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Comparison of Tuberculous meningitis in children with or without BCG Scar

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Abstract

Background: Most serious form of tuberculosis in children is tubercular meningitis. TBM remains a significant cause of hospitalization, death, and permanent neurological disability in children in India. Even though the BCG vaccine has been used from past 80 years, there remains a shadow of doubt about its value in protection against tuberculosis children. Adapted clinical presentation of tuberculous meningitis (TBM) in children vaccinated with BCG has been defined in the literature. It is significant to recognize the full clinical spectrum of TBM in BCG vaccinated children so that the diagnosis is not overdue. With more children being vaccinated nowadays, the clinical spectrum of TBM changing. We, therefore, started this prospective study to compare the clinical, biochemical and radiological skins of TBM in BCG vaccinated and unvaccinated progenies.

Methods: It was a prospective cross- sectional study conducted with a total of 100 successive hospitalized children with tubercular meningitis.(76 vaccinated, 24 unvaccinated).They all satisfied predefined criteria for the diagnosis of TBM. Clinical, bio-chemical and radiological features of children with/without a BCG scar were compared.

Results: Univariate analyses showed that the vaccinated children with TBM had significantly lower rates of altered sensorium and focal neurological deficits and higher mean Glasgow Coma Scale score and cerebrospinal fluid cell count. Signs of raised intracranial tension were more common in the unvaccinated group. Hydrocephalus and tuberculoma were more common in unvaccinated children. Short-term outcome was significantly better in the vaccinated group. Mortality was more in the unvaccinated group.

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

Keywords: TBM, BCG.

Introduction

Tuberculosis is a major public health problem all over the world. India bears a major portion of this burden globally harbouring nearly one-third of all cases. The most dangerous form of tuberculosis seen in children is Tubercular meningitis (TBM). TBM is an important cause of hospitalisation, death, and morbidity in the form of permanent neurological disability in children in India. Although the BCG vaccine has been used for a decade, there remains a shadow of doubt regarding its role in protection against tuberculosis. BCG vaccination is held to be useful in preventing the spread of and improving the prognosis of tuberculosis in children.

There are few reports in the literature that describe a distinctive clinical profile of TBM in BCG vaccinated children.[7-12] It is necessary to recognize the full clinical spectrum of TBM in BCG vaccinated children so that the diagnosis and treatment are not delayed. With more children being vaccinated nowadays, the clinical spectrum of TBM has been changed. This prospective study was done to compare the radiological and clinical features of TBM in BCG vaccinated and unvaccinated children.

Patients and Methods

It was a prospective cross-sectional study conducted with a total of 100 consecutive hospitalised children with tubercular meningitis. (76 vaccinated, 24 unvaccinated) between December 2014 to December 2015 at Patna Medical College and Hospital, Patna. They all satisfied predefined criteria for the diagnosis of TBM. Clinical, biochemical and radiological features of children with/ without a BCG scar were compared in this study. The diagnostic standards for TBM:

- Record of fever of more than 15 days along with any neurological sign and a progressive course.
- CT scan of cranium showing two or more of the following :
  - hydrocephalus
  - basal enhancement
  - tuberculoma
- cerebrospinal fluid:
  - pleocytosis>10 cells/mm^3,Mostly lymphocytes.
  - Increased protein, low sugar, and ADA more than 10.

Methods

- Detailed history,
- Examination,
- Investigations (biochemical and radiological) and follow up.

The Glasgow Coma Scale was used to assess the sensorium of children.

Following investigations were done:

1) Complete blood count
2) Test of tuberculin with 5TU PPD (tuberculin purified protein derivative),

3) Chest X-ray.
4) CSF examination for cells, protein, and sugar, bacterial and mycobacterial cultures, and a cranial contrast-enhanced CT scan.

- Ventricular size was measured and there are three ways to measure hydrocephalus graded as mild, moderate, or severe according to Meese et al.[13] Similarly, Enhancement BASAL was also graded as mild, moderate, or severe according to Bhargava et al.[14] If the fourth ventricle was also dilated Hydrocephalus was classified as communicating and as obstructive if the fourth ventricle was normal.

All the patients were started on a four drug anti-tubercular treatment along with a steroid.

