

Pulmonary Manifestations of Primary Immunodeficiencies in Children - A Review

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Abstract

Primary immunodeficiency diseases (PIDs) are inherited defects of the innate or adaptive arms of the immune system that differs from secondary immunodeficiencies. Respiratory disorders are significant causes of morbidity and the leading causes of death (30% -65%) in both children and adults with PIDs. The spectrum of respiratory manifestations is extremely wide due to PIDs. PIDs are broadly classified according to the components of the immune system that is primarily disrupted. Predominant antibody deficiency disorders are the most frequent and comprise approximately 70-75% of all PIDs. The most common clinical manifestations are infections involving the respiratory tract e.g. rhinosinusitis, otitis media, bronchitis, bronchiectasis and recurrent pneumonia (30% -65%). Recurrent respiratory infections are often the first warning sign. Timely diagnosis and appropriate therapy can improve or at least decelerate the progression of these complications. Infectious and non-infectious respiratory complications determinate the patient's prognosis. These complications are associated with significant morbidity and mortality in PID patients. Appropriate awareness of these manifestations is essential, especially for the pulmonologist to reduce morbidity and mortality in PID patients.

Keywords: Primary immunodeficiency, Pulmonary manifestations, Children

Introduction:

Primary immunodeficiency diseases (PIDs) are inherited defects of the innate or adaptive arms of the immune system.¹ PIDs result in a wide range of manifestations including susceptibility to infections, autoimmunity, inflammation, allergy and malignancy. PIDs are distinct from secondary immunodeficiencies that may result from other causes, such as viral or bacterial infections, malnutrition or treatment with drugs that induce immunosuppression.² Recurrent or persistent infection is the major manifestation of PIDs.³ All forms of PIDs are rare and the overall prevalence of PID is not known but it is estimated to be 1:10,000 live births. However, IgA deficiency occurs more frequently, as many as 1: 333 individuals may be affected.⁴ The accurate and timely diagnosis of these disorders requires a high index of suspicion

and specialized testing.⁵ The treatment modalities for PID mainly include immunoglobulin replacement, antibiotics and bone marrow transplantation.³ It is important to recognize children with PID before significant end organ damage occurs to maximize the opportunity for successful treatment and a normal life span.⁶

Respiratory disorders are significant causes of morbidity and the leading cause of death (30% -65%) in both children and adults with PIDs.⁷ Recurrent respiratory infections are often the first warning sign. The spectrum of respiratory manifestations is extremely wide, including acute and chronic infections, immune dysregulation (e.g. autoimmunity, allergy and lymphoproliferative disorders), structural abnormalities and malignancies.⁸ Timely diagnosis and appropriate therapy can improve or at least decelerate the progression of these complications.⁷

The aim of this review is to highlight the pulmonary manifestations and complications in pediatric patients with PIDs.

Brief overview of common PIDs

PIDs are broadly classified according to the component of the immune system that is primarily disrupted: adaptive or innate immunity.⁹

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Received: 13 April 2018

Accepted: 21 June 2018

Predominantly Antibody Deficiency

Antibody- deficiency disorders are the most frequent and comprise approximately 70-75% of all PIDs.¹⁰ The most common clinical manifestations are infections involving the respiratory tract e.g. rhinosinusitis, otitis media, bronchitis, bronchiectasis and pneumonia.¹¹ Recurrent pneumonia is one of the most frequent, important and characteristic sign of primary humoral deficiencies.

X-linked agammaglobulinemia (XLA): Patients with XLA typically present after 6-9 months of age when the level of protective maternal IgG starts going down.¹² The disorder is characterized by markedly reduced levels of circulating B-cells and serum IgG, IgA and IgM.

Common variable immunodeficiency (CVID): CVID is a heterogeneous disorder characterized by markedly reduced serum concentration of IgG, low levels of IgA and/or IgM and poor or absent responses to immunization.

