Review Article

Chronic Granulomatous Disease (CGD): Epidemiology, Pathogenesis, Clinical Phenotype, Diagnosis, Prognosis and Management

Farimah Fayyaz[1], Kiavash Khashayar[2], Matineh Nirouei[2], Zahra Tavakol[3,4], Marzieh Tavakol[5]

[1] Student Research Committee, Alborz University of Medical Sciences, Karaj, Iran

[2] Alborz University of Medical Sciences, Karaj, Iran

[3] Department of Sports and Exercise Medicine, Imam Khomeini Complex Hospital, Tehran University of Medical Sciences, Tehran, Iran

[4] Sports Medicine Research Center, Neuroscience Institute, Tehran University of Medical Sciences, Tehran, Iran

[5] Non-Communicable Diseases Research Center, Alborz University of Medical Sciences, Karaj, Iran

Abstract

Chronic granulomatous disease (CGD) is a relatively rare inborn error of immune system caused by some defects in the phagocyte nicotinamide adenine dinucleotide phosphate (NADPH) oxidase complex, which leads to the impaired production of reactive oxygen species (ROS) and ineffective function of phagocyte. Moreover, genetic defects of any one of proteinaceous components of NADPH oxidase complex results in CGD. The most common type of CGD (65-70%) is caused by X-linked mutations in the CYBB gene encoding gp91phox, followed by autosomal recessive mutations in the NCF1, NCF2, CYBA and NCF4 genes, which encode p47phox, p67phox, p22phox, and p40phox, respectively. In this regard, Dihydrorhodamine (DHR) 123 oxidation and nitroblue tetrazolium (NBT) tests are both used for the diagnosis of CGD that should be confirmed by genetic testing at first. CGD patients generally present with recurrent infections caused by uncommon pathogens such as aspergillus, staphylococcus aureus, burkholderia cepacia, serratia marcescens, Aspergillus species, and nocardia. They usually manifest with deep seated abscess formation, genitourinary and gastrointestinal granuloma development, autoimmunity, and malignancy. Apart from comprehensive treatment of acute infections, the management of CGD is performed based on reducing bacterial and fungal infections as well as minimizing the inflammatory symptoms. Also, antibiotics, anti-fungal, and IFN-γ are used for prophylaxis. Allogeneic hematopoietic stem cell transplantation from a human leucocyte antigen identical donor is currently considered as the only proven curative treatment for CGD. Accordingly, gene therapy is known as an alternative novel therapeutic approach in near future.

Keywords: Chronic Granulomatous Disease (CGD), Dihydrorhodamine (DHR) test, Nitroblue tetrazolium (NBT) test

* Corresponding author: Marzieh Tavakol

1. Non-Communicable Diseases Research Center, Alborz University of Medical Sciences, Karaj,

E-mail: marziyeh.tavakol@gmail.com

Introduction

Chronic granulomatous disease (CGD) is a relatively rare hereditary immunodeficiency disorder (1:200,000 to 1:250,000 of live births in the United States and Europe) caused by some defects in the phagocyte nicotinamide adenine dinucleotide phosphate (NADPH) oxidase complex leading to the impaired production of reactive oxygen species (ROS) and ineffective pathogen removal (1, 2). NADPH oxidase complex is composed of 5 proteins (gp91^{phox}, p22^{phox}, p47^{phox}, p67^{phox}, and p40^{phox}) and stabilized by a sixth protein, called EROS (that is essential for reactive oxygen species) (3). Genetic defects of any one of these proteins results in CGD. Mutations in the CYBB gene encoding gp91^{phox} are X-linked, which affect about 65-70% of cases. Also, the mutations in the NCF1, NCF2, CYBA and NCF4 genes encoding p47^{phox}, p67^{phox}, p22^{phox}, and p40^{phox}, are autosomal recessive respectively (4). The tests used for the diagnosis of CGD are dihydrorhodamine (DHR) 123 oxidation and nitroblue tetrazolium (NBT) that should be confirmed by genetic testing at first (5).

