Chronic pediatric pulmonary disease and primary humoral antibody based immune disease

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Summary
Chronic inflammation of the larger airways is a common occurrence in children. A number of factors such as younger age, premature birth, male gender, exposure to environmental smoke or pollution, and crowded housing can increase a child’s susceptibility to chronic lung disease. Chronic bronchitis may be caused by an underlying humoral immunodeficiency if the clinical course is recurrent or prolonged. Primary humoral immunodeficiency accounts for approximately 70% of all immunodeficiencies. The differential of chronic bronchitis also includes Cystic Fibrosis, ciliary defects and immune cellular and phagocytic defects.1,2 This review will summarize the most common humoral antibody based immune based deficiencies associated with chronic pulmonary disease.

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Contents

Introduction ........................................................................ 512
X-Linked agammaglobulinemia .................................................... 512
Selective IgA deficiency ............................................................ 512
IgG subclass deficiency ............................................................ 512
Combined variable immunodeficiency (CVID) .................................................. 512
Hyperimmunoglobulin E or job syndrome ................................................... 513
Hyper-IgM deficiency ................................................................ 513
Specific diagnostic evaluations ............................................................ 513
Conclusions ......................................................................... 514
Conflict of interest ................................................................... 514
References ........................................................................... 514

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Introduction

Primary Immune Deficiency is an identified cause of chronic bronchitis and recurrent pneumonia. The early identification and management of primary humoral immunodeficiency may help preserve lung function and lung growth. Failure to thrive and secondary heart disease may occur once bronchitis is established. Most patients with humoral immunodeficiency do not have fungal, mycobacterial or non-enteroviral disease.

The presentation of humoral deficiency trends to occur in the first years of life rather than at birth, since there is a passive transfer of maternal IgG, and a delay in fetal production of antibodies. Preventive strategies include the use of secretion mobilization, vaccination and possibly prophylactic inhaled or oral antibiotics. The mainstay of therapy for most of the diseases described in this review is intravenous immunoglobulin (IVIG). The goal of this review is to describe the pathophysiology, clinical diagnosis and management of chronic lung diseases caused by primary humoral immunodeficiency.

X-Linked agammaglobulinemia

X-Linked agammaglobulinemia (XLA) is one of the primary immunodeficiencies, and is inherited by presence of a mutation located on the X chromosome, encoding for tyrosine kinase, a key regulator of B cell maturation. There have been hundreds of mutations in the Bruton’s tyrosine kinase gene identified. As a result in XLA, otherwise known as Bruton’s disease, B cell numbers are low and B cell function is affected. T cell function and numbers are preserved and cell-mediated responses are normal. The clinical presentation commonly includes an uneventful course for the first six to nine months of life. Once maternal antibodies wane, there is a dysfunction in Ag-presenting cell differentiation occurs in patients with Bruton’s agammaglobulinemia. There is sometimes associated neutropenia. CD3, CD4, and CD8 lymphocyte populations are preserved, but CD19/20 lymphocyte subsets are significantly diminished. Delayed-type hypersensitivity and in vitro T cell proliferation are normal, while specific antibody responses are weak.

Typical respiratory pathogens include Hemophilus Influenzae, Pseudomonas aeruginosa, Streptococcus pneumoniae, ECHO virus, and Mycoplasma pneumoniae. Patients will typically respond to appropriate antibiotics and intravenous immunoglobulin (IVIG) replacement therapy. Some patients who have underlying lung damage at the time of treatment will present with bronchiectasis.

Selective IgA deficiency

As the most common primary humoral immunodeficiency, as many as 1 in 333 caucasians may be affected with IgA deficiency. Asians and African Americans are generally less commonly afflicted. Both environmental and genetic risk factors contribute to the condition, and it is often present in healthy individuals. Some patients present with increased susceptibility to gastrointestinal and respiratory infections, while others have an increased risk for allergic or autoimmune diseases.

