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Bacillus Calmette-Guérin (BCG) complications associated with primary immunodeficiency diseases

Sayna Norouzi[a], **Asghar Aghamohammadi**[b], **Setareh Mamishi**[a], **Sergio D. Rosenzweig**[c], and **Nima Rezaei**[b,d,e,*]

[a]Pediatric Infectious Diseases Research Center, Tehran University of Medical Sciences, Tehran, Iran

[b]Research Center for Immunodeficiencies, Pediatrics Center of Excellence, Children's Medical Center, Tehran University of Medical Sciences, Tehran, Iran

[c]Infectious Diseases Susceptibility Unit, Laboratory of Host Defenses, Primary Immunodeficiency Clinic, National Institutes of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, USA

[d]Molecular Immunology Research Center, Department of Immunology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran

[e]Department of Infection and Immunity, School of Medicine and Biomedical Sciences, The University of Sheffield, Sheffield, UK

Summary

Primary immunodeficiency diseases (PIDs) are a group of inherited disorders, characterized by defects of the immune system predisposing individuals to variety of manifestations, including recurrent infections and unusual vaccine complications. There are a number of PIDs prone to Bacillus Calmette-Guérin (BCG) complications. This review presents an update on our understanding about the BCGosis-susceptible PIDs, including severe combined immunodeficiency, chronic granulomatous disease, and Mendelian susceptibility to mycobacterial diseases.

Keywords

vaccination; Complications; Primary immunodeficiency diseases; Severe combined immunodeficiency; Mendelian susceptibility to mycobacterial diseases

Introduction

Tuberculosis (TB) is a common deadly infectious disease, caused by various strains of mycobacteria, including *Mycobacterium tuberculosis* (*M. Tuberculosis*).[1,2] Emergence of multiple-drug resistant *M. Tuberculosis* strains and notable increase in the rate of non-

*Corresponding author. Research Center for Immunodeficiencies, Children's Medical Center Hospital, Dr Qarib St, Keshavarz Blvd, Tehran 14194, Iran. Tel.: +9821 6692 9234; fax: 9821 6692 9235. rezaei_nima@yahoo.com, rezaei_nima@tums.ac.i(N. Rezaei).

tuberculous mycobacteria are features mandates paying more attention to identify the potential conditions, which can predispose individuals to acquire such infections.[3–5] Bacillus Calmette-Guérin (BCG) vaccination aims to prevent early-life infections with *M. Tuberculosis*.[3,4] The BCG vaccine was developed by Albert Calmette and Camille Guerin in France between 1908 and 1921. The original BCG strain (*Mycobacterium bovis* BCG) was an attenuated form of *M. bovis*, resulting from 231 3-week-subcultures in a media aimed to preserve the microorganism's immunogenicity minimizing its virulence. Nowadays, several substrains derived from the original preparation are used in the manufacturing of the currently used different BCG vaccines.[6] World Health Organization (WHO)-recommended vaccination of newborns with BCG takes place in several countries, especially those with high burden of TB or neighboring such regions, to prevent from miliary and meningeal forms of TB.

The BCG vaccination itself is believed to be merely safe for a competent immune system. However, a potentially lethal infection could be expected in immunocompromised hosts. In fact immunocompromised patients are vulnerable not only to mycobacterial diseases, but also to adverse complications of BCG vaccine.[6–8] Hence, a close scrutiny for primary immunodeficiency diseases (PIDs) is required at the time of detecting an overwhelming infection following the vaccination, a condition ranging from regional disease (BCGitis) to disseminated disease (BCGosis).[9]

Primary immunodeficiency diseases (PIDs) are inherited immune system disorders that lead to a variety of manifestations, including recurrent infections, autoimmunity, and malignancies; more than 150 types of PIDs with distinct underlying gene defects have been identified so far.[10] It has been shown that some PIDs tend to remain undiagnosed until the appearance of the presumed complications, including BCGosis.[6,11] Meanwhile a number of PIDs are susceptible to severe mycobacterial disease following vaccination with BCG, including severe combined immunodeficiency (SCID), chronic granulomatous disease (CGD), and Mendelian susceptibility to mycobacterial diseases.[12] There are a number of reports that investigated underlying PIDs in those with disseminated BCG (Table 1). This review is to present PIDs that prone to BCG complications, whilst vulnerability to other mycobacterial infections in any of these BCGosis-susceptible PIDs is discussed as well.

