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Evaluation of Children with Complication of BCG Vaccination in North of Iran

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Abstract

Background: Although the efficacy of Bacillus Calmette-Guerin (BCG) vaccine in the prevention of tuberculosis has been noted consistently, the use of BCG vaccine is not without risk. In this study we aimed to evaluate immunologically, children with complication of BCG vaccination in North of Iran.

Materials and Methods: This case-control study began in 30 Jan 2013 and was completed in 2 Jul 2015. In case group 35 patients with moderate to severe complications of BCG vaccination for Tuberculosis (TB), have been enrolled. The control group included 35 patients with mild complication and patients had no complications due to BCG vaccine. Routine and specific tests for evaluation of immunological function were performed.

Results: Out of total number of 35 patients in case group, 3(8.6%) patients had severe complication, also they diagnosed as BCG-osis; 32(91.42%) cases had moderate symptoms. In the control group 25 (71.4%) patients had mild complications and 10(28.57%) patients had no complications. The mean of IL-23 level in the two groups had significant difference ($P= 0.027$). There was a significant relationship about interleukin and interferon deficiency among patients with severe complications. Patients with mild to moderate complications of BCG vaccine were not associated with immunodeficiency. Patients with severe complications of BCG vaccine, were associated with Mendelian susceptibility to mycobacterial disease (MSMD) primary immunodeficiency (PID).

Conclusion: Severe complications of BCG vaccine could be due to MSMD and it may be associated with immune deficiency in IL 12/23. BCG vaccination must be deferring in newborns in families with a history of death following presumed BCG or early death or recurrent infection, until suitable screening immunological tests exclude the PID.

Key Words: Bacillus Calmette Guerin Vaccine, Complications, Iran, Primary immunodeficiency.

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1- INTRODUCTION

The BCG vaccine is administered to all newborns in countries where tuberculosis is endemic (1-3). Although the efficacy of BCG vaccine in the prevention of miliary or meningeal tuberculosis among children has been noted consistently, the use of BCG vaccine is not without risk (4). Patients with human immunodeficiency virus infection or primary immunodeficiency and immunocompromised hosts are prone to serious complications from this vaccine (5). Complications after BCG vaccine include local reactions in 0% to 5% of recipients and systemic complications such as osteitis and disseminated infection. Factors associated with the development of local complications include the type, dose and strength of the vaccine strain, age, technique of inoculation, race, purified protein derivative (PPD) skin reaction and immune status of the recipient. Other adverse reactions are ulcer formation, lymphangitis, keloids formation and suppurative adenitis. Local reactions occurred as early as two weeks after vaccine administration in 30% of patients, but could be seen 90 days after the procedure (6-9).

Although the diagnosis of these complications are usually based on clinical grounds, histopathological and microbiological examinations is helpful (10). Severe complications caused by the vaccine and the global incidence has been 100-1000 and one to seven hundred, and two in a million, respectively (11, 12). In the Mahmoudi et al. study in Pediatric Infectious Disease Research Center, Tehran University of Medical Sciences, among 46 cases with BCG complication during the 2 years period, disseminated BCG was detected in 8 patients (17%)(7). Complication after BCG vaccine is consistently indicated the presence of an underlying impaired immunity, such as MSMD (13). MSMD, a rare

immunodeficiency and heterogeneous syndrome, conferring predisposition clinical disease, either disseminated or localized and recurrent, caused by weakly pathogenic mycobacteria such as BCG vaccines and nontuberculous environmental mycobacteria (14, 15). MSMD was first reported, in an Algerian child with disseminated BCG disease in 1951 (16). Patients with MSMD are otherwise healthy and are not prone to other unusually severe infections, with the notable exception of systemic nontyphoidal salmonellosis, which is documented in about half the patients, including some without mycobacterial diseases. Mycobacterial disease generally begins in childhood, more rarely during adolescence and adulthood (17).

MSMD is as a clinical phenotype extends beyond mycobacterial diseases. MSMD also serves as a useful reminder that isolated infectious diseases may be genetically driven (18-20). In countries practicing BCG vaccination at birth this event represents their first encounter with mycobacteria, usually resulting in severe clinical infection. MSMD should to be considered in all patients presenting with infections due to nontuberculous mycobacteria such as *Mycobacterium bovis*. Most typical clinical manifestations of disseminated infection in MSMD include: fever, malaise, fatigue, weight loss or failure to thrive; skin papules, nodules or ulcers; lymphadenitis; lung infections; liver and/or spleen enlargement; osteomyelitis; mechanical obstructions of the respiratory or gastrointestinal tracts; malabsorption of nutrients and diarrhea can also be seen (21-23). MSMD is due to partial interferon gamma receptor 1 (IFN-gammaR1), partial interferon gamma receptor 2 (IFN-gamma R2), complete interleukin 12 receptor, beta 1 (IL-12R-beta1), complete interleukin 12b (IL12B), complete interferon-stimulated gene 15

