

Adult patients living with primary immune deficiency and bronchiectasis require early diagnosis and prompt medical treatment to improve and maintain their health status

Primary immune deficiency in bronchiectasis

In this article...

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- › Link between primary immune deficiency and bronchiectasis
- › Management of respiratory problems

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The primary purpose of the immune system is to protect the body from infection. Failure of the immune system can lead to repeated infections. The aim of this review is to discuss primary immune deficiency (PID) and its relationship with bronchiectasis in adults. It examines treatment options for patients with PID and provides practical details of how nurses can empower these patients to reduce their risk of respiratory infections.

Our body's immune system is designed to protect us against invading pathogens. It is made up of different elements that fight infections. Having an immune deficiency means the immune system is not functioning properly.

Primary immune deficiency (PID) is an umbrella term for more than 200 diseases where part of the body's natural defence mechanisms to fight infection is ineffective or absent altogether, leaving patients prone to infections. There are several types of PID, including common variable immune deficiency (CVID) and X-Linked-agammaglobulinaemia (XLA). Patients with CVID or XLA are predisposed to respiratory diseases, such as bronchiectasis (chronic dilation of one or more bronchi), because they produce no or too few immunoglobulins (antibodies) to fight infections. Early treatment with immunoglobulin replacement therapy protects patients

from acquired infections and progression of disease, and in turn reduces hospital admission rates, antibiotic use and time away from work.

The immune system

The immune system is primarily intended to protect the body against microbial pathogens and cancers. For protection to be effective, it is important that the system can differentiate between "self" and "non-self" cells, so the body does not work against healthy cells. Protecting the lungs against infection involves both innate and adaptive immune response mechanisms.

Innate immunity

The innate immune response is activated immediately in response to the presence of microbial pathogens and cancers, while the adaptive immune response takes longer and offers protection against re-exposure to the same pathogens. The receptors of innate immunity are activated when pathogens enter the body: the innate system senses danger and activates the adaptive immune system to respond. The function of innate immunity is to gather information about the pathogen and determine the best way to respond.

Adaptive Immunity

The key components of the adaptive immune response are B and T cells (lymphocytes), providing a second-line defence against invading pathogens (Abbas et al, 2012). T-helper cells stimulate the immune response of B cells to produce antibodies. T-suppressor cells control the level and quality of the immune response and Killer-T cells recognise and destroy infected cells and activate phagocytes to destroy the

5 key points

1 Antibody deficiency can cause susceptibility to respiratory infection

2 Recurrent lung infections drive an inflammatory response, which may lead to bronchiectasis

3 Treatment of patients with primary antibody deficiency and bronchiectasis is immunoglobulin replacement therapy

4 Patients who have repeated courses of antibiotics should be referred for investigation of their immune system

5 Diagnosis of PID is often delayed, resulting in increased morbidity, diminished quality of life and life expectancy

pathogens they have identified (Public Health England, 2013).

B cells can be easily distinguished by the presence of a protein on the outer surface known as a B cell receptor, and it is these proteins that bind to a specific antigen. When a B cell encounters an antigen it recognises, it proliferates and produces large numbers of lymphocytes, which secrete antibodies to bind to the antigen. This initial response results in the body being primed with immunocompetent B lymphocytes able to recognise the antigen on subsequent exposure.

B cells produce five different antibody classes known as immunoglobulins (Table 1). Although all immunoglobulin classes derive from blood plasma, there are only two major sources of immunoglobulins in lung secretions and sinus mucosa: IgG and IgA. They identify the bacteria involved and tag them for destruction by other cells of the immune system, such as neutrophils and macrophages.

If the B cells of the immune system do not mature due to an inherited genetic fault, there will be a depletion of antibody production. This deficiency can range from either having inadequate levels of B cells, causing hypogammaglobulinaemia in which the patient will have low levels of IgG, IgA and IgM, to complete absence of any type of immunoglobulin, which is known as agammaglobulinaemia.

Primary immune deficiency

PID is under-diagnosed and the prevalence can range from 1 in 500 to 1 in 500,000 in the general population (Kelleher et al, 2012). PID can contribute to the development of bronchiectasis because malfunction of the immune response mechanism leads to repeated and persistent infections that cause inflammation in the respiratory airways and, over time, structural damage to the bronchi (Bondioni et al, 2007). Two PIDs linked to bronchiectasis are discussed in this article: XLA and CVID.

