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Abstract

Introduction and objective: Tuberculosis is an infectious disease with global spread and BCG vaccine is the only vaccine available against this disease. The disseminated infection caused by the BCG vaccine is a rare, but dangerous complication of this vaccine. This study was conducted with the aim of evaluating the prevalence of clinical and paraclinical findings in hospitalized children with the disseminated infection caused by BCG vaccine in the pediatric ward of Ali ibn Abi Talib Hospital in 2015. **Materials and methods:** In this descriptive study, the files of all children who were hospitalized in the pediatric ward of Ali ibn Abi Talib Hospital in Zahedan with the diagnosis of the disseminated infection caused by the BCG vaccine during the years 2011-2015 were selected as census and they were examined. Six files were excluded from the study due to a lack of information. Information about the clinical and laboratory findings of the patients was extracted from the files. Descriptive information was displayed using SPSS ver.21 software. **Findings:** The files of 27 children were studied in this study; 16 children (59.3%) were boys and 11 children (40.7%) were girls. The most common clinical findings included fever in 23 patients (85.2%), lymphadenopathy in 20 patients (74.1%), weight loss in 15 patients (55.6%), hepatomegaly in 4 patients (14.8%), and splenomegaly in 4 patients (14.8%). The most common hematological findings were anemia and leukocytosis. **Discussion and Conclusion:** According to the results of this study, the diagnosis of the disseminated infection caused by BCG vaccine should be considered in all newborns and children with fever, lymphadenopathy, hepatosplenomegaly, any abnormal hematologic or radiological findings, and the history of BCG vaccine inoculation.

Keywords: BCG vaccine, Tuberculosis, Children



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Introduction:

Tuberculosis is an old infection that has been widely spread in the world and has an ancient history. This disease is caused by *Mycobacterium tuberculosis*. The usual site of the disease is in the lungs; however, other organs can also be affected. The *Bacillus Calmette–Guérin* is the only available vaccine against tuberculosis. This name comes from the name of two French who discovered it, and it was first used orally in 1921. The primary organism is *Mycobacterium bovis*, which its weakened form is used to produce the vaccine. This vaccine stimulates the cell-dependent immunity to provide protection against tuberculosis infection. Only the live form of the vaccine should be used for immunization (1).

It's estimated that every 4 seconds a person in the world gets infected with tuberculosis, and every 10 seconds someone in the world dies of tuberculosis. With this in mind, over a decade, nearly 300 million people get infected with tuberculosis (2). Tuberculosis appears in both pulmonary and extra-pulmonary forms. Pulmonary tuberculosis accounts for 85% of cases and its extrapulmonary form accounts for 15% of cases. The incidence rate of tuberculosis in Iran in 2008 is estimated to be 13.4 per 100,000 people, with the highest incidence rate being in the Sistan and Baluchestan Province, which is estimated to be between 40 and 70 per 100,000 people in recent years (3, 4). Concerns about controlling the tuberculosis are delayed diagnosis and treatment of the disease, which according to the World Health Organization (WHO) in 2006, this delay in Iran has been 127 days from the onset of symptoms until the onset of the treatment, with the highest delay being related to delay in diagnosis. By 2013, the World Health Organization has estimated the detection of pulmonary tuberculosis cases by smear microscopy method as up to 70% (2). The first and most important step in controlling tuberculosis is locating the infected cases and treating them, in which the transmission of infection between the cases near each other is interrupted. Another primary way to prevent tuberculosis infection is vaccine inoculation, which is usually safe in a host with a healthy immune system (5). Currently, the only effective vaccine for tuberculosis is the BCG vaccine, which is inoculated in the hospital on the first day of birth with a dose of 0.05% as a dried form and by an intradermal method (6). Disseminated infection caused by BCG vaccine (disseminated BCG infection), according to the definition, is referred to the clinical spread of infection to at least two areas beyond the inoculation site of the BCG vaccine (7), and it has a prevalence of about 0.1 to 1.3 cases in one million vaccinated people (8, 9). Disseminated tuberculosis infection, as the most serious complication of BCS vaccine, can be due to disorders of immune deficiency in children. The severe immunodeficiency and cellular immunodeficiency can be cited as some of these disorders (10, 11). However, this disseminated disease can be idiopathic and developed in healthy children (12, 13). Disseminated BCG disease develops various symptoms that the most prevalent clinical symptoms of which are: fever, weight loss, localized or disseminated involvement of lymph nodes especially prolonged lymphadenitis accompanied by prolonged fistulization, various skin manifestations, soft tissue involvement, and hepatosplenomegaly (16-14). In a study by Dr. Karimi et al., conducted in Tehran Children's



