THE PROTECTIVE EFFECT OF BCG IN CHILDREN AGAINST COMPLICATED TUBERCULOSIS: THE P.G.H. EXPERIENCE

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ABSTRACT

From August 1-September 1, 1995, there were 50 cases of extra-pulmonary/complicated tuberculosis seen and/or admitted at the Department of Pediatrics, Philippine General Hospital. An interview with the parents/caretakers of these patients was made on immunization status. Patients were examined for the presence of BCG scar. Others which were seen and/or admitted during the study period were likewise interviewed and examined. Of the 614 patients, the immunization rate was 52%, and 45% had a BCG scar. Among the 50 cases of extra-pulmonary/complicated tuberculosis, there are prominent clinical features namely: a) age - infants and adolescents, b) male sex, c) severe malnutrition, and d) exposure to tuberculous adults. Even if there is a BCG scar, there is still a significant chance ($p < 0.01$) of extra-pulmonary/complicated tuberculosis, especially with the clinical features mentioned.

INTRODUCTION

The advances in technology have offered a lot of progress in the prevention and treatment of tuberculosis. Yet nearing the third millenium, tuberculosis remains one of the leading causes of morbidity and mortality in the pediatric population, particularly in developing countries, like the Philippines.[3, 19, 25]

This illness is prevented worldwide by means of BCG vaccination to provide protection against extra-pulmonary/complicated tuberculosis. Although BCG does not protect against primary infection, it is believed BCG limits the spread and progression of tuberculosis in the re-challenged host.[1-3, 5, 7-8, 11-13]

In controlled studies conducted since 1935, the protective efficacy of BCG has been shown to be 75-80%. It is worth noting however, that these studies were done in developed nations where socio-economic conditions are vastly different from developing ones and where tuberculosis is not endemic. Studies done from developing nations like India and the Philippines gave a much varied protective rate (0-80%).[9-16, 19, 21-24] The wide variation may be due to differences in study design, genetics and race involving the trial population, and the presence of environmental mycobacteria.[7-8]

Despite the national health policy of advocating BCG vaccination in neonates and of the use of effective anti-microbials, there is still the unabated spread of tuberculosis thus making it necessary to review the current practices.[19, 22, 25] This study aims to compare between the presence of a BCG scar and extra-pulmonary/complicated tuberculosis and to study the clinical features of patients having this disease.

METHODOLOGY

The parents or caretakers of patients seen and/or admitted at the Philippine General Hospital, Department of Pediatrics Out-Patient Division (Subspecialty Clinics namely Pulmonology, Neurology, Infectious Diseases and Gastroenterology) and In-Patient Section, were interviewed about the primary immunization of their children/wards. The patients were examined and inspected for the BCG scar. Those confirmed to have extra-pulmonary/complicated tuberculosis formed the test group while the rest formed the control group. Factors which might have contributed to the diminished protective effect of the vaccine were also studied, notably: malnutrition and other immunecompromised states, presence of systemic steroids and other immunosuppresant drugs, effect of measles and other concomittant infections, age groups and exposure to tuberculous adults. The relationship between the presence of the BCG scar and extra-pulmonary/complicated tuberculosis was studied using Fischer's exact probability test.

RESULTS

There were 614 patients who were seen and/or admitted from August 1-September 1, 1995 at the Philippine General Hospital Department of Pediatrics. There were 398 patients at the Out-Patient Division (Subspecialty Clinics namely: Pulmonology, Neurology, Infectious Diseases and Gastroenterology) and 216 patients at the wards. (Table 1)

Table 1. Profile of patients seen and admitted at PGH, Department of Pediatrics, August 1- September 1, 1995. (n = 614)

Profile	Number	(%)
Where patients were seen:		
Out-Patient Clinic:	398	(65%)
Neurology	201	(33%)
Pulmonology	112	(18%)
Gastroenterology	61	(9%)
Infectious Diseases	24	(4%)
In-Patient:	216	(35%)
(+) Primary immunization:	320	(52%)
OPD patients	208	(34%)
In-patients	112	(18%)
(+) Primary immunization done at Local Health Center:	306	(50%)
OPD patients	199	(32%)
In-patients	107	(18%)
(+) BCG scar:	277	(45%)
OPD patients	175	(29%)
In-patients	102	(17%)

There were 320 (52%) patients who had primary immunization; of these, 306 (95.6%) had their immunization at the local health center, the rest in private clinics. Out of the 320 patients whose mothers/caretakers reported to have primary immunization, only 277 (86.6%) had BCG scar or 45% of the total population seen/examined during the study period. (Table 1)

