

Tuberculous meningitis in BCG vaccinated and unvaccinated children

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Background: A modified clinical presentation of tuberculous meningitis (TBM) in children vaccinated with BCG has been described in the literature. However, most reports are old and not based on actual comparisons and tests of significance. Also, neuroimaging features were not compared. With large scale BCG coverage, it becomes pertinent to describe the "modified" presentation and identify any significant differences between vaccinated and unvaccinated children with TBM.

Methods: A total of 150 consecutive hospitalised children (96 unvaccinated, 54 vaccinated) were enrolled. They all satisfied predefined criteria for diagnosis of TBM. Clinical and radiological features of children with/without a BCG scar were compared.

Results: Univariate analysis revealed that the vaccinated children with TBM had significantly lower rates of altered sensorium (68.5% v 85.4% unvaccinated; OR 2.2 (1.1 to 6.2); $p=0.019$) and focal neurological deficits (20.3% v 39.5% unvaccinated; OR 2.6 (1.1 to 6.0); $p=0.016$), and higher mean (SD) Glasgow Coma Scale score (10.2 (3.4) v 8.76 (2.7) unvaccinated; $p=0.010$) and cerebrospinal fluid cell count (210.9 v 140.9 unvaccinated; $p=0.019$). No significant radiological differences were seen. Short term outcome was significantly better in the vaccinated group with 70% of the total severe sequelae and 75% of the total deaths occurring in the unvaccinated group ($p=0.018$).

Conclusion: Children with TBM who have been vaccinated with BCG appear to maintain better mentation and have a superior outcome. This may in part be explained by the better immune response to infection, as reflected in the higher CSF cell counts in this group in the present study.

Tuberculosis continues to be a major public health problem globally. India is a major contributor to this global burden, harbouring nearly a third of all cases.¹ Tuberculous meningitis (TBM) is the most dangerous form of tuberculosis and is, in particular, seen in children. TBM remains an important cause of hospitalisation, death, and permanent neurological disability in children in India. Over the years there has been no noteworthy decline in the incidence of this deadly disease, despite the claims of high vaccination coverage with the bacille Calmette Guérin (BCG) vaccine.^{2,3} Although the BCG vaccine has been used for over 80 years, there remains a shadow of doubt regarding its value in protection against tuberculosis.^{4,5} In large community trials the protective efficacy of BCG varies from 0% to 80%.^{6–9} The BCG vaccine trial in the Chingleput district in southern India showed no protective effect of the vaccine against adult pulmonary tuberculosis.¹⁰

Although the protective efficacy of BCG vaccination in adult forms of the disease is doubtful, it is held to be useful in preventing the spread of and improving outcome of tubercular infection.^{11–13} Vaccinated children mobilise their cellular immune responses more effectively compared with unvaccinated children when exposed to natural tuberculous infection, thereby experiencing fewer haematogenous complications such as miliary tuberculosis and TBM. However, even this protection is only relative and may be overcome in presence of a heavy infecting dose from a household contact, in the presence of severe malnutrition, and because of waning immunity many years after vaccination.^{14–16}

There are few reports in the literature that describe a distinctive clinical presentation of TBM in BCG vaccinated children.^{17–22} These reports are not based on actual comparisons and statistical differences between vaccinated and unvaccinated children and were mostly anecdotal in nature. Also, most of these studies were conducted in the

pre-computed tomography (CT) era and radiological features were not reported.

It is important to recognise the full clinical spectrum of TBM in BCG vaccinated children so that the diagnosis is not delayed. With more children being vaccinated nowadays, the clinical spectrum of TBM may be changing. We therefore undertook this prospective study to compare the clinical and radiological features of TBM in BCG vaccinated and unvaccinated children.

PATIENTS AND METHODS

We conducted this cross-sectional study over a period of two years, from July 2002 to July 2004, in the pediatric wards of King George Medical University Hospital, Lucknow, India. We included those children between one month and 12 years of age, who were admitted to the hospital and satisfied certain predefined criteria for diagnosis of TBM, provided that they had not received antitubercular treatment in the last three months. The diagnostic criteria for TBM were:

- clinical presentation with fever of 14 days or more along with any neurological manifestation and a progressive course
- cranial CT scan showing two or more of the following:
 - hydrocephalus
 - enhancement in basal cisterns or sylvian fissures
 - tuberculoma
- cerebrospinal fluid (CSF) pleocytosis (>10 cells/mm³).

