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Clinical features and outcomes of Bacille Calmette-Guérin (BCG)-induced diseases following neonatal BCG Tokyo-172 strain immunization

Rattanachai Rermruay, Supattra Rungmaitree, Sunsanee Chatpornvorarux, Chantapat Brukesawan, Orasri Wittawatmongkol, Keswadee Lapphra, Wanatpreeya Phongsamart, Nantaka Kongstan, Benjawan Khumcha, Kulkanya Chokephaibulkit *

Department of Pediatrics, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand

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ABSTRACT

Background: Bacille Calmette-Guérin (BCG) vaccination at birth may cause mild and benign local adverse effects (AE). More serious AE are rarely reported.
Objective: To describe clinical features and outcomes of BCG (Tokyo-172 strain)-induce diseases (BCG-ID) that required medical attention at a tertiary care center in Bangkok, Thailand.
Method: We retrospectively reviewed medical records from January 2007 to December 2016 that were selected by ICD-10 codes. The inclusion criteria were the patients under 3 years of age who developed lymphadenitis, osteitis, or disseminated infections of which BCG was a possible pathogen. Cases were classified into suspected (clinically compatible without laboratory confirmation), probable (suspected cases with *M. tuberculosis complex* identified), and confirmed BCG-ID (probable cases with molecular confirmation of *M. bovis* BCG strain).
Results: 95 children were identified; 57 (60.0%) were male, and the median age at presenting symptom was 3.5 (range: 0.6–28.7) months. Of these, 25 (26.3%) were suspected, 49 (51.6%) were probable, and 21 (22.1%) were confirmed BCG-ID. Overall, 87 (92%) children had regional lymphadenitis corresponding to the BCG site, 5 (5%) had osteitis, and 3 (3%) had disseminated BCG. Of those with lymphadenitis, average size was 2.2 (range 0.7–5) cm. in diameter and 53% (46/87) had pulmonary involvement. Five children with immunodeficiency; three had disseminated BCG and two had lymphadenitis. Eight (9.2%) patients with lymphadenitis underwent needle aspiration; 57 (65.5%) had surgical excision. All children with BCG osteitis underwent surgical intervention in combination with anti-tuberculosis treatment. One patient with osteitis experienced long-term leg length discrepancy.
Conclusion: Regional lymphadenitis was the most common feature of BCG-ID requiring medical attention. That none of the BCG osteitis were immunocompromised hosts suggested the potential virulence of BCG in neonates. A systematic national surveillance and reporting system is needed to develop accurate estimates of population incidence and support development of effective vaccine policy.

1. Introduction

The World Health Organization (WHO) recommends Bacille Calmette-Guérin (BCG) vaccination to all infants in tuberculosis (TB) high burden countries. Several studies have reported BCG effectiveness against disseminated TB and TB meningitis of approximately 80%, and 50% against pulmonary TB [1]. BCG vaccine is administered to approximately 100 million infants globally each year [2].

Thailand is classified by the WHO as one of the 22 countries with a high TB burden [3]. The prevalence of TB in Thailand in 2014 was estimated at 236 while the incidence was 171 per 100,000 population [3]. Since1977, every healthy newborn infant in Thailand receives a single dose of BCG vaccination intradermal immediately after birth. The neonates who are sick and require hospitalization will receive BCG vaccination at the time of hospital discharge. The BCG vaccine used in Thailand has been strain Tokyo-172 manufactured by the Thai Red Cross since 1953. This strain has been reported to be relatively less reactogenic as compared to Pasteur and Copenhagen strains [2], and has been used in several countries including Taiwan [4–6], South Korea [7], Japan and Malaysia [8].

* Corresponding author at: Department of Pediatrics, Faculty of Medicine, Siriraj Hospital, Mahidol University, Wanglang Road, Bangkok-noi, Bangkok 10700, Thailand.
E-mail address: kulkanya.cho@mahidol.ac.th (K. Chokephaibulkit).

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Local site reactions following BCG vaccination are common and usually mild with red induration that progresses to an ulcerated crust and scar formation within 6–10 weeks after vaccination [2]. The overall adverse reactions have been reported in 1–2%, mostly local abscesses at the inoculation site and regional lymphadenitis [9]. The severe local reactions such as regional lymphadenitis with or without suppuration was found in 1:1,000–10,000 infants that received the vaccine [2,10]. The ipsilateral axillary lymph node is the most common site, while supraclavicular and cervical lymphadenitis have also been described [1,2,8,11].

BCG osteomyelitis/osteitis is a rare but serious complication that typically presents in children before the age of 5 years [12]. The incidence varies in different settings and is typically associated with certain BCG vaccine strains [2,13]. A study from Finland found the incidence of BCG osteitis while using the BCG-Glaxo strain during 1978–1988 of 1.7–10.1 per 100,000 vaccinated infants [13]. The onset of BCG osteitis may be subtle, progress slowly, and lead to delayed diagnosis with long-term sequelae. Disseminated BCG is a rare complication with an incidence of two per one million vaccinated. It has an 80% mortality rate and occurs exclusively in those with severe immunodeficiency [14]. A study of Tokyo-172 BCG vaccine in Taiwan reported the incidence of BCG osteomyelitis/osteitis and disseminated BCG infection of 3.68 and 0.9 per million doses, respectively [4,5]

Adverse events following BCG vaccination may be influenced by factors such as diagnostic criteria, injection technique, dose and strain. Here we report BCG-induced diseases (BCG-ID) following neonatal BCG vaccination that required medical attention which included clinical pictures, management, and outcomes during a 10-year period.