Selective IgA deficiency (SIgAD): SIgAD is a milder antibody deficiency disorder characterized by low or absent levels of serum IgA in the presence of normal levels of IgG and IgM.⁹

IgG subclass deficiency (IgGSD): The term IgGSD refers to a significant decrease in the serum concentrations of one or more subclasses (IgG1, IgG2, IgG3, IgG4) of IgG in a patient whose total IgG concentration is normal.¹³ IgGSD may occur independent of IgA deficiency or in association with IgA deficiency. They may present with recurrent infection.⁴

Transient hypogammaglobulinemia of infancy (THI): It is characterized by low serum IgG concentration with good antibody responses to protein antigens such as tetanus and spontaneous resolution of the hypogammaglobulinemia, sometimes after 2 yrs of age.¹⁴

Combined B cell and Tcell immunodeficiency

T-cell disorders are rare and account for 9% of primary immunodeficiency diseases in the European Society for Immunodeficiencies (ESID) registry.¹⁵ Patients with specific T-cell defects may be lymphopenic and neutropenic.

Severe combined immunodeficiency (SCID): It is the most severe form of combined immunodeficiency. There is virtual lack of functional T cells and immune

function. Even if B cells are present, antibody production is impaired because of lack of T helper cell.⁴

Hyper-IgM syndrome (HIGM): In HIGM syndrome S. IgM remains normal or increased but decreased or absent levels of other immunoglobulin isotypes.

Other well-defined PIDs

DiGeorge syndrome (DGS) : It results from a developmental defect in the third and fourth pharyngeal pouches resulting in impaired formation of the thymus, parathyroid glands, congenital heart disease and hypocalcemia.

Ataxia telangiectasia (AT) : Patients with AT can present at the age of 6 months to 5 years with gait abnormalities or neurodevelopmental delay, progressive cerebellar ataxia and telangiectasia.¹⁶ They also have pneumonia, chronic lung disease and increased risk of different malignancies, especially lymphoreticular.¹⁷

Wiskott-Aldrich syndrome (WAS): WAS patients present with eczema, petechiae and recurrent sino-pulmonary manifestations.¹⁸ Thrombocytopenia with low mean platelet volume gives important clue to diagnosis of WAS.¹⁹

Hyper-IgE syndrome (HIES): Eczema in infancy and recurrent staphylococcal skin boils and pneumonia with pneumatocele formation are the commonest presenting manifestations of HIES.¹⁶ In general, in HIES, the lung symptoms are very common and have early presentation of the disease.

Congenital defects of phagocyte number and function

These types of disorders account for 12.5% of primary immunodeficiency diseases in the ESID registry.

Chronic granulomatous disease (CGD): It is the most common phagocytic disorder in the ESID registry.¹⁵ It is characterized by pneumonia, abscesses, suppurative adenitis and gastrointestinal infections. The first manifestation may be omphalitis in infants.²⁰

Leukocyte adhesion deficiency (LAD) type1: It usually presents within the first few weeks of life. Delayed separation of the umbilical cord (more than four weeks after birth) or erosive perianal ulcers can be early signs.²⁰ Persistent neutrophilia even in the absence of active infection is a common feature of LAD-1.

Severe congenital neutropenia (SCN): Omphalitis can occur in SCN.¹⁵ In SCN, child has persistently low absolute neutrophil counts (ANC) with elevated monocytes and eosinophils counts. Patients with cyclic neutropenia present with drop in ANC every 3-4 weeks with fever, infections and mouth ulcers.¹⁹

Complement deficiency

Complement disorders account for 2% of primary immunodeficiency diseases in the ESID registry.¹⁵ Patients with complement deficiency present later in life usually after 5 years of age. Autoimmune diseases, serious infections from *Neisseria* species, recurrent pneumonia (*S. pneumoniae*), meningitis and peritonitis are seen in different complement deficiencies.²¹

Disorders of immune dysregulation

Familial Hemophagocytic Lymphohistiocytosis (FHL) and Autoimmune Lymphoproliferative syndrome (ALPS) are the most common groups of diseases in this category.¹²

The ESID registry has suggested 10 warning signs for suspicion of PID²² :

- Four or more new ear infections within 1 year
- Two or more serious sinus infections within 1 year
- Two or more months on antibiotics with little effect
- Two or more pneumonias within 1 year
- Failure of an infant to gain weight or grow normally
- Recurrent, deep skin or organ abscesses
- Persistent thrush in mouth or fungal infection on skin
- Need for intravenous antibiotics to clear infections
- Two or more deep-seated infections including septicemia
- A family history of PID

Respiratory diseases are the main and initial manifestations in most cases and the most common complications. Since the spectrum of pulmonary manifestations in PID is broad, those are divided into upper respiratory and lower respiratory tract manifestations.²³

Upper respiratory tract

The most frequent presentations are sinusitis, otitis media and laryngeal angioedema.

