

Disseminated bacille Calmette-Guérin disease in Saudi children: clinical profile, microbiology, immunology evaluation and outcome

E. BUKHARI¹, F. ALAKLOBI², H. BAKHEET¹, A. ALRABIAAH¹, F. ALOTIBI³, F. ALJOBAIR², M. ALSHAMRANI², E. ALAKI⁴, F. ALNAHDI⁵, A. ALODYANI⁵, F. ALZAMIL¹

¹Prince Abdullah Ben Khalid Celiac Disease Research Chair, Department of Pediatric, College of Medicine, King Saud University, Riyadh, Saudi Arabia

²Department of Pediatric Infectious Diseases, King Saud Medical City, Riyadh, Saudi Arabia

³Department of Pathology, King Khalid University Hospital and King Saud University, College of Medicine, King Saud University Medical City, Riyadh, Saudi Arabia

⁴Department of Pediatric Allergy and Immunology, King Saud Medical City, Riyadh, Saudi Arabia

⁵Department of Pediatric Infectious Diseases, Prince Sultan Military Medical City, Riyadh, Saudi Arabia

Abstract. – OBJECTIVE: The bacille Calmette Guérin (BCG) vaccine is administered worldwide to prevent tuberculosis. Although, Post BCG vaccination complications like disseminated BCG infections are rare and immunocompromised children are at high risk of developing BCG-related complications including BCG-lymphadenitis and other disseminated diseases.

PATIENTS AND METHODS: This was a prospective study of children who developed disseminated BCG after vaccination who were admitted in three tertiary care hospital in Riyadh, Saudi Arabia, in the year 2015. The clinical presentation, microbiological/immunological evaluation and outcome will be discussed.

RESULTS: 12 cases (7 males and 5 females) of disseminated BCG infections after vaccination were documented with age ranges 3 and 32 months. Eight (66%) patients had interleukin IL-12 deficiency and 3 (25%) had severe combined immune deficiency (SCID) and 1 (8%) had Interferon gamma receptor II deficiency. 9 (75%) patients presented with generalized lymphadenopathy. Hepatosplenomegaly was present in 6 (50%) patients. 2 (16%) patients presented with a recurrent skin infection and persistent oral candidiasis in one patient and pneumonia in the other. Five (41%) families were from 1st degree consanguineous marriage. Tuberculosis (TB) culture and sensitivity were positive for *Mycobacterium bovis* from gastric aspirate (GA) in 4 patients and the lymph node in 9 patients and 1 patient had culture positive from both skin lesion and lymph nodes. *Mycobacterium bovis* PCR was positive in 4 patients. All patients received anti-tuberculosis therapy; all patients survived except one who died due to multi-organ failure.

CONCLUSIONS: These results indicate that the prevalence of disseminated BCG vaccine in

immunocompromised Saudi children is significantly high. Since in our region we have a high consanguinity rate and a high number of primary immune deficiency disorder (PID), we believe that BCG vaccination should be postponed till a child reaches one-year-old and appropriate tests exclude the diagnosis of primary immunodeficiency diseases.

Key Words

BCG vaccination, Complications, Primary immunodeficiency diseases.

Introduction

The BCG vaccine was developed by Albert Calmette and Camille Guérin in France between 1908 and 1921¹. Bacillus Calmette-Guérin (BCG) vaccine was derived by in vitro attenuation of *Mycobacterium bovis* strains in 1906, and the World Health Organization (WHO) incorporated the vaccine in the Expanded Program of Immunization (EPI) in 1974². The efficacy of the BCG vaccine for tuberculosis prevention is controversial. However, it has a relatively high protective efficacy against meningeal and disseminated *Mycobacterium tuberculosis*³⁻⁵. A recent meta-analysis has shown a summary of the protective BCG effect of 73% (95% confidence interval, CI: 67-79) against tuberculous meningitis and 77% (95% CI: 58-87) against miliary tuberculosis⁶. In Saudi Arabia, BCG SSI vaccine

