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Original Research Article

A Hospital Based Assessment of Different Clinical Manifestations and Outcome of TBM in Relation to BCG Vaccinated, Non-Vaccinated and Nutritional Status of the Children

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Abstract

Aim: The objective of the present study was to evaluate the different clinical manifestations and outcome of TBM in relation to BCG vaccinated, non- vaccinated and nutritional status of the children.

Methods: The present study was conducted at department of Pediatrics, JLNMCH, Bhagalpur, Bihar, India and 50 children with definite or probable tuberculous meningitis (TBM) were included. Permission for the study was obtained from the College authorities prior to commencement. Duration of the study was one year. Local cultural values and ideas were respected. Confidentiality was assured. The nature and purpose of the survey were explained in detail to them in their own language.

Results: The common symptoms observed were fever 90%, altered sensorium 62%, vomiting 60% and convulsions 56%. Other symptoms observed were cough, headache. The common signs present were GCS below 10 in 57% of cases, meningeal irritation in 64%, and McEvan's sign in 60%. Also seen were hemiparesis 43%, CN palsy 43%, fundal changes25%. All signs were significantly more common in malnourished children except GCS10-14. Tuberculomas, conscious variety and focal involvements are seen more commonly in well-nourished group among vaccinated patients. All atypical features of TBM are more common in well-nourished group when compared to malnourished children except encephalopathy. Other typical features found were Ophthalmoplegia (3), brain stem syndromes (2), serous meningitis (2), conscious type (3), encephalopathy (2) and focal infarcts in 4 cases.

Conclusion: It was concluded that clinical patterns in TBM vary according to nutritional status of the child and severe malnutrition carry very poor prognosis. Knowing different clinical patterns of the disease helps in early prognosis and thus in preventing deaths due to TBM among children.

Keywords: Tuberculous Meningitis, BCG immunisation status, Severe Malnutrition.

Introduction

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 Guerin (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]

Also, the results of BCG vaccination in malnourished children are often disappointing in our country. [17] Classical or generalized TBM, military TB, disseminated TB and other serious complications of primary infection go on occurring in malnourished BCG vaccinated children. [17,18] Hence it is useful to relearn the new patterns of tuberculous disease if any, in relation to vaccination status and nutritional status of the children. The published data regarding, the various clinical forms and outcome of TBM and relation to BCG vaccination status are limited. [19] Also wide availability of CT scan and neurosonogram has contributed to a better understanding of the clinical features of TBM and its management.

The objective of the present study was to evaluate the different clinical manifestations and outcome of TBM in relation to BCG vaccinated, non-vaccinated and nutritional status of the children.

Materials and Methods

The present study was conducted at department of Pediatrics, JLNMCH, Bhagalpur, Bihar, India for one year and 50 children with definite or probable tuberculous meningitis (TBM) were included.

Inclusion criteria/case definition

1. Patients who satisfy clinical case definition of TBM, which includes history, clinical features, fundoscopy, etc.
2. Demonstration of acid-fast bacilli in the CSF or fulfillment of the following criteria.

A. Essential: CSF showing:

a. Predominant lymphocyte pleocytosis >50/mm^3.
b. Protein > 60 mg %.
c. Sugar<2/3 of blood sugar.

B. Supportive

Along with essential ones, two or more of the following clinico-investigational criteria must be present:

a. History of fever of two weeks or more.
b. Positive family history of tuberculosis.
c. Generalised lymphadenopathy.
d. Mantoux test (5TU) >10mm.
e. Positive radiological evidence of tuberculosis elsewhere in the body.
f. Isolation of AFB from gastric lavage or other sites.

g. CT scan evidence of basal exudates or CNS tuberculosis.
h. Histologically proven tubercular lymphadenitis

Nutritional status of the children is assessed according to IAP classification i.e., Nutritional subcommittee of the Indian Academy of Paediatrics (standard value).

Exclusion criteria: A child with any neurological symptom with proven etiology like CSF positive for specific etiology like pyogenic meningitis, positive for J E virus, malaria parasite etc.

Permission for the study was obtained from the College authorities prior to commencement. Duration of the study was one year. Local cultural values and ideas were respected. Confidentiality was assured. The nature and purpose of the survey were explained in detail to them in their own language.

All studies were performed after obtaining informed consent in patient's native language. All these individuals were subjected to detailed clinical and neurological examination and various laboratory tests, including complete Haemogram, ESR, Mantoux test, biochemistry, LP for CSF Analysis, Transcranial neurosonogram / CT scan brain or both in majority of cases for the evidence of chronic meningitis changes and its complications. Patients were considered as immunized with BCG if there is a clear BCG scar on the left deltoid region.