(ISG15), partial signal transducer and activator of transcription 1 (STAT1) and partial interferon regulatory factor 8 (IRF8) deficiencies and MSMD due to partial X-linked recessive (XR) mutations are usually less severe (20, 23). Only about half of patients with MSMD have an identified genetic etiology. Nine genes are known to be responsible for MSMD. Seven of them are inherited autosomal (IFN-gammaR1, IFN-gammaR2, STAT1, IL12B and more recently IRF8 and ISG15) and 2 are X-linked. Diagnosis is made by laboratory analysis. High plasma concentrations of IFN-gamma suggest a complete IFN-gamma R deficiency (15, 18, 24-26). In this study we aimed to evaluate immunologically children with complication of BCG vaccination in North of Iran.

2- MATERIALS AND METHODS

2-1. Study design and populations

This case-control study began in (30 Jan 2013), and was completed in (2 Jul 2015). The sample size in each group was calculated based on previous studies including that performed by Rezai et al. (1). The sample size was calculated as 35 based on the following formula.

$$n = \frac{2 * (z_{1-\frac{\alpha}{2}} + z_{1-\beta})^2 \bar{P}(1-\bar{P})}{(p_1 - p_2)^2} = 35$$

$$p_1 = 0.6$$

$$p_2 = 0.3$$

$$z_{1-\frac{\alpha}{2}} = 1.96$$

$$z_{1-\beta} = 0.84$$

In coordination with Vice Chancellor for Health of Mazandaran University of Medical Sciences, first all supervisor of tuberculosis physicians in health networks across the Mazandaran province were informed about the project by correspondence or personally. A booklet

containing project information, as well as complications of BCG vaccine has been in their possession. Participants visited by supervisor of tuberculosis in health networks. All participants were referred to pediatric infectious disease subspecialty doctor in Bu Ali Sina hospital (teaching hospital of pediatric), located in Sari city, for diagnosis and treatment and they have been enrolled in the project. A pediatric resident helped in visiting the patients, filling out the questionnaire and analysis of statistical results.

The case group was included 35 patients with moderate to severe complicated caused by BCG vaccination such as injection-site complications; Ulcer larger than a centimeter, abscess-wound exudate and oscar, Lymphadenopathy; refers to nodes that are abnormal in size, consistency or number and disseminated BCG infection; 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 diarrhea, related parents, family history of immunodeficiency, recurrent or persistent oral candidiasis, pneumonia, osteomyelitis, anemia (hemoglobin < 10), hepatomegaly and splenomegaly. Mild complications caused by BCG vaccination included; injection site papule (onset 2-4 weeks), mild ulceration (1-2 months), and scar (2-5 months). (7, 27-30).

The control group consisted of 35 patients (similar in age and gender with case group), whom 25 patients had mild complications and 10 patients had no complications after BCG vaccination. The diagnosis of BCG complication was clinical and performed by pediatrics infectious disease subspecialty. We gathered information that included demographic and clinical characteristics, medical history such as vaccination

history, family history, and history of infant death, immune deficiency and abnormal weight.

2-2. Routine tests and evaluation of immunological function

For each group, complete blood count (CBC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), interleukin 12 and interleukin 23 level and IFN-gamma mediated immunity was investigated. IL-12/23 level and IFN-gamma concentrations were determined by sandwich enzyme-linked immunosorbent assay (ELISA) according to the manufacturers' guidelines. The specific Platinum ELISA kits were purchased from (eBioscience, U.S.A). Routine immunological tests were done by a doctor of laboratory sciences and an expert immunologist

2-3. Specific tests evaluated for case group

For diagnosis of immunodeficiency in case group, serum immunoglobulin G (IgG) subclasses levels [IgG1, IgG2, IgG3, IgG4], immunoglobulin M (IgM), immunoglobulin E (IgE), and immunoglobulin A (IgA), were evaluated by immunofixation electrophoresis. For bcgosis patients bone marrow aspiration was done to cell culture and study of IL-12/23 and IFN-gamma receptors. Nitroblue tetrazolium blood test (NBT), and cluster of differentiations (CD3, CD4, CD8, CD19, CD20) surface markers level were determined by flow cytometry assay. 50% haemolytic complement (CH50) activity of serum was performed by ELISA. Specific immunological tests were done by a doctor of laboratory sciences and an expert immunologist

2-4. Statistical analyses

Statistical analyses were performed by using SPSS software (version 18.0) and descriptive statistics were used. The mean and standard deviation (SD) for

quantitative variables, Chi-Square test and T-test were used for analyze and compare of complications with regard to each of the underlying variables.

