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Disseminated *Mycobacterium bovis* Infection after BCG Vaccination

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ABSTRACT

The Calmette-Güerin vaccine (BCG) is administered to all the newborns in Iran in order to prevent tuberculosis. Complications of this vaccine are uncommon. We report disseminated BCG disease in 17 patients less than 10 years old.

This is a retrospective study of total of 17 cases who were admitted in Children Medical Center Hospital with systemic syndrome compatible with Mycobacterium disease with evidence of histopathologic demonstration of acid-fast bacilli during 1995-2004.

Fourteen cases occurred in children younger than 1 year old. Nine patients were female. Ten of the 17 total cases were associated with an immune deficiency including severe combined immunodeficiency, chronic granulomatous disease and cell mediated immune defect. Response to therapy was ineffective and 10 of them (58.8%) died.

Disseminated BCG disease is an uncommon but devastating complication of vaccination that should be considered in the appropriate clinical setting. Immune-compromised infants are at greatest risk and they respond poorly to standard therapies.

Key words: BCG; Children; Tuberculosis; Vaccination

INTRODUCTION

The original BCG (Bacillus Callmette – Güerin) strain of *Mycobacterium bovis* was derived from multiple passages of wild-type *Mycobacterium bovis*.[1] BCG vaccine is administered to prevent tuberculosis (TB) specially miliary and meningeal TB in childhood. It is considered to be safe however, some complications may occur, including abscesses at the site of inoculation and localized lesions such as osteitis.[2]

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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,[3] and impaired IL12 and IFNγ mediated immunity.[4] However it may cause severe disease in otherwise healthy children with no overt immunodeficiency.[5] In infants with immunodeficiency BCG vaccination is contraindicated, but they are vaccinated prior to diagnosis, and immunodeficiency may be diagnosed after the development of BCG complications.[6]

In Iran BCG substrain Pasteur vaccine, is administered to children at birth to prevent

tuberculosis. In this study we reviewed 17 cases of disseminated bacillus calmette- Güerin infection.

PATIENTS AND METHODS

During a retrospective study in Children Medical Center, a referral teaching hospital affiliated to Tehran University of Medical Sciences, we found 30 cases who had been admitted due to complication of BCG vaccine from 1995 to 2004.

We accepted 17 of 30 patients that showed all of following conditions:

1. positive history of the inoculation of BCG vaccine
2. Two or more signs and symptoms of a systemic syndrome compatible with mycobacterial disease including fever, weight loss, lymphadenopathy or cutaneous abscesses, pneumonia, osteomyelitis, hepatomegaly and splenomegaly.
3. Evidence of BCG infection includes a histopathologic demonstration of acid- fast bacilli; at two or more anatomic sites beyond the region of vaccination such as lymph nodes or cutaneous abscesses outside the region of inoculation, liver biopsy, gastric aspiration and bone marrow aspiration.

The competency of the immune system was evaluated by different tests including measurement of Immunoglobulins, Isohemaglotination test, phagocyte activity by NBT (slide test), T-cell and B-cell counts by flowcytometry, delayed type hypersensitivity test (DHT). HIV test performed only in 5 cases by ELIZA. These tests were performed by standard procedures and by trained laboratory personnel in the laboratories of the Children Medical Center.

RESULTS

We reviewed 17 cases with disseminated BCG disease (9 female and 8 male), who complied with inclusion criteria of this study. These data are summarized in table 1. There was a history of complications of BCG infection or death due to other infections in family of patients in 41.17% (6 cases).The rate of consanguinity was 82.35% (14 cases) in affected families.

Table 1. Summary of data on 17 cases of disseminated BCG disease.

