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CORRELATION OF NEUROTUBERCULOSIS WITH BCG VACCINATION IN CHILDREN-A CROSS SECTIONAL OBSERVATIONAL STUDY

Dr.Akhilesh Ahirwar, Dr. Samriddhi Jain, Dr.Ananya Ganguly , Dr.Mayur jain , Dr.Rahul Gedam

Senior resident ,Dept of neonatology
NSCB medical college and superspeciality hospital Jabalpur (M.P.)

Corresponding author -Dr. Samriddhi Jain
Senior Resident,Dept. Of Paediatrics,Gandhi Medical College,
Bhopal (M.P.)
Senior Resident, Department of Pediatrics,Nscgmc khandwa(M.P.)
Senior resident ,Dept of neonatology ,NSCB medical college and superspeciality hospital Jabalpur (m.p.)
Designation- senior resident ,Department- Pediatrics
Institute- Netaji Subhash Chandra Bose Medical College Jabalpur(M.P.)

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ABSTRACT

Background: Although pulmonary TB is more common, neuro-tuberculosis is the more severe form of tuberculosis, causing death or major neurological sequelae in children despite of treatment

Aim: The primary objective of this study is socio-demographic and clinical evaluation of neuro-tuberculosis children and its correlation with the BCG vaccination

Materials and methods: Total 45 **c**confirmed tuberculosis Children of 6 months-12 years of age presenting with neurological manifestations were enrolled in this study. Detailed socio-demographic history, presenting symptoms, neurological examination and BCG immunization status of the child was documented. All relevant investigation was done in each recruited subject

Results: Majority of the children (85.7%) belonged to >5 years of age, predominantly males. No significant association was shown between BCG vaccination and demographic variables ($p>0.05$). Meningeal irritation and abnormal movements were most common clinical signs of neuro-tuberculosis among BCG vaccinated children and half of them had tubercular meningitis stage 1. HIV status was positive in significantly higher proportion of children with no BCG scar ($P<0.05$). However, no significant association of BCG scar with Mantoux test and BCG vaccination and mortality in neuro-tuberculosis children ($p>0.05$).

Conclusion: Identifying and managing factors responsible for neuro-tuberculosis can prevent morbidity and mortality associated with the neuro-tuberculosis in children

Keywords: Neuro-tuberculosis, BCG vaccination, Mantoux test, Children

INTRODUCTION

Tuberculosis (TB) is caused by mycobacterium tuberculosis; it remains a substantial health problem and is one of the leading causes of death worldwide [1]. Though tuberculosis is primarily a pulmonary disease, extra pulmonary involvement is also common [2]. Once the infection is acquired, its control relies on both the adaptive and innate immune responses, and protective immunity against Mycobacterium tuberculosis varies considerably between individuals [3]. Tuberculosis may affect all the organ systems, most common being respiratory, central nervous system, gastrointestinal (GI) system, musculoskeletal system, lymphoreticular system, reproductive system etc [4]. The tuberculosis of central nervous system is termed neuro-tuberculosis, and it can affect meninges, spinal cord, brain alone or in combination [5]. The spectrum of neuro-tuberculosis include tuberculous meningitis, encephalopathy, military tuberculosis involving neural structure, vasculopathy, tuberculoma, tubercular abscess, Pott's spine, spinal meningitis etc [6]. Neuro-tuberculosis usually results from the Hematogenous spread of the tubercle bacilli from primary rich foci (most commonly pulmonary foci) whereas direct spread from extra cranial or intracranial foci is rare [7]. Neuro-tuberculosis is a rare condition attributing to approximately1% of the total tuberculosis cases, but has been associated with significant mortality. Amongst various forms of neuro-tuberculosis, tuberculous meningitis (TBM) is the most common cause responsible for CNS tuberculosis [8]. The common risk factors predispose the children to CNS tuberculosis; these include malnutrition, HIV coinfection, measles infection, malignancies, immunosuppressed children, family history of tuberculosis and children on immunosuppressive agents [7]. BCG, an attenuated strain of Mycobacterium bovis (M.bovis), remains the only approved vaccine against TB for clinical use since 1921 [9]. World Health Organization (WHO) included BCG vaccination in Expanded Programme on Immunization (EPI), which was dedicated for infant vaccination worldwide [9]. The BCG vaccine is one of the most widely used vaccines globally. The World Health Organization (WHO) recommends vaccinating neonates residing in high-incidence TB and/or Leprosy settings with a single dose of the BCG vaccine at birth [10]. Furthermore, neonates residing in low-incidence settings and at high risk of contracting TB disease and/or Leprosy should also be considered for vaccination [9]. High-risk neonates, defined as those with close contact to currently or previously infected individuals. Repeat BCG vaccination is not currently recommended by the WHO as evidence arguing its efficacy is insufficient [11]. Despite its wide range of purported efficacy in preventing primary TB, with many studies predicting efficacy anywhere between 0 and 80%, the BCG vaccine continues to be a mandatory vaccine for much of the world [9, 11]. The vaccine's strong safety profile, measured as one major side effect from vaccine administration per one million doses administered to immunocompetent individuals, may also be a reason for its continued use in TB endemic countries [11].

