Respiratory Manifestations of Humoral Primary Immunodeficiencies

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Abstract

Primary immunodeficiencies comprise a genetically heterogeneous group of rare disorders that are caused by genetic defects or developmental defects of the immune system.

The most typical manifestations are recurrent infections, but other associated conditions can also be observed, such as severe allergic reactions, asthma, lymphoid hematopoietic neoplasia, autoimmune diseases, chronic inflammatory bowel disease and endocrinopathies.

Antibody deficiencies are predominantly accompanied by sinopulmonary infections caused by extracellular encapsulated bacteria and secondarily accompanied by gastrointestinal infections. Severe forms of congenital agammaglobulinemia or variable common immunodeficiency can evolve with complications such as bronchiectasis, gastrointestinal diseases, malignancies and autoimmune diseases.

The main therapeutic tool for patients with antibody deficiencies is gammaglobulin replacement by the intravenous or subcutaneous route. This treatment has proved to be highly effective in reducing the number and severity of infections and the number of hospitalizations, in addition to presenting a good safety profile and very low risks for serious adverse reactions.

Keywords: Antibodies; Gammaglobulin; Immunodeficiency; Infections; Respiratory Manifestations

Introduction

Primary immunodeficiency diseases (PID) are inherited defects of the immune system which predispose affected individuals to severe and recurrent infections, malignancy, immune dysregulation with autoimmune disease and abnormal inflammatory responses. So far more than 150 different genetic kinds of PID have been identified [1,2].

The prevalence of PID is approximately 1 individual in 2,000 live births, especially when consanguinity is present [3].

The most typical manifestations of PID are recurrent or prolonged infections caused by specific microorganisms or by pathogens of low virulence, height and weight growth retardation, an inadequate response to habitually used antibiotic therapy, high risks of complications and hospitalizations, and severe reactions to attenuated vaccines [2]. In countries where the BCG (Bacillus Calmette-Guérin) vaccine is used, pediatricians must be alert to its severe or fatal complications in other family...
members because this is a warning sign and can be an important tool for the early diagnosis of severe combined immunodeficiency (SCID) or of other severe forms of PID [4].

The pattern of the organ systems affected as well as the characteristic pathogen varies according to the type of PID and are presented in Table 1 [5]. Thus it is important to identify, as much as possible, the foci of infections as well as the pathogens involved and the response to treatment.

Table 1: Main clinical characteristics of PID. Adapted from Woroniecka & Ballow (5).

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>T cell defects</th>
<th>Antibody defects</th>
<th>Phagocyte defects</th>
<th>Complement defects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of onset</td>
<td>Early</td>
<td>Early</td>
<td>Early</td>
<td>Early age</td>
</tr>
<tr>
<td>Most common pathogens</td>
<td>Mycobacterium</td>
<td>Listeria</td>
<td>salmonella</td>
<td>Neutropenia (NK)</td>
</tr>
<tr>
<td>Most common alterations</td>
<td>Malformations in the gonads, persistent candidiasis</td>
<td>Lymphopenia, autoantibodies, monoclonal gammopathy, vasculitis, immuno-osseous dysplasia</td>
<td>Cytopenia, sepsis, opportunistic infections</td>
<td>Neutropenia, Leukopenia</td>
</tr>
<tr>
<td>Special characteristics</td>
<td>Childhood disease caused by maternal cells or non-vaccinated blood, inflammation after BCG vaccination, hypercalcemia</td>
<td>Increased production of antibodies due to defects of B cells or flaws of interaction between T and B cells</td>
<td>Vascular, synovial, skin, dermatoosseous, pneumo-osseous infections</td>
<td>Neutropenia, Leukopenia</td>
</tr>
</tbody>
</table>

However, malignancy and inflammatory and autoimmune disturbances are also often seen in several PID. Most of the malignancies are hematologic in origin (lymphoma and leukemia) [6]. Autoimmune diseases arise as a result of the same immunologic defect and include vasculitides, inflammatory arthropathies and autoimmune cytopenias [7].

