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Common Infections and Target Organs Associated with Chronic Granulomatous Disease in Iran

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Abstract
Recurrent severe bacterial and fungal infections are characteristic features of the rare genetic immunodeficiency disorder chronic granulomatous disease (CGD). The disease usually manifests within the first years of life with an incidence of 1 in approximately 200,000 live births. The incidence is higher in Iran and Morocco where it reaches 1.5 per 100,000 live births. Mutations have been described in the 5 subunits of NADPH oxidase, mostly in gp91^{phox} and p47^{phox}, with fewer mutations reported in p67^{phox}, p22^{phox}, and p40^{phox}. These mutations cause loss of superoxide production in phagocytic cells. *CYBB*, the gene encoding the large gp91^{phox} subunit of the transmembrane component cytochrome b_{558} of the NADPH oxidase complex, is localized on the X-chromosome. Genetic defects in *CYBB* are responsible for the disease in the majority of male CGD patients. CGD is associated with the development of granulomatous reactions in the skin, lungs, bones, and lymph nodes, and chronic infections may be seen in the liver, gastrointestinal tract, brain, and eyes. There is usually a history of repeated infections, including inflammation of the lymph glands, skin infections, and pneumonia. There may also be a persistent runny nose, inflammation of the skin, and inflammation of the mucous membranes of the mouth. Gastrointestinal problems can also occur, including diarrhea, abdominal pain, and perianal abscesses. Infection of the bones, brain abscesses, obstruction of the genitourinary tract and/or gastrointestinal tract due to the formation of granulomatous tissue, and delayed growth are also symptomatic of CGD. The prevention of infectious complications

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in patients with CGD involves targeted prophylaxis against opportunistic microorganisms such as *Staphylococcus aureus*, *Klebsiella* spp., *Salmonella* spp. and *Aspergillus* spp. In this review, we provide an update on organ involvement and the association with specific isolated microorganisms in CGD patients.

Introduction

Chronic granulomatous disease (CGD) is an inherited primary immunodeficiency disorder (PID) characterized by defective granulocytes (neutrophils and eosinophils), monocytes, and macrophages. In CGD patients, these cells are unable to kill pathogens due to a deficiency in nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activity. This limits the production of reactive oxygen species (ROS) that are essential for intracellular killing of many types of fungi and bacteria [1–3]. The complex formation of the cytosolic and membrane components of NADPH oxidase results in the activation of this enzyme. NADPH in the cytosol can then bind and donate electrons, which are transported within the enzyme via flavin adenine dinucleotide and 2 heme groups to molecular oxygen on the luminal side of the membrane. As a result, superoxide and other ROS are produced within the phagosome, which helps in killing the ingested pathogens (Fig. 1) [4]. Granulocyte death is regulated by the cell surface expression of sialic acid-binding immunoglobulin-like lectins (Siglecs). Siglec-9 ligation, in particular, enhances neutrophil cell death via an NADPH/ROS-mediated process [5]. In CGD patients, where NADPH is absent due to a genetic defect, it is probable that Siglec-mediated cytoxicity does not occur, leading to prolonged neutrophil survival and delayed resolution of inflammation. This may be especially important in the regulation of some clinical features of disease including abscess formation. Mutations in any of the components of NADPH oxidase (gp91^{phox}, p22^{phox}, p40^{phox}, p47^{phox} and p67^{phox}) can lead to CGD. The most common molecular defect in CGD is a mutation in the *CYBB* gene (cytochrome *b*, beta subunit) that is located on the X chromosome and encodes gp91^{phox} [6]. About 70% of all CGD cases result from mutations in *CYBB*. Autosomal recessive (AR) expression due to mutations in *CYBA* (<5% of cases), *NCF1* (about 20% of cases), and *NCF2* (<5% of cases) genes, encoding the p22^{phox}, p47^{phox}, and p67^{phox} subunits, respectively, has also been reported [7]. Recent studies have also reported mutations in the *NCF4* gene encoding p40^{phox} [8, 9].

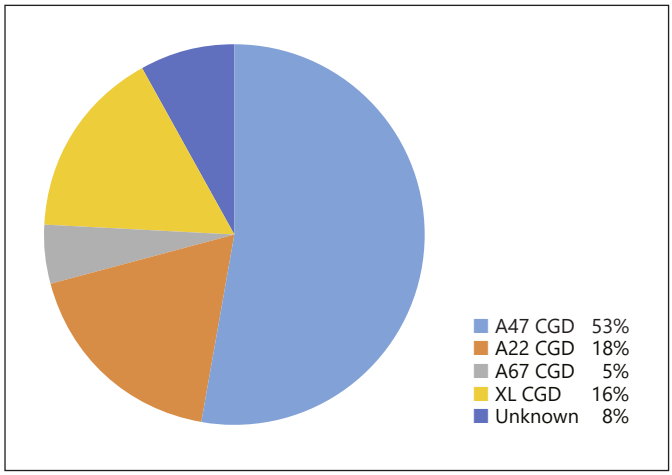

Fig. 1. Subtypes of CGD in Iranian patients. Unlike in most countries, in Iran the highest percentage is related to the autosomal form of CGD and includes 53% A47 CGD, 18% A22 CGD and 5% A67 CGD. XL CGD is therefore one of the less common subtypes in Iranian patients.

CGD is the second-most common PID in Middle-Eastern countries such as Iran, and accounts for 20% of these patients [10], with the AR form of CGD (AR-CGD) being the most common [11]. Patients with CGD are susceptible to variety of recurrent bacterial and fungal infections. The most common bacteria include *Staphylococcus aureus*, *Klebsiella* spp., *Salmonella* spp., and the most common fungal infections are due to *Aspergillus* spp. [12]. Candida, the enteric Gram-negative bacteria *Serratia marcescens*, *Burkholderia cepacia* complex, and *Mycobacterium tuberculosis* (MTB) have also been detected [2].

