

Adverse reactions to *Mycobacterium bovis* bacille Calmette-Guérin vaccination against tuberculosis in Iranian children

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Purpose: There are considerable variations in the number of adverse reaction reports related to vaccine from different countries. The aim of this study was to review the development of adverse reactions to bacille Calmette-Guérin (BCG) vaccination among hospitalized patients in an Iranian referral hospital.

Materials and Methods: We identified hospitalized patients with BCG complications in Pediatric Infectious Disease Research Center, Tehran University of Medical Sciences, Tehran, Iran during January 2007-April 2009. Data on demographics, clinical features, laboratory findings, personal history (including vaccination history), family history, and outcomes were retrieved from medical records.

Results: There were 46 cases with BCG complication during the 2 years period. All of the children received vaccination at birth. Twenty-eight patients (61%) were male. The mean age of the patients was 13.5 ± 11.3 months (range, 1 to 52 months; median, 10 months). The majority of children (57%) with BCG complication were less than 1 year old. Among hospitalized patients due to BCG complications, suppurative lymphadenitis was occurred in 28 children (61%) and lymphadenopathy was seen in 9 children (20%). Disseminated BCG was detected in 8 patients (17%) and only 1 child (2%) was presented with abscess. In 7% (n = 3) of children, the family history of BCG complications were positive.

Conclusion: The most common side effect of the BCG vaccine in our study was suppurative lymphadenitis. Disseminated BCG infection in complications leading to hospitalization in our study was 17%. With regard to the difficulty in implementing such a guideline in settings where BCG is given to all newborns, registration of Iranian primary immunodeficiency disorders (PID) patients would be helpful to increase the awareness of medical community of Iran to investigate underlying disease. In addition, BCG vaccination should postpone in each newborn with a family history of PID until the definite condition has been ruled out.

Keywords: Bacille Calmette-Guérin, Complication, Children

Introduction

Bacille Calmette-Guérin (BCG) is a live attenuated *Mycobacterium bovis* vaccination which is currently recommended for all newborns in Iran [1]. The type of vaccine which is administrated in our country is *M. bovis* [French (Pasteur) strain 1173-P2] with 1 mg/mL concentration [2].

The BCG vaccine is administered to 100 million children each year and global coverage rates exceed 80% in countries endemic for tuberculosis [3]. The reported descriptions of adverse reactions to BCG vaccination are well recognized in all regions that routinely administer the vaccination [4]. Complications due to BCG vaccination can be classified into mild and severe [5]. Erythema, induration, papule, injection site ulceration, injection site abscess and fistula are some of its early complications, while osteomyelitis, lymphadenitis, prolonged ulceration of injection site for more than 4 months and disseminated BCG infection are reported as late complications [2].

There are considerable variations in the number of adverse reaction reports from different countries. The variation is thought to be due to a number of factors, including the level of case finding and the diagnostic criteria employed, route of administration and technique, the age and immune status of the vaccinee and the quality, strain and dose of the BCG vaccine delivered [3,6].

Local and regional adverse reactions to BCG vaccination are generally self-limiting and require no treatment [5]. The most serious complication of BCG is disseminated disease that is suggested to result from impaired immunity of the children such as severe combined immunodeficiency, cellular immune defect, chronic granulomatous disease, and impaired interleukin-12 (IL-12) and interferon- γ (IFN- γ) mediated immunity [7]. It has been reported that nearly 1 in 2,500 vaccinees were presented with localized BCG-associated complications, while 1 in 100,000 individuals presented with disseminated complications [6,8].

The aim of this study was to review the development of adverse reactions to BCG vaccination among hospitalized patients in an Iranian referral Hospital.

Materials and Methods

We identified hospitalized patients with BCG complications in a Pediatric Infectious Disease Research Center, Tehran University of Medical Sciences, Tehran, Iran during January 2007- April 2009. Data on demographics, clinical features, laboratory findings, personal history (including vaccination history), family history, and outcomes were retrieved from medical records.

The diagnosis of BCG complication such as suppurative BCG lymphadenitis, lymphadenopathy, abscess and disseminated BCG was clinical, by pediatric infectious disease spe-

cialists in the department.

