Congenital hypothyroidism — what's new?

Nicholas P Mann

Abstract

Screening for congenital hypothyroidism has been available for more than 30 years. Recent developments have included improvements in lab TSH screening with lower cut-off points usually at 6 mU/litre, earlier commencement of levothyroxine therapy and high dose treatment regimens. Normalization of TSH levels during the first 2 years with frequent thyroid function testing is likely to be beneficial to outcome. Children with agenesis of the thyroid gland or low free T4 at diagnosis still show significantly reduced IQ results at assessment years later.

Keywords congenital; dosage; dysgenesis; hypothyroidism; iodine; levothyroxine

Congenital hypothyroidism has an incidence of between 1 in 2500 and 4000 newborns and there are some indications that the incidence is rising. In the majority of affected infants there are no clinical features so diagnosis is by neonatal blood screening which was developed more than 30 years ago after dramatic improvements in neuro-developmental outcome were found. The condition is twice as common in girls as boys.

Thyroid development

The thyroid gland is the first fetal endocrine gland to develop and this starts at 3 weeks of gestation. The gland originates from the median surface of the developing pharyngeal floor which is part of the first and second pharyngeal pouches and descends down the neck. This series of events is under control of transcription factors and patterning genes which can be deleted or mutate.

The two lobes are located on either side of the midline and are connected via an isthmus. Initially the thyroid is connected to the tongue via the thyroglossal duct which is normally entirely obliterated by 7—10 weeks of gestation. Further descent of the thyroid gland leads to descent anterior to both the hyoid bone and laryngeal cartilages. As the thyroid gland descends, it forms its final shape, with a median isthmus connecting two lateral lobes. Descent is complete by the seventh gestational week when the gland reaches its final location immediately anterior to the trachea.

Physiology

Thyroid stimulating hormone (TSH) produced from the pituitary gland starts being detectable in fetal serum at 12 weeks and gradually rises to a maximum 6—8 mU/litre towards the end of pregnancy. Iodine freely crosses the placenta and is drawn into the fetal thyroid gland under this hormone influence. Initially small amounts of thyroxine are produced but the thyroid becomes more sensitive to endogenous TSH from mid-pregnancy. Thus free thyroxine (free T4) levels increase rapidly from this time and are under TSH regulation by 24—27 weeks gestation. In parallel thyroglobulin (TBG) production which is the specific carrier protein for thyroxine increases and levels rise from the second trimester of pregnancy.

Prior to 30 weeks the majority of thyroxine is metabolized by the placenta into a metabolically inactive form called reverse T3 (rT3) and this peaks at 18 weeks. Most thyroid hormone production into the circulation is in the form of thyroxine however the active thyroid hormone triiodothyronine (T3) is produced from 30 weeks in peripheral tissues once placental rT3 production ceases. Therefore it is not until this time during the last 10 weeks of pregnancy that serum free T3 the active thyroid hormone starts showing rapidly increasing levels.

When there is an abnormality of this fetal thyroid axis because the gland is absent or there is no thyroxine production then some maternal thyroid hormones can cross the placenta to the developing fetus so cord blood samples in term babies show free T4 at 25—50% of normal levels. The developing brain needs thyroid hormones to mature and this maternal transplacental leak gives some degree of brain protection when the fetal thyroid axis is totally non-functional.

Clinical features

Most cases are sporadic but geographical areas with endemic iodine deficiency have an increased incidence (see below). The majority of infants have no clinical features at birth nevertheless severe cases can still present soon after birth prior to the results of Guthrie screening results becoming available at 10—12 days of age. Thus the possible presentations up to 2 weeks of age are listed in Table 1. A goitre is very unusual but may occur when

Clinical features of hypothyroidism in first 2 weeks

None present (80%)
Coarse features
Large for dates
Constipation
Goitre
Jaundice (unconjuagated)
Poor feeding
Sleepy/lethargic
Large anterior or posterior fontanelle
Protruding tongue
Bradycardia
Hypothermia
Floppiness
Dry skin
Noisy breathing — nasal obstruction
Cold extremities
Oedema/myxoedema
Cardiomegaly/pericardial effusion

Table 1

Nicholas P Mann *MD FRCP FRCPCH DCH is a Consultant Paediatrician at the Royal Berkshire Hospital, Reading, UK. Conflicts of interest: none.*

there is a dyshormonogenesis or iodine deficiency. It is always worth considering the diagnosis of congenital hypothyroidism in infants admitted to hospital at a few days of age with sleepiness, jaundice, poor feeding and these babies have a tendency to hypothermia.

