Abstract. – OBJECTIVE: The bacille Calmette Guérin (BCG) vaccine is administered worldwide to prevent tuberculosis. Although, Post BCG vaccination complications like disseminated BCG infections are rare and immunocompromised children are at high risk of developing BCG-related complications including BCG-lymphadenitis and other disseminated diseases.

PATIENTS AND METHODS: This was a prospective study of children who developed disseminated BCG after vaccination who were admitted in three tertiary care hospital in Riyadh, Saudi Arabia, in the year 2015. The clinical presentation, microbiological/immunological evaluation and outcome will be discussed.

RESULTS: 12 cases (7 males and 5 females) of disseminated BCG infections after vaccination were documented with age ranges 3 and 32 months. Eight (66%) patients had interleukin IL-12 deficiency and 3 (25%) had severe combined immune deficiency (SCID) and 1 (8%) had Interferon gamma receptor II deficiency. 9 (75%) patients presented with generalized lymphadenopathy. Hepatosplenomegaly was present in 6 (50%) patients. 2 (16%) patients presented with a recurrent skin infection and persistent oral candidiasis in one patient and pneumonia in the other. Five (41%) families were from 1st degree consanguineous marriage. Tuberculosis (TB) culture and sensitivity were positive for Mycobacterium bovis from gastric aspirate (GA) in 4 patients and the lymph node in 9 patients and 1 patient had culture positive from both skin lesion and lymph nodes. Mycobacterium bovis PCR was positive in 4 patients. All patients received anti-tuberculosis therapy; all patients survived except one who died due to multi-organ failure.

CONCLUSIONS: These results indicate that the prevalence of disseminated BCG vaccine in immunocompromised Saudi children is significantly high. Since in our region we have a high consanguinity rate and a high number of primary immune deficiency disorder (PID), we believe that BCG vaccination should be postponed till a child reaches one-year-old and appropriate tests exclude the diagnosis of primary immunodeficiency diseases.

Key Words: BCG vaccination, Complications, Primary immunodeficiency diseases.

Introduction

The BCG vaccine was developed by Albert Calmette and Camille Guerin in France between 1908 and 1921. Bacillus Calmette-Guérin (BCG) vaccine was derived by in vitro attenuation of Mycobacterium bovis strains in 1906, and the World Health Organization (WHO) incorporated the vaccine in the Expanded Program of Immunization (EPI) in 1974. The efficacy of the BCG vaccine for tuberculosis prevention is controversial. However, it has a relatively high protective efficacy against meningeal and disseminated Mycobacterium tuberculosis. A recent meta-analysis has shown a summary of the protective BCG effect of 73% (95% confidence interval, CI: 67-79) against tuberculous meningitis and 77% (95% CI: 58-87) against miliary tuberculosis. In Saudi Arabia, BCG SSI vaccine
Disseminated bacille Calmette-Guérin disease (Danish strain 1331) is administered at birth to all the newborns and is injected intradermally, above the distal insertion of the deltoid muscle of the left arm. Although it is generally considered safe, there are secondary complications. The most frequent complications are regional lymphadenitis 0.4-1 per 1,000 vaccinated children. Another important complication is a life-threatening disseminated BCG infection. Meanwhile, a number of PIDs are susceptible to severe mycobacterial disease following vaccination with BCG, including severe combined immunodeficiency (SCID), chronic granulomatous diseases (CGD), complete DiGeorge syndrome (CDGS), Acquired Immune Deficiency Syndrome (AIDS) and the Mendelian susceptibility to mycobacterial disease (MSMD). Patients with an isolated inborn error of the IL-12/23-IFN-γ pathway are exclusively prone to low-virulence mycobacterial and non-typhoid Salmonella infections, also known as, Mendelian susceptibility to the mycobacterial disease (MSMD) phenotype (for example, IFN-γ receptor 1/2 deficiencies, IL-12/23 receptor b1 chain deficiency, IL-12p40 deficiency, STAT1 deficiency and NEMO deficiency) in contrast. The occurrence of disseminated BCG disease ranged from 0.06 to 3.4 cases per million vaccination, with a high mortality rate that reached up (60-83%) in immunocompromised patients. Disseminated BCG disease can be confirmed by histopathological findings of acid-fast bacilli at two or more anatomic sites (e.g., lymph nodes) outside the region of vaccination, in gastric aspiration or bone marrow aspiration. Furthermore, disseminated BCG disease can be confirmed through the identification of an isolate such as M. bovis BCG using a multiplex polymerase chain reaction (PCR) assay that distinguishes M. bovis BCG from other members of the M. tuberculosis complex. Further laboratory investigations, including screening laboratory tests, complete blood count and differential count (platelet volume, absolute lymphocyte count, neutrophil and eosinophil counts), immunological tests were performed to determine the underlying defects including serum immunoglobulin levels (IgG, IgM and IgA), lymphocyte subpopulations including CD19+ B-cells, CD3+ T-cells, CD56+ natural killer (NK) cells, and also CD4+ CD8+ were measured by double staining of lysed whole blood followed by flow cytometric analysis. Other screening tests such as tests for HIV (Human Immunodeficiency Virus), nitroblue tetrazolium (NBT) for chronic granulomatous disease (CGD) were also taken.