Abbreviations: BCG, bacille Calmette Guérin (vaccine); CSF, cerebrospinal fluid; TBM, tubercular meningitis

All enrolled children underwent a work-up in accordance with a predesigned protocol including a detailed history taking, physical examination, investigations, and follow up. We assessed the children's nutritional status by weight for age percentage using standards derived from Indian children,²³ and recorded the presence/absence of a BCG scar on the left shoulder. The sensorium was assessed using the Glasgow Coma Scale modified for children. Bradycardia with hypertension and/or an abnormal breathing pattern were considered as features of raised intracranial tension.

The investigations carried out included complete blood count, tuberculin test with 5TU PPD (tuberculin purified protein derivative), chest x ray, CSF examination for cells, protein, and sugar, bacterial and mycobacterial cultures, and a cranial contrast-enhanced CT scan. The latter was usually done within 72 hours of admission with a third generation scanner, and 10–12 axial cuts were taken. We measured ventricular size and graded the hydrocephalus as mild, moderate, or severe according to Meese *et al.*²⁴ Basal enhancement was also graded as mild, moderate, or severe according to Bhargava *et al.*²⁵ Hydrocephalus was classified as communicating if the fourth ventricle was also dilated and obstructive if the fourth ventricle was normal.

We followed the hospital's protocol with regard to therapy. All the patients were started on a four drug antitubercular treatment along with steroids. The antitubercular regimen consisted of:

- intramuscular injection of streptomycin 30 mg/kg per day for two months
- pyrazinamide (tablet) 30 mg/kg per day for two months
- rifampicin (tablet) 10 mg/kg per day for 12 months
- isoniazid (tablet) 5 mg/kg per day for 12 months.

Steroids were given in the form of oral prednisolone 1–2 mg/kg per day for four to six weeks and tapered off.

As all of the children were hospitalised, we could check compliance daily by questioning their attendants. We recorded the daily progress in hospital. Outcome at discharge was classified as follows:

- normal
- mild sequelae, such as isolated focal neurological deficit, but ambulatory and able to perform daily activities
- severe sequelae, such as frank mental regression, frank motor deficits leading to inability to perform routine activities, blindness, deafness, or vegetative state
- death.

Statistical analysis

We entered data in a Microsoft Excel worksheet and used SPSSwin software for data analysis. The clinical features, results of the investigations, and outcome of the children with and without a BCG scar were compared by univariate analysis; two sample *t* tests were used for continuous variables and χ^2 tests for nominal and ordinal variables to identify features associated with BCG vaccination. The sample size was calculated for difference between proportions. With $\alpha = 0.05$, $\beta = 0.2$, and smaller proportion = 0.2, and to detect a difference of 20% between the two groups, the sample size was calculated to be 54 per group.²⁶

Ethical approval

We did not obtain formal ethical approval because the study was purely observational and patients' identities were not revealed. However, informed verbal consent was obtained from the guardian of each child.

RESULTS

A total of 150 children with TBM were enrolled in the study, of whom 54 had a BCG scar. Tables 1–4 provide comparisons of the symptoms, signs, investigative findings, and outcomes between BCG vaccinated and unvaccinated children. Of the 10 demographic/historical features compared in table 1, only altered sensorium was significantly different in the two groups, being higher in the non-vaccinated group. Of the 13 clinical signs shown in table 2, the Glasgow Coma Scale at admission was significantly lower and prevalence of neurological deficits was significantly higher in the unvaccinated group. Comparison of the investigative findings (table 3) revealed significant differences between the groups only in the CSF cell count, which was higher in the vaccinated group. Finally, outcome was significantly better in the vaccinated group (table 4).