Although CGD can present at any age, the majority of cases are diagnosed before the age of 5 years old (6). This disease is characterized by recurrent, severe bacterial and fungal infections, and excessive inflammation like granuloma formation, which is the most prominent one in gastrointestinal and genitourinary tracts. Accordingly, these infections are mostly caused by catalase positive organisms and the common organisms including aspergillus, staphylococcus aureus, burkholderia cepacia, serratia marcescens, and nocardia (7). Notably, the most affected site usually is the lung. Formerly, most CGD patients did not get through their first decade of life. However, currently, due to the use of prophylactic antimicrobial agents and immediate diagnosis and treatment of infections, patients live up to the end of their first decade at least. Therefore, new concerning complications such as inflammatory and autoimmune disorders of this disease, have come to light.

In this review, we aimed to clarify the immune-based manifestations and complications of CGD as well as summarizing the pathogenesis, diagnosis, management, and prognosis of this disease.

Epidemiology

As a typical primary immunodeficiency disorder of early years of life, CGD manifestations generally occur over the first five years of the patients' life. Although it could manifest at any age and in milder forms, in a subject who have some NADPH oxidase enzyme activity remained, it may present in adulthood. It has been shown that the annual incidence of CGD is approximately as twice as the number of severe combined immunodeficiency disorders. According to the fact that CGD is more prevalent in some populations such as Arab population of Israel dwellers, which is estimated to be 1.5 in 100,000 live births compared to 1 in 200,000-250,000 live births among American and European citizens, it is deemed that the incidence of CGD can be affected by ethnic background. Given the main type of inheritance, which is X-linked, there is a gender difference in patients, in a way that men are affected approximately twofold more than women (8-10). The most prevalent genetic type is X-linked followed by autosomal recessive form, among which p47^{phox} defect is known as the most frequent one. Nonetheless, it is not universal and the frequency pattern is different in those countries that have high rates of consanguinity. Although the survival rate until the age of 7 years old used to be less than 40% in the past (about 60 years ago), the patients' lifespan has considerably increased over the last 10 years, and currently more than 50% of patients at least live up to 25 years from the time of diagnosis (11, 12). Except the defective gene, the type and location of the mutation are also important in the survival rate. Patients with X-linked forms mostly present earlier and with more severe clinical patterns as well as less duration of life (9, 10).

Pathogenesis of CGD

The NADPH oxidase complex (NOX2) is composed of the membrane-bound heterodimer (p22^{phox} and gp91^{phox}) and 3 cytosolic subunits (p47^{phox}, p67^{phox}, and p40^{phox}), which is also stabilized by another protein named EROS. After phagocytosis, cytosolic subunits translocate into membrane-bound component. Afterward, the activated NADPH oxidase complex can produce superoxide metabolites. Correspondingly, this process is called respiratory burst. Reactive oxygen species (ROS) besides the destruction of ingested microorganisms are able to activate proteases (3, 13, 14). Defective respiratory burst could be resulted from the absence of EROS which is needed for p22^{phox} and gp91^{phox} stabilization, which is caused by homozygous mutation of CYBC1 (15).

In CGD, there is a genetic defect in any one of the components of NADPH oxidase complex. Genes encoding of these proteins are as follows: CYBB gene on Xp21.1-p11.4 (gp91phox); NCF1 on 7q11.23 (p47phox); and CYBA on 16q24.3 (p22phox), NCF2 (p67phox), and NCF4 (p40phox). CYBB mutations are inherited in an X-linked manner, and are also known as the most common causes of CGD. Notably, all the other mutations are inherited in an autosomal recessive fashion (16).

Clinical manifestations in patients with (CGD)

Pulmonary diseases

The most frequently affected site in CGD is recognized to be the lung. The pulmonary manifestations are also observed in two-thirds of adult with CGD (17). It was found that various infectious and inflammatory processes occur during this disease. Notably, one of the major concerns in this regard is pulmonary infection. Particularly invasive fungal infections have the highest morbidity and mortality rates. Also aspergillus fumigatus followed by aspergillus nidulans are the most common pathogens affecting the lungs (7, 18-20). CGD has the highest prevalence rate of invasive aspergillus infection among primary immunodeficiency disorders (21).