Results

We found that there were 7 males and 5 females; age ranges between 3 months and 32 months. Nine patients presented with generalized lymphadenopathy. Hepatosplenomegaly was present in 6 patients. Two patients presented with failure to thrive, recurrent skin infection and persistent oral candidiasis. One patient presented with pneumonia. Consanguineous marriage was defined as partners who have at least one ancestor in common, with the ancestor being no more distant than a great grandparent. Five families were within the 1st degree of consanguineous marriage. The family history of early onset severe infections leading to death in infancy was documented in two families. Five patients had a family history suggestive of an underlying immune deficiency. All the patients had an underlying immune deficiency: 8 patients had in-
terleukin IL-12 deficiency and three have severe combined immune deficiency SCID and one had Interferon gamma receptor II deficiency. The diagnosis was confirmed by TB culture and sensitivity. The culture was positive for *Mycobacterium bovis* from gastric aspirate in four patients and the lymph node in nine patients, and one patient had positive culture from both skin lesion and lymph node. *Mycobacterium bovis* PCR was positive in four patients. Ultrasound and CT scan abdomen revealed the presence of Hepatosplenomegaly and the chest X-ray (CXR) revealed lung involvement (perihilar infiltrates, right pleural effusion/consolidation) Table I. All patients received anti-tuberculosis treatment and improved on the treatment except one (Interferon gamma receptor II deficiency) who died in the intensive care with multi-organ failure. Seven patients were discharged home with anti-tuberculosis treatment and given a regular follow up with the infectious disease and immunology clinic. Two patients with SCID were transferred to the transplant center and one patient was sent for hematopoietic stem cell transplantation (HSCT) from cord blood. One patient received bone marrow transplantation (BMT).

**Discussion**

Till date, there is no consensus on the number of cases of disseminated BCG infection in Saudi Arabia. In this study, disseminated BCG infection was documented in twelve Saudi children following BCG vaccination. The age of presentation of the patients was their first two years of life ranging between 3 and 32 months. A study from Tunisia reports four cases of disseminated BCG infection occurring in children from three months to four years of age. In another study from Iran, the ages of their 17 patients were between 3.5 to 72 months. Six children (36.3%) were younger than 6-months and 13 patients (76%) were younger than 12-months. The preliminary prominent symptoms of our patients were generalized lymphadenopathy and hepatosplenomegaly. In a similar report from Iran, 8 patients (4 males and 4 females) were diagnosed with disseminated BCG infection; all patients had SCID. Axillary adenitis was detected in seven patients, and hepatosplenomegaly was also found in seven patients. Unfortunately, all the patients died due to severe disseminated BCG infection. In another study, lymphadenopathy and weight loss were the most common symptoms of disseminated BCG disease. The assessment of the immune status of the patients in the current study showed that all the patients have a different underlying immune deficiency: 8 patients have interleukin IL-12 deficiency and three have severe combined immune deficiency SCID and one had Interferon gamma receptor II deficiency. Shanbestari et al similarly reported 11 cases with disseminated BCG infection and almost all of them had immunodeficiency as follows: seven cases had severe combined immunodeficiency and one case had a chronic granulomatous disease. MSMD was found in two cases and IL12 R deficiency in another one. In this study, almost half of the families were within the 1st degree of consanguineous marriage, with a significant history of early onset severe infections leading to death in infancy. A similar result was reported from Iranian study in which consanguineous was found in more than half of patients (7 cases) and family history of disseminated BCG infection or immunodeficiency was found in nearly one-third of patients (3 cases).