Clinical presentation with recurrent or problematic viral or bacterial pulmonary infections is common and similar to those associated with XLA. The infections can be controlled with appropriate use of antibiotics. Since patients have a normal IgG and possibly anti-IgA antibodies, there is no role for the use of intravenous replacement. IgA deficiency unlike XLA is a selective defect in the defense of mucosal surfaces, and replacement strategies are therefore not as effective.

Diagnostic laboratory results include a significantly diminished IgA, with a normal IgG, T cell function and number. Since children do not reach adult levels of IgA until around eight years of age, the diagnosis is often delayed until the child is at least four years old. IgA deficiency is also found in association with IgG2 deficiency and CVID. There is also a defect in T cell priming by antigens in most patients. As a result there is a dysfunction in Ag-presenting cells and increased production of IFN-gamma by CD8+ cells, enhanced rates of apoptosis, and often a presence of auto anti-IgA antibodies.

IgG subclass deficiency

Most patients with IgG subclass deficiency are without symptoms, but some patients do have recurrent sino-pulmonary infections. IgG2 deficiency in particular results in lack of production of antibodies against polysaccharides and recurrent infection with encapsulated bacteria. Diagnostic workup should include specific antibody levels to a broad array of protein and polysaccharide antigens to provide a mechanistic correlate to the IgG subclass deficiency. As noted above some patients also may have IgA deficiency. There are no described T or B cell proliferation defects, and IVIG may be useful in some patients.

Combined variable immunodeficiency (CVID)

Combined Variable Immunodeficiency (CVID) is a heterogeneous group of disorders characterized by hypogammaglobulinemia and defective specific antibody
production. CVID involves multiple different genetic disorders, with an estimated incidence of 1: 10,000. Thus, it is far rarer than IgA deficiency. It tends to present later in childhood with recurrent sino-pulmonary infections caused by similar pathogens as found with XLA or IgA deficiency. CVID patients have normal blood T and surface Ig-bearing B cells and are able to defend normally against fungal and viral infections. Approximately 10% of CVID patients have recurrent wheezing. In contrast to XLA, the pattern of inheritance is thought to be autosomal dominant and it presents later in life. As a result of low levels of all major immunoglobulins, XLA and CVID share many more clinical features in comparison to IgA deficiency. The presentation in CVID unlike XLA, rarely involves entero viral meningocerephalitis. On physical exam, patients with CVID have normal tonsillar tissue, and approximately 15–25% exhibit lymphadenopathy or splenomegaly.

CVID is associated with enhanced risk for cancer, lymphoproliferative and autoimmune diseases. Diagnostic evaluation is characterized by, normal CD3, 4, 8 lymphocyte levels, anemia, decreased immunoglobulin levels, with weak specific antibody levels. Treatment is similar to Bruton’s agammaglobulinemia which uses intravenous immunoglobulin and antibiotics to prevent ongoing lung damage and subsequent infections.

**Hyperimmunoglobulin E or Job syndrome**

Since Buckley et al. reported the details of the clinical presentation of patients with hyperimmunoglobulin E (IgE) in patients with hyperimmunoglobulin E syndrome, recurrent cystic lung disease has been recognized as one of the later features of the disease. Underlying molecular causes of this rare disease (1:1,000,000) include mutations of signal transduction and activation of transcription 3 (STAT3) gene. The pulmonary manifestations begin with recurrent viral infections and subsequent chronic cystic lung disease. The pulmonary problems typically present after recurrence of staphylococcal skin abscesses. Patients who inherit the disorder in an autosomal recessive manner tend to lack pneumatocele formation. The patients with autosomal dominant disease have severe pulmonary disease and pneumatocele formation which can lead to early mortality. Pneumatoceles are associated with recurrent pneumonia in 80% of patients. Despite the presence of high levels of IgE, patients with Jobs syndrome do not typically have wheezing or bronchial hyperresponsiveness. In contrast, children present with chronic cough productive of purulent sputum, rhonchi and rales on physical examination. Diagnostic evaluation should include CT scans of the lung to detect pneumatoceles, pulmonary function testing and possibly broncho-alveolar lavage to identify typical organisms. Specific pathogens which are common include *S. aureus*, *S. pneumoniae* and *H. influenzae*. Secondary organisms infecting pneumatoceles are *Pseudomonas*, *Aspergillus* and non tuberculosis species. Investigational studies on peripheral blood mononuclear cells may show low IFN-gamma responses to *S. aureus*. Immunoglobulin E (IgE) levels above two standard deviations are also characteristic of the diagnosis. Among infants, the IgE level may be lower than anticipated in suspected cases of Jobs syndrome.