PID are classified and divided into 8 groups according to a combination of mechanistic and clinical characteristics. These categories include defects of the adaptive immune response which are subdivided into humoral or antibody deficiencies and the combined deficiencies that compromise both cellular and humoral mechanisms. A different category of immunodeficiency syndromes with characteristic phenotypes is distinguished, along with autoimmune syndromes, defects of innate immunity, disorders of immune dysregulation, defects of phagocytes, and complement deficiencies (Table 2). Among these categories, humoral deficiencies are the most frequent, corresponding to about half the cases [8].

Table 2: Categories of PID. Adapted from Chapel, 2012 (6).

| 1. Deficiencies predominantly of antibodies |
| 2. Combined deficiencies (T and B cells) |
| 3. Other well-defined immunodeficiencies |
| 4. Diseases of immunologic dysregulation |
| 5. Congenital phagocyte defects |
| 6. Inborn immunity defects |
| 7. Autoinflammatory diseases |
| 8. Deficiencies of the complement system |

Humoral Primary Immunodeficiencies

The humoral primary immunodeficiencies (HPID) are a group of disorders characterized by deficient production of antibodies due to defects of B cells or flaws of interaction between T and B cells.

The evaluation of humoral response competence is essential to define the diagnosis of HPID. The list of laboratory tests for humoral immunity can be found in Table 3.

Table 3: Laboratory tests for humoral immunity.

<table>
<thead>
<tr>
<th>Screening tests</th>
<th>Advanced tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum immunoglobulin levels</td>
<td>Flow cytometry to enumerate T cell subsets</td>
</tr>
<tr>
<td>Serum specific antibody levels</td>
<td>Flow cytometry to enumerate B cell subsets</td>
</tr>
<tr>
<td>Antibody response to booster immunizations</td>
<td>Flow cytometry to enumerate total B cells</td>
</tr>
</tbody>
</table>

The laboratory spectrum of the diseases is variable. All kinds of agammaglobulinemia (x-linked and autosomal recessive forms) are associated with very low numbers of B cells as well as very reduced levels of all immunoglobulins. Patients with common variable immunodeficiency (CVID) usually present variable reduction of two or more major immunoglobulin classes, impairment of specific antibody response and B cell numbers that can be reduced or not. Specific antibody deficiency, selective IgA deficiency, IgG subclass deficiency and transient hypogammaglobulinemia of infancy are milder antibody deficiencies and can be associated with variably low levels of immunoglobulin classes or subclasses in serum and impairment of specific antibody production [8].

About 60% of patients with HPID present lung abnormalities. Recurrent and prolonged infections of the upper and
lower respiratory tract are the major clinical manifestations in these patients, because the immune response mediated by antibodies is the principal defense mechanism against respiratory pathogens [2,9,10]. The main causes of the respiratory infections are extracellular encapsulated bacteria.

Recurrent infections and lung damage are the most common causes of morbidity and mortality in patients with HPID [11]. Some patients with HPID, especially CVID, can present clinical manifestations in adulthood [12-14].

**X-Linked Agammaglobulinemia**

This immunodeficiency is characterized by a disorder of B cell maturation arising from defects in a signal transduction molecule called Bruton's tyrosine kinase (BTK), which is required for the maturation of B-lymphocytes. Patients with X-linked agammaglobulinemia have less than 2% circulating B cells and very low levels of all immunoglobulins, especially IgG (usually < 200 mg/dL) [15].

In most patients, clinical manifestations start at 9 months of life. Before that, the presence of the mother's antibodies prevents infections.

Recurrent sinopulmonary infections are very frequent in these patients. The main microorganisms involved are Streptococcus pneumoniae, Haemophilus influenzae, Pseudomonas aeruginosa, Echovirus and Mycoplasma pneumoniae. A retrospective study of 842 patients with immunodeficiency (50.4% had HPID) showed that patients with X-linked agammaglobulinemia had a higher frequency of chronic rhinosinusitis compared to patients with other HPID [15].

Late diagnosis increases the risk of bronchiectasis and a variety of other forms of infiltrative and inflammatory lung disease. This is an important component of overall mortality, morbidity and quality of life [16].

