TÜRK PEDİATRİ ARŞİVİ
TURKISH ARCHIVES of PEDİATRİCS

Original Article

Frequency of *Mycobacterium bovis* and mycobacteria in primary immunodeficiencies

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Cite this article as: Ulusoy E, Edeer Karaca N, Aksu G, Çavuşoğlu C, Kütükçüler N. Frequency of *Mycobacterium bovis* and mycobacteria in primary immunodeficiencies. Turk Pediatri Ars 2017; 52: 138-44.

Abstract

Aim: Susceptibility to mycobacterial diseases is observed in some primary immunodeficiency diseases. In this study, we aimed to evaluate mycobacterial infections in primary immunodeficiency diseases.

Material and Methods: Patients under follow-up by Ege University Pediatric Immunology Department for severe combined and combined immunodeficiencies, interleukin 12/ interferon gamma receptor deficiency, nuclear factor kappa-beta essential modulator deficiency and chronic granulomatosis disease were evaluated retrospectively in terms of the frequency and characteristics of mycobacterial infections using a questionnaire form for demographic properties, clinical features and laboratory tests.

Results: A diagnosis of mycobacterial infection was made clinically in a total of 25 patients including five (11.3%) of 45 patients who had severe combined immune deficiency, 12 (52.3%) of 21 patients who had chronic granulomatous disease, four patients (100%) who had interferon gamma receptor 2 partical deficiency, two patients (100%) who had interleukin 12 receptor beta 1 deficiency and one patient (100%) who had nuclear factor kapa-beta essential modulator deficiency. Mycobacterium strain could be typed in 14 (33%) of these 25 patients including *Mycobacterium bovis, Mycobacterium chelonea, Mycobacterium elephantis, Mycobacterium fortuitum*, and *Mycobacterium tuberculosis*. All patients were treated with anti-tuberculosis therapy. Thirty-six percent of these 25 patients underwent hematopoietic stem cell transplantation. Eight patients (five before, three after transplantation) died.

Conclusions: Non-tuberculosis mycobacteria including mainly *Mycobacterium bovis* were observed with a higher rate compared to Mycobacterium tuberculosis in primary immunodeficiencies, especially in those affecting the interleukin 12/interferon gamma pathway. Early diagnosis of primary immunodeficiencies with neonatal screening program and preventing administration of the Bacille Calmette-Guerin vaccine in these patients is important.

Keywords: Bacille Calmette-Guerin, interleukin 12, interferon gamma, mycobacteria, *Mycobacterium tuberculosis*, primary immunodeficiency

Introduction

Innate immunity against *Mycobacterium tuberculosis*, non-tuberculosis mycobacteriae, and the mycobacterial group including the Bacille Calmette-Guerin (BCG) vaccine strain is related with operation of the interleukin 12-23/interferon gamma (IL-12/23-IFN-γ) pathway (1, 2). Mycobacterial infections are observed commonly in patients with severe forms of primary immunodeficiency, including severe combined immune deficiency (SCID), complete Di George syndrome, X-linked hyper immunoglobulin (Ig)-M syndrome (HIGM type 1, CD154 deficiency), CD40 deficiency, immune deficiencies accompanying ectodermal dysplasia (nuclear factor kappa-beta essential modulator (NEMO), IKBA), chronic granulomatous disease (CGD), interleukin 12-interferon gamma (IL-12/IFN-γ) receptor disorders, and hyper IgE syndrome, and these diseases have been examined under the title of Mendelian Susceptibility to Mycobacterial Diseases (MSMD) (3-12). In this group of patients, non-tuberculosis mycobacteriae are predominantly observed. Weakly virulent mycobacteriae including the Bacille Calmette-Guerin vaccine may lead to regional disease including BCG-itis or diffuse disease including BCG-osis. More virulent bacteriae including *Mycobacterium (M) tuberculosis* may lead to lung tuberculosis or

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Received: 07.01.2017 **Accepted:** 23.03.2017

DOI: 10.5152/TurkPediatriArs.2017.5240

diffuse tuberculosis. In this study, the frequency and characteristics of mycobacterial infections were investigated in patients with primary immune deficiency.

