Iranian Journal of Pediatric Society
Volume 1, Number2, 2007: 43-47

Original Article

Type of Immunodeficiency, Treatment and Outcomes of Serious BCG Vaccine Complications: A 15 Year Survey

Samileh Noorbakhsh [1], Ahmad Siadati [2], Setareh Mamishi [3], Lida Fereidoni [4], Jalil Kooh Paiezadeh [5]

[1] Assistant Professor of Pediatric Infectious Disease, Research center of pediatric infectious diseases, Iran University of Medical Sciences, [2] Professor of Pediatric Infectious Disease, Research center of pediatric infectious diseases, Central Children Hospital. Tehran University of Medical Sciences, [3] Associate Professor of Pediatric Infectious Disease, Central Children Hospital, Tehran University of Medical Sciences, [4] Pediatrician, Central Children Hospital, Tehran University of Medical Sciences, [5] Iran University of Medical Sciences .

ABSTRACT

***Background**: To describe the immunologic characteristics and outcomes of the patients with serious BCG complication in a 15- year survey.*

***Materials and Methods:** A descriptive and retrospective study was performed in 2 referral pediatric infectious wards of central Children Hospital, and Rasool Akram Hospital Tehran, Iran between 1989 and 2004.*

***Results:** We studied 76 patients (72% male and 28% female) with serious BCG complications. mean age of 14.41± 1.43 months the results were follows:*

severe combined immunodeficiency 15.7 % of cases Leukopenia 1.4%; lymphopenia in 2.8%; cell mediated immunodeficiency in 26.3 %, chronic granulomatous disease in 11.2%, common variable immunodeficiency 6.5 %; NK cell deficiency in 5.2%; isolated CD4 deficiency in 5.1 %; hyper IgM syndrome in 1.4 %, mild abnormality in nitroblue tetrazolium (NBT) test 4.2 %;mild hypogammaglobulinemia in 4.2 % and idiopathic disseminated BCG infection in 15.7% of patients. Nineteen patients died due to progressive disseminated mycobacterial infections.

***Conclusion:** N.k cell deficiency has yet reported as a risk factor for progression and complication of BCG infection. we suggest combination therapy with IFN-δ and chemotherapy in all cases of" idiopathic disseminated BCG infections.*

***Key words:** BCG compliacation, Gamma Interferon, BCG vaccine, Immunodeficiency.*

***Corresponding author*:** *Samileh Noorbakhsh MD*
***Address*:** *Center of Pediatric Infectious Diseases, Hazrat Rasool Hospital, Niayesh street, Satarkhan Avenue, Tehran, 14455 Islamic Republic of Iran*
***Tel**: 09121823797; **Fax**: +98-281- 3344088*
***Email:** Samileh_noorbakhsh @yahoo.com/Saminoor@hbi.or.ir*

INTRODUCTION

Bacille Calmette-Guérin (BCG) vaccination has been used to prevent tuberculosis since 1921. It was incorporated in the World Health Organisation's Expanded Program on Immunization in 1974 to strengthen the fight against childhood tuberculosis in developing countries. BCG vaccine has a low incidence of serious adverse reactions, and is considered to be a safe-vaccine (1,2). BCG lymphadenitis is the most common complication resulting from this vaccination (3,4).

Disseminated BCG infections occur in patients with severe T-cell defects, serious immunodeficiency states like severe combined immunodeficiency, acquired immunodeficiency syndrome (AIDS) and chronic granulomatous disease(1,2,).

Seven cases of IL-12R beta-1 deficiency with mycobacterial infection have been reported through 1998 (8-13). Insufficient IFN-γ production appears to be the main pathogenic mechanism in IL-12R beta-1 deficient patients. Complete IFN-γ-R deficiencies can also lead to more severe and fatal infections with mycobacteria of low grade virulence, usually before 3 years of age (18-19).

The aim of present study is to describe the immunologic characteristics of the patients with serious BCG complication in a 15- year period.