The intracellular survival of ingested bacteria leads to the development of granulomata in the lymph nodes, skin, lungs, liver, gastrointestinal tract, brain, and bones [13]. Although the exact incidence of CGD in Iran is unknown, in the USA and Western Europe it is about 1 case per 200,000–250,000 live births [14, 15]. The diagnosis is usually determined with dihydrorhodamine-1,2,3 (DHR) and nitroblue tetrazolium (NBT) tests; the former measures intracellular NADPH oxidase activity by flow cytometry and the latter is a microscopic-slide test that yields information about the NADPH oxidase activity in each separate cell. Subsequent molecular and genetic studies are needed to confirm the diagnosis by demonstrating specific mutations [7, 12]. CGD is generally diagnosed in infancy or childhood [14, 16] and the mean age of detection in Iran is 5.5 years [17].

Generally, strategies for treating CGD patients are based on the early diagnosis of infection, the prevention

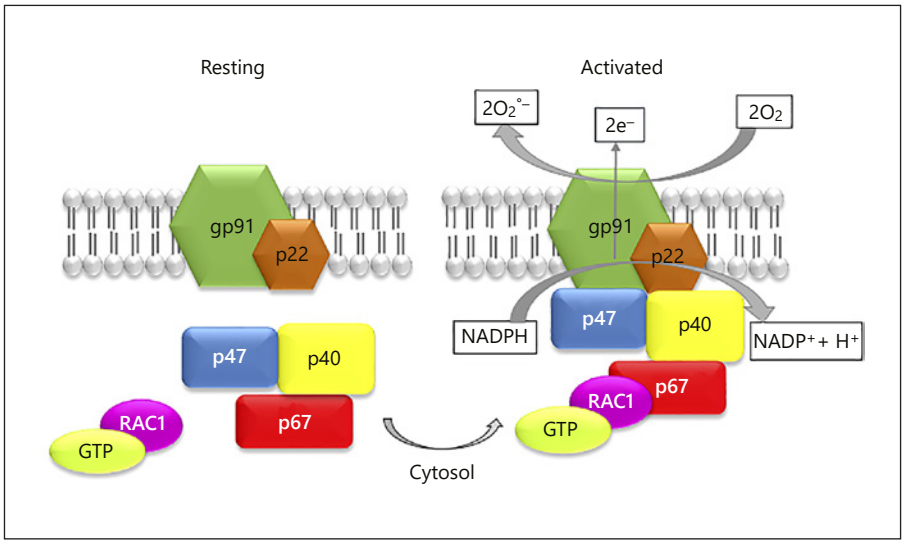

Fig. 2. Schematic representation of the activated and resting forms of NADPH oxidase. The membrane-associated component of the enzyme, flavocytochrome b_{558}, is composed of $gp91^{phox}$ and $p22^{phox}$. $P47^{phox}$, $p67^{phox}$, and $p40^{phox}$ are cytoplasmic components that bind to flavocytochrome b_{558} after activation of the cells. The small GTPase Rac, with GDP bound in the resting state, sheds GDP and binds GTP, and then translocates to the membrane upon cell activation. After the enzyme has been assembled, it generates superoxide (O_2^-) by transporting electrons from cytoplasmic NADPH to molecular O_2 on the other side of the membrane. In this way, O_2^- is generated in the phagosome or on the outside of the cells. Other ROS are subsequently generated from O_2^-.

of bacterial and fungal infections, and the timely management of the complications of infection. Prevention of infection utilizes a combination of an antibacterial (trimethoprim-sulfamethoxazole) and an antifungal (itraconazole) agent, with or without immunomodulatory therapy with interferon (IFN)-γ [18–21]. In a study on 76 patients with CGD, immunotherapy with IFN-γ reduced the rate of serious infection by 67% [22]. IFN-γ therapy is used in addition to antimicrobial antibiotics for CGD management in Iran. Allogeneic hematopoietic stem cell transplantation (HSCT) is also performed in Iran, particularly in adults. Ramzi et al. [23] reported the first cases in Iran that underwent HSCT treatment. A 22-year-old man with X-linked CGD (XL-CGD) was successfully treated and his condition improved. In this review, we provide a comprehensive picture of CGD, its prevalence, and common agents of infection in Iran.

Pathogenesis of CGD

In this section, we discuss genomic analysis and the relationship with specific mutations involved in CGD. Approximately 53% of CGD patients in Iran possess an AR mutation in the *NCF1* gene encoding $p47^{phox}$. Other major causes of AR-CGD are mutations in *CYBA* and *NCF2,* which encode $p22^{phox}$ and $p67^{phox}$, respectively (Fig. 2). Teimourian et al. [24] evaluated mutations in 43 patients with AR-CGD and reported that 32 (74%) had a $p47^{phox}$ deficiency (A47 CGD), 9 (20%) a $p22^{phox}$ deficiency (A22 CGD), and 2 (5%) a deficiency in $p67^{phox}$ (A67 CGD). Moreover, Fattahi et al. [11] evaluated 93 CGD patients with (81 AR CGD) and reported 67% with A47 CGD, 25% with A22 CGD, and 7% with A67 CGD. Although the NCF2 mutation is less common, Badalzadeh et al. [25] detected 2 different homozygous mutations in *NCF2* in 4 Iranian A67 CGD patients.