(Danish strain 1331) is administered at birth to all the newborns and it is injected intradermally, above the distal insertion of the deltoid muscle of the left arm. Although it is generally considered safe, there are secondary complications. The most frequent complications are regional lymphadenitis 0.4-1 per 1,000 vaccinated children⁷. Another important complication is a life-threatening disseminated BCG infection. Meanwhile, a number of PIDs are susceptible to severe mycobacterial disease following vaccination with BCG, including severe combined immunodeficiency (SCID), chronic granulomatous diseases (CGD), complete DiGeorge syndrome (CDGS), Acquired Immune Deficiency Syndrome (AIDS) and the Mendelian susceptibility to mycobacterial disease (MSMD). Patients with an isolated inborn error of the IL-12/23- IFN- γ pathway are exclusively prone to low-virulence mycobacterial and non-typhoid *Salmonella* infections, also known as, Mendelian susceptibility to the mycobacterial disease (MSMD) phenotype (for example, IFN- γ receptor 1/2 deficiencies, IL-12/23 receptor b1 chain deficiency, IL-12p40 deficiency, STAT1 deficiency and NEMO deficiency) in contrast⁸⁻¹⁰. The occurrence of disseminated BCG disease ranged from 0.06 to 3.4 cases per million vaccination, with a high mortality rate that reached up (60-83%) in immunocompromised patients¹¹⁻¹². The diagnosis of disseminated BCG infection that affects mainly infants and young children and is characterized by a clinical presentation with fever, weight loss, lymphadenopathy, and hepatosplenomegaly¹³. After examining the documented cases of disseminated BCG disease in Saudi children, we are reporting new cases and discussing the clinical, diagnostic evaluation, and its underlying defects.

Patients and Methods

Twelve patients with disseminated BCG after vaccination were diagnosed between January 2015 and January 2016 at three tertiary care hospitals in Riyadh, Saudi Arabia. These hospitals have a specialist pediatric infectious disease and immunology services. Patient data were obtained daily from hospital and laboratory records. The data collected included demographic information, clinical presentation, laboratory and radiological studies, treatment and outcome (Table I).

Case definitions of disseminated BCG disease were defined as the isolation of *Mycobacterium bovis* BCG from one or more clinical

sample regional lymph nodes, respiratory secretions, blood, bone marrow or cerebrospinal fluid, taken at sites distant from the vaccination site, in the presence of a clinical syndrome consistent with disseminated BCG disease¹⁴. Disseminated BCG disease can be confirmed by histopathological findings of acid-fast bacilli at two or more anatomic sites (e.g., lymph nodes) outside the region of vaccination, in gastric aspiration or bone marrow aspiration. Furthermore, disseminated BCG disease can be confirmed through the identification of an isolate such as *M. bovis* BCG using a multiplex polymerase chain reaction (PCR) assay that distinguishes *M. bovis* BCG from other members of the *M. tuberculosis* complex¹⁵. Further laboratory investigations, including screening laboratory tests, complete blood count and differential count (platelet volume, absolute lymphocyte count, neutrophil and eosinophil counts), immunological tests were performed to determine the underlying defects including serum immunoglobulin levels (IgG, IgM and IgA), lymphocyte subpopulations including CD19+ B-cells, CD3+ T-cells, CD56+ natural killer (NK) cells, and also CD4+ CD8+ were measured by double staining of lysed whole blood followed by flow cytometric analysis. Other screening tests such as tests for HIV (Human Immunodeficiency Virus), nitroblue tetrazolium (NBT) for chronic granulomatous disease (CGD) were also taken.

Results

We found that there were 7 males and 5 females; age ranges between 3 months and 32 months. Nine patients presented with generalized lymphadenopathy. Hepatosplenomegaly was present in 6 patients. Two patients presented with failure to thrive, recurrent skin infection and persistent oral candidiasis. One patient presented with pneumonia. Consanguineous marriage was defined as partners who have at least one ancestor in common, with the ancestor being no more distant than a great grandparent¹⁶. Five families were within the 1st degree of consanguineous marriage. The family history of early onset severe infections leading to death in infancy was documented in two families. Five patients had a family history suggestive of an underlying immune deficiency. All the patients had an underlying immune deficiency: 8 patients had in-

terleukin IL-12 deficiency and three have severe combined immune deficiency SCID and one had Interferon gamma receptor II deficiency. The diagnosis was confirmed by TB culture and sensitivity. The culture was positive for *Mycobacterium bovis* from gastric aspirate in four patients and the lymph node in nine patients, and one patient had positive culture from both skin lesion and lymph node. *Mycobacterium bovis* PCR was positive in four patients. Ultrasound and CT scan abdomen revealed the presence of Hepatosplenomegaly and the chest X-ray (CXR) revealed lung involvement (perihilar infiltrates, right pleural effusion/consolidation) Table I. All patients received anti-tuberculosis treatment and improved on the treatment except one (Interferon gamma receptor II deficiency) who died in the intensive care with multi-organ failure. Seven patients were discharged home with anti-tuberculosis treatment and given a regular follow up with the infectious disease and immunology clinic. Two patients with SCID were transferred to the transplant center and one patient was sent for hematopoietic stem cell transplantation (HSCT) from cord blood. One patient received bone marrow transplantation (BMT).

