Risk of BCG infection in primary immunodeficiency children. Proposal of diagnostic, prophylactic and therapeutic guidelines for disseminated BCG based on experience in the Department of Immunology, Children’s Memorial Health Institute in Warsaw between 1980-2006

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Abstract
The increasing number of reports of disseminated BCG infection (BCG-itis) is very serious, and is almost always in children with immunocompromising conditions such as HIV, SCID, or with another severe form of congenital immunodeficiency. Vaccination at birth is a constant element of vaccination programmes in Central and Eastern Europe, due to the high prevalence of tuberculosis. Difficulties in the diagnosis and therapy of BCG infections in primary immunodeficiency patients, hospitalised in the Department of Immunology, Children’s Memorial Health Institute in Warsaw, during the last 25 years have recently been published in Emerg Infect Dis 2007; 13(5): 799. Based on our experience, we would like to propose a set of novel criteria for diagnosis and prophylaxis, and therapeutic guidelines for BCG infection.

Key words: disseminated BCG infection, primary immunodeficiency.

Introduction
Control of tuberculosis is based on prevention due to BCG vaccination. BCG vaccines belong to the most widely-used vaccines in the world. BCG vaccination at birth is constant element in vaccination programmes in Central and Eastern Europe, due to the high prevalence of tuberculosis. There is evidence that BCG vaccination provides consistent and reliable protection against tuberculous meningitis and miliary disease with one dose of BCG vaccine [1-3]. Though BCG vaccines are considered to be very safe, they are also among the most reactogenic vaccines currently in use. Vaccines differ in reactogenicity, varying with differ strains and the number of viable bacilli [4, 5]. Systemic BCG infection has been seen in children with severe

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immune deficiencies [6-9]. A fatal course of BCGitis mostly occurs in children with cellular immunity disorders, both primary immunodeficiency children and in individuals with symptomatic HIV infection [10-14]. However, occasionally BCGitis can occur in the course of other clinical disorders or even in individual healthy children [15, 16].

The development of diagnostic guidelines and treatment strategies has been initiated for a cohort of diseases under the guidance of the European Society for Immunodeficiencies (ESID), http://www.esid.org. The initial attempt to identify the diagnostic and treatment regimens for a single disease demonstrated a rather large variation among different centres. The task force of the Polish Working Group for PID is to develop diagnostic and therapeutic guidelines with the aim of harmonising its strategy, http://www.immunologia.czd.pl.

In this paper we present proposal for diagnostic and therapeutic guidelines for disseminated BCG infection in children with primary immunodeficiencies, developed from experience in diagnosis and therapy for children hospitalized in the Department of Immunology, Children’s Memorial Health Institute in Warsaw, between 1980 and 2006.

Patients and Methods

Nine hundred and forty-six cases of primary immunodeficiencies were diagnosed in Department of Immunology, Children’s Memorial Health Institute in Warsaw between 1980-2006.

Table 1. Adverse events following BCG vaccination in children with primary immunodeficiencies registered in the Department of Immunology, Children’s Memorial Health Institute in the years 1980-2006 (total PID number – 946)

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Local Disseminated</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCID (n=29)</td>
<td>9 4</td>
</tr>
<tr>
<td>IFN-γ receptor deficiency (n=4)</td>
<td>1</td>
</tr>
<tr>
<td>IL-12 receptor deficiency (n=2)</td>
<td>2</td>
</tr>
<tr>
<td>CGD (n=41)</td>
<td></td>
</tr>
<tr>
<td>Di George syndrome (n=10)</td>
<td></td>
</tr>
<tr>
<td>unclassified PID</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 2. Adverse events following BCG vaccination in children with severe combined immunodeficiencies

<table>
<thead>
<tr>
<th>Number of patients registered</th>
<th>Mild local reaction (unhealed inflammation at site of BCG injection &lt;10 mm )</th>
<th>Severe local reaction (ulceration &gt;10 mm and local suppurative lymphadenitis, no evidence of disseminated process)</th>
<th>Disseminated BCG infection (at least 2 involved sites beyond injection area)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCID n=29</td>
<td>8</td>
<td>2</td>
<td>4*</td>
</tr>
</tbody>
</table>

* Confirmation of diagnosis:
  clinical symptoms + histopathology (in autopsy) – 2 patients;
  clinical symptoms + positive PCR + positive culture + histopathology (in autopsy) – 1 patient;
  clinical symptoms + histopathology + positive PCR – 1 patient.

BCGitis following vaccination was recognised in 8 children (table 1). Three children with severe combined immunodeficiency died due to of BCGitis with multiorgan involvement. In one boy with X-linked SCID we observed disseminated BCG infection after a BMT procedure with skin, liver and bones involved. After 15 months of antitubercular treatment full recovery and full post-transplant immunological reconstitution was observed. One boy with SCID due to RAG 2 deficiency developed severe local inflammation at the site of a BCG injection 3 months after bone marrow transplantation (BMT), with a good response to antitubercular treatment. A successfully treated severe local reaction was observed also in one boy with undefined combined immunodeficiency.

One child with IFN-γ receptor deficiency, one girl died due to BCGitis. One boy with unclassified PID recovered on antitubercular treatment. In two girls with a severe local reaction at the site of a BCG injection and purulent adenitis deficiency of IL-12 receptor and BCGitis were diagnosed. All children except one were vaccinated on the first day of life with BCG vaccine containing Brazilian strain (Biomed, Poland), according to the compulsory scheme. The recognition of BCGitis beyond the site of vaccination is possible in cases of fever, cachexia, and at least two other areas of involvement such as lymph nodes, skin, soft tissues, lungs, spleen, liver or bones. Mycobacterium tuberculosis complex molecular analysis was determined by a PCR (MTD Gen-Probe) test, and a culture of mycobacterium in the BACTEC 460 Tb system was made. More clinical data are available in Emerg Infect Dis 2007; 13(5): 799.

The study was conducted according to the principles expressed in the Helsinki Declaration, with informed consent obtained from each patient’s family.

Results

Following our experience in the diagnosis and therapy of BCGitis in primary immunodeficiencies, we
would like to propose a set of novel criteria for diagnosis and prophylaxis, and therapeutic guidelines for BCG infection (tables 3 and 4).

**Discussion**

More than two hundred cases of BCG disseminated diseases have been described in the literature, most of them in infants and young children with clinically and immunologically well-defined SCID, INF-γ and IL-12 receptor-deficiency [6-11, 17]. In one of the largest series, generalized complications of BCG vaccination were retrospectively analysed by Casanova et al. [17]. Apart from a reaction in local lymph nodes those cases presented involvement of at least two other organs, including other lymph nodes, skin, lung, spleen, liver or bones. The frequency of fatal BCGitis is estimated about 0.06-1.56 cases per million doses of vaccine administered [17]. Based on 9 documented cases reported to the Polish Registry of Adverse Events Following Vaccination and those published in medical journals, the risk of BCGitis is estimated to be 0.0061/1 000 000 vaccinated newborns [18, 19]. This could reflect the high number of undiagnosed BCGitis cases in the country where 98% of newborns are vaccinated at birth every year. No one case of BCGitis was noted up to 2000 [20-22].

On the other hand, differences in reactogenicity between vaccines are also noticed recently and in the past, varying for particular strains and the number of viable bacilli. The Pasteur, Tokyo and Copenhagen strains have generally been found to be more reactogenic than the Glaxo or Brazilian (Moreau) strains [4, 5, 17]. The majority of described
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