Material and Methods

Patients who were treated by Ege University, Faculty of Medicine, Division of Pediatric Immunology for severe combined and combined immune deficiency (n=45), IL-12/IFN-γ receptor disorder (n=7), NEMO disorder (n=1), and chronic granulomatous disease (n=21) were evaluated retrospectively in terms of mycobacterial infections. Questionnaires including demographic properties (age, sex, consanguinity), and clinical and laboratory findings were completed. Patients with lymph node involvement alone without systemic involvement were considered to have BCG-itis and those with both lymph node involvement and systemic involvement were considered to have BCG-osis. Participants with respiratory findings and a positive tuberculin skin test (PPD) (a value above 15 mm was considered positive) and/or quantiferon positivity and positive X-ray findings were considered clinically to have lung tuberculosis. Mycobacteria typing was made with culture and polymerase chain reaction (PCR) anaylsis in lymph node biopsy preparations, sputum, fasting gastic fluid (FGF) or skin abscess.

Ethics approval for our study was obtained from the ethics comittee of Ege University on 12.09.2016 (number: 16-11/12). Informed consent was obtained from the relatives of the patients included in the study.

Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS Inc.; Chicago, IL, USA) 16.0.1 program and the results are expressed as mean±standard deviation and percentage.

Results

A diagnosis of mycobacterial infection was made clinically in a total of 25 patients, including five of 45 patients with severe combined immune deficiency (11.3%), 12 of 21 patients with chronic granulomatous disease (52.3%), four patients who had partial IFN-γ receptor 2 (IFNGR2) deficiency (100%), one patient with complete IFN-γ receptor 1 deficiency (100%), two patients who had IL-12 receptor beta 1 (IL12RB1) defects, and one patients who had NEMO defect (100%). BCG-itis was present in 14 of 25 patients (56%), both lung tuberculosis and BCG-itis were present in three patients, lung tuberculosis was present in five patients, tuberculosis abscesses were present in one patient, and BCG-osis was present in two patients (Table 1). In the patient with CGD who developed BCG-osis, lung tuberculosis was also subsequently observed. In the patient who was found to have complete IFNGR1 deficiency, BCG-itis was observed primarily and lung tuberculosis caused by *M. tuberculosis*, and *M. avium* was also observed in the follow-up. Mycobacteriae were isolated in 14 of 25 patients (Table 2).

Triple anti-tuberculosis treatment (isoniazid, rifampicin, pyrazinamide) was given to 66% of the patients and quadruplet treatment (isoniazid, rifampicin, pyrazinamide, ethambutol or streptomycine) was given to 34%. Ten of 21 patients who had chronic granulomatous disease received isoniozid prophylaxis in addition to antibacterial and antifungal prophylaxis because of PPD positivity. Isoniazid prophylaxis was given to all patients with IL12-interferon gamma pathway disorder and all patients with SCID who developed BCG-itis. In addition, IFN-γ (50 mcg/m^2) treatment was also given to 11 patients (44%) [CGD (n=7), NEMO (n=1), partial IFN-γ receptor 2 deficiency (n=2), IL-12 receptor beta 1 deficiency (n=1)].

Six (24%) patients who were found to have mycobacterial infection were female and 19 (76%) were male. The mean age at the time of onset of symptoms was 9.8±19.8 months, and the mean age at the time of diagnosis was 33±36.4 months. Consanguineous marriage was present in the parents of 76% of the patients and a familial history of primary immunodeficiency was present in 24%. The manifestations at the time of first presentation before primary immune deficiency was diagnosed included lymphadenitits in 40%, recurrent lung infections in 32%, superficial skin abscess in 12%, and recurrent gastroenteritis in 8%.

When the clinical charactersitics of the patients were evaluated, it was found that the weight and height percentiles at the time of diagnosis were below the 3rd percentile in 36%. Accompanying findings included hepatomegaly in 60%, splenomegaly in 44%, and chronic lung disease in 24%.

