

ROSTRUM

How primary immune deficiencies impact the lung in children

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ABSTRACT

Primary immune deficiencies (PID) encompass a heterogeneous group of genetically determined disorders that affect development and/or function of innate or adaptive immunity. Consequently, patients with PID suffer from recurrent and/or severe infections that frequently involve the lung. Pulmonary complications, which are largely dependent on the components of the immune system that are defective, cause significant morbidity and mortality. Even though the pattern of lung damage and the types of microorganisms involved may provide insights into potential defects in innate, humoral, or cell-mediated immunity, there is a substantial overlap in lung complications among the different types of PID. Consequently, thorough laboratory investigations are necessary to establish a definitive diagnosis and to prompt appropriate treatment. Furthermore, the identification of a large number of PID-causing genes allows early, even presymptomatic diagnosis, thus representing an essential tool for prevention of lung damage.

IMPACT STATEMENT: This article describes the most common forms of PID, their cellular and molecular bases, and the associated lung abnormalities, and reports on available treatment.

INTRODUCTION

Primary immunodeficiency diseases are a heterogeneous group of inherited disorders of the immune system in which one or several immune components are decreased, missing, or of non-appropriate function (1). In the immune system, three primary cell lineages can be identified, all originating from a shared lymphoid precursor cell (LPC). If the LPC migrates to the thymus, it will differentiate into the T cell lineage, characterized by two main subsets: CD3+ CD4+ (associated with helper activity) and CD3+CD8+ (associated with cytotoxic activity). The latter plays a crucial role in the defense against intracellular pathogens, such as viruses and fungi. If the LPC migrates to the bone marrow, it will differentiate, based on the local microenvironment, either into the B cell lineage, a precursor of the immunoglobulin-secreting plasma cells, or into the myeloid lineage, ultimately leading to the differentiation into neutrophils. Immunoglobulins play a crucial role in protecting against extracellular pathogens, whereas neutrophils contribute to protection against both intra and extracellular pathogens. Regardless of the defective cell line, the lungs are a major target in PID, and pulmonary manifestations vary in etiopathogenesis, type, and severity according to the specific branch of the immune system which is compromised.

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ABBREVIATIONS

ARA: Autosomal Recessive Agammaglobulinemia
CGD: Chronic Granulomatous Disease
CVID: Common Variable Immune Deficiency
GLILD: Granulomatous Lymphocytic Interstitial Lung Disease
HIES: Hyper IgE Syndromes
ILD: Interstitial Lung Disease
PID: Primary Immune Deficiencies
SCID: Severe Combined Immunodeficiencies
XLA: X-linked Agammaglobulinemia

KEY WORDS

Interstitial lung disease; granulomatous lymphocytic interstitial lung disease; hyper IgE syndromes; chronic granulomatous disease; severe combined immunodeficiencies; X-linked agammaglobulinemia; autosomal recessive agammaglobulinemia; primary immune deficiencies; common variable immune deficiency.

This article will focus on the different patterns of pulmonary involvement in selected forms of PID where one or more immune components are defective.

AGAMMAGLOBULINEMIA

Agammaglobulinemia is a primary immune deficiency characterized by low or absent immunoglobulin serum levels, impaired antibody production, and a severely reduced or absent peripheral B cell population (<2%) due to early arrest of B cell development. Since the T and myeloid cell lineages are normal, agammaglobulinemia can be considered the prototype of primary antibody deficiencies. There are two different forms of agammaglobulinemia: the X-linked (XLA or Bruton disease), affecting males, which is due to mutation in BTK, the gene encoding for Bruton's tyrosine kinase, a cytoplasmic protein essential for early B-cell development, and the autosomal recessive (ARA) form which affects both males and females and is due to mutations in genes encoding for different components of the B cell receptor (BCR), such as μ heavy chain, $\lambda 5$, $Ig\alpha$, $Ig\beta$ or for cytoplasmic proteins (e.g., BLNK deficiency, E47 deficiency, p85 α deficiency, ZIP7 deficiency), all crucial for B cell development (2).

Typically, agammaglobulinemic patients suffer from recurrent infections, commonly affecting the upper and lower respiratory tracts. In a recent survey of a large cohort of agammaglobulinemic patients (3), respiratory infections were the most frequent clinical symptom at diagnosis, with one or more episodes of pneumonia recorded in 40% of patients. Of note, at the time of diagnosis, 13% of patients were already affected by chronic lung disease (CLD), as indicated by the results of a lung computed tomography scan which showed the presence of bronchiectasis, peri bronchial wall thickening, and atelectasis. The most common pathogens causing pneumonia include encapsulated bacteria such as *Hemophilus influenzae* and *Streptococcus pneumoniae*. Over a mean follow-up period of 8.35 years per patient (range 1-18 years), respiratory infections remained the most common clinical manifestation persisting even with immunoglobulin replacement therapy (IRT). Specifically, episodes of pneumonia and sinusitis were recorded in 34 and 56% of patients, respectively. It is noteworthy that, despite regular IRT, the percentage of patients with CLD increased from 13% to

35% during follow-up, allowing to calculate the cumulative risk of CLD, which is equal to 47% at 50 years of age. The occurrence of CLD already at diagnosis and during follow-up may be partially explained by various factors, such as advanced age, delayed diagnosis, and, in some cases, initial treatment with intramuscular immunoglobulins. It is known that intramuscular immunoglobulins are considerably less effective than intravenous or subcutaneous immunoglobulins in reducing the incidence of respiratory infections. The development of CLD during follow-up suggests that regular IRT may not completely prevent the development of lung complications, likely due to the administered immunoglobulins' inability to reach the mucosal surface. Furthermore, the administered immunoglobulins contain only IgG, which are not selected on antigen specificity and cannot compensate for the lack of IgA at the mucosal surface (3, 4, 5). As pathogens more frequently responsible for pneumonia are encapsulated bacteria, the most common radiological pattern observed in these patients is lobar consolidation, often accompanied by pleural effusion or empyema, depending on the severity of the infectious episode (**Figure 1A**). This radiological pattern is common to all forms of agammaglobulinemia, regardless of the underlying genetic defect. This contrasts with what is observed in common variable immunodeficiency (see below). Repeated episodes of pneumonia may result in bronchiectasis during the course of the disease (**Figure 1B**). Early diagnosis and a timely and consistent IRT are crucial for controlling long-term lung complications. Furthermore, considering the impact of CLD on daily life and especially on long-term outcome, each acute infectious episode should be promptly treated with antibiotics. Additionally, a personalized respiratory physio-

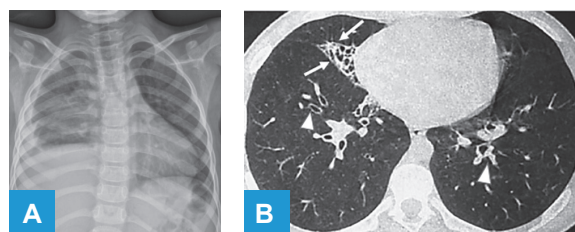


Figure 1. (A) Frontal chest radiograph in a 6-year-old boy with XLA demonstrates extensive parenchymal consolidation in the right lower lobe with pleural effusion caused by *Str. Pneumoniae*; (B) CT scan in a 18-year old boy with XLA shows middle lobe collapse with cylindrical bronchiectasis (arrows); other bronchiectasis are visible in both lower lobes (arrowheads).

therapy program and/or antibiotic prophylaxis regimen should be considered (5, 6).