Among the 277 patients with BCG scars, the scars were mostly on the right deltoid (186/277 or 67%), the rest were on the left deltoid (91/277 or 33%). (Table 2)

Table 2. Location of BCG scars of patients seen and admitted at PGH Department of Pediatrics, August 1-September 1, 1995. (n = 277)

Location of BCG Scar	Number	(%)
A. Patients with complicated TB	32	(11%)
Right deltoid	22	(7%)
Left deltoid	10	(4%)
B. Patients without complicated TB	245	(90%)
Right deltoid	164	(67%)
Left deltoid	81	(33%)
TOTAL	277	(100%)

There were 50 patients (prevalence rate of 8%) confirmed to have extra-pulmonary/complicated tuberculosis. 30 (60%) of these were seen at the Out-Patient Division at the above-mentioned subspecialty clinics and 20 (40%) were admitted at the wards. According to age, there were 4 (8%) patients who were less than 1 year old, 4 (8%) who were between 1-2 years old, 12 (24%) were 2-7 years old, and 30 (60%) were more than 7 years old. According to sex, there were 30 (60%) males and 20 (40%) females. There were 19 (38%) patients with identified and confirmed exposure from adults. There were only 2 (4%) patients with concurrent illnesses, these were both post-measles cases. There were no patients receiving systemic steroids or other immunosuppressant drugs upon diagnosis. (Table 3)

Table 3. Profile of patients with extra-pulmonary/complicated tuberculosis seen or admitted at PGH Department of Pediatrics, August 1-September 1, 1995. (n = 50)

Profile	Number	(%)
A. According to source:		
1. Out-Patient Clinic:		
Pulmonology	15	(30%)
Infectious Diseases	7	(14%)
Neurology	5	(10%)
Gastroenterology	3	(6%)
2. In-Patient:	20	(40%)
TOTAL	50	(100%)
B. According to age (in years):		
≤ 1 yr. old	4	(8%)
> 1-2 yrs. old	4	(8%)
> 2-< 7 yrs. old	12	(24%)
≥ 7 yrs. old	30	(60%)
TOTAL	50	(100%)
C. According to sex:		
Male	30	(60%)
Female	20	(40%)
TOTAL	50	(100%)
D. According to presence of severe malnutrition:	19	(38%)
E. According to presence of other illnesses (measles):	2	(4%)
F. According to identified source of exposure:	18	(36%)

Regarding the BCG scars of these patients, among those who were less than 1 year old to 2 years old, only 2 (1 or 2% for each age group stratified) had BCG scars . Those who were between 2-7 years old, there were 9 (18%) and 21 (42%) of those who were more than 7 years old had BCG scars. (Table 4)

Table 4. Presence of BCG scar and age group of patients with extra-pulmonary/complicated tuber-culosis. (n = 50)

Age (in years)	BCG scar	
	Positive	Negative
≤ 1 yr. old	1 (2%)	3 (6%)
> 1-2 yrs. old	1 (2%)	3 (6%)
≥ 2-7 yrs. old	9 (18%)	3 (6%)
≥ 7 yrs. old	21 (42%)	9 (18%)
TOTAL	32 (64%)	18 (36%)

Table 5 presents the laboratory results and ancillary procedures used to confirm the diagnosis of extra-pulmonary/complicated tuberculosis. 36 (72%) of the cases were confirmed using chest and bone radiographs, as well as computed tomography of the head, chest and abdomen. 17

Table 5. Laboratory and ancillary procedures that confirmed tuberculosis in patients diagnosed to have extrapulmonary/complicated tuberculosis, seen and admitted at PGH Department of Pediatrics, August 1- September 1, 1995.

Laboratory/Ancillary Evidence	Number	(%)
Radiographs (including CT scan)	36	(72%)
Immunologic:	10	(20%)
accelerated BCG reaction	7	(14%)
(+) PPD reaction	3	(6%)
Positive AFB smears:	17	(34%)
gastric fluid	12	(24%)
endotracheal aspirate	2	(4%)
urine	2	(4%)
ear discharge	1	(2%)
Biopsy	13	(26%)
Others:		
CSF analysis	8	(16%)
pleural fluid analysis	6	(12%)
elevated ESR	6	(12%)

Table 6. Sex and age group distribution among patients with positive AFB smear. (n = 17)