Search strategy and selection criteria

We searched PubMed and ISI Web of Science, and EMBASE for articles published in English with no time and language limitations on date up to January 2012. We used free text and MESH terms to search the Medline electronic bibliographical Database (accessing via PubMed) combining terms for study patients/population, problem and intervention. We did not include terms for the comparison groups (more sensitive, less specific search) and did not put "Methodological filter" (study type filter) for our search strategy, as our preliminary search revealed that there were no randomized controlled trial identifiable for the review question. In our preliminary search, we made use of built-in search filters of PubMed "clinical queries" and did a rapid search on PubMed and the ISI Web of Science. We also used free texts to search EMBSE (accessing via Ovid). BCG complications, including BCGitis and BCGosis (disseminated disease) were searched through the literature and

articles were selected for their relevance to the analysis of underlying disorders. Indeed, cohort and case reports/series of patients with severe combined immunodeficiency, chronic granulomatous disease, and Mendelian susceptibility to mycobacterial diseases, including their subtypes (*IFN- γR1*, *IFN- γR2*, *IL-12Rβ1*, *IL12p40*, *STAT1*, and *IKBKG* deficiencies) were enrolled and BCG complications were investigated in the selected articles. Each article was then assessed for its methodological quality and the relevance of its results. Preference was given, but not restricted to, clinical studies with large number of cases and definite diagnosis. Additional references were identified from citations in retrieved articles.

Severe combined immunodeficiency

Severe combined immunodeficiency (SCID) is the most severe forms of PIDs, which are genetically deficient in development and function of T-lymphocytes and could also be associated with decreased numbers of B-lymphocytes and NK-cells.[13] SCID is considered as an emergency of pediatric practice, whilst early detection of SCID and appropriate treatment is life-saving and could prevent further complications, such as BCGosis following BCG vaccination.[14–16] Severe combined immunodeficiency is a lethal disease, if timely diagnosis and appropriate treatment, e.g. bone marrow transplantation, is not made.[17,18] Therefore, screening for SCID has been started as a routine program for newborns in some countries (e.g., United States since 2008), and is under evaluation in some others. In the US project, T-cell receptor excision circles (TRECs) are detected by polymerase chain reaction (PCR) from Guthrie cards, as a marker of thymic activity and thymic output.[19]

Several gene defects responsible for SCID phenotype have been identified so far; therefore SCID could be sub-classified to four groups based on lymphocyte subpopulation (Table 2). Indeed, without a normally functional specific arm of the immune system such as CD4 T helper (Th) lymphocytes (e.g., Th1, Th2, Treg, Th17), innate arm of the immune system like macrophages, even with an abundant quantity, could not play its proper role.[19–21] In addition to above-mentioned classification, SCID could also be divided into four groups regarding to the defective mechanism involved in pathogenesis, including purine metabolism defect which lead to premature lymphocyte precursor cell death, defective signaling through the common gamma chain dependent cytokine receptor, defective pre T-cell receptor (TCR)/TCR signaling, and defective V(D)J recombination.[22,23]

BCG complications including BCGosis, as the adverse reaction to BCG vaccination, could be seen in all underlying genetic types of SCID. So far, there are no identifiable differences described between rates of infections among the various types of SCID; however, large multicenter international studies would be necessary to confirm or refute this and other concepts related to BCG complications in SCID patients. Several reports described BCGosis in patients with SCID (Table 3). Numerous reports on this group of patients were related to adverse complication of early BCG vaccination,[24] whilst in the majority of cases, BCGosis is the preliminary sign of the underlying disease.

In contrary to high incidence rate of BCGosis in patients with SCID, reports investigating vulnerability of SCID to NTM are rare. Although there are few reports of disseminated infection with *Mycobacterium avium* or *Mycobacterium marinum*,[25,26] infection with *M. tuberculosis* in SCID is not noteworthy[27] and probably due to lack of exposure.