The anti-tubercular regimen consisted of:-

- Intramuscular injection of streptomycin 20 mg per kg per day for two months.
- pyrazinamide (tablet) 30 mg/kg per day for two months
- rifampicin (tablet) 15 mg/kg per day for 12 months
- Isoniazid (tablet) 10 mg/kg per day for 12 months.

Dose of steroids was 1–2 mg/kg per day of oral prednisolone for four to six weeks and tapered off in next two weeks.

Statistical Analysis

Dose of steroids was 1–2 mg/kg per day of oral prednisolone for four to six weeks and tapered off in next two weeks.

Entered data in a Microsoft Excel worksheet and SPSS software for data analysis was used. 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 $\chi 2$ tests for nominal and ordinal variables to identify features associated with BCG vaccination .Consent was obtained from the guardian of each child.

Tables 1 to 5 provides a comparison of symptoms, signs, stages of diseases, investigative findings, and outcomes between BCG-vaccinated and unvaccinated children. Period of illness was maximum in the unvaccinated group. Tonic spasms, seizure frequency, decreased vision and altered sensorium were more common in the non-vaccinated group but the distinctness was not significant. In both the group's a headache, vomiting and fever were equally common. Table 2 unveils that patients of the unvaccinated group had a more severe stage of disease on admission as compared to the vaccinated group. The GCS was significantly lower in the unvaccinated children as compared to vaccinated children. The ubiquity of neurological deficits was also significantly higher in the unvaccinated group. Papilledema, meningeal signs, and cranial nerve palsies occurred more frequently in unvaccinated children. There was significant differences in the CSF cell count of the two groups, which was higher in the vaccinated group. Hydrocephalous was more frequent in unvaccinated children. Finally, the prognosis was significantly better in the vaccinated group (Table 4). Hospital stay was shorter in vaccinated children.

Table 1: Distribution of symptoms

	BCG Scar		P value
	Absent	Present	
No. of children	24	76	
Age (in months)	12-36	24-72	
Duration of illness(days)	18	8	>0.05
Tonic spasms	4	6	>0.05
Seizures	8	15	>0.05
Headache	13	38	>0.05
Vomiting	11	32	>0.05
Decreased vision	11	20	>0.05
Fever	18	45	>0.05
Altered sensorium	6	9	>0.05
Contact history	2	1	>0.05

Table 2: Stage of disease on admission

	BCG Scar	
	Present	Absent
Stage I	65%	43%
Stage II	29%	35%
Stage III	6%	22%

Table 3: Comparison of clinical signs

	BCG Scar		P value
	Absent	Present	
No. of children	24	76	
Glasgow Coma Scale(average)	6-7	12-13	>0.05
Fundus blurring/ papilledema	11	29	>0.05
Fundus pallor/ atrophy	4	7	>0.05
Meningeal signs	20	55	>0.05
Focal deficits	2	5	>0.05
Cranial nerve palsy	1	3	>0.05
Generalised raised tone	2		>0.05
Clonus	3	2	>0.05
Plantar extensor	2	1	>0.05
Abnormal movements	1	1	>0.05
Decerebration	0	0	>0.05
Signs of raised intracranial tension	5	3	>0.05

Table 4: Investigative findings in children with or without BCG Scar

	BCG scar		P value
	Absent	**Present**	
No of children	24	76	
CSF			>0.05
Cells	16	59	
Polymorphonuclear leucocytes%	14	52	
Protein	12	66	
Sugar	10	50	
X- Ray chest(military or consolidation)	12	34	>0.05
CT Scan			>0.05
Hydrocephalus	11(45.8 %)	21(27.6 3%)	
Basal enhancement	3	4	
Tuberculoma	6	12	

Table 5: Prognosis of children with or without BCG Scar

		BCG Scar		P value
		Absent	**Present**	
No of children		24	76	
Hospital stay(days)		14	10	>0.05
Shunt surgery				
Outcomes	**Total**			
Normal	24	4	20	>0.05
Mild sequalae	47	16	31	
Severe sequalae	22	15	7	
Death	5	4	1	
Not known	2	2	0	

Discussion

The sequence of TBM is altered in BCG vaccinated and unvaccinated children. The radiological features in these two groups of children have been related by some authors. The clinical outline of the disease (TBM) has changed over past few years due to increase in the proportion of children being vaccinated.