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Medical Center during 1997-2001, in a 5-year follow-up 8 cases of this disease in vaccinated children were reported (16). Also, Karaca et al. (2012), in a case report in Turkey, described a disseminated and severe infection following inoculation of BCG vaccine in an 8-month-old infant with interferon-dependent immune deficiency. The manifestations and clinical findings of the patient included fever, lymphadenopathy, hepatosplenomegaly and cutaneous infection. In the performed biopsies, there was skin, lung, liver, spleen, abdomen and lymph nodes involvement (17). The disease led to death of the child (17). Considering the possibility of complications caused by BCG vaccine, and on the other hand, its risks, especially if accompanied by undiagnosed immunodeficiency disorders in children, we decided to conduct a study with the aim of evaluating the epidemiological, clinical, laboratory, and radiological findings in children with the disseminated infection caused by BCG vaccine, so if significant relationships are achieved, provide a background for further studies, as well as useful strategies for timely diagnosis and treatment, and consequently reduction of its subsequent complications.

Materials and Methods:

This cross-sectional study was conducted on 25 children vaccinated with BCG vaccine who had complications from the vaccine during a 5-year follow-up, from March of 2011 up to March of 2016, and they were hospitalized in the pediatric ward of Ali ibn Abi Talib Hospital in Zahedan. That is, following the necessary coordination with the hospital management, the records of all studied children were taken from the Imam Ali Hospital's archives, and necessary information including age, sex, clinical findings (including fever, weight loss, lymphadenopathy, hepatomegaly, splenomegaly, skin involvement, osteomyelitis and positive mantoux test), laboratory findings (including hemoglobin levels, white blood cell and platelet count of the patient), and radiographic findings (including chest X-ray, and abdominal and pelvic ultrasound) were examined and recorded in the prepared information form. If the file was incomplete, it was excluded from the study. According to the hematologic values table in infancy and childhood, based on the Nelson Essentials of Pediatric Medicine (18), paraclinical findings including anemia, leukocytosis, and leukocytopenia were evaluated. Finally, the data, after being collected, were statistically analyzed using SPSS ver.21 software.

Findings:

The number of patients present in this study was 27, who had disseminated BCG infection according to the diagnosis of a pediatric infectious diseases specialist. In all patients, BCG vaccine was inoculated at birth. 11 patients (40.7%) were girls and 16 (59.3%) were boys. The mean and standard deviation of patients' age and age of onset of symptoms in patients were 31.05 ± 47.82 and 3.96 ± 3.74 months, respectively.

Clinical findings in the studied children in order of the prevalence are presented in Table 1. **Table 1. Determining the prevalence of clinical findings in studied children**



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Clinical Clinical	Percent	Number
Fever	85/2	23
Weight Loss	55/6	15
Lymphadenopathy	74/1	20
Hepatomegaly	14/8	4
Splenomegaly	14/8	4
Skin involvement	44/4	12
Osteomyelitis	7/4	2

There were abnormal findings in chest radiography of 11 patients (40.7%). There were also abnormal findings in ultrasound of 13 patients (56.5%).

Paraclinical findings are indicative of the presence of anemia in 18 patients (66.7%), leukocytosis in 11 patients (40.7%), leukopenia in 1 patient (3.7%), and thrombocytopenia (platelet of less than 150,000 per microliter) in 3 patients (11.1%).