MATERIALS AND METHODS

This retrospective study was performed on 108 children from 3 months to 14 years old admitted in the pediatric infectious ward of Rasool Akram Hospital and Central Children Hospitalbased on diagnostic parameters for BCG complications during a 15-year period (1989-2004).

The inclusion criteria included patients with multiple BCG lymphadenitis or other serious complications, [defined with no other] identifiable or known cause in these cases.

Exclusion criteria included: presence of fever, tenderness, and other constitutional symptoms for pyogenic adenitis. On the other hand, once suppuration has supervened; consisted of positivity of microbial culture of lymph node.

Initially, a questionnaire was filled in from files of each patient. It considered of the number and sites of lymphadenitis, peresence of organomegaly and other finding on systemic examination of patients, laboratory indices including nitroblue tetrazolium (NBT) test and flowcytometeric studies and qualitative determination of serum immunoglobulin (IgM, IgG and IgA).

Data were analyzed by SPSS software ver 10.

RESULTS

During a 15-year- period, 108 patients were admitted in our wards due to serious BCG complications. Twenty-seven had insufficient blood sampling and other immunologic studies in initial admission or follow-up. In 4 cases, immunologic studies were not done due to blood clotting of the sample. They did not return for repeating these tests.

2 cases were died before immunological study.

Finally, we studied 76 patients with mean age of 14.41+1.43 months. (72 % male and 28% female)

Types of Immunodeficiency are presented in Table 1.

Table 1. Type of Immunedeficiency in 76 patients

Type of Immunodeficiency	Number	Percent
Leukopenia	1	1.3%
Lymphopenia	2	2.7 %
SCID (severe combined immunodeficiency)	12	15.7 %
CMID (cell mediated immunodeficiency)	20	26.4 %
CGD (chronic granulomatous disease)	9	11.8 %
CVID (common variable immunodeficiency)	5	6.7 %
NKC (natural killer cell deficiency)	4	5.2 %
Isolated CD4 /or CD3/ or CD19 deficiency	4	5.2 %
Hyper IgM	1	1.3 %
Mild CGD* (NBT test activity less than 10%)	3	4 %
Mild hypogammaglobulinemia (less than 10% for normal age)	3	4 %
Idiopathic disseminated BCG infection (Unknown immunodeficiency type) observed	12	15.7 %
Total	76	100%

* NBT: nitroblue tetrazolium

Outcomes:

Nineteen patients died due to progressive disseminated mycobacterial infections although other non-mycobacterial infections occurred in them, too.

Those patients with mild immunodeficiency (mild lymphopenia and CD19 deficiency) had no previous recurrent infections and were not diagnosed as immunodeficient cases until admission in hospital. They had good response to antimycobacterial drugs.

N.K cell deficiency has not yet reported as a risk factor for progression and complication of BCG infection.

N.K cell deficient (5%) and isolated CD4 deficient cases responded well to 3 antimycobacterial drugs with immunomodulator drugs.

Cases with idiopathic disseminated BCG infection (unknown immunodeficiency type) responded well to 3 antimycobacterial drugs combined with gamma-interferon. They had no history of other agents except mycobacterium bovis. Unfortunately,we could not detect beta-1chain of the IL-12 receptor which is another possible explanations for this predilection.

DISCUSSION

Serious immunodeficiency states like severe combined immunodeficiency and AIDS are associated with increased incidence of local as well as systemic disseminated BCG infection after vaccination (3,4).

At least 3 studies on disseminated BCG infections were done in Tehran during the last decades. (5-7).

Siadati et al reported 27 cases included SCID in 7(26%); CMID in 7(26%) and CGD in 4 (13%); CVID in 3(12%); and hyper IgM syndrome in 1 case(4%). In 5 cases (19%) no known type of immunodeficiency diagnosed. Eleven cases died. Male/ female ratio was 21/8, and mean age was 34.8 months ranging from 2.5 to108 months (5).