Statistical Methods: Descriptive statistics like mean, percentages were used. Chi square test was applied to find out the statistical significance of TBM in relation to BCG vaccination and different grades of nutrition. P value of <0.05 was considered statistically significant and <0.001 as highly significant.

Clinical data: The neurological status of all patients with TBM was evaluated on admission and during follow up and the clinical manifestations were classified as follows

Classical TBM

Stage I: Prodromal stage: No definite neurological symptoms at admission or in the history before admission.

Stage II: Stage of meningeal irritation: meningitis signs, drowsiness or lethargy, cranial nerve palsies.

Stage III: Stage of diffuse or focal cerebral involvement: severe clouding of consciousness, stupor or coma, convulsions, gross paresis or paralysis. Modified forms of TBM: Any isolated /unusual CNS feature with or without global encephalopathy

a. Serous tubercular meningitis.
b. Isolated tuberculous encephalopathy.
c. Multiple intracranial tuberculomas (meningeal).
d. Localised lesions manifestations due to infarctions in the territory of large intracranial arteries and / or small arteries with lacunar infarct with resultant large number of syndromes.
e. Localised meningitis in the posterior fossa.
f. Isolated spinal tuberculous meningitis.

Therapy and outcome:

Therapy: All patients received ATT (anti-tubercular treatment) according to body weight. 2HRZE+ 10HRE regimen was followed.

In addition, children received steroid for 10-12 weeks.

Anti-edema and other measures were considered whenever indicated.

Outcome: At discharge and at 3 months follow up outcome was graded into 3 groups according to modified British medical research council clinical criteria.

Outcome I = complete recovery.

Outcome II = partial recovery with residual deficits/disability.

Outcome III = Death.

Results

Mean age of study subjects was 3.4 years with range between 6months to 12 years. Majority were in the age group of 1-5 years (64%) followed by infants (16%). The male to female ratio was 1:1. Mean duration of illness was about 12.6 days prior to establishment of diagnosis at our hospital. The mean duration of stay of the cases at our hospital was 18.1 days. Majority of the study subjects belonged to low socio economic group (80%).

Table 1: Clinical Profile of tuberculous meningitis among study subjects

Clinical characteristics	N%
Classical symptoms	
Fever	45 (90)
Convulsions	28 (56)
Vomiting	30 (60)
Altered Sensorium	31 (62)
Cough	17 (34)
Headache	27 (54)
Classical signs	
Meningeal irritation	30 (60)
Hemiparesis	23 (46)
Cranial nerve palsy	26 (52)
Fundal changes	14 (28)
McEwan's sign	37 (74)
GCS =15	20 (40)
10-14	21 (42)
<10	25 (50)
Atypical Features	
Isolated ophthalmoplegia	3 (6)
Brain stem syndromes	2 (4)
Serous meningitis	2 (4)
Localised meningitis/edema(CT scan)	5 (10)
Conscious type	3 (6)
Encephalopathy (CT scan)	2 (4)
Meningeal tuberculoma (CT scan)	6 (12)
Focal infarcts (CT scan)	4 (8)

The common symptoms observed were fever 90%, altered sensorium 62%, vomiting 60% and convulsions 56%. Other symptoms observed were cough, headache. The common signs present were GCS below 10 in 57% of cases, meningeal irritation in 64%, and McEvan's sign in 60%. Also seen were hemiparesis 43%, CN palsy 43%, fundal changes25%. All signs were significantly more common in malnourished children except GCS10-14. Tuberculomas, conscious variety and focal involvements are seen more commonly in well-nourished group among vaccinated patients. All atypical features of TBM are more common in well-nourished group when compared to malnourished children except encephalopathy. Other typical features found were Ophthalmoplegia (3), brain stem syndromes (2), serous meningitis (2), conscious type (3), encephalopathy (2) and focal infarcts in 4 cases.

Table 2: Classical and Atypical Features of TBM in Relation to Vaccination Status and nutritional status.

Immunization status	Classical	Atypical	Total
BCG +ive	14 (53.84)	12 (46.16)	26
BCG –ive	10 (41.66)	14 (58.34)	24
Nutritional Status			
Well-nourished	6 (23.07)	20 (76.93)	26
Poorly nourished	20 (83.34)	4 (16.66)	24

Among the vaccinated patients, 53.84% had classical disease and 46.16% had atypical disease. In non-vaccinated group 41.66% had classical disease and 58.34% had atypical disease. This difference was not statistically significant (p value >0.05). Among the well-nourished patients, 23.07% had classical disease and 76.93% had atypical disease. In severely malnourished children 83.34% had classical disease and 16.66% had atypical disease. This difference was statistically significant (P value <0.05).