The mean hemoglobin levels, platelet and white blood cell count, and erythrocyte sedimentation rate in studied children were 10.10 ± 2.40 gr/dl, 13722.22 ± 6158.06 per μ l and 424.96 ± 206.78 thousand per μ l, and 47.18 ± 13.17 mm/h, respectively.

The frequency of studied children based on the age group is shown in Table 2.

Table 2. *Frequency of studied children based on the age group*

Age category	Percent	Number
Less than 6 months	18/5	5
6 to 9 months	40/8	11
10 to 36 months	14/8	4
37 months and more	25/9	7
Total	100	27



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Discussion & Conclusion:

BCG vaccine is one the least dangerous vaccines introduced, but disseminated tuberculosis caused by the injection of this vaccine is very rare, with an occurrence of about one case per one million inoculation doses (19, 20). This complication is the most dangerous complication of the vaccine and has a high mortality rate. Most of these children have some form of immunodeficiency (21), however, there is also old reports of this complication occurring in children with normal immunity, and even some new studies suggest that up to half of the patients are with no apparent immune deficiency and they have called these cases as idiopathic forms, for which a type of genetic background without a particular hereditary plan has also been suggested for them (22).

Of the studied children, 11 were (40.7%) girls and 16 (59.3%) were boys. In the majority of studies (23, 24, 16, 21) in line with the present study, this complication was more prevalent in males, which may be due to the more prevalence of some of the congenital immune defects in males. Due to the lack of determination of the presence of absence of immunodeficiency in affected children in the present study, further studies are needed to determine the exact role of gender. The mean age of patients and the age of onset of symptoms after vaccination were 31.05 and 3.96 months, respectively. The age range of children in the study by Afshar et al. (2006), was reported between 3 and 42 months (13), in the study by Galal et al. (2012), between 6 and 192 months (25), and in the study by Shahmohammadi et al. (2014), between 3.5 and 72 months (24).

The most common clinical findings in children in the present study were fever (85.2%), lymphadenopathy (74.1%), weight loss (55.6%), skin involvement (44.4%), hepatomegaly (8.8% 14%), splenomegaly (14.8%) and osteomyelitis (7.4%), respectively. The most common clinical findings in the study by Afshar et al (2006) reported as fever (88.3%), weight loss (88.3%), lymphadenopathy (82.3%), hepatomegaly (70.5%), splenomegaly (9.9% 52%), pneumonia (47%), skin involvement (35.2%) and osteomyelitis (17.6%), respectively (13). In the study by Jadali et al. (2007), all four children referred with clinical signs of fever and server and acute respiratory distress. The study of the frequency of involvement of organs in the studied children indicated adenopathy (2 patients), hepatomegaly (4 patients), splenomegaly (4 patients), skin involvement (2 patients), pulmonary lesions (3 patients), abdominal lesions (4 patients), and brain involvement (1 patient) (26). Comparison of the findings from various studies shows that fever and neoplasm are present in the vast majority of patients with disseminated tuberculosis caused by BCG vaccine inoculation, and in the subsequent degrees, hepatomegaly and splenomegaly are the most common clinical findings in these patients. According to the obtained results, doctors need to be aware of the dangerous but low prevalence complications of BCG vaccine, and they should perform a full examination during the examination of a child with fever and adenitis caused by the vaccine, and examine the adjacent armpit lymph nodes and cervical lymph nodes and pay attention to hepatosplenomegaly, because if the above cases exist, they should check for disseminated BCG infection. Paraclinical findings of the present study indicated the presence of anemia in 18 patients



