

ORIGINAL ARTICLE

OVERDIAGNOSIS OF TUBERCULOSIS AND ROLE OF TUBERCULIN TEST

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ABSTRACT

This is a retrospective analysis of children who were referred to our tuberculosis (TB) clinic from March 2010 to Feb 2011 but were not started on ATT and none of them subsequently developed TB. Interpretation of tuberculin test as a means of diagnosis was analysed.

Results: Thirty-four (11.2%) children were overly diagnosed as TB. Seventeen out of 28 referred children were tuberculin positive and 8 were tuberculin negative. Also, 12 of tuberculin positive children had a reading of ≥ 15 mm, yet none of them developed active disease. Although 2 TU is the recommended standard dose for tuberculin testing in India, in our study no child had received 2 TU, 23.5% of tuberculin positive patients had received a 5 TU dose and 35.3% a 10 TU dose.

Conclusion: Most children with over-diagnosis of TB receive TT with more than 2TU units. The size of tuberculin reaction needs to be interpreted carefully.

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Introduction

A major challenge of childhood tuberculosis (TB) is establishing an accurate diagnosis. Less than 15% of cases are sputum acid-fast bacilli smear positive, and mycobacterial culture yields are 30%–40%.¹ Diagnosis of most paediatric TB cases is dependent on the tetrad of 1) careful history (including history of TB contact and symptoms consistent with TB). 2) Clinical examination (including growth assessment). 3) Tuberculin Skin Testing with Tuberculin test (TT) 4) Lesions suggestive of active TB on chest radiography. However, in developing and endemic countries, most individuals acquire latent infection and become tuberculin positive in childhood itself and chest radiography can be difficult to assess.

With difficulty of conclusive diagnosis, it can lead to overdiagnosis of TB. This retrospective study was undertaken to assess the overdiagnosis of TB, and to discuss the role of TT for treatment of TB, with emphasis on the prevalent practices of administration and interpretation of TT.

Methods & Materials

A retrospective study was carried out in the paediatric department of a tertiary care hospital in Mumbai. During the study period of March 2010 to Feb 2011, all patients who were diagnosed as TB and were referred from other centres to our TB clinic for starting Anti tuberculous therapy (ATT) were assessed. These

children were diagnosed as TB based on either a positive tuberculin test; or symptoms suggestive of TB; or history of contact with a patient suffering from TB; or ultrasound (USG) abdomen showing abdominal lymph nodes; or palpable cervical lymph nodes.

Children were assessed by detailed history, through physical examination and diagnostic investigations. In the history- details on the presence of TB contact, previous TB infection, BCG vaccination status and symptoms of illness in the form of cough, fever, weight loss and loss of appetite were enquired. Investigation reports of child having undergone past tuberculin testing, the results of recent (within previous one month) tuberculin test done in other centres and findings of abdominal USG for lymph nodes was noted. Examination included general physical examination and assessment of nutritional status. Routine hemogram, and Chest X ray was done for all patients. In interpreting the tuberculin test, as per general practice, induration ≥ 10 mm was considered as positive with 5 TU unit. No patient had been investigated with cervical lymph node biopsy, TB Elisa, or QuantiFERON Gold Assay.

Patients were not started on ATT if TT was positive with 10 TU units; if cervical nodes are less than 1cm and discrete; if abdominal nodes were non-matted, non-caseous; if the contact suffering from tuberculosis was not having open TB; patient had a recent positive TT with 5 TU units but also had a previous positive TT in the past; patient had recent TT with 5 TU units but had been treated with anti-tuberculous therapy in the past, and/or symptoms of the patient relieved in 2 weeks with other therapy.

Data was analysed based on descriptive statistics. SPSS version 18 was used for statistical correlation of data with Fischer exact test.

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Results

Out of the 250 children who presented to the TB clinic from March 2010 to Feb 2011, 34 patients were not started on ATT. All these patients had received BCG. Six children were lost to follow up. None of the remaining 28 children were found to subsequently develop TB on a mean follow up of 2.5 months and median of 3 months. The male to female ratio was 1:1.4. The median age at presentation was 8 years with the youngest being 1.5 years and the oldest being 13 years. Twenty-one children were ≥ 5 years of age. None of the children were known to be HIV positive. Clinical features based on which referral was made is given in Table 1. One out of 17 patients with a positive TT showed evidence of pneumonia on chest radiography and improved symptomatically with management of pneumonia. Out of 8 patients, with cervical adenopathy, 6 were tested with tuberculin test and 50% had a positive result. Out of 4 patients with abdominal adenopathy, 75% had a positive tuberculin test.

A history of recent positive tuberculin test reaction was seen in 17 patients, a negative tuberculin reaction in 8 patients and tuberculin test was not done in 3 patients. Comparison of results of tuberculin testing with clinical, investigational, and demographic data is depicted in Table 2. The difference in tuberculin positivity in children above 5 years and those below 5 years was not statistically significant. ($p=0.56$). Eight patients have been treated for TB in the past of which 6 (75%) had a current TT positive and 4 (50%) also had a positive TT in the past. The tuberculin unit used for testing were 10 TU in 6 patients (all of them tested positive), 5 TU in 4 patients (all tested positive). In 15 patients, the strength of tuberculin unit used was not known of which 7 tested positive and 8 tested negative.