The mean laboratory values were as follows: white cell count: 12,708±7375/mm^3, erythrocyte sedimentation rate: 66±43 mm/s (12-105 mm/s), purified protein derivative (PPD) induration diameter: 16.4±6.4 mm (9-24 mm), IgG level: 1584±760 mg/dL, IgA level: 145±128 mg/dL, and IgM level: 160±132 mg/dL. Anemia was found in 76% of patients, thrombocytopenia was found

Table 1. Foci of mycobacterial infection by diagnoses

		Focus of mycobacterial infection					
		BCG-itis	**Lung tuberculosis**	**BCG-osis**	**Skin abscess**	**BCG-itis and lung tuberculosis**	**Total**
Diag-	CGD	3	5	1	0	3	12
nosis	IFNGR2	4	0	0	0	0	4
	IFNGR1	1	0	0	0	0	1
	IL12 RB1	2	0	0	0	0	2
	SCID	4	0	0	1	0	5
	NEMO	0	0	1	0	0	1
Total	14	5	2	1	3	25	

BCG: Bacille Calmette-Guerin; CGD: chronic granulomatous disease; IFNGR2: IFN-γ receptor 2; IFNGR1: IFN-γ receptor 1; IL12R1: interleukin 12 receptor beta 1; NEMO: nuclear factor kappa beta essential modulator SCID: severe combined immune deficiency

Table 2. Mycobacteriae that could be grown by diagnoses

	Number of individuals / tissue where isolation was realized						
Diagnosis	***M. bovis***	***M. chelonae***	***M. elephantis***	***M bovis, M. fortiutum, M.tuberculosis and M. avium intracellulare***	***M.fortiutum and M.chlonea***	***M.tuberculosis***	**Total number of patients**
CGD	1 individual/ liver	0	0	0	0	3 individuals sputum and FGF	4
Partial defect of IFNGR2	1 individual/ lymph node	0	1 individual/ lymph node	0	0	0	2
Complete defect of IFNGR1	0	0	0	1 individual/ *M. bovis* and *M.fortiutum* in lymph node, *M.tuberculosis* in the bone marrow, *M. avium* intracellulare in FGF	0	0	1
IL12 R1 defect	0	1 individual/ lymph node	0	0	1 individual/ lymph node	0	2
SCID	1 individual/ skin abscess 3 individuals / lymph node	0	0	0	0	0	4
NEMO	1 individual/ skin abscess, CNS and lymph node	0	0	0	0	0	1
Total number of patients	7	1	1	1	1	3	14

CGD: chronic granulomatous disease; FGF: fasting gastric fluid; IFNGR2: IFN-γ receptor 2; IFNGR1: IFN-γ receptor 1; IL12RB1: interleukin 12 receptor beta 1; NEMO: nuclear factor kappa beta essential modulator, SCID: severe combined immune deficiency

in 16%, neutropenia was found in 24%, and lymphopenia was found in 16%. Various bacterial infections accompanied in 67% of patients including non-typhoidal salmonella in two patients. *Giardia lamblia* infection was observed in one patient and *Cryptosporidium parvum* infections were identified in two patients.

Stem cell transplantation was performed in nine (36%) of 25 patients (CGD [n=3], SCID [n=5], complete IFN-γ receptor 1 deficiency [n=1]). Five patients (20%) were lost before transplantation (one patient because of BCG-osis and the others because of various infections). A total of eight (32%) patients died. Symptoms occured

