Immunity status in children with Bacille Calmette–Guérin adenitis

A prospective study in Tehran, Iran

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ABSTRACT

Objective: To determine the immunity status of children with Bacille Calmette-Guerin (BCG) lymphadenitis (patient group) and unaffected children (control group) in Iran.

Methods: We performed this longitudinal case-control study on 75 children between 2 months to 14 years old in Rasool Akram and Markaz Tebbi Hospital, Tehran, Iran during the period of 2 years (2000-2002).

Results: Ninety percent of patients had normal immunoglobulin, 10% had low level, 96.1% had normal nitro blue tetrazolium test and 3.9% had lower activity. There was a significant difference in the total lymphocyte CD3, CD8, CD19, CD16/CD56 and natural killers (NK) cell but no significant difference in the CD4/CD8 ratio and CD4 between case (n=75) and control (n=100) groups. Thirty-eight cases with mild lymphopenia, isolated CD4, CD3, CD19, NK cells (CD16/CD56) deficiency in 3 (22%); idiopathic disseminated BCG infection (unknown immunodeficiency type) in 3 (22%) patients were observed. Thirty-eight cases were diagnosed as mild immune deficient without any previous recurrent infections (mild lymphopenia; Isolated CD4; CD3 or CD19 deficiency. Natural killers (CD16/CD56) deficiency in 3 (22%); idiopathic disseminated BCG infection (unknown immunodeficiency type) in 3 (22%) patients. The natural killers (CD16/CD56) deficient cases responded well to 3 antimycobacterial drugs without immunomodulator. Natural killers cell deficiency not yet reported as a risk factor for progression and complication of BCG infection. All cases of idiopathic disseminated BCG infection (unknown immunodeficiency type) with nonlethal and indulgent BCG infections responded well to needle aspiration and antimycobacterial drugs with immunomodulator (gamma interferon).

Conclusion: In cases with multiple and recurrent BCG lymphadenitis without any previous recurrent infection complete immunological studies should be carried out. Most cases with mild immune deficiency usually response well to needle aspiration alone or combine with antimycobacterial drugs. The combination of IFN-gamma and chemotherapy in cases of idiopathic disseminated infections caused by BCG and without previous recurrent other infection except mycobacterium species, can limit the disease

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Bacille Calmette-Guérin (BCG) vaccination has been used to prevent tuberculosis since 1921, and it was incorporated in the World Health Organization's Expanded Programme on Immunization in 1974 to

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strengthen the fight against childhood tuberculosis in developing countries.[1,2] Bacille Calmette-Guérin vaccine has a low incidence of serious adverse reactions, and is considered to be a safe vaccine.[3,4] Bacille Calmette-Guérin lymphadenitis is the most common complication resulting from this vaccination.[2-14] Two forms of BCG lymphadenitis can be recognized in its natural course.[11,13] The non-suppurative form, also called simple BCG lymphadenitis,[3,13] occurs in the beginning and frequently resolves spontaneously without any sequelae, within a period of few weeks.[7,11] In some cases, however, the affected lymph nodes (LNs) may enlarge progressively and develop suppuration, marked by the appearance of fluctuations in the swelling with erythema and edema of overlying skin.[8,10-16] Suppurative lymphadenitis can also develop abruptly within 2-4 months of BCG vaccination.[8,13] Once suppuration has supervened, the subsequent course is usually distinguished by the occurrence of spontaneous discharge and sinus formation. Though BCG lymphadenitis may develop as early as 2 weeks after vaccination, most of the cases appear within 6 months, and almost all cases occur within 24 months.[5–7,11] Ipsilateral axillary glands are involved in more than 95% of the cases, though supraclavicular or cervical glands may occasionally be enlarged in isolation or in association with enlarged axillary nodes.[5,6,11,12] In majority of cases, there are only one or 2 enlarged nodes, though multiple glands may be palpable in some cases.[6] The finding of isolated enlarged axillary (rarely supraclavicular or cervical) LNs ipsilateral to the site of BCG vaccination, with no other identifiable cause for adenitis, is usually sufficient for making the diagnosis in the majority of cases.[10,13,17] Absence of fever, tenderness, and other constitutional symptoms differentiates it from pyogenic adenitis.[11] Differentiation from tuberculous lymphadenitis may be difficult, but cases of isolated axillary glandular tuberculosis are very rare.[5] Investigations have a limited role in the diagnosis of BCG lymphadenitis, and are not routinely indicated. Definitive identification of BCG that would require phase typing or gene analysis[14,19] and immune work-up are not usually needed unless disseminated BCG infection is suspected.[11,14,15] Treatment of BCG lymphadenitis has remained controversial.[20-29] Disseminated BCG infections occur in patients with severe Tcell defects.[7] Severe combined immunodeficiency and phagocytic dysfunction (especially chronic granulomatous disease).[30-37] Complete IFN-gamma-R deficiencies can also lead to more severe and fatal infections with mycobacteria of low grade virulence, usually before 3 years of age.[37-44] The aim of the present study is to compare the immunity status of children with recurrent and multiple BCG lymphadenitis with unaffected children by conducting a case control study.