BCG adenitis was labeled based on the following criteria: isolated axillary (or supraclavicular/cervical) lymph node enlargement, history of BCG vaccination on the same side, absence of tenderness and raised temperature over the swelling, absence of fever and other constitutional symptoms [9]. Lymphadenopathy refers to nodes that are abnormal in size, consistency or number. Inclusion criteria for patients with disseminated BCG infection were lymphadenitis, abscesses or fistula in the site of BCG vaccination or another site or BCG ulceration with two or more signs and symptoms of a systemic syndrome compatible with mycobacterial disease, including fever $>38^{\circ}\text{C}$ more than two weeks, weight loss, recurrent or persistent diarrhoea, related parents, family history of immunodeficiency, recurrent or persistent oral candidiasis, pneumonia, osteomyelitis, anaemia (hemoglobin <10), hepatomegaly and splenomegaly. In addition, evidence of BCG infection was confirmed by histopathological findings of acid-fast bacilli at two or more anatomic sites beyond the region of vaccination [10]. In addition, evidence of BCG infection was confirmed by histopathologic findings of acid-fast bacilli at two or more anatomic sites beyond the region of vaccination [7]. Although some complications generally clear up without treatment, aspiration and drainage and treatment was carried out if it was appropriate.

Results

There were 46 cases with BCG complication during the 2 years period. All of the children received vaccination at birth. Twenty-eight patients (61%) were male. The mean age of the patients was 13.5 ± 11.3 months (range, 1 to 52 months; median, 10 months). The majority of children (57%) with BCG complication were less than 1 year old. Thirteen patients (28%) were 1 to 2 years old, while 7 (15%) were older than 2 years. The median age of complication onset after vaccination was 3 months.

The mean length of hospitalization was 6.1 ± 10.9 days (median, 3 days) and the highest length of hospital stay was 63 days. The mean duration of each complication onset after vaccination are indicated in the Table 1.

Among hospitalized patients due to BCG complications, suppurative lymphadenitis was seen in 28 children (61%) and lymphadenopathy was occurred in 9 children (20%). Disseminated BCG was detected in 8 patients (17%) and only 1 child (2%) was presented with abscess.

Table 1. The complication of BCG vaccination among hospitalized children in an Iranian referral Hospital

Complication	No.	Male	Female	Duration of onset after vaccination (mean ± SD [Median])	Length of hospital stay (day)			Familial history
					0-3	3-10	≥ 11	
Lymphadenopathy	9	6	3	141 ± 119 (150)	8	1	0	1
Lymphadenitis	28	12	16	185 ± 231 (90)	21	7	0	1
Abscess	1	1	0	14 (14)	1	0	0	0
Disseminated BCG	8	2	6	230 ± 227 (117)	1	3	4	1
Total	46	18	28	180 ± 209 (90)	31	11	4	3

BCG, bacille Calmette-Guérin.

In 7% (n=3) of children the family history of BCG complications were positive. Immune defects were identified in 4 subjects (9%) (2 cases with severe combined immunodeficiency, 1 case with chronic granulomatous disease, and 1 with humoral immune system defect). Seven cases (15%) did not show any abnormality in immune system and in 35 cases (76%) the results of immunodeficiency was not sufficient.

Birth weight of less than 2,500 g was found in 7 patients (15%). The mean of birth weight among hospitalized patients was 2,983 g (median, 3,000 g). Among 8 patients with disseminated BCG, 5 (62.5%) were low birth weight (LBW) (p=0.006), while only 2 (7%) were LBW among 28 patients with lymphadenitis.

Among 46 patients, fever was found in 10 cases (22%). Half of the patients with disseminated BCG disease had fever, while it did not report in any of the patients with lymphadenopathy. Among patients with lymphadenopathy, 6 patients (21%) had experienced fever. Skin rash was found in half of the patients with disseminated BCG. Erythema and induration at the BCG vaccination site was found in 21 patients (46%). Hepatosplenomegaly was described in 10 cases (22%). Five out of 28 patients (18%) with lymphadenitis had hepatosplenomegaly. In 1 patient with abscess, no hepatosplenomegaly was found while it was described in more than half of the patients (n=5, 62.5%) with disseminated complications.

Among all patients, the result of purified protein derivative (PPD) test was recorded for 13 cases and 3 (23%) had positive result among them. Among patients with disseminated BCG, only 2 patients had the results of PPD test that in both of them were negative.

The result of the erythrocyte sedimentation rate (ESR) was reported in 37 patients. Among these patients, only 2 cases had less than 10 mm/hr, while 15 and 20 cases had ESR value of 10-50 mm/hr and more than 50 mm/hr, respectively.