The mortality rate in this work was 8% as one patient died of multi-organ failure in spite of intensive treatment. However, overall, the mortality rate was high in other researches. Mahnaz et al similarly reported a death rate of 72.8% (8 cases) in which 7 cases of them were SCID and one had CGD. In another study, 25% of the patients died. Aelami et al found an immunodeficiency state detected in 50% of the patients and the overall mortality rate was 58.8% (20 of 34). BCG vaccine is still part of the routine vaccination program for all newborns in Saudi Arabia since 1968. Many factors require considering the review and change of the time of administration of the BCG vaccine. Those factors included: 1. The incidence rate of TB is decreasing, reaching up to 17/100,000 of the population reported annually from this the country. 2. The consanguinity rate is very high in Saudi population reaching up to (58%) in the world and significant association of genetic disorders. 3. The prevalence of most of the PID’s predisposing BCG infections within the Saudi Arabian population is much higher (CGD- 5.2 cases/100000 live births, SCID 219 cases/100,000 live births) than any other population in the world. In literature BCG use has been controversially discussed, it has been recommended in tumors and it has also been suggested that BCG should be avoided in immune disorders until the age of one year.
Table I. Clinical characteristics of twelve patients with disseminated BCG post vaccination.

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Sex</th>
<th>Age</th>
<th>Clinical features</th>
<th>Underlying immune deficiency</th>
<th>Laboratory positive TB culture</th>
<th>Radiology positive finding</th>
<th>Family history</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>6M</td>
<td>Generalized lymphadenopathy pus discharge left axillary lymph node (LN) with hepatosplenomegaly</td>
<td>Interleukin-12 deficiency</td>
<td>Mycobacterium bovis PCR: positive and culture: positive</td>
<td>CXR: right hilar infiltration with right pleural effusion CT scan abdomen: hepatosplenomegaly</td>
<td>She had 1 brother may have similar illness but not investigated</td>
<td>Discharge home with regular follow up with ID &amp; immunology clinic</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>18M</td>
<td>Left axillary LN and splenic abscess</td>
<td>IL-12 Deficiency</td>
<td>Mycobacterium bovis culture positive (from LN)</td>
<td>CXR: normal CT scan abdomen: splenomegaly</td>
<td>Negative</td>
<td>Discharge home with regular follow up with ID &amp; immunology clinic</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>14M</td>
<td>Skin lesion, splenomegaly</td>
<td>Sever combined immunodeficiency (SCID)</td>
<td>Mycobacterium bovis PCR: positive from gastric aspirate and skin lesion</td>
<td>CXR: bilateral perihilar infiltration</td>
<td>Negative</td>
<td>Discharge home with regular follow up with ID &amp; immunology clinic</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>6M</td>
<td>Generalized lymphadenopathy with hepatosplenomegaly</td>
<td>IL-12 Deficiency</td>
<td>Mycobacterium bovis PCR and culture positive (from LN)</td>
<td>CT scan abdomen: Hepatosplenomegaly</td>
<td>Unknown</td>
<td>Discharge home with regular follow up ID clinic</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>3M</td>
<td>Generalized lymphadenopathy (Lt. axillary LN + inguinal LN) massive hepatosplenomegaly, consolidation &amp; atelectatic changes in both lungs</td>
<td>Interferon gamma receptor II deficiency (homozygous mutation,Y235X in IFNGR2 gene &amp; her mother is heterozygous)</td>
<td>Gastric aspirates (GA)3 consecutive positive samples positive for AFB and culture positive for mycobacterium bovis (from LN)</td>
<td>US abdominal: revealed hepatosplenomegaly, no ascites. CT scan chest, abdomen &amp; pelvis: bilateral lung consolidation more on the left side, hepatosplenomegaly. Bone survey: normal; CT scan brain: normal.</td>
<td>Positive family history of early infantile deaths</td>
<td>She died in the PICU with multi-organ failure.</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>7M</td>
<td>Generalized lymphadenopathy</td>