Methods. This longitudinal case-control study was performed on 108 children between 2 months to 14 years old referred to the pediatric infectious clinics of Rasool Akram Hospital affiliated with Iran University of Medical Science and Markaz Tebbi Kodakan affiliated with Tehran University of Medical Science based on diagnostic parameters for BCG complications within 2 years (2000-2002).

Patients were included if the ipsilateral regional LN enlargement after BCG vaccination, particularly, supraclavicular or cervical glands in isolation or in association with enlarged axillary nodes or multiple glands. The finding of isolated enlarged axillary/supraclavicular or cervical/lymph nodes ipsilateral to the site of BCG vaccination, with no other identifiable cause for adenitis in these cases. In cases with suppuration, spontaneous discharge and sinus formation or needle aspiration by physician may occurred. Exclusion criteria were presence of fever, tenderness, and other constitutional symptoms for pyogenic adenitis. In cases with suppuration; positivity of microbial culture of LN; and known case of immune deficiency.

The control group comprised children in the same range of age with prior BCG vaccination at birth and absence of BCG complications. Initially each patient with BCG lymphadenitis completed the questionnaire by the help of the authorized physician, followed by clinical examinations in existence of number and sites of lymphadenitis, presence of organomegaly and other systemic examination of these patients. For laboratory studies, 3 ml blood samples were taken from each patient, 1 ml in ethylene diamine tetra-acetate (EDTA) contained tube for NBT test and flow cytometric studies (Simol set V1.1; Beckton Dickenson; Canada) by Sysmex; 2 ml of blood restored in another tube. Blood samples were centrifuged and transferred to the Research Laboratory for immunoglobulin examination. In the control, we carried out flowcytometric examination in taking blood samples. Qualitative determination of immunoglobulin in the serum were accomplished with gel electrophoresis method. We evaluated the IgM, IgG and IgA by using commercial kits (Radim; Italy) as suggested by the manufacture.

Statistical Package for Social Sciences Version 9 and EPI6 were used for statistical analysis. Descriptional statistics were constructed with the mean and standard deviation. Chi square for comparing positive results with confidence interval of 95% (CI=95%) was used. *P*-value of <0.05 is considered significant.