DISCUSSION

A number of workers have remarked on the modified pattern of TBM in BCG vaccinated children but most observations have been anecdotal in nature. To date there are only a few studies in the world literature that have compared clinical features of BCG vaccinated and unvaccinated children with TBM.^{20–21} Further, there is scant literature comparing the radiological (neuroimaging) features in these two groups of children.²⁰ As more and more children are being vaccinated with BCG, the clinical spectrum of the disease (TBM) may be changing. It is important to document the clinical and radiological differences so as to recognise the full spectrum of the disease.

Table 1 Demographics of and distribution of symptoms in BCG vaccinated and unvaccinated children with tuberculous meningitis

	BCG scar		OR (95% CI)	p value
	Absent	Present		
No of children	96	54		
Age (in months)†	45.63 (37.5)	46.5 (36.1)		0.754
Duration of illness (days)†	45.2 (52.3)	35.1 (38.3)		0.157
Tonic spasms‡	44 (45.8)	23 (42.5)	1.1 (0.5 to 2.4)	0.701
Generalised clonic seizures‡	38 (39.5)	16 (29.6)	1.6 (0.7 to 3.4)	0.272
Partial seizures‡	11 (11.4)	4 (7.4)	2.7 (0.7 to 10.8)	0.097
Convulsion frequency† per day	5.19 (4.9)	3.8 (4.7)		0.485
Headache‡	46 (47.9)	29 (53.7)	0.9 (0.4 to 2.2)	0.899
Vomiting‡	72 (75.0)	41 (75.9)	0.8 (0.4 to 1.8)	0.670
Altered sensorium‡	82 (85.4)	37 (68.5)	2.2 (1.1 to 6.2)	0.019*
Contact history‡	45 (46.8)	32 (59.2)	0.6 (0.3 to 1.3)	0.145

*Significant.

†Values are mean (SD). A two sample *t* test was used for comparison of means.

‡Values are n (%). χ^2 tests were used for comparison of proportions.

Table 2 Comparison of clinical signs in vaccinated and unvaccinated children

	BCG scar		OR (95% CI)	p value
	Absent	Present		
No of children	96	54		
Weight for age %†	67.9 (13.8)	70.5 (12.8)		0.470
Glasgow Coma Scale score†	8.76 (2.7)	10.2 (3.4)		0.010*
Fundus blurring/papilloedema‡	40 (41.6)	21 (38.8)	1.1 (0.5 to 2.3)	0.739
Fundus pallor/atrophy‡	22 (22.9)	14 (25.9)	0.8 (0.4 to 2.0)	0.678
Meningeal signs‡	64 (66.6)	35 (64.8)	1.1 (0.5 to 2.2)	0.818
Focal deficits‡	38 (39.5)	11 (20.3)	2.6 (1.1 to 6.0)	0.016*
Cranial nerve palsy‡	40 (41.7)	18 (33.3)	1.4 (0.7 to 2.8)	0.353
Generalised ↑ tone‡	68 (70.6)	32 (59.2)	1.7 (0.8 to 3.6)	0.148
Clonus‡	20 (20.8)	17 (31.4)	0.6 (0.2 to 1.3)	0.146
Plantar extensor‡	81 (84.3)	40 (74.0)	2.0 (0.8 to 5.1)	0.087
Abnormal movements‡	30 (31.2)	12 (22.2)	1.6 (0.7 to 3.7)	0.237
Decerebration‡	25 (26.0)	11 (20.3)	1.4 (0.6 to 3.3)	0.435
Signs of ↑ intracranial tension‡	42 (43.7)	16 (29.6)	1.8 (0.9 to 4.0)	0.088

*Significant.

†Values are mean (SD). A two sample *t* test was used for comparison of means.‡Values are n (%). χ^2 tests were used for comparison of proportions.