Discussion

Till date, there is no consensus on the number of cases of disseminated BCG infection in Saudi Arabia. In this study, disseminated BCG infection was documented in twelve Saudi children following BCG vaccination. The age of presentation of the patients was their first two years of life ranging between 3 and 32 months. A study from Tunisia¹⁷ reports four cases of disseminated BCG infection occurring in children from three months to four years of age. In another study from Iran¹⁸, the ages of their 17 patients were between 3.5 to 72 months. Six children (36.3%) were younger than 6-months and 13 patients (76%) were younger than 12-months. The preliminary prominent symptoms of our patients were generalized lymphadenopathy and hepatosplenomegaly. In a similar report from Iran, 8 patients (4 males and 4 females) were diagnosed with disseminated BCG infection; all patients had SCID. Axillary adenitis was detected in seven patients, and hepatosplenomegaly was also found in seven patients. Unfortunately, all the patients died due to severe disseminated BCG infection¹⁹. In another study²⁰, lymphade-

nopathy and weight loss were the most common symptoms of disseminated BCG disease. The assessment of the immune status of the patients in the current study showed that all the patients have a different underlying immune deficiency: 8 patients have interleukin IL-12 deficiency and three have severe combined immune deficiency SCID and one had Interferon gamma receptor II deficiency. Shanbestari et al²¹ similarly reported 11 cases with disseminated BCG infection and almost all of them had immunodeficiency as follows: seven cases had severe combined immunodeficiency and one case had a chronic granulomatous disease. MSMD was found in two cases and IL12 R deficiency in another one. In this study, almost half of the families were within the 1st degree of consanguineous marriage, with a significant history of early onset severe infections leading to death in infancy. A similar result was reported from Iranian study²² in which consanguineous was found in more than half of patients (7 cases) and family history of disseminated BCG infection or immunodeficiency was found in nearly one-third of patients (3 cases).

The mortality rate in this work was 8% as one patient died of multi-organ failure in spite of intensive treatment. However, overall, the mortality rate was high in other researches. Mahnaz et al²¹ reported a death rate of 72.8% (8 cases) in which 7 cases of them were SCID and one had CGD. In another study²² 25% of the patients died. Aelami et al²³ found an immunodeficiency state detected in 50% of the patients and the overall mortality rate was 58.8% (20 of 34). BCG vaccine is still part of the routine vaccination program for all newborns in Saudi Arabia since 1968. Many factors require considering the review and change of the time of administration of the BCG vaccine. Those factors included: 1. The incidence rate of TB is decreasing, reaching up to 17/100,000 of the population reported annually from this the country^{24,25}. 2. The consanguinity rate is very high in Saudi population reaching up to (58%) in the world and significant association of genetic disorders^{26,27}. 3. The prevalence of most of the PID's predisposing BCG infections within the Saudi Arabian population is much higher (CGD- 5.2 cases/100000 live births, SCID 219 cases/100,000 live births) than any other population in the world²⁸⁻²⁹. In literature BCG use has been controversially discussed, it has been recommended in tumors³⁰ and it has also been suggested that BCG should be avoided in immune disorders until the age of one year³¹.

Table 1. Clinical characteristics of twelve patients with disseminated BCG post vaccination.