Aims & objectives: The present study was conducted to correlate neuro-tuberculosis patient with the BCG vaccination status in our tertiary care hospital

MATERIAL AND METHODS

This was a cross sectional observational hospital based study conducted in the department of pediatrics at Gandhi Medical College, Bhopal, India. The study duration was 18 months from March 2021 to Sept.2022.

Inclusion Criteria:

- Children of 6 months-12 years of age with both genders
- All confirmed tuberculosis cases presenting with neurological manifestations
- All patients whose parents or guardian provided written informed consent

Exclusion Criteria:

- Children less than 6 months or more than12 years of age
- Known cases of underlying neurological disease other than tubercular etiology
- Patients whose parents not giving consent

Detailed data regarding socio-demographic variables, clinical history, presenting symptoms, history of contact with tuberculosis, dietary history and immunization status of the child was enquired and documented. All the children were then subjected to detailed anthropometric, general and systemic examination with special emphasis on neurological examination. The level of consciousness (modified Glasgow coma scale (GCS)), signs of raised intracranial pressure (ICP) and meningeal irritation was noted.

Neuro-tuberculosis was suspected based on following features:

- Fever and/or a cough for ≥2 weeks, neurological symptoms (irritability, refusal to feed, headache, vomiting, altered sensorium, abnormal movements or seizure) with weight loss or poor weight gain.

All the recruited children were then subjected to following investigations: chest X-ray, Mantoux test, complete hemogram, gastric aspirate for acid-fast Bacilli (AFB), ultrasonography of abdomen, Cerebrospinal fluid CSF) analysis and CBNAAT of Gastric aspirate

All the children underwent neuro-imaging (plain and contrast enhanced computed tomography or magnetic resonance imaging (MRI).

STATISTICALANALYSIS

Data analysis was done with the help of IBM SPSS software version 20. Categorical data was represented as frequency and proportions whereas continuous quantitative data was expressed as mean and standard deviation. Association of various variables was done using chi square test. P value of <0.05 was considered statistically significant.

RESULT

A total of 45 children with TB presenting with neurological manifestation were analysed.

Table 1 showing correlation of BCG vaccination with the socio-demographic variables of the study subjects. About 85.7% children who were not showing BCG scar belonged to more than 5 years of age and majority of children who did not receive BCG scar were males and belonged to lower middle socioeconomic class. Most of children had chronic under nutrition. We observed no significant association of BCG scar with socio-demographic variables (p>0.05).

Table1: Association of BCG scar with socio-demographic variables

Socio-demographic variables		BCG scar		P value
		No (N=7)	**Yes (N=38)**	
Age	6 months to 3 years	0 (0%)	8 (21.1%)	0.23
	3 to 5 years	1 (14.3%)	10 (26.3%)	
	>5years	6 (85.7%)	20 (52.6%)	
Sex	Male	5 (71.4%)	18 (47.4%)	0.24
	Female	2 (28.6%)	20 (52.6%)	
Socio economic status	Upper middle	0 (0%)	2 (5.3%)	0.68
	Lower middle	4 (57.1%)	16 (42.1%)	
	Lower	3 (42.9%)	20 (52.6%)	
Nutritional status	Normal	2 (28.6%)	10 (26.3%)	0.99
	Mild to moderate malnutrition	1 (14.3%)	7 (18.4%)	
	Severe malnutrition	1 (14.3%)	6 (15.8%)	
	Chronic under nutrition	3 (42.9%)	15 (39.5%)	

Our study observed the most common clinical signs of neuro-tuberculosis were meningeal irritation and abnormal movements among BCG vaccinated children, no significant association of signs of neuro-tuberculosis with BCG scar (p>0.05).

Table 2: Association of BCG scar with neuro-tuberculosis signs

Signs	BCG scar		P value
	Yes (N=38)	**No (N=7)**	

Meningeal irritation		21 (55.3%)	3 (42.9%)	0.55
Hemi-paresis		1 (2.6%)	0 (0%)	0.66
Quadriparesis		4 (10.5%)	1 (14.3%)	0.77
Abnormal movements		19 (50%)	5 (71.4%)	0.29
Level of consciousness	**<7**	5 (13.2%)	0 (0%)	0.50
	7 to 10	15 (39.5%)	4 (57.1%)	
	>10	18 (47.4%)	3 (42.9%)	
Raised ICP		12 (31.6%)	2 (28.6%)	0.87

Half of the neuro-tuberculosis patients with BCG scar have tubercular meningitis stage 1. Our study observed no significant association of BCG scar with stage of TBM (p>0.05).

