TUBERCULOSIS IN BCG VACCINATED AND UNVACCINATED CHILDREN

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ABSTRACT

One hundred, non-consecutive, non-randomized, cases of tuberculosis divided in 2 groups i.e. Group A including 50 BCG vaccinated children and Group B including 50 unvaccinated children were studied to determine the pattern of tuberculosis and the role of protein energy malnutrition in the pathogenesis of tuberculosis. Thirty four per cent of Group A and 52 per cent of Group B had severe protein energy malnutrition. Sixty eight per cent in Group A and 76 per cent in Group B had intrathoracic forms of tuberculosis. Twelve (24%) patients in Group A and 11 (22%) in Group B suffered from serious forms of tuberculosis including tubercular meningitis, miliary tuberculosis and disseminated tuberculosis. The difference was not statistically different ($p>0.05$). However, in severe form of tuberculosis, the morbidity in vaccinated group was less. Sixty six per cent of vaccinated children with disseminated forms of tuberculosis had features of severe protein energy malnutrition. BCG is not effective in preventing tubercular infection in children of preschool age. It is effective to a certain extent in localizing the infection to a particular organ. Severe protein energy malnutrition is a contributing factor in the genesis of tuberculosis in preschool children vaccinated with BCG at or immediately after birth.

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KEYWORDS : BCG vaccine; Protein energy malnutrition; Tuberculosis.

Introduction

The control of tuberculosis in an individual today is not difficult and there is reasonable certainty of cure. However at the community, national and global level this promising vista is not seen. Tuberculosis affects all age groups, with 1.3 million cases of tuberculosis and 40,000 deaths occurring in children under 15 years in developing countries [1]. Of the nearly 2.5 million tuberculosis deaths in 1990, 0.6 million were in India. Six to 10 per cent of the total admissions to a paediatric ward are due to tuberculosis.

The BCG vaccine was discovered in 1924 and is in use for nearly 70 years. It has not made the impact that was expected. Several epidemiological studies have shown very wide variations in the protection offered by BCG vaccine [2]. The little protection that the vaccine provides in turn modifies the disease pattern. Studies have demonstrated the changing spectrum of tuberculosis in children

who have been vaccinated [3]. Protein energy malnutrition (PEM), common in preschool children also plays a role in aggravating the risk for tuberculosis. This study attempted to :

- i) study the pattern of tuberculosis in the vaccinated child,
- ii) determine the role of protein energy malnutrition in pathogenesis of tuberculosis,
- iii) examine the role of BCG vaccine in tuberculosis control.
- iv) suggest remedial measures in overcoming the problem of tuberculosis in children.

Material and Methods

This was a prospective study during the period from Jan 94 to Jul 95. Hundred non-consecutive, non-randomized cases of tuberculosis in children below 12 years of age were included in the study. Group A included 50 vaccinated children and Group B included 50 unvaccinated children. A

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child with history of BCG vaccination and having a scar was considered to be a vaccinated child. A child with history but no scar was considered as unvaccinated. Each child underwent thorough detailed history taking including history of contact with an adult case of tuberculosis, nutritional assessment as per Indian Academy of Pediatrics classification, and clinical examination [4]. Suspected cases of tuberculosis were investigated to confirm the diagnosis. Investigations done included the following :

a) Mantoux test : 1 TU PPD with tween 80, procured from BCG Laboratory Guindy, Madras was used for the study. An induration of 10 mm or more at 72 hr was taken as positive.

b) BCG diagnostic test : This test was done in those children in whom the Mantoux test was negative. 0.1 mL of BCG vaccine was used. This test was graded according to Udani's criteria [5].

c) Radiological investigations such as chest radiography, ultrasonography, CT scan of brain, barium meal studies and intravenous pyleography were done as applicable in individual cases.

d) Histopathological examination of tissues was included in appropriate cases.

e) Isolation of acid fast bacilli from different specimen was attempted by direct smear and culture technique in all cases.

The diagnosis of tuberculosis in each child was based on the scoring system of Udani in which each parameter in history, clinical examination and laboratory test is scored with points ranging from 0 to 4. Readers are referred to original reference for the details [5]. The interpretation of the scoring in each child was done as follows :

5 and below : Probably negative, but high risk subjects may require chemoprophylaxis. 6 and 8 : Probably positive and needs further evaluation.

9 and above : Established tuberculous disease.

Observations

This was a cross-sectional hospital study wherein 100 paediatric patients of tuberculosis occurring in the age group below 12 years were studied. There were 54 male and 46 female patients. Majority of the cases (87/100) were below the age of 10 years. Further, of these 87 cases, 63 were in the age group of 2 to 9 years. Mean age at diagno-

sis was approximately same in both groups i.e. about 5 years (Group A 3.85 years and Group B 6.0 years). The youngest patient in both groups was a month old infant (Table 1). Thirty nine per cent of children were found to have severe protein energy malnutrition. Another 38 per cent exhibited signs of mild malnutrition. The difference between the two groups as regards severe malnutrition was not statistically significant (52% Gp B; 34% GpA). Approximately equal proportion (18%) of children in both groups were of normal nutritional status. Positive history of contact was elicited in 13 patients in Group A and 16 in Group B.