These measures are used by pediatricians throughout India. Except for fungal meningitis, which is the occasional entity, other meningo-encephalitis are unlikely to be misclassified as TBM by these criteria. The Indian Academy of Pediatrics Working Group on Tuberculosis has placed special emphasis on cranial CT scan for the diagnosis of TBM. The most sensitive tests like CSF culture for tubercle bacilli or polymerase chain reaction for mycobacterial DNA in CSF were not usually obtainable to us and the results would have been available only after several weeks. So, these were not used as diagnostic criteria. Weight for age was accepted as the criterion for grading malnutrition.

A BCG scar at the insertion of left deltoid was considered as the sign for vaccination. In India, patients rarely keep a record of vaccinations and thus the BCG scar is the most practical method of checking prior vaccination with BCG.

24% of children with TBM in the present study were unvaccinated. Our hospital caters in particular to the poor and extremely sick children of the city of Patna and its nearby areas. Therefore, it is likely that we see a large proportion of the individual's anguish with TBM in this area, particularly in an advanced stage. Whether this replicates the true vaccination analysis in the community is, however, doubtful. The assessment of clinical history in the vaccinated and unvaccinated groups publicized a significantly higher proportion with transformed sensorium in the unvaccinated group. Table 1 indicates that the average extent of symptoms at admission was 10 days longer in the unvaccinated group. The difference was not statistically noteworthy. Unvaccinated children likely come from poorer socioeconomic backgrounds and illiterate families who are not able to distinguish their child's symptoms timely. On investigation, the Glasgow Coma Scale score was considerably lower in this group. From 1973 to 1975 80 cases has been studied, Udani et al witnessed that the "conscious" kind of TBM was three times commoner in vaccinated children. They also found that localized forms of TBM happened more commonly in BCG vaccinated children, whereas "classic" TBM was seen twice as often in the unvaccinated children studied. Several brain stem syndromes due to localized brain involvement have been described in vaccinated children by these innovators in the field. Even though we didn't witness such brain stem syndromes or cranial nerve palsies more commonly in our vaccinated group, our study supports Udani et al remarks that BCG- vaccinated children have a suggestively higher rate of conscious-type TBM. We also found ominously higher rate of focal neurological deficits in the unvaccinated group. The average CSF cell count was greater in the vaccinated group. This may replicate a better immune response plus cellular reaction to the infection. However, Udani et al informed a higher rate of "serous" TBM (51.3% v 18.7% in unvaccinated) in their sequence. We didn't discover any occurrences of serous TBM in the present study because one of our criteria for diagnosis was CSF pleocytosis. The radiological outcomes of the two sets were not ominously different. Even though communicating hydrocephalus was seen in 45.8% of the unvaccinated children in contrast with 27.6% in the vaccinated group, this difference just failed to reach statistical significance.

Lastly, our study designates that result of TBM was better in the vaccinated children; however, we studied the short period outcome only. This has been stated by earlier personnel also. Guller *et al* (1998) calculated the consequence of neonatal BCG-vaccination on laboratory and clinical profiles of and mortality among children with TBM in Turkey. Although the incidence of contact

of tuberculosis, clinical features, age distribution and laboratory research were not significantly dissimilar between the vaccinated and unvaccinated children, mortality was only a third in the vaccinated group. Udani also specified that one of the most vital factors affecting prognosis is BCG vaccination in TBM, and found that death rate due to miliary tuberculosis and TBM was twice as high in unvaccinated children. BCG vaccination is one of the factors influencing the outcome of TBM but there are also other factors that might play a role in age, stage of disease at diagnosis, immune and nutritional status, household contact, compliance and coexistence of other illnesses. Out Of these, the later four may be influenced by socioeconomic factors and living circumstances. We did not assess the socioeconomic status of our patients but data on nutritional status and household contact were collected and compliance was confirmed because the patients were hospitalised. Even though this univariate inspection suggests an association between BCG vaccination status and better result in TBM, it would be fascinating to undertake a multivariate inspection of factor influencing consequence of TBM to see if this association holds true even after controlling for the effect of other variables.

Conclusion

Even though BCG vaccination cannot thwart occurrence of TBM, still our results support earlier studies suggesting that vaccinated children appear to maintain better mentation and ultimately have a better result than unvaccinated children. Our study did not disclose any significant difference in neuro-radiological features to describe this outcome. The better result may in part be explained by the better mobilisation of cell-mediated immune response to infection as is reflected in the higher average CSF cell count in vaccinated children.

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