2-5. Ethics

This study was approved by the ethics committee of Mazandaran university of medical sciences (ID number: 91251). We obtained the written informed consent from parents, who on behalf of the children enrolled in the study.

3- RESULT

Totally 70 children were evaluated included 35 in case group and 35 in control group. In case group 12(34.3%) were girls and 23(65.7%) were boys. In control group 15(42.9%) were girls and 20(57.1%) were boys. There was no significant relationship between gender in two groups ($P=0.46$). Geographical distribution of children in two groups is shown in **Figure.1**.

Out of the total number of 51 (72.85 %) children had complications. A variety of complications among the children has been shown in the **Table.1**. There was a significant relationship about some manifestations such as fistula, lymphadenitis and Lymphadenitis with ($2*1$) cm² size between two groups ($P\leq.0001$). Classification of complication is shown in **Table.2**.

Characteristics of patients with severe complication is shown **Table.3**. There was a significant relationship between severities of complications among case and control groups ($P\leq.0001$). In two groups' family history, medical history, history of infant death, immune deficiency and abnormal weight were not seen. Mean and standard deviation (SD) of birth weight and current weight and the level of interferon and interleukin are shown in the **Table.4**. According to univariate analysis, independent t-test for IL-23 mean in two groups, there was a significant relationship ($P=0.027$). Average level of interferon-

gamma, interleukin-12 and interleukin- 23 in patients with mild, severe, moderate and non-complications due to BCG vaccine is

shown in **Table.5**. The level of IL-23 between case and control group was significantly different (P=0.02)

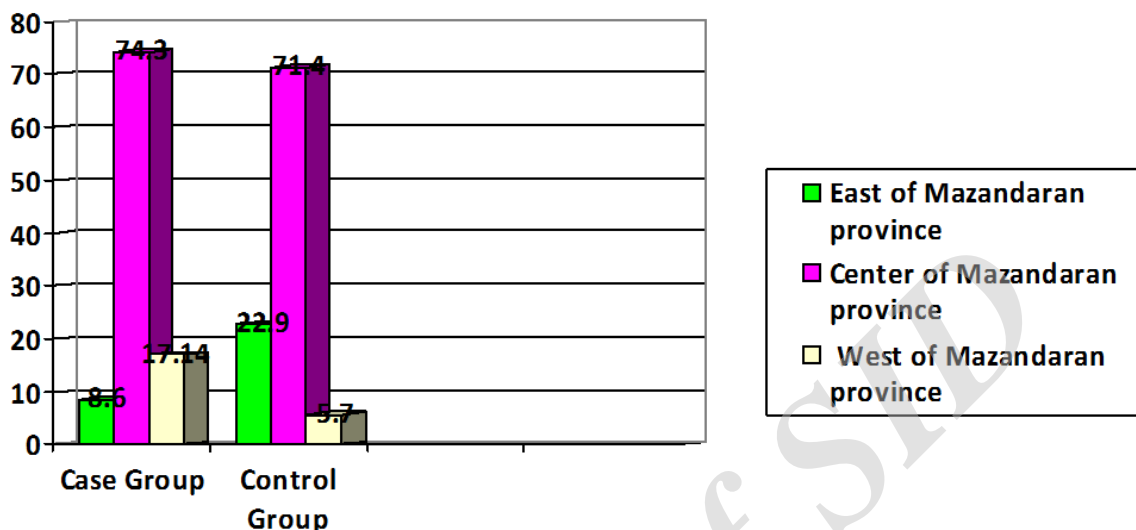


Fig.1: Geographical distribution of patients (The numbers are percentages).