COMMON VARIABLE IMMUNODEFICIENCY

Common variable immunodeficiency (CVID) is the most common symptomatic primary immunodeficiency. It is characterized by markedly reduced serum levels of IgG, IgA, and IgM, usually less severe than that observed in agammaglobulinemia. In addition to reduced immunoglobulin levels, individuals with CVID exhibit the inability to mount functional antibody responses to immunization or infection. Peripheral T (CD3) and B (CD20 or 19) cell counts are generally within the normal range, whereas a more in-depth investigation of T and B cell subsets may reveal subtle abnormalities, contributing to the clinical heterogeneity of this disorder (7-9).

In fact, analysis of extensive patient datasets reveals that CVID patients can be broadly categorized in two major clinical groups. The first group predominantly presents infections, with recurrent bacterial infections of the upper and/or lower respiratory tracts being the most common clinical manifestation that often prompts diagnosis of the immune defect. Pneumonia, often caused by *Streptococcus pneumoniae* and *Hemophilus influenzae*, is identified in up to 60% of patients with CVID. The recurrence of pneumonia may lead to the development of structural airway changes, such as bronchiectasis, affecting up to 40-60% of patients (10-13). Therefore, in terms of lung involvement, this patient group shares similarities with those having agammaglobulinemia. Thus, an early diagnosis and a timely and consistent IRT are crucial for controlling long-term lung complications. Furthermore, prompt antibiotic treatment for each acute infectious episode and a personalized respiratory physiotherapy program and/or antibiotic prophylaxis regimen should be considered.

The other group (complex CVID) is characterized by a prevalence of non-infectious complications, including autoimmunity (cytopenia, thyroiditis, enteropathy), inflammatory and/or lymphoproliferation, splenomegaly, lymphoma, nodular hyperplasia, and granulomatous manifestations (9, 14). These complications may occur simultaneously or sequentially over the disease course. They are thought to derive from dysregulated innate and adaptive cellular activation responses due

to underlying pathogenetic mechanisms that affect the maintenance of tolerance (14-16). Consequently, lung complications in this group are more severe than those of the first group and encompass, in addition to bronchiectasis, interstitial and parenchymal lung disease (ILD).

These two distinct clinical phenotypes likely result from distinct genetic defects causing CVID, falling broadly into two categories: those that almost exclusively affect B cell development, differentiation, activation, and/or survival, such as genes encoding for the cluster of differentiation 19, 20, 21, or 27 (first group), and those that control/affect crosstalk between B and T cells (*i.e.*, mutations in LRBA, CTL-4, NFKB1, NFKB2, PIK3CD, STAT3), causing immune dysregulation ultimately leading to ILD (second group) (9, 14). CVID-related ILD is presumed to be unrelated to bacterial infections, as it can be observed also in the absence of bronchiectasis, it is not significantly associated with a history of pneumonia and frequently occurs in conjunction with lymphoid hyperplasia in other tissues, such as lymph nodes, spleen, and the mucosal lymphoid tissue of the gastrointestinal tract (17). This phenotypic distinction also has important clinical implications because the risk of death due to lung complications is significantly higher for patients with ILD as compared to those without (9, 14, 18). Lymphoid ILD, found in 8-20% of CVID patients (19), exhibits various pulmonary histological patterns, including follicular bronchiolitis, nodular lymphoid hyperplasia, granulomatous lung disease, lymphocytic interstitial pneumonia, and organizing pneumonia. Since these patterns may coexist in the same patient, the term "Granulomatous and Lymphocytic Interstitial Lung Disease (GLILD)" was coined to identify a distinct clinico-radio-pathological interstitial lung disease characterized by a lymphocytic infiltrate and/or granuloma in the lungs (20, 21).

The main computed tomography (CT) features of ILD/GLILD are nodules, ground glass opacities, reticulations, consolidation, and interstitial fibrosis (**Figure 2A**). Immunohistochemical analysis of pulmonary lymphoid hyperplasia has documented the presence of distinct B-cell follicles and T-cell zones, demonstrating lymphopoiesis as a feature of lymphoid hyperplasia and implicating B lymphocytes in the pathogenesis of this complication (21). Since ILD is very rare or absent in

X-linked and autosomal recessive agammaglobulinemia, two disorders characterized by absence of B cells, it is tempting to speculate that B cells, by acting as antigen-presenting cells, producing proinflammatory chemokines and cytokines, or both, might perpetuate leukocyte accumulation within the lung, leading to lymphoid hyperplasia (21). This is supported by the adoption of B cell depletive therapy, either alone or in combination with other immunosuppressive drugs, as a fundamental component of CVID-related ILD/GLILD treatment (22, 23) (**Figure 2B**). Since this complication causes significant morbidity and mortality, there is a need for effective treatments. However, currently, there is no standardized treatment protocol. IRT has greatly reduced the number of infections, but it does not appear to prevent or ameliorate most inflammatory and autoimmune conditions. Because the mechanisms underlying CVID-related ILD/GLILD are only partially elucidated, immunosuppressive treatment either as monotherapy or as a combination of different drugs, has been tried with varying results (24). Glucocorticosteroids are considered the first line therapy for ILD/GLILD (20). However, the response may be short-lived or unsatisfactory, and there are significant side effects associated with protracted use. Additionally, a proportion of patients are refractory. Thus, besides glucocorticoids, other immunosuppressive drugs (ciclosporin, mycophenolate mofetil, azathioprine, hydroxychloroquine, infliximab, rituximab, abatacept) have been administered with varying success (24). Finally, HSCT may be an option when other treatments have failed, but the reported mortality rate is still relatively high compared to the overall survival of patients transplanted for other types

of PID (24, 25). A better understanding of the pathogenic mechanisms underlying ILD/GLILD may lead to the development of safer and more effective therapies.