X-Linked-agammaglobulinaemia

XLA is a genetic condition characterised by virtual absence of all immunoglobulin isotypes and circulating B lymphocytes but with normal T lymphocyte function. It is a rare genetic condition affecting approximately 200 patients in the UK (Webster, 2006). XLA usually presents in early childhood with recurrent bacterial sino-pulmonary, ear and gut infections with low serum immunoglobulins levels.

Improvements in outcome are linked with early diagnosis and treatment with immunoglobulin replacement therapy.

TABLE 1. CATEGORIES OF IMMUNOGLOBULIN

IgG	Found in the lower airways but makes up around 75% of antibodies in the blood. IgG half-life is around 23 days – four to ten times longer than other isotypes. It reacts against bacteria and viruses, and is transferred from the mother during pregnancy to the foetus so that the new-born infant is protected specifically against pathogens to which the mother has been exposed
IgM	Typically the first class of antibody made in a response to pathogens, IgM is commonly found in the lower airways. It is efficient at making large immune complexes that can underpin unwanted inflammation and disease. The production of IgM is down-regulated as soon as IgG is sufficiently generated
IgA	Found commonly in the upper airways: sinuses and mucosal secretions as well as in tears and sweat. IgA is also found in breast milk which can protect the gut of a new-born infant against infections. IgA is less abundant in blood than IgG as it is immediately transported into secretions
IgE	Involved in the allergic response and in defence against parasites. Their main property is to bind with mast cells and promote degranulation
IgD	A category of immunoglobulin of uncertain function and it is believed that it does not have a role in host defence
Source: Playfair et al (2013), Sompayrac (2012)	

Prevention of lung disease in XLA patients remains the challenge as there are no randomised controlled studies that have assessed the long-term benefits of antibiotic prophylaxis and specialist respiratory physiotherapy regimens. Long-term prognosis has improved with aggressive treatment from intravenous immunoglobulin treatment and antibiotic therapy although chronic lung disease remains a significant cause of death (Brown et al, 2011).

Common variable immune deficiency

The most common PID is CVID, with a European prevalence of 20.7% of all PIDs (Gathmann et al, 2009). CVID is defined by the European Society of Immunodeficiencies (2014) as a marked decrease in IgG and a marked decrease of IgA with or without low IgM (Table 1); with the presence of clinical criteria, which include:

- » Poor antibody response to vaccines;
- » Increased susceptibility to infections;
- » Auto-immune manifestations;
- » Granulomatous disease;
- » Unexplained polyclonal lymphoproliferation e.g. malignant lymphoma;
- » Affected family member with antibody deficiency.

Males and females are equally affected and it is commonly diagnosed in childhood and the second to the fourth decades of adult life.

It is thought that around 5% of patients do not have many infections, and come to medical attention due to the onset of

inflammatory or autoimmune complications, such as rheumatoid arthritis, and it is these factors that contribute to an average delay of around six to seven years in diagnosis (Resnick et al, 2012).

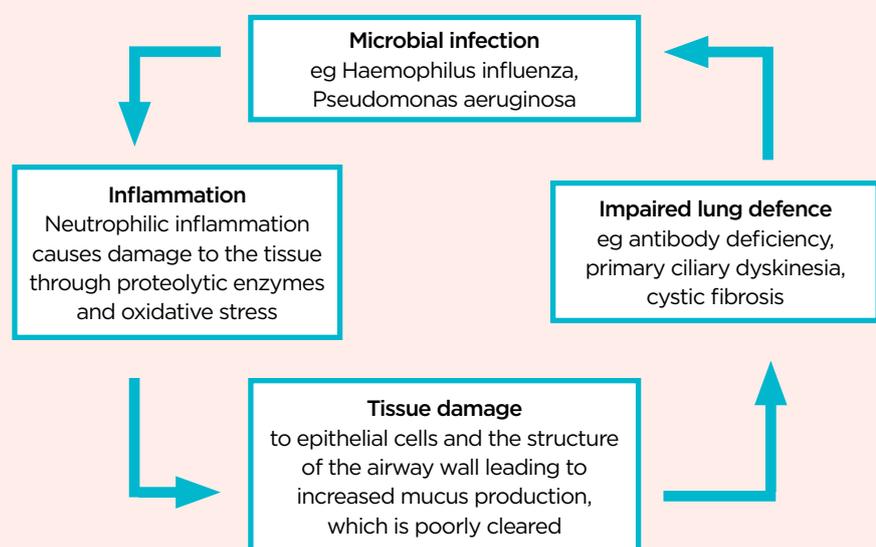
Improvements in outcome are linked with early diagnosis and treatment with immunoglobulin replacement therapy. Many patients will have long periods of good health, attend school, and have successful careers, but regular patient reviews by both the respiratory physicians and clinical immunologists will be required to maintain their health status.

