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

EWA BERNATOWSKA[1], BEATA WOLSKA-KUŚNIERZ[1], MAŁGORZATA PAC[1], MAGDALENA KURENKO-DEPTUCH[1], BARBARA PIETRUCHA[1], ZOFIA ZWOLSKA[2], BARBARA PIĄTOSA[3], KAZIMIERZ ROSZKOWSKI[2], BOŻENA MIKOŁUĆ[4], MAJA KLAUDEL-DRESZLER[1]

[1]Department of Immunology, Children's Memorial Health Institute, Warsaw, Poland; [2]National Institute of Tuberculosis and Lung Diseases, Warsaw, Poland; [3]Histocompatibility Laboratory, Children's Memorial Health Institute, Warsaw, Poland; [4]Department of Propedeutics of Pediatrics, The Medical University, Białystok, Poland

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.*

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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

Correspondence: Ewa Bernatowska, Department of Immunology, The Children's Memorial Health Institute, Av. Dzieci Polskich 20, 04-730 Warsaw, Poland. Phone number: +48 22 815 18 39, Email: bernatowskae@yahoo.com

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

Number of patients	Local	Disseminated
SCID (n=29)	9	4
IFN-γ receptor deficiency (n=4)		1
IL-12 receptor deficiency (n=2)		2
CGD (n=41)		
Di George syndrome (n=10)		
unclassified PID		1

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.

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 by our experience in the diagnosis and therapy of BCGitis in primary immunodeficiences, we

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

Number of patients registered	Mild local reaction (unhealed inflammation at site of BCG injection <10 mm)	Severe local reaction (ulceration >10 mm and local suppurative lymphadenitis, no evidence of disseminated process)	Disseminated BCG infection (at least 2 involved sites beyond injection area)
SCID n=29 28 vaccinated with BCG	8	2	4*

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

Table 3. Diagnostic Criteria for BCG disseminated infections in Primary Immunodeficiencies

definitive	A male or female patient with systemic symptoms, such as fever or subfebrile states, weight loss, or stunted growth, and at least two areas of involvement beyond the site of a BCG vaccination, such as lymph nodes, skin, soft tissues, lungs, spleen, liver or bones. Identification by the *Mycobacterium bovis* BCG substrain from the patient's organs by culture and/or standard PCR, as well as typical histopathological changes with granulomatous inflammation.
probable	Systemic symptoms such as fever or subfebrile states, weight loss or stunted growth, and at least two areas of involvement beyond the site of a BCG vaccination, such as lymph nodes, skin, soft tissues, lungs, spleen, liver or bones. Identification of *M. tuberculosis* complex from the organs by PCR, without differentiation of *M. bovis* BCG substrain *or* other members of the *M. tuberculosis* complex and with negative mycobacterial cultures, with the presence of typical histopathological changes with granulomatous inflammation.
possible	Systemic symptoms such as fever or subfebrile condition, weight loss or stunted growth, and at least two areas of involvement beyond the site of a BCG vaccination, such as lymph nodes, skin, soft tissues, lungs, spleen, liver or bones. No identification of mycobacteria by PCR or culture, with the presence of typical histopathological changes with granulomatous inflammation.
spectrum of disease	A male or female patient with severe combined immunodeficiencies, deficiency of IFN-γ receptor, IL-12 receptor deficiency, or other genetically – confirmed primary immunodeficiency with disseminated BCG infection.
exclusion criteria	Any inflammation without typical histopathological changes, with no identification of *Mycobacterium tuberculosis* complex by PCR analysis in male and female with primary immunodeficiency.
differential diagnosis	Severe, long-term inflammation with granuloma formation in primary immunodeficiency patients.

Table 4. Prophylaxis and therapeutic guideline for BCG disseminated infection in severe combined immunodeficiency

No signs of local changes at the site of the BCG injection, and no signs of BCGitis Careful observation
Local changes at the site of the BCG injection Anti-TB treatment include IHN and RMP should be initiated and continued till complete immunological reconstitution occurs after HSCT.
BCGitis with regional lymph node involvement Anti-tuberculosis treatment with at least triple anti-TB therapy, followed by long-term prophylactic treatment, as above.
BCGitis Anti-tuberculosis treatment including four or more anti-TB drugs, until the patient fully recovers. Then, a prophylactic programme with two drugs should be continued, until complete immunological reconstitution after HSCT is achieved.

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

BCGitis cases come from France, where Pasteur strain has been used [10, 17]. After World War Two, until the mid-fifties, Copenhagen 1331 vaccine strain was widely used in the National Immunisation Programme in Poland [21, 22]. At that time serious local reactions such as axillary and cervical lymphadenitis were reported very often [21, 22]. In 1955 the immunisation schedule was shifted to the Brazilian (Moreau) strain. Since that time, the frequency of local adverse events, reported from 1989 to 1997, has been about 0.2 per 1 000 of vaccinated children, with 43.6% of them presented lymphadenitis , and others developing only local adverse events at the innoculation site [20].There have also been anecdotal cases of pseudo-lupoidal lesions, but no cases of osteitis have been published [20-22]. Reactogenicity of other strains used in Finland, Sweden, Japan and Czechoslovakia have been reported with an increased level of osteitis to over 0.3 per 1 000 vaccinated children [5, 23-26].

One could conclude that the ten times lower frequency of the reported disseminated BCG infection in Poland could result not only from undiagnosed cases, but it could also be related to the lower reactogenicity of the Brazilian (Moreau) strains used in Poland since 1955. Recently, differences in reactogenicity of BCG vaccine between Czech and Polish SCID patients has been observed [27]. Changing BCG vaccine in the National Vaccination Programme in the Czech Republic to a vaccine contained Copenhagen 1331 strain resulted in higher reactogenecity and mortality in the course of BCGitis. This alarmin observation caused a delay in BCG vaccination to 4 months of age, instead of vaccination at birth. Recently, a dramatically increased number of cases of BCGitis has been found in HIV positive infants in South Africa, where vaccine contained Copenhagen 1331 strain is used in the National Immunisation Programme [28, 29]. The Global Advisory Committee on Vaccine Safety, WHO, concerning the clinical relevance of using different BCG vaccines, has taken into account other issues including vaccine quality control and the genetic diversity of different strains [30]. The Committee emphasized that the most important safety consideration with regard to vaccination policy is the potential for disseminated BCG disease in immunocompromised children with special vaccine strains, rather than reactogenecity in the general target population. The Global Advisory Committee on Vaccine Safety and the WHO Working Group on BCG vaccines, as well as the Vaccine subcommitte of the TB Partnership, should be consulted for broader discussion on the clinical relevance of using different BCG vaccines [31].

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