case No.	sex	Age	Clinical features	Underlying immune deficiency	Laboratory positive TB culture	Radiology positive finding	Family history	Prognosis
1	F	6M	Generalized lymphadenopathy plus discharge left axillary lymph node (LN) with hepatosplenomegaly	Interleukin-12(IL-12) deficiency	Mycobacterium bovis PCR: positive and culture: positive	CXR :right perihilar infiltration with right pleural effusion CT scan abdomen: hepatosplenomegaly	She had 1 brother may have similar illness but not investigated	Discharge home with regular follow up with ID & immunology clinic
2	M	18M	Left axillary LN and splenic abscess	IL-12 Deficiency	Mycobacterium bovis culture positive (from LN)	CXR : normal CT scan abdomen: splenomegaly	Negative	Discharge home with regular follow up with ID & immunology clinic
3	M	14M	Skin lesion, splenomegaly	Sever combined immunodeficiency (SCID)	Mycobacterium bovis PCR: positive from gastric aspirate and skin lesion	CXR: bilateral perihilar infiltration	Negative	discharge home with regular follow up ID clinic
4	F	6M	Generalized lymphadenopathy with hepatosplenomegaly	IL-12 Deficiency	Mycobacterium bovis PCR and culture positive (from LN)	CTscan. abdomen: Hepatosplenomegaly	Unknown	Discharge home with regular follow up ID clinic
5	F	3M	Generalized lymphadenopathy (lt. axillary LN +inguinal LN) massive hepatosplenomegaly, consolidation & atelectatic changes in both lungs	Interferon gamma receptor II deficiency (homozygous mutation,Y235x in IFNGR2 gene & her mother is heterozygous).	Gastric aspirates (GA)3 consecutive samples positive for AFB and culture positive for mycobacterium bovis (from LN)	U/S abdomen: revealed hepatosplenomegally, no ascites. CT scan chest, abdomen & pelvis: bilateral lung consolidation more on the left side, hepatosplenomegally. Bone survey: normal CT scan brain: normal.	Positive family history of early infantile deaths	She died in the PICU with multi-organ failure.
6	M	7M	Generalized lymphadenopathy	IL-12 deficiency	Culture positive for Mycobacterium bovis from LN	None	He had 1 sister with similar illness	Discharge home with regular follow up ID clinic
7	F	4M	Generalized lymphadenopathy	IL-12 deficiency	Culture positive for Mycobacterium bovis from LN.	None	She had 1 brother with similar illness	Discharge home with regular follow up ID clinic
8	F	9M	Generalized lymphadenopathy	IL-12 deficiency	Culture positive for Mycobacterium bovis from LN	None	Negative	Discharge home with regular follow up ID clinic

9	M	12M	FTT, recurrent boils and cutaneous abscess formation, persistent oral thrush, BCGitis with generalized lymphadenopathy (left axillary lymphadenitis, inguinal LN)	SCID	FNA aspiration from It axillary lymph node is showing +ve AFB on ZN stain, Mycobacterium bovis C/S:	Ultra sound left axillary area: multiple enlarged LNS measuring 1.5x1.1 cm in size. Bone survey: normal. CT chest: B/L bronchial thickening & air space disease at rt. upper lung. CT brain: lt. occipital ill defined hypodense lesion. MRI brain: old inferior cerebellar infarction, B/L subdural hygromas. U/S abdomen: hepatosplenomegally. CT chest, abdomen & pelvis: ground glass opacification, atelectasis & few lung nodules, hepatosplenomegally, nephromegally, with multiple hypodense lesions in spleen mostly infection, extra-medullary hematopoiesis or infarction. CXR: bilateral perihilar infiltration CT: splenomegaly	Negative	Patient was transferred to another hospital (KFSH) for HSCT from cord blood pneumonitis.
10	M	19M	FTT, BCGitis with no LNS involvement, pneumonitis massive hepatosplenomegally with ascitis	SCID	Gastric aspirates 3 samples were +ve for AAFB for ZN stain, +ve for TB PCR, C/S of gastric aspirate +ve for Mycobacterium bovis	1st degree consanguineous marriage with History of death of the patient brother at the age of 4 months with meningitis, hepatosplenomegally, he, died without diagnosis positive History of deaths of 2 daughters of the patient aunt the age of 4-6 months with similar clinical presentation		KFSH for bone marrow transplant (BMT) from his HLA matched sister
11	M	2.5 year	Generalized lymphadenopathy draining lymph node sinus & splenomegaly	IL-12 Deficiency	FNA aspiration from axillary lymph node is showing +ve AFB on ZN stain, culture positive for Mycobacterium bovis from LN. mycobacterium bovis PCR: positive		Negative	Discharge home with regular follow up ID clinic
12	M	2.8 year	Left axillary lymphadenopathy and bilateral neck swelling, weight loss abdominal distention and chronic cough	IL-12 Deficiency	Culture positive for Mycobacterium bovis from LN & from gastric aspirate. Positive gene expert test PCR	Chest, abdomen and pelvis CT with contrast showed bilateral mild plural effusion, hepatomegaly, ascitis, axillary, mediastinal, hilar abdominal, inguinal lymphadenopathy	Negative	Discharge home with regular follow up ID clinic

Conclusions

Based on this data, the need for BCG vaccination should be further evaluated. As most congenital immunodeficiency disorders are apparent by one year of age, BCG vaccination should be avoided in patients with immune disorders until the age of 12 months. The data available about the magnitude of disseminated BCG among Saudi children is limited; therefore, more studies on national bases need. Furthermore, we also advise to reconsider the routine BCG time to be postponed until 12 months of age. By this time most congenital immunodeficiency disorders have become apparent.