PID and its association with bronchiectasis

Bronchiectasis is caused by weakness and destruction of muscular and elastic components of the bronchial wall. With loss of ciliated epithelium (the lining of the lungs that assists in removing secretions), the small airways and alveoli becomes collection points for mucus to accumulate. This collection of stationary mucus acts as an ideal environment for bacteria to grow and is the source of recurrent infections (Ozerovitch et al, 2011). The presence of infective bacteria leads to chronic inflammation and subsequent immune responses in the lungs, which in turn causes further damage to the walls of the bronchi, causing a vicious cycle with progressive lung disease. This is illustrated in Figure 1.

The presence of recurrent infective symptoms and upper respiratory tract infections in patients with bronchiectasis, that are present from childhood, gives a

FIG 1. A VICIOUS CYCLE OF INFECTION AND INFLAMMATION IN BRONCHIECTASIS



Source: Ozerovitch (2013)

- » Sputum specimens to detect respiratory infection;
- » Sputum cell count (neutrophils and eosinophils);
- » Physiotherapy assessment and when appropriate referral to dietetic; ear, nose and throat team, and gastroenterology team.

Treatment considerations Immunoglobulin therapy

Although there is no current cure for PID, treatment is based on replacing the missing immunoglobulin through the various parenteral administration routes (Ozerovitch, 2013). In most cases, respiratory patients receiving immunoglobulin treatment have fewer lung infections and those that occur are less serious particularly when replacement is coupled with prompt antibiotic treatment and chest physiotherapy regimens. Studies into intravenous immunoglobulin replacement therapy show higher doses reduce lung function decline and exacerbation frequency in patients with immune deficiencies and chronic co-morbidities (Chen et al, 2011; Orange et al, 2011).

Patients receiving subcutaneous immunoglobulin have reported better quality of life outcomes in terms of reduced time spent in hospital, fewer antibiotics and fewer days missed from work or school when compared to conventional hospital-based intravenous immunoglobulin replacement therapy (Eades-Perner et al, 2007; Gardulf et al, 2006).

Quarterly blood tests are used to monitor the effectiveness of the treatment (Kelleher et al, 2012). A record of upper and lower respiratory tract infections, antibiotic use and sputum bacteriology results, are useful measures of patient stability and effectiveness of treatment.

Patients prescribed either immunosuppressant or corticosteroids drugs need regular clinic reviews. Immunosuppressants are used to prevent rejection of a transplanted organ and corticosteroids, a type of immunosuppressant, are used to suppress inflammatory disease, such as in rheumatoid arthritis, whereby the body attacks its own tissue. However, when using immunosuppressant medication, the body's ability to fight infections becomes suppressed, which can lead to immune deficiency disorders, for example, following chemotherapy. Concomitant medication needs to be considered when commencing patients on immunoglobulin replacement therapy with the aim to achieve maximal patient improvement on the lowest tolerated dose.

strong suggestion of an immune dysfunction (King et al, 2006a; Pasteur, 2000). Furthermore, the more that is discovered about lung immunity, the less likely bronchiectasis will be labelled as idiopathic (a condition of unknown cause).

Bronchiectasis is reported as an established disease complication in 18-68% of patients with CVID and in 32% of adult XLA patients (Pasteur et al, 2010; Howard et al, 2006).

King et al (2006b) acknowledge that although the immune system plays an essential part in bronchiectasis, few studies have assessed the immune function in this condition. Advances in scientific techniques, such as whole genome sequencing – a process that identifies new genes involved in the pathogenesis of PID – will help to enhance our understanding.

Screening for PID in general practice

Community and practice nurses should be aware of patients who require repeated courses of antibiotics to resolve underlying chest infections. Where a diagnosis of bronchiectasis is established, a screening process for antibody deficiency should be considered.