Age Group	Sex	
	Male	Female
≤ 1 yr. old	2 (12%)	3 (6%)
1-2 yrs. old	0	1 (6%)
2-< 7 yrs. old	5 (29%)	0
≥ 7 yrs. old	5 (29%)	3 (18%)
TOTAL	12 (71%)	5 (30%)

Table 7. Age distribution of patients with severe malnutrition with extra-pulmonary/complicated tuberculosis. (n = 19)

Age	Number	(%)
≤ 1 yr. old	4	(21%)
1-2 yrs. old	4	(21%)
2-< 7 yrs. old	7	(37%)
≥ 7 yrs. old	4	(21%)
TOTAL	19	(100%)

(34%) had positive AFB smears, mostly from the gastric fluid aspirate (12 or 24%), the rest were from the endotracheal aspirate (2 or 4%), urine (2 or 4%) and ear discharge (1 or 2%). 13 had biopsies which were consistent with tuberculosis. 5 (10%) of the biopsy specimen were from the lymph nodes, 5 (10%) from the liver, 1 (2%) from the bone, 1 (2%) from percutaneous lung biopsy, and 1 (2%) from pericardial tissue. 10 (20%) had immunologic evidence of the disease.

Table 8 presents the organ involvement of the patients with extra-pulmonary/complicated tuberculosis. 16 (32%) involved solely the respiratory system, and these were pleural effusion (6 or 12%) with either fibrothorax, consolidation or cavitary lesions, 2 (4%) with consolidation and/or fibrothorax, 2 (6%) with pneumonia and consolidation, 2 (6%) with consolidation and/or bronchiectasis, 1 (2%) with empyema and consolidation, 1 (2%) with cavitary and cicatricial changes, 1 (2%) had pneumonia, bronchiectasis and cicatricial changes, and 1 (2%) with pneumonia, cavitation and endobronchial spread. 14 (28%) had CNS involvement. 12 (24%) had tuberculous meningitis but there were only 8 who had CSF available for analysis since the rest had

Table 8. Organ involvement of patients diagnosed and confirmed to have extra-pulmonary/complicated tuberculosis, seen and admitted at PGH Department of Pediatrics, August 1-September 1; 1995. (n = 50)

Organ Involved	Number	(%)
Pulmonary	16	(32%)
CNS	14	(28%)
Disseminated	8	(16%)
- Pulmonary/CNS/bone	1	(2%)
- Pulmonary/CNS	1	(2%)
- Pulmonary/cardiac	1	(2%)
- Pulmonary/middle ear	1	(2%)
- Renal/liver	1	(2%)
- Pulmonary/cutaneous/ lymph nodes	1	(2%)
- Pulmonary/renal	1	(2%)
- Pulmonary/liver	1	(2%)
Lymph nodes	5	(10%)
Gastrointestinal	4	(8%)
Cardiac	1	(2%)
Bone	1	(2%)
Renal	1	(2%)
TOTAL	50	(100%)

uncontrolled increased intracranial pressure. 2 presented with tuberculous granuloma confirmed by cranial CT scan. There were 8 (16%) patients diagnosed to have disseminated infection; 7 of these had pulmonary involvement consisting of bronchiectasis, miliary spread, pneumonia, and pleural effusion. 5 (10%) had involvement of the lymph nodes, namely the cervical, axillary and inguinal lymph nodes; the diagnosis was confirmed by fine needle aspiration biopsy. 4 (8%) patients had involvement of the gastrointestinal system, confirmed by percutaneous liver biopsy.

The relationship between the presence of the BCG scar and the extra-pulmonary/complicated tuberculosis was studied using the Fischer's exact probability test. It showed that there is still a significant chance of having the disease ($p = 0.008$) even in the presence of a BCG scar. (Table 9)

Table 9. Relationship of BCG scar and presence of extrapulmonary/complicated tuberculosis.

	Disease		Total
	Positive	Negative	
(+) BCG scar	32 (5.2%)	245 (39.9%)	277 (45.1%)
(-) BCG scar	18 (2.9%)	319 (51.9%)	337 (54.9%)
Total	50 (8.1%)	564 (91.9%)	614 (100.0%)

$p = 0.008$, Fischer's exact probability test

DISCUSSION

The characteristics of patients in our study reflected some of the data from the National Tuberculosis Prevalence Survey done in 1981-1983. The survey showed that in the unvaccinated population, the natural infection was evident in 54%. Prevalence was 2% in infants < 1 yr.old, 7% at 1-4 yrs. old, 16% at 5-9 yrs. old, and 42% at 10-14 yrs. old.[19] Note that this is in the unvaccinated population but the data is still comparable when our data was stratified according to age alone (Table 1) and when we stratified our data according to presence/absence of BCG scar and age group. (Table 4)

Likewise, the data of the Philippine Health Statistics of 1989 show that the true incidence of significant clinical disease in children is most probably understated since majority have negative AFB smears.[2-5, 9, 11, 16, 19-20, 23-24] Only 17 (34%) of our patients had a positive AFB smear, mostly from gastric fluid aspirate.

