Congenital Hypothyroidism

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KEYWORDS

• Congenital hypothyroidism • Neonatal thyroid • Development • Levothyroxine
• Dysgenesis • Dyshormonogenesis

KEY POINTS

- Thyroid hormone is critical for neurodevelopment, and congenital hypothyroidism can lead to severe neurocognitive impairment.
- Most congenital hypothyroidism is caused by thyroid dysgenesis, of which the underlying causes are poorly understood; a minority of patients have a normally placed thyroid gland, while rare patients have central congenital hypothyroidism.
- Universal newborn screening is a valuable but imperfect tool for diagnosis of congenital hypothyroidism; clinical judgment and repeat screening are important in high-risk infants.
- Careful evaluation usually reveals the etiology of congenital hypothyroidism, which may inform treatment and prognosis.
- Prompt diagnosis and treatment with adequate doses of levothyroxine lead to excellent neurodevelopmental outcomes in most patients with congenital hypothyroidism.

INTRODUCTION

Thyroid hormone has important effects on almost every organ system and plays a crucial role in normal growth and neurologic development. Congenital hypothyroidism affects nearly 1 in 2000 newborns and can have devastating effects on neurocognitive development if not detected and treated early and effectively. Although the introduction of universal newborn screening has nearly eliminated congenital hypothyroidism as a cause of severe neurologic impairment in the developed world, it remains a leading cause of preventable intellectual disability in areas of the world where access to prompt diagnosis or treatment is not available. An understanding of the pathophysiology of congenital hypothyroidism and of the principles and pitfalls of newborn screening are required to appropriately identify, evaluate, and treat this condition in the newborn period. Optimal diagnosis and therapy of congenital hypothyroidism is critical to ensuring excellent outcomes, particularly in high-risk infants.

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THYROID PHYSIOLOGY

Function and Regulation of the Thyroid

The primary function of the thyroid gland is to produce and secrete thyroid hormones, which exert important physiologic effects throughout the body. Thyroxine (T4), the predominant hormone produced by the thyroid, is a prohormone that is converted in peripheral tissues to the biologically active hormone triiodothyronine (T3), which has a 15-fold greater affinity for the thyroid hormone receptor than T4. Most circulating T3 (80%) is derived from peripheral conversion of T4, and the remaining 20% is secreted directly from the thyroid. In the serum, both T4 and T3 are bound tightly to serum proteins including T4-binding globulin (TBG), albumin, and prealbumin, and only the tiny fraction of T4 (0.02%) and T3 (0.3%) that exists in the unbound or "free" state is able to enter cells and exert its biological actions.

The function of the thyroid gland is regulated by thyroid-stimulating hormone (TSH), which is secreted by thyrotrope cells in the anterior pituitary. Binding of TSH to its receptor on the thyroid follicular cell stimulates the synthesis and secretion of thyroid hormone, as well as growth of the thyroid gland. The production of TSH by pituitary thyrotropes is stimulated, in turn, by thyrotropin-releasing hormone (TRH), which is produced by specific neurons in the hypothalamus. Circulating thyroid hormones inhibit the secretion of both TRH and TSH, completing a negative feedback loop that maintains normal thyroid homeostasis.

Congenital hypothyroidism is an inborn condition in which the thyroid gland does not produce sufficient thyroid hormone to meet the body's needs. The causes of congenital hypothyroidism can be divided into those that directly impair thyroidal synthesis of thyroid hormone (primary hypothyroidism) and those that disrupt hypothalamic or pituitary control of the thyroid gland by decreasing the secretion and/or bioactivity of TSH (central hypothyroidism). Primary hypothyroidism is far more common than central hypothyroidism.

In primary hypothyroidism, the hypothalamus and pituitary respond appropriately to decreased thyroidal production of thyroid hormones by increasing the serum concentration of TSH. Because TSH increases significantly in responses to small changes in serum free T4 (FT4) levels, TSH is the most sensitive test for primary hypothyroidism, and in mild cases the serum TSH becomes elevated before FT4 concentrations fall below normal. In central hypothyroidism, serum concentrations of thyroid hormones are low, but owing to the hypothalamic or pituitary defect, serum levels of TSH do not increase appropriately, but instead remain normal or low.

Fetal Thyroid Development and Physiology

The fetal thyroid gland begins to form about 3 weeks after conception as a thickening of cells (thyroid anlage) in the floor of the primitive pharynx, at what will become the base of the tongue (foramen cecum). The anlage forms a thyroid bud that descends caudally over the next few weeks to its final position in the anterior neck. During this descent, the connection to the pharynx (thyroglossal duct) is normally obliterated, although remnants can persist and cause thyroglossal duct cysts. By week 10 of gestation, the fetal thyroid is able to trap iodide and synthesize thyroid hormones; however, hypothalamic and pituitary control is not established until the second trimester, and the axis continues to mature throughout the third trimester.

Thyroid hormone plays a critical role in brain development beginning in the first trimester and through the first few years of life. Hypothyroidism during this period can have devastating neurodevelopmental consequences.[1,2] During the first trimester, before the onset of fetal thyroid hormone synthesis, the embryo is completely