Based on these findings, the susceptibility of SCID patients to overwhelming BCG infection is of substantial importance, particularly in countries with national wide vaccination programs. Although this relationship is not surprisingly, given the impact of SCID on cell-mediated immunity which is required for immunity against BCG, the topic is surprisingly underestimated on the SCID literature. It should be emphasized that BCG vaccination is more frequent in developing countries where other comorbidity factors have a strong influence on child mortality, while SCID could be under-diagnosed frequently in these regions. How age at BCG vaccination, the administration rout, the type of vaccination strain or which variant of SCID is more susceptible to BCG complications, are still unanswered questions.

Altogether, precise control and measures aiming in order to avoid administration of BCG at birth in those with family history of recurrent infections and immunodeficiency is highly recommended. BCG vaccination could be done later once screening tests rule out underlying immunodeficiencies.

Chronic granulomatous disease

Chronic granulomatous disease (CGD) is a heterogeneous genetic disorder in which the phagocytes (neutrophils, monocytes and macrophage) are not capable to kill microorganisms as a result of a defect in production of reactive oxygen spicies (ROS) due to impaired nicotinamide adenine dinucleotide phosohate oxidase (NADPH) activity.[28] Therefore patients with CGD usually suffer from recurrent bacterial and fungal infections.[28,29] This increased infectious susceptibility results of the impairment of at least three reactive oxygen spices (ROS)-dependent antimicrobial mechanisms[29]: i) decreased phox-generated ROS with intrinsic antimicrobial activity; ii) decreased phox-mediated activation of microbicidial granule proteases; and iii) decreased phox-mediated release of neutrophil extracellular traps.[29–31] Besides, these patients are also characterized for presenting dysregulated inflammation and increased granuloma formation.

Constitutional inactivating mutations in *CYBB* [Cytochrome *b*(-245), beta subunit, OMIM*300481] gene leads to X-linked (XL) form of CGD, where as mutations in the *CYBA* [Cytochrome *b*(-245), beta subunit, OMIM+608508], *NCF1* [Neutrophil cytosolic factor 1, OMIM*608512] and *NCF2* [Neutrophil cytosolic factor 2, OMIM*608515] genes that encode subunits of phagocyte NADPH oxidase result in autosomal recessive (AR) forms of CGD.[32,33] More recently, mutations in *NCF4* (Neutrophil cytosolic factor 4, p40^{phox}, OMIM*601448) were also described to be associated to AR forms of CGD.[34]

The patients with CGD are vulnerable to infections caused by Staphylococci, Burkholderia, Serratia, Salmonella, and Aspergillus; although an increased predisposition to infections with *M. tuberculosis* has been documented in some CGD patients, it is still a debate. It has been shown that the oxidative burst plays an important role in host defense against mycobacterium infections[35]; however, phagocytes in CGD patients are not capable to destroy intracellular BCG *in vitro*.[36]

Also in practice, vaccination with attenuated *M. bovis* BCG vaccine could result in BCGosis in these patients.[35,37] These patients are sacrifice to the BCG vaccination to show up their

underlying disease.[9] Review of literature reveals several reports on complications of BCG in CGD patients (Table 4), while no BCG complication was reported in few studies.[38] CGD patients are more likely to show BCG lymphadenitis.[39] However, they are more prone to cure with anti-TB regimen in contrast to the SCID patients.[37,40,41]

BCG vaccination is contraindicated in infants with CGD, but due to its administration at birth in some countries, most patients are diagnosed with CGD after being vaccinated and developing BCG complications.[40]

Nowadays, CGD patients are showing increased survival rates compared to a few decades ago. This is probably the natural consequence of aggressive prophylactic and diagnostic measures, better antifungal medications and the very promising results of hematopoietic stem cell transplantation. As diagnosis of underlying immunodeficiencies before BCG vaccination could be beneficial and life-saving, postponing BCG vaccination could be suggested as a short-term solution for those suspicious to immunodeficiency with positive family history of recurrent infections and immunodeficiencies. Indeed usage of safer antituberculosis vaccines could be advised in order to prevent BCG complications in immunodeficient patients.