The $p22^{phox}$ defect is the second most prevalent cause of AR-CGD in Iranian patients [24]. Badalzadeh et al. [26] evaluated mutations and clinical presentation in 22 CGD patients with $p22^{phox}$ deficiency. The most common clinical signs were lymphadenitis (68.1%), abscesses (59%), pneumonia (50%), osteomyelitis (27%), Aspergillosis (18.2%), aphthous lesions (14%), and urinary tract infections (UTI) (14%), observed over time in all 22 patients. Eighteen patients had received the Bacillus Calmette-Guerin (BCG) vaccine and, as a result, 6 were affected by BCGitis and 7 by BCGosis. In addition, *CYBA* gene mutational analysis determined 12 different mutations, including 3 that were novel. These mutations are described in Table 1. Teimourian et al. [27] described 8 CGD patients (6 males and 2 females), all with a $p22^{phox}$ deficiency. Direct sequencing of *CYBA* showed 6 different novel mutations. The characteristics of these 8 patients, along with the precise mutations, are listed in Table 1.

XL-CGD is the other form of CGD in Iran and several cases have been reported. Rezvani et al. [28] published the first report of a 4-year-old male patient with XL-CGD with a stop mutation in the *CYBB* gene in exon 8. This patient also presented with a mutation in the *CYBB* promoter region. Other cases are described in detail in Table

Table 1. Characterization of 65 Iranian CGD patients

No.	Gender	Age	Clinical features	CGD subtype	Gene	Mutation	Nucleotide chain	Protein change	Ref.
1	F	6.5 years	Axilliary lymphadenopathy, BCGitis, hepatomegaly, hepatitis, and meningitis	AR ($p67^{phox}$)	*NCF2*	nonsense (homo-zygous)	exon 4, c.304C>T	p.Arg102Ter	[25]
2	M	9 years	Liver abscess and fever, abscessified lymphadenopathies in the neck	AR ($p67^{phox}$)	*NCF2*	ca deletion (homo-zygous)	exon 13, c.1038_1039delCA	p.Ser347CysfsTer33	[25]
3	F	4.5 years	Hand-swelling, wrist arthritis, severe diarrhea, and vomiting	AR ($p67^{phox}$)	*NCF2*	ca deletion (homo-zygous)	exon 13, c. 1038-1039delCA	p.Ser347CysfsTer33 same family	[25]
4	F	6 years	UTI, septicemia, recurrent osteomyelitis, and septic arthritis	AR ($p22^{phox}$)	*CYBA*	missense	exon 4, c.269G>A	p.Arg90Gln	[26]
5	M	18 years	BCGitis, recurrent oral aphthous lesions, chronic face and nose ulcers, recurrent pneumonia, soft-tissue infections of upper and lower limbs, osteomyelitis, and submandibular salivary gland abscess	AR ($p22^{phox}$)	*CYBA*	missense	exon 3, c.136G>A	p.Gly46Ser	[26]
6	M	3 years	Cervical lymphadenitis, liver abscesses, and pneumonia	AR ($p22^{phox}$)	*CYBA*	deletion	exon 3, c.174delG	p.Arg59fsTer15	[26]
7	F	8 months	Severe diarrhea and UTI	AR ($p22^{phox}$)	*CYBA*	deletion	exons 3–5, large deletion	p.Ile43MetfsTer66	[26]
8	F	6 years	Recurrent axillary and parotid lymphadenitis, recurrent pneumonia, and recurrent pyelonephritis	AR ($p22^{phox}$)	*CYBA*	deletion	exons 3–5, large deletion	same family	[26]
9	M	2 months	Recurrent otitis media, UTI, pneumonia, submandibular abscess, liver abscess, axillary lymphadenitis, and septic arthritis	AR ($p22^{phox}$)	*CYBA*	deletion	exons 3–5, large deletion	same family	[26]
10	M	8 years	Axillary and cervical lymphadenitis which eveloped into an abscess, submandibular abscess, and pneumonia	AR ($p22^{phox}$)	*CYBA*	deletion	exons 3–5, large deletion	same family	[26]
11	M	7 years	Recurrent abscess and aspergillosis	AR ($p22^{phox}$)	*CYBA*	deletion	exon 6, c.385_388delGAGC	p.Glu129SerfsTer61	[26]
12	F	5 months	Recurrent abscess and cervical osteomyelitis	AR ($p22^{phox}$)	*CYBA*	deletion	exon 6, c.385_388delGAGC	p.Glu129SerfsTer61 same family	[26]