Sinusitis: Sinusitis or rhinosinusitis is defined as a common inflammatory condition of the paranasal sinuses and nasal cavity that can be acute or chronic (>12 weeks). In a systematic review, 10% to 54% of patients with chronic sinusitis had PID.²⁴ One study reported considerable differences in the incidence of sinusitis in PIDs, such as agammaglobulinemia (11.52%), CVID (9.4%), SCID(1.8%), IgGSD (13.41%), SIgAD (6.58%) and HIGM (0.7%).⁸ In general, broad spectrum antibiotics, saline nasal washes, anti-inflammatory agents and immunoglobulin replacement therapy could reduce the frequency and severity of sinusitis in PID patients.²⁵

Otitis Media: Recurrent otitis media is considered to be one of the most common infections in PID, although its frequency varies between the different forms of PIDs.²⁶ It is more common in primary antibody deficiency (PAD) than in combined immunodeficiency.¹⁰ Yazdani et al. demonstrated 81.1% of XLA patients manifested acute otitis media.²⁷ They also found a lower rate of otitis media in CVID patients.²⁸ Infection is more severe in patients with IgGSD and SIgAD.²⁹

Laryngeal angioedema: Hereditary angioedema (HAE), which is clinically manifested by recurrent angioedemas in different parts of the body. Potentially life threatening is the angioedema located to larynx.³⁰ Several types of PIDs should be considered in patients with HAE. Decreased level or dysfunction of C1 esterase inhibitor (C1INH) has been estimated to have a prevalence of 1 case per 50,000 individuals causing HAE. C1INH deficiency patient should be treated with purified or recombinant C1INH and bradykinin receptor antagonists.¹⁰

Lower respiratory tract

Bronchiolitis and infantile wheeze: Bronchiolitis and infantile wheeze are the most frequent causes of typical wheezing symptoms during infancy. In fact, recurrent lower respiratory tract viral infections have been reported as associated to transient hypogammaglobulinemia of infancy.³¹ However, persistent wheezing symptoms resistant to B2 adrenergic-agonist and anti-cholinergic therapies should be considered for hypogammaglobulinemia and if the child experiencing life threatening

symptoms, IVIG should be administered. Persistent bronchiolitis by RSV may occur in patients with SCID. The infections are severe, prolong and complicated.³²

Bronchitis: Acute bronchitis is characterized by cough due to acute inflammation of the trachea and large airways when there is no evidence of pneumonia. Cough associated with acute bronchitis typically lasts about 2-3 weeks.³³ Patients with antibody deficiencies are at increased risk of bronchitis. In one study, 54.4% of CVID patients presented with bronchitis as the first manifestation.³⁴ In another study, 78% patients with XLA had bronchitis.

Pneumonia : Recurrent pneumonia is one of the most common and characteristic signs of PAD. Almost two-thirds of CVID patients have experienced at least 1 episode of pneumonia before diagnosis and many experienced multiple prior episodes.³⁵ A high rate of pneumonia has been also observed in patients with XLA (62%)³⁶, X-linked HIGM (81%)³⁷ and WAS (45%).³⁸ Recurrent pneumonias are typical clinical features for all the three types of HIES. Pneumonia and chronic lung disease can be observed also in the patients with DNA repair deficiencies (AT, Bloom syndrome),³² CGD,³⁹ SCN⁴⁰ and deficiency of C3 complement.⁴¹ In patients with PID, pneumonia can be severe and require high-dose immunoglobulin replacement therapy, intravenous antibiotics, and/or hospitalization. Immunoglobulin replacement therapy is useful in PID patients with pneumonia, as it increases the level of IgG to at least the mid-normal range.⁴² By preventing pneumonia, treatment with immunoglobulin can also decrease accompanying complications, such as bronchiectasis and chronic lung disease.⁴³