Mendelian susceptibility to mycobacterial diseases

Mendelian susceptibility to mycobacterial diseases (MSMD) describes a group of PIDs highly vulnerable to weakly virulent species of mycobacterium.[42] Not a particular ethnic group or geographic region is specific for MSMD patients. These individuals are usually presented with supreme disseminated mycobacterial infections,[9,43] especially BCG[9,44,45] (Table 5).

Although most of MSMD are likely prone to disseminated BCG infection or NTMs,[43] infection with *M. tuberculosis* yet comprises a considerable number of case presentations. Different clinical features of this disease may arise from the variable existing gene mutations.[46]

All genetic types of MSMD seem to have defects in IFN-γ mediated immunity. It seems that IFN-γ is mandatory for efficient immune response to Mycobacterial species. Moreover, it has been shown that IL12/23 axis is necessary for promotion of a competent IFN-γ secretion. Therefore, any mutation which leads to a defect in IFN-γ or IL12/23 receptors or signal transduction pathways would lead to incomplete response to Mycobacterial infections.[47,48]

Mutations in several gene loci have been detected for MSMD: *IFN- γR1*, *IFN- γR2*, *IL-12Rβ1*, *IL12B*, *STAT1*, and *IKBKG* (Table 6). However, it is worthy to declare that in numerous cases of MSMD, no genetic defect has been discovered.

IFN-γ receptor is composed of two chains; IFN-γR1 and IFN-γR2. Mutations in the genes encoding these receptors would result in a defect in the action of IFN-γ.[48–51] *STAT1* mutations lead to diminished Gamma Activating Factor (GAF, STAT1 homodimers) - mediated response to IFN-γ. *IL12RB1* mutations bring about β1 chain deficiency in IL12/23

receptor complex. NK and T cells activity are dependable on the above-mentioned pathways. *IKBKG* mutations, as an XL form of MSMD, cause NF-kB essential modulator (NEMO) deficiency.[46,50–52] NEMO deficiency clinically presents with a hypohydrosis, hypotricosis, peg-shaped teeth and immunodeficiency syndrome called ectodermal dysplasia anhydrotic with immunodeficiency (EDA-ID). Some patients show a more severe phenotype of EDA-ID with osteopetrosis and lymphoedema (OL-EDA-ID), while others present with immunodeficiency with no (or very minimal) ectodermal manifestations. Moreover, high serum levels of IgM, and low levels of IgG, IgA resembling Hyper IgM syndromes have also described found in a subset of these cases. IKBKG-hypomorphic mutated patients are highly susceptible to of BCG complications and NTMs infections.[53–55]

Interferon Regulatory Factor 8 (*IRF8*, OMIM*601565) gene controls the development of dendritic cells, as well as differentiation of granulocytes and macrophages IRF8 also plays a fundamental role in regulation of function of hematopoitic cells. One of the reported mutations of the *IRF8*, K108E, is inherited as an AR pattern leading to a syndrome manifested by early onset disseminated BCG. Lack of monocytes and dendritic cells in this patient was associated with opportunistic infections. A distinct mutation, T80A, has also been reported with AD pattern of inheritance resulting in a less severe immunodeficiency picture. These patients also show susceptibility to BCG infection.[56,57]

Recently, macrophage $gp91^{phox}$ deficiency, which is due to mutation in *CYBB* gene, has been classified under category of MSMD,[58] in addition to CGD,[8] while a group of these patients are identified who has isolated susceptibility to mycobacteria.[58]

Under certain cultural or religious precepts, cousin to cousin marriage is still an ongoing ritual. In countries with high rates of consanguineous marriage, AR forms of MSMD (as other AR diseases) are significantly more prevalent than autosomal dominant (AD) or XL forms of the diseases. Besides, most of these countries are also the ones encouraging strong neonatal BCG vaccination policies. In such cases the BCG complications are manifested in the child of otherwise clinically healthy parents.

Other PIDs associated with BCG complications

In addition to SCID, CGD, and MSMD, other PIDs have increased vulnerability to BCG infection; however BCG vaccination complications are usually less prevalent and severe than in the diseases mentioned above.