SEVERE COMBINED IMMUNODEFICIENCIES

Severe combined immunodeficiencies (SCID) encompasses a heterogeneous group of genetic disorders characterized by a profound impairment of T cell development and/or function. In some forms of SCID, the numbers of circulating B and/or NK cells is variably affected, but B cell function is impaired due to the lack of adequate helper T cell activity. Based on the number, function, and origin of circulating T cells, SCID may be classified into two categories: typical and atypical forms. The former is characterized by a very low number of circulating T cells (<300 cells/ μ l) and no or very low T cell function, ($<10\%$ of lower limit of normal of T cell proliferation to phytohemagglutinin). Typical SCID also includes the form characterized by the presence of circulating maternal T cells (maternal engraftment). Atypical SCID includes a reduced number (>300 cells/ μ l) of circulating T cells for age, in the absence of documented maternal engraftment, and $<30\%$ of lower limit of normal proliferative response to phytohemagglutinin. Atypical SCID is sometimes referred to as “leaky” SCID (26). The full blood count becomes, therefore, the most accessible and practical first-level diagnostic test. Yet the absolute lymphocyte counts are often overlooked. Lymphocyte counts are higher in infancy than in adulthood, and it is not widely appreciated that an absolute lymphocyte count of less than 2,800 cells/ μ l is 2SD below the mean. When infants with infections have a count lower than this, it is highly likely they have SCID (27, 28). Following immunophenotyping of blood lymphocytes, SCID patients can be classified, according to the presence or absence of different lymphocyte subsets, into 4 different subgroups: T-B-NK $^{+}$; T-B-NK $^{-}$; T-B $^{+}$ NK $^{-}$; T-B $^{+}$ NK $^{+}$ (29). A normal lymphocyte count does not preclude a SCID diagnosis. In fact, the presence of B lymphocytes in the absence of T cells, as well as the presence of maternal engraftment and a distinctive phenotype characterized by the presence of autologous, oligoclonal, and activated T cells (Omenn syndrome), may obscure lymphopenia. The identification of the genetic defects underlining different immunophenotypes (29) has helped to clarify

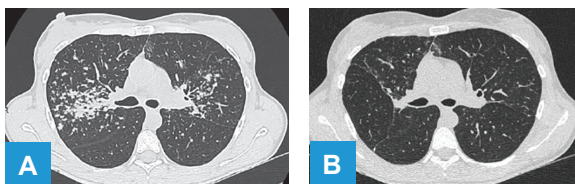


Figure 2. A 37-year-old female with CVID, admitted to the hospital because of productive cough, mild fever, and dyspnea on exertion. Her clinical history was remarkable for autoimmune thyroiditis, psoriasis, and multiple allergic reactions to drugs. (A) CT scan shows multiple nodules in both lungs, more pronounced in the right one; culture of bronchoalveolar lavage fluid excluded bacterial infections, mycobacteria, and pneumocystosis. Lung biopsy revealed numerous non-necrotizing epithelioid cell granulomata and interstitial lymphocytic infiltrates, suggestive of GLILD (data not shown); (B) CT scan after treatment with Rituximab shows complete resolution.

the mechanisms of functional T cell development. Furthermore, precise identification of the gene defect has a relevant impact on treatment, as exemplified using by use of enzyme replacement therapy in Adenosine deaminase deficiency.

Infants with SCID typically appear healthy at birth. However, due to the lack of adequate T cell function, most of them will manifest severe and potentially life-threatening opportunistic infections within the first year of life if not promptly diagnosed and treated. The most frequent reason for seeking medical attention is respiratory tract infections, often associated with other symptoms such as diarrhea, failure to thrive, or thrush (30). Respiratory symptoms in infants with SCID can resemble those of bronchiolitis, including persistent cough, tachypnoea, increased work of breathing, grunting or nasal flaring, and wheezing or rales on chest auscultation. Despite supportive therapy, these symptoms persist beyond the expected duration and can worsen to the point of requiring admission to the pediatric intensive care unit (PICU). In fact, it is widely recognized that patients with SCID are often diagnosed in a PICU, where they were admitted for severe, prolonged, and complicated respiratory infections. Imaging features usually reveal an interstitial pneumonia with varying patterns of consolidation. Opportunistic pathogens, such as *Pneumocystis jirovecii*, cytomegalovirus, adenovirus, parainfluenza virus type 3, and respiratory syncytial virus, are most commonly isolated from bronchoalveolar lavage (Figure 3A, B, C, D). Invasive bacterial and fungal infections also occur, with the former mostly resulting from impaired humoral immunity secondary to defects in T-cell immunity.

The definitive cure of SCID involves restoration of the immune system through allogeneic hematopoietic stem cell transplantation (HSCT) or gene therapy. Prophylaxis of infections with antibiotics, immunoglobulin substitution, antiviral and antifungal drugs can, at best, marginally prolong survival (26). The outcome of HSCT is largely dependent on the presence or absence of active infection at the time of HSCT, with increased mortality for patients with an active infection at the time of transplantation compared to those without (31, 32). This raises the question of the need of an early diagnosis of these disorders, just before the occurrence of infections. Early diagnosis can be

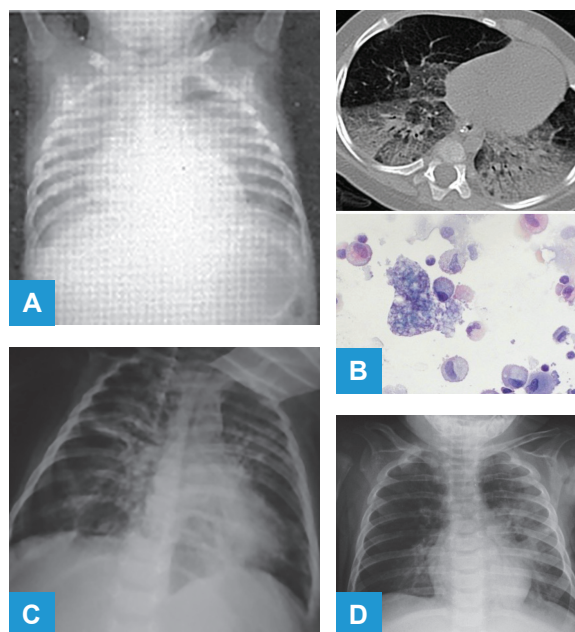


Figure 3. Lung involvement in SCID patients. (A) chest radiograph in a 4-month-old male shows bilateral, perihilar interstitial infiltrates, due to CMV infection; (B) lung CT scan in a 6-month-old female showing diffuse interstitial infiltrates in the right lung associated with parenchymal consolidation in the left lung. *Pneumocystis jirovecii* was isolated from bronchoalveolar lavage fluid; (C) chest radiograph of a 6-month-old male showing bilateral parenchymal consolidations in the context of interstitial infiltrates; bronchoalveolar lavage fluid yielded *Stenopneumococcus maltophilia*; (D) chest radiograph in a 5-month-old male showing inhomogeneous parenchymal consolidation in the left paracardiac site and another in the right paracardiac site; bronchoalveolar lavage fluid yielded adenovirus. Absence of thymic shadow is documented in c and d cases.

