Bruton’s Agammaglobulinaemia

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

- 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 Agammaglobulinaemia, eMedicine, Sept 2008

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