Results. Of 108 patients referred to our clinic due to BCG complications, 18 were not satisfied for blood sampling and other immunologic studies and 2 had blood clotted. Flowcytometry and NBT test were not carried out and they did not return for retest. In 88 patients, physical and immunological examinations had completed, but 13 patients excluded from the study due to severe immune deficiencies [5 severe combined immune deficiency (SCID); 6 cell mediated immune deficiency (CMID) and 2 chronic granulomatosis disease (CGD)]. Of this 13, 6 died due to progressive disseminated mycobacterial infections. Of the 88 patients, 75 met the inclusion criteria (40 males and 35 females; mean age 14.41±14.30 years; age range 82 years). The site of lymphadenopathy: 47.3% axillary, 6.8% supraclavicular, 8.1% axillary and supraclavicular, 12.2% other sites (sub mandible, neck, humerus, and so forth), 16.8% concomitant in axillary, supraclavicular and other sites, 9.5% were disseminated in the liver, spleen, bone marrow, intra abdominal LN and abscess. The number of needle aspiration or drainage performed were 39.3% one time; 32.8% twice; 13.1% thrice; 9.8% 4 times; 3.3% 5 times and 1.6% 6 times. **Table 1** reports the serum immunoglobulin and NBT activity of the 75 patients included in this study. **Table 2** illustrates the flowcytometric studies in case (n=75) and control (n=100) groups. Significant difference in total lymphocyte (p=0.000); CD3 (p=0.0002); CD8 (p>0.038); CD19 (p=0.000) and natural killers (NK) cell (CD16/CD56) (p=0.0004) but no significant difference in the CD4/ CD8 ratio and CD4 between case and control groups. Thirty eight cases had mild lymphopenia and isolated CD4; CD3 or CD19 deficiency. Natural killers cell (CD16/CD56) deficiency in 3 cases (22%). Idiopathic disseminated BCG infection (unknown immunodeficiency type) in 3 (22%) cases were observed. These mild immune deficient patients had no previous recurrent infections and not diagnosed as immune deficient cases; they had good response to needle aspiration; antimycobacterial drugs and antimycobacterial combine immunomodulator drugs.

Table 1 - Serum immunoglobulin and NBT activity in 75 patients.

Serum IgG ratio	Mean	Min	Max	Range
IgG mg/dl	982.36 ± 931	66.70	4000	3933
IgM mg/ml	162.4 ± 137.38	5	540	540
IgA mg/ml	70.35 ± 84.33	0.0	410	394
IgE mg/ml	5865.36 ± 931	2	35000	34998
% NBT activity	81.90 ± 29.5	000	100	100

NBT - nitroblue tetrazolium test, IgG - Immunoglobulin

Discussion. Bacille Calmette-Guérin lymphadenitis defined as the development of ipsilateral regional LN enlargement after BCG vaccination, is the most common complication resulting from this vaccination.[2–4] The diagnosis of BCG lymphadenitis is clinical. This is also called "normal BCG-itis" in the course of successful BCG vaccination.[5] However, there is no easy way to differentiate "normal" from "abnormal" and there is no agreed definition as to what constitutes BCG lymphadenitis, particularly with regards to the size of LN enlargement, and its onset after vaccination.[5,7-10] It has been recommended that the term BCG lymphadenitis be used to refer to the cases where LNs have become large enough to be easily palpable and a cause of concern for the parents.[5,6] Previously, 3 studies were carried out in Tehran for dissemination of BCG in children. In 10 years survey reported by Siadati et al[44] 29 cases were included: SCID in 7 (29%), CMID in 7 (37.5%), CGD in 4 (17%), CVID in 3 (12.5%), hyper IgM syndrome in one case (4%), 5 cases (19%) with unknown type of immune deficiency diagnosed and 11 died. Mansoori et al[45] found one case of DiGeorge

Table 2 - Flowcytometric changes in patients (N=75) and control group (N=100).

