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Congenital Hypothyroidism in Newborns: Current Approaches to Diagnosis and Treatment

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Abstract. Congenital hypothyroidism is a deficiency of thyroid hormone present at birth. Clinical signs are often subtle in the neonatal period, although prolonged hormone deficiency can impair brain development. This narrative review examines newborn screening, diagnostic confirmation, and early treatment. Dried blood spot screening based on thyroid-stimulating hormone (TSH) identifies most cases of primary congenital hypothyroidism. An abnormal screening result requires prompt measurement of serum TSH and free thyroxine (FT4), interpreted using age-specific reference intervals. Two diagnostic challenges deserve particular attention. Preterm or critically ill newborns may have a delayed TSH rise, while infants with central hypothyroidism may have low FT4 without a marked TSH elevation. For infants with confirmed primary congenital hypothyroidism, oral levothyroxine is the treatment of choice and should begin as soon as possible, ideally within the first two weeks of life. Thyroid imaging can clarify the underlying cause and should not delay treatment. Follow-up combines serial thyroid function testing with assessment of growth and neurodevelopment. The benefit of newborn screening depends on timely confirmation, prompt treatment, and sustained biochemical control throughout early childhood.

Keywords: congenital hypothyroidism, newborn screening, neonatal diagnosis, thyroid-stimulating hormone, free thyroxine, levothyroxine, neurodevelopment.

Introduction

Congenital hypothyroidism is a deficiency of thyroid hormone present at birth. Its clinical importance lies in the timing of diagnosis: thyroid hormone is essential for early brain development, yet many affected newborns have few recognizable signs in the first days of life. Newborn screening makes it possible to identify these infants and begin

treatment before prolonged hormone deficiency causes irreversible neurodevelopmental impairment. Screening programs report primary congenital hypothyroidism in approximately 1 in 2,000 to 3,000 newborns, although the observed incidence varies with the screening method and diagnostic threshold.

The main diagnostic challenge is that the result of a newborn screen depends on which hormone is measured and when the sample is collected. In primary congenital hypothyroidism, abnormal thyroid development or impaired hormone synthesis typically leads to an increase in thyroid-stimulating hormone (TSH), which can be detected in a dried blood spot. In central congenital hypothyroidism, impaired hypothalamic or pituitary stimulation can leave an infant with low free thyroxine (FT4) despite a TSH concentration within the screening reference range. Preterm and critically ill newborns present a different challenge because the rise in TSH may be delayed. These differences explain why some infants require repeat screening and why an abnormal result requires prompt confirmation with serum TSH and FT4 interpreted against age-specific reference intervals.

For infants with confirmed primary congenital hypothyroidism, oral levothyroxine should begin promptly, ideally within the first two weeks of life. Thyroid imaging can clarify the underlying cause, but arranging imaging should not delay hormone replacement. Subsequent care requires dose adjustment as the infant grows, guided by serial hormone measurements and assessment of growth and neurodevelopment. This narrative review examines the clinical decisions that connect newborn screening to effective treatment, with particular attention to interpreting early test results, recognizing infants who may be missed on the first screen, and maintaining adequate thyroid hormone replacement during infancy.

Literature Review

Newborn screening and diagnostic confirmation. Newborn screening changed the diagnosis of congenital hypothyroidism by making it possible to identify thyroid hormone deficiency before clinical signs become apparent. The choice of screening

marker determines which infants a program is likely to detect. Measuring thyroid-stimulating hormone (TSH) in a dried blood spot is effective for detecting primary congenital hypothyroidism, in which the pituitary responds to inadequate thyroid hormone production by increasing TSH secretion. Adding a thyroxine measurement can also identify infants with central congenital hypothyroidism, whose TSH may remain within the screening range despite low circulating thyroxine. Both the European consensus guidelines and the American Academy of Pediatrics emphasize prompt confirmation of an abnormal screen with serum TSH and free thyroxine (FT4), interpreted using age-specific reference intervals.