Mansoori et al reported 7 cases of disseminated BCG infections. DiGeorge syndrome was diagnosed only in 1 case. A known immunodeficiency disorder was not diagnosed in 6 patients. Five cases died and one case improved. The male/female ratio was 5 /2, and mean age was 8 months ranged from 2 to 76 months (7).

Farhoodi et al reported 35 cases included SCID in 1(2.8%); CMID in 12(34.2%); CGD in 9 (25.7%); isolated Tcell defect in 1(2.8%); malignancy with CMID in 2(5.7%) and undiagnosed immune deficiency in 2(5.7%) cases (7).

In the present study, the range of age in our patients (2- 84 months; mean=14.41months) is near to the above studies but the sex predilication (male /female ratio: 40/35) is different.

Therefore, the results of this study, like as previous studies in Iran, showed that lethal disseminated BCG infections usually occurred in patients with severe T-cell defects (CMI; SCID) or CGD (5-7).

In contrsat to previous studies, we observed mild nospecific host defects like mild lymphopenia and mild isolated CD 19 deficiency in 50% of cases (1, 5-7).

In 4 cases a N.K cell deficiency (5.4%) was diagnosed. All of thses cases responded well to 3 antimycobacterial drugs with immunomodulator drugs.

N.K cell deficiency has not yet been reported as a risk factor for progression and complication of BCG infection.

The multiple and severe form of BCG lymphadenitis (but not disseminated) in N.K cell and isolated CD4 deficient patients in this study may be due to lower amount of IFN-gamma (below normal level) which produced by N.K cells and T helper 1 lymphocytes.

Twelve cases (15.7%) with unknown immunodeficiency type were diagnosed as idiopathic disseminated BCG infection. The incidence of idiopathic disseminated BCG infection in this

study (15.7%) is near to Siadati's study (17%). They had nonlethal and indulent BCG infection. They were not susceptible to infections with many agents other than mycobacteria or had previous recurrent infections. All of them responded well to treatment included needle aspiration plus antimycobacterial drugs plus immunomodulator drugs (gamma-interferon).

Probably, susceptibility of these patients to mycobacterial infections resulted from an intrinsic impairement of the IFN-γ pathway response to these particular intracellular pathogens.

IFN-γ is produced by N.K cells and T-helper 1 lymphocytes, and its production is up-regulated by interleukin-12(IL-12) which is produced and released by macrophages and dendritic cells (9,10).

It has been reported that IL-12- dependent IFN-γ secretion is essential and specific for protective immunity to mycobacterial infections (11-14). IL-12 is a powerful inducer of IFN- γ production by T and NK cells.

The mutated receptor chain results in unresponsiveness of the cells of patients to IL-12 and thus inadequate IFN- γ production. T helper 1 responses appeared to be normal in these patients (15-18).

Insufficient IFN- γ production appears to be the main pathogenic mechanism in IL-12R beta 1-deficient patients. The underlying immune disorder is genetically heterogeneous and related to cell-mediated immunity response to intracellular pathogens (17,18).

Unfortunately; we were not able to detect beta-1chain of the IL-12 receptor which are other possible explanations for this predilection.

CONCLUSIONS

The multiple and severe form of BCG lymphadenitis(but not disseminated) in N.K cell deficient (5%) and isolated CD4 deficient cases may be due to lower (than normal) amount of IFN- γ produced by natural killer cells and T helper (CD3 and CD4) lymphocytes. We successfully treated all N.K cell deficient or isolated CD4 deficient patients with chemotherapy and antimycobacterial drugs without immunomodulator drugs.

The incidence of idiopathic disseminated BCG infection in this study was 15.7%. Unfortunately, we did not detect β-1 chain of the IL-12 receptor in our patients.

According to previous experiences in other studies and difficulty in detecting of IFN-γ receptor (R1 and R2), we suggest combination therapy with IFN-γ and chemotherapy in all cases of" idiopathic disseminated infections" caused by B. C.G vaccination.