Case No.	Age/ Sex	Immune defect	Sites of evidence of BCG infection	Antimicrobial therapy	Outcome
1	6 mo/M	None	Skin ,Liver	INH,RMP, SM EMB,	Survived
2	3Y/M	None	DLN,Liver	INH, RMP , PZA ETM	Survived
3	5mo/F	CGD	Liver–DLN	INH, RMP	Died
4	11mo/M	SCID	DLN ,Lung	INH, RMP	Died
5	4.5mo/F	None	DLN,Liver BM	INH, RMP, PZA SM	Died
6	11 mo/M	CMI	DLN,BM	INH, RMP, ETM SM	Died
7	9 mo/M	SCID	DLN -Gastric aspiration	INH, RMP, ETM SM	Died
8	8 mo/F	SCID	DLN,BM	INH, RMP, SM	Died
9	3mo/M	SCID	Skin DLN,Lung	INH, RMP, ETM	Died
10	3mo/M	None	Skin – BM	INH, RMP, ETM, SM	Survived
11	3 Y/F	None	DLN- pelvic abscess	INH, RMP, PZA, ETM,	Survived
12	7mo/M	SCID	Scalp abscess,Lung	INH, RMP, ETM, SM	Died
13	4 mo/F	SCID	BM,Lung,Liver	INH, RMP, ETM	Died
14	6 mo/F	SCID	DLN,Lung	INH, RMP, ETM, SM	Survived
15	5 mo/F	SCID	DLN,Liver	INH, RMP, ETM, SM	Died
16	8 mo/F	None	Gastric aspiration,DLN	INH, RMP, ETM, SM	Survived
17	2Y/F	None	BM,Lung	INH, RMP, ETM, SM	Survived

CGD= chronic granulomatous disease, CMI=cell–mediated immune defect, SCID= severe combined immunodeficiency, DLN= Distant lymph node, INH= isoniazid, RMP=Rifampin, ETM= ethambutol, SM=streptomycin, BM=Bone marrow, NONE=no immune deficient (including: CGD, SCID, CMI)

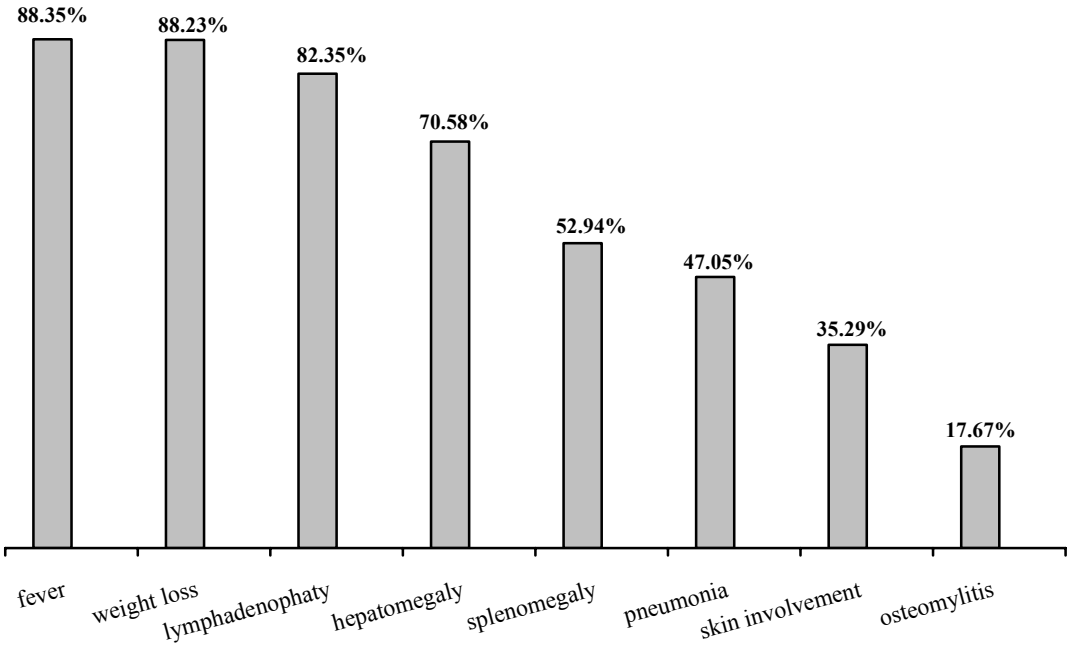

Figure 1. Signs and symptoms in the patients with disseminated BCG disease.

