Original Article

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Paediatrics Section

Study of Tuberculin Reactivity in Clinically Suspected Cases of Pulmonary Tuberculosis in Children & Adolescents

SANTHOSH JOSE, MOHAMAD ISMAEL K

ABSTRACT

Introduction: India harbors highest number of tuberculosis (TB) patients globally. Few studies have focused on TB in young children who constitute a vulnerable population and lack of early diagnosis results in increased morbidity.

Aim: To study the tuberculin reactivity in clinically suspected cases of pulmonary tuberculosis in children and adolescents attending Paediatrics OPD in a tertiary care centre and to study the effect of nutritional status of children on tuberculin reactivity.

Study design: Cross sectional study was conducted in Department of Pediatrics of MES Medical college Hospital, Perinthalmanna, for a period 1 year starting from 01/01/2013 to 31/12/2013. In all 1120 subjects were considered for the study out of which 111 patients lost follow-up hence a final sample size of 1009 was obtained.

Materials and Methods: Children aged between 1 to 18 years with suspected TB were prospectively enrolled at a Tertiary Hospital in Malappuram district, Kerala, India. Children were specifically examined for BCG scar. Tuberculin testing was done in all children using the purified protein derivative (PPD).

Results: Tuberculin reactivity among clinically suspected cases of Pulmonary tuberculosis using 1TU PPDRT23 was only 4.8 % as per our study which is in concordance with new sputum positive /case detection rate in Malappuram district, ie; 22-25 per lakh per year. Malnourished children had more tuberculin reactivity than normal children in our study.

Conclusion: Tuberculin test has a sensitivity only of 4.8% among all clinically suspected cases of tuberculosis, and malnutrition and tuberculosis often co-exist and worsen each other.

Keywords: Mantoux test, Mid upperarm circumference, Weight for age

INTRODUCTION

Tuberculosis is an infectious disease caused by *Mycobacterium tuberculosis*. There is increased incidence of extra pulmonary tuberculosis in children [1]. It is estimated that one third of the world's population is infected with *Mycobacterium tuberculosis* [2].

Around 74,000 children who were HIV-negative died of TB in 2012 and an estimated 5,30,000 children became ill with TB. Of the whole world's population, more than 30% is infected with *Mycobacterium tuberculosis* [3]. The TB mortality rate has decreased to 45% since 1990, and the 2015 global target of a 50% reduction in mortality is now within reach [4].

The Annual Risk of Tuberculosis Infection (ARTI) is the proportion of the population per lakh who gets infected (or reinfected) with tubercle bacilli during the course of one year. ARTI for India is 1.5 %, whereas for Kerala it is 1%. NSP/CDR (New sputum Positive /Case Detection Rate) is 22-25 in Malappuram District [5]. Reliable data on the burden of all forms of TB amongst children in India are not available [1]. Recovery of tubercle bacilli which establishes the diagnosis with certainty is difficult in children. Even investigations like GeneExpert have got limitations. Main drawback being limited availability, increased cost etc. Even chest x-ray is not diagnostic. Hence, Tuberculin test, a good old method which has stood the test of time is still routinely practiced worldwide. The present study was undertaken to correlate the clinical symptoms of tuberculosis and tuberculin reactivity using 1 TU PPD RT 23.

MATERIALS AND METHODS

This cross sectional study was conducted in Department of Pediatrics, MES Medical college Hospital, Perinthalmanna, Malappuram District of Kerala, India for the duration of 1 year starting from 01/01/2013 to 31/12/2013. Total 1120 subjects who fulfilled the criteria for clinical suspicion of tuberculosis were selected for the study, out of which 111 patients lost follow-up hence 1009 was considered as a final

sample size. Our study population includes children of 1-18 years age group who attended the Pediatric OPD during the study period.

Inclusion Criteria

a) Persistent fever and or cough >2 weeks

b) Loss of weight/no weight gain*

c) History of contact with infectious TB case. **

*loss of weight more than 5% of body weight as compared to highest weight recorded in the past 3 months .

*No weight gain in the past three months [6].