achieved only through a newborn screening for SCID (SCID-NBS). The efficacy of this approach has been documented in a recent paper showing improved survival of SCID-transplanted patients in countries where SCID-NBS has been implemented (33).

DEFECTS OF PHAGOCYtic COMPARTMENT

Neutrophils play a significant role in the clearance of bacterial and fungal infections, making immunodeficiencies due to phagocytic dysfunction notable for infections caused by these organisms. Phagocytic dysfunction, accounting for 10% to 15% of primary immunodeficiencies, impairs neutrophil function in a wide range of inherited disorders. Among these, chronic granulomatous disease, leukocyte adhesion deficiency, congenital neutropenia, and Chediak-Higashi syndrome are some of the most well-known. This section focuses on lung involvement in CGD, offering a key illustration of PID caused by impaired neutrophil function.

Chronic granulomatous disease (CGD) is a genetically heterogeneous disorder characterized by recurrent, life-threatening infections with bacteria and fungi, along with dysregulated granuloma formation. CGD commonly arises from defects in any of the genes encoding the structural subunits of the NADPH oxidase, the enzyme responsible for the phagocyte respiratory burst and the generation of phagocyte superoxide, which is crucial for intracellular killing of ingested microorganisms. NADPH oxidase consists of 2 membrane-bound proteins (gp91^{phox} and p22^{phox} that constitute the cytochrome b₅₅₈), and 4 cytosolic components (p47^{phox}, p67^{phox}, p40^{phox}, and RAC). CGD caused by mutations in gp91^{phox} is inherited as an X-linked trait (affecting 65% of patients), while mutations in p47^{phox}, p67^{phox}, p40^{phox}, and RAC, lead to autosomal recessive inheritance. The recently recognized EROS (encoded by CYBC1) is required for assembly and transport of cytochrome b₅₅₈ (34, 35).

In CGD, infections typically have an early onset and are mainly caused by catalase-positive microorganisms, such as *Staphylococcus aureus*, *Burkholderia cepacia*, *Serratia marcescens*, *Nocardia*, and *Aspergillus* species. In addition to skin infections, lymphadenitis, and liver abscesses, the lungs are frequently involved (36). This includes recurrent pneumonia, which is the most common infection occurring in 50-80% of CGD patients, hilar lymphadenopathy, empyema, or lung abscesses (37, 38). Radiologically, bacterial pneumonia may manifest as segmental or lobar parenchymal consolidation (Figures 4A, B, 5A, B). The presence of pneumatocele is suggestive of staphylococcal pneu-

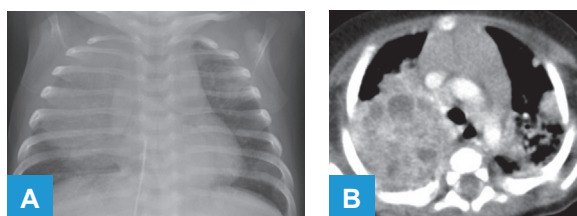


Figure 4. (A) frontal chest radiograph in a 2-month-old male with X-linked CGD demonstrates an extensive parenchymal consolidation in the right lung and another consolidation in the suprabasal area of the left lung; (B) CT scan of the same patient shows extensive parenchymal consolidation in the right lung, with multiple hypodense rounded areas, compatible with colliquative necrotic material (abscess lesions). Similar small areas of rounded morphology are also observed in the left lung. *Staphylococcus aureus* was isolated from bronchoalveolar lavage fluid.

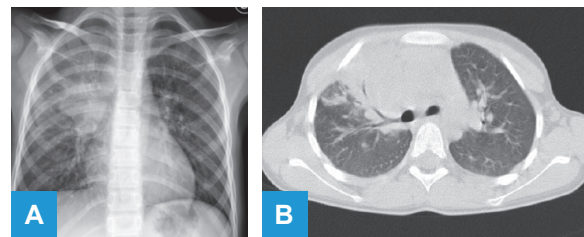


Figure 5. (A) frontal chest radiograph of a 2-year-old girl with CGD showing a parenchymal opacity with irregular profiles in the right perihilar area; (B) CT scan of the same patient shows a parenchymal consolidation with a broncogram in the right upper lobe. *Burkholderia gladioli* was isolated from bronchoalveolar lavage fluid.

monia and usually occurs 10-14 days after the onset of infection, when the patient is clinically improving (39). Patients with CGD are particularly susceptible to developing pulmonary aspergillosis. Typically, the focal consolidations characteristic of pulmonary aspergillosis often exhibits a distinct “halo” of ground-glass attenuation (Figure 6A, B), indicative of hyphae proliferation into the endobronchial tree, ultimately invading pulmonary vessels and resulting in thrombosis and infarction of the lungs (40). In some cases, especially during the early phase of the disease, *Aspergillus* nodules may be small and lack the characteristic “halo sign”, making it challenging to differentially diagnose between infectious or inflammatory (granulomatous) origins of the nodules (40, 41).

Infections caused by uncommon organisms, such as those mentioned above, should prompt an investigation for CGD in patients of any age who lack other predisposing factors. The diagnosis of CGD is established by assays that rely on superoxide production. These methods include direct measurement of superoxide production, ferricytochrome c reduction, chemiluminescence, NBT reduction, or the flow cytometry-based test dihydrorhodamine oxidation (DHR).

