A case of an abnormal thyroid screen

Neonatal thyroid screening aims to detect congenital hypothyroidism to ensure timely therapy and prevent delayed development and irreversible neurological disability. This article describes the case of an asymptomatic newborn female with an abnormal thyroid test. Her medical evaluation revealed a diagnosis of secondary congenital hypothyroidism that required further hormonal and radiological testing. A brief summary of 10 years of follow-up is presented.

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Key points

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1. The newborn thyroid screen is an important tool for early diagnosis of congenital hypothyroidism.
2. Healthcare professionals should be able to interpret the results of thyroid testing in the newborn period.
3. Primary congenital hypothyroidism is due to deficiency of thyroid gland activity with under-production of thyroxine.
4. Secondary congenital hypothyroidism is due to deficiency of thyroid stimulating hormone (TSH) secretion from the pituitary gland, which reduces thyroxine secretion from the thyroid gland.

A six-week-old female presented to the paediatric endocrinology clinic for evaluation of an abnormal thyroid screening test. She was referred by her paediatrician with a reported low thyroxine (total T4) level, although the actual level was not supplied. The infant was born asymptomatic and at full term with a birthweight of 3.3kg. She was feeding on formula milk and growing well. The mother reported no constipation, dry skin or vomiting. The infant was not taking any medications and her immunisations were up-to-date. Her past medical history was significant for a sepsis evaluation at birth with negative cultures. The review of body systems was negative. The family history was unremarkable; there was no family history of thyroid diseases.

The infant's physical examination was unremarkable:

- Weight: 4.2kg (approximately 50th centile)
- Length: 51cm (50th centile)
- The infant was alert and active
- The infant's head was normocephalic with soft fontanelles. There was no mid-line facial defect
- The thyroid gland was palpable
- The lungs were clear to auscultation and the heart had a regular rhythm
- The abdomen was soft with no organomegaly; liver span was less than 5cm
- The skin was non-jaundiced
- A neurological examination showed normal reflexes and tone
- A genital examination showed normal female genitalia with no ambiguity.

On the day of her visit to the paediatric endocrinology clinic, a thyroid panel revealed the following:

- Normal thyroid stimulating hormone (TSH): 2.7mIU/L (normal range for a full term newborn = 1.3-16mIU/L)
- Normal total T4: 68.2nmol/L (normal range = 58-161nmol/L)
- Low free T4: 7.3pmol/L (normal range for 1-3 months of age = 11-33pmol/L).

Discussion, management and follow-up

In the UK, neonates are screened at birth for TSH and T4 levels using blood taken via a pinprick as part of the newborn screening programme. Newborn screening tests may not always detect secondary hypothyroidism[1] yet a diagnosis of congenital hypothyroidism should be made early so that therapy can be started as soon as possible to prevent delayed development and irreversible neurological disability[2,3]. Factors that may interfere with thyroid neonatal screening include: prematurity, euthyroid sick syndrome and thyroxine-binding globulin (TBG) deficiency. These may affect total T4 levels[4] but are unlikely to cause low free T4.

The infant had an initial abnormal neonatal screen (with a low total T4 level reported to the primary care provider) and a low free thyroxine level (free T4) by repeated laboratory analysis. Since the thyroid function test in the paediatric endocrinology clinic showed a normal TSH level, it was unlikely that the diagnosis was primary hypothyroidism but rather, secondary (**TABLE 1**). When faced with a low free T4 level, the level of TSH may help to differentiate between primary and secondary hypothyroidism.

Prior to starting therapy with levothyroxine (L-thyroxine) other hormonal deficiencies should be ruled out, especially ACTH (adrenocorticotropic

	Primary (glandular) congenital hypothyroidism	Secondary (pituitary) congenital hypothyroidism
Aetiology	Deficiency of thyroid gland activity with under-production of thyroxine. This is usually due to dysgenesis or absence of the gland.	Deficiency of TSH secretion from the pituitary gland, which reduces thyroxine secretion from the thyroid gland.
Features	Usually associated with high TSH and low free T4 levels.	Usually associated with low to normal TSH levels and low free T4 levels.

TABLE 1 Comparison of primary and secondary congenital hypothyroidism.

hormone)/cortisol deficiency[5], since isolated secondary hypothyroidism is extremely rare. Starting the infant on levothyroxine therapy, while failing to diagnose secondary adrenal insufficiency, may precipitate adrenal crisis or unmask adrenal failure. In this case, the diagnosis of congenital hypothyroidism was almost certain but there was an immediate need to rule out secondary adrenal insufficiency[5,6].