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(66.7%), leukocytosis in 11 patients (40.7%), leukopenia in 1 patient (3.7%) and thrombocytopenia in 3 patients (11.1%). Limited studies have evaluated the laboratory findings of children with disseminated tuberculosis complication caused by the vaccine. Jadali et al (2007) showed that anemia is present in each of the four children examined. White blood cell count (thousand per cubic millimeters) in this study in 4 patients was reported as 3200 (70% lymphocyte), 14500 (40% lymphocyte), 14000 (25% lymphocyte) and 5000 (30% lymphocyte), respectively (26). In the study by Karimi et al. (2003), 8 patients were also examined. The white blood cell count in 7 patients was normal, or leukocytosis was brief, and leukopenia was shown in one patient. All of the patients had anemia, but severe anemia (hemoglobin less than 7 g/dL) was seen in only 3 patients. Three cases of thrombocytopenia were observed (16).

Although the results of laboratory tests in this study and other similar studies do not show a specific finding in the tests, however, the incidence of anemia and leukocytosis can be considered as a contributing factor in the diagnosis of the disease.

In the radiologic examination of the chest of affected children in the study, it was found that 16 (59.3%) patients had normal chest radiography. Therefore, normal chest X-ray images in the early stages of tuberculosis is expected, therefore, it should be noted that normal radiography does not reject tuberculosis. On the other hand, there was abnormal findings in radiographies of 11 patients (40.7%). Abnormal ultrasound finding was also seen in 13 patients (56.5%). These findings suggest that familiarity with the different radiographic findings of tuberculosis in chest X-ray, as one of the most common and inexpensive imaging methods, is necessary in early examinations of pulmonary tuberculosis, as well as the evaluation of its complications. These findings can be a significant help in early diagnosis and timely treatment of the disease, which itself prevents the transmission and emergence of the disease or at least minimizes its complications in the future.

This study was based on the results of tests and findings of initial imaging of the patients before the onset of treatment. Therefore, it is suggested that similar studies be carried out to determine the effect of duration of the disease, as well as the time of onset of treatment on laboratory and radiographic findings of pulmonary tuberculosis. The results of this study showed that fever and lymphadenopathy, and in further degrees, weight loss and hepatosplenomegaly, are the most common clinical findings in children with disseminated tuberculosis caused by BCG vaccine, and anemia and leukocytosis are the most common paraclinical findings in these patients. Also, due to the high abnormal findings of chest X-ray imaging and abdominal and pelvic ultrasound imaging, using these two methods is very helpful in diagnosing this condition.



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Reference:

1. Dr. Maryam Seif Hashemi et al. Study of Complications of BCG Vaccine in Semnan Children. *Iranian Children's Diseases Journal*. Volume 15, Issue 3, Autumn 2005.
2. WHO. Treatment of tuberculosis: guidelines. Geneva, Switzerland: WHO Press; 2010.
3. Incidence of tuberculosis in Iran. Ministry of Health and Medical Education. Center for Disease Control. Available from: <http://www.cdc.hbi.ir/> Accessed January December 26, 2010.
4. Moghtaderi A, Alavi-Naini R, Rahimi-Movaghar V. Tuberculous myelopathy: current aspects of neurologic sequels in the southeast of Iran. *Acta Neurol Scand* 2006;113:267–272
5. Fitzgerald D, Sterling T, Haas D. Mandell G, Benett J, Dolin R. Mandell, Douglas, and Bennetts principles and practice of infectious diseases. 7th ed. Philadelphia: Churchill Livingstone/ Elsevier; 2010.
6. Bani Fazl, Mohammad, Ramezani, Amitis, Babaei Moghaddam, Mohammad Reza. "TB disease textbook". Tehran: Poursina Publishing House, 2002.
7. Trevenen CL, Paqtakhan RD. Disseminated tuberculoid lesions in infants following BCG vaccination. *Can Med Assos J* 1988;127(6):502-4.
8. Penelope HD, Georges Peter. Active immunizing agents. In: feigin, Cherry, Demmler. Kaplan's text book of pediatric infectious diseases. 5th ed. Philadelphia: Saunders; 2004.
9. Szczua L. Adverse events following immunization with BCG vaccine in Poland 1994-2000. *Przegl Epidemiol* 2002;56(2):205-16.
10. 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.
11. Lotte A, Wasz-Hockert O, Poisson N, Dumitrescu N, Verron M, Couvet E. BCG complications: estimates for the risks among vaccinated subjects and statistical analysis of their main characteristics. *Adv Tuberc Res* 1994;2:107–93.
12. Levin M, Newport MJ, D'Souza S, Kalabalikis P, Brown IN, Lenicker HM, et al. Familial disseminated atypical mycobacterial infection in childhood: a human mycobacterium susceptibility gene. *Lancet* 1995;345:79-83.
13. Afshar Paiman SH, Siadati A, Mamishi S, Tabatabaie P, Khotae GH. Disseminated *Mycobacterium bovis* Infection after BCG Vaccination. *Iran J Allergy Asthma Immunol* 2006;5(3):133-137.
14. Torriani R, Zimmermann A, Morel A. BCG sepsis as a total complication of BCG vaccination. *Schweiz Med Wochenschr* 1979;109(19):708-15.