Continuous antimicrobial prophylaxis with co-trimoxazole and azole antifungal drugs has proven effective in reducing the incidence of severe infections in CGD patients. However, the long-term prognosis of CGD remains controversial, and it is advisable to consider HSCT. Allogeneic HSCT is currently the only known cure for CGD. Earlier use of myeloablative regimens led to disease resolution but relatively high risk of mortality (34, 42). More recent application of reduced intensity conditioning regimens has greatly reduced regimen-related toxicity, enabling transplantation

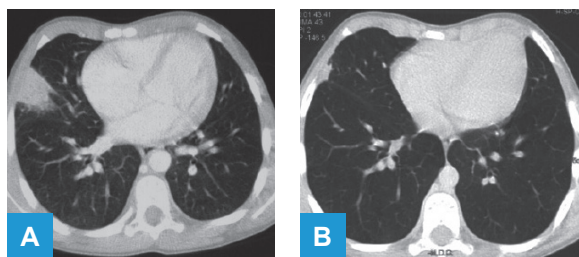


Figure 6. (A) CT scan in an 8-year-old male with X-linked CGD shows focal consolidation in the middle right lobe surrounded by a noticeable «halo sign» at the periphery, suggestive of alveolar hemorrhage. A specimen of the infiltrate obtained with a CT-guided biopsy showed growth of *Aspergillus*; (B) despite long-term antifungal treatment, CT scan performed almost 1 year later shows persistent focal pleural thickening.

even in the presence of active infection. With these regimens, survival rates range from 80% to 90%, with comparable survival outcomes among patients with matched related, matched unrelated, and umbilical cord donors (34, 43-45). Moreover, promising results have been recently obtained with gene therapy for the X-linked form of CGD (46, 47).

THE HYPER IGE SYNDROMES (HIES): STAT3 DEFICIENCY AS REPRESENTATIVE EXAMPLE OF THE STAT3-RELATED HIES

Hyper-IgE syndromes are primary immune deficiencies characterized by the triad of high serum IgE levels, eczema, and recurrent skin and pulmonary infections. Both autosomal dominant and autosomal recessive forms of the disorder have been described (29, 48, 49). Some types of HIES share common clinical features, including immunological and non-immunological skeletal and connective tissue abnormalities, with a strong involvement of the STAT3 dependent pathway. These conditions, resulting from mutations in genes such as STAT3, IL6ST, IL6R, PGM3, ZFN341, ERBIN and TGFBR, are collectively termed "STAT3-related HIES". Other forms of non-STAT3-related HIES have been reported (50). The diagnosis of HIES is typically made based on elevated serum IgE levels along with specific clinical symptoms. However, as the symptoms of different forms of HIES overlap to some extent, molecular-genetic testing is required for a definitive diagnosis of HIES.

This section focuses on the lung involvement observed in STAT3 deficiency, commonly known as Job syndrome, as an illustrative example representing the

broader category of STAT3-related HIES. STAT3 deficiency, resulting from a dominant negative mutation in the STAT3 gene, is the most frequent form of HIES among the STAT3-related HIES and in the general spectrum of HIES. The lung represents one of the main target organs in STAT3 deficiency, and the prognosis is strongly dependent on the degree of lung disease. Recurrent pyogenic pneumonias, commonly caused by *Staphylococcus aureus*, *Streptococcus pneumoniae* and *Hemophilus influenzae*, typically manifest in the first few years of life. Most patients have at least one episode of pneumonia, with over 50% having three or more episodes before receiving a diagnosis (51). The systemic signs of infection are often attenuated, leading to delayed diagnosis of pneumonia. For instance, *S. aureus* lobar pneumonia may present with minimal fever, normal peripheral white blood cell count, and normal inflammatory markers.

Aberrant healing, likely resulting from connective tissue abnormalities and the necessity of normal STAT3 signaling for physiological repair of bronchiolar and alveolar epithelium after damage (52), is frequently observed following pulmonary infections. This predisposes individuals to the development of pneumatoceles and/or bronchiectasis, affecting up to 75% of patients (51) (Figure 7A, B, C, D). Once the lung

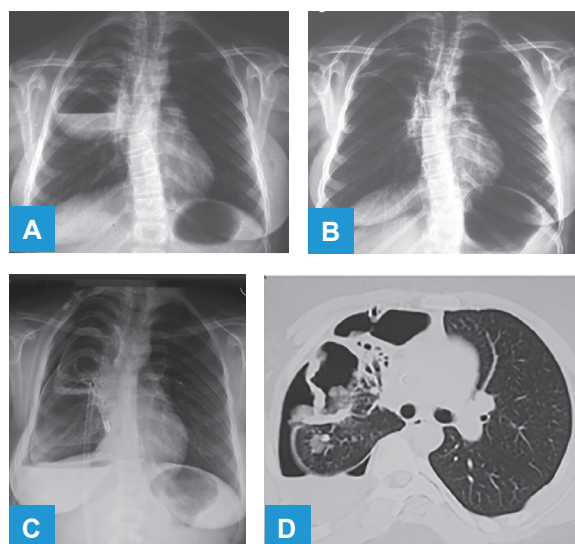


Figure 7. (A) chest X ray in a 12-year-old girl with STAT3 deficiency reveals, in the right lung, a large cavitation (pneumatocele) with air-fluid level, a finding suggestive of an abscess; (B) following long-term medical therapy, the air-fluid level resolved; (C) one year later, the patient presented with hydropneumothorax, and (D) a CT scan showed an aspergilloma inside the pneumatocele. Scoliosis is part of the skeletal and connective tissue abnormalities typical of STAT3 deficiency.

parenchyma has been altered by pyogenic pneumonias, the spectrum of infecting microbes expands to include non-tuberculous mycobacteria, molds such as *Aspergillus* and *Scedosporium*, and persistent gram-negative bacilli such as *Pseudomonas*. Infections by molds and gram-negative bacilli, often occurring in areas of pre-existing pneumatoceles and bronchiectasis, cause chronic infections which represent the major causes of morbidity and mortality in these patients (53-55).

Treatment of patients with STAT3 deficiency primarily focuses on aggressively treating and preventing bacterial and fungal respiratory tract infections. In some patients, immunoglobulin replacement therapy may also be considered. Due to the absence or limited presence of normal inflammatory signs, even subtle indications of infection must be carefully monitored and investigated, especially when the disease has progressed substantially (42). Antifungals may not always be effective in treating aspergillomas forming inside pneumatoceles (48). Thus, resection is generally accepted as the preferred therapy and offers the possibility of a permanent cure; however, this surgical procedure carries a high rate of complications and recurrence (54, 56, 57). Given that STAT3 expression is ubiquitous, replacing the hematopoietic lineage alone may not be entirely curative. Although HSCT has shown some promising results from an infectious and inflammatory perspective, more studies are needed before a clear pattern can be established (48).