Flowcytometric changes	Case				Control		
	Mean	Minimum	Maximum	Range	Mean	Minimum	Maximum
Total Lymphocyte	47.07 ± 21.59	1.90	78	76.10	61.66 ± 11	36	84
% CD19	27.57 ± 19.05	0.6	98	96.70	18.42 ± 5.4	2.9	38
% CD3	51.84 ± 2.139	1	90	89	67.3 ± 2.1	51	78
% CD4	33.35 ± 16.42	0.4	21	62.60	36.18 ± 5.32	23	48
% CD8	32.83 ± 34.81	0.6	66	64.40	25.85 ± 4.76	14	37
% Natural killers cell (CD16/56)	12.55 ± 6.80	1	29.10	28.10	9.39 ± 4.69	2.1	29
CD4/CD8 ratio	1.39 ± 0.6557	0.6	3	2.40	1.41 ± 1.15	-	-

syndrome and 6 with unknown immunodeficiency disorder in 7 cases of disseminated BCG infections. In another study,[46] they found SCID (2.8%), CMID (34.2%), CGD (25.7%), isolated Tcell defect (2.8%), malignancy with CMID (5.7%), and undiagnosed immune deficiency (5.7%) in their cases.

In Siadati et al[44] study, the gender ratio was 1:8, mean age was 2.9 years and range of age was 2.5 - 108 months. In Mansoori et al[45] study, however, gender ratio was 5:2, mean age was 2.8 years and range of age was 2-76 months.

The range of age (2-84; mean=14.41 month) in our study was similar to that of other study; however, the gender predilection was significantly different. In the present study, the normal NBT was observed in 96.1% and the abnormal NBT were seen in 3.9%, which is comparable to Siadati et al[44] study (56% normal and 44% abnormal). In our study, abnormality of NBT test are less frequent than Siadati study. The mean and range of 3 classes of immunoglobulin amount in the present study compare with Siadati study were observed: IgG mg/dl (mean=982.36; 66.70-4000 versus 566; 25-2200), IgM mg/dl (mean=162.4; 5-540 versus 125; 17-931). IgA mg/dl (mean=70.35; 0- 410; versus 52; 0.21-280). The mean of immunoglobulins amount in this study are higher compared with Siadati et al[44] study. Because we studied all type of BCG lymphadenitis (which includes disseminated BCG). In this study, 13 cases of severe immune deficiency were observed: SCID in 5, CMI in 6 and CGD in 2 patients. Six patients (50%) died due to progressive disseminated mycobacterial infections although other non-mycobacterial infections were also observed on their study. The mortality rate in our study was almost equal to the study of Siadati et al[44] Therefore, our results agree with the previous studies in Iran that lethal disseminated BCG infections usually occur in patients with severe Tcell defects (CMI; SCID) or disorders of phagocyte function patients.[7] The flowcytometric indexes had meaningful difference with healthy group in total lymphocyte, CD3, CD8, CD19, NK cell but no significant difference in the CD4/CD8 ratio and CD4 between case and control groups. But, in contrast to prior study, they found mild non-specific host defect in their cases such as mild lymphopenia and mild isolated CD4; CD3 or CD19 deficiency. The flowcytometric indexes were the same as healthy control group after exclusion of these cases. Three NK cell deficient (22%) cases were detected. They responded well to 3 antimycobacterial drugs without immunomodulator. Natural killers cell deficiency are not yet reported as a risk factor for progression and complication of BCG infection. Three cases (22%) with idiopathic disseminated BCG infection (unknown immunodeficiency type) were observed, they found it in 2 boys and one girl with a positive previous history of death of her brother with the same clinical signs. They had nonlethal and indulgent BCG infections, not to be susceptible to infections with many agents other than mycobacteria or had previous recurrent infections. They had not yet diagnosed as immune deficient cases but, we identified them as an idiopathic disseminated BCG infection. They responded well to treatment including needle aspiration and 3 antimycobacterial drugs with immunomodulator (gamma interferon). There are other possible explanations for this predilection. Susceptibility of these patients to mycobacterial infections results from an intrinsic impairment of the gamma IFN pathway response to these particular intracellular pathogens. Probably, insufficient IFN-gamma production appears to be the main pathogenic mechanism in IL-12R beta 1-deficient patients.[20-27] The underlying immune disorder was genetically heterogeneous and related to cell-mediated immunity to intracellular pathogens. Unfortunately, we can not detect beta-1chain of the IL-12 receptor in our patients. The incidence of idiopathic disseminated BCG infection in this study is approximately 17% of Siadati study.[44] The major effector mechanism of cell-mediated immunity against intracellular pathogens including mycobacteria, is thought to be the activation of infected macrophages by interferon-gamma (IFN-gamma). Interferon-gamma is produced by NK cell and TH1 lymphocytes, and its production is up-regulated by interleukin-12 (IL-12), which is produced and released by macrophages and dendritic cells.[28-37] It has been reported that IL-12-dependent IFN-gamma secretion is essential and specific for protective immunity to mycobacterial infections.[28-39] In recent reports, idiopathic disseminated infections caused by non-tuberculous mycobacteria have been described in a few children without well-defined immunodeficiencies (severe combined immuno deficiency and chronic granulomatous disease). All of these children appeared not to be susceptible to infections with many agents other than mycobacteria; apparently results from an intrinsic impairment of the gamma IFN pathway response to these particular intracellular pathogens. The first was found in a 2.5 month-old Tunisian girl who had fatal idiopathic disseminated BCG infection and in 4 children from Malta who had disseminated atypical mycobacterial infection in the absence of a recognized immunodeficiency. They had a functional defect in the upregulation of TNF-production by their blood macrophages in response to stimulation with IFN-gamma. Each was also found to have a mutation in

