Disseminated *Mycobacterium bovis* Infection after BCG Vaccination

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**ABSTRACT**

The Calmette-Güerin vaccine (BCG) is administered to all the newborns in Iran in order to prevent tuberculosis. Complications of this vaccine are uncommon. We report disseminated BCG disease in 17 patients less than 10 years old.

This is a retrospective study of total of 17 cases who were admitted in Children Medical Center Hospital with systemic syndrome compatible with Mycobacterium disease with evidence of histopathologic demonstration of acid-fast bacilli during 1995-2004.

Fourteen cases occurred in children younger than 1 year old. Nine patients were female. Ten of the 17 total cases were associated with an immune deficiency including severe combined immunodeficiency, chronic granulomatous disease and cell mediated immune defect. Response to therapy was ineffective and 10 of them (58.8%) died.

Disseminated BCG disease is an uncommon but devastating complication of vaccination that should be considered in the appropriate clinical setting. Immune-compromised infants are at greatest risk and they respond poorly to standard therapies.

**Key words:** BCG; Children; Tuberculosis; Vaccination

**INTRODUCTION**

The original BCG (Bacillus Calmette – Güerin) strain of *Mycobacterium bovis* was derived from multiple passages of wild-type *Mycobacterium bovis*.¹ BCG vaccine is administered to prevent tuberculosis (TB) specially miliary and meningeal TB in childhood. It is considered to be safe however, some complications may occur, including abscesses at the site of inoculation and localized lesions such as osteitis.²

The most serious complication of BCG is disseminated disease that is suggested to result from impaired immunity of the children such as severe combined immunodeficiency, cellular immune defect, chronic granulomatous disease,³ and impaired IL12 and IFNγ mediated immunity.⁴ However it may cause severe disease in otherwise healthy children with no overt immunodeficiency.⁵ In infants with immunodeficiency BCG vaccination is contraindicated, but they are vaccinated prior to diagnosis, and immunodeficiency may be diagnosed after the development of BCG complications.⁶

In Iran BCG substrain Pasteur vaccine, is administered to children at birth to prevent...
tuberculosis. In this study we reviewed 17 cases of disseminated bacillus calmette- Güerin infection.

PATIENTS AND METHODS

During a retrospective study in Children Medical Center, a referral teaching hospital affiliated to Tehran University of Medical Sciences, we found 30 cases who had been admitted due to complication of BCG vaccine from 1995 to 2004.

We accepted 17 of 30 patients that showed all of following conditions:
1. positive history of the inoculation of BCG vaccine
2. Two or more signs and symptoms of a systemic syndrome compatible with mycobacterial disease including fever, weight loss, lymphadenopathy or cutaneous abscesses, pneumonia, osteomyelitis, hepatomegaly and splenomegaly.
3. Evidence of BCG infection includes a histopathologic demonstration of acid-fast bacilli; at two or more anatomic sites beyond the region of vaccination such as lymph nodes or cutaneous abscesses outside the region of inoculation, liver biopsy, gastric aspiration and bone marrow aspiration.

The competency of the immune system was evaluated by different tests including measurement of Immunoglobulins, Isohemaglotination test, phagocyte activity by NBT (slide test), T-cell and B-cell counts by flowcytometry, delayed type hypersensitivity test (DHT). HIV test performed only in 5 cases by ELIZA. These tests were performed by standard procedures and by trained laboratory personnel in the laboratories of the Children Medical Center.

RESULTS

We reviewed 17 cases with disseminated BCG disease (9 female and 8 male), who complied with inclusion criteria of this study. These data are summarized in table 1. There was a history of complications of BCG infection or death due to other infections in family of patients in 41.17% (6 cases). The rate of consanguinity was 82.35% (14 cases) in affected families.

Table 1. Summary of data on 17 cases of disseminated BCG disease.

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age/ Sex</th>
<th>Immune defect</th>
<th>Sites of evidence of BCG infection</th>
<th>Antimicrobial therapy</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6 mo/M</td>
<td>None</td>
<td>Skin, Liver</td>
<td>INH, RMP, SM EMB,</td>
<td>Survived</td>
</tr>
<tr>
<td>2</td>
<td>3Y/M</td>
<td>None</td>
<td>DLN, Liver</td>
<td>INH, RMP, PZA ETM</td>
<td>Survived</td>
</tr>
<tr>
<td>3</td>
<td>5mo/F</td>
<td>CGD</td>
<td>Liver-DLN</td>
<td>INH, RMP</td>
<td>Died</td>
</tr>
<tr>
<td>4</td>
<td>11mo/M</td>
<td>SCID</td>
<td>DLN, Lung</td>
<td>INH, RMP</td>
<td>Died</td>
</tr>
<tr>
<td>5</td>
<td>4.5mo/F</td>
<td>None</td>
<td>DLN, Liver BM</td>
<td>INH, RMP, PZA SM</td>
<td>Died</td>
</tr>
<tr>
<td>6</td>
<td>11 mo/M</td>
<td>CMI</td>
<td>DLN, BM</td>
<td>INH, RMP, EMT SM</td>
<td>Died</td>
</tr>
<tr>
<td>7</td>
<td>9 mo/M</td>
<td>SCID</td>
<td>DLN, Gastric aspiration</td>
<td>INH, RMP, EMT SM</td>
<td>Died</td>
</tr>
<tr>
<td>8</td>
<td>8 mo/F</td>
<td>SCID</td>
<td>DLN, BM</td>
<td>INH, RMP, SM</td>
<td>Died</td>
</tr>
<tr>
<td>9</td>
<td>3mo/M</td>
<td>SCID</td>
<td>Skin DLN, Lung</td>
<td>INH, RMP, EMT</td>
<td>Died</td>
</tr>
<tr>
<td>10</td>
<td>3mo/M</td>
<td>None</td>
<td>Skin – BM</td>
<td>INH, RMP, EMT, SM</td>
<td>Survived</td>
</tr>
<tr>
<td>11</td>
<td>3 Y/F</td>
<td>SCID</td>
<td>DLN- pelvic abscess</td>
<td>INH, RMP, PZA, ETM</td>
<td>Survived</td>
</tr>
<tr>
<td>12</td>
<td>7mo/M</td>
<td>SCID</td>
<td>Scalp abscess, Lung</td>
<td>INH, RMP, EMT</td>
<td>Died</td>
</tr>
<tr>
<td>13</td>
<td>4 mo/F</td>
<td>SCID</td>
<td>BM, Lung, Liver</td>
<td>INH, RMP, EMT</td>
<td>Died</td>
</tr>
<tr>
<td>14</td>
<td>6 mo/F</td>
<td>SCID</td>
<td>DLN, Lung</td>
<td>INH, RMP, EMT, SM</td>
<td>Survived</td>
</tr>
<tr>
<td>15</td>
<td>5 mo/F</td>
<td>SCID</td>
<td>DLN, Liver</td>
<td>INH, RMP, EMT</td>
<td>Died</td>
</tr>
<tr>
<td>16</td>
<td>8 mo/F</td>
<td>None</td>
<td>Gastric aspiration, DLN</td>
<td>INH, RMP, EMT</td>
<td>Survived</td>
</tr>
<tr>
<td>17</td>
<td>2Y/F</td>
<td>None</td>
<td>BM, Lung</td>
<td>INH, RMP, EMT, SM</td>
<td>Survived</td>
</tr>
</tbody>
</table>