CONCLUSIONS

The lungs are the most affected organ in PID, and associated complications are often the first warning signs of PID. The nature and severity of respiratory symptoms, the specific etiological agents, and the radiological findings play a crucial role in guiding the diagnostic suspicion towards a particular type of immunodeficiency.

Patients with agammaglobulinemia, characterized by a B cell defect, are more susceptible to recurrent pneumonias caused by extracellular pathogens, particularly encapsulated bacteria. This susceptibility can result in the development of structural airway changes, such as bronchiectasis. Similar structural

airway changes are observed in patients with CVID presenting only/predominantly with infections. On the contrary, the spectrum of pulmonary complications in CVID patients with symptoms of immune dysregulation (non-infectious complications) is more extensive and encompasses both structural airway disease as well as interstitial or parenchymal lung disease (ILD). Patients with SCID are more prone to respiratory infections by extracellular (encapsulated bacteria) and intracellular pathogens such as viruses and fungi due to the lack of adequate T cell function. In CGD, respiratory infections by catalase-positive microorganisms with suppurative complications are characteristic, whereas the development of pneumatocele is suggestive of hyper-IgE associated with skeletal and connective tissue abnormalities.

Nevertheless, even though the pattern of lung damage and the types of microorganisms involved may provide insights into potential defects in innate, humoral, or cell-mediated immunity, there is a substantial overlap in lung complications among the different types of PID. Consequently, thorough investigations are necessary to establish a definitive diagnosis.

COMPLIANCE WITH ETHICAL STANDARDS

Conflict of interests

The Authors have declared no conflict of interests.

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Author contributions

All the Authors confirmed the contribution to the manuscript's conception and approved its final version.

Ethical approval

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N/A.

Animal studies

N/A.

Data sharing and data accessibility

Data are available upon motivated request to the Corresponding Author.

Publication ethics

Plagiarism

All original studies are cited as appropriate.

Data falsification and fabrication

All the data correspond to the real.

REFERENCES

- Picard C, Bobby Gaspar H, Al-Herz W, Bousfiha A, Casanova JL, Chatila T, et al. International Union of Immunological Societies: 2017 Primary Immunodeficiency Diseases Committee Report on Inborn Errors of Immunity. *J Clin Immunol*. 2018;38(1):96-128. doi: 10.1007/s10875-017-0464-9.
- Plebani A, Lougaris V. Agammaglobulinemia. In: Sullivan KE, Stiehm ER. *Stiehm's Immune Deficiencies. Inborn Errors of immunity*. Academic Press, Elsevier inc., 2020;pp.443-63.
- Lougaris V, Soresina A, Baronio M, Montin D, Martino S, Signa S, et al. Long-term follow-up of 168 patients with X-linked agammaglobulinemia reveals increased morbidity and mortality. *J Allergy Clin Immunol*. 2020;146(2):429-37. doi: 10.1016/j.jaci.2020.03.001.
- Hernandez-Trujillo, Zhou C, Scalchunes C, Ochs HD, Sullivan KE, Charlotte Cunningham-Rundles C, et al. A registry study of 240 patients with X-linked agammaglobulinemia living in the USA. *J Clin Immunol*. 2023;43(6):1468-77. doi: 10.1007/s10875-023-01502-x.
- Plebani A, Soresina A, Rondelli R, Amato GM, Azzari C, Cardinale F, et al. Clinical, immunological, and molecular analysis in a large cohort of patients with X-linked agammaglobulinemia: an Italian multicenter study. *Clin Immunol*. 2002;104(3):221-30. doi: 10.1006/clim.2002.5241.
- Milito C, Pulvirenti F, Cinetto F, Lougaris V, Soresina A, Pecoraro A, et al. Double-blind, placebo-controlled, randomized trial on low-dose azithromycin prophylaxis in patients with primary antibody deficiencies. *J Allergy Clin Immunol*. 2019;144(2):584-93. doi: 10.1016/j.jaci.2019.01.051.
- Cunningham-Rundles C, Bodian C. Common variable immunodeficiency: clinical and immunological features of 248 patients. *Clin Immunol*. 1999;92(1):28-34. doi: 10.1006/clim.1999.4725.
- Quinti I, Soresina A, Spadaro G, Martino S, Donnanno S, Agostini C, et al. Long-term follow-up and outcome of a large cohort of patients with common variable immunodeficiency. *J Clin Immunol*. 2007;27(3):308-16. doi: 10.1007/s10875-007-9075-1.
- Ho He, Cunningham-Rundles C. Non-infectious Complications of Common Variable Immunodeficiency: Updated Clinical Spectrum, Sequelae, and Insights to Pathogenesis. *Front Immunol*. 2020;11:149. doi: 10.3389/fimmu.2020.00149.
- Schutz K, Alecsandru D, Grimbacher B, Haddock J, Bruining A, Driessen G, et al. Imaging of bronchial pathology in antibody deficiency: data from the European Chest CT Group. *J Clin Immunol*. 2019;39(1):45-54. doi: 10.1007/s10875-018-0577-9.
- Bondioni MP, Soresina A, Lougaris V, Gatta D, Plebani A, Maroldi R. Common variable immunodeficiency: computed tomography evaluation of bronchopulmonary changes including nodular lesions in 40 patients. Correlation with clinical and immunological data. *Comput Assist Tomogr*. 2010;34(3):395-01. doi: 10.1097/RCT.0b013e3181cad9da.
- Quinti I, Soresina A, Spadaro G, Martino S, Donnanno S, Agostini C, et al. Long-term follow-up outcome of a large cohort of patients with common variable immunodeficiency. *J Clin Immunol*. 2007;27(3):308-16. doi: 10.1007/s10875-007-9075-1.
- Hampson FA, Chandra A, Screation NJ, Condliffe A, Kumararatne DS, Exley AR, et al. Respiratory disease in common variable immunodeficiency and other primary immunodeficiency disorders. *Clin Radiol*. 2012;67(6):587-95. doi: 10.1016/j.crad.2011.10.028.
- Lui VG, Ghosh T, Rymaszewski A, Chen S, Baxter RM, Kong DS, et al. Dysregulated lymphocyte antigen receptor signaling in common variable immunodeficiency with granulomatous lymphocytic interstitial lung disease. *J Clin Immunol*. 2023;43(6):1311-25. doi: 10.1007/s10875-023-01485-9.
- Berbers RM, Drylewicz J, Ellerbroek PM, van Montfrans JM, Dalm V, vanHagen PM, et al. Targeted Proteomics Reveals Inflammatory Pathways that Classify Immune Dysregulation in Common Variable Immunodeficiency. *J Clin Immunol*. 2012;41(2):362-73. doi: 10.1007/s10875-020-00908-1.
- Hultberg J, Ernerudh J, Larsson M, Nilsson-Augustinsson Å, Nyström S. Plasma protein profiling reflects TH1-driven immune dysregulation in common variable immunodeficiency. *J Allergy Clin Immunol*. 2020;146(2):417-28. doi: 10.1016/j.jaci.2020.01.046.
- Maglione PJ. Chronic lung disease in primary antibody Deficiency: diagnosis and management. *Immunol Allergy Clin North Am*. 2020;40(3):437-59. doi: 10.1016/j.iac.2020.03.003.
- Fischer A, Provot J, Jais JP, Alcais A, Mahlaoui N, Adoue D, et al. Autoimmune and inflammatory manifestations occur frequently in patients with primary immunodeficiencies. *J Allergy Clin Immunol*. 2017;140(5):1388-93. doi: 10.1016/j.jaci.2016.12.978.
- Scarpa R, Cinetto F, Milito C, Gianese S, Soccodato V, Buso H, et al. Common and Uncommon CT Findings in COVID-Related GL-ILD: Correlations with Clinical Parameters, Therapeutic Decisions and Potential Implications in the Differential Diagnosis. *J Clin Immunol*. 2023;43(8):1903-15. doi: 10.1007/s10875-023-01552-1.
- Hurst JR, Verma N, Lowe D, Baxendale HE, Jolles S, Kelleher P, et al. British Lung Foundation/United Kingdom Primary Immunodeficiency Network Consensus Statement on the Definition, Diagnosis, and Management of Granulomatous-Lymphocytic Interstitial Lung Disease in Common Variable Immunodeficiency Disorders. *J Allergy Clin Immunol Pract*. 2017;5(4):938-45. doi: 10.1016/j.jaip.2017.01.021.
- Maglione PJ, Ko HM, Beasley MB, Strauchen JA, Cunningham-Rundles C. Tertiary lymphoid neogenesis is a component of pulmonary lymphoid hyperplasia in patients with common variable immunodeficiency. *J Allergy Clin Immunol*. 2014;133(2):535-42. doi: 10.1016/j.jaci.2013.08.022.
- Tessarini G, Baronio M, Gazzurelli L, Rossi S, Chiarini M, Moratto D, et al. Rituximab Monotherapy Is Effective as First-Line Treatment for Granulomatous Lymphocytic Interstitial

