BCG DISSEMINATION IN 40 PATIENTS AND THE REVIEW OF "LEUKOCYTE MYCOBACTERIUM DEFECT" IN ONE PATIENT

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ABSTRACT

We have reviewed the medical records of 40 patients with disseminated (Bacille Calmette-Guerin) BCG from 1996 to 1999 in the Immunology Department of the Children Hospital, Medical Center, Tehran university. These patients are divided into 3 groups:

1. Patients who had disseminated (Bacille Calmette-Guerin) BCG after vaccination and their diagnosis was chronic granulomatous disease.

2. Patients who had disseminated (Bacille Calmette-Guerin) BCG and were diagnosed as having cell-mediated immunodeficiency.

3. Patients whose Nitroblue Tetrazulium and CMI were around normal, but they could not kill intracellular mycobacterium, because of confirmed deficiency of interferon-gamma receptor and IL-12 receptor.

Interferon-gamma receptor or CD119 was checked in 6 patients. In one patient interferon-gamma receptor deficiency was confirmed by flowcytometric analysis. In other patients, this marker was around normal, but presumably they had IL-12 receptor deficiency, which we were unable to detect in our laboratory. In some patients this marker should be checked after preparation of more laboratory facilities.

Key words: Interferon-Gamma Receptor Deficiency, Interleukin-12 Receptor Deficiency, Leukocyte Mycobacterium Defect.

INTRODUCTION

After the discovery of BCG and the beginning of the immunization in children against the mycobacterium tuberculosis, the morbidity and mortality by mycobacterium decreased significantly. Usually there are more advantages and less disadvantages during BCG vaccination. The advantages of BCG vaccination are very common such as: immunity against tuberculosis and also the protection of the body against malignant diseases like acute lymphocytic leukemia(1).

On the other hand, many reports have been
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published regarding local or systemic disseminated BCG complications (2). Some of these patients suffered from BCG adenitis, which developed into an abscess or generalized lymphadenitis and hepatosplenomegaly and did respond well to the anticylococcal agents. In spite of receiving appropriate antibiotic, a few patients did not respond, the disease progressed and the diagnosis of disseminated BCG was confirmed. During the last decade, several reports concerning disseminated BCG have been published which are summarized as follows:

It has been reported that in human and mice, some are sensitive to BCG and others are resistant to it, which causes positive and negative skin reactions.(4).

Adverse reactions induced by BCG vaccination were observed in several related family members in 1999. WHO's classifications revealed that the phagocytosis defect of mycobacterium by leukocytes, could be considered as the cause of the BCG dissemination.(5). Interferon gamma receptor deficiency like IL12 receptor deficiency predisposes to severe infections. As mentioned above, leukocyte mycobacterium defects (LMD) due to interferon-gamma receptor 1 deficiency has been identified as a cause of fatal BCG infection, but partial interferon-gamma receptor and IL-12 receptor deficiency have also been reported in children.(6). Furthermore, combined immunodeficiency (CIMD) and CGD patients could develop disseminated BCG.(7). Defective interferon-gamma receptor deficiency could be type I and II. Several familial disseminated BCG infections were described and genetic etiology suggested.(8).

Interleukin-12 (IL-12) is a monokine which plays a critical role in resistance to mycobacterium tuberculosis infection.(9). We reported 2 cases of disseminated BCG who had cell mediated immunity defects(10), then 40 patients who were suffering from severe complications of BCG vaccination. Immunological investigations revealed that one group had chronic granulomatous disease and the second group had cell mediated immunodeficiency(7). The 3rd group whose T-cell and NBT were around normal range, had interferon-gamma and IL-12 receptors deficiencies. Interleukin-12 is known to be a strong inducer of interferon-gamma and plays a vital role in activating the immune surveillance system against intracellular pathogen(11), and malignant tumors(1).

MATERIALS & METHODS

In this survey, 40 patients with complications following BCG vaccination were examined. Complications were as follows: lymphadenopathies, abscesses formation and fistulization at the site of vaccination. In some patients, BCG infection became disseminated which caused generalized lymphadenopathies, hepatosplenomegaly and ascitis. The competency of the immune system was evaluated by different tests. Immunoglobulins by radial Immunodiffusion (RDI), phagocytes activity by NBT (slide test) and chemiluminescence test, T and B cells counts and detection of IFN-γ receptor (mouse antihuman CD119, serotec MCA1450) by FACSTAR flowcytometry Invivo and invitro T-cell evaluation by DCH and LTT were performed respectively.

RESULTS

The patients were divided into 3 groups according to the laboratory data. The 1st group consisted of 5 patients who had defective phagocytosis, low NBT and chronic granulomatous disease (CGD). Table 1 shows the frequency of these patients. The 2nd group consisted of 11 patients who had low T-cell population. CD3, CD4, CD8, CD16-56, CD45 RO were measured. One, two or more of these CD markers were found to be decreased. Some of them had negative delayed type hypersensitivity tests. Cell mediated immunodeficiency was proved in the second group of patients. Table 2 shows the frequency of this group. The 3rd group whose NBT and CM1 tests were in normal range had disseminated BCG infection and complications following the vaccine. Interferon-gamma receptor or CD119 were checked in 6 patients. In one patient flowcytometric analysis showed that the patient's leukocytes could not bind a monoclonal antibody specific for the alpha chain IFN-γ receptor, in other words, he had IFN-γ receptor deficiency. This
patient is a 14-year-old boy. He had both recurrent salmonella and mycobacterial cervical adenitis during the past years but, now he is healthy and infection free with prophylactic antibiotics.