The strengths of the present study include the prospective enrolment of children and careful documentation using a standardised predesigned data collection form. The case definition of TBM was also predefined. These TBM criteria are used by paediatricians throughout India. Except for fungal meningitis, which admittedly is a rare entity, other meningoencephalitis are unlikely to be misclassified as TBM by these criteria. The Indian Academy of Pediatrics Working Group on Tuberculosis has laid special emphasis on cranial CT scan for diagnosis of TBM.²⁷ We deliberately kept our diagnostic criteria sufficiently broad so that we could include as wide a spectrum of the disease as possible. Although diagnosis based on CSF culture for mycobacteria or on polymerase chain reaction for mycobacterial DNA in CSF yield the widest possible range of disease, these investigations were not usually available to us and the results would have been available only after several weeks. Weight for

age was adopted as the criterion for grading malnutrition. Other parameters such as skinfold thickness or mid-arm circumference may have added to the measure of nutritional status, but weight for age is the single most important parameter that is widely used in assessment of nutritional status and grading of malnutrition. A BCG scar was considered as the marker for vaccination. In India, patients seldom keep a record of vaccinations given, and thus the BCG scar is the most practical method of ascertaining prior vaccination with BCG. However, scars could have faded in a small proportion of patients. We assessed short term outcome only even though we often see the neurological status of patients with TBM improve over months or years, and therefore some of our poor outcomes may change for the better with time. However, in the present study patients with good outcome would at least have been correctly classified.

Table 3 Comparison of investigative findings in vaccinated and unvaccinated children

	BCG scar		OR (95% CI)	p value
	Absent	Present		
No of children	96	54		
Cerebrospinal fluid				
Cells†	140.9 (156.6)	210.9 (288.4)	–	0.019*
Polymorphonuclear leucocytes %†	35.4 (31.4)	32.7 (33.0)	–	0.431
Protein†	134.3 (143.9)	135.1 (189.7)	–	0.403
Sugar†	37.3 (20.9)	38.3 (21.4)	–	0.306
X ray chest (miliary or consolidation)‡	26 (27.0)	14 (25.9)	1.0 (0.4 to 2.4)	0.923
Computed tomography scan				
Hydrocephalus‡	94 (97.9)	54 (100)	0.0 (0.0 to 7.3)	0.285
Communicating‡	44 (45.8)	16 (29.6)	2.0 (0.9 to 4.3)	0.051
Obstructive‡	44 (45.8)	31 (57.4)	0.6 (0.3 to 1.3)	0.173
Basal enhancement‡	81 (84.3)	44 (81.4)	1.2 (0.5 to 3.2)	0.648
Degree of enhancement:				
1	4	1	–	0.425
2	15	5		
3	30	17		
4	3	1		
Periventricular leak‡	70 (72.9)	37 (68.5)	1.2 (0.6 to 2.7)	0.567
Tuberculoma‡	8 (8.3)	4 (7.4)	1.1 (0.3 to 4.8)	0.840
Infarct‡	17 (17.7)	9 (16.6)	1.1 (0.4 to 2.9)	0.871
Ventricular size				
0	1	1	–	0.457
1	11	5		
2	32	15		
3	16	5		

*Significant.

†Values are mean (SD). A two sample *t* test was used for comparison of means.‡Values are n (%). χ^2 tests were used for comparison of proportions.

Table 4 Comparison of outcomes of vaccinated and unvaccinated children with TBM

	BCG scar		p value
	Absent	Present	
No of children	96	54	
Hospital stay†	20.7 (12.3)	22.3 (14.2)	0.65
Shunt surgery (n=63)‡	20/41 (48.7)	11/22 (50.0)	1.000
Outcome†§	Total no (%)		
Normal	16 (10.6)	8 (50.0)	0.018*
Mild sequelae	47 (31.3)	26 (55.3)	
Severe sequelae	60 (40.0)	42 (70.0)	
Death	20 (13.3)	15 (75.0)	
Not known	7 (4.6)	7 (100)	

*Significant

†A two sample t test was used for comparison of means. Values are mean (SD).

‡ χ^2 tests were used for comparison of proportions. Values are n (%). Data available on 63 patients.§ χ^2 test for trend.

Our statistical comparisons of the two groups included 38 variables, of which five showed significant differences. It can be argued that the few significant differences could have occurred by chance. However, it must be taken into account that the significant differences were found among related variables from the history and physical examination—this shows a true association. We did not adjust the level of significance. In fact, if the cut-off for the p value had been lowered to 0.01 or 0.005, none of the differences would have been significant.

