Common Variable Immunodeficiency

Common variable immunodeficiency (CVID) is the most common symptomatic primary immune deficiency in adults. It is often diagnosed late when there is less scope to prevent complications. An account published by a patient and the accompanying medical view highlights important issues for better diagnosis and management.[1]

CVID is an umbrella diagnosis in that it encompasses a group of genetic disorders which result primarily in hypogammaglobulinaemia or failure of antibody production.[2] Often, specific genetic defects cannot be identified, unlike with some of the other immunodeficiency disorders. Patients typically present with recurrent infections, particularly of the respiratory tract. Gastrointestinal disease, autoimmune and inflammatory features and lymphoma are also more common in CVID.

Attempts to produce a universally accepted definition of CVID have proved difficult. The current definition, produced in 1999, relies on three criteria, all of which need to be met:[3]

1. Hypogammaglobulinaemia with IgG levels two standard deviations below the mean.
2. Impaired vaccine responses or absent isohaemagglutinins.
3. Exclusion of other causes of hypogammaglobulinaemia.

Whilst this definition is useful to assist in management decisions it has been criticised on the grounds that it does not take account of clinical symptoms and leads to over-reliance on the response to vaccines in the diagnosis of the condition.

Pathophysiology

In CVID there are, as implied in the name, many and varied immune-system abnormalities. To understand these, some understanding of immunology is helpful. The most common defect is in antibody formation but there are related defects in both humoral and cell-mediated lymphocytic responses.

- Defective humoral responses:
  - Failure in differentiation of B lymphocytes.
  - A variety of defects at a cellular level has been described, including defects in surface molecules, absence of IgA and IgG production, increased rates of apoptosis, impaired DNA repair and others.
  - There is a deficiency of isotype switched memory B cells in peripheral blood. This is associated with problematic clinical complications and outcomes such as inflammatory and autoimmune conditions.

- Defective cell-mediated responses. These are complex but can be summarised as:
  - Defective T-cell signalling.
  - Defective interactions between T and B lymphocytes.

CVID is characterised by:

- Low levels of most or all of the immunoglobulin classes.
- Lack of B lymphocytes or plasma cells capable of producing antibodies.
- Frequent bacterial infections.

CVID is diverse in clinical presentation, the types of deficiency and the presence of associated diseases. The sequelae of this antibody deficiency syndrome include:

- Impaired terminal B-cell differentiation which leads to varying degrees of hypogammaglobulinaemia:
  - Reduced levels of IgG and IgA, which are characteristic.
  - 50% of patients also having reduced IgM levels.
- 50% of patients have T-lymphocyte dysfunction as well.
- Susceptibility to recurrent infection by encapsulated bacteria (mainly *Streptococcus pneumoniae* and *Haemophilus influenzae* type b).

However, CVID, like other immunodeficiency disorders, is further complicated by a plethora of systemic immunopathology, such as autoimmune disease, lymphoproliferative disease, malignancy and sarcoid-like granulomas.

Aetiology[2]

- There are defects in both the innate and adaptive immune systems but the cause is unknown.[4]
• Genetic factors:
  • A disease-causing gene for an autosomal dominant CVID/IgA deficiency has been found on chromosome 4q. [5]
  • 10% of patients with CVID have a first-degree family member with IgA deficiency. [6]
  • No clear pattern of inheritance has been identified.
  • There is a possible association with use of antirheumatic or anti-epileptic drugs. [7, 8]

Epidemiology [2]
• It is found in one per 25,000-50,000 subjects, depending on the ethnicity of the population. The frequency may be lower in some populations such as those in Northeast Asia. [9]
• It affects male and females equally. [9]
• Females have more switched memory B cells and tend to be diagnosed later and live longer. [4]

Presentation
CVID can present in infants, young children, adolescents and adults.
• The diagnosis is usually made between the ages of 20 and 40 years but in 20% of cases it is diagnosed before the age of 20. [2]
• CVID presents often with recurrent bacterial infection:
  • The most common are sinusitis, pneumonia, bronchitis, otitis, conjunctivitis and gastrointestinal infection. [10]
  • Septicaemia and central nervous system infections can also occur.
  • Persistent diarrhoea and malabsorption (causing failure to thrive in children) from gastrointestinal infections. These include *Giardia lamblia* (the most common), salmonella, shigella and campylobacter. [11]
• Some patients present with mycobacterial or fungal infection.
• Some present with *Pneumocystis jirovecii*.
• Viral infection is uncommon although some may suffer from recurrent herpes zoster infection.
• There may be associated diseases particularly:
  • Autoimmune diseases
  • Malignancies
  • Granulomatous disease
  • Dermatological manifestations

Differential diagnosis
Other diseases which may need to be excluded are:
• Cystic fibrosis.
• Immotile cilia syndromes.
• Allergy.
• Other primary immune deficiencies including:
  • Selective IgG subclass deficiency.
  • IgA deficiency.
  • Selective deficiency in the response to polysaccharide antigens.
  • Bruton’s agammaglobulinaemia.
  • Severe combined immunodeficiency.
• Protein-losing enteropathy.
• Thymoma.
• Transient hypogammaglobulinaemia secondary to infection.