TABLE I
Age distribution in 100 children with tuberculosis

Age	Vaccinated (Group A) (n= 50)	Unvaccinated (Group B) (n=50)
< 23 months	11 (22%)	9 (18%)
2 - 5 years	19 (38%)	11 (22%)
6 - 9 years	15 (30%)	20 (40%)
> 10 years	5 (10%)	10 (20%)

The pattern (clinical spectrum) of tuberculosis in the two groups is highlighted in Table 2. Primary complex and progressive primary complex cases were diagnosed on the basis of chest radiography and scoring criteria. The 7 cases of disseminated tuberculosis were diagnosed on the basis of clinical signs, radiological appearance, ultrasonographic findings and, in one patient, liver biopsy. Two patients with skeletal tuberculosis in the unvaccinated group were indeed disseminated forms and diagnosed on histopathological basis. Tubercular lymphadenitis was diagnosed in 5 patients based on histopathology. Glancing at the figures it is apparent that the type (pattern) of tuberculosis including severe forms i.e. tuberculous meningitis, disseminated tuberculosis, and miliary forms occurred in almost equal number of vaccinated and unvaccinated children. In other words, immunized children exhibited similar pattern of illness as the unimmunised. Further analyzing the data in the two groups it seems that in vaccinated children, the localized forms are three times commoner than disseminated forms. The apparently more number of disseminated forms in vaccinated children as

compared to that of unvaccinated children was not statistically significant ($p>0.05$).

TABLE 2
Clinical spectrum of tuberculosis (n=100)

Type of tuberculosis	Vaccinated Group A (n=50)	Unvaccinated Group B (n=50)
Pulmonary	34 (68%)	38 (76%)
Primary complex	12 (35.2%)	7 (18.4%)
Progressive primary complex	22 (64.8%)	26 (68.4%)
Pleural effusion	nil	4 (10.5%)
Cavitary	nil	1 (2.7%)
Extrathoracic	12 (24%)	11 (22%)
Tubercular meningitis	7 (58.3%)	4 (36.4%)
Disseminated tuberculosis	4 (33.3%)	3 (27.4%)
Miliary tuberculosis	1 (8.4%)	2 (18.1%)
Skeletal	nil	2 (18.1%)
Tubercular lymphadenitis	4 (8%)	1 (2%)

The clinical presentation of tubercular meningitis in the vaccinated and unvaccinated children were different. The diagnosis of tuberculous meningitis was based on CSF analysis and CT scan findings. Vaccinated children with tuberculous meningitis had clinically less morbidity i.e. presence of altered sensorium, seizures and neurological deficits. Seven children in Group A underwent CT scan of brain. Basal exudates and hydrocephalus were seen in 4 cases. Two had isolated tuberculoma and 1 child had evidence of infarct only (Table 3). In the present study positivity of Mantoux test was equal in both groups (29 and 30 cases). In 41 children who had negative mantoux test, BCG diagnostic test was positive in 12 patients in each group. Attempt to isolate AFB was done in all 100 cases using different specimens. In children below 6 years gastric lavage aspirate was taken for culture studies. In only 2 cases could AFB be isolated, in both cases from sputum specimens. Presence of granuloma suggestive of tubercular infection was seen in 11 children. Using Udani's scoring criteria, 86 children scored above 9, 13 scored between 6 and 8 and none scored below 5. Sixty six per cent of vaccinated children with disseminated forms of tuberculosis had features of

severe PEM. The associated immune dysfunction in children with PEM could have been a major factor responsible for the high percentage of disseminated forms of tuberculosis in vaccinated children.

TABLE 3
Investigation profile in 100 children with tuberculosis

Investigation	Vaccinated Group A	Unvaccinated Group B
Mantoux test	n=50	n=50
< 9 mm (negative)	21	20
> 10 mm (positive)	29	30
BCG diagnostic test	n=21	n=20
accelerated	12	12
X-ray chest	n=50	n=50
Adenopathy	20	23
Segmental lesion	10	10
Bronchiectasis	2	nil
Cavitary lesion	nil	1
Pleural effusion	nil	4
Pneumonia	12	10
Miliary	1	1
Normal	5	1
CT scan findings	n=7	n=3
Basal exudates	3	3
Hydrocephalus	4	2
Tuberculoma	2	1
Infarcts	2	2
Histopathology - granuloma	n=7	n=3
Lymph node	4	1
Bone	1	2
Peritoneum	1	nil
Liver	1	nil
Acid fast bacilli	n=50	n=50
Gastric aspirate	nil	nil
Sputum	nil	1
Bronchoalveolar lavage	1	nil
Udani scoring criteria	n=50	n=50
< 5	nil	nil
6-8	6	7
> 9	44	43

Discussion

Childhood tuberculosis in India constitutes a problem of tremendous magnitude, compounded and perpetuated by the large pool of infectious adults [6]. With a high pool of infectious cases

(1.5 million new cases), nearly 1.9 million children under the age of 5 years get primary infection annually [7]. In a study of 300 paediatric tuberculosis patients from the underprivileged population who attended the indoor and outdoor services of a hospital in south India, 91 per cent were below the age group of 9 years and over 57 per cent below the age of 5 years. About 58 per cent children under 5 years had serious forms of tubercular disease like meningitis and miliary tuberculosis [8].

