Immunodeficiency (Primary and Secondary)

These are classified as primary and secondary/acquired.

Primary immunodeficiency syndromes

- Mostly these are inherited single-gene disorders that present in infancy or early childhood with the exception of common variable immunodeficiency which usually occurs in adults.[1]
- Mutations/deletions of genes governing stem cell differentiation have been identified and over 150 disorders have been described.[2]
- Once thought to be rare, symptomatic primary immunodeficiencies are now considered to range from 1:500 to 1:500,000 in the general population in the USA and Europe.[3]
- The age of presentation varies widely.[4] 70% occur in males due to X-linked inheritance in many syndromes.[5]
- B-cell defects account for 50% of primary immunodeficiency.
- T-cell defects account for 30%, phagocytic deficiencies 18% and complement deficiencies 2%. Knowledge about the function and diversity of B cells in health and disease has now become quite detailed but there is still much to learn.[6]

The conditions are sometimes classified according to which component is faulty (T cells, B cells, phagocytic cells or complement) or according to individual clinical syndromes. The International Union of Immunological Societies Expert Committee for Primary Immunodeficiency has identified main categories as follows:

- Combined immunodeficiencies.
- Combined immunodeficiencies with associated or syndromic features.
- Predominantly antibody deficiencies.
- Complement deficiencies.
- Congenital defects of phagocyte number, function, or both.
- Defects in innate immunity.
- Autoinflammatory disorders.
- Phenocopies of primary immunodeficiencies (presenting as inherited disorders but arising from acquired mechanisms).

One study found that the four most common primary immunodeficiencies seen in paediatric practice (apart from physiological hypogammaglobulinaemia of infancy) were transient hypogammaglobulinaemia of infancy (THI), IgG subclass deficiency, partial antibody deficiency with impaired polysaccharide responsiveness (IPR) and selective IgA deficiency (IgAD).[1]

- Antibody deficiency syndromes: this is a group of conditions characterised by an inability to produce antibodies in sufficient quantity or of sufficient quality.
  - Common variable immunodeficiency: this is a heterogeneous syndrome characterised by various degrees of hypogammaglobulinaemia, commonly associated with autoimmunity.[7] See the separate Common Variable Immunodeficiency article for more details.
  - Thymoma and hypogammaglobulinaemia: this is characterised by low numbers of B cells and a distinctive T-cell type.[8]
  - X-linked (Bruton's agammaglobulinemia): the agammaglobulinemia is an X-linked immunodeficiency in which there is a failure to produce mature B-lymphocyte cells. The defect in this disorder is a fault in the enzyme in Bruton's tyrosine kinase, a key regulator in B-cell development.[9] Novel genetic defects have been found.[10]
  - Selective IgAD occurs in about 1/400 people.[7] There is a selective severe deficiency or total absence of IgA in serum and body secretions.

- Cell-mediated immunity can be subject to a number of genetic defects affecting the function of the T cells:[11]
  - Thymic aplasia (DiGeorge syndrome): there are genetic defects of the thymus and often the parathyroid glands and heart, associated with T-cell dysfunction and significant immune deficiency.[12]
  - Severe combined immunodeficiency disease: this is in fact a group of rare congenital diseases in which there is severe and usually fatal immune deficiency. It has gained the attention of the media in the past and has been known as 'bubble boy disease'.[13]
  - Inherited syndromes associated with immunodeficiency: a wide range of inherited immunodeficiency conditions has been identified, many involving a single gene.[14]

Secondary immunodeficiencies

There are many possible causes and so it is difficult to obtain exact epidemiological data. It is known that the current epidemics of AIDS and tuberculosis have caused global increases in the condition.

Secondary immunodeficiency is common in people who are hospitalised for:

- Lymphoreticular malignancy.
- Drugs - particularly cytotoxic drugs and immunosuppressants.
• Viruses - eg, HIV.
• Malnutrition - the most common cause worldwide.
• Metabolic disorders - eg, renal disease requiring peritoneal dialysis.
• Trauma or major surgery.
• Protein loss - for example, due to nephrotic syndrome.

Presentation
The most common presenting feature is frequent infections. Recurrent respiratory infections are common but this is by no means pathognomonic, as every GP will be aware of the 'sickly child' who seems to acquire infections from his or her siblings frequently.