Mulch pneumonitis is an emergency presentation of CGD. During mulching, severe exposures may occur to aerosolized fungi. This can consequently lead to respiratory symptoms such as fever, cough, dyspnea, and hypoxia. In a clinical series performed on fulminant mulch pneumonitis, patients had diffuse bilateral infiltrations by passing 3 days from the onset of symptoms. Also, aspergillus pathogens were found in lung biopsy specimens (22). Although the initial symptoms in this disease are similar to viral infections, bacterial pneumonia and hypersensitivity pneumonitis, the failure of treatment and the history of immune defect should guide the clinician to consider some other etiologies. In fact, fulminant mulch pneumonitis at any age in the absence of any known immune deficiency should prompt the consideration of CGD. Therefore, early treatment with antifungal and steroid is critical, because it can prevent death. It is reported that early use of high-dose steroid (1mg/kg/day for 1 week and then tapering) can reduce the acute pulmonary inflammation in these patients (2, 22).

Non-infectious pulmonary events, which are more frequent in the X-linked group of CGD patients, may also involve the lungs in CGD patients (17, 23). Granulomatous lung disease and interstitial pulmonary fibrosis are some of the known inflammatory pulmonary manifestations of CGD (24). In a case series, 40% of these events were indicated to be associated with an infection. Also, it was shown that immune modulator therapy is effective on the consolidations associated with an infection, but pulmonary involvement in interstitial pneumonia persists after performing this therapy (17).

Allergic diseases

Hypersensitive pneumonitis (HP) or extrinsic allergic alveolitis is a respiratory inflammatory reaction that could be considered as a type 2 or 4 hypersensitivity reaction to the inhaled antigens (25, 26). The occurrence of HP in children is rare, which should prompt investigation. More-

over, CGD increases the risk of HP, so it should be ruled out in this setting (27-32). The presentations of HP usually include a history of exposure to a potential inciting antigen, lymphocytosis in bronchoalveolar lavage fluid, negative fungal and bacterial cultures, compatible imaging features, loosely formed granulomas with no central micro-abscesses on lung biopsy, and favorable response to systemic glucocorticoids (27, 30, 31). As indicated previously, HP presentations are not as acute, rapid, and fatal as fulminant mulch pneumonitis and the culture results are negative for Aspergillus (22, 31, 33). Although the mechanism of hyperinflammation in CGD patients is not well understood yet, the decreased inhibition of inflammatory cytokines production due to the reduced ROS still is under investigation (34). The management of HP in CGD patients consists of avoidance of allergen exposure and high-dose steroid or other inflammatory drugs (anti-TNFα, hydroxychloroquine, and thalidomaide). Notably, careful surveillance for infection and antimicrobial prophylaxis in these patients are mandatory (29, 31).

Allergic bronchopulmonary aspergillosis (ABPA) is a hypersensitivity disorder induced by aspergillus antigens that, despite considering to be common amongst asthmatic and cystic fibrosis patients, it rarely occurs in CGD patients (35, 36). Correspondingly, its symptoms include wheezing, productive cough, hemoptysis, low-grade fever, malaise, and fatigue (37). The elevated aspergillis specific IgE, total IgE, aspergillus specific IgG, eosinophilia, and positive skin prick test have also aid clinicians in the diagnosis (38). Positive sputum culture for aspergillus supports the diagnosis; however, it is not specific. In addition, the therapeutic approach to ABPA includes systemic glucocorticoide and antifungal agents (39).

Adverse reactions to BCG vaccination at birth including abscess formation, severe ulcer at the injection site, and swelling and calcification of ipsilateral axillary lymph nodes, may be considered as the first presentations in CGD patients, which should guide the clinician to the underlying disease (31). The attack rate of BCG adverse effects were reported to be 40% and 22% in National Institute of Paediatrics in Mexico and European Experience on CGD, respectively (1, 40).

