ORIGINAL ARTICLE

ROLE OF TUBERCULIN TEST AS A DIAGNOSTIC TOOL FOR TUBERCULOSIS

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Background: Childhood Tuberculosis remains one of the major public health concerns in developing countries like Pakistan and is responsible for high rates of morbidity and mortality in children. Although tuberculin skin test is very commonly used by physicians all over the world, its interpretation always remains difficult and challenging. The objective of this study was to determine the frequency of positive tuberculin skin test in vaccinated and unvaccinated children suffering from tuberculosis. **Methods:** This Cross-sectional study was conducted in the department of Paediatric Ayub Teaching Hospital, Abbottabad from 1st February 2015 to 30th April 2016. A total of 150 patients were observed in this study. Children of either gender who were aged 1–15 years admitted in ward with tuberculosis were included in the study by using non-probability convenient sampling technique. We injected 0.1 ml (10 units) of tuberculin purified protein derivative (PPD) into the anterior surface of the forearm and induration was read at 72 hours after administration. Data was entered and analysed using SPSS version 10. **Results:** Out of 150 children, 84 (56%) were males and 66 (44%) were females. The mean age was 7.8±3.84 years. Of these 75 (50%) were vaccinated and 75 (50%) were unvaccinated. In vaccinated Group 5.3% children had positive tuberculin skin test while in unvaccinated Group 2.7% children had positive tuberculin skin test and this difference was found statistically insignificant (*p*-value=0.40). Pulmonary TB was the diagnosis in 67 (44.7%), TBM in 65 (43.3%), abdominal TB in 7 (4.7%), disseminated TB in 4 (2.7%) and military TB in 7 (4.7%) patients. **Conclusions:** The positivity of tuberculin skin test in vaccinated and unvaccinated children suffering from tuberculosis was found to be insignificant in our study. We conclude that Tuberculin Skin Test should not be used as a sole diagnostic tool for diagnosing the disease in children of our region.

Keywords: Vaccinated; Unvaccinated; Tuberculin skin test; Children; Tuberculosis

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INTRODUCTION

Tuberculosis is a serious cause of public health concern in Pakistan and Pakistan ranks 5th amongst the highest tuberculosis burden countries in the world.[1] It is associated with high mortality rates and across the globe nearly one third of the total world population is thought to be affected with tuberculosis. Figures in 2013 shows that worldwide an estimated 9 million people had tuberculosis that caused mortality in about 1.5 million.[2] Prevalence of all tuberculosis cases in Pakistan is estimated as 342 per 100,000 individuals.[3]

BCG vaccination was started in Pakistan in 1949 and became part of EPI in 1970 and was supposed to be given to babies immediately after birth or in the first month of life. BCG vaccination estimates vary between 63–86% in pediatric population aged 12–23 months in different areas of country.[4]

Paediatric patients with tuberculosis are more prone to develop serious complications of the disease eventually leading to high mortality. Children having latent tuberculosis infection, act as the hub of infection as they grow up to become adults.[5] Therefore, accurate and early diagnosis of the disease in paediatric population is very crucial to start early appropriate therapy and infection control measures.[6] Adult population infected with mycobacterium tuberculosis are easily diagnosed due to its classical symptoms and signs. However, diagnosing a case of tuberculosis in paediatric population poses a huge challenge due to its atypical clinical presentation and difficulty in expectoration.[7]

The timely and correct diagnosis of tuberculosis is of profound importance not only for the patient himself but also for devising means to control its spread and eventual elimination from the whole region.[8]

The modern diagnostics for mycobacterium tuberculosis include two new blood tests T-SPOT-TB and Quantiferon TB-Gold.[9]

Apart from these, a fully automated system GeneXpert MTB/RIF (Xpert) assay is being widely

used with reported sensitivity and specificity of 77.3% and 98.2% respectively.[10]