Table 3: Association of BCG scar with stage of TBM

Stage of TBM	**BCG scar**		**P value**
	Yes (N=38)	**No (N=7)**	
I	19 (50%)	2 (28.6%)	0.14
II	8 (21.1%)	4 (57.1%)	
III	11 (28.9%)	1 (14.3%)	

Among BCG vaccinated children, Mantoux test was positive in 81.6%, CBNAAT was positive 84.2% and chest X-ray were positive in 89.5% respectively. On neuro-imaging findings most of the study children showed meningeal enhancement (52.6%) followed by Peri-ventricular edema (15.8$). HIV status was positive in significantly higher proportion of children with no BCG scar (P<0.05). However, no significant association of BCG scar with other investigations (p>0.05).

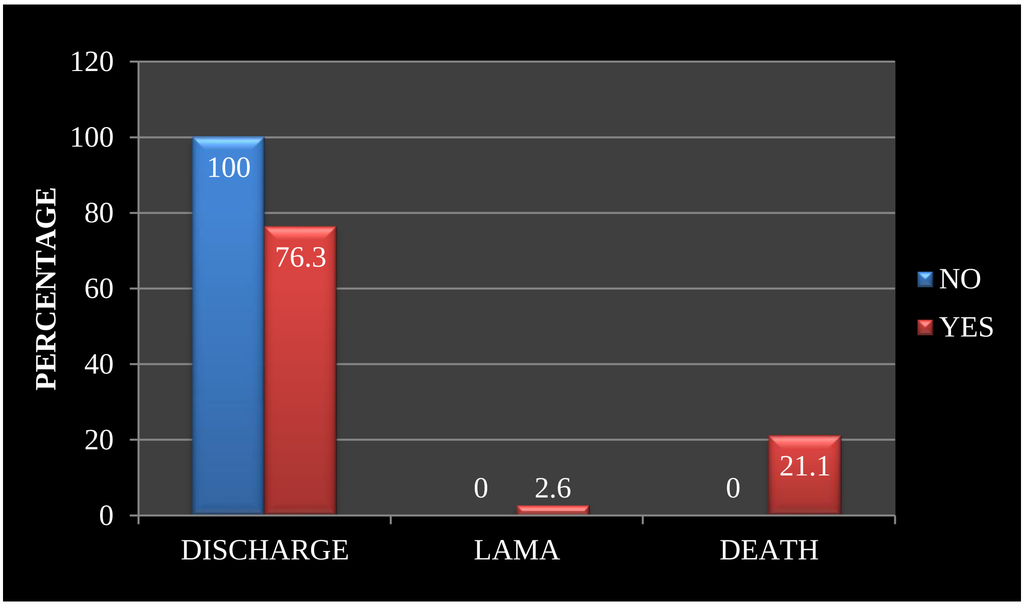
Table 4: Association of BCG scar with investigations

Investigations		**BCG scar**		**P value**
		Yes (N=38)	**No (N=7)**	
Mantoux	Negative	7 (18.4%)	0 (0%)	0.22
	Positive	31 (81.6%)	7 (100%)	
CBNAAT	Negative	6 (15.8%)	5 (71.4%)	0.50
	Positive	32 (84.2%)	2 (28.6%)	

Chest X-ray	Normal	34 (89.5%)	6 (85.7%)	0.88
	Abnormal	4 (10.5%)	1 (14.3%)	
HIV	Negative	38 (100%)	6 (85.7%)	**0.018**
	Positive	0 (0%)	1 (14.3%)	
Neuro-imaging	Meningeal enhancement	20 (52.6%)	3 (42.9%)	0.46
	Hydrocephalous	2 (5.3%)	1 (14.3%)	
	Peri-ventricular edema	6 (15.8%)	0 (0%)	
	Infarcts	2 (5.3%)	0 (0%)	
	Tuberculoma	5 (13.2%)	1 (14.3%)	