Autoimmunity

Various studies demonstrated that discoid lupus and systemic lupus erythematous are frequently reported in X-linked CGD female carriers (2, 41). In a case series performed on 19 X-linked female carriers (41), photosensitive skin rashes, mouth ulcers, and joint pain were frequently reported (58%, 42%, and 37%, respectively). On the other hand, the result of anti-nuclear antibody (ANA) was mostly negative. It was suggested that negative serology should not prevent the clinician from starting the treatment, because the symptoms may respond well to it. In another case series (42), Battersby et al. established that there is no clear correlation between the degree of neutrophil function or autoantibodies and the development of SLE manifestations. Although the pathogenesis of this manifestation is not clear yet, there has been studies suggesting that polyclonal hypergammaglobulinemia resulted from the repeated antigenic stimulation of partial phagocyte defect, along with antigenic exposure of damaged host cells, may lead to SLE like manifestations (43). More recently, it was reported that abnormal apoptosis along with the impaired clearance of apoptotic cells in these carriers can result in the increased risk of SLE (44-46). It should be noted that gene polymorphism in encoding molecules of inflammatory responses including mannose binding lectin and Fc gamma receptors, seems to be associated with some autoimmune disorders in CGD (47).

Also, SLE manifestations frequently occur in patients with CGD (2, 48-51). Moreover, the other autoimmune manifestations reported in CGD patients were as follows: idiopathic thrombocytopenia purpura (ITP) (2, 52), myasthenia gravis (2), chorioretinitis (2), glomerulonephritis (53, 54), antiphospholipid syndrome (55), recurrent pericardial

effusion (55, 56), juvenile idiopathic arthritis (55, 57), rheumatoid arthritis (57), IgA nephropathy (55, 58, 59), sarcoidosis (60), and crohn-like inflammatory bowel diseases (61).

Additionally, there are multiple factors associated with autoimmunity in CGD patients. Except the impaired apoptotic clearance, decreased neutrophil apoptosis, increased proinflammatory protein expression, and reduced ROS-mediated inflammasome dampening (45, 62-65), it has been recently revealed that effector regulatory T cells have also decreased in gp91^{phox}- deficient CGD patients (64).

Gastrointestinal Disorders

GI inflammation is considered as one of the main manifestations of CGD, which affects almost half of the patients. Its prevalence among different genotypes of CGD is relatively similar to that was shown in a cohort on CGD patients in France (24). Although in cohort of National Institute of Health (NIH), it was previously reported that the GI involvement was much higher in gp91^{phox} deficiency forms (61). In this regard, the common symptoms were abdominal pain, diarrhea with or without blood, nausea and vomiting, and constipation (61).

One of the most common GI manifestations in CGD patients is a form of inflammatory bowel disease (IBD) similar to Crohn's disease; however, it is a distinct entity. Accordingly, it can be described as a type of colitis that is complicated by fistulae, fissures, and perianal abscesses (61, 66).

Endoscopic examination of CGD patients has revealed that erosions and aphthoid ulcers, particularly in left colon leading to "lead pipe like" appearance, are usually observed in CGD-IBD patients. Despite these chronic inflammatory lesions, GI dysplasia or malignancy was not reported. Upper tract disease also is common among these patients; however, it is not as severe as colitis (67). In several case reports, dysphagia have been reported with some radiographic abnormalities (68-70).

In a study, histopathology of CGD patients with acute colitis was shown to be associated with cryptitis and crypt abscess. Also, chronic colitis was associated with lymphoplasmacytic infiltration in the lamina propria. Moreover, Ulceration, eosinophilic microabscesses, microgranulomas, and pigmented macrophages were also found (71, 72). In another study, the staining of CD68 in colon biopsies, which is expressed by macrophages, was significantly less than that of Crohn's disease patients and normal colon biopsies. Therefore, CD68 could be used as a marker to distinguish CGD-IBD from Crohn's disease (73).

Since CGD patients are susceptible to infections, management and treatment of CGD-IBD are challenging and not well-established yet. So, in this setting, systemic glucocorticoid therapy accompanied with antibacterial and antifungal drugs are often used. Immunomodulatory therapy, including azathioprine, hydroxychloroquine, thalidomide, and cyclosporine can also be used (74-76). It should be noted that, although anti-TNFα is beneficial for closure of fistulae, it is associated with serious infections in CGD patients , so it is not recommended (77). In severe cases or in cases of stricture and fistulizing, surgery or hematopoietic stem cell transplantation should be considered (78).