That BCG vaccine does not prevent the natural infection in the lungs is now beyond doubt. All children who are vaccinated when they come in contact with the large pool of sputum positive pulmonary tuberculosis adults, are likely to be infected. Hence the incidence of intrathoracic tuberculosis has markedly increased. In a study of 2000 BCG vaccinated children, the author has found the incidence to be 91 per cent [9]. In the present study 68 per cent of children in the vaccinated group had pulmonary form of tuberculosis. And of these 44 per cent had progressive primary complex and 24 per cent had primary complex. BCG has a protective value against the dissemination of the disease and it contains the infection because the T cells in vaccinated child are highly sensitized with the result that though the infection may be present in the lungs and the lymph nodes the incidence of hematogenous spread is small [3]. This has brought down the cases of generalized tuberculous meningitis from 4.5 per cent of total paediatric admissions in early 1950's to less than 1.5 per cent [10]. In the present study, of 50 cases of tuberculosis in children who were vaccinated, 7 had tubercular meningitis. The spectrum of illness in these 7 cases were different from those in unvaccinated cases. The fact that even in tubercular meningitis, the infection has a tendency to localize in vaccinated children, has been highlighted by Udani [11]. Isolated organ disease, in the form of tubercular ascitis, hepatomegaly, osteomyelitis, and iridocyclitis in vaccinated children were seen in the study. Similar reports are seen in other studies [5,12].

Without going into the intricacies of statistical analysis and the resulting data, it is very apparent that a vaccinated child also suffers from tuberculosis with maximum incidence around 4 to 5 years. Being a cross-sectional study, the apparently more

number of disseminated forms of tuberculosis in the vaccinated group might have occurred by chance. Secondly in a population based study, with a high percentage of BCG coverage (80%), it is likely that inherently more number of vaccinated children have been studied. However one clear fact emerges i.e. even if a vaccinated child does suffer from tuberculosis, the nature of illness has a tendency to localize to a particular organ, even in severe forms such as tubercular meningitis.

However the question remains whether BCG is effective? Why so many children develop tuberculosis despite being vaccinated? One possible explanation is the correlation of PEM and incidence of tuberculosis. In the present study, nearly 66 per cent of vaccinated children had severe PEM and disseminated tuberculosis - a strong correlation. Many studies have demonstrated local impairment of afferent or sensitized limb of delayed hypersensitivity response in PEM [13]. The degree of immunological impairment parallels degree of PEM. Chandra has demonstrated numerical and functional deficiency of CD 4 and Helper cells in PEM which forms the basis of the clinical manifestations of PEM [14]. Hence children below 5 years of age, despite being vaccinated, on becoming malnourished and getting exposed to infectious cases, develop tuberculosis in a moderately severe form. In a hospital based study, the authors have shown the result of BCG vaccination in malnourished children. Classical or generalized tubercular meningitis, miliary tuberculosis, disseminated form, and serious complications of primary go on occurring in malnourished BCG vaccinated children [15].

Therefore if BCG vaccine is not effective or is less effective, do we have an alternative? There is no ready answer for the question. However certain remedial measures have been suggested. Firstly, the need to improve the nutritional status of children in the age group of 5 years and below. Secondly, the role of booster dose of BCG vaccine in preschool period. It is well-documented that BCG immunity wanes within a year or so in children. Hence Udani suggested that it was worthwhile to give a booster dose of BCG vaccination at 2 years to reduce the incidence of these serious hematological complication of primary tuberculosis [16]. IUATLD [17] has commented on various reasons

for revaccination at school age so as to boost the immunity and induce longer protection. The third strategy, again related to BCG vaccine was suggested by Udani in 1989. He indicated that it would be worthwhile to carry out a trial giving BCG vaccine by inhalation or nebulisation in the first 3 months of life. This route will stimulate the T cells and alveolar macrophages in the airways and may prevent natural tuberculous infection, which cannot be achieved with the present technique of giving BCG by intradermal route [15]. In a recent paper in 1994, Lagranderie et al [18] have demonstrated the role of mucosal lymphoid system of the respiratory tract. They have demonstrated, in guinea pigs, that the alveolar route of BCG administration activated broncho-alveolar macrophages more effectively than the intradermal route and induced higher local cellular immune responses and substantially improved protective effect both locally and systematically. The fourth strategy, and the most effective in the present era, would be identify and adequately treat all infectious cases - as adult tuberculosis acts as the fountain head of childhood tuberculosis.

Nearly 90 million tuberculosis cases and 30 million deaths due to tuberculosis are expected to occur during the present decade at the present level of interventions. For a disease where intervention is known to be cost-effective this is truly staggering. A sincere efforts at all levels of health care delivery system is the need of the day.

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