- Lung Disease (GLILD) in CVID Patients. *J Clin Immunol*. 2023;43(8):2091-103. doi: 10.1007/s10875-023-01587-4.
23. Matson EM, Abyazi ML, Bell KA, Hayes KM, Maglione PJ. B Cell Dysregulation in Common Variable Immunodeficiency Interstitial Lung Disease. *Front Immunol*. 2021;11:622114. doi: 10.3389/fimmu.2020.622114.
 24. Lamers OAC, Smits BM, Leavis HL, de Bree GJ, Cunningham-Rundles C, Dalm VASH, et al. Treatment Strategies for GLILD in Common Variable Immunodeficiency: A Systematic Review. *Front Immunol*. 2021;12:606099. doi: 10.3389/fimmu.2021.606099.
 25. Laberko A, Gennery AR. Clinical considerations in the hematopoietic stem cell transplant management of primary immunodeficiencies. *Expert Rev Clin Immunol*. 2018;14(4):297-306. doi: 10.1080/1744666X.2018.1459189.
 26. Candotti F, de Villartay JP, Moshous D, Villa A, Notarangelo LD. Severe Combined Immunodeficiencies. In: Sullivan KE, Stiehm ER. *Stiehm's Immune Deficiencies. Inborn Errors of immunity*. Academic Press, Elsevier inc., 2020;pp.153-205.
 27. Gennery AR, Cant AJ. Diagnosis of severe combined immunodeficiency. *J Clin Pathol*. 2001;54(3):191-5. doi: 10.1136/jcp.54.3.191.
 28. Comans-Bitter WM, de Groot R, van den Beemd R, Neijens HJ, Hop WCJ, Groeneveld K, et al. Immunophenotyping of blood lymphocytes in childhood. *J Pediatr*. 1997;130(3):388-93. doi: 10.1016/s0022-3476(97)70200-2.
 29. Tangye SG, Al-Herz W, Bousfiha A, Cunningham-Rundles C, Franco JL, Holland SM, et al. Human Inborn Errors of Immunity: 2022 Update on the Classification from the International Union of Immunological Societies Expert Committee. *J Clin Immunol*. 2022;42(7):1473-07. doi: 10.1007/s10875-022-01289-3.
 30. Jesenak M, Banovcin P, Jesenakova B, Babusikova E. Pulmonary manifestations of primary immunodeficiency disorders in children. *Front Pediatr*. 2014;2:77. doi: 10.3389/fped.2014.00077.
 31. Crooks BN, Taylor CE, Turner AJ, Osman HK, Abinun M, Flood TJ, et al. Respiratory viral infections in primary immune deficiencies: significance and relevance to clinical outcome in a single BMT unit. *Bone Marrow Transplant*. 2000;26(10):1097-102. doi: 10.1038/sj.bmt.1702656.
 32. Yun-Pai S, Logan BR, Griffith LM, Buckley RH, Parrot RE, Dvorak CC, et al. Transplantation Outcomes for Severe Combined Immunodeficiency, 2000-2009. *N Engl J Med*. 2014;371(5):434-46. doi: 10.1056/NEJMoa1401177.
 33. Thakar MS, Logan BR, Puck JM, Dunn EA, Buckley RH, Cowan MJ, et al. Measuring the effect of newborn screening on survival after haematopoietic cell transplantation for severe combined immunodeficiency: a 36-year longitudinal study from the Primary Immune Deficiency Treatment Consortium. *Lancet*. 2023;402(10396):129-140. doi: 10.1016/S0140-6736(23)00731-6.
 34. Leiding JW, Holland SM. Chronic granulomatous disease. In: Sullivan KE, Stiehm ER. *Stiehm's Immune Deficiencies. Inborn Errors of immunity*. Academic Press, Elsevier inc., 2020;pp.829-47.
 35. Thomas DC, Charbonnier LM, Schejtman A, Aldhekri H, Coomber EL, Dufficy ER, et al. EROS/CYBC1 mutations: decreased NADPH oxidase function and chronic granulomatous disease. *J Allergy Clin Immunol*. 2019;143(2):782-5. doi: 10.1016/j.jaci.2018.09.019.
 36. Notarangelo LD, Plebani A, Mazzolari E, Soresina A, Bondioni MP. Genetic causes of bronchiectasis: Primary immunodeficiency and the lung. *Respiration*. 2007;74(3):264-75. doi: 10.1159/000101784.
 37. Martire B, Rondelli R, Soresina A, Pignata C, Broccolletti T, Finocchi A, et al. Clinical features, long term follow-up and outcome of a large cohort of patients with Chronic Granulomatous Disease: an Italian multicenter study. *Clin Immunol*. 2008;126(2):155-64. doi: 10.1016/j.clim.2007.09.008.
 38. Donowitz GR, Mandell GL. Clinical presentation and unusual infections in chronic granulomatous disease. In: Gallin JI, Fauci AS. *Advances in host defence mechanisms*. New York Raven, 1983;pp.55-75.
 39. Khanna G, Kao SC, Kirby P, Sato Y. Imaging of chronic granulomatous disease in children. *Radiographics*. 2005;25(5):1183-95. doi: 10.1148/rq.255055011.
 40. Copley SJ. Application of computed tomography in childhood respiratory infections. *Br Med Bull*. 2002;61:263-79. doi: 10.1093/bmb/61.1.263.
 41. Bondioni MP, Lougaris V, Di Gaetano G, Lorenzini T, Soresina A, Laffranchi F, et al. Early identification of lung fungal infections in Chronic granulomatous Disease (CGD) using multidetector computed tomography. *J Clin Immunol*. 2017;37(1):36-41. doi: 10.1007/s10875-016-0342-x.
 42. Seger RA, Gungor T, Belohradsky BH, Blanche S, Bordigoni P, Di Bartolomeo P, et al. Treatment of chronic granulomatous disease with myeloablative conditioning and an unmodified hemopoietic allograft: a survey of the European experience, 1985-2000. *Blood*. 2002;100(13):4344-50. doi: 10.1182/blood-2002-02-0583.
 43. Khandelwal P, Bleasing JJ, Davies SM, Marsh RA. A single-center experience comparing alemtuzumab, fludarabine, and melphalan reduced intensity conditioning with myeloablative busulfan, cyclophosphamide, and anti-thymocyte globulin for chronic granulomatous disease. *Biol Blood Marrow Transplant*. 2016;22(11):2011-8. doi: 10.1016/j.bbmt.2016.08.013.
 44. Parta M, Kelly C, Kwatema N, Theobald N, Hilligoss D, Qin J, et al. Allogeneic reduced-intensity hematopoietic stem cell transplantation for chronic granulomatous disease: a single-center prospective trial. *J Clin Immunol*. 2017;37(6):548-58. doi: 10.1007/s10875-017-0422-6.
 45. Slatter MA, Gennery AR. Hematopoietic Stem Cell Transplantation for Chronic Granulomatous Disease. *J Clin Med*. 2023;12(18):6083. doi:10.3390/jcm12186083.
 46. Cavazzana M, Bushman FD, Miccio A, Andre-Schmutz I, Six E. Gene therapy targeting haematopoietic stem cells for inherited diseases: progress and challenges. *Nat Rev Drug discovery*. 2019;18(6):447-62. doi: 10.1038/s41573-019-0020-9.