The infant was brought back to the clinic on the same day that the results came back. A low dose synthetic ACTH test was performed by administering 0.02µg/kg of synthetic ACTH (total dose was 0.08µg) and obtaining cortisol levels at baseline and one hour later. The blood sample was sent to the laboratory for immediate processing; the results suggested a reasonable cortisol reserve:

- Baseline cortisol level prior to synthetic ACTH injection: 41nmol/L
- Stimulated cortisol level at one hour after injection: 610 nmol/L (normal range for age = 110-607nmol/L).

A repeated thyroid panel on the same blood sample revealed a normal TSH level of 2.1mIU/L and a low free T4 level of 8.75pmol/L. The electrolyte panel was normal as was the blood glucose level. The diagnosis of secondary congenital hypothyroidism was therefore confirmed and the infant was started on levothyroxine at 9µg/kg/day (total daily dose = 37.5µg).

Since the infant was diagnosed with secondary hypothyroidism there was no need to visualise the thyroid gland, but rather the pituitary gland[5]. An MRI of the pituitary gland and brain revealed a small pituitary gland with an ectopic posterior lobe. There were no other abnormalities in the brain.

Monitoring the blood level of thyroid hormone is very important after starting therapy with levothyroxine. The best way to do this in secondary hypothyroidism is to measure the level of free T4 on a regular basis. Monitoring developmental milestones and growth are the most important clinical factors to ascertain that the baby is clinically euthyroid[2,3].

During the first year of life, the child remained euthyroid but had a slow growth velocity of 8cm per year (normal = 25cm per year). She grew at the third centile for weight and the first centile for length. The growth velocity remained between 3-5cm per year (normal = 12cm per year in the second year of life, 8cm in the third year and 5cm in early childhood) until the age of five years. The genetic family target height was at the 25th centile. The patient had normal vision and no neurological symptoms.

The later years

A poor growth velocity had been noticed and monitored since the child's first year of life. The mother was counselled about a possible diagnosis of growth hormone deficiency and the need for monitoring all pituitary hormones to evaluate pituitary function[6].

The best indicators for growth hormone deficiency are the levels of IGF1 (insulin-like growth factor 1) and IGFBP3 (insulin-like growth factor-binding protein 3)[7]. The level of IGF1 is influenced by age and nutritional status and has a wide normal range in infancy. At the age of five years the child's levels were:

- Low IGF1: 48µg/L (normal range for age = 82-262µg/L)
- Low IGFBP3: 1.1mg/L (normal range for age = 1.5-3.4mg/L)

The mother was advised to consider growth hormone therapy but declined due to concerns about daily injections and potential side effects. At the age of six, the patient had a growth velocity of 3cm per year (normal = 5cm per year) and her height was below the first centile. The repeated IGF1 and IGFBP3 levels were low (36µg/L and 1mg/L, respectively). The yearly cortisol, ACTH, glucose and liver enzyme measurements were normal. The patient remained euthyroid clinically and had normal free T4 levels.

A growth hormone level was obtained; the level was 1.9ng/mL (post-clonidine stimulation), which is considered low (below 10ng/mL)[7]. The bone age was delayed at four years and six months. After discussing the need for growth hormone therapy again, the mother agreed and the patient was started at a dose of 0.3mg/kg/week. Her growth velocity jumped to 16cm per year in the first year of therapy.

Strict life-long follow-up of hypopituitarism is necessary because patients may develop new hormonal deficiencies later on in life[6]. At the age of ten years, the patient was at the 23rd centile for height and the eighth centile for weight. She was taking levothyroxine and growth hormone and was clinically euthyroid with no complications. On physical examination, her Tanner stage was 1 (prepubertal).

Because of the possibility of gonadotropin deficiency, the mother was consulted about the need to watch for the status of puberty. The mother had menarche at the age of 14 years, indicating that her puberty onset was late. The plan is to continue the patient on current therapies and test gonadotropin and oestradiol levels if the girl fails to enter puberty within the coming two years. The patient has also been referred to a genetic clinic to evaluate potential mutations of genes encoding pituitary transcription factors[6].

Conclusion

Healthcare providers should be familiar with the newborn screening programme. The thyroid screen aims for early diagnosis of congenital hypothyroidism so that therapy can be started as soon as possible to prevent poor growth and irreversible neurological disability. A primary versus secondary hypothyroidism diagnosis should be clearly made since the latter may need further pituitary hormonal evaluation and potential therapies that may involve ACTH, growth hormone and gonadotropin deficiencies. Careful evaluation of general well-being, growth and puberty progression is needed throughout childhood and the patient's whole life.

In the case presented here the early referral by the primary care provider, the extensive medical work-up and the timely

commencement of therapy allowed the patient to become euthyroid and attain normal development.

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