Liver involvement also is another common GI manifestation of CGD. Many CGD patients suffer from liver abscesses, and unlike pyogenic abscesses, they are multiloculated and possess a thickened pseudocapsule (7). In this regard, a cohort study demonstrated that nonoperative approaches to CGD liver abscesses including steroid and antimicrobial therapies are effective and safe approaches, which also improve liver function (79). Liver dysfunction may also occur due to portal hypertension and nodular regenerative hyperplasia. Non-cirrhotic portal hypertension is an indicator of poor prognosis, which could be evaluated by platelet count decline. Systemic infections, drug-induced liver injury, and repeated liver abscesses may increase the risk of portal hypertension. Also, portal hypertension itself can increase the risk of infection by decreasing bacterial clearance and increasing bacterial translocation (80).

Table 1. Case reports of malignancy in CGD patients in literature.

Author (reference)	Gender	Type of Malignancy	Age of Diagnosis of Malignancy	Age of Diagnosis of CGD	Genetic Defect of CGD
Weel et al. (83)	Male	Retinoblastoma Ocula Dextra	At birth	14 years old	P47^{phox} deficiency (autosomal recessive)
Weel et al. (83)	Female	Malignant Melanoma	26 years old	13 years old	P47^{phox} deficiency (autosomal recessive)
Weel et al. (83)	Male	Rhabdomyosarcoma of the Liver	7 years old		gp91^{phox} deficiency (X-linked)
Geramizadeh et al. (85)	Male	Primary Splenic Hodgkin's Disease	20 years old	-	-
Lugo Reyes et al. (84)	Male	Hodgkin Lymphoma	14 years old	7 years old	gp91^{phox} deficiency (X-linked)
Lugo Reyes et al. (84)	Female	Hodgkin Lymphoma	10 years old	10 years old	P47^{phox} deficiency (autosomal recessive)
Aguilera et al. (87)	Female	Glioblastoma Multiforme	13 years old	2 years old	P67^{phox} deficiency (autosomal recessive)
Wolach et al. (86)	Male	Acute Lymphoblastic Leukemia	16 months	4 months	gp91^{phox} deficiency (X-linked)

Malignancy

It has been demonstrated that primary immunodeficient patients are at the increased risk of malignancy (81, 82). Furthermore, in a study conducted on 42 CGD patients identified in The Netherlands, the increased relative risk of malignancy was also reported (83). However, those reported cases of CGD complicated by cancer are limited and sporadic. In addition, the reported cases of malignancy in CGD patients include the following: Hodgkin lymphoma (84, 85), acute lymphoblastic leukemia (86), giloblastoma multiforme (87), retinoblastoma (83), malignant melanoma (83), and rhabdomyosarcoma of liver (83) (**Table 1**).

Diagnosis

CGD should be taken into account in the evaluation of every patient presenting with the recurrent infections, especially when it is caused by uncommon pathogens such as aspergillus, staphylococcus aureus, burkholderia cepacia, serratia marcescens, Aspergillus species, and nocardia. Also, deep seated abscess formation, mucocutaneous manifestations, and genitourinary and gastrointestinal granuloma development should undergo diagnostic test for CGD (12).

The amounts of oxygen utilization as well as superoxide or hydrogen peroxide creation are considered as the different methods of the assessment of NADPH oxidase activity (10). Moreover, the procedure of reducing ferricytochrome c and chemiluminescence is recognized as the diagnostic test for CGD confirmation (12). The evaluation of the NADPH oxidase complex activity in the stimulated neutrophils has been generally used to confirm the CGD diagnosis in a patient with suspicious clinical features. Measuring the extent of superoxide production by neutrophils exposed to NBT dye and aroused by phorbol myristate acetate (PMA), called NBT test, has also been utilized as the diagnostic test for CGD. The NBT dye color, which is typically yellow will change to dark blue after being reduced to formazan by NADPH oxidase complex in normal stimulated neutrophils in contrast to the defective neutrophils, which remain yellow. The result of the NBT test is reported by the percentage of color change within neutrophils, which is seen by the technician using a light microscope. This test may also be utilized to identify the carrier women who have some affected neutrophils due to lyonization. By considering the fact that NBT