13	F	20 days	Cervical abscess and BCGosis	AR ($p22^{phox}$)	*CYBA*	deletion	exon 1, deletion	–	[26]
14	F	6 months	BCGosis, submandibular and postauricular ulcers, and pulmonary abscess	AR ($p22^{phox}$)	*CYBA*	deletion	exon 1, deletion	–	[26]
15	M	28 years	TB, cervical and abdominal abscess, recurrent oral and genital aphthous lesions, pneumonia, and liver abscess	AR ($p22^{phox}$)	*CYBA*	missense	exon 6, c.371C>T	p.Ala124Val	[26]
16	M	21 years	Pneumonia, oral aphthous lesions, and BCGosis	AR ($p22^{phox}$)	*CYBA*	missense	exon 6, c.371C>T	p.Ala124Val same family	[26]
17	F	3 years	BCGosis and paronychia	AR ($p22^{phox}$)	*CYBA*	missense	exon 6, c.371C>T	p.Ala124Val same family	[26]
18	M	1.5 years	Recurrent pneumonia, recurrent abscess (skin, cervical, axillary, pulmonary, and intestinal), osteomyelitis, and aspergillosis	AR ($p22^{phox}$)	*CYBA*	splice site	intron 5, c.369+1G>A	exon 5 deleted	[26]
19	M	40 days	Aspergillosis, axillary and cervical abscess, anal abscess, osteomyelitis, brain abscess, pulmonary abscess, liver abscess, and pyelonephritis	AR ($p22^{phox}$)	*CYBA*	splice site	intron 5, c.369+1G>A	exon 5 deleted? same family	[26]
20	F	3 months	Lymphadenitis, pneumonia, and osteomyeliti	AR ($p22^{phox}$)	*CYBA*	nonsense	exon 6, c.388C>T	p.Gln130Ter	[26]
21	F	3.5 years	BCGosis, aspergillosis and axillary skin abscess	AR ($p22^{phox}$)	*CYBA*	splice site	intron 4, c.287+1G>A	exon 4 deleted?	[26]
22	M	4 months	Axillary abscess (BCGitis) and pneumonia	AR ($p22^{phox}$)	*CYBA*	missense	exon 4, c.269G>A	p.Arg90Gln	[26]
23	M	20 years	Pneumonia, pulmonary abscess, and oral ulcers	AR ($p22^{phox}$)	*CYBA*	missense	exon 4, c.269G>A	p.Arg90Gln	[26]
24	M	3.5 years	BCGosis	AR ($p22^{phox}$)	*CYBA*	missense	exon 6, c.373G>A	p.Ala125Thr	[26]
25	F	1 year	Recurrent pneumonia and fever	AR ($p22^{phox}$)	*CYBA*	missense	exon 2, c.70G>A	p.Gly24Arg	[26]
26	M	3 years	Multiple liver abscesses and cervical lymphadenitis	AR ($p22^{phox}$)	*CYBA*	deletion (homo-zygous)	exon 3, c.174delG	p.Arg59GlyfsTer15	[27]
27	M	4 years	Recurrent pneumonia, cutaneous abscesses, and inguinal adenopathies	AR ($p22^{phox}$)	*CYBA*	deletion (homo-zygous)	exon 4, c.223delG	p.Ala75ProfsTer3	[27]
28	F	6 years	Recurrent multiple lymphadenitis	AR ($p22^{phox}$)	*CYBA*	gross deletion (homo-zygous)	encompassing exons 3–5	p.Ile43MetfsTer66	[27]
29	F	8 years	Right axillary adenitis following BCG vaccination and liver abscess	AR ($p22^{phox}$)	*CYBA*	deletion (homo-zygous)	exon 6, c.385_388delGAGC	p.Glu129SerfsTer61	[27]
30	M	6 years	Chronic otitis media, recurrent skin infections, diarrhea, and leg abscess	AR ($p22^{phox}$)	*CYBA*	deletion (homo-zygous)	exon 6, c.385_388delGAGC	p.Glu129SerfsTer61 same family	[27]
31	M	13 years	Pneumonia, right lower lobe fungal abscess, and draining to the chest wall	AR ($p22^{phox}$)	*CYBA*	splice site (homo-zygous)	intron 5 c.369+1G>A	exon 5 deleted	[27]
32	M	11 years	Recurrent diarrhea, recurrent skin infections, liver abscess and pneumonia, fungal endocarditis, and heart failure	AR ($p22^{phox}$)	*CYBA*	splice site (homo-zygous)	intron 5 c.369+1G>A	exon 5 deleted	[27]
33	M	20 years	Pneumonia, liver abscesses, and recurrent infections	AR ($p22^{phox}$)	*CYBA*	missense (homo-zygous)	exon 6, c.373G>A	p.Ala125Thr	[27]
34	M	26 years	Weight loss, fever, hepatosplenomegaly and coughing, lymphadenopathy, and pulmonary sarcoidosis	AR ($p47^{phox}$)	*NCF1*	deletion (homo-zygous)	exon 2, c.75_76delGT	p.Tyr26HisfsTer26	[68]
35	M	4 years	Recurrent episodes of bacterial infection	XL ($gp91^{phox}$)	*CYBB*	nonsense	exon 8, c.868C>T	p.Arg290Ter	[28]