Bronchiectasis: PID is one of the most common causes of bronchiectasis. Chronic airway inflammation, such as in recurrent pulmonary infections and autoimmune disease is supposed to be the primary cause of bronchiectasis. In PID, recurrent pulmonary infections and chronic inflammatory airways lead to bronchiectasis.⁴⁴ There is chronic and abnormal dilatation of the airways in bronchiectasis. Patients with PADs are at a significantly increased risk for developing bronchiectasis.⁴⁵ About 37.5% of patients with bronchiectasis were diagnosed with defects in antibody-mediated immunity that was indicated in a study.⁴⁶ More than 70% of CVID patients develop bronchiectasis indicating that bronchiectasis is a well-

recognized complication of CVID.⁴⁷ The incidence of bronchiectasis in patients with XLA is almost 32%.⁴⁸ In SIgAD and IgGSD, bronchiectasis is much lower than that of XLA and CVID.⁴⁹ The incidence of bronchiectasis in HIGE is < 2.5 % and in phagocyte defect is <1% to 10%.⁵⁰ High resolution computed tomography (HRCT) is considered a reliable test for assessing bronchiectasis in patients with PID.⁵¹ They are in general cylindrical, bilateral and diffuse. It is most commonly found in the middle or lower lobes and less frequently in the upper lobes.¹⁰ Bronchiectasis secondary to PID in childhood is not always a progressive condition and there is a potential to slow or prevent disease progression with appropriate treatment.⁵² The aggressive antibiotic treatment, physiotherapy and substitution therapy with immunoglobulins are the most important preventive strategy. The appropriate treatment may delay the development and also alter the natural course of bronchiectasis. The earlier the immunoglobulin substitution is started, the lower probability of bronchiectasis development.⁵³

Interstitial lung diseases (ILDs) and PIDs : In patients with PIDs having recurrent respiratory infections, ILD is frequent and much more prevalent than expected from general population especially in antibody deficiencies.⁵⁴ ILDs are a group of chronic inflammatory diseases and are major complications of PIDs. It is asymptomatic in initial stage but symptoms appear at later stages of disease course such as pulmonary hypertension, cor pulmonale and respiratory failure and is associated with fibrosis.⁵⁵ ILDs rarely occur in childhood. CVID-associated ILD is known as granulomatous-lymphocytic interstitial lung disease (GLILD). Lung pathology of GLILD includes lymphocytic interstitial pneumonia, follicular bronchiolitis, granulomatous lung disease and organizing pneumonia.⁴³ GLILD is the most common ILD and associated with poor outcome. Spirometry reveals restrictive lung disease in ILD by decreasing the diffusing capacity of lungs for carbon monoxide.⁵⁶ HRCT is the diagnostic choice for early detection and confirmation of suspected ILD.⁵⁷ Immunoglobulin replacement therapy is effective for prevention of GLILD. However, corticosteroids are first line approach in several studies. Combination therapies are also indicated in some studies.⁵⁸ Antifibrotic agents, especially pirfenidone and nintedanib, can be used in patients with ILD.⁷

Tumors of respiratory tract: Malignancy is the second most leading cause of death in PIDs (6%-10% worldwide). Tumors are often associated with Epstein-Barr virus (EBV) in 30%-60% cases. Non-Hodgkin lymphoma is found in as many as 8% of patients with CVID.⁵⁹ Patients with ALPS are at a higher risk of developing the Non-Hodgkin and Hodgkin lymphoma.²¹ There is increased risk of lymphoreticular malignancy in patients with AT.³² The incidence of EBV associated lymphoma is also high in WAS.¹⁹ Pulmonary compromise due to metastasis (origin from e.g. gastric carcinoma) is more often seen than primary pulmonary malignancy.¹⁰

Conclusion:

Pulmonary manifestations are the most common form of presentations of different PIDs in children. Infectious and non-infectious respiratory complications determinate the patient's prognosis. These complications are associated with significant morbidity and mortality in PID patients. Pulmonary manifestations should be recognized accurately in early stage to improve patient's survival. Appropriate awareness of these manifestations is essential, especially for the pulmonologist to reduce morbidity and mortality in PID patients.

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