Table-1: A variety of complications among children

Type of complication	Groups		P-value
	Case Number (%)	Control Number (%)	
Osteomyelitis, fistula, and lymphadenitis (4*5) cm ²	1(2.9)	0	0.32
Fistula and lymphadenitis (4*5) cm ²	32(91.4%)	0	≤.0001
Fistula and organomegaly	1(2.9)	0	0.32
Skin lesion and organomegaly	1(2.9)	0	0.32
Lymphadenitis (1*1) cm ²	0	2(12.5)	0.1
Lymphadenitis (2*1) cm ²	0	14(87.5)	≤.0001
Total	35(100)	16(100)	

Table-2: Classification of complications in case and control groups

Classification of complications	Group		Total Number (%)
	Case Number (%)	Control Number (%)	
Mild	0	25(71.4)	25(35.7)
Severe	3(8.6)	0	3(4.3)
moderate	32(91.4)	0	32(45.7)
No complication	0	10(28.6)	10(14.3)
Total	35(100)	35(100)	70(100)

Table-3: Characteristics of patients with severe complication

Variables	Patient number 1	Patient number 2	Patient number 3
Age (month)	24	8	8
Age of onset (month)	7	2	8
Gender	B	G	G
Presentation	BCG -osis	BCG -osis and Diarrhea	BCG -osis
Fever	+	-	-
Loss weight	-	-	-
Tenderness	+	+	+
Skin lesion	+	-	-
Lymphadenitis axillary	+	+	+
Leukocytosis	+	+	+
Humoral immunity deficiency	-	-	-
Cell-mediated immunity deficiency	-	-	-
IgG1, IgG2, IgG3, IgG4	N	N	N
IgM	N	N	N
IgE	N	N	N
IgA	N	N	N
NBT	N	N	N
CH50	N	N	N
CD3, CD4, CD8, CD19, CD20	N	N	N
IFNGRs deficiency	+	+	+
IL12 receptors deficiency	-	+	-
IL23 receptors deficiency	-	-	+
Type of Immunodeficiency	MSMD	MSMD	MSMD
Vaccination	+	+	+
Salmonella	-	+	-
submandibular lymphadenopathy	-	-	+
Hepatosplenomegaly	-	+	-
Osteomyelitis	+	-	-
Abdominal sonography	N	Liver and spleen sizes were larger than normal	lymph nodes around mesenteric & multiple liver abscesses
CXR	N	N	N
Treatment	INH, RMP,SM,IFN	Ceftriaxone, INH, RMP,SM,IFN	INH, RMP,SM,IFN
Outcome	Cured	Cured	Cured

G: Girl; B: Boy; IFNGR: Interferon gamma receptor; N: Normal; NBT: Nitro blue tetrazolium test; MSMD: Mendelian susceptibility to mycobacterial diseases; INH: Isoniazid; RMP: Rifampin; SM: Streptomycin; EMB: Ethambutol; IFN: Interferon.

Table-4: Average of Birth weight, Current weight, IFN-gamma, IL23, IL12 in case and control group

Variables	Group	Mean	Standard deviation
Birth weight (Kg)	Case	3.21	0.285
	Control	3.16	0.358
Current weight (Kg)	Case	7.92	2.267
	Control	7.33	2.807
IFN-gamma (pg/ml)	Case	11.18	22.491
	Control	6.58	6.335
IL23 (pg/ml)	Case	0.77	4.393
	Control	10.13	24.163
IL12 (pg/ml)	Case	1.95	4.550
	Control	3.17	12.894

Interferon-gamma: IFN-gamma; Interleukin-23: IL23; Interleukin- 12: IL12.

Table-5: Average of Interferon-gamma, interleukin-12 and interleukin- 23 level in patients with mild, severe, moderate and none complications due to BCG vaccine

Variables	Classification of complication	Number	Mean	Standard deviation
INF, (pg/ml)	Mild	25	7.60	7.231
	Severe	3	0.00	0.000
	Moderate	32	12.23	23.272
	No complication	10	4.05	1.477
	Total	70	8.88	16.655
IL23, (pg/ml)	Mild	25	12.00	27.019
	Severe	3	0.00	0.000
	Moderate	32	0.85	4.594
	No complication	10	5.46	15.001
	Total	70	5.45	15.001
IL12, (pg/ml)	Mild	25	3.70	15.13
	Severe	3	0.00	0.000
	Moderate	32	2.13	4.723
	No complication	10	1.84	3.875
	Total	70	2.56	9.671

Interferon-gamma: IFN-gamma; Interleukin-23: IL23; Interleukin- 12= IL12.