Prior to introduction of neonatal thyroid screening in 1979–1981 when there were no newborn features the diagnosis of congenital hypothyroidism was delayed for several years and was subsequently identified because of juvenile myxoedema in first few years. Late presentation will still occur in developing countries where screening has not been introduced, when there have been laboratory errors or occasionally in secondary hypothyroidism due to a pituitary problem when screening is only from TSH. Table 2 lists the clinical features that may be encountered in these later presentations.

Aetiology

Most cases of permanent congenital hypothyroidism (80–85% of total) are labelled as **dysgenesis** which are due to developmental abnormalities of the thyroid gland at embryogenesis – see Table 3. In some infants the gland is absent (agenesis) or poorly developed (hypoplasia) with a thyroid remnant and this may be accompanied by failure to descend into the neck (ectopia). One variety of the latter is the lingular thyroid that can be seen as a mass at the back of the tongue. Dysgenesis seems to occur sporadically and only rarely have specific genes been implicated. No doubt as understanding of mechanisms improves more genetic causes will be identified.

Thyroid **dyshormogenesis** (10–15% of total) includes a large group of disorders of thyroxine production which are mostly recessive in inheritance, can present with a goitre and are more common in consanguineous families. Abnormalities of thyroid peroxidise activity make up many of these cases. The metabolic pathway for production of thyroid hormone uses hydrogen peroxides in an enzymatic process to couple iodine to thyroglobulin to form thyroxine. This complex group of disorders of thyroid hormone production is well reviewed in an article by Rastogi and LaFranchi. Pendred syndrome is one example with an organification defect due to an abnormal pendrin gene on chromosome 7q22-31. It has been linked to mutations in the *PDS gene* which codes for the pendrin protein and it may present with goitre, hypothyroidism and sensori-neural deafness often in later childhood.

Central hypothyroidism is due to a pituitary or hypothalamic cause associated with TSH deficiency. There is an increased risk with mid-line cleft lip/palate and septo-optic dysplasia and it may be associated with panhypopituitarism that is difficult to diagnose in neonates. Refractory hypoglycaemia in the first few weeks of life is one presentation of panhypopituitarism, others include mid-line cranio-facial anomalies, holoprosencephaly or poorly developed genitalia in males from gonadotropin deficiency. A number of genes regulate pituitary gland development including HESX1, LHX4, PIT1 and PROP1 and specific deletions or missense mutations may be identified. Newborn screening with TSH widely used in Europe will fail to identify these cases.

Deficiency of iodine has adverse effects on both pregnant women and infants and is an essential element for production of thyroid hormones. Thyroxine contains four iodide molecules whereas the T3 molecule has only three attached. The term endemic cretinism is used to describe clusters of infants with hypothyroidism (with or without a goitre) in areas deficient in iodine. In the 1920s dietary supplementation with iodine was found to prevent endemic goitre and cretinism so iodization of salt was established as a standard measure to prevent iodine deficiency. Before this iodine deficiency was common around the Great Lakes, Appalachian, and North Western U.S regions and in most of Canada. The World Health Organization (WHO) has not been able to completely eliminate iodine deficiency throughout the world so endemic cretinism is still observed in some countries such as regions of Bangladesh, Chad, China, Indonesia, Nepal, Peru, and Zaire.

It is estimated that worldwide there are 50 million children affected. As newborns are so susceptible to iodine deficiency neonatal TSH monitoring provides a useful guide to the prevalence of iodine deficiency in the population. Thus when screening shows more than 3% of TSH levels in newborns >5 mU/litre then there is almost certainly local iodine deficiency. Children with iodine deficiency leading to hypothyroidism can suffer from stunted growth, with mental retardation and problems in movement, speech or hearing. Recommended daily intake of iodine is 150 μg for adults, 90 μg for infants but if premature 40 μg and 200 μg for pregnant mothers.

Clinical diagnosis of hypothyroidism in infancy and early childhood

Growth failure/short stature
Large protruding tongue
Hoarse cry/voice
Juvenile myxoedema – puffy face or cretinous appearance
Hypotonia
Goitre
Developmental delay
Dry skin
Hair loss/thin scalp hair/thin eyebrows
Dry skin
Cold hands/feet
Infantile appearance/features
Visible lingular thyroid
Anaemia

Table 2

Aetiology of congenital hypothyroidism

Thyroid dysgenesis (85%)
- Agenesis (16%)
- Hypoplasia/ectopic (68%)

Dyshormonogenesis (10–15%)
Hypopituitarism/TSH deficiency (2–5%)
Resistance to TSH (rare) e.g. pseudohypoparathyroidism Type 1A
Iodine deficiency (common cause in a few countries; not currently seen in most)

Table 3