About two thirds of children with TBM in the present study were unvaccinated. To enrol 54 vaccinated children with TBM, we therefore had to enrol 96 unvaccinated children. Our hospital caters in particular to the poor and seriously sick children of the city of Lucknow and its surrounding areas. Therefore, it is likely that we see a large proportion of the individuals contracting TBM in this area especially when the disease reaches an advanced stage. Whether this reflects the true vaccination coverage in the community is, however, doubtful. Since this was a hospital based study, it is possible that unvaccinated children, who have a higher risk of getting TBM, are seen more frequently by us.

The comparison of clinical history in the vaccinated and unvaccinated groups revealed a significantly higher proportion with altered sensorium in the unvaccinated group. Table 1 shows that the average duration of symptoms at admission was 10 days longer in the vaccinated group. The difference was not statistically significant. Unvaccinated children likely come from lower socioeconomic backgrounds and uneducated families who are less aware of or simply not able to recognise or report their child's symptoms early on. On examination the Glasgow Coma Scale score was significantly lower in this group. In a study of 80 cases between 1973 and 1975, Udani *et al* observed that the "conscious" type of TBM was three times commoner in vaccinated children.²² They also found that localised forms of TBM occurred more commonly in BCG vaccinated children, whereas "classic" TBM was seen twice as often in the unvaccinated children studied. Various brain stem syndromes due to localised brain involvement have been described in vaccinated children by these pioneers in the field.²¹ Although we did not observe such brain stem syndromes or cranial nerve palsies more commonly in our vaccinated group, our study supports Udani *et al*'s observations that BCG vaccinated children have a significantly higher rate of conscious-type TBM. We also found significantly higher rate of focal neurological deficits in the unvaccinated group.

The only investigation that was significantly different between the groups was the mean CSF cell count, which was higher in the vaccinated group. This may reflect a better immune response and cellular reaction to the infection. However, Udani *et al* reported a higher rate of "serous" TBM (51.3% v 18.7% in unvaccinated) in their series.²¹ We did not find any instances of serous TBM in the present study because one of our criteria for diagnosis was CSF pleocytosis. The radiological findings of the two groups were not significantly different. Although communicating hydrocephalus was seen in 45.8% of the unvaccinated children in contrast with 29.6% in vaccinated group, this difference just failed to reach statistical significance.

Finally, our study indicates that outcome of TBM was better in the vaccinated children; however, we studied the short term outcome only. This has been reported by earlier workers also. Guller *et al* (1998) studied the effect of neonatal BCG vaccination on clinical and laboratory profiles of and mortality among children with TBM in Turkey.²⁰ Although the rate of family contact of tuberculosis, age distribution, clinical features, and laboratory investigations were not significantly different between the vaccinated and unvaccinated children, mortality was only a third in the vaccinated group. Udani also stated that one of the most important factors affecting prognosis in TBM is BCG vaccination, and found that death rate due to miliary tuberculosis and TBM was twice as high in unvaccinated children.^{12, 22} BCG vaccination may be one of the factors influencing the outcome of TBM. Other factors that might play a role include age, stage of disease at diagnosis, immune and nutritional status, household contact, compliance and coexistence of other illnesses. Of these, the latter four may be influenced by socioeconomic factors and living conditions. We did not evaluate the socioeconomic status of our patients but data on nutritional status and household contact were collected and compliance was ensured because the patients were hospitalised. Although this univariate analysis suggests an association between BCG vaccination status and better outcome in TBM, it would be interesting to undertake a multivariate analysis of factors influencing outcome of TBM to see if this association holds true even after controlling for the effect of other variables.

CONCLUSION

Although BCG vaccination does not totally prevent occurrence of TBM our results support earlier studies suggesting that children who have been vaccinated with BCG appear to maintain better mentation and ultimately have a better outcome than unvaccinated children. Our study did not reveal any significant differences in neuroradiological features to explain this finding. The better outcome may in part be explained by the better mobilisation of cell mediated immune response to infection as is reflected in the higher mean CSF cell count in vaccinated children in our study.

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