Patients with hyper-immunoglobulin E syndrome (HIES or Job's syndrome), as an autosomal dominant syndrome due to mutations in the *Signal Transducer and Activator of Transcription 3* (*STAT3*, OMIM*102582) gene, develop skeletal abnormalities, abnormal faces and delay in shedding of primary teeth. These patients could show early (even neonatal) eczema and respiratory infections. There are few reports of BCG infection in HIES; however, the patients have shown more vulnerability to BCG or NTM infections than *M. tuberculosis*.[59–62]

One of the rare hereditary disorders in T-cells activity is X-linked hyper IgM syndrome (XL-HIGM) due to mutations in the *CD40 Ligand* (*CD40L*, OMIM*300386) gene. There

are few reports of regional or disseminated BCG in these patients. It is noteworthy that the AR forms of hyper IgM syndrome affecting B-cell intrinsic function are not more susceptible to mycobacterial disease.[13,63–65]

Conclusions

Occurrence of severe BCG complications in a patient is strongly suggestive of an underlying immunodeficiency, primary or secondary.[66,67]

PIDs could show BCG complications with different severity, ranging from a regional-localized disease, or BCGitis, to a more severe, life-threatening disseminated form, so called BCGosis.

Interestingly, not only severity of BCG complications in PIDs is different, but also the onset of this disease is not the same in various types of PIDs. In general, BCG complications are manifested earlier and in more severe forms in SCIDs and MSMDs, than in any other forms of PIDs. Both molecular (e.g., genetic form of PIDs) and vaccine-associated factors (e.g., BCG strain, age at vaccination) might influence the type of outcome after BCG vaccination. For CGD, most of the patients are prone to exhibit BCG lymphadenitis, although disseminated cases have also been reported. In contrast to SCID and MSMD, patients with CGD are usually more successful in clearing BCG infection. Moreover, the prevalence and severity of BCG complications in XL-HIGM and HIES is lesser than the above-mentioned PIDs, and if present are more likely to be controlled with anti-mycobacterial regimens.

According to these findings, the most important arm in defending against BCG infections is the pathways facilitated by IFN-γ, a cytokine produced by T-cells and NK-cells in response to IL12/23 stimulation. Hence, SCID and MSMD patients, as a result of bearing deficiency in these pathways, develop the most critical complications to BCG.

In summary, preventing BCG complications in patients with PIDs could be achieved through different and not mutually exclusive approaches: screening for SCID in the general population; for MSMD, CGD or other PIDs in suspicious families; or delaying BCG vaccination as another option. As AR pattern of inheritance is the most frequent type of PIDs, such diseases should be considered more precisely in the regions with high rates of consanguinity. To the best of our knowledge, taking a good family history in such patients could be beneficial and might lead to a timely diagnosis, which in its turn would result in early intensive treatment and could be life-saving in these patients.

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Table 1

Selected reports of primary immunodeficiency diseases in the patients with BCG complications.

Study	Year	Country/Origin	No. of patients with BCG complications	No. of Patients with PIDs	No. of SCID patients	No. of CGD patients	No. of MSMD patients	No. of other PIDs patients	Ref.
Toida & Nakata	2007	Japan	39 (review)	19(48.7%)	4	5	4 IFN-γR1 deficiency	6 cell-mediated immune defects	68
Li et al	2010	China	18	12(66.7%)	3	7	2 IL-12/IFN-γ pathway deficiency	–	69
Lee et al	2009	Taiwan	18	18(100%)	12	2	3 IFN-γR1 deficiency	1 chronic mucocutaneous candidiasis	70
Afshar Paiman et al	2006	Iran	17	10(58.8%)	8	1	–	1 cell-mediated immune defects	40
Sadeghi-Shabestari et al	2009	Iran	11	11(100%)	7	1	1 IL12R deficiency 2 Other MSMD	–	71
Scoazec et al	1984	France	11	11(100%)	5	3	–	1 Di George's syndrome, 3 unclassified conditions	72
Gonzalez et al	1989	Chile	9	9(100%)	2	3	–	4 cell-mediated immune defects	73
Lee et al	2009	Taiwan	8	4(50%)	2	–	–	1 primary autoimmune neutropenia, 1 chronic mucocutaneous candidiasis	74
Jacob et al	1996	Brazil	4	4(100%)	1	1	–	1 cell-mediated immune defects, 1 chemotaxis defect	75
Abramowsky et al	1993	Chile-USA	4	4(100%)	2	–	–	2 cell-mediated immune defects	76
Romanus et al	1993	Sweden	4	3(75%)	–	–	–	–	77
Verma et al	2008	India	3	3(100%)	2	–	–	1 CD8 deficiency	78
Santos et al	2010	Portugal	3	3(100%)	1	–	2 IFN-γR1 deficiency	–	11
Bustamante et al	2007	France	3	3(100%)	–	–	3 Novel XL-MSMD	–	79
Antaya et al	2001	Qatar- Panama	2	2(100%)	1	–	–	1 cell-mediated immune defects	80
Pasic et al	1998	Yugoslavia	1	1(100%)	–	–	–	1 hyper-immunoglobulin E syndrome	62
Talbot et al	1997	Brazil	1	1(100%)	–	–	–	1 cell-mediated immune defects	6
Fischer et al	1980	France	1	1(100%)	–	–	–	1 cell-mediated immune defects	81
Mackay et al	1980	Scotland	1	1(100%)	–	–	–	1 cell-mediated immune defects	82