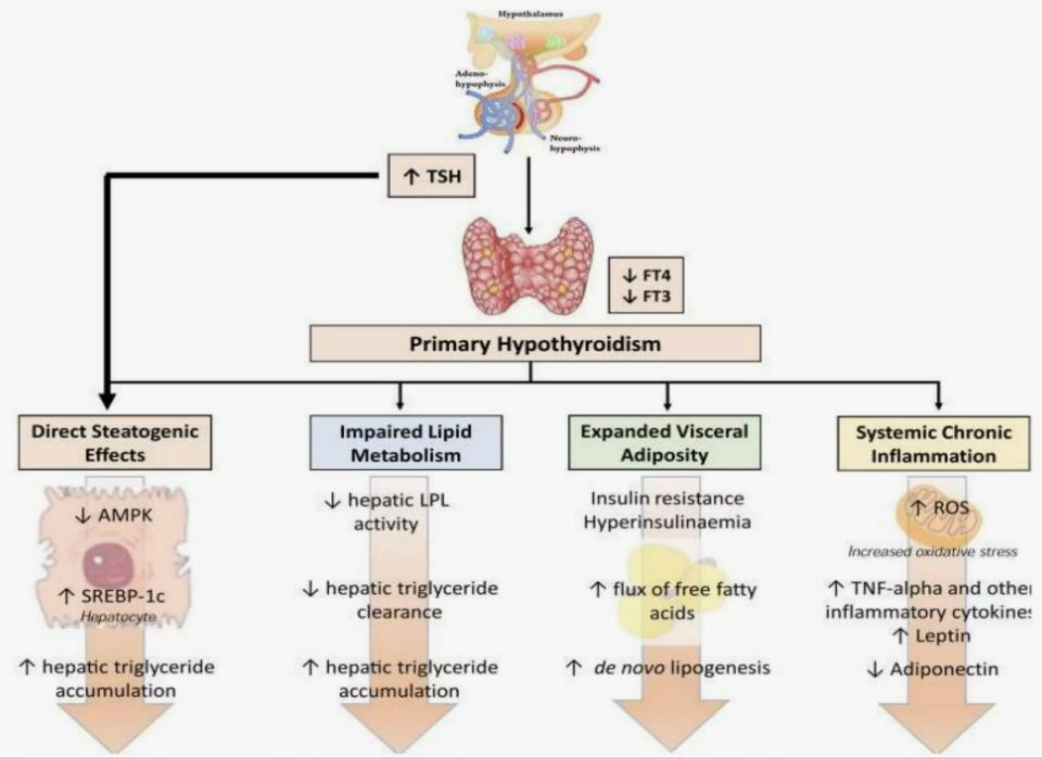

Figure 1. Primary hypothyroidism and its proposed effects on hepatic lipid metabolism

Definition. Primary congenital hypothyroidism is a deficiency of thyroid hormone present at birth that originates in the thyroid gland. In overt cases, reduced production of thyroxine leads to a low serum free thyroxine (FT4) concentration. The pituitary responds by increasing secretion of thyroid-stimulating hormone (TSH). This pattern of low FT4 and elevated TSH, interpreted using age-specific reference ranges, supports the

diagnosis in newborns.

The upper panel illustrates the hormonal feedback response to primary thyroid failure. The lower panels depict proposed pathways linking hypothyroidism to fat accumulation in the liver, including altered triglyceride metabolism, insulin resistance, and inflammation. Their relevance to the neonatal diagnosis is limited; newborn evaluation relies on thyroid function testing.

