Childhood and Congenital Hypothyroidism

Congenital hypothyroidism (CH) can be defined as a lack of thyroid hormones present from birth. If it is not detected and treated early it is associated with irreversible neurological problems and poor growth.

Some infants develop a lack of thyroid hormones after birth. This is thought to represent primary hypothyroidism rather than CH. Children with untreated primary hypothyroidism do not experience the irreversible neurological problems that are seen with untreated CH.

Epidemiology

- In the UK, 1 in 4,000 live births have CH.
- The incidence is twice as common in girls. [1]
- Areas with iodine deficiency associated with endemic CH are Bangladesh, China, Peru and Zaire. This has in part been counteracted by compulsory iodination of salt.
- Italian screening for CH suggests it is more prevalent in multiple pregnancies - the cause of which remains unclear. [2]

Aetiology

Congenital hypothyroidism (CH) may be due to defects in the pituitary gland, the thyroid gland or the thyroid hormones themselves.

Thyroid gland defects

- A missing, ectopic or poorly developed thyroid gland. This condition accounts for 75% of all cases of CH.
- It is not inherited, so that chances of another sibling being affected are low.

Disorders of thyroid hormone metabolism

- These account for 10% of cases of CH. [3]
- Examples include TSH unresponsiveness and defects in thyroglobulin structure.
- These conditions are usually inherited and so there is a risk that further children may also be affected.

Hypothalamic or pituitary dysfunction

- Hypothalamic-pituitary dysfunction accounts for 5% of cases of CH. Pituitary hypothyroidism usually occurs with other disorders of pituitary dysfunction - eg, lack of growth hormone.
- Hypothalamic causes include tumours, ischaemic damage or congenital defects.

Transient hypothyroidism

- This accounts for 10% of cases and is usually related to either maternal medications (eg, carbimazole) or to maternal antibodies. In maternal thyroid disease, IgG auto-antibodies can cross the placenta and block thyroid function in utero; this improves after delivery.

A number of genetic defects have been associated with CH. This includes mutations in the ‘paired box gene 8’ (PAX8) and the ‘dual oxidase 2 gene’ (DUOX2). The PAX8 gene is particularly linked to the formation of the kidney and thyroid gland. [1] The DUOX2 gene encodes an enzyme called dual oxidase 2 which is crucial to the production of thyroid hormones. [1]

Presentation

Infants are usually clinically normal at birth, due to the presence of maternal thyroid hormones.

Symptoms

- Feeding difficulties
- Somnolence
- Lethargy
- Low frequency of crying
- Constipation

Signs

- Large fontanelles
- Myxoedema - with coarse features and a large head and oedema of the genitalia and extremities
- Nasal obstruction
- Macroglossia
- Low temperature (often <35°C) with cold and mottled skin on the extremities
- Jaundice - prolongation of the physiological jaundice
- Umbilical hemia
- Hypotonia
- Hoarse voice
- Cardiomegaly
- Bradycardia
- Pericardial effusion - usually asymptomatic
- Failure of fusion of distal femoral epiphyses
- The growing child will have short stature, hypertelorism, depressed bridge of nose, narrow palpebral fissures and swollen eyelids
- Refractory anaemia
- A goitre may be present (more likely with dyshormonogenesis, thyroid hormone resistance and transient hypothyroidism)

5% of patients will also have other congenital defects - eg, atrial septal defects or ventricular septal defects.

Infants not treated early may have delayed mental development, learning difficulties and poor co-ordination.

**Diagnosis**

All babies in the UK are screened at birth using blood taken via a pinprick and analysed for TSH and T4. This is part of the UK Newborn Screening Programme (the blood is also analysed for phenylketonuria, cystic fibrosis and sickle cell disease).[^4]^[5]

- A high TSH and low T4 confirm the diagnosis.[^6]
- Thyroglobulin levels can also be measured - usually total T4 is low with a normal TSH; however, free T4 and T3 are within the normal range. This would require no further treatment.
- Thyroid auto-antibodies are also measured.
- Infants may need to have thyroid ultrasound scanning and/or thyroid radionuclide scanning.
- False positive results are usually due to intercurrent illness and thyroglobulin deficiency.^[7]

20% of infants may only have a slight increase in TSH - these patients need to be observed and TFTs repeated in a few months.

**Management**

The aim of treatment is **early detection and early thyroid hormone replacement** to ensure that infants do not develop irreversible neurological disability.

- Thyroxine hormone replacement with L-thyroxine is given once daily and titrated to TFTs.[^8] There is no evidence at present to suggest that higher starting doses of thyroxine have more beneficial effect on outcome compared with standard doses.[^9]
- TFTs need to be monitored on a regular basis. The frequency of blood tests can be reduced after the first two years of life once adequate replacement is achieved.
- T4 should ideally be kept in the upper half of the normal range.
- Transient hypothyroidism need not be treated unless the low T4 and raised TSH persist beyond two weeks. Treatment is usually terminated after three to five months.[^10]

**Monitoring**

- Regular monitoring of TFTs.
- Cross-sectional reference growth charts should be used to monitor child growth.
- Monitor achievement of childhood milestones.
- Monitor mental development - four areas need to be reviewed: communication and personality behaviour, language ability, motor ability and adaptive behaviour.[^10]

**Adverse sequelae**

The main adverse effects are related to the lack of adequate thyroid hormone replacement leading to hypothyroidism, or excessive thyroid hormone replacement leading to hyperthyroidism, manifesting as tachycardia, anxiety and a disturbed sleep pattern.

**Prognosis**

If CH is detected early in infants and treatment begun, normal development of mental function can occur.[^11] If treatment is delayed, spasticity, gait problems and dysarthria and profound mental disability may result.

Poor self-esteem and depression are amongst several factors that lead to a poorer quality of life in patients who have been treated for CH.[^12] A high index of suspicion with careful questioning is required to pick up on these aspects.
Acquired childhood hypothyroidism

The most common cause of childhood hypothyroidism is lymphocytic thyroiditis, also known as Hashimoto's autoimmune thyroiditis.

- This is typically seen in adolescence, but can occur earlier.
- There is a high incidence in children with Turner syndrome and Down's syndrome.
- First signs are slowing of growth (often unrecognised) with other typical signs of hypothyroidism - eg, skin changes, cold intolerance, sleepiness and low energy.
- Typically puberty is delayed, although younger children may have galactorrhoea or precocious puberty.
- One particular issue is poor medication compliance in adolescents, which can lead to apparently unexplained deterioration in thyroid function.[13]

The cause may be iatrogenic (eg, treatment for hyperthyroidism). Rarer causes include acute suppurative thyroiditis and subacute non-suppurative thyroiditis (de Quervain's disease).

Subclinical hypothyroidism (SH) in children

This is quite common in children and adolescents. It is a remitting process with a low risk of evolution toward overt hypothyroidism. See separate article Subclinical Hypothyroidism.

Further reading & references

- Congenital hypothyroidism - Initial Clinical Referral Standards and Guidelines; British Society for Paediatric Endocrinology and Diabetes and UK Newborn Screening Programme Centre (Jan 2013)
- Rastogi M, LaFranchi SH; Congenital hypothyroidism. Orphanet J Rare Dis. 2010 Jun 10;5:17.
- Adherence to Treatment in Adolescents; Paediatrics & Child Health, Jan 2008

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