Table 2

Gene defects associated with various SCID phenotypes, based on lymphocyte subpopulation.

SCID groups	Subtype	Genetic defects	Gene Symbol	Cytogenetic location	OMIM
T-B+NK-SCID	*γc deficiency*	*INTERLEUKIN 2 RECEPTOR, GAMMA*	*IL2RG*	Xq13.1	*308380
	JAK3 deficiency	*JANUS KINASE 3*	*JAK3*	19p13.1	*600173
T-B+NK + SCID	*IL7-Rα deficiency*	*INTERLEUKIN 7 RECEPTOR*	*IL7R*	5p13	*146661
	CD45 deficiency	*LEUKOCYTE-COMMON ANTIGEN; or PROTEIN-TYROSINE PHOSPHATASE, RECEPTOR-TYPE, C (PTPRC)*	*LCA*	1q31-q32	*151460
	CD3γ deficiency	*CD3 ANTIGEN, GAMMA SUBUNIT*	*CD3G*	11q23	+186740
	CD3δ deficiency	*CD3 ANTIGEN, DELTA SUBUNIT*	*CD3D*	11q23	*186790
	CD3ε deficiency	*CD3 ANTIGEN, EPSILON SUBUNIT*	*CD3E*	11q23	+186830
	CD3ξ deficiency	*CD247 ANTIGEN*	*CD247*	1q22-q23	*186780
	Coronin 1a deficiency	*CORONIN 1A*	*CORO1A*	16p11.2	*605000
	Winged-helix-nude (WHN) deficiency	*WINGED HELIX NUDE; or FORKHEAD BOX N1 (FOXN1)*	*WHN*	17q11-q12	*600838
T-B-NK+ SCID	*RAG 1 deficiency*	*RECOMBINATION-ACTIVATING GENE 1*	*RAG1*	11p13	*179615
	RAG 2 deficiency	*RECOMBINATION-ACTIVATING GENE 2*	*RAG2*	11p13	*179616
	Artemis deficiency	*DNA CROSS-LINK REPAIR PROTEIN 1C*	*DCLRE1C*	10p13	*605988
	DNA ligase IV deficiency	*LIGASE IV, DNA, ATP-DEPENDENT*	*LIG4*	13q33-q34	*601837
	Cernunnos deficiency	*NONHOMOLOGOUS END-JOINING FACTOR 1*	*NHEJ1*	2q35	*611290
	DNA-dependent protein kinase deficiency	*PROTEIN KINASE, DNA-ACTIVATED, CATALYTIC SUBUNIT*	*PRKDC*	8q11	*600899
T-B-NK- SCID	*ADA deficiency*	*ADENOSINE DEAMINASE*	*ADA*	20q13.12	*608958
	PNP deficiency	*PURINE NUCLEOSIDE PHOSPHORYLASE*	*PNP*	14q13.1	*164050
	Reticular dysgenesis	*ADENYLATE KINASE 2*	*AK2*	1p34	*103020

Table 3

Selected reports of severe combined immunodeficiency associated with BCG complications.