Diagnostic challenges in preterm infants and central hypothyroidism. Prematurity and central hypothyroidism illustrate two different reasons why a newborn with thyroid hormone deficiency may initially have an unremarkable TSH result. McGrath et al. (2019) studied delayed TSH elevation in preterm infants and found that a single repeat screen at two weeks would still have missed some affected infants. Their findings show that the timing of repeat sampling matters when interpreting screening results in this population. In central hypothyroidism, the difficulty lies in an inadequate pituitary response to low FT4. A review of central congenital hypothyroidism found that the diagnosis was sometimes missed even in hospitalized newborns with hypoglycemia, feeding difficulties, or prolonged jaundice. In this setting, measuring FT4 alongside TSH can reveal a deficiency that TSH screening alone may overlook. Associated pituitary hormone deficiencies, particularly adrenal insufficiency, also influence the safe initiation of treatment.

Early levothyroxine treatment and neurodevelopment. The strongest evidence for prompt levothyroxine replacement concerns infants with overt congenital hypothyroidism. European consensus guidelines recommend beginning treatment as soon as the diagnosis is confirmed and no later than two weeks after birth in infants detected on the initial screen. Evidence on longer-term outcomes comes largely from observational cohorts. Albert et al. (2013) compared 44 children who received early levothyroxine treatment and close biochemical monitoring with 53 unaffected siblings. At a median age of nine years, the investigators found no significant difference in overall IQ between the groups. The sibling comparison helps account for shared family

influences on development. Because early treatment and close follow-up were delivered together, the study cannot isolate the contribution of the starting dose from that of subsequent dose adjustment.

Mild abnormalities and the limits of current evidence. A less settled question is how to manage otherwise healthy newborns with a modestly elevated serum TSH and an FT4 concentration within the age-specific reference range. This biochemical pattern can resolve during follow-up, and the developmental benefit of immediate treatment in every mild case remains uncertain. For an infant with a TSH of 6–20 mIU/L beyond 21 days of age and normal FT4, the European consensus allows either treatment followed by later reassessment or repeat testing within one to two weeks before deciding. The distinction is clinically important: evidence supporting urgent treatment of overt hormone deficiency cannot, on its own, establish the benefit of treating an isolated mild TSH elevation. Serial measurements help determine whether the abnormality resolves, persists, or progresses to a fall in FT4.

Results and Analysis

Two published cohorts examined different stages of care for congenital hypothyroidism (CH). McGrath et al. (2019) evaluated whether repeat screening identified preterm infants whose thyroid-stimulating hormone (TSH) rose after the first newborn screen. Albert et al. (2013) examined cognitive outcomes in children who received early levothyroxine treatment and close biochemical monitoring. Table 1 presents the findings separately because the studies measured different outcomes.

Table 1

Repeat screening and cognitive outcomes in published cohorts of children with

congenital hypothyroidism

Study	Population	Outcome	Result
McGrath et al. (2019)	53 infants born before 33 weeks of gestation who were subsequently diagnosed with CH	Delayed TSH elevation that the first newborn screen did not detect	27/53 (50.9%)
McGrath et al. (2019)	27 infants with delayed TSH elevation	Cases that would have been missed if repeat screening had occurred only once, at two weeks of age	13/27 (48%)
McGrath et al. (2019)	The same 27 infants with delayed TSH elevation	Severe hormone deficiency at diagnosis, defined as serum free thyroxine (FT4) below 5.5 pmol/L	4/27 (14.8%)
Albert et al. (2013)	44 children treated early for CH and 53 unaffected siblings	Overall IQ at a median age of nine years	No statistically significant difference between groups

Diagnostic findings. In the McGrath cohort, the 50.9% figure describes delayed TSH elevation among very preterm infants ultimately diagnosed with CH. It cannot be used to estimate the prevalence of CH among all preterm newborns. The investigators collected repeat samples weekly until 37 weeks' corrected gestational age. This allowed them to determine that a single repeat test at two weeks would still have missed 13 affected infants. Four infants in the delayed-elevation group already had severely reduced FT4 at diagnosis, demonstrating that a delayed TSH rise can accompany clinically important hormone deficiency.