• The development of severe, persistent recurrent bacterial infection is a better indicator. A common scenario is repeated episodes of sore throat or upper respiratory tract infection which lead to sinusitis, chronic otitis and bronchitis. Another feature is the ease with which complications develop. For example, bronchitis progresses to pneumonia, bronchiectasis and respiratory failure.[15]
• Opportunistic infections are common, such as *Pneumocystis jirovecii* or cytomegalovirus, especially in patients with T-cell deficiencies. Infection of the skin and mucous membranes occurs frequently, including resistant thrush, oral ulcers and periodontitis. Conjunctivitis, pyoderma, severe warts, alopecia, eczema and telangiectasia are also prominent features.
• Common gastrointestinal symptoms include diarrhoea, malabsorption and failure to thrive or losing weight. The diarrhoea is usually non-infectious, although a range of organisms, including rotavirus, *Giardia lamblia*, *Cryptosporidium* spp. and cytomegalovirus may be involved.
• Less commonly, haematological abnormalities such as autoimmune haemolytic anaemia, leukopenia, or thrombocytopenia can occur.
• Neurological problems (such as seizures and encephalitis) and autoimmune conditions (such as vasculitis and arthritis) are also sometimes seen. There is also a higher incidence of gastric carcinoma and liver disease.
• Paradoxically, autoimmune diseases can be associated with primary immunodeficiencies.[16]
History

- Check family history. There may be a familial tendency to early death, similar disease, autoimmunity, allergy, early malignancy or intermarriage.
- Check for risk factors - diabetes, medications, illicit drug use and sexual history.
- A history of adverse reactions to immunisations or complications of viral infections may be significant.
- Enquiry should be made about the frequency of previous antibiotic prescriptions and any history of relevant surgery - eg, splenectomy, tonsillectomy, adenoidectomy.
- A history of radiation therapy to the thymus or nasopharynx may also be a pointer to the diagnosis.

Examination

- Patients with immunodeficiency often look ill on presentation, with pale skin, general malaise, cachexia and a distended abdomen. Various skin manifestations may be apparent, such as rashes, vesicles, pyoderma, eczema and telangectasia.
- The eyes may be inflamed and infected.
- Signs of chronic ENT disease, such as scarred eardrums, encrusted nostrils and postnasal drip may be evident.
- There may be a chronic cough with crepitations in both lungs.
- Hepatomegaly and splenomegaly may be detected in the abdomen.
- In infants, crusting around the anus may be a sign of chronic diarrhoea. Delayed developmental milestones or ataxia may be evident.

Investigation

Specialist tests are often required to elucidate the exact diagnosis but screening tests can be done in primary care. These should include:

- FBC, IgG, IgM and IgA levels and tests to confirm the presence and type of any infection. A systematic review called for screening in patients with recurrent infections, irrespective of age.[17]
- An elevated ESR may indicate chronic infection and CXR and sinus X-ray may confirm the source.
- Appropriate microbiological swabs should be taken, as dictated by the clinical picture.
- More advanced investigations include:[18]
  - Assays of lymphocyte response.
  - Antibody response to immunisation of diphtheria, tetanus and pneumococcal polysaccharides.
  - Phagocytosis assay and quantitation of individual complement components.
  - Flow cytometry.

Management

- General measures include making sure that patients have a healthy lifestyle and are protected as far as possible from infection. This includes having regular dental checks and their own accommodation.[19] There may be an element of social isolation and psychological issues may need to be addressed.
- If there is any evidence of antibody response, the standard regime of killed vaccines should be given. Live vaccines are contra-indicated in T-cell deficiency.
- Bacterial and fungal infection should be recognised and treated early. Swabs should be taken before treatment so that empirical treatment failures can be rectified rapidly. Continuous prophylactic antibiotics may be appropriate in some circumstances. Chest infections may require physiotherapy and lung exercises.
- Antiviral therapies such as amantidine and ramantadine may be life-saving in the management of viral infections.
- Intravenous or subcutaneous immunoglobulin replacement is the first-line treatment for most immunoglobulin deficiency states.[19] Subcutaneous therapy is preferred by many patients because it is more convenient and they can be more independent.[20] Immunoglobulin replacement is contra-indicated in selective IgAD, as serious anaphylactic reactions can be caused. Fortunately, selective IgAD is a relatively mild disease and usually responds to general support measures and appropriate treatment of infections.
- The best treatment for T-cell deficiency conditions is bone marrow transplant, if a donor can be found.
Other treatment options, some of which are still in the experimental phase, include:
- Cytokines [21]
- Thymic transplants [22]
- Gene therapy [23]
- Stem cell transplantation [24]

Prognosis (primary)

Most primary immunodeficiencies are genetic and lifelong. Some conditions such as selective IgAD have a good prognosis. Many patients have a normal lifespan, especially if the condition is diagnosed early and infections are treated regularly. The prognosis in other conditions, such as severe combined immunodeficiency disease is less optimistic. Many patients have chronic illness and require intensive treatment.

Prognosis (secondary)

This depends on the underlying cause. Many conditions secondary to acute disease resolve when the underlying pathology is treated.

Prevention (primary)

Prevention of primary immunodeficiency depends on the identification and genetic counselling of likely carriers in families with a positive history. X-linked disorders may be excluded by sex determination.

National registries in the UK and other countries continue to provide information that is used to inform further research. [14]

Further reading & references

9. Bruton Agammaglobulinemia Tyrosine Kinase, BTK; Online Mendelian Inheritance in Man (OMIM)
13. Severe combined immunodeficiency, Genes and Disease

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