Study	Year	Country/Origin	No. of SCID patients	No. of BCG complications	SCID type	Reference
Stephan et al	1993	France	117	10(8.5%)[a]	Unknown	18
Yeganeh et al	2008	Iran	40	18(45%)	Unknown	83
Kohn et al	1991	Germany	18	18(100%)	Unknown	84
Sadeghi-Shabestari & Rezaei	2009	Iran	8	8(100%)	4 T-B-NK+3 T-B+NK− 1 T-B+NK+	85
Yan et al	1997	China	4	1(25%)	Unknown	86
Heyderman et al	1991	UK	2	2(100%)	Omenn syndrome ADA deficiency	87
Case reports						
Norouzi et al	2011	Iran	1	1	T-B+NK−	88
Bacalhau et al	2011	Portugal	1	1	T-B-NK−	89
Akaihata et al	2011	Japan	1	1	Unknown	90
Sadeghi-Shabestari et al	2009	Iran	1	1	T-B-NK+	91
Marchand et al	2008	France	1	1	T-B NK−	92
Pariyaprasert et al	2008	Thailand	1	1	T-B+NK+	93
Culic et al	2004	Croatia	1	1	Unknown	94
López-Herrera et al	2004	Mexico	1	1	T-B-NK−	95
Hung et al	2003	Taiwan	1	1	Unknown	96
Ikincioğullari et al	2002	Turkey	1	1	T-B+NK−	97
Su et al	2001	Taiwan	1	1	Unknown	98
McKenzie et al	2000	South Africa	1	1	Unknown	99
Han et al	2000	Korea	1	1	Unknown	100
Uysal et al	1999	Turkey	1	1	Unknown	101
Jung et al	1997	Japan	1	1	T-B+NK−	102
Skinner et al	1996	UK	1	1	Unknown	103
Hugosson et al	1991	Saudi Arabia	1	1	Unknown	104
Minegishi et al	1985	Japan	1	1	Unknown	105

[a]Some of enrolled cases were vaccinated with BCG.

Table 4

Selected reports of chronic granulomatous disease associated with BCG complications.

Study	Year	Country/Origin	No. of CGD patients	No. of BCG complications[a]	Reference
van den Berg et al	2009	Europe	429	34(7.9%)	39
Fattahi et al	2011	Iran	93	52(55.9%)	106
Movahedi et al	2004	Iran	41	7(17.1%)	107
Lee et al	2008	China	17	8(47.1%)	35
Bakri et al	2009	Jordan	15	2(13.3%)	108
Köker et al	2009	Turkey	12	4(33.3%)	109
Teimourian et al	2008	Iran	11	4(36.4%)	110
Ortega et al	1980	Spain	6	1(16.7%)	111
Köker et al	2007	Turkey	2	1(50%)	112
Case reports					
Movahedi et al	2010	Iran	1	1	37
Kusuhara et al	2009	Japan	1	1	113
Fehon et al	2008	Australia	1	1	114
Bustamante et al	2007	France	1	1	115
Kawashima et al	2007	Japan	1	1	116
Vieira et al	2004	Portugal	1	1	41
Cerdá de Palou et al	2003	Netherlands	1	1	117
Kabuki et al	2003	Japan	1	1	118
Hódsági et al	1986	Hungary	1	1	119
Kobayashi et al	1984	Japan	1	1	120
Smith et al	1984	South Africa	1	1	121
Verronen et al	1974	Finland	1	1	122

[a] It should be noted that a proportion of enrolled cases were not vaccinated with BCG.

Table 5

Selected reports of mendelian susceptibility to mycobacterial diseases associated with BCG complications.