Treatment and developmental outcomes. In the Albert cohort, children who received early levothyroxine and close follow-up achieved overall IQ scores comparable to those of their unaffected siblings. The sibling comparison helped account for shared family influences on cognitive development. Because the children received early treatment and subsequent dose adjustments as part of the same care program, the study cannot determine how much each component contributed to the outcome. Taken together, the studies support attention to two distinct points in neonatal care: detecting delayed biochemical abnormalities in very preterm infants and maintaining adequate thyroid

hormone replacement after diagnosis.

Discussion

The findings highlight two points at which the outcome of congenital hypothyroidism can be influenced: when hormone deficiency is first detected and how consistently thyroid hormone replacement is maintained during early development. The preterm screening study by McGrath et al. (2019) addresses the first question, while the sibling comparison by Albert et al. (2013) informs the second. Their results support complementary conclusions, although neither study followed infants from a comparison of screening strategies through to long-term developmental assessment.

The most clinically relevant finding from McGrath et al. concerns the timing of repeat screening. Among 53 infants born before 33 weeks of gestation who were subsequently diagnosed with congenital hypothyroidism, 27 had a delayed rise in thyroid-stimulating hormone (TSH). A single repeat screen at two weeks would have missed 13 of those 27 infants. Four infants in the delayed-elevation group had a free thyroxine (FT4) concentration below 5.5 pmol/L at diagnosis. Thus, a reassuring first result can precede substantial hormone deficiency in a very preterm infant. These data support serial testing in this high-risk population, although the study design does not establish the optimal interval between samples.

A normal screening TSH has a different interpretation when central congenital hypothyroidism is suspected. In this condition, inadequate pituitary stimulation can leave FT4 low while TSH remains within the screening range. Repeating TSH alone may therefore reproduce the initial result. Persistent hypoglycemia, feeding difficulties, or prolonged jaundice can justify measuring serum FT4 alongside TSH, particularly when other features suggest pituitary dysfunction. The distinction has practical consequences: delayed TSH elevation calls attention to when the sample is collected, whereas suspected central disease also requires attention to which hormone is measured.

For infants with confirmed primary congenital hypothyroidism, the developmental evidence supports prompt levothyroxine treatment followed by close biochemical

monitoring. Albert et al. found no statistically significant difference in overall IQ between 44 treated children and 53 unaffected siblings at a median age of nine years. The sibling comparison helps account for shared family influences on cognitive development. However, a nonsignificant difference in a cohort of this size cannot establish equivalence, and the study cannot separate the contribution of the initial dose from that of subsequent dose adjustments. Its findings are best understood as evidence of the outcomes achievable when early treatment and sustained follow-up are delivered together.

The principal uncertainty concerns infants with a modest, isolated TSH elevation and an FT4 concentration within the age-specific reference range. The developmental benefit of immediately treating every infant with this biochemical pattern remains unclear. Serial TSH and FT4 measurements can distinguish a resolving abnormality from persistent or progressive dysfunction. A priority for future research is to determine which infants with persistent mild TSH elevation gain a measurable developmental benefit from treatment, accounting for gestational age, initial FT4 concentration, and the duration of the abnormality

Conclusion

Early detection and prompt levothyroxine treatment can protect neurodevelopment in infants with congenital hypothyroidism. Screening results must be interpreted in light of gestational age and the hormones measured. Very preterm infants may develop a delayed rise in thyroid-stimulating hormone (TSH), and a single repeat screen at two weeks can still miss affected infants. Central congenital hypothyroidism presents a different challenge because free thyroxine (FT4) may be low despite a TSH concentration within the screening range. These findings support repeat screening in high-risk infants and prompt measurement of serum TSH and FT4 when screening results or clinical findings raise concern.

For screen-detected primary congenital hypothyroidism, levothyroxine should begin as soon as the diagnosis is confirmed, ideally within the first two weeks of life. Follow-up requires regular biochemical assessment, dose adjustment as the infant grows,

and monitoring of development. Evidence for immediate treatment is strongest in overt hormone deficiency. When TSH is only mildly elevated and FT4 remains within the age-specific reference range, repeat testing helps determine whether the abnormality resolves or persists.

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