REFERENCES

1. Talbot EA, Perkins MD, Silva SF, Frothingham R. Disseminated bacille Calmette-Guérin disease after vaccination: case report and review. ***Clin Infect Dis*** 1997; 24(6):1139-46. Review.
2. O'Brian KL, Ruff AJ, Louis MA, et al. Bacillus Calmette-Guerin complications in children born to HIV-infected women with a review of literature. ***Pediatrics*** 1995;95:414–8.
3. Goraya JS, Virdi VS. Treatment of Calmette-Guérin bacillus adenitis: a metaanalysis. ***Pediatr Infect Dis J*** 2001;20(6):632-4.
4. Goraya JS, Virdi VS. Bacille Calmette-Guérin lymphadenitis. ***Postgrad Med J*** 2002;78(920):327-9.
5. Siadati A, Khotaei GH, Saboni F. Disseminated BCG lymphadenitis. ***Iranian J Ped Inf Dis*** 1995; 1 & 2: 41-48.
6. Mansoori M, Tabatabaei A, Golcar H, Masjedi SA.Immunologic study of disseminated BCG infection. ***J Trop Inf Dis*** 1996; 4: 54-58.
7. Farhoodi A, Bazargan N, Arshi S, Poorpak ZB. BCG dissemination in forthy patients and the review of leukocyte mycobactria defect in one patient. ***Iranian Journal of Allergy and Asthma Immunology*** 2000; 1: 63-67.

8. Altare F, Lammas D, Revy P, Jouanguy E, Döffinger R, Lamhamedi S, et al. Inherited interleukin 12 deficiency in a child with bacille Calmette-Guérin and Salmonella enteritidis disseminated infection. ***J Clin Invest*** 1998;102(12):2035-40.
9. Altare F, Durandy A, Lammas D, Emile JF, Lamhamedi S, Le Deist F, et al. Impairment of mycobacterial immunity in human interleukin-12 receptor deficiency. ***Science*** 1998;280(5368):1432-5.
10. Frucht DM, Holland SM. Defective monocyte costimulation for IFN-gamma production in familial disseminated Mycobacterium avium complex infection: abnormal IL-12 regulation. ***J Immunol*** 1996;157(1):411-6.
11. Zhang M, Gong J, Presky DH, Xue W, Barnes PF. Expression of the IL-12 receptor beta 1 and beta 2 subunits in human tuberculosis. ***J Immunol*** 1999;162(4):2441-7.
12. Altare F, Jouanguy E, Lamhamedi S, Döffinger R, Fischer A, Casanova JL. Mendelian susceptibility to mycobacterial infection in man. ***Curr Opin Immunol*** 1998;10(4):413-7.
13. Jouanguy E, Altare F, Lamhamedi S, Revy P, Emile JF, Newport M, Levin M, Blanche S, Seboun E, Fischer A, Casanova JL. Interferon-gamma-receptor deficiency in an infant with fatal bacille Calmette-Guérin infection. ***N Engl J Med*** 1996;335(26):1956-61.
14. Pierre-Audigier C, Juanguy E, Lamhamedi S, et al. Fatal mycobacterium smegmatis infection in a child with inherited interferon-gamma receptor deficiency. ***Clin Infect Dis*** 1997; 24:982-4.
15. De Jong R, Altare F, Haagen IA,et al. Severe mycobacterial and Salmonella infections in interleukin-12 receptore deficient patients. ***Science*** 1998; 280:1435-8.
16. 17.Dorman SE, Holland SM. Mutation in the signal-transducing chain of the interferon-gamma receptor and susceptibility to mycobacterial infection. ***J Clin Invest*** 1998; 101:2364-9.
17. Doffinger R, Jouanguy E, Dupuis S, et al. Partial interferone-gamma receptore signaling chain deficiency in a patient with bacile Calmette-Guerin and Mycobacterium abscessus infection. ***J infect Dis*** 2000;181:379-84
18. Ottenhoff HM, kumararatne D, Casanova JL. Novel human immunodeficiencies reveal the essential role of type-1 cytokines in immunity to intracellular bacteria. ***Imunol Today*** 1998; 19: 491- 4.