In other patients, this marker was around normal, but presumably they had IL-12 receptor deficiency, which we were not able to detect in our laboratory. In some patients this marker should be checked after preparation of more laboratory facilities.

Table 1. Frequency of disseminated BCG in CGD patients.

<table>
<thead>
<tr>
<th>SN</th>
<th>Sex</th>
<th>NBT</th>
<th>Chemiluminescence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>O</td>
<td>0.85/1552</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>O</td>
<td>6.2/1662</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>O</td>
<td>4.8/1098</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>O</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>O</td>
<td>0.73/1162</td>
</tr>
</tbody>
</table>

**DISCUSSION**

IFN-γ receptor is located on the cell surface of neutrophils, macrophages, B cells and natural killer cells. This receptor has two chains: alpha chain or ligand binding chain called CD 119 (IFN gamma R1) and Beta chain (IFN-gamma RII). IFN-gamma R1 or CD 119 deficiency has been classified by WHO as a “defect of phagoocyte number and function” (5). It is an autosomal recessive inherited immune disorder (12). Mutations in the IFN-γ R1 are associated with severe infections due to mycobacteria. However, several aspects of the phenotype of IFN-gamma R1 deficient children have recently been found to vary from case to case (13). IL-12 and its receptors help the expression IFN-gamma receptors in resistance to mycobacterium (9,11). Mutations of the gene of IFN-gamma or IL-12 receptors result in disseminated BCG and recurrent salmonella infections in 50% (11) and Listeria monocytogenes as well (14). In our survey only one patient had CD 119 deficiency which was confirmed by flowcytometry, but the other patients had similar clinical findings. Presumably, these patients had deficiency of IL-12 or its receptor, which we could not detect in vitro. The mechanisms involved in leukocyte mycobacterium defect (LMD) are shown in figure 1.

As shown in this figure, the macrophages and NK cells of patients with disseminated BCG could not genetically express receptors of IL-12 and IFN-gamma. The expression of the IL-12 and IFN-gamma receptors are coexistantly necessary for resistance to mycobacteria and salmonella infections (9,11). During the last decade several reports concerning BCG disseminated were published, which will be summarised as follows: The human and mice have diverse genetic patterns against BCG vaccination. Some of them are resistant while the others are sensitive to BCG. The genetic locus of sensitivity to BCG is located on chromosome 1 in

![Diagram](image-url)
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Table 2. Clinical and immunological data in disseminated BCG patients with cell mediated immunodeficiency

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Patient T Cell (%)</th>
<th>CD3%</th>
<th>CD4%</th>
<th>CD8%</th>
<th>CD4/CD8</th>
<th>CD16/56%</th>
<th>CD45 RO%</th>
<th>Clinical Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>38/60</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>lymphadenopaties, abscess, prolonged oral candidiasis</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>64/76</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>lymphadenopaties, candidiasis (sibling of case 1)</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>47/62</td>
<td>64</td>
<td>55</td>
<td>19.5</td>
<td>17</td>
<td>5</td>
<td>24</td>
<td>lymphadenopaties, candidiasis, recurrent diarrhea</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>42/65</td>
<td>55</td>
<td>33</td>
<td>11.5</td>
<td>1.4</td>
<td>12</td>
<td>20</td>
<td>Generalized lymphadenopaties, prolonged candidiasis</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>-</td>
<td>48</td>
<td>32</td>
<td>15</td>
<td>2.1</td>
<td>14</td>
<td>14</td>
<td>lymphadenopaties and abscess, hepatomegaly, fever</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>33/66</td>
<td>32</td>
<td>16</td>
<td>11.5</td>
<td>1.4</td>
<td>12</td>
<td>20</td>
<td>lymphadenopaties, abscess and fistulae</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>42/66</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Axillary lymphadenopaties and mastitis</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>-</td>
<td>61</td>
<td>22</td>
<td>31</td>
<td>0.8</td>
<td>2.5</td>
<td>21</td>
<td>lymphadenopaties</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>-</td>
<td>55</td>
<td>32</td>
<td>14.5</td>
<td>0.02</td>
<td>8.4</td>
<td>21</td>
<td>Abscess following BCG, recurrent pneumonia, candidiasis</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>50/65</td>
<td>47</td>
<td>17</td>
<td>25</td>
<td>6.6</td>
<td>1.29</td>
<td>18</td>
<td>Generalized lymphadenopaties, recurrent diarrhea</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>-</td>
<td>71</td>
<td>48</td>
<td>18</td>
<td>2.5</td>
<td>1.3</td>
<td>8.16</td>
<td>lymphadenopaties and abscess</td>
</tr>
</tbody>
</table>
mouse and chromosome 23 in human, and is called BCG²/BCG³ gene (4).

Some of our patients probably were genetically susceptible to fatal and generalized BCG after vaccination(10). However, IFN-gamma and IL-12 receptors deficiencies are newly recognized disorders (15) and more informations are needed for shedding new lights on these topics.

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REFERENCES