Acknowledgements

This work was supported financially by King Saud University. Through vice Deanship of Scientific Research, Prince Abdullah bin Khalid, Coeliac Disease Research Chair.

Conflict of Interests

The Authors declare that they have no conflict of interests.

References

- NOROUI S, AGHAMOHAMMADI A, MAMISHI S, ROSENZWEIG SD, REZAEI N. Bacillus Calmette-Guérin (BCG) complications associated with primary immunodeficiency diseases. *J Infect* 2012; 64: 543-554.
- WHO/UNICEF. Expanding immunization coverage. Immunization, vaccines and biological. Available from URL: http://www.unicef.org/immunization/index_coverage.html, cited date: Jan 2016.
- HAWN TR, DAY TA, SCRIBA TJ, HATHERILL M, HANEKOM WA, EVANS TG. Tuberculosis vaccines and prevention of infection. *Microbiol Mol Biol Rev* 2014; 78: 650-671.
- ROMANUS V, FASTH A, TORDAI P, ERIK WILHOLM B. Adverse reactions in healthy and immunocompromised children under six years of age vaccinated with the Danish BCG vaccine, strain Copenhagen 1331: implications for the vaccination policy in Sweden. *Acta Paediatr* 1993; 82: 1043-1052.
- O'BRIEN KL, RUFF AJ, ALBERT LOUIS M, DESORMAUX J, JULES JOSEPH D, MC BRIEN M. Bacillus Calmette-Guérin complications in children born to HIV-1-infected women with a review of the literature. *Pediatrics* 1995; 95: 414-418.
- TRUNZ BB, FINE P, DYE C. Effect of BCG vaccination on childhood tuberculous meningitis and miliary tuberculosis worldwide: a meta-analysis and assessment of cost-effectiveness. *Lancet* 2006; 367: 1173-1180.
- BUKHARI E, ALZHRANI M, ALSUBAIE S, ALRABIAAH A, ALZAMIL F. Bacillus Calmette Guerin lymphadenitis: A six year experience in two Saudi hospitals. *Ind J Pathol Microbiol* 2012; 55: 202-205.
- HUNG GY, CHIOU TJ, LIN CY. Transplantation of related histocompatible marrow and peripheral blood stem cells in a patient with severe combined immunodeficiency and disseminated BCG infection. *J Chin Med Assoc* 2003; 66: 72-75.
- REICHENBACH J, ROSENZWEIG S, DOFFINGER R, DUPUIS S, HOLLAND SM, CASANOVA JL. Mycobacterial diseases in primary immunodeficiencies. *Curr Opin Allergy Clin Immunol* 2001; 1: 503-511.
- LEE WI, HUANG JL, YEH KW, JAING TH, TZOU-YIEN LIN TY, HUANG YC, CHIU CH. Immune defects in active mycobacterial diseases in patients with primary immunodeficiency diseases (PIDs). *J Formosan Med Assoc* 2011; 110: 750-758.
- TALBOT EA, PERKINS MD, SILVA SF, FROTHINGHAM R. Disseminated Bacillus Calmette-Guérin disease after vaccination: case report and review. *Clin Infect Dis* 1997; 24: 1139-1146.
- IKINCIÖGULLARI A, DOĞU F, CİFTÇİ E, GERAMIZADEH B, POURABBAS B, MARDANEH J. An intensive approach to the treatment of disseminated BCG infection in a SCID patient. *Bone Marrow Transplant* 2002; 30: 45-47.
- BERNATOWSKA EA, KUSNIERZ BW, PAC M, KURENKO-DEPTUCH M, ZWOLSKA Z, CASANOVA JL. Disseminated bacillus Calmette-Guérin infection and immunodeficiency. *Emerg Infect Dis* 2007; 13: 799-801.
- HESSELING AC, RABIE H, MARAIS BJ, MANDERS M, LIPS M, SCHAAF HS, GIE RP, COTTON MF, VAN HELDEN PD, WARREN RM, BEYERS N. Bacille Calmette-Guérin vaccine-induced disease in HIV-infected and HIV-uninfected children. *Clin Infect Dis* 2006; 42: 548-558.
- TALBOT EA, WILLIAMS D, FROTHINGHAM R. PCR identification of Mycobacterium bovis BCG. *J Clin Microbiol* 1997; 35: 566-569.
- REZAEI N, POURPAK Z, AGHAMOHAMMADI A, FARHOUDI A, MOVAHEDI M, GHARAGOZLOU M, ET AL. Consanguinity in primary immunodeficiency disorders; the report from Iranian primary immunodeficiency registry. *Am J Reprod Immunol* 2006; 56: 145-151.
- BAHRI IT, BOUDAWARA S, MAKNI M, KHARRAT A, TRIKI S, HAMED R. Disseminated BCG infection: a four case study. *Méd Mal Infect* 2001; 31: 549-553.
- SHAHMOHAMMADI S, SAFFAR MJ, REZAI MS. BCG-osis after BCG vaccination in immunocompromised children: case series and review. *J Pediatr Rev* 2014; 2: 47-54.
- SADEGHI-SHABESTARI M, REZAEI N. Disseminated bacille Calmette-Guérin in Iranian children with severe combined immunodeficiency. *Int J Infect Dis* 2009; 13:420-423
- PAIMAN SA, SIADATI A, MAMISHI S, TABATABAIE P, KHOTAEI G. Disseminated Mycobacterium bovis infection after BCG vaccination. *Iran J Allergy Asthma Immunol* 2006; 5: 133-137.
- SADEGHI-SHANBESTARI M, ANSARIN K, MALJAEI SH, RAFEEY M, PEZESHKI Z, KOUSHA A, BARADARAN R, CASANOVA JL, FEINBERG J, DE VILLARTAY JP. Immunologic aspects of patients with disseminated bacilli Calmette-Guérin disease in north-west of Iran. *Ital J Pediatr* 2009; 35: 42.