Clinical signs and symptoms had begun before 1 year of age in 82.35% of them. Impaired immunity was detected in 10 cases (58.82%) including: severe combined immunodeficiency in 8 cases (80%), chronic granulomatous disease in 1 case (10%), and cell mediated immune defect in 1 case(10%).

HIV was not identified in any of the cases that we evaluated for it. The most common sites of acid- fast bacilli were lymph nodes (70.58%). The most commonly reported symptoms and signs are indicated in fig.1. Fever, weight loss and lymphadenopathy were seen in more than 80% of the patients. Unfortunately 10 patients (58.8%) died.

DISCUSSION

Immunization of children with BCG is recommended by the world health organization in communities with a high prevalence of tuberculosis.[7] BCG vaccines are safe in immunocompetent hosts, however possible complications including hypersensitivity, localized lymphadenitis, fistula formation and rarely disseminated disease and death may occur.[8] Disseminated disease is the most serious complication of BCG vaccine that may develop in children with immunodeficiency disorders,[9] although, there are a few reports of disseminated BCG infection in normal hosts.[10]

The records of our review showed that most of patients with disseminated BCG disease had immunodeficiency. Immune defects were identified in 10 subjects. The other cases did not show any abnormality in immune system. However they were not investigated for disorders of IL-12 and IFN-γ mediated immunity that have recently been identified as possible cause of susceptibility to infection with intracellular microorganisms such as mycobacterium and salmonella.[11] In a study by Farhoudi, et al.[12] in this center, one of the 6 cases had INF-γ receptor deficiency, however they were not investigated for detection of IL-12 receptor deficiency.

In the retrospective review of disseminated BCG disease by Lotte, et al.,[13] all the 60 patients took part in that study, had cellular immunodeficiency and 31 of these patients died. Additionally, in study of Talbot et al.,[14] immunodeficiency was identified in 24 out of 28 subjects. In another review of nine children by Gonzalez et al.,[15] all of their patients had immunodeficiency disorders.

There have been many reports of local and disseminated complications in patients with HIV infection,[16] but HIV test in our patients was found to be negative. Most of the clinical signs in our study comprised of fever, weight loss and lymphadenopathy. Also in study by Casanova, et al.,[3] fever and cachexia were common in the patients. Positive family history of BCG complications and high degree of consanguinity in patients′ families, support the hypothesis of inherited susceptibility to disseminated BCG disease. This finding is compatible with the study of Casanova, et al.[3] There is little information about suitable treatment for disseminated BCG disease. Antimycobacterial regimens used for the treatment of patients in our study were isoniazid, rifampin, ethambutol, and streptomycine. In a Spanish review,[17] 10 immunocompetent patients with non-BCG *Mycobacterium bovis* infection were treated with isoniazid, rifampin and ethambutol. Nine of the patients were cured and had no relapses and one patient died of other causes. Most of our patients died despite aggressive management. This result was compatible with the finding of Talbot, et al.[13] who reported mortality rate of more than 70% in immunodeficient patients with disseminated BCG infection. Also in Casanova, et al, study[3] the prognosis of BCG infection was poor and mortality rate reported as 43%. These results may be due to immunodeficiency in patients, delay in diagnosis or resistance of Bacillus Calmet-Gurin to drugs which had been used. Finally we conclude that despite benefits of BCG immunization against mycobacterium tuberculosis infections, development of a more effective, safer, affordable vaccine with fewer side effects are a major necessity because infants with immunodeficiency usually are vaccinated prior to diagnosis in many countries.