is a semi-quantitative analysis, manually was reported instead of being an automatically proper quantitative test and NBT reduction occurs even in the presence of a little amount of residual enzyme activity, the interpretation is challenging in the carrier patients with AR inheritance, and also in women with X-linked mutation and heterogeneous lyonization who have a combination of normal and defective gene expression in their neutrophils. Other factors with considerable impacts on NBT reliability are operator expertise and necessity of using fresh blood sample to carry out the assay (10, 88). Since the last years of 20th century, NBT has been substituted by dihydrorhodamine (DHR) test, which is a new quantitative method currently considered as the gold standard for the identification of CGD. DHR assay, which is based on the flow cytometric analysis of neutrophil respiratory burst, has not only higher sensitivity and reliability, but also is an easier procedure compared to NBT. In the first step, PMA is utilized to stimulate the neutrophils similar to the NBT. However, in the next step of this technique, the aroused neutrophils are exposed to DHR 123, which is reduced to rhodamine 123 by NADPH oxidase created hydrogen peroxide. By applying the fluorescent emission produced by rhodamine 123 in the green band (525-575 nm) after being stimulated by 488 nm light, neutrophils with normal NADPH oxidase complex activity could be distinguished using flow cytometry. It has been shown that there is a direct relationship between the strength of the emitted fluorescent and the amount of reactive oxygen species. Therefore, this technique offers a quantitative assessment of NADPH oxidase activity. Consequently, DHR test could be applied, not only to confirm the diagnosis of CGD, but also to predict the patients' survival rate, differentiate the type of inheritance, and the amount of lionization among X-linked female carriers. Compared to the NBT, it was shown that DHR test need no fresh blood sample. However, the effect of temperature on cellular

living time sample should be considered during the transportation of the sample and also the test ought to be done in the first 48 hours. Performing a DHR test after the stimulation of the phagocytes by serum-opsonized E.coli is used to confirm the diagnosis of the NCF4/p40phox deficiency. The role of myeloperoxidase (MPO), which is needed for DHR 123 oxidation in consort with NADPH oxidase, should not be ignored in the interpretation of DHR test. Hence, the diagnosis of CGD in patients with an abnormal DHR should be validated using the genetic assessment (10, 15, 89).

Management

The goal of the management of CGD is to reduce bacterial and fungal infections, besides minimizing the inflammatory symptoms. Antibiotics, anti-fungal, and IFN-γ are also used for prophylaxis. Furthermore, the management of acute infections is essential.

Prophylactic trimethoprim / sulfamethoxazole (5 mg/kg/day based on trimethoprim) reduces the frequency of major infections (90, 91). Itraconazole prophylaxis showed a significant efficacy in the prevention of fungal infections in CGD (100 mg daily for patients <13 years old or <50 kg; 200 mg daily for those ≥13 years old or ≥50 kg weight) (90, 92). Prophylactic IFN-γ (50 μg/m2) reduces the infection rates, so it is suggested in number of articles, despite having some controversial results (90, 93).

A short course of corticosteroid therapy in patients with autoimmune manifestations is the treatment of choice (61, 93). Marciano et al. reviewed 140 patients with CGD as well as 41 patients with GI manifestations. They used prednisone (1 mg/kg/day) and then tapered it to _0.25 mg/kg every other day for a period of 12 to 20 weeks, which demonstrated that steroids could rapidly reduce symptoms and induce remission. Thereafter, by discontinuation of steroids, relapse occurred in 71% (61).