The treatment strategies for the management of pulmonary infections in Job’s syndrome include IVIG, vaccines and regular visits to the specialist to evaluate lung function.

**Hyper-IgM deficiency**

Patients with autosomal recessive and X-linked forms of Hyper-IgM have elevated total IgM and very low levels of IgG, IgA and IgE, but retain normal T cells function. The disease is rare with an estimated incidence as low as 1/1 million live births. The autosomal forms are caused by defective enzymes (activation-induced cytidine deaminase or Uracil nucleoside glycolyase) needed for B cell development and antibody production. In the autosomal form, cellular immunity is typically not affected. The clinical pulmonary presentation reflects the loss of resistance to encapsulated bacteria and patients have recurrent sino-pulmonary infections. On physical exam, there is lymphoid hyperplasia in the autosomal forms of the disease. The treatment includes prevention of infection and IVIG administration. In a study of 79 patients from 60 unrelated families with X-linked hyper-IgM syndrome, over 90% had developed symptoms by age 4 years. The same study reported that the most prominent infection was pneumonia (81%). The underlying infectious cause of the pneumonias included encapsulated bacteria, CMV, histoplasmosis and *P. jiroveci*. Compared to isolated defects of humoral immunity, and those with the autosomal form of Hyper-IgM syndrome, patients with the X-linked form are at risk for fungal pneumonias, such as those caused by Candida, Cryptococcus and Histoplasma.

**Specific diagnostic evaluations**

Chronic bronchitis is associated with slowly resolving or persistent symptoms such as productive cough, sputum production and intermittent fevers. Chest radiographic findings are atelectasis, bronchiectasis or focal consolidation. A sputum analysis for bacterial as well as viral agents such as adenovirus is helpful in guiding antibiotic therapy and providing a pattern of infection with certain pathogens.

An appropriate first step in diagnosis is a complete blood count with differential (CBC). This will establish whether lymphopenia or anemia is present. Normal lymphocyte counts in infants are typically higher than in adults. The CBC remains a basic and inexpensive screening test if aged based normals are used in its interpretation. If there is a lymphocyte count of less than 3000 lymphocytes/cubic mm or age specific normal values, then a flow cytometry is indicated to identify specific lymphocyte subsets which may be abnormal. The use of flow cytometry is also indicated if there is clinical suspicion. Among very young patients, flow cytometry may be more useful, since maternally derived lymphocytes may still be present and an absolute count alone would not distinguish the source. For functional analysis, cutaneous delayed-type hypersensitivity testing (DTH) is used to document a positive response. A positive DTH suggests that uptake, processing by antigen presenting cells to helper T cells and subsequent activation of monocytes and macrophages is intact. The drawbacks of this test are that: it requires intracutaneous antigen injection; is often suppressed during an infection or use of immunoregulatory drugs;
and is unreliable in children under the age of one year. The response necessitates that the patient return to have the skin test read at 48 or 72 h after injection. Induration of more than 5 mm is considered positive.  

Other essential screening tests are total serum immunoglobulins, IgG, IgA and IgM along with subclass levels of IgG. If X-linked disease is suspected, carrier detection is performed, in which 50% of mothers are expected to be carriers.  

Table 1 summarizes the pulmonary manifestations of each of the diseases discussed, along with the key immunologic diagnostic findings.

### Conclusions

Primary immunodeficiency is a common cause of recurrent bronchitis or bronchiectasis.

The identification of primary humoral immunodeficiencies begins with clinical suspicion and relies on accurate history, family history and physical exam and pathogen analysis. The preliminary screening tests may be performed in the office or clinic setting, before referral to an immunologist for further evaluation.

### Conflict of interest

None and the author has no disclosures, related to this manuscript.

### References