Table 1 (continued)

No.	Gender	Age	Clinical features	CGD subtype	Gene	Mutation	Nucleotide chain	Protein change	Ref.
36	M	5 years	Recurrent diarrhea	XL ($gp91^{phox}$)	*CYBB*	nonsense (hemizygous)	exon 10, c.1272G>A	p.Trp424Ter	[29]
37	M	4 years	Skin and liver abscesses	XL ($gp91^{phox}$)	*CYBB*	nonsense	exon 7, c.676C>T	p.Arg226Ter	[29]
38	M	3 years	Axillary and cervical lymphadenitis following BCG vaccination, pneumonia	XL ($gp91^{phox}$)	*CYBB*	nonsense (hemizygous)	exon 10, c.1272G>A	p.Trp424Ter	[29]
39	M	8 years	BCG adenitis, perianal abscess, and cutaneous tuberculosis	XL ($gp91^{phox}$)	*CYBB*	deletion	exon 7, c.703_704delAG	p.Ser235PhefsTer5	[29]
40	M	7 years	Recurrent skin and pulmonary infections, brain abscess	XL ($gp91^{phox}$)	*CYBB*	nonsense	exon 3, c.217C>T	p.Arg73Ter	[29]
41	M	6 years	recurrent lymphadenitis, BCG axillary lymphadenitis, and pulmonary aspergillosis	XL ($gp91^{phox}$)	*CYBB*	nonsense	exon 8, c.868C>T	p.Arg290Ter	[29]
42	M	8 years	Osteomyelitis, pneumonia, liver abscess, and fungal infection	XL ($gp91^{phox}$)	*CYBB*	nonsense	exon 4, 271C>T	p.Arg91Ter	[29]
43	M	2 years	Right axillary and supraclavicular BCG adenitis, diarrhea	XL ($gp91^{phox}$)	*CYBB*	nonsense	exon 9, c.1011G>A	p.Trp337Ter	[29]
44	M	4 years	Subauricular lymphadenopathy, neck mass, and axillary lymphadenopathy	XL ($gp91^{phox}$)	*CYBB*	nonsense	exon 8, c.868C>T	p.Arg290Ter	[29]
45	M	9 years	Osteomyelitis, lymphadenitis, and gastric pyloric stenosis	XL ($gp91^{phox}$)	*CYBB*	nonsense (hemizygous)	exon 8, c.810G>A	p.Trp270Ter-novel	[29]
46	M	1 year	Cervical and axillary adenopathy	XL ($gp91^{phox}$)	*CYBB*	splice site	exon 9, c.1150_1151delAAGT	exon 9 deleted	[29]
47	M	4 years	Fever, abdominal pain, axillary lymphadenopathy, recurrent lymphadenitis, splenomegaly, and hepatomegaly	XL ($gp91^{phox}$)	*CYBB*	deletion	exon 4, c.316delT	p.Trp106GlyfsTer1	[31]
48	M	7 months	Lymphadenopathy and an abscess of the neck lymph nodes	XL ($gp91^{phox}$)	*CYBB*	nonsense	exon 3, c.271C>T	p.Arg91Ter	[30]
49	M	1 year	Diarrhea and prolonged fever	XL ($gp91^{phox}$)	*CYBB*	nonsense	exon 3, c.271C>T	p.Arg91Ter same family	[30]
50	M	3 months	Fungal pneumonia, osteomyelitis, and axillary lymphadenopathy	XL ($gp91^{phox}$)	*CYBB*	nonsense	exon 5, c.448G>T	p.Glu150Ter	[30]
51	M	6 months	Fever and axillary lymphadenopathy due to BCGitis	XL ($gp91^{phox}$)	*CYBB*	missense	exon 9, c.1012C>G	p.His338Asp	[30]
52	M	2.5 years	Fever and axillary lymphadenopathy	XL ($gp91^{phox}$)	*CYBB*	deletion	exon 3, c.316delT	p.Trp106Glyfs Ter1novel	[30]
53	M	6 months	Abscessified neck adenopathy and otitis media	XL ($gp91^{phox}$)	*CYBB*	missense	exon 3, c.334T>C	p.Ser112Pro	[30]
54	M	3 years	Fever and pneumonia	XL ($gp91^{phox}$)	*CYBB*	deletion	exons 3–5, large deletion	exons 3–5 deleted	[30]
55	M	13 months	Perianal abscess, fistula, and BCGitis	XL ($gp91^{phox}$)	*CYBB*	nonsense	exon 5, c.469C>T	p.Arg157Ter	[30]
56	M	8 months	Fever and lymphadenopathy	XL ($gp91^{phox}$)	*CYBB*	deletion	exon 1, large deletion	exon 1 deleted	[30]
57	M	3 years	BCG dissemination, otitis media, perianal abscess, pneumonia, and pulmonary abscess	XL ($gp91^{phox}$)	*CYBB*	nonsense	exon 4, c.388C>T	p.Arg130Ter	[30]

XLR, X-linked recessive; AR, autosomal recessive. This Table does not show the actual percentage of the different types of CGD in Iran and only describes some of the reported cases and mutated genes.

1. Teimourian et al. [29] analyzed the clinical features and molecular diagnosis of 11 XL-CGD patients suffering from recurrent severe infections. DNA analysis of 13 exons and the promoter region of the *CYBB* gene revealed 9 different nonsense mutations, 2 of which were novel and are described in Table 1. Teimourian et al. [30] also reported 4 novel mutations in 10 XL-CGD patients, described in Table 1. Moreover, one 4-year-old Iranian boy with XL-CGD has been reported to have a novel deletion in exon 4 in the *CYBB* gene [31].

Rezaei et al. [32] examined the frequency of consanguineous marriages in families with PID. The records of 515 Iranian PID patients (324 men and 191 women) seen over a 25-year period (1980–2005) were reviewed. Eighty-nine of these patients (17%) were suffering from CGD, and consanguineous marriages were reported in 68 cases (76%). Overall, whilst the overall incidence of consanguineous marriages in Iran was 39%, the incidence rose to 66% for those with PIDs. In patients with defects of phagocytic function, the incidence of consanguinity was 73%.

Clinical Evidence

Clinical manifestations and disease severity are different between p47 deficiency and the other forms of CGD; p47 deficiency (A47 CGD) has a milder course of disease whilst p22 and p67 deficiency are as serious as XL-CGD [33].