Investigations
Greater awareness of the primary immunodeficiency disorders among generalists is still needed to avert late diagnosis and subsequent chronic ill health in patients. [1] Detailed investigation is complex and beyond the scope of general practice. Basic investigations may give some general clues with the history but referral for diagnosis is needed.

Generally, serum immunoglobulins are reduced. Serum hypogammaglobulinaemia is the key finding present in all patients with CVID but tests of immune function should also be used. [9] Further investigation is required to exclude other causes of antibody deficiency, especially in the over 50 age group. Investigation to exclude: B-cell lymphoproliferative disease, protein-losing diseases and iatrogenic or drug-related causes. The possible investigations can be summarised as:
Laboratory studies:
- FBC.
- Autoantibody testing.
- Serum electrophoresis.
- Immunoelectrophoresis.
- Radial immunodiffusion methods.
- Immunoturbidimetric methods.
- Assessment of antibody response.
- Assessment of T and B lymphocytes by flow cytometry.
- In vivo measures of T-cell function by assessing localised immunological skin responses.
- Other measures of T-cell activity.

- Imaging. This is likely to be required and may have to be extensive, including different modalities (CT scanning, MRI) according to the clinical manifestations of disease.
- Further investigations, such as pulmonary function tests, bronchoscopy, microbiological and histological testing, may be required to diagnose associated diseases.

Associated diseases

Patients with CVID may have:

- **Bronchiectasis** (particularly if presenting later), which is common.
- Autoimmune diseases occurring more often than in the general population, including:
  - Immune thrombocytopenia
  - Thyroid disease
  - Pernicious anaemia
  - Haemolytic anaemias
  - Autoimmune neutropenias
  - Vitiligo
  - Autoimmune hepatitis
  - Primary biliary cirrhosis
  - Atrophic gastritis
  - Aphthous stomatitis
  - Inflammatory bowel disease

- **Granulomatous disease** affecting:
  - Lungs
  - Spleen
  - Liver
  - Skin

Granulomatous diseases affect 15% of patients at presentation.

- **Malignancy:**
  - B-cell lymphomas occur more commonly.
  - The risk of **gastric cancer** is 50 times greater in CVID.
  - **Malignant melanomas** occur in CVID.

- **Dermatological diseases:**
  - Alopecia areata.
  - Skin granulomas - both sarcoid-like (non-necrotising) and tuberculoid (necrotising).
  - More widespread granulomatous disease.
  - Increased risk of **squamous cell carcinomas** and **actinic keratosis**.
  - Increased risk of **polymorphic light eruption** and **atopic dermatitis**.

Such dermatological diseases are not markers for the disease and CVID should only be considered if there are other manifestations which might implicate CVID as the cause (for example, recurrent infections).

Management\[2, 3\]

It is likely that referral will be required to establish the diagnosis and plan treatment of the disease, the varied associated diseases and complications. It is an uncommon and complicated disease requiring both a multidisciplinary approach to care and the employment of good shared care arrangements. This involves sharing information with patients and their GPs. Information for patients and GPs about the disease and the management of the disease is essential for good care of patients.

- Antibiotics for bacterial infection, usually chest or sinus infection.
- Postural drainage where bronchiectasis has developed.
Immunoglobulin replacement therapy:
- This can be given intravenously (most commonly) or subcutaneously.
- Patients may require lifelong three-weekly infusions to maintain IgG levels above 7-8 g/L (immunoglobulins have a three-week half-life).
- Infusions may delay progression to bronchiectasis by reducing the number of infections.
- They may improve life expectancy and quality of life.
- Unfortunately, infusions have no effect on the autoimmune or granulomatous disease which accompanies CVID.
- Infusions carry a risk of acquiring transmissible infections, particularly hepatitis C.

- Corticosteroids
- TNF-alpha antagonists have also been used with some degree of success. [7]

Immunisations
- The measles, mumps and rubella (MMR) and varicella vaccines are not recommended in patients receiving replacement immunoglobulin therapy, because the vaccines may be inactivated.
- Inactivated vaccines can be given to patients with CVID but these may not be effective because of the underlying antibody deficiency.
- The influenza vaccine is commonly recommended annually.

Complications
There are many potential complications due to the wide-ranging nature of the disease.
Prognosis

This depends on the extent of lung damage as a consequence of infection, severity of autoimmune disease and the development of a malignancy. Numbers of switched memory B cells may also play an important role. Women tend to be diagnosed later and live longer.

Further reading & references


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