** Contact with a smear positive case of pulmonary tuberculosis in household.

Exclusion Criteria

a) All children already diagnosed as pulmonary tuberculosis with or without treatment.

b) Past history of tuberculosis.

c) History of live vaccine injection (<1 month), measles, mumps (<3 months), malignancies, immunodeficiency diseases, steroid therapy (<1month).

Anthropometrical measurements were measured using standard techniques. Length was measured <2yrs using infantometer and height >2yrs using stadiometer. Height for age was plotted in CDC growth chart 2000 and interpreted accordingly. Weight was measured using minimal cloth using an electronic weighing machine with a resolution of (+/-100gm). Nutritional status was assessed based on weight for age and plotted on CDC growth chart 2000, and also classified as per IAP classification of Malnutrition for children below 5 years of age [7]. Mid Upper Arm Circumference (MUAC) was measured and classified as per Arnold classification [8].

Mantoux Test

Children were specifically examined for BCG scar. Tuberculin testing was done using the purified protein derivative (PPD) supplied by Span Diagnostics Pvt. limited, Udhana, Surat, India. It is claimed by manufacturers that the test material is caliberated agaist PPD RT23 produced from Statens Serum Institute Denmark. The PPD was diluted with a special buffer with Tween 80 as stabilizing agent. The strength of PPD used was 1 tuberculin units (TU) per 0.1 mL. Children were given, 0.1 mL of the standard 1TU of PPD RT23 taken in a disposable tuberculin syringe, immediately intradermally on volar surface of the forearm. The Mantoux-test was read after 48 to 72 hrs of injection. A reactive area of >10 mm was considered positive.

STATISTICAL ANALYSIS

Statistical methods applied are a) Descriptive statistics; b) Correlation coefficient; and c) Kruskal Wallis test. Data was analyzed using SPSS16 trial version software.

RESULTS

In our study population majority of the children were in the age group of (0-5 years) and least were found in the age group of (10-18 years). In our study, fever and cough (99.6-99.9%) was the commonest presenting symptom in a suspected case of pulmonary tuberculosis. Loss of weight was present in 46.9% of cases as it is a clue for clinical suspicion of pulmonary tuberculosis. There was history of contact with sputum smear positive case within their household among 31.3% of cases [Table/Fig-1]. Clinical pallor was noted in 37.3% of cases [Table/Fig-1]. In our study group, majority of the children had normal weight as per (CDC 2000) growth chart, while 17.6% were under nourished (below 5th Percentile) Among the age group (0-5 years), 82.6% of them were normal,16.4% had grade1 protein energy malnutrition (PEM) as per IAP classification and 1% had grade 2 PEM [Table/Fig-2].

Tuberculin Reaction in Relation to Nutritional Status

Malnutrition is one of the causes for false negative reactions [9]. Among the normal weight children in the age group (0-5 years) 3.7 %had positive tuberculin test 95.5 % had negative and 1.1 % had borderline reaction. Among Grade 1 PEM cases, 8.2 % had tuberculin positivity, 88.7 % had negative and 3.1 % had borderline reaction. Among Grade 2 PEM cases, none were positive, all were negative which was statistically significant (p=0.04). Among the normal weight children in the age group (5-18 years) as per CDC 2000 Growth chart, 4.7% had tuberculin positivity, 94.2% had negative reaction and 1.2% had borderline reaction. Among the undernourished children, 5.3% had tuberculin positivity, 93% were negative, and 1.8% had borderline reaction. Which was statistically not significant (p=0.92).

Symptoms	Yes/No	Count	Percentage (%)
Fever	Yes	1008	99.9
	No	1	0.1
Cough	Yes	1005	99.6
	No	4	0.4
Loss of Weight	Yes	473	46.9
	No	536	53.1
Presence of Pallor	Yes	376	37.3
	No	633	62.7

[Table/Fig-1]: Distribution according to symptoms.

Weight	Count	Percentage (%)
Normal	488	82.6
Grade 1	97	16.4
Grade 2	6	1.0

[Table/Fig-2]: Distribution according to weight for age: (0 – 5 years) IAP classification.

As per our study 94.8% of the children had normal height whereas 5.2% were below 5th percentile as per CDC 2000 [Table/Fig-3]. It was observed that among the age group (1-5 years), 93.7% were normal and 6.3% had mild to moderate malnutrition as per mid arm circumference in Arnold's classification [Table/Fig-4].