Table 3. Patients and their chacteristics

Patient	Diagnosis	Sex	Age at the time of onset of symptoms	Age at the time of diagnosis	Clinical finding	Mycobacterium strain isolated	HSCT	Final state
1	CGD	M	12 months	60 months	Lung tb, Lymphadenopathy, HSM	*M. tuberculosis* (Sputum)	Not performed	Exitus
2	CGD	M	12 months	96 months	Lymphadenopathy, HSM	None	Not performed	Exitus
3	CGD	M	3.5 months	10 months	Lung tb, Lymphadenopathy, HM	*M. tuberculosis* (FGF)	Not performed	Living
4	CGD	M	3 months	84 months	Lymphadenopathy, HM	None	Not performed	Living
5	CGD	M	3 months	12 months	Lung tb, Lymphadenopathy, HSM	None	Performed	Living
6	CGD	M	18 months	36 months	Lung tb, Lymphadenopathy	None	Not performed	Exitus
7	CGD	M	4 months	18 months	Lung tb, Lymphadenopathy, HM	None	Performed	Living
8	CGD	F	4 months	12 months	Lung tb, Lymphadenopathy, HSM	None	Not performed	Living
9	CGD	M	4 months	19 months	Lymphadenopathy, HM	None	Performed	Exitus
10	CGD	F	12 months	14 months	Lymphadenopathy	None	Not performed	Living
11	CGD	M	3 months	6 months	Lung tb, HSM	None	Not performed	Living
12	CGD	F	6 months	12 months	Lung tb	*M. tuberculosis* (FGF)	Not performed	Exitus
13	Partial IFNGR2 deficiency	F	4 months	5 months	HSM, Lymphadenopathy	*M. bovis* (Lymph node)	Not performed	Living
14	Partial IFNGR2 deficiency	M	2 months	96 months	Lymphadenopathy	*M. elephantis* (Lymph node)	Not performed	Living
15	Partial IFNGR2 deficiency	M	36 months	36 months	HSM, Lymphadenopathy	None	Not performed	Living
16	Partial IFNGR2 deficiency	M	7 months	7 months	Lymphadenopathy	None	Not performed	Living
17	NEMO	M	7 months	30 months	HSM, Lymphadenopathy, Abscesses in the body	*M. bovis* (Lymph node, abscess, CNS, liver)	Not performed	Exitus
18	IL12 R1 defect	F	1 months	96 months	Lymphadenopathy, SM	*M. cholenae* (Lymph node)	Not performed	Living
19	IL12 R1 defect	M	96 months	120 months	Lymphadenopathy, HSM	*M. fortiutum* and *M. chlonea* (Lymph node)	Not performed	Exitus
20	SCID	M	2 months	18 months	Abscesses in the body	*M. bovis* (Abscess)	Performed	Living
21	SCID	M	1 months	6 months	Lymphadenopathy	None	Performed	Living
22	SCID	F	2.5 months	11 months	Lymphadenopathy	*M. bovis* (Lymph node)	Performed	Exitus
23	SCID	M	1 months	5 months	Lymphadenopathy, HSM	*M. bovis* (Lymph node)	Performed	Living
24	SCID	M	3 months	7 months	Rash, Lymphadenopathy	*M. bovis* (Lymph node)	Performed	Living
25	Complete IFNGR1 deficiency	M	6 months	10 months	Lymphadenopathy, HSM	*M. bovis, M. fortuitum* (Lymph node) *M. tuberculosis* (Bone marrow) *M. avium intracellulare* (FGF)	Performed	Exitus

CGD: chronic granulomatous disease; HM: hepatomegaly; HSCT: hematopoetic stem cell transplantation; HSM: hepatosplenomegaly; IFNGR2: IFN-γ receptor 2; IFNGR1: IFN-γ receptor 1; IL12R1: interleukin 12 receptor beta 1; NEMO: nuclear factor kappa beta essential modulator; SCID: severe combined immune deficiency; SM: splenomegaly

after transplantation in two patients who had severe combined immune deficiency and developed BCG-itis. The general characteristics of the patients are given in Table 3.

Discussion

Mendelian Susceptibility to Mycobacterial Diseases (MSMD) is a rare condition and infections with mycobacteriae with low virulence including the BCG vaccine may be observed more commonly in this group of patients compared with the healthy population without hematologic and immunologic disorders (10-14). Mendelian Susceptibility to Mycobacterial Diseases MSMD has especially been associated with defects in the IL12B, IL12RB1, IRF8, ISG15, NEMO, IFNGR1, IFNGR2, STAT1, IRF8, and CYBB genes (15-22). In addition, susceptibility to mycobacterial infections may be observed in combined immune deficiencies and X-linked hyper IgM syndrome (2).