Table 3: Outcome of TBM among BCG vaccinated children in relation with nutritional status

Stage	Outcome 1 n (%)	Outcome 2 n (%)	Outcome 3 n (%)	Total
Well nourished				
Stage1	4 (100)	0 (0)	0 (0)	4
Stage 2	4 (50)	3 (38.5)	1 (12.5)	8
Stage 3	0	0	0	0
Malnourished				
Stage1	0	0	0	0
Stage 2	1 (20)	3 (60)	1 (20)	5
Stage 3	0 (0)	4 (36)	6 (54)	10

In BCG +ive normally nourished group 33% presented in grade I disease with full recovery (outcome1). 67% presented in grade II disease of which 43% recovered completely, 43% partially recovered and 14% died. None were in grade III disease. In poorly nourished children, none had grade I disease, 5 had grade II disease in which 2 recovered partially, 1 recovered fully and 1 died. 10 patients had grade III disease, one patient was referred to higher centre, 4 patients recovered partially and 5 patients died.

Table 4: Outcome of TBM among BCG non-vaccinated children (n=20) in relation with nutritional status

Stage	Outcome 1 n (%)	Outcome 2 n (%)	Outcome 3 n (%)	Total
Well nourished				
Stage1	1 (100)	0	0	1
Stage 2	4 (67)	2 (33)	0 (0)	6
Stage 3	0 (0)	1 (100)	0 (0)	1
Malnourished				
Stage1	0	0	0	0
Stage 2	0 (0)	2 (100)	0 (0)	2
Stage 3	0 (0)	4 (50)	4 (50)	8

Among the BCG –ive normally nourished patients, 1 patient was in grade I disease and recovered fully. 7 (35%) patients were in grade II, 4 patients recovered fully, 3 partially and none died. Only one patient was in grade III disease which recovered partially. Among the malnourished patients, none had grade I meningitis. Only 1 was in grade 2 which recovered partially. Majority, 10 (50%) were in grade III disease among which one went against medical advice, one referred to higher centre. In the remaining 8 patients half recovered partially and half died.

Discussion

The World health organization (WHO) estimates that one third of the world's population is infected with mycobacterium tuberculosis, with the highest prevalence of tuberculosis in Asia. [20] The prevalence of childhood tuberculosis is largely underestimated, usually as a result of diagnostic problems. Clinical manifestations like lethargy, fever, vomiting, weight loss, altered mental status, photophobia being nonspecific particularly in the early stages of the disease, tuberculosis remains easily misdiagnosed, under diagnosed or paradoxically over treated. Only 30-40% childhood cases are confirmed even in tertiary care institutions. [21]Younger children also experience more severe disease such as meningitis and disseminated disease. [22]

80% of cases in the present study were below 5 years of age depicting that majority of cases occurring in less than 5 years children. As compared to present study slightly higher incidence was found in Benakappa et al [23] study and slightly lower incidence was found in Udani et al. [12] Gender distribution was found to be equal in his study whereas in other studies have shown a slight male preponderance. Male preponderance could be due to more outdoor exposure to TB patients and preference given by parents in seeking health care. In the present study fever was the most common symptom followed by altered mental status and vomiting. The variations in symptoms could be because history is indirect as perceived by parents and other family members rather than directly told by patient. Similar to the present study other studies also found fever as one of the most common symptom (Ramachandra, Benakappa, Udani peter décor). [12,23,24]

Atypical clinical features were present in 33% cases, most common being meningeal tuberculomas (one third cases) followed by local meningitis. Present study reported that mean duration of illness before seeking medical advice was 12.6 days. In contrast, Kondo S studies reported longer mean duration of illness. [25] In the present study no statistically significant difference in clinical manifestations was seen between vaccinated and non-vaccinated children.

Significant difference was observed in clinical features like neck rigidity, cranial nerve deficits, focal neurological signs between well-nourished and severely malnourished children in this study. No comparative studies were available for the same although Udani et al and Awasthi series proposed similar opinions. [12,26] There was no significant difference in mortality between vaccinated (29%) and non-vaccinated children (22%). This could be due to poor immunity, secondary to malnutrition and poor living conditions. Al Abbasil reported lower case fatality rate in BCG vaccinated (13%) than non-vaccinated children (26%). [27,28]

Conclusion

Tuberculous meningitis (TBM) is an important cause of admission in children with tuberculosis in the present study area. The disease can present in many different forms. The clinical features and outcome of TBM may vary between well-nourished and severely malnourished children. There appears to be no difference in clinical

features and outcome of disease in vaccinated and non-vaccinated children.

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