In our study among 1009 cases with clinical suspicion of tuberculosis, 93.8% had induration less than 5mm, 1.4% had between 5-10mm, and only 4.8% had induration more than 10mm [Table/Fig-5] i.e. 947 cases were negative, 14 were border line and 48 of them had positive tuberculin test. Among the normal weight children, 3.7% had positive tuberculin test, 95.5 %had negative and 0.8% had Borderline reaction. Among Grade 1 PEM cases, 8.2% had tuberculin positivity, 88.7% had negative and 3.1% had borderline reaction. Among Grade 2 PEM cases, none were positive, all were negative (p=0.04) [Table/Fig-6]. Among the normal height children with clinical symptoms, 4.6% had positive tuberculin reactivity, 94.3% had negative and 1.1% had borderline reaction. Among the cases, below 5th percentile as per CDC 2000 growth chart, positivity was noted among 7.7%, 86.5% had negative reaction and 5.8% had borderline reaction [Table/Fig-7].

As per mid upper arm circumference among the children in the age group (1-5 years), with normal MUAC (>13.5) as per ARNOLD classification, 3.6% had tuberculin reactivity and 95.7% were negative and 0.7% had borderline reaction. On the other hand, among mild-moderate malnutrition (MUAC 12.5-13.5cm), 12.2% had positive reaction and 80.5% were negative and 7.3% were Borderline [Table/Fig-8] which was statistically significant (p=0.01).

Among the normal height children (0-18 years) with clinical symptoms as per CDC 2000 growth chart, 4.6% had positive tuberculin reactivity, 94.3% had negative and 1.1% had borderline reaction. Among the cases, below 5th percentile, positivity was noted among 7.7%, 86.5% had negative reaction and 5.8% had borderline reaction which was statistically significant (p=0.01).

Height	Count	Percentage (%)
Normal	957	94.8
Below 5th percentile.	52	5.2

[Table/Fig-3]: Distribution according to height for age: (0-18 years) (CDC 2000).

MUAC	Count	Percentage (%)
> 13.5	610	93.7
12.5 - 13.5	41	6.3

[Table/Fig-4]: Distribution according to MUAC: (Arnold's Classification).

Size of Induration	Count	Percentage (%)
< 5 mm (negative)	947	93.8
5 - 10 mm (border line)	14	1.4
> 10 mm (positive)	48	4.8

[Table/Fig-5]: Tuberculin reactivity.

Weight	Positive		Negative		Borderline		Kruskal Wallis Test	
	Count	Percentage (%)	Count	Percentage (%)	Count	Percentage (%)	Z	p-values
Normal	18	3.7	466	95.5	4	0.8	6.41*	0.041
Grade 1	8	8.2	86	88.7	3	3.1		
Grade 2	0	0.0	6	100.0	0	0.0		

[Table/Fig-6]: Association of weight and tuberculin reactivity (0 – 5 years).
*: - Significant at 0.05 level
Grade 1 71-80% of expected weight, grade 2 61- 70% of expected weight as per IAP classification of PEM. Statistically significant (p= 0.041)

Height	Positive		Negative		Borderline		Kruskal Wallis Test	
	Count	Percentage (%)	Count	Percentage (%)	Count	Percentage (%)	Z	p-values
Normal	44	4.6	902	94.3	11	1.1	8.88*	0.012
Below 5th percentile	4	7.7	45	86.5	3	5.8		

[Table/Fig-7]: Association of height for age and tuberculin reactivity.
*: - Significant at 0.05 level

MUAC	Positive		Negative		Borderline		Kruskal Wallis Test	
	Count	Percentage (%)	Count	Percentage (%)	Count	Percentage (%)	Z	p-values
> 13.5	22	3.6	584	95.7	4	0.7	23.59**	0.010
12.5 - 13.5	5	12.2	33	80.5	3	7.3		

[Table/Fig-8]: Association of muac and tuberculin reactivity.
** Significant at 0.01 level

Even though malnutrition is one of the causes of false negative tuberculin reaction our results were different. In the present study tuberculin positivity was more in malnourished (IAP classification) group 8.2% as compared to normal children 3.7%.