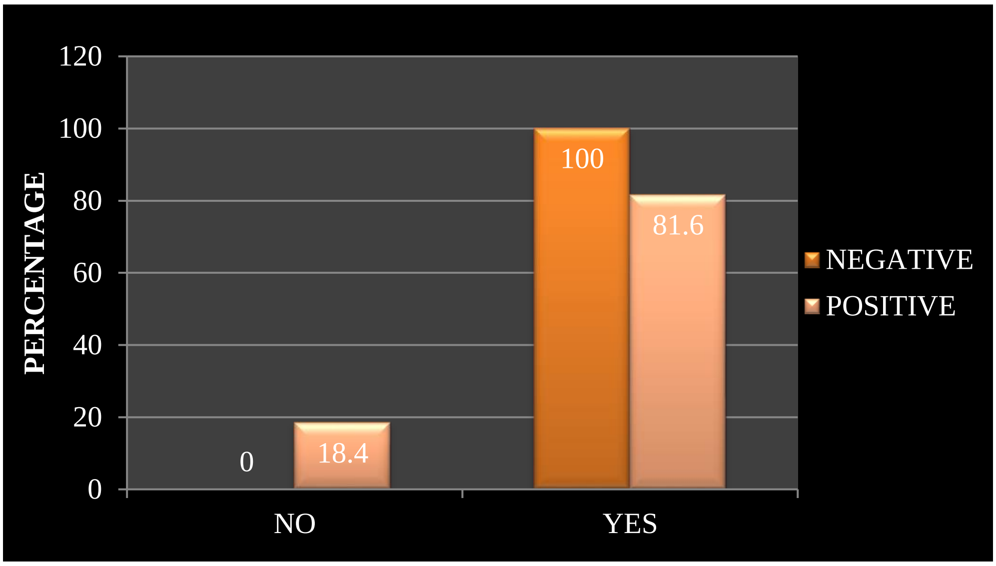
Though mortality was reported in higher proportion of cases with history of BCG scar (21.1%), the observed association was statistically insignificant (p>0.05).

Graph 1: Association of BCG scar with outcome



Out of 38 cases with positive Mantoux test, 81.6% cases had history of BCG scar. The observed association of BCG scar with Mantoux test was statistically insignificant (p>0.05).

Graph 2: Association of BCG scar with Montoux test



DISCUSSION

In this study majority of the children who were not showing BCG scar belonged to more than 5 years of age group and predominantly males, similar finding were reported by Renji S et al [12].

We have observed no significant association between BCG scar with socio-demographic variables of neuro-tuberculosis patients ($p>0.05$), in agreement with the Kuan et al [13].

In the children with extra pulmonary tuberculosis group, neuro-tuberculous was the commonest form, the incidence of neuro-tuberculous was higher in BCG unvaccinated children in current research, concordance findings were reported by Col R Gupta, et al [14] and L Martinez, et al [15].

We have found that Chronic under nutrition or severe malnutrition in children were associated with the neuro-tuberculosis, concordant with the findings of Dahiphale R et al [16], in which about 75.7% cases with neuro-tuberculosis had malnutrition.

In our study, the common clinical symptoms were fever and seizures whereas common clinical signs meningeal irritation and abnormal movements among neuro-tuberculosis children, comparable with the Rock, et al [17].

We have reported that most of the patients had tubercular meningitis stage I and no significant association of BCG scar with stage of tubercular meningitis, our results constant with the Dewan P et al [18] and Mengjin Qua, et al [19].

Mantoux test is one of the commonly performed investigation for diagnosis of childhood tuberculosis, in this study 84.4% patients were mantoux positive, consistent to the a study done by Verma J et al [20].

Present study observed meningeal enhancement and peri-ventricular edema were most common findings on neuro-imaging, our results correlate with the Cherian A, et al [21].

HIV status was positive in significantly higher proportion of children not vaccinated with BCG as compared to BCG vaccinated children (P<0.05) and HIV positive status also significantly correlated with the neuro-tuberculosis, similar findings were reported by Huang, et al [22].

The mortality rate in our study was 17.8%, accordance with the Solarte RA et al [23] reported overall mortality rate of 17%.

Current study reported there was no significant association between BCG vaccination and mortality among neuro-tuberculosis children, whereas Sharma P, et al [24] reported mortality rate of 22% in neuro-tuberculosis and documented focal neurological deficits, advanced stage of TBM, HIV positive status, and BCG unimmunized status were independently associated with poor prognosis in neuro-tuberculosis.

Israni AV et al [25] documented mortality in 23.4% cases and higher mortality was reported in non vaccinated children.

CONCLUSION

In conclusion, the study showed a high incidence neuro-tuberculosis was seen in BCG unvaccinated children. The underlying risk factors were poor socio-economic status; chronic malnutrition and poor immunization coverage contribute to childhood neuro-tuberculosis. These factors should be taken into consideration for prevention of morbidity and mortality due to neuro-tuberculosis

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Conflicts of interest: none

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