the gene on chromosomes 6q22-23 that encodes the IFN-gamma receptor 1. A second type of defect with disseminated mycobacterial infections is mutations in the beta-1chain of the IL-12 receptor. Interleukin-12 is a powerful inducer of IFN- production by T and NK cells. The mutated receptor chain resulted in unresponsiveness of these patients cells to IL-12 and inadequate IFN-production. TH1 responses appeared to be normal in these patients.[28-39] Altare et al[30] diagnosed a homozygous deletion within the LI-12 p40 subunit gene in a child with disseminated BCG and Salmonella enteritidis infection which was the first discovered human disease resulting from a cytokine gene defect. Besides, mutations in the IL-12 p40 gene, mutations causing complete IFN-gamma receptor (R) 1 and R2 deficiencies and partial IFN-gamma-R1 deficiency were also found. Interluken-12 binds to high affinity beta 1/beta 2 heterodimeric IL-12 receptor (IL-12R) complexes on NK cell and TH1 lymphocytes.[29-34,43-44] Recently recessive mutation in IL-12 beta 1 chain genes have been identified in a number of patients with disseminated mycobacterial infections such as *Mycobacterium avium* and *Mycobacterium bovis*. Rapidly growing mycobacterial species have been cultured in patients with complete IFN-gamma-RI and IFN-gamma-R2 deficiency.[37-44] Seven cases of IL-12R beta 1 deficiency with mycobacterial infections have been reported through 1998. Complete IFN-gamma-R deficiencies could also lead to more severe and fatal infections with mycobacteria of low-grade virulence, usually before 3 years of age.[37-44] Insufficient IFN-gamma production appears to be the main pathogenic mechanism in IL-12R beta 1-deficient patients. In contrast to these disorders, patients with IL-12R beta 1 deficiency often develop milder infections, which manifest at a later age and can usually be cured by extensive chemotherapy. These patients resemble children with partial IFN-gamma-R deficiency, and they display a milder histopathologic phenotype, at least in the case of infection with BCG.[32-44] The multiple and severe form of BCG lymphadenitis (but not disseminated) in NK cell and isolated CD4 deficient patients in this study may be due to lower than normal amount of IFN-gamma is produced by NK cell and TH1 in patients.

Therefore, according to previous experiences in Iran and other studies and difficulties in detecting of IFN-gamma receptor (R1 and R2) in all of these cases, we suggest combination of IFN-gamma and chemotherapy in cases of idiopathic disseminated infections caused by BCG without well-defined immunodeficiencies (SCID; CMID; phagocyte dysfunction) in routine immunological profile and without previous recurrent other infection except mycobacterium species.

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