2. Patients and methods

2.1. Study design and population

We retrospectively reviewed the medical records at Siriraj hospital, a tertiary care center in Bangkok, Thailand from January 2007 to December 2016. The records were selected by ICD-10 codes. (I88: I88.0 – 88.9 Non-specific lymphadenitis, L04: L04.0 – 04.9 Acute lymphadenitis, A18.2 Tuberculous peripheral lymphadenopathy, A 19.1 Acute miliary tuberculosis of multiple sites, A 19.2 Acute miliary tuberculosis, unspecified, A19.8 Other miliary tuberculosis, A19.9 Miliary tuberculosis, unspecified and A18.0 TB bone and joint, acute or chronic osteomyelitis). Patients were eligible for inclusion if they were less than 3 years of age and developed regional lymphadenitis at the site of the BCG scar and osteitis or disseminated infections of which BCG was a possible pathogen. Patients with an alternative diagnosis or another pathogen identified were excluded. BCG-ID was classified into suspected, probable and confirmed cases, in accordance with case definitions provided by the Bureau of Epidemiology, Thailand Ministry of Public Health. Suspected cases were defined as children who had ipsilateral regional lymphadenitis near the vaccination site, or with other clinical features compatible with TB or BCG-ID. Probable cases were suspected cases with pus or tissue positive for acid fast bacilli (AFB) stain or positive for *M. tuberculosis* complex by polymerase chain reaction (PCR), tissue culture or histopathology. Confirmed cases were defined as probable cases with PCR confirmation of the *M. bovis* BCG strain.

2.2. Evaluation of immunological function

All patient records were reviewed to identify the history of any illness that suspected to primary immunodeficiency (PID). In patient who developed a BCG osteitis/disseminated infection of BCG, to exclude the immunodeficiency disorder, the immunological function was evaluated by different tests including complete blood count and differential count (absolute lymphocyte count, neutrophil and eosinophil counts), measurement of immunoglobulin levels (IgA, IgG, IgM and, IgE), phagocyte activity by DHR analysis, T-cell, B-cell, NK-cell flow cytometry, and HIV ELISA test. For the patients with normal immune function according to the prior tests, the further analysis of IL12 and IFN gamma receptor would be performed to rule out mendelian susceptibility to mycobacterial diseases (MSMD).

2.3. Molecular diagnosis of *M. bovis* BCG strain

Since 2009, our center has routinely tested and archived all isolates of *M. tuberculosis* complex from clinical specimens of children under 3 years of age for *M. bovis* by PCR. The laboratory was accredited by the College of American Pathologists (CAP) and ISO15189:2007. Culture was performed on both automated liquid and Löwenstein-Jensen medium. Because the RD1 region appeared to have potential as a specific marker for *M. bovis* BCG strain, a multiplex PCR that targets the RD1 was developed. The BCG vaccine (Thai Red Cross, Bangkok) and *M. tuberculosis* strain H37Rv were used as positive controls.

2.3.1. PCR methods

The PCR template for *M. tuberculosis* complex and *M. bovis* were prepared by using 50 μl reaction mixer of 5 μl DNA and PCR primers: ET1, 5′-AAGCGGTTGCCGCCGACCGACC-3′; ET2, 5′-CTGGCTA TATTCCTGGGCCCGG-3′; and ET3, 5′-GAGGCGATCTGGCGGTTT-GGGG-3′in 1x of the PCR reaction mix (KAPA Taq Ready Mix, KAPA biosystems) as previous described by Talbot et al. [15]. Fig. 1 demonstrates agarose gel detection of 150-bp product indicating RD1 region deletion in the patients' isolates similar to the BCG control band.

2.4. Statistical analysis

A case record form was developed to capture demographic, clinical presentation, medical management, outcomes, and laboratory data. Patients were categorized into three groups according to the site of the principal clinical presentation; lymphadenitis, osteitis, and disseminated infection. Patients who presented with lymphadenitis underwent chest X-ray. Patients with disseminated infections were those who had evidence of BCG infection in other organ systems or mycobacteremia. Demographic data were compared using Chi-Square and Fisher Exact test, as appropriate. Statistical analysis was performed using IBM SPSS Statistics for windows, version 20.0 (Armonk, NY: IBM Corp).

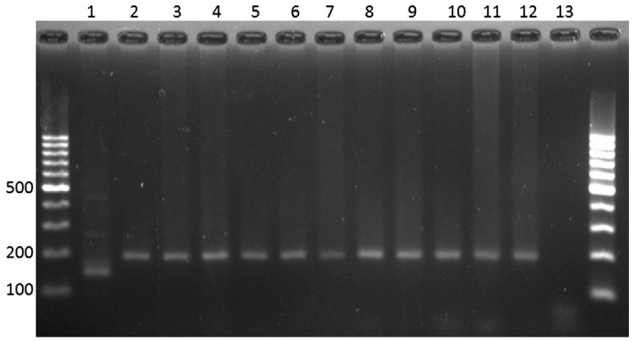

Fig. 1. PCR products in agarose gel electrophoresis. Lane 1, *M. tuberculosis* control; 2, BCG control; 3–12, patients' isolates present 150-bp product indicating RD1 region deletion. Molecular size markers are shown on the right and the left side (in base pairs).

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