In this study, patients who were treated for severe combined immune deficiency, IL-12/IFN-γ receptor deficiency, NEMO deficiency, and chronic granulomatous disease were evaluated in terms of mycobacterial infections. Clinical mycobacterial infections were observed in 9% of patients with severe combined immune deficiency, 47.3% of patients with chronic granulomatous disease, and in all patients with partial IFNGR2 deficiency, IFNGR2 deficiency, IL12RB1 deficiency, and NEMO deficiency. Most patients with IL12B, IL12RB1, NEMO, IFNGR1, IFNGR2 deficiencies present with mycobacterial infections and are diagnosed as a result of investigations for diseases that might cause a predisposition to mycobacterial infections. In most of these patients, BCG strain (*M. bovis*) or non-tuberculosis mycobacteriae including *M. chelonea, M. fortuitum, M. mageritense, M. peregrinum, M. Smegmatis* and *M. scrofulaceum* are observed (23-26). In our study, 76% of our patients were diagnosed as having BCG-itis. Mycobacteriae could be isolated in 14 (33%) the patients. The most common mycobacterium was *M. bovis* and the other mycobacteriae included *M. tuberculosis, M. chelonae, M. fortiutum* and *M. elephantis*. In addition, multiple mycobacterial infections were observed in three patients, one of whom had CGD and two had IL12/ IFN-γ pathway defects. Mycobacterium should be isolated to confirm the diagnosis of mycobacterial infection. However, this is not alway possible in patients with immune deficiency. The symptoms of patients in whom mycobacterium could not be isolated, but a diagnosis of mycobacterial disease was made using different clinical, laboratory, and X-ray findings regressed with antituberculosis treatment.

In these patients, a predisposition to infections including non-typhoidal salmonella, coccidioidomycosis, paracoccidioidomycosis, histoplasma, nocardia, lysteria, cryptococcus, and cryptosporidium is also observed (27, 28). In this study, non-typhoidal salmonella infection was observed in two patients including one with partial IFNGR2 deficiency, and one with IL-12 receptor 1 deficiency, and cryptosporidium infection was observed in two patients, including one who had partial IFNGR2 deficiency and one who had CGD.

Immune deficiencies usually manifest in early childhood. Very rarely, onset of symptoms is observed in adolescence or adulthood. The mean age at the time of onset of symptoms was 9.8±19.8 months and the mean age at the time of diagnosis was 33±36.4 months in our patients, and the period from onset of symptoms to the time of diagnosis was 27 months (Table 3). This suggests that physicians should be more careful in terms of primary immune deficiencies in the presence of infections caused by non-tuberculosis mycobacteriae in order to make the diagnosis earlier in conditions that lead to a predisposition to mycobacterial infections.

In many immune deficiencies, the definite treatment is stem cell transplantation, which is lifesaving (29). Stem cell transplantation was performed in 36% of our patients. Cure was obtained in 66% of patients who underwent transplantation.

The facts that our study was a retrospective study and mycobacterium could not be typed in all patients were limitations of our study. Rare diseases with a predisposition to mycobacterial infections may be observed in Turkey because consanguineous marriages are common. This study is important in terms of describing these diseases and potential mycobacterial infections.

In conclusion, disorders affecting the IL12/IFN–γ pathway are observed predominantly in MSMD and infections caused by atypical mycobacteria including mainly *M. bovis and M. chelonae, M. fortuitum, M. mageritense, M. peregrinum, M. smegmatis, M. scrofulaceum* are common. In these types of infections, primary immune deficiencies should definetely be considered. Early diagnosis of primary immune deficiencies through neonatal screening programs will enable prevention of *M. bovis* infections by halting administration of BCG vaccines to these patients. Examination in terms of primary immune deficiency should definetely be performed in children with a positive familial history before administration of BCG vaccine.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Ege University School of Medicine (9.12.2016/16-11/12).

Informed Consent: Written informed consent was obtained from the parents of the patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - E.U., N.E.K.; Design - E.U., N.E.K.; Supervision - G.A., N.K.; Resources - E.U., Materials - E.U.; Data Collection and/or Processing - E.U.; Analysis and/or Interpretation - E.U., N.E.K., G.U., N.E.K., C.Ç.; Literature Search - E.U., N.E.K.; Writing Manuscript - E.U.; Critical Review - N.E.K., G.U., N.K.; Other - E.U., N.E.K.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

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