The tuberculin skin test (TST) has long been used as a standard tool for diagnosis of patient exposed to tuberculosis.[11] It is used widely throughout the world due to its low cost and simplicity of administration.[12] Although tuberculin skin test is very commonly used by physicians throughout the world but its interpretation is always difficult and different in different conditions.[13] Multiple factors like age, immunological status, co-morbid conditions and prior BCG vaccination etc. can affect the positivity of TST.[12] A Tuberculin Skin Test induration of 10 mm or more after 72 hours of administration is usually considered positive but in BCG vaccinated children the tuberculin skin test induration of 15 mm or more is considered positive and this is due to tuberculosis infection and cannot be ascribed to previous BCG vaccination.[11]

This study aimed to determine the frequency of positive Tuberculin Skin Test in vaccinated and unvaccinated children suffering from tuberculosis. Our results will help to modify the diagnostic protocols for the accurate and timely diagnosis of childhood tuberculosis and to institute early appropriate clinical management and infection control measures and to prevent serious tuberculosis diseases like disseminated tuberculosis and Tuberculous meningitis.

MATERIAL AND METHODS

This Cross-sectional study was conducted in the Paediatric Department of Ayub Teaching Hospital, Abbottabad from 1st February 2015 to 30th April 2016. This study was conducted after approval from hospital's ethical and research committee. Sample size was calculated using the WHO software for sample size determination in health studies by keeping confidence level of 95%, frequency of positive tuberculin skin test in children suffering of Tuberculosis 52%[9] and Absolute Precision of 8%. Children of either gender who were aged 1–15 years admitted in ward with tuberculosis were included in the study by using non-probability convenient sampling technique. Children having HIV infection, on immunosuppressive drugs and with other chronic diseases including Hodgkin lymphoma, Non-Hodgkin lymphoma, diabetes mellitus, and chronic renal failure were excluded from this study. Tuberculosis in the study subjects was diagnosed by using modified Kenneth Jones Criteria. A child scoring 7 or more points was diagnosed as a case of tuberculosis. The vaccination status of the children against tuberculosis was determined by the presence or absence of BCG scar. The procedure was explained to patients and parents and an informed written consent was obtained before enrolling the patients into this study. Every child was injected with 0.1 ml of tuberculin purified protein derivative (PPD) into the anterior surface of the forearm and induration was read at 72 hours after administration. Tuberculin Skin Test was considered positive if the induration was 10 mm or more.[22] The age of patient, sex, type of tuberculosis, presence of BCG scar and positivity of tuberculin skin test was recorded in a predesigned pro forma. All the data was analyzed using software SPSS version 10. Mean±SD was calculated for numerical variable like age. Percentage and frequencies were calculated for categorical variables like gender, presence of BCG scar, positivity of tuberculin skin test and type of tuberculosis.

RESULTS

In this study a total of 150 patients were observed. Of these 84 (56%) children were males and 66 (44%) were females. The mean age of the patients was 7.8±3.84 years. Age distribution among two groups were analyzed in vaccinated Group 25 (33.3%) children were in age range 1–5 years, 28 (37.3%) children were in age range 6–10 years, 22 (29.3%) children were in age range 11–15 years. In Unvaccinated Group, 23 (30.7%) children were in age range 1–5 years, 29 (38.7%) children were in age range 6–10 years, and 23 (30.7%) children were in age range 11–15 years (Table-1)

Tuberculin skin test among two groups was analyzed as in vaccinated Group 4 (5%) children had positive tuberculin skin test while 71 (95%) children had negative tuberculin skin test. In unvaccinated Group 2 (3%) children had positive tuberculin skin test while 73 (97%) children had negative tuberculin skin test (Table-5). Overall TST was positive in only 6(4%) cases.