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REFERENCES

1. Lugosi L. Theoretical and methodological aspects of BCG vaccine from the discovery of Calmette and Guerin to molecular biology. A review. Tuber Lung Dis 1992; 73(5):252-61
2. kröger L, Korppi M, Brander E, Kroger H, Wasz-Hockert O, Backman A, et al. Osteitis caused by bacille Calmette-Guerin vaccination: a retrospective analysis of 222 cases. J Infect Dis. 1995; 172(2):574-6.
3. Casanova JL, Blanche S, Emile Jf. Jouanguy E, Bordigoni P, Lambamedi S, et al. Idiopathic disseminated Bacillus calmette – Güerin infection: A French National retrospective study. Pediatrics 1996; 98 (4):774-8.
4. Doffinger R, Dupuis S, Picard C, Fieschi C, Feinberg J, Bacenas-Morales G, Casanova JL. Inherited disorders of IL-12- and IFN gamma-mediated immunity: a molecular genetics update. Mol Immunol 2002; 38:903-9.
5. Levin M, Newport MJ, D'Souza S, Kalabalikis P, Brown IN, Lenicker HM, et al. Familial disseminated atypical mycobacterial infection in childhood: a human mycobacrurid susceptibility gene. Lancet 1995; 345:79-83.
6. Han TI, Kim IO, Kim WS, Yeon KM. Disseminated BCG infection in a patient with severe combined immunodeficiency. Kor J Radiol 2000; 1(2):114-7.
7. Fine PEM, Carneiro IAM, Milsteen JB, Clements CJ. Issues relating to the use of BCG in immunization programs, Department of vaccines and biologicals. World Health organization Geneva 1999. www.who.int/gpv-documents.
8. Grange JM. Complications of bacilli calmette-Güerin (BCG) vaccination and immunotherapy and their management. Commune Dis Public Health 1998; 9:84-8.
9. Pedersen FK, Engbaek HC, Hertz H. Fatal BCG infection in an immunocompetent girl. Acta Paediatr Scand 1978; 67(4):519-23.
10. Katzir Z, Okon E, Ludmirski A. Generalized Lymphadenitis following BCG vaccination in an immunocompetent 12 years old boy. Eur J Pediatr 1984; 141(3):165-70.
11. Fieschi C, Cosanova JL. The role of interleukin-12 in human infectious diseases: only a faint signature. Eur J Immunol 2003; 33(6):1461-4.
12. Farhoudi A, Bazargan N, Arshi S, Pourpak Z. BCG dissemination in 40 patients and review of leukocyte mycobatericidal defect in one patient. Iran J Allergy Asthma Immunol 2000; 1(2):63-7.
13. Lotte A, Wasz-Hockert O, Poisson N, Dumitrescu N, Verron M, Couvet E. BCG complications. Estimates of the risks among vaccinated subjects and statistical analysis of their main characteristics. Adv Tuberc Res 1984; 21:107-9.

14. Talbot EA, Perkins MD, Silva SF, Frothingham R. Talbot EA, Perkins MD, Silvas FM. Disseminated bacille Calmette-Guerin disease after vaccination: case report and review. Clin Infect Dis. 1997; 24:1139-46.
15. Gonzalez B, Moreno S, Burdach R, Valenzuela MT, Henrigueza A, Ramos MI, et al. Clinical presentation of Bacillus Calmette-Guerin infections in patients with immunodeficiency syndromes. Pediatr Infect Dis J. 1989; 8(4):201-6
16. O'Brien kL, Ruff AJ, Louis MA. Bacillus calmette-Güerins complication in children born to HIV-1 – infected women with a review of the literature. Pediatrics 1995; 95(3):414-8.
17. Sauret J, Jolis R, Ausina V, Castro E, Cornudella R. Human tuberculosis due to *Mycobacterium bovis*: report of 10 cases. Tuber Lung Dis 1992; 73(6):388-91