- 22) MAHMOUDI S, KHAHESHI S, POURAKBARI B, AGHAMOHAMMADI A, VALIAN SK, BAHADOR A, SABOUNI F, RAMEZANI A, MAMISHI S. Adverse reactions to Mycobacterium bovis bacille Calmette-Guérin vaccination against tuberculosis in Iranian children. *Clin Exp Vaccine Res* 2015; 4: 195-199.
- 23) AELAMI MH, ALBORZI A, POULADFAR G, GERAMIZADEH B, POURABBAS B, MARDANEH J. Post-vaccination disseminated bacillus Calmette Guérin infection among children in Southern Iran. *Jundishapur J Microbiol* 2015; 8: e25663.
- 24) DYE C, SCHEELE S, DOLIN P, PATHANIA V, RAVIGLIONE MC. Global burden of tuberculosis estimated incidence, prevalence, and mortality by country. *JAMA* 1999; 282: 677-686.
- 25) AL-HAJJOJ S, MEMISH Z, ABULJADAYE N, ALHAKEEM R, ALRABIAH F, VARGHESE B. Molecular confirmation of bacillus Calmette Guérin vaccine related adverse events among Saudi Arabian children. *PLoS One* 2014; 9: e113472.
- 26) ELMOUZAN MI, ALSALLOUM AA, ALHERBISH AS, OURACHI MM, ALOMAR AA. Consanguinity and major genetic disorders in Saudi children: a community-based cross-sectional study. *Ann Saudi Med* 2008; 28: 169-173.
- 27) EL-HAZMI MA, AL-SWAILEM AR, WARSY AS, AL-SWAILEM AM, SULAIMANI R, AL-MESHARI AA. Consanguinity among the Saudi Arabian population. *J Med Genet* 1995; 32: 623-626.
- 28) SULIAMAN F, AL-GHONAIUM A, HARFI H. High incidence of severe combined immune deficiency in the eastern Province of Saudi Arabia. *Pediatr Asthma Allergy Immunol* 2006; 19: 14-18.
- 29) SULIAMAN F, AMRA N, SHEIKH S, ALMUHSEN S, ALSMADI O. Epidemiology of chronic granulomatous disease of childhood in eastern province, Saudi Arabia. *Pediatr Asthma Allergy Immunol* 2009; 22: 21-26.
- 30) LEOPARDO D, CECERE SC, DI NAPOLI M, CAVALIERE C, PISANO C, STRIANO S, MARRA L, MENNA L, CLAUDIO L, PERDONÀ S, SETOLA S, BERRETTA M, FRANCO R, TAMBARO R, PIGNATA S, FACCHINI G. Intravesical chemo-immunotherapy in non muscle invasive bladder cancer. *Eur Rev Med Pharmacol Sci* 2013; 17: 2145-2158.
- 31) AL-MOUSA H. An infant with disseminated bacillus Calmette-Guérin infection (BCGitis). *Int J Pediatr Adolesc Med* 2014; 1: 89-92.