Twelve patients had an induration of >15 mm with TT of which 5 (41.7%) has received 10 TU, 3 (25%) had received 5 TU and in 4 (33.3%) TU strength was not known. Four (33.3%) of these 12 patients had been treated for TB in the past. In 2 patients, the induration dimensions were not documented. Three patients had an induration of 10-14 mm of which one each had received 10 TU, 5 TU and unknown strength TU respectively and all 3 of them had been treated for TB in the past.

Table 1. Clinical profile of patients of overly diagnosed tuberculosis (TB).

Clinical Features	Number of Children (N=28)
Cough	16 (57.1%)
Loss of appetite	10 (35.7%)
Loss of weight	7 (25%)
Fever	12 (42.9%)
Recent Tuberculin positive	17 (60.7%)
TB contact	11 (39.3%)
Cervical lymphadenopathy	8 (28.6%)
Abdominal lymphadenopathy	4 (14.3%)

Discussion

Out of the 250 patients, 11.2% of patients who presented to our clinic for treatment were overly diagnosed as tuberculosis. This study aims to bring to light this phenomenon of overdiagnosis of tuberculosis. Clinical judgement and tuberculin testing are the mainstays of diagnosis of TB in children since many cases present as sputum negative. The tuberculin test is only a method of detection of infection with tubercle bacilli and not a marker of active disease. The usefulness of the test lies not only on proper technique of administering a standard dose of a standard tuberculin and reading of the reactions by trained personnel but also in its careful interpretation.

The recommended dose for tuberculin testing in India is 2 TU², however there is a lack of widespread availability of this standard dose. In our study no child had received the 2 TU dose, 23.5% of tuberculin positive patients had received a 5 TU dose and 35.3% a 10 TU dose (in rest of the patients- dose given not known). Though skin reaction is not a linear function of tuberculin dose, it can alter results since cut off values used are the same, irrespective of dose. Stuart et al³ found a statistically significant 1.5 mm increase in induration, when 10 TU was used as opposed to 5 TU within individuals. In their study, this small increase was enough to increase the number of positive individuals by 11% when a 10mm cut off was used and by 0.7% when a 15mm cut off was used. Even in our study, more numbers of wrongly diagnosed patients based on tuberculin testing had received 10 TU dose (41.7% of patients with ≥ 15 mm induration and 35.3% of patients with 10- 14mm induration) as compared to 5 TU dose (25% of patients with ≥ 15 mm induration and 23.5% of patients with 10-14mm induration).

In tuberculin testing with 2 TU, a very high probability of M. Tuberculosis infection (latent or active) in an endemic country like India is taken as ≥ 15 mm of induration, 10 mm–14 mm of induration is considered borderline (can be due to infection with atypical mycobacteria or BCG sensitivity).⁴

It is important to note that though 12/28 children had a tuberculin positive of ≥ 15 mm, none of them developed active disease. This can be attributed to 33.3% children receiving a dose of 10 TU for testing, history of past TB in 33.3% children indicating the positivity could simply be due to past latent infection and not necessarily active flare up of old disease. Other factors like improper technique of administration and improper reading could also play a role. Thus, although a higher cut off 15mm should be used as one of the parameters for deciding indication of chemotherapy, it is not useful alone and should be interpreted with caution, keeping in mind clinical picture of presentation and other differentials. Note should be taken of history of tuberculosis and history of TB contact. In our study 6/17(35.5%) for 10mm cut off and 4/12 (33.3%) for 15mm cut off, of patients who had past TB; and 7/12(41.2%) for 10mm cut off and 4/12 (33.3%) for 15 mm cut off, of patients with TB contact had a positive tuberculin test but did not develop active disease.

Studies have shown that the hypersensitivity to tuberculin secondary to BCG vaccination significantly

waned beyond 2.5 years of age and even if present normally shows an induration between either less than 10mm or between 10 and 14 mm.^{4,5} In older children, latent infection acquired from the environment often gives rise to a positive tuberculin test. Though the correlation between tuberculin positivity in the absence of active disease and age was not significant in our study ($p=0.560$), it can be attributed to a small sample size. Nevertheless, the tuberculin test should be interpreted with extreme caution in children less than 2.5 years and more than 5 years of age.

Chest X ray is an important diagnostic tool to rule out pneumonia as a differential and to identify lesions of active pulmonary tuberculosis. Only one out of 17 patients with a positive tuberculin reaction showed evidence of pneumonia on chest radiography and improved symptomatically with management of pneumonia.

Cervical lymphadenopathy is common in children, mostly reactive in nature. In our study 8 children were referred with cervical lymph nodes, and a positive and negative tuberculin test was seen in 3 children each. However, none of them went on to develop active disease. In absence of matted lymph nodes, a fine needle aspiration cytology (FNAC) of enlarged lymph node can be done to look for evidence of caseation before suspecting TB. Three out of 4 children with abdominal lymphadenopathy had a positive tuberculin test, however, these patients also did not show any progression on follow up suggestive of other causes of abdominal adenopathy such as atypical infections, acute mesenteric lymphadenitis. Thus, non-matted, non-caseous abdominal nodes even with a positive tuberculin test may be considered inconclusive and requires further assessment.

Conclusion

Overdiagnosis of TB leads to unnecessary chemotherapy with hepatotoxic drugs. If in doubt the clinician can adopt an approach of careful observation and follow up. The usefulness of the tuberculin test lies in standard procedure/dose of administration and careful interpretation. The diagnosis of active tuberculosis infection cannot be directly correlated only with size of reaction; the diagnosis should be based on a multipronged approach of careful history, examination, tuberculin testing and chest radiography.

Compliance with Ethical Standards

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Conflict of Interest: None

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