Bruton's agammaglobulinaemia is an X-linked immunodeficiency characterised by failure to produce mature B lymphocyte cells and is associated with a failure of immunoglobulin heavy chain rearrangement.

**Epidemiology**
- The incidence is approximately 1 in 250,000 but this may be an underestimate.¹
- One third of cases are thought to arise from new mutations.

**Presentation**
- Most likely to be diagnosed when unusually severe or recurrent respiratory tract infections occur in a male infant. The most common infections are due to *Streptococcus pneumoniae*, *Haemophilus influenzae* type b, *Staphylococcus* spp., *Neisseria meningitidis* and *Moraxella catarrhalis*.
- The infant may also present with persistent diarrhoea and failure to thrive. Diarrhoea is often caused by *Giardia* spp. and *Campylobacter* spp. Enteroviral infections are potentially fatal, including those due to the attenuated vaccine strain of poliovirus.
- Herpes simplex infections are more likely to be recurrent. Patients can defend against other viruses such as measles and varicella.
- Family history is important, as about one third of patients have an affected family member. Female carriers have no clinical manifestations.

**Differential diagnosis**
- Other causes of hypogammaglobulinaemia, chronic and recurrent respiratory tract infections, chronic diarrhoea and failure to thrive.
- T-cell disorders.
- Severe combined immunodeficiency.
- X-linked immunodeficiency with hyper-IgM.
- Lymphoproliferative disorders.
- Cystic fibrosis and other causes of severe, recurrent respiratory tract infections.

**Investigations**
- Quantitative measurements of immunoglobulins.
- Confirmation requires low or absent expression of CD19 lymphocytes and normal or increased numbers of mature T lymphocytes.
- Specific IgG antibody responses to T-cell dependent and T-cell independent antigens administered as immunisations.
- Liver function tests are recommended at yearly intervals to monitor for autoimmune hepatitis and hepatitis C.
- Respiratory function tests in older children, to monitor the progressive nature of chronic lung disease. Both restrictive and obstructive chronic lung disease may occur.
- Imaging studies include chest X-ray and CT scans of the sinuses and lungs.
- Bronchoscopy.
- Upper and lower gastrointestinal endoscopy to assess the extent of inflammatory bowel disease.
- Prenatal diagnosis is possible for families known to carry a mutated gene.

**Associated diseases**
- Autoimmune disorders such as arthritis, autoimmune haemolytic anaemia, autoimmune thrombocytopenia, and autoimmune neutropenia may be associated either at presentation, or develop later.
- Increased incidence of allergic diseases, eg atopic dermatitis, allergic rhinitis, asthma.
- Increased risk of malignancy, especially lymphomas and gastrointestinal malignancy.
- Inflammatory bowel disease is usually chronic.
- Hypogammaglobulinaemia is also associated with a high incidence of hepatitis.²
Management\[1\]

- The mainstay of treatment is intravenous immunoglobulin, which decreases and delays both morbidity and mortality.\[3\]
- Antibiotic therapy is required at high dosage and for a longer duration of therapy than is usually recommended. Inhaled bronchodilators and steroids are usually required.
- Sinusitis is chronic in older patients and is treated with nasal steroids, saline nasal sprays, and often requires surgical intervention.
- Chronic eczema is treated in the usual way with moisturising creams and topical steroids but has a high risk of bacterial infection.
- Chronic lung disease may require surgical intervention.

Complications

- Chronic lung disease, eg bronchiectasis.
- Chronic infection, including chronic enteroviral infection of the central nervous system.

Prognosis

- Viral and pulmonary infections cause more than 90% of mortalities.
- Patients who begin immunoglobulin replacement therapy before the age of 5 years have a more prolonged survival rate and decreased morbidity.
- Some patients now survive into their late forties.

Prevention

*Gene therapy* is not yet available and stem cell transplantation is not considered appropriate because of its risk and because of improved outcomes with immunoglobulin replacement therapy.

Further reading & references

- *Bruton Agammaglobulinemia Tyrosine Kinase, BTK; Online Mendelian Inheritance in Man (OMIM)*
  1. Chin T; Bruton Agammaglobulinemia, eMedicine, Sept 2008

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