MTB/RIF had sensitivity and specificity of 71.4% (CI – 41.9–91.6%) and 54.5% (CI – 23.3–83.2%).

Xpert MTB/RIF had 100% sensitivity (CI – 79.4–100%) and specificity (CI – 76.8–100%) for the detection of rifampicin resistance. About 53.3% (16/30) of the isolates were resistant to rifampicin and isoniazid. All samples that were rifampicin resistant on Xpert MTB/RIF were also resistant to isoniazid tested by conventional drug sensitivity test. Resistance to moxifloxacin was noted in 78% (11/14) while ofloxacin was resistant in 50% of the isolates (7/14).

DISCUSSION

Childhood TB often masquerades as other diseases, making clinical diagnosis difficult. To add to this, obtaining a microbiological confirmation, in cases where it is suspected, is difficult given the paucibacillary nature of the disease and the poor sensitivity of the traditional screening tests like fluorescent microscopy. In our study, fluorescent microscopy had a sensitivity of 37.2% in pulmonary samples of children with clinically suspected pulmonary TB. This was far lower than the sensitivity of Xpert MTB/RIF that tested positive in 75% of the cases with clinically suspected pulmonary TB. In children with culture-positive TB, the sensitivity of fluorescent microscopy was 42.2% while that of Xpert MTB/RIF was 75.0%. The WHO in its policy update systematically analyzed the existing data and quoted the sensitivity of Xpert MTB/RIF to vary from 50% to 77% for sputum samples and 55% to 81% for gastric lavage samples. The same update reported the sensitivity of microscopy to vary from 30 to 60% in sputum and 0–50% in gastric lavage samples in children with culture-positive TB.[2] This review included analysis from both traditional ZN stain and LED fluorescent microscopy. A study from India compared LED fluorescent microscopy with Xpert MTB/RIF and found that the latter outperformed the former in all type of samples.[4]

Apart from rapid detection of the bacilli, the ability of Xpert MTB/RIF to reliably detect rifampicin resistance is the other major advantage attributed to it. In our study, Xpert MTB/RIF had 100% sensitivity in detecting rifampicin resistance. In addition, all samples that showed rifampicin resistance on Xpert MTB/RIF also had resistance to isoniazid acting as a surrogate marker for MDR TB. Boheme *et al*. reported 99.1% sensitivity of Xpert MTB/RIF for the detection of rifampicin resistance.[5]

An appalling finding in our study is the high rates of multidrug resistance. In North India, the prevalence of drug-resistant TB is estimated to be 13% in 2015 where some states like Uttar Pradesh, it is estimated to be as high as 35%.[6] A study of epidemiology of drug-resistant TB in children in the city of Mumbai estimated the prevalence of drug-resistant TB to be around 9.6%.[7] Furthermore, disturbing is the high resistance to the second-line fluoroquinolones found in our

isolates. The easy over-the-counter access of these antibiotics[8] and irrational use to treat viral respiratory illness may be the cause for this high burden of drug resistance in TB.

Traditional screening tests like Mantoux test, which picked up only 20% of the microbiologically proven cases in our studies, have long proven to be unreliable resulting in its removal from various diagnostic algorithms.[9]

The main limitation in our study is the sample size, which had to be restricted due to limited funds.

Xpert MTB/RIF is now endorsed by the WHO and has been included in the RNTCP guideline. However, the practical applicability is limited due to financial constraints in resource-limited settings like India. Furthermore, Xpert MTB/RIF though an excellent diagnostic test cannot replace liquid culture and drug sensitivity test, considering the high resistance to other first-line and several second-line antitubercular therapy.

In this day and age of multidrug resistance, it may be worthwhile chasing a microbiological diagnosis in children. With increasing sensitivities of the nucleic acid amplification tests, paucibacillary disease can no longer be an excuse to start empiric antitubercular medications. Obtaining adequate, appropriate samples, and utilization of all the available diagnostics efficiently by health-care providers and financial aid to replace low yielding, labor intensive investigations like smear microscopy with more reliable nucleic acid amplification tests at district and rural centers by governments will help plan the treatment more efficiently and will eventually contribute toward the goal of disease eradication.

CONCLUSIONS

In this day and age of multidrug resistance, it may be worthwhile chasing a microbiological diagnosis in children. With increasing sensitivities of the nucleic acid amplification tests, paucibacillary disease can no longer be an excuse to start empiric antitubercular medications. Obtaining adequate, appropriate samples, and utilization of all the available diagnostics efficiently by health-care providers and financial aid to replace low yielding, labor intensive investigations like smear microscopy with more reliable nucleic acid amplification tests at district and rural centers by governments will help plan the treatment more efficiently and will eventually contribute toward the goal of disease eradication.

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