Isolation of acid fast bacillus (AFB) staining and culture or polymerase chain reaction from bone marrow or lymphaden-

itis secretion was described in 43% of patients (6 out of 14). Among 8 cases with disseminated complications, 6 (75%) had positive AFB.

In our study, 14 biopsies (30%) were histologically proved to be necrotizing granulomas. It was seen in 40% of patients with lymphadenitis or lymphadenopathy and in 25% of cases with disseminated BCG.

Among 8 patients who had the nitro-blue tetrazolium test, 7 cases had normal result while the low level of this test was reported in only 1 patient with disseminated complications.

Among 3 patients with disseminated complications who had the result of CD4 and CD8 marker, 2 had low level of these two markers. Among all patients with disseminated BCG, 2 patients (25%) who had defined immunodeficiency died.

Discussion

Across the range of BCG vaccine which has been used, adverse reactions have rarely been reported [3]. However, the safety of BCG remains of primary concern wherever it is used [3].

Adverse reactions and complications of BCG vaccination such as suppurative lymphadenitis, localized abscess and, very rarely, disseminated BCG might occur due to BCG vaccination [11]. The most common side effect of the BCG vaccine in our study was suppurative lymphadenitis that was similar to other studies [2,4,10,12]. In this study, injection-site abscesses accounted for only one patient that was lower than other reports [4,13]. Following the inoculation of the vaccine, abscess is usually self-limiting and can be resolved without the need for treatment; therefore, only limited number of patients requiring hospitalization and invasive procedures.

Disseminated BCG infection in complications leading to hospitalization in our study was 17% that was similar to Sadeghi-Shanbestari et al.'s report [14], while there are some studies that did not report this complication [4,13,15] or has reported this complication less than 1% [12].

In our previous report in Pediatric Infectious Disease Research Center, Tehran University of Medical Sciences, Tehran, Iran, an Iranian refereral pediatrics hospital, 44 patients were found with disseminated BCG disease through 10 years evaluation [10].

In our study, the majority of patients with disseminated BCG were female (75%) that was in contrast to the previous report that 80% of patients were male [1]. Among patients with this complication, 25% died that was lower than other reports [1,7,16].

The most commonly reported symptoms in the hospitalized patient with BCG complications were fever, lymphadenopathy, and erythema. Among patients with disseminated BCG, the most prevalent symptoms were lymphadenopathy and hepatosplenomegaly that was similar to previous report [1], while in Afshar Paiman et al's study [7] weight loss, fever, lymphadenopathy and hepatomegaly were the most common symptoms.

In our study, LBW was significantly associated with disseminated BCG. However, LBW could not be considered as an etiologic factor for disseminated BCG infection, possible presence of immunodeficiency and its impacts on fetal growth can be mentioned as probable cause of LBW.

Further researches on potential role of LBW on this complication should be evaluated by designing of matched case and control groups to eliminate the effect of confounding factors.

The records of our review showed that 25% of patients with disseminated BCG disease had confirmed immunodeficiency while the higher rate of immunodeficiency were reported in the previous reports from Iran [1,7,14].

Generally, BCG complications can be induced by several factors such as vaccine strains, viability of bacteria in the final vaccine formulation, overdose, improper administration, vaccination during neonatal period and any type of disturbance to cellular immunity [17]. In our study, appropriate diagnosis such as investigating of IL-12 and IFN- γ mediated immunity immunodeficiency disorders as well as mutation analysis did not perform. Since disseminated BCG largely depends on the host immune system, defect in IFN- γ or IL12/23 receptors or signal transduction pathways [18] might play an important role in our patients particularly those with disseminated BCG [19]. As with any retrospective study, the lack of adequate clinical or laboratory detail should be considered. Our analysis only included children who received BCG vaccinations and were hospitalized due vaccine complications; therefore, these children might not be representative of the entire pop-

ulation.

There was an increasing trend in recognition of more primary immunodeficiency disorders (PID) in Iran in the recent years [20]. The occurrence of BCG complication particularly disseminated BCG due to vaccine should alert the pediatrician to the possibility of PID [21]. Further efforts must be taken by increasing the coverage of Iranian PID registry via electronically registration and even referral system in order to estimate the PID and reduce the number of undiagnosed cases [22].

In addition, BCG vaccination should be postpone in each newborn with a family history of PID until the definite condition has been ruled out [21]. With regard to the difficulty in implementing such a guideline in settings where BCG is given to all newborns, registration of Iranian PID patients would be helpful to increase the awareness of medical community of Iran to investigate underlying disease.

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