Type of tuberculosis among two groups was analyzed as in vaccinated Group 42 (56%) children had pulmonary tuberculosis, 23 (31%) children had tuberculous meningitis, 4 (5%) children had abdominal tuberculosis, 2 (3%) children had disseminated tuberculosis and 4 (5%) children had miliary tuberculosis. In unvaccinated Group 25 (33%) children had pulmonary tuberculosis, 42 (56%) children had tuberculosis meningitis, 3 (4%) children had abdominal tuberculosis, 2(3%) children had disseminated tuberculosis and 3 (4%) children had miliary tuberculosis. (Table-2). All cases with positive tuberculin skin test 6(4%) had pulmonary TB. (Table-4)

Table-1: Vaccination status of children with respect to age groups

Age of patients	Vaccination status		Total	*p*-value
	Vaccinated	Unvaccinated		
1–5 years	25 (33.3%)	23 (30.7%)	48 (32.0%)	0.94
6–10 years	28 (37.3%)	29 (38.7%)	57 (38%)	
11–15 years	22 (29.3%)	23 (30.7%)	45 (30.0%)	
Total	75 (100%)	75 (100%)	150 (100%)	

Table-2: Types of tuberculosis and vaccination status

	Vaccination status		Total	*p*-value
Types of TB	Vaccinated	Unvaccinated		
Pulmonary TB	42 (56.0%)	25 (33.3%)	67 (44.7%)	0.518
TBM	23 (30.7%)	42 (56.0%)	65 (43.3%)	
Abdominal TB	4 (5.3%)	3 (4.0%)	7 (4.7%)	
Disseminated TB	2 (2.7%)	2 (2.7%)	4 (2.7%)	
Miliary TB	4 (5.3%)	3 (4.0%)	7 (4.7%)	
Total	75 (100.0%)	75 (100.0%)	150 (100.0%)	

Table-3: Gender of patients and Tuberculin skin test

Gender of patients	Tuberculin skin test		Total	*p*-value
	Positive	Negative		
Male	2 (2.4%)	82 (97.6%)	84 (100%)	0.25
Female	4 (6.1%)	62 (93.9%)	66 (100%)	
Total	6 (4%)	144 (96.0%)	150 (100%)	

Table-4: Types of Tuberculosis and Tuberculin skin test

Types of Tuberculosis	Tuberculin skin test		Total	*p*-value
	Positive	Negative		
Pulmonary TB	6 (100%)	61 (42.4%)	67 (44.7%)	0.101
Tuberculous Meningitis	0 (0.0%)	65 (45.1%)	65 (43.3%)	
Abdominal TB	0 (0.0%)	7 (4.9%)	7 (4.7%)	
Disseminated TB	0 (0.0%)	4 (2.8%)	4 (2.7%)	
Miliary TB	0 (0.0%)	7 (4.9%)	7 (4.7%)	
Total	6 (100%)	144 (100%)	150 (100%)	

Table-5: Tuberculin skin test and vaccination status

Tuberculin skin test	Vaccination status		Total	*p*-value
	Vaccinated	Unvaccinated		
Positive	4 (5.3%)	2 (2.7%)	6 (4.0%)	0.40
Negative	71 (94.7%)	73 (97.3%)	144 (96.0%)	
Total	75 (100%)	75 (100%)	150 (100%)	

DISCUSSION

Tuberculosis is one of the leading causes of deaths all over the world, with approximately 1.5 million deaths each year.[13] Childhood tuberculosis is estimated to account for approximately 15–40% of all cases of tuberculosis.[14]

In our study majority of the patients were of pulmonary tuberculosis (44.7%) and tuberculous meningitis (43.3%). In a study by Zulqarnain *et al* in Multan, 52% children had tuberculous meningitis and 34% children suffered pulmonary tuberculosis.[15] In another study conducted by Imran in Peshawar, 43.9% children had pulmonary tuberculosis and 40% children had tuberculous meningitis.[16]

In present study, among vaccinated Group 4 (5%) children had positive tuberculin skin test, while in unvaccinated Group 2 (3%) children had positive tuberculin skin test. Overall Tuberculin Skin Test was positive in only 4% of the cases (p=0.40).