Study	Year	Country/Origin	No. of MSMD patients	No. of BCG complications[a]	Genetic forms	Reference
de Beaucoudrey et al	2010	France (from 30 countries)	141	65(46.1%)	IL-12Rβ1 deficiency	123
Dorman et al	2004	USA (from worldwide)	60	20(33.3%)	IFN-γR1 deficiency	124
Fieschi et al	2003	France (from 17 countries)	41	18(43.9%)	IL-12Rβ1 deficiency	125
Sologuren et al	2011	Spain, Chile, Portugal	14	6(42.9%)	IFN-γR1 deficiency	126
Picard et al	2002	Pakistan, India, Saudi Arabia	13	11(84.6%)	IL-12Rβ1 deficiency	127
Lichtenauer-Kaligis et al	2003	Turkey	11	8(72.7%)	IL-12Rβ1 deficiency	128
Sasaki et al	2002	Japan	6	6(100%)	IFN-γR1 deficiency	129
Chapgier et al	2006	France	5	4(80%)	STAT1 deficiency	130
Elloumi-Zghal et al	2002	Tunisia	5	5(100%)	3 IL-12Rβ1 deficiency 2 IL12B deficiency	131
Jouanguy et al	2000	Algeria, Turkey, France/Portugal	4	4(100%)	IFN-γR1 deficiency	132
Altare et al	1998	Morocco, Turkey, Cyprus	4	2(50%)	IL-12Rβ1 deficiency	133
Tanir et al	2006	Turkey	3	2(66%)	IL-12Rβ1 deficiency	134
De Jong et al	1998	The Netherlands	3	1(33%)	IL-12Rβ1 deficiency	135
Pedraza-Sánchez et al	2010	Mexico	2	2(100%)	IL-12Rβ1 deficiency	136
Lee et al	2008	China	2	2(100%)	IL-12Rβ1 deficiency	137
Mansouri et al	2005	Iran	2	2(100%)	IFN-γR2 deficiency IL12B deficiency	138
Ulrichs et al	2005	Slovakia	2	2(100%)	IL-12Rβ1 deficiency	139
Rosenzweig et al	2004	Qatar	2	1(50%)	IFN-γR2 deficiency	140
Dupuis et al	2003	Saudi Arabia	2	2(100%)	STAT1 deficiency	141
Altare et al	2001	Morocco	2	1(50%)	IL-12Rβ1 deficiency	142
Jouanguy et al	1997	Portugal	2	1(50%)	IFN-γR1 deficiency	50
Imamura et al	2011	Japan	1	1(100%)	NEMO deficiency	143
van de Vosse et al	2010	Netherlands	1	1(100%)	IL-12Rβ1 deficiency	144
Rosenzweig et al	2010	Argentina	1	1(100%)	IL-12Rβ1 deficiency	145
Enkai et al	2009	Japan	1	1(100%)	NEMO deficiency	146
Okada et al	2007	Japan	1	1(100%)	IFN-γR1 deficiency	147

Study	Year	Country/Origin	No. of MSMD patients	No. of BCG complications[a]	Genetic forms	Reference
Döffinger et al	2000	Portugal	1	1(100%)	IFN-γR2 deficiency	[148]

[a] It should be noted that a proportion of enrolled cases were not vaccinated with BCG.

Table 6

Genetic defects that cause mendelian susceptibility to mycobacterial diseases.

Genetic defects	Gene Symbol	Locus	Inheritance	OMIM
INTERFERON, GAMMA, RECEPTOR 1	*IFNGR1*	6q23-24	Autosomal recessive & dominant	*107470
INTERFERON, GAMMA, RECEPTOR 2	*IFNGR2*	21q22	Autosomal recessive	*147569
INTERLEUKIN 12 RECEPTOR, BETA-1	*IL-12RB1*	19p13	Autosomal recessive	*601604
INTERLEUKIN 12B or IL12, SUBUNIT p40	*IL12B*	5q31	Autosomal recessive	*161561
SIGNAL TRANSDUCER AND ACTIVATOR OF TRANSCRIPTION 1	*STAT1*	2q32	Autosomal recessive & dominant	*600555
INHIBITOR OF KAPPA LIGHT POLYPEPTIDE GENE ENHANCER IN B CELLS, KINASE OF, GAMMA or NF-KAPPA-B ESSENTIAL MODULATOR	*IKBKG or NEMO*	Xq28	X-linked	*300248
CYTOCHROME b(-245), BETA SUBUNIT	*CYBB*	Xp11.4	X-linked	*300481
INTERFERON REGULATORY FACTOR 8	*IRF8*	16q24.1	Autosomal dominant	*601565