CGD= chronic granulomatous disease, CMI=cell-mediated immune defect, SCID= severe combined immunodeficiency, DLN= Distant lymph node, INH= isoniazid, RMP=Rifampin, EMT= ethambutol, SM=streptomycin, BM=Bone marrow, NONE=no immune deficient (including: CGD, SCID, CMI)
Clinical signs and symptoms had begun before 1 year of age in 82.35% of them. Impaired immunity was detected in 10 cases (58.82%) including: severe combined immunodeficiency in 8 cases (80%), chronic granulomatous disease in 1 case (10%), and cell mediated immune defect in 1 case (10%).

HIV was not identified in any of the cases that we evaluated for it. The most common sites of acid-fast bacilli were lymph nodes (70.58%). The most commonly reported symptoms and signs are indicated in fig.1. Fever, weight loss and lymphadenopathy were seen in more than 80% of the patients. Unfortunately 10 patients (58.8%) died.

**DISCUSSION**

Immunization of children with BCG is recommended by the world health organization in communities with a high prevalence of tuberculosis.\(^7\) BCG vaccines are safe in immunocompetent hosts, however possible complications including hypersensitivity, localized lymphadenitis, fistula formation and rarely disseminated disease and death may occur.\(^6\) Disseminated disease is the most serious complication of BCG vaccine that may develop in children with immunodeficiency disorders,\(^9\) although, there are a few reports of disseminated BCG infection in normal hosts.\(^10\)

The records of our review showed that most of patients with disseminated BCG disease had immunodeficiency. Immune defects were identified in 10 subjects. The other cases did not show any abnormality in immune system. However they were not investigated for disorders of IL-12 and IFN-\(\gamma\) mediated immunity that have recently been identified as possible cause of susceptibility to infection with intracellular microorganisms such as mycobacterium and salmonella.\(^11\) In a study by Farhoudi, et al.\(^12\) in this center, one of the 6 cases had INF-\(\gamma\) receptor deficiency, however they were not investigated for detection of IL-12 receptor deficiency.

In the retrospective review of disseminated BCG disease by Lotte, et al.,\(^13\) all the 60 patients took part in that study, had cellular immunodeficiency and 31 of these patients died. Additionally, in study of Talbot et al.,\(^14\) immunodeficiency was identified in 24 out of 28 subjects. In another review of nine children by Gonzalez et al.,\(^15\) all of their patients had immunodeficiency disorders.
There have been many reports of local and disseminated complications in patients with HIV infection, but HIV test in our patients was found to be negative. Most of the clinical signs in our study comprised of fever, weight loss and lymphadenopathy. Also in study by Casanova, et al. fever and cachexia were common in the patients. Positive family history of BCG complications and high degree of consanguinity in patients' families, support the hypothesis of inherited susceptibility to disseminated BCG disease. This finding is compatible with the study of Casanova, et al. There is little information about suitable treatment for disseminated BCG disease. Antimycobacterial regimens used for the treatment of patients in our study were isoniazid, rifampin, ethambutol, and streptomycine. In a Spanish review, 10 immunocompetent patients with non-BCG Mycobacterium bovis infection were treated with isoniazid, rifampin and ethambutol. Nine of the patients were cured and had no relapses and one patient died of other causes. Most of our patients died despite aggressive management. This result was compatible with the finding of Talbot, et al. who reported mortality rate of more than 70% in immunodeficient patients with disseminated BCG infection. Also in Casanova, et al. study the prognosis of BCG infection was poor and mortality rate reported as 43%. These results may be due to immunodeficiency in patients, delay in diagnosis or resistance of Bacillus Calmette-Guerin to drugs which had been used. Finally we conclude that despite benefits of BCG immunization against mycobacterium tuberculosis infections, development of a more effective, safer, affordable vaccine with fewer side effects are a major necessity because infants with immunodeficiency usually are vaccinated prior to diagnosis in many countries.

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REFERENCES

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