The Handbook on Tuberculosis in Infancy and Childhood of the Task Force of Tuberculosis of the Philippine Pediatric Society states that there is no difference in the incidence between sexes, except in bacteriologically proven cases ≥ 10 yrs. old which shows a male predominance.[19] Our data show a male predominance (30 or 60%), similar to Galicia's series,[8] but which may be due to the small number of our cases. Even if the data were stratified according to age group and the presence of (+) AFB smears, it would still show a male predominance in all age groups. (Table 6)

The BCG scar rate of our patients is 45%, again similar to Galicia's series of 45.44%.[8] This may be due to the fact that Galicia's and ours were done in the same medical center, thus catering to the same population, even if the studies were done 2 years apart.

In all of the patients, BCG immunization was administered during the first three months of life, and no patient had a booster dose, even those who are above 7 years old.

It would have been ideal if all of the patients underwent PPD testing. This was not possible since PPD was not always available, but the test was positive in all the patients tested. BCG acceleration test was positive in 2/3 patients who underwent the test. They were all severely malnourished. BCG was likewise not readily available thus was not used as a tool to screen patients, particularly the severely malnourished ones.[1, 9-11, 14, 15, 17-19]

The prominent features of patients with the disseminated form of tuberculosis are as follows: 4/8

(50%) were females more than 7 years old, 7/8 (88%) had pulmonary involvement, 5/8 (63%) had severe malnutrition, 4/8 (50%) had a BCG scar, and 2/8 (25%) had a confirmed exposure.

The impact of severe malnutrition likewise remains prominent. All (8/8) of our patients 2 years old and less had severe malnutrition. In the 2-7 years old age group, 7 of 12 (58%), and in those more than 7 years old, 4/30 (13%) were severely malnourished. Overall, our data showed that 19 (38%) of our patients were severely malnourished. (Table 3) (Table 7)

The 8 cases that were 2 years old and below are described as follows: as previously noted, all had severe malnutrition. 3/8 (38%) had a BCG scar so they may have acquired the disease before the immunization. 2/8 (25%) had a confirmed exposure. 3/8 (38%) had the disseminated form of the disease. 1 had the miliary form on chest radiographs. 1 had stage III tuberculous meningitis and is on a chronic vegetative state.

One patient had consolidation, bronchiectasis, pulmonary arterial hypertension, and required oxygen support on discharge. This patient who was 5 months old on diagnosis may belong to the group of patients described by Abughali who were diagnosed to have congenital tuberculosis but did not present with hepatosplenomegaly. He may have contracted the disease during delivery or soon after birth. Teeratakulpisarn reported a similar case of a 5 month old with the extensive form of pulmonary involvement.[1, 20]

Thus, as the current local statistics show, morbidity and mortality are highest in infancy and adolescence.[19] In this study, there were more adolescents with the disease but those under 2 years old had the more extensive form of the disease, compared to the other age groups.

Notable too was the fact that as of the time of the study, in 18 (36%), there were identified sources of exposure, these were mostly adults who lived in the same household. (Table 3)

CONCLUSIONS AND RECOMMENDATIONS

The conclusions that can be derived from this study are:

1. There is a 52% immunization rate, mostly given at the local health center (95.6%) among the patients included.

2. There is a 45% rate of BCG scar in the study.

3. There are clinical features associated to the development of the disease namely:
   a. age - infants and adolescents
   b. male sex
   c. exposure to tuberculous adults
   d. severe malnutrition

4. There is still a significant chance of developing extra-pulmonary/complicated tuberculosis even in the presence of a BCG scar, especially with the clinical features mentioned.

The following are recommended:

1. A more effective health education program on immunization should be implemented.

2. After BCG vaccination at the local health center, infants must be followed up to ensure that a BCG scar was formed at the expected time; if negative, there must be a repeat BCG vaccination.

3. There must be a booster BCG vaccination upon school entry.

4. In a country where tuberculosis is endemic, there must be routine screening programs to be conducted regularly among schoolchildren. These programs must include facilities for evaluation and treatment of children found positive.[26]

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