Patients experiencing persistent respiratory infections who have low or absent pneumococcal response identified by a blood test, should receive the pneumococcal polysaccharide vaccine, followed by re-assay of the individual specific antibody response after 21 days (Pasteur et al, 2010). Despite having normal levels of

serum immunoglobulins, some patients have an inadequate response to the pneumococcal vaccine which, if left untreated, predisposes them to persistent bacterial and viral infections. This type of immune “selective” impairment is known as specific polysaccharide antibody deficiency (SPAD). Further screening tests may be required but should be undertaken in a specialist centre. Patient education plays an important role in preparing the patient for these tests and potential treatment options.

Specialist investigations

At the trust where I work, adult patients suspected of having bronchiectasis will receive a series of personalised investigations based on their clinical history and presenting complaint. These investigations are known as the “Host defence workup” and include:

- » Lung function tests;
- » High resolution CT scan to assess lung structure;
- » Nitric oxide tests to screen for primary ciliary dyskinesia (a relatively rare condition that affects lungs, sinuses and ears and is characterised by abnormal beating cilia);
- » Brush biopsy of the nasal epithelium to measure beat frequency of the cilia and structure;
- » Blood tests to screen for immune dysfunction and other markers of health status;
- » Skin prick tests for allergy;
- » Genetic screening for cystic fibrosis;

Antibiotics

Some patients may be offered long courses of oral prophylactic antibiotic treatment during the winter, to help them manage their daily respiratory symptoms. Those who remain well, meanwhile, can be considered for an antibiotic pause during the summer months on the understanding that treatment restarts in the late autumn. In a few cases where symptoms persist or accelerate, it may be necessary to consider rotating the classes of oral antibiotic, as this might reduce the likelihood of the emergence of antibiotic-resistant strains. However, there are no published studies to underpin this approach (Pasteur et al, 2010).

Physiotherapy

Chest physiotherapy is the bedrock of bronchiectasis management (Bott et al, 2009). Patients are taught chest clearance techniques and receive regular reviews in line with their medical out-patient appointments. Personalised techniques aim to remove secretions, reduce the risk of an exacerbation and reduce the sensation of breathlessness.

Influenza vaccine

A study by Bijl et al (2011) showed that some CVID patients are capable of producing antibodies in response to the influenza antigens. They suggest that although data on safety and responses to other vaccines is lacking, it is reasonable to offer a seasonal-flu vaccine to patients with CVID. XLA patients however do not mount any response to the influenza vaccination (Bijl et al, 2011).

Close family members and carers of people with PID should also be vaccinated as this will protect the patient from catching flu from them. It is advisable to get the flu vaccine as soon as it becomes available and, if possible, by October before the flu "season" starts.

Self-management

Patients with bronchiectasis require a self-management plan based on sputum bacteriology and symptom history. It is worth noting that, with bronchiectasis, the presence of mucopurulent or purulent sputum alone or the isolation of a pathogen alone is not necessarily an indication for antibiotic treatment if the patient is clinically well (Pasteur et al, 2010).

Keeping a patient diary of infections, such as recording the number of infective exacerbations and antibiotic treatment outcomes with a record of sputum production (noting colour, consistency and

volume when feeling unwell) is an invaluable resource for the clinical nurse specialist, immunologist and respiratory physician. Other key metrics include the patient's expose to stress and hours of sleep, as these aspects can negatively affect the immune system.

Travel

Patients diagnosed with PID and bronchiectasis can live a normal life. They may require specialist support from immunologists and clinical nurse specialists when planning holidays abroad with advice on travel vaccinations and continuing their immunoglobulin replacement therapy.

A travel letter from a health professional explaining the patient's underlying condition, medication and a listing of equipment required for the administration of immunoglobulin therapy (which should be carried in hand luggage) is helpful to airport security and overseas medical personnel. A course of rescue antibiotics is also advisable to have on standby and can be prescribed by the clinical team before the date of travel. Patients on longer vacations who are on intravenous immunoglobulin replacement therapy will require arrangements for infusions to be set up prior to departure.

Conclusion

With prompt medical treatment, coupled with early diagnosis, adult patients living with PID and bronchiectasis can expect to experience fewer lung infections and improvement in health status. In the UK the future of immunoglobulin usage is reliant on the Department of Health's Demand Management Programme to show commissioners that immunoglobulin therapy is being administered to specific conditions which have the best evidence-base (www.ivig.nhs.uk). Over the years the use and indication of immunoglobulins has continued to grow. Hopefully with improvement in understanding, the mechanisms of action will lead to improving treatment options available to bronchiectasis patients with PID. **NT**

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