In general, patients with X-linked agammaglobulinemia respond appropriately to antibiotics and intravenous immunoglobulin therapy [17].

**Transient hypogammaglobulinemia**

This is a very common pediatric condition. Most patients show a reduction of serum IgG levels (possibly accompanied by reduced IgA and/or IgM levels) at least 2 standard deviations below the mean for normal individuals of the same age range, with levels returning to normal spontaneously between 2 and 3 years of age. In some patients, however, this reduction is prolonged up to 4 or 5 years of age. Characteristically, the patients show normal production of isohemagglutinins and antibodies in response to immunization, as well as unchanged cell immunity [18].

Usually patients are asymptomatic. However, eventually patients can present with mild recurrent viral and bacterial infections, especially of the respiratory tract like otitis, sinusitis [19] and pneumonia [18]. Usually the infections are self-limited and have a good prognosis, with a low rate of hospitalizations and a satisfactory response to antimicrobial agents when they are necessary [18,19].

The most common etiologic agents are extracellular bacteria such as Streptococcus pneumoniae, Haemophilus influenzae, Staphylococcus aureus and enteroviruses [19,20].

Allergic diseases are also frequently observed in patients with transient hypogammaglobulinemia, affecting up to 30% of cases, such as asthma, allergic rhinitis, atopic dermatitis, and food allergy [19, 21,22].

A definitive diagnosis is possible only in a retrospective manner after normalization of immunoglobulin levels [19]. No specific therapeutic measures are recommended for asymptomatic patients or patients with few infections, who only require clinical follow-up and appropriate antimicrobial treatment, since transient hypogammaglobulinemia is self-limited and tends to correct itself by up to 36 months of age [21,23].

Routine intravenous immunoglobulin replacement is not indicated, but may be recommended for patients with serious and invasive infections [24].

**Common Variable Immunodeficiency**

This is a heterogeneous syndrome characterized by immunoglobulin deficiency, with reduced serum IgG levels (more than 2 standard deviations below the appropriate value for the age range), and also possibly accompanied by reduction of IgA and IgM levels, and by the inability to produce antibodies against specific antigens after exposure, with reduced or absent isohemagglutinin titers [25,26].

Even though CVID is a primarily humoral immunodeficiency based on B cell abnormalities, more than 50% of the patients also show changes related to cell immunity such as abnormal T lymphocyte proliferation in vitro, accelerated apoptosis of these cells, insufficient production of interleukins 2 and 10, and dendritic cell dysfunction [25].

Common variable immunodeficiency usually does not occur during the first years of life, being of later onset. This disease has 2 peaks of incidence: from 2 to 5 years and from 16 to 20 years of age. However, it is more frequently diagnosed after the second decade of life [26].

Common variable immunodeficiency belongs to a group of rare diseases with highly variable clinical presentation. The most common clinical manifestations of this
immunodeficiency are recurrent infections of the respiratory tract (otitis, sinusitis, tonsillitis and pneumonia) and of the gastrointestinal tract [25,26]. Due to the large number of respiratory infections and their chronicification, the patients frequently develop severe complications such as bronchiectasis, chronic obstructive pulmonary disease, interstitial lung disease and pulmonary fibrosis, causing irreversible injury to pulmonary tissue which can lead the patients to respiratory failure [25,27].

The most common causes of respiratory infections are Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catharralis and Mycoplasma pneumoniae [24].

Patients with CVID can present with other kinds of infections like conjunctivitis (especially caused by non-capsulated Haemophilus influenzae), septic arthritis (caused by Mycoplasma sp and Ureaplasma urealyticum), bacterial meningitis, sepsis and opportunistic infections (though uncommon) caused by viruses, fungi and protozoan [5,24].

Infections can commonly be also associated with granulomas, autoimmune, lymphoproliferative and atopic processes.

Multisystemic granulomatous disease is a well documented complication, with the lungs being the organs most affected, although other organs may also be compromised [25,28].