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15. Kumar PV, Banuni SA. Fine needle aspiration findings in generalized post-Calmette-Guerin bacillus lymphadenitis presenting as an abdominal mass. *Acta Cytol* 1994;38(2):165-8.
16. Karimi, Abdullah; Nateghian, AliReza; Memoshi, Star. "A report of 8 cases of diffuse tuberculosis due to inoculation of BCZ vaccine at the Tehran Children's Medical Center during the years of 80-76". *Journal of Mazandaran University of Medical Sciences*, vol 13, no. 38, 2003.
17. Edeer Karaca N, Boisson-Dupuis S, Aksu G, Bustamante J, Kandiloglu G, Ozsan N, et al. Granulomatous skin lesions, severe scrotal and lower limb edema due to mycobacterial infections in a child with complete IFN- γ receptor-1 deficiency. *Immunotherapy* 2012; 4(11): 1121-7.
18. Munoz FM, Starke JJR. Tuberculosis. In: Behrman RE, Kliegman M, Jensen B: *Nelson Textbook of Pediatrics*. 17th ed. Philadelphia: Saunders; 2004.
19. Strake J, Smith M. Tuberculosis. In: Feigin & Cherry's textbook of pediatrics infectious disease. 4th ed. Saunders Company; 1998.
20. Davidson P, Genshemier K, Melius J, et al. The role of BCG vaccine in the prevention and control of tuberculosis in the United States. *CDC weekly report and recommendation*. 1996;26(45):1-18.
21. Talbu EA, Perkins MD, Silva SF, Forthingham R. Disseminated bacille Calmette-Guerin disease after vaccination: case report and review. *Clin Infect Dis*. 1997;24(6):1139-46.
22. Babac S, Franulvic J. Familial liability to complication after BCG vaccination. *Acta Padiatry*. 1997;86(8):899-903.
23. Gantzer A, Neven B, Picard C, Brousse N, Lortholary O, Fraitag S, et al. Severe cutaneous bacillus Calmette-Guérin infection in immunocompromised children: the relevance of skin biopsy. *J Cutan Pathol* 2013;40(1):30-7.
24. Shahmohammadi SH, Saffar MJ, Rezai MS. BCG-osis after BCG vaccination in immunocompromised children: Case series and review. *J Pediatr Rev* 2014;2(1):47-54.
25. Galal N, Boutros J, Marsafy A, Kong XF, Feinberg J, Casanova JL, et al. Mendelian susceptibility to mycobacterial disease in egyptian children. *Mediterr J Hematol Infect Dis* 2012;4(1):e2012033.
26. Jadali F, Karimi A, Armin SH, Gharib A, Fallah A, Sharifian M. Detection of Disseminated Mycobacterial Infection Due to BCG Vaccination (BCGosis) in 4 Suspected Infant Autopsies by PCR Method. *Iranian Journal of Pathology* 2007;2(3):89- 93.