DISCUSSION

As per socioeconomic status, majority belonged to upper lower class followed by lower middle class, lower class, and upper class, as per modified Kuppuswamy classification, supporting the incidence of tuberculosis among the low socioeconomic class population as reported by Faridi MMA et al., [10] and Sharifi et al., [11].

Tuberculin Reactivity

In our study, Tuberculin positivity was 4.8% with 1 TU PPDRT23, which was comparable with Indian studies by Chadha et al.,[12], similar observation was also found among international studies as well with lesser cut off for induration done by Hennessey KA et al., [13].

Following could be the reasons for low reactivity:

a) New Sputum Positive /Case Detection Rate (NSP/CDR) in Malappuram district is as low as 22-25 cases/lakh/year, which is in concordance with the present study.

b) We had used 1 TU PPD RT 23 for the study provided by Central TB division through RNTCP, but latest recommendation of RNTCP is 2 TU which was not available.

c) As per selection criteria, which includes- fever for more than 2 weeks. Many children with symptoms would have been treated for fever with antibiotics with Anti-tuberculosis action during 2 weeks period.

Relationship between Tuberculin Reactivity and BCG scar Status

Previous vaccination with BCG can cause a reaction to Tuberculin Test. As per our study, BCG scar was present among majority of cases 76.6 %. Tuberculin reactivity among BCG vaccinated children was more (5.3%) compared to non vaccinated group (3%).

Mustaf et al.,[14] did a similar study with 1 TU PPD RT 23, tuberculin positivity was more among BCG vaccinated children (16.5%) as compared to non-vaccinated group (6.5%)

Serene VT et al., [15] showed contradictory results where 18.2% with BCG Scar and 20% without BCG Scar were Tuberculin positive. Kulkarni ML et al., [16] also confirmed that tuberculin reactivity was more (11.4%) among BCG vaccinated children as compared to non-vaccinated group (7.4%).

Tuberculin Reaction in Relation to Nutritional Status

Even though malnutrition is one of the causes of false negative tuberculin reaction our results were different. In the present study, tuberculin positivity was more in malnourished (IAP classification) children group 8.2% as compared to normal children 3.7%. Similar observation was made by other workers like Shah et al., [17] and Ganapathy KT et al., [18] also.

The degree of suppression is proportional to the severity of malnutrition. It is also possible that these children had more exposure to *Mycobacterium tuberculosis* and hence the increased number of tuberculin positivity. The other factor which may be responsible for the nonspecific determinants which include various social factors, like those associated with poor quality of life namely over crowding, sub-standard housing, ignorance, low level of education, poor sanitation, poverty and large families etc.

LIMITATIONS

Main limitation of study is lesser number of study population, further studies with higher number of children should be considered. Other tests like Gene Xpert would have been used in diagnosis of tuberculosis which had better specificity and sensitivity.

CONCLUSION

Positive tuberculin reactivity of more than 10mm induration was found in 4.8% of clinically suspected cases of pulmonary tuberculosis. Tuberculin positivity was more among BCG vaccinated children (5.3%) as compared to non-immunized group (3%), (p=0.23) not significant. and malnutrition and tuberculosis often coexist and worsen each other. Thus, despite all its limitations tuberculin test gives a reliably sensitive results matching at par with New Sputum Positive / Case Detection Rate (NSP/CDR) in Malappuram district. So until newer and more reliable techniques like GeneXpert are easily available tuberculin test should be continued as an investigation of paediatric TB diagnosis.

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AUTHOR(S):
1. Dr. Santhosh Jose
2. Dr. Mohamad Ismael K

PARTICULARS OF CONTRIBUTORS:
1. Associate Professor, Department of Paediatrics, MES Medical College, Perinthalmanna, Kerala University of Health Sciences, Kerala, India.
2. Assistant Professor, Department of Paediatrics, MES Medical College, Perinthalmanna, Kerala University of Health Sciences, Kerala, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Mohamad Ismael K
Assistant Professor, Department of Paediatrics,
MES Medical College, Perinthalmanna,
Kerala University of Health Sciences, Kerala, India.
E-mail: hensapapa@gmail.com

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