Autoimmunity is observed in about 20 to 25% of patients with CVID. Immune thrombocytopenic purpura and autoimmune hemolytic anemia are the conditions most frequently detected [25]. Other autoimmune diseases may be present, such as autoimmune thyroiditis, diabetes mellitus, dermatomyositis, Graves’ disease, systemic lupus erythematosus, vitiligo, primary biliary cirrhosis, ulcerative colitis, Chronic’s disease, idiopathic intestinal inflammatory disease, Sjögren’s syndrome, and psoriasis [25,29].

Benign lymphoproliferative diseases may be associated with CVID, such as generalized lymphadenomegaly, splenomegaly and nodular lymphoid hyperplasia [25,29]. The risk of malignancy is higher in CVID patients than in the general population.

There is also the possibility of coexistence of CVID and atopy, with the probability of a CVID diagnosis, as well as a diagnosis of other primary immunodeficiencies, being higher among atopic patients. This association may be possibly due to an intrinsic deregulation of the humoral immune response [30].

Interestingly, common variable immunodeficiency is the most frequent immunodeficiency in adults. This disease tends to appear later in childhood.

Immunoglobulin replacement has proved to be highly effective by significantly reducing the incidence of acute respiratory infections, especially pneumonias, and reducing the risk for chronic lung disease. In addition, immunoglobulin replacement reduces the frequency of hospitalizations due to infection, with a consequent reduction of mortality and an improvement of quality of life [31,32].

**Selective IgA Deficiency**

Selective IgA deficiency is defined as serum IgA levels lower than 7 mg/dL, normal IgG and IgM levels and a normal response to vaccine antigens in male or female patients aged 4 years or more [33].

Partial IgA deficiency is defined as serum IgA levels at least 2 standard deviations below the mean concentration for each age range but with normal IgG and IgM levels, in children aged 4 years or more. Patients with partial deficiency may spontaneously progress to remission [34].

Selective IgA deficiency may be frequently associated with autoimmune, neoplastic, allergic and infectious diseases.

The autoimmune diseases most frequently associated are systemic lupus erythematosus, rheumatoid arthritis, ankylosing spondylitis, scleroderma, Henoch-Schönlein purpura, psoriasis, myastenia gravis, celiac disease, ulcerative colitis, active chronic hepatitis, and diabetes mellitus [35].

Although there is controversy about a greater predisposition to the development of cancer in patients with selective IgA deficiency, case studies have shown the occurrence of some forms of neoplasias in these patients, such as adenocarcinoma of the stomach, jejunal B cell lymphoma [36], colon carcinoma, lymphosarcoma, melanoma, and thymoma [37].

There is evidence of an association between selective IgA deficiency and allergic diseases, especially rhinoconjunctivitis, asthma, urticaria and atopic dermatitis [38]. There may also be an increased frequency of food allergy [35] and of high serum IgE levels [39].

Another relevant aspect is that many patients with selective IgA deficiency, especially those with associated IgG2 deficiency, may develop anti-IgA antibodies [40]. Thus, post-transfusional anaphylactic systemic reactions may occur; although infrequently.

Although approximately 50% of patients with selective IgA deficiency may be asymptomatic or oligosymptomatic, those who have other associated immunodeficiencies, especially IgG2 and antipolysaccharide antibody deficiency, may have recurrent sinopulmonary respiratory infections [41,42] and gastrointestinal infections, especially giardiasis.
A retrospective study conducted in Spain evaluated 331 pediatric patients with selective IgA deficiency and showed that 47% of them had upper respiratory infections, 19% were submitted to adenoidecotomy, 24% had otitis and 11.8% had recurrent otitis. Regarding lower respiratory tract infections, 17.8% had pneumonia, 6% recurrent pneumonias and 1.8% had complications with sequelae like bronchiectasis in six patients and lobectomy in two patients [43].

There is no specific treatment for symptomatic patients with selective IgA deficiency. Because of their increased risk of parasitic infection, these patients should be instructed about proper cleaning of legumes, fruits and vegetables and about the intake of treated water. Specific therapeutic measures are recommended for the associated comorbidities such as allergic and autoimmune diseases and infections. In special situations, particularly during the winter, systemic and/or intranasal antibiotic prophylaxis may be indicated. In patients with associated polysaccharide antibody deficiency and IgG2 deficiency refractory to antibiotic treatment, intravenous immunoglobulin replacement may be instituted [44,45].