Table 2. Clinical features of Iranian CGD patients expressed as a percentage of patients

	Movahedi et al. [17], 2004	Fattahi et al. [11], 2011
Total number of patients	41	93
Lymphadenopathy	76	66
Pulmonary involvement	66	57
Pneumonia	49	–
Lung tuberculosis	32	–
Pulmonary aspergillosis	10	–
Pulmonary abscess	7	–
Hydatid cyst	2	–
Bronchiectasis	2	–
Skin involvement	63	54
Subcutaneous abscess	54	–
Cellulitis	30	–
Skin fistula	7	–
Gastrointestinal disorders	56	33
Chronic diarrhea	27	–
Oral candidiasis	17	–
Hepatitis	12	–
Hepatic abscess	10	29
Gastric outlet obstruction	5	–
BCG complications		
BCGitis	–	56
BCGosis	23	–
Failure to thrive	15	–
Bone and joint infections	30	–
Osteomyelitis	22	30
Septic arthritis	20	–
Upper respiratory tract	27	–
Otitis media	24	8
Acute sinusitis	12	–
Mastoiditis	2	–
Central nervous system	2	11
Genitourinary infections	–	15
Vision	–	5
Cardiovascular system	–	4

The prevalence of symptoms and the diagnosis of XL-CGD occur at an earlier age than with A47 CGD. The most common clinical feature in XL-CGD patients is lymphadenopathy (66%) followed by pulmonary (57%) and skin involvement [14, 15, 33]. Fattahi et al. [11] showed that XL-CGD patients have more severe infectious manifestations than A47-CGD patients and that AR-CGD is more prevalent in females (57%) than males (43%). The severity of the disease was greater in patients with A22 CGD, compared to other forms of AR-CGD, whilst the age of diagnosis was earlier. A summary of the clinical features and presenting complications in Iranian CGD patients is provided in Table 2 [17].

The clinical, radiological, and pathologicial features of 13 children with CGD (10 males and 3 females) in Iran over a 6-year period have been reported [26]. The most common manifestations seen were pulmonary infections, skin involvement, and lymphadenopathy. *Aspergillus* spp. were detected in the pulmonary secretions of 38% of these patients. In contrast, hypergammaglobulinemia, hepatomegaly, and splenomegaly were diagnosed in 80% of patients with CGD in southern Iran [34].

In a study on 32 patients (20 males and 12 females) with PID referred to Mofid Children's Hospital over a 10-year period, CGD was the most frequent PID seen (22%) [35]. The infections observed in the CGD patients included pneumonia, lymphadenitis, inguinal and perianal abscesses, lung abscess, BCGosis, peritonitis, mouth ulcers, sinusitis, mastoiditis, and respiratory infections. *S. aureus*, MTB, and *Aspergillus*, *Enterobacter*, and *Enterococcus* spp. were the most common pathogenic microorganisms reported in these patients.

Infections in Iranian CGD Patients

Patients with CGD are susceptible to a variety of bacterial and fungal infections. Some of the most important infectious agents affecting CGD patients in Iran are summarized in Table 3.

S. aureus

S. aureus is one of the most common pathogens in CGD patients. Farhoudi et al. [36] reviewed the medical course of an 8-year-old girl with AR-CGD who had initially presented with dermal staphylococcal abscesses at the age of 3 months. She suffered from several episodes of *Staphylococcus*, *Salmonella*, and *Aspergillus* spp. infection with pulmonary involvement. Esfandbod and Kabootari [37] reported a 12-year-old boy with CGD who had suffered from recurrent pneumonia since the age of 5 years and other complications such as finger-clubbing, splenomegaly, and massive lymphadenopathy in the cervical, axillary, and preauricular areas. Blood culture confirmed the presence of *S. aureus* infection. Finally, Afrough et al. [38] described a 24-day-old male CGD patient with vesiculopustular rash in the periorbita, genitalia, foot, and sacroiliac regions. Gram-positive cocci were seen in a direct smear from skin lesions and culture was positive for *S. aureus*.

Mycobacterium *spp.*

MTB is an intracellular pathogen that can infect monocytic cells, including macrophages and dendritic

Table 3. Overview of infecting pathogens in Iranian CGD patients

	Movahedi et al. [17], 2004	Mamishi et al. [54], 2005	Teimourian et al. [27], 2008	Fattahi et al. [11], 2011	Bassiri-Jahromi and Doostkam [53], 2012	Babaie et al. [35], 2017
Total number of patients	41	7	8	93	12	7
Infecting organism[a]						
Staphyloccocus spp.	–	–	3	7	–	3
Escherichia coli	1	–	–	2	–	–
Salmonella spp.	–	–	3	6	–	–
Serratia marcescens	–	–	–	1	–	–
Pseudomonas spp.	–	–	–	1	–	–
Mycobacterium spp.	–	–	–	18	–	2
Nocardia spp.	–	–	–	1	–	–
Shigella	–	–	1	2	–	–
Bacillus subtilis	–	–	1	1	–	–
Klebsiella	–	–	–	2	–	–
Enterobacter	–	–	–	–	–	1
Enterococcus	–	–	–	–	–	1
Proteus mirabilis	–	–	–	1	–	–
Aspergillus spp.	4	7	2	26	3	1
Candida spp.	–	–	–	2	–	–
Fusarium	–	–	–	–	2	–

[a] Values express the number of patients infected by each organism in each of the 6 studies.

cells, resulting in the formation of granulomas [39]. Nontuberculous mycobacteria (NTM) refer to all *Mycobacterium* spp. which may cause human disease but do not cause tuberculosis [40]. NADPH oxidase is an important component of human immunological defense against mycobacterial infection, and reduced ROS-induced killing increases the survival of MTB. Soroush et al. [41] first described in Iran a heterozygous carrier of CGD combined with MTB and NTM, whilst Khotaei et al. [42] described a 3-year-old girl with a 3-week fever and chills who was diagnosed with tuberculous meningitis and CGD.

Immunodeficient patients are susceptible to mycobacterial disease after receiving the BCG vaccine (derived from *Mycobacterium bovis*) [43, 44]. This can lead to lymphadenitis that can result in BCGitis (local disease) and eventually BCGosis (disseminated disease) [45]. Osteomyelitis and disseminated BCG infection are rare adverse reactions to the BCG vaccine seen in immunodeficient diseases such as CGD. Rezai et al. [46] described 15 children in Iran with disseminated BCG infection, 9 of whom had PID, including 2 with CGD. Furthermore, in a retrospective study, 1/17 patients with BCG complications was suffering from CGD [47] and 1/11 patients with BCGosis was found to have CGD [48].