<td>IL-12 deficiency</td>
<td>Culture positive for Mycobacterium bovis from LN</td>
<td>None</td>
<td>He had 1 sister with similar illness</td>
<td>Discharge home with regular follow up ID clinic</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>4M</td>
<td>Generalized lymphadenopathy</td>
<td>IL-12 deficiency</td>
<td>Culture positive for Mycobacterium bovis from LN</td>
<td>None</td>
<td>She had 1 brother with similar illness</td>
<td>Discharge home with regular follow up ID clinic</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>9M</td>
<td>Generalized lymphadenopathy</td>
<td>IL-12 deficiency</td>
<td>Culture positive for Mycobacterium bovis from LN</td>
<td>None</td>
<td>Negative</td>
<td>Discharge home with regular follow up ID clinic</td>
</tr>
<tr>
<td>Age</td>
<td>Sex</td>
<td>Symptoms</td>
<td>Diagnoses</td>
<td>Investigations</td>
<td>Outcome</td>
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<tr>
<td>9 M</td>
<td>12M</td>
<td>FTT, recurrent boils and cutaneous abscess formation, persistent oral thrush, BCGitis with generalized lymphadenopathy (left axillary lymphadenitis, inguinal LN)</td>
<td>SCID</td>
<td>FNA aspiration from left axillary lymph node is showing +ve AFB on ZN stain, Mycobacterium bovis C/S: Ultra sound left axillary area: multiple enlarged LNS measuring 1.5x1.1 cm in size. Bone survey: normal. CT chest: B/L bronchial thickening &amp; air space disease at r.t upper lung. CT brain: lt occipital ill defined hypodense lesion. MR1 brain: old inferior cerebellar infarction, B/L subdural hygromas. LNS involvement, Gastric aspirates at B/L subdural hygromas. PCR: positive for Mycobacterium bovis</td>
<td>Negative Patient was transferred to another hospital (KFSH) for HSCT from cord blood pneumonitis.</td>
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<tr>
<td>10 M</td>
<td>19M</td>
<td>FTT, BCGitis with no LNS involvement, pneumonitis massive hepatosplenomegally with ascitis</td>
<td>SCID</td>
<td>Gastric aspirates 3 samples were +ve for AFB, -ve for TB PCR, C/S of gastric aspirate +ve for Mycobacterium bovis</td>
<td>1st degree consanguineous marriage with History of death at age of 4-6 months with similar clinical presentation KFSH for bone marrow transplant (BMT) from his HLA matched sister.</td>
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<tr>
<td>11 M</td>
<td>2.5 year</td>
<td>Generalized lymphadenopathy draining lymph node sinus &amp; splenomegaly</td>
<td>IL-12 Deficiency</td>
<td>FNA aspiration from axillary lymph node is showing +ve AFB on ZN stain, culture positive for Mycobacterium bovis from LN. Mycobacterium bovis PCR: positive CXR: bilateral perihilar infiltration CT: splenomegaly</td>
<td>Negative Discharge home with regular follow up ID clinic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 M</td>
<td>2.8 year</td>
<td>Left axillary lymphadenopathy and bilateral neck swelling, weight loss abdominal distention and chronic cough</td>
<td>IL-12 Deficiency</td>
<td>Culture positive for Mycobacterium bovis from LN &amp; from gastric aspirate. Positive gene expert test PCR Chest, abdomin &amp; pelvis CT with contrast showed bilateral mild plural effusion, hepato megaly, ascitis, axillary, mediastinal, hilar abdominal, inguinal lymphadenopathy</td>
<td>Negative Discharge home with regular follow up ID clinic</td>
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</tbody>
</table>
Conclusions

Based on this data, the need for BCG vaccination should be further evaluated. As most congenital immunodeficiency disorders are apparent by one year of age, BCG vaccination should be avoided in patients with immune disorders until the age of 12 months. The data available about the magnitude of disseminated BCG among Saudi children is limited; therefore, more studies on national bases need. Furthermore, we also advise to reconsider the routine BCG time to be postponed until 12 months of age. By this time most congenital immunodeficiency disorders have become apparent.

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Conflict of Interests

The Authors declare that they have no conflict of interests.

References