Allogeneic hematopoietic stem cell transplantation from a human leucocyte antigen identical donor currently is the only proven curative treatment for

CGD. Therefore, it should be considered in CGD patients with a suitable stem cell donor, who have recurrent serious infections. However, on contrast, being on anti-microbial – and in some cases, IFN-γ – prophylaxis or they show severe steroid-dependent or steroid resistant inflammatory complications (94). Soncini et al. also analyzed the outcome of 20 patients with CGD who underwent HSCT from matched sibling or unrelated donors following myelo-ablative or reduced-intensity conditioning, and showed 100% engraftment with 90% survival. In their study, it was demonstrated that HSCT is an effective treatment for patients who have well-matched donor at young age and those who are at low-risk for GVHD. By following the patients, they found out that these patients showed no failure of growth or puberty (95).

Primarily, gene therapy appeared as an ideal treatment, since CGD is a monogenic defect, it can be reconstituted in vitro, and only 5-10% of corrected cells could be enough for phenotypic correction of the disease (90, 93). It is noteworthy that, the first gene therapy for CGD patients was done by Malech et al. in 1997. In this study, patients with p47 or gp91^{phox} deficient CGD received infusions of genetically modified cells without any conditioning and 6 months after the last infusion the cells were detectable at low levels (96). Ott et al. have also tried gene therapy using spleen focus forming virus (SFFV) retroviral vector, along with transplant conditioning on 2 patients with X-linked CGD. Initially, marking levels in peripheral blood leukocytes were between 10% and 30% for the first 3–4 months; however, ultimately oligoclonality and myelodysplasia have occurred (97). Kang et al. used MFGS-based retroviral vector encoding the gp-91^{phox} gene for gene therapy and then conditioned the recipients with a total of 10 mg/kg of busulfan. Patient 1 had 1% of the genetically corrected cells after 2 years and he experienced the reduced infections. Moreover, Patient 2 had 5% of the genetically corrected cells; however, he died due

to infection before being able to proceed to an unrelated donor transplant (98). Therefore, CGD patients treated with gene therapy were limited and not as successful as it was predicted.

Prognosis

Currently, due to lifelong use of prophylactic antimicrobial agents including trimethoprim-sulfamethoxazole and itraconazole, combined with immediate diagnosis and treatment of infections, the survival rate of CGD patients has substantially increased. However, this has led to the emergence of inflammatory and autoimmune complications of the disease. It should also be noted that the survival rates of CGD patients with autosomal recessive pattern are much higher than X-linked CGD (7).

In a case series published in 2008, by analyzing medical records of 94 CGD patients in UK and Ireland, it was shown that the estimated survival rate was 88% during 10 years, but 55% within 30 years (6). Examining the records of 268 CGD patients followed for over 4 decades in United States demonstrated that the median age at death have increased from 15.53 years before 1990 up to 28.12 years in the last decade (7). In a European survey on 429 patients, median survival of 38 years for X-linked CGD and 50 years for autosomal recessive CGD were shown (1)

Studies conducted on curative treatment with hematopoietic cell transplantation look promising, which may increase the survival rate in CGD patients in years to come. Gene therapy also is another approach for definitive correction of the disease. However, the studies on gene therapy are still limited, so there is a need for more research.

Conclusion

CGD, as a hereditary disorder causing phagocyte dysfunction, is characterized by recurrent bacterial and fungal infections. Due to the use of prophylactic antimicrobial agents as well as immediate diagnosis and treatment of infections, there has been an increase in survival rates in recent

years. However, increase in life expectancy has led to the emergence of inflammatory and auto-immune complications with high morbidity rates.

In this review, we focused on the inflammatory, autoimmune, and allergic presentations of CGD. The pathogenesis of these manifestations is still obscure. However, the impaired apoptotic clearance, decreased neutrophil apoptosis, increased proinflammatory protein expression, reduced ROS-mediated inflammasome dampening, and decreased effector regulatory T cells are likely to be involved in this process. In most cases, steroid therapy is known as the treatment of choice. Therefore, clinicians should be aware of the other presentations of CGD. It is predicted that by early diagnosis and treatment of these manifestations, there would be a dramatic increase in the quality of life in these patients.

HCT, as a curative treatment, is a revolutionary approach, which should be considered in young patients with severe or autoimmune manifestations who have a well-matched donor. However, the experimental data on gene therapy, as a curative treatment in CGD, are rather controversial and not successful yet.

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgements

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