47. Ferrari G, Thrasher AJ, Aiuti A. Gene therapy using haematopoietic stem and progenitor cells. *Nat Rev Genet.* 2020;22(4):216-34. doi: 10.1038/s41576-020-00298-5.
48. Milner JD. Primary immune deficiencies associated with a Th2 diathesis In: Sullivan KE, Stiehm ER. *Stiehm's Immune Deficiencies. Inborn Errors of immunity.* Academic Press, Elsevier inc., 2020;pp.393-410.
49. Bousfiha A, Jeddane L, Picard C, Al-Herz W, Ailal F, Chatila T, et al. Human Inborn Errors of Immunity: 2019 Update of the IUIS Phenotypical Classification. *J Clin Immunol.* 2020;40(1):66-81. doi: 10.1007/s10875-020-00758-x.
50. Fadil I, Ben-Ali M, Jeddane L, Barbouche MR, Bousfiha A. The seven STAT-related hyper IgE syndromes. *J Clin Immunol.* 2021;41(6):1384-9. doi: 10.1007/s10875-021-01041-3.
51. Yong PFK, Freeman AF, Engelhardt KR, Holland S, Puck JM, Grimbacher B. An update on the hyper-IgE syndromes. *Arthr Res Ther.* 2012;14(6):228. doi: 10.1186/ar4069.
52. Tadokoro T, Wang Y, Barak LS, Bai Y, Randell SH, Hogan BL. IL-6/STAT3 promotes regeneration of airway ciliated cells from basal stem cells. *Proc Natl Acad Sci USA.* 2014;111(35):E3641-9. doi: 10.1073/pnas.1409781111.
53. Freeman AF, Olivier KN. Hyper-IgE syndromes and the lung. *Clin Chest Med.* 2016;37(3):557-67. doi: 10.1016/j.ccm.2016.04.016.
54. Gernez Y, Freeman AF, Holland SM, Garabedian E, Patel NC, Puck JM, et al. Autosomal dominant Hyper-IgE syndrome in the USIDNET registry. *J Allergy Clin Immunol Pract.* 2018;6(3):996-1001. doi: 10.1016/j.jaip.2017.06.041.
55. Carrabba M, Dellepiane RM, Cortesi M, Baselli LA, Soresina A, Cirillo E, et al. Long term longitudinal follow-up of an AD-HIES cohort: the impact of early diagnosis and enrollment to IPINet centers on the natural history of Job's syndrome. *Allergy, Asthma Clin Immunol.* 2023;19(1):32. doi: 10.1186/s13223-023-00776-5.
56. Dureault A, Tcherakian C, Poiree S, Catherinot E, Danion F, Jouvion G, et al. Spectrum of pulmonary aspergillosis in Hyper-IgE syndrome with autosoma-dominant STAT3 deficiency. *J Allergy Clin Immunol Pract.* 2019;7(6):1986-95. doi: 10.1016/j.jaip.2019.02.041.
57. Mahdavian SA, Ghadimi S, Fallahi M, Hashemi-Moghaddam SE, Chavoshzadeh Z, Puel A, et al. Interventional pulmonary procedures and their outcomes in patients with STAT3 hyper IgE syndrome. *BMC Surgery* 2023;23(1):289. doi: 10.1186/s12893-023-02193-2.