**IgG Subclass Deficiency**

The four IgG subclasses (IgG1: 58–71.5%; IgG2: 19–31%; IgG3: 5–8.4%; IgG4: 0.7–5%), exert distinct biological activities. The humoral immune response to a certain antigen may be restricted to one subclass. Isolated or combined immunoglobulin subclass deficiencies, even without a decrease in total serum IgG concentrations, have been described [46].

The IgG1 and IgG3 subclasses correspond to antibodies against protein antigens, including bacterial, viral and autologous proteins. On the other hand, the IgG2 subclass predominates in the response to polysaccharide antigens [47].

Patients with a complete IgG subclass deficiency are usually asymptomatic [47]. However, the absence or deficiency of one or more IgG subclasses has been associated with an increased risk of sinopulmonary infections, especially for IgG2 deficiencies, which is associated with the inability to mount a specific antibody response against polysaccharides [48]. Interestingly, the severity of clinical manifestations is not related to the degree of IgG subclass deficiency [46].

Severe asthma in children has also been reported to be associated with IgG subclass deficiency, especially IgG3 deficiency. However, IgG subclass deficiency appears not to be a suitable predictor of the development of infections in asthmatic children [47].

Usually no specific treatment is required for patients with isolated IgG subclass deficiency. However, some patients with deficiency of IgG subclasses (especially IgG2) associated with IgA deficiency or with defects in the production of specific antipolysaccharide antibodies can benefit from regular treatment with intravenous gammaglobulin [32].

**Specific Antibody Deficiency**

Specific anti-polysaccharide antibody deficiency is a very common and non-life threatening primary immunodeficiency. Many patients can recover spontaneously, especially when they are less than 5 years old. Thus, in young children this immunodeficiency is often transient and probably simply constitutes a delay in the physiological maturation of the response to polysaccharide antibodies [49].

For the evaluation of complete immune function, specific antibody titers to both protein and polysaccharide antigens should be obtained [50].

Antibody levels to protein vaccine antigens such as diphtheria and tetanus are often determined [24]. With respect to polysaccharide antigens, antibody levels measured after natural exposure or immunization with unconjugated pneumococcal vaccine are indicative of an adequate polysaccharide response. Newer conjugated pneumococcal vaccines couple the polysaccharide to a protein carrier and the response to these vaccines is indicative of a good protein response [24].

IgG specific for the serotypes included in currently used pneumococcal vaccines may be determined by a standardized ELISA method and expressed in micrograms per milliliter (51). Protection against invasive pneumococcal infection and colonization is associated with antibody levels of 1.3 µg/mL or higher [52].

Thus, current diagnostic criteria consider a response to be adequate when post-vaccination levels determined after 4 weeks are 1.3 µg/mL or higher or when there is at least a 4-fold increase for 50% of the tested serotypes (children between 2 and 5 years old) and for 70% of the tested serotypes (children over 5 years old) [24]. This criterion is not reliable for detecting this immunodeficiency in children less than 2 years of age because in this age group the response to polysaccharide antigens may be physiologically impaired [49].

This immunodeficiency can affect up to 11% of children with recurrent respiratory infections. The most common infections are acute otitis media, sinusitis and pneumonia caused by Streptococcus pneumoniae [49].

Symptomatic patients can benefit from prophylactic antibiotics or intravenous gammaglobulin [53]. However, this treatment may not be necessary in most young children with this immunodeficiency [49].
Conclusions

HPID correspond to almost 50% of all PID.

The major clinical manifestations are recurrent and prolonged infections of the upper and lower respiratory tract, mainly caused by extracellular bacteria.

However, malignancy, autoimmune and inflammatory disturbances can also be found in some HPID.

Bronchiectasis, chronic obstructive pulmonary disease, interstitial lung process, lung fibrosis and granuloma are the main causes of lung damage and contribute to a poor prognosis.

These immunodeficiencies should be rapidly diagnosed so that treatment may be instituted as early as possible in order to prevent these complications and to improve the survival and quality of life of the patients.

References