Nocardia *and* Actinomyces

Nocardia and *Actinomyces* spp. are important infectious agents in CGD patients. *Nocardia* can lead to bone and brain disease and lymph node involvement in both immunocompetent and immunocompromised human hosts. *Actinomyces* spp. are commensal oral flora and become pathogenic in only a few conditions, such as CGD, where oral mucosal injury can allow the bacteria to penetrate the mucous barrier [49, 50]. Between 2001 and 2008, 2/12 CGD patients were found to be infected with *Nocardia* and *Actinomyces*: 1 a 14-year-old male who suffered from osteomyelitis due to *Nocardia asteroides*, and the other a 12-year-old girl who presented with a painful swelling on the upper right neck and fever and who was culture-positive for *Actinomyces* [51]. *Actinomyces* usually induces pulmonary and abdominal disease manifestations [50].

Aspergillosis

Aspergillosis is a key infectious agent in CGD patients. The incidence of aspergillosis in the USA was reported to be 78% of all fungal infections in 245 cases of CGD [52], with *Aspergillus fumigatus* being the major cause of invasive aspergillosis [14]. *Aspergillus* can infect the lungs, chest, and bone. For example, Bassiri-Jahromi and Doostkam [53] evaluated 12 CGD patients in Iran (7 males and

5 females) with suspected fungal infection. Fungal infections were diagnosed in 5 patients (41.7%), 3 with *Aspergillus* spp. that affected the bones, lung, and chest, and 2 with *Fusarium* spp. that were detected in the bone and lung. These 2 fungal infections cause life-threatening complications in CGD patients and increase the mortality rate.

Aspergillus was detected in the lung and bones of a 5-year-old boy with CGD who suffered from osteomyelitis of the ribs and hepatic abscess, and with a history of pneumonia and inflammation of the wrists and legs [54]. *Aspergillus* infection was described in a 20-year-old female CGD patient complaining of cough, fever, anorexia, night sweats, and weight loss [55]. Furthermore, Mamishi et al. [56] reported 7 CGD patients with invasive *Aspergillus* spp. (5 with *A. fumigatus*, 1 with *A. flavus*, and 1 with an unknown species) which had infected the lung, liver, chest, and brain.

Excessive inflammation due to *Aspergillus* infection can, in rare cases, lead to a necrotic mass in the CGD patient's airway, as demonstrated in a 19-year-old female who complained of productive cough and massive hemoptysis. Chest X-ray, CT scan, and bronchoscopy were performed, and showed a necrotic obstructive mass at the right middle bronchus [57]. In addition, Movahedi et al. [58] described a 3.5-year-old girl with an axillary mass, progressing toward the anterior chest wall. An examination of aspirated fluid from the chest abscesses showed the presence of *Aspergillus*.

Fusarium

Fusarium infection is a rare disease that is often seen in immunocompromised patients. The disseminated form of this infection occurs in patients with prolonged neutropenia and acute leukemia. Skin lesions that occur commonly in the trunk and face are the most common complications of the infection [59]. Mansoory et al. [60] described a 54-year-old female CGD patient who had suffered from skin lesions for 3 years from which *Fusarium solani* was cultured.

Paecilomyces

Paecilomyces spp. rarely causes infections in humans. We described the first *Paecilomyces formosus* infection in an 18-year-old female CGD patient complaining of cough, dyspnea, and fever. She had a history of thrombocytopenia (from the age of 9 years), and a chest X-ray showed diffuse pulmonary infiltrations. Culturing of a bronchoscopy specimen showed the presence of *P. formosus* [61] along with *Botryotrichum* infection [62].

Organ Involvement in CGD Patients

Pulmonary Involvement

The lungs are the most common site of infection in CGD patients [2, 14, 15, 63, 64]. Pulmonary CT scans of 24 CGD patients collected over a 10-year period (2001–2012) showed consolidation in in the upper lobes of 19 (79%) patients. Small pulmonary nodules (more common in the right than in the left lung) were present (58%), as was mediastinal lymphadenopathy (38%), and pleural thickening (25%). In contrast, unilateral hilar lymphadenopathy, axillary lymphadenopathy, bronchiectasis, abscess formation, pulmonary large nodules or masses, and free pleural effusion were only rarely observed [65].

Tafti et al. [66] described an Iranian family with 8 children, 6 of whom (5 males and 1 female) were diagnosed with CGD, with diffuse sterile granulomatous lesions particularly in the lung. Three children died due to a delayed diagnosis and a lack of proper treatment. Laboratory tests were performed on the 3 other children and on the parents. The parents were healthy and all 3 infected children were asymptomatic. The 3 children were treated and are still alive.

Our own group previously reported a 40-year-old man with a history of granulomatous lesions in the lung, and recurrent abscesses of the skin and soft tissue, who presented with respiratory symptoms. Open-lung biopsy revealed lymphocytic bronchiolitis, and subsequently a diagnosis of CGD was confirmed [67]. Moreover, we also described for the first time, pulmonary *Aspergillus terreus* infection in a 26-year-old man with AR-CGD on long-term corticosteroid treatment. The combination of the molecular characterization of the inherited CGD and the sequencing of fungal DNA enabled the disease-causing agent to be determined and the correct treatment to be instigated [68].