Our findings were much different from that observed by Zulqarnain *et al* in which the positivity of Tuberculin Skin Test was found to be 52% in paediatric patients suffering from tuberculosis.[15] Imran in a clinical study conducted in Peshawar reported that tuberculin skin test was positive in 52% of children suffering from tuberculosis.[16]

A study conducted by Göçrnen *et al* showed that Mantoux test was positive in 44.5%.[17] Results of a Nigerian study spanned over 4 years conducted by Gofama *et al*, showed positivity to Mantoux test in 15.5% of paediatric patients suffering from various form of tuberculosis.[18]

In relation to sex of the patients, the differences were not found to be statistically significant regarding BCG vaccination or TST positivity (p=0.254). In our study although Mantoux test was positive only in children infected with pulmonary tuberculosis but it was statistically insignificant (p=0.101).

The high percentage of false negative tuberculin skin tests in our study can be attributed to huge prevalence of malnutrition in our area. This aspect could not be taken into consideration in this study. Malnutrition causes immunosuppression in children leading to negative TST. A study conducted by Pelly *et al* showed that patients with decreased body proteins, as determined by anthropometric measurements like mid upper arm circumference were prone to be TST negative (p=0.02) which suggest that under-nutrition does affect positivity of Tuberculin Skin test.[19]

Another factor which contributes to the high rate of false-negative results could be improper storage and handling of PPD antigens. Exposure to light and temperature for more than 20 minutes significantly affect the quality of PPD antigens and result in negative Mantoux test. Further studies are needed to investigate this factor.[20]

In our study although Tuberculin Skin test was more positive in vaccinated children 4 (5%) compared to unvaccinated children 2 (2%) but this difference was statistically insignificant (p=0.40). A previous study by Bozaykut *et al* showed that BCG vaccination at the age of 0–2 months effects TST positivity for a sufficiently long period of time and this effect of BCG vaccination does not alter significantly until 6 years of age.[21] A recent review of literature studying the effect of BCG immunization on outcome of Tuberculin skin test suggest that in children who received BCG vaccine at birth, the effect on size of induration after TST wanes off quite quickly so that by 10 years of age or more, less than 1% of immunized paediatric population will exhibit an induration of 10 mm or more to Mantoux Test.[22] A study conducted in Canada, found that BCG vaccination at birth significantly increase the probability of a positive tuberculin skin test. However, this impact of BCG vaccination on the positivity of TST was less after 15 years of age. They concluded that induration of 15 mm or more is more likely to be attributed to tuberculosis infection rather than previous BCG vaccination.[23] Results from a study in Spain suggest that BCG vaccination at birth has an effect on the results of TST in patients below three years of age in the form of false positive results. However, this effect wanes off after 3 years of age.[24] Some studies suggest that in previously immunized patients, an induration greater than or equivalent to 15 mm should be regarded as positive.[25] Presently, management protocols for tuberculosis in paediatric population recommend an induration of 10 mm to be significant regardless of the immunization status of the patients.[26]

CONCLUSION

Our study concludes that tuberculin skin test is highly nonspecific for the diagnosis of tuberculosis among children in our area irrespective of status of BCG vaccination. This could be attributed to mass prevalence of malnutrition in our area. Another factor which contributes to the high rate of false-negative TST results could be improper storage and handling of PPD antigens. Further studies are needed to investigate these factors.

We therefore recommend that further studies should be conducted to determine reasons behind the high percentage of negative TST results in our setup and to devise reliable, accurate and reproducible investigations for early and precise diagnosis of tuberculosis because tuberculosis and malnutrition are highly prevalent in our region.

AUTHORS' CONTRIBUTION

MUR: Conceptualization of study design, Literature search, Data collection, write-up. SB, SYHG: Data analysis, Data interpretation. I, ZK, ASK: Proof reading.

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