4- DISCUSSION

Systemic infection caused by weakly pathogenic mycobacteria and salmonella is related to mutations in genes encoding cytokine axis and should be screened for MSMD (25). Disseminated Bacillus Calmette–Guerin infection after BCG vaccination require investigation for underlying immunodeficiency such as defects in the IL12/IL23 dependent IFN-gamma pathway (1, 31). This study reports the first immunologically evaluation focused on IL12/23 and IFN-gamma pathway among patients with complications after BCG vaccination in North of Iran. The mean and standard deviation of IL 12/23 and IFN-gamma variables in terms of birth weight and current weight and the amount of interferon and interleukin were obtained in case and control group. Based on univariate analysis, independent t-test, the mean of IL-23 level the two groups had significant difference ($P = 0.027$), and for the rest of the variables (such as IL 12 and IFN-gamma) were not significantly different. There was a significant relationship for interleukin or interferon deficiency among patients with severe complications. The ratio of each type of PID is different among BCG-osis. In

contrast with Norouzi et al. and Casanova et al. findings , that severe combined immunodeficiency (SCID), was the most common form of immunodeficiency in children with BCG-osis, in our study all patients with BCG-osis had MSMD (32, 33). Patients with MSMD in our study have been confirmed with a cell culture and stimulation test. Ying et al. surveyed the clinical and immunogenetical features in a cohort of Chinese patients with BCG-osis and they found, among 74 confirmed cases of BCG-osis during 2007–2012, chronic granulomatous disease (CGD), was the most PID and MSMD were the second form of PID among BCG-osis patients (28).

In our study, patients with mild to moderate complications of BCG vaccine were not associated with any immunodeficiency by routine immunological function evaluation, but we found patients with severe complications of BCG vaccine were associated with immunodeficiency. Many researchers reported that 50% to 76% of BCG-osis had immunodeficiency (4, 32). Complications of BCG vaccine usually develops 5 months to 5 years after vaccination (29, 34). In our study the age of patients with severe complication was lower

than 2 years old. Behjati et al. in an analytical prospective follow up study among 480 consecutive newborns reported 5.8% cases of lymphadenitis due to BCG vaccine (35). Reported rates of lymphadenopathy are vary widely, ranging from 0% to 17.6% (36). Some factors have been shown to influence the incidence of local reactions, included dose, viability and strain of vaccine, quality of the intradermal injection, age of the recipient and characteristics of the recipient population (36). In a prospective national study of adverse reactions of BCG vaccine among 918 cases in Australia, 5% had local complications and lymphadenopathy (37).

Also, fistula, lymphadenopathy and local complications were the most common complication in our patients. We found the incidence of lymphadenopathy was 8.57% in case group. Lymphadenitis in case group and control group were 94.28% and 45.71%, respectively. Segal et al. reported a case with osteomyelitis of the humerus complicating 6 months after BCG vaccination with a proximal pathological fracture and a number of lytic lesions (38). Also, in our study, a patient had lytic lesions in the first finger of the right hand and arm and forearm on the same side. In comparing with de Beaucoudrey et al. study, the incidence of salmonellosis with BCG diseases in our patients was high (one case among three cases). de Beaucoudrey et al. found 21 salmonellosis with BCG diseases among 132 MSMD patients from 30 countries in the Americas, Europe, Africa, and Asia (39). In our study MSMD patients were treated with anti-tuberculosis drug and IFN-gamma. The patient with salmonellosis and BCG disease cured by Ceftriaxone in addition to anti-TB drug and IFN γ treatment. Patients with mild to moderate complications after BCG vaccine were treated in the two-year follow and they were not becoming BCG-osis. An accurate molecular diagnosis is indeed crucial to determine the optimal treatment strategy for individual patients. Antibiotics should not be discontinued and bone marrow

transplantation may be considered in children with complete IFN-gammaR1 or IFN-gamma R2 deficiency, in whom IFN-gamma treatment is ineffective and mycobacterial infections overwhelming. In children with partial IFN-gammaR1, IFN-gamma R2, and STAT-1 deficiencies, anti-TB drug may be sufficient but IFN gamma therapy may also be benefit. Antibiotics and IFN-gamma treatment are likely to be effective in patients with complete interleukin-12 subunit p40 (IL-12 p40) or IL-12R-beta1 deficiency. In contrast, the treatment of patients with severe BCG and non-tuberculous mycobacteria (NTM) infections but no known genetic defect remains empirical (4).

4-1. Limitations of the study

Due to financial matters, cell culture did not perform for all samples.

5- CONCLUSION

During the 2 years period, we found that MSMD was the most common PID exists in cases with severe complications due to BCG vaccine. Patients with severe complications of BCG vaccine were associated with immunodeficiency in IL12/23. BCG vaccination must be deferring in newborns in families with a history of death following presumed BCG or early death or recurrent infection, until suitable screening immunological tests to exclude a diagnosis of PID. This is particularly important in countries such as Iran where consanguinity is high and newborns immunization with BCG is routine. Precautionary measures against food or water-borne salmonella infections and avoidance of live typhoid vaccines is necessary for MSMD patients.

6- CONFLICT OF INTEREST: None.

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