Interstitial lung disease (ILDs) constitute a diverse group of lung diseases with different etiologies that all reduce the ability of the lung to exchange respiratory gases due to an accumulation of inflammatory cells and fibroblasts within the alveolar tissue. The group includes idiopathic pulmonary fibrosis, hypersensitivity pneumonitis, sarcoidosis, and connective tissue disease-associated ILD, and these are all are associated with high morbidity and mortality [69]. ILD is a rare complication in CGD patients, and the number of reports in the field is limited. Moghtaderi et al. [70] described an 11-year-old patient with CGD who suffered from chronic cough, dyspnea, and recurrent lower respiratory tract infections. Pulmonary function tests and CT scan revealed the presence of ILD.

The Gastrointestinal Tract and Skin

These organs are exposed to many pathogenic organisms and contain a large population of reticuloendothelial cells, which are important sites of infection in CGD patients [17]. Movahedi et al. [71] evaluated the gastrointestinal manifestations of CGD in 57 patients (38 males and 19 females) over a 24-year period (1980–2004). Twenty-four cases (42%) were diagnosed with gastrointestinal manifestations, with the most common complication being diarrhea detected in 12 cases (21%). Other complications were (in descending order) oral candidiasis (12%), hepatitis (9%), hepatic abscess (7%), and gastric-outlet obstruction (4%). Failure to thrive was detected in 6 patients (11%) and 4 patients died (7%). Over 50% of the patients showed symptoms by the age of 5 months, whilst the age of the onset of symptoms in the other patients varied from 2 to 14 years.

Similarly, Sedighipour et al. [72] investigated skin manifestations in 52 children with CGD over 2 years. The most common complaint was lymphadenopathy which was reported in 65% of patients. Twenty-nine patients (55%) suffered from frequent skin or soft-tissue abscesses, and the presence of a skin abscess was the first manifestation in 11% of patients. Carbuncles were seen in a further 10 patients (19%) and, overall, skin involvement was reported in 39 (75%) of the patients.

Amyloidosis

Amyloidosis is a clinical disorder caused by the extracellular and/or intracellular deposition of insoluble abnormal amyloid fibrils that alter the normal function of tissues [73]. This condition is rarely seen in CGD patients. However, Darougar et al. [74] reported a 22-year-old man who was hospitalized due to frequent respiratory infections and distress. Chest tomography and pulmonary biopsy indicated CGD with lung involvement, which was confirmed by NBT testing. A kidney biopsy was performed, as the patient suffered from continuous proteinuria due to the amyloidosis. This suggests that amyloidosis should be considered as an inflammatory condition in CGD patients with proteinuria.

Hepatic Abscess

Hepatic abscesses are a known complication of CGD and one-third of hepatic abscesses in children are caused by CGD. Mahlouji et al. [75] reported a 2.5-year-old female with abdominal pain that did not respond to antibiotics. Two masses in the liver were detected by abdominal CT scan, and subsequent pathological, microbiological, NBT, and DHR tests indicated that these abscesses resulted from underlying CGD.

Juvenile Idiopathic Arthritis

Juvenile idiopathic arthritis (JIA) is a heterogenous group of diseases associated with chronic arthritis in children or adolescents <16 years, and it persists for at least 6 weeks [76]. JIA is rare in CGD patients, and only 1 case has been reported in Iran. This was a young boy with CGD who suffered from JIA with pelvic pain at the age of 2 years with CGD symptoms including sinusitis, cervical lymphadenitis, and pneumonia evident by 6 years of age [77].

CGD and Autoimmunity

Although initially it seems improbable that immunodeficiency and autoimmunity can occur simultaneously, these 2 conditions are often linked [78, 79]. Due to the presence of frequent infections, patients with CGD produce large quantities of immunoglobulins, including autoantibodies. Approximately 15% of children with CGD have autoimmune diseases such as discoid lupus erythematosus and Crohn's disease [79]. In a study on 93 CGD patients by Fattahi et al. [11], autoimmune complications were reported in 15 (16.1%), including systemic lupus erythematosus, discoid lupus erythematosus, autoimmune enteropathy, rheumatoid arthritis, lupus-like erythmatosus lesions, idiopathic thrombocytopenia, chorioretinitis, and selective IgA deficiency. Moreover, Shamsian et al. [80] described a 10-year-old Iranian girl with AR-CGD with a deficiency in $p47^{phox}$ who also suffered from selective IgA deficiency. She also developed the autoimmune condition refractory immune thrombocytopenic purpura.

Conclusion and Future Perspectives

Defective NADPH oxidase function in phagocytes leads to CGD, a PID. The prevalence of CGD in Iran is increasing and there is an increasing awareness of the increased risk in children from consanguineous marriages. Many studies have reported the clinical problems, the response to existing therapies, the genetic aspects of CGD, and its diagnosis. Overall, hereditary AR-CGD is more predominant in Iran rather than the XL-CGD form which is prevalent in most other countries. This likely reflects the high incidence of consanguineous marriages in Iran.

Most of the existing strategies for controlling the disease can be implemented in Iran due to early detection, particularly as the clinical features of CGD are well known. Pulmonary inflammatory problems, pneumonia,

and skin problems are common in these patients; however, further studies are necessary to explore the link between genotype and phenotype of disease and the specific organ involvement. Better understanding this correlation will provide improved treatments for these patients. Overall, bacterial infections are reported less frequently in CGD patients in Iran than in other regions. This may reflect a lack of detection of the bacterial species or possibly a greater exposure to environmental fungal species. It is necessary to mention that any remaining NADPH oxidase activity in the patients' neutrophils is crucial for expectations about clinical course and survival [33, 81].

Disclosure Statement

The authors have no conflicts of interest to declare.

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