A global perspective on newborn congenital hypothyroidism screening

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ABSTRACT

Congenital hypothyroidism (CH) is a thyroid hormone deficiency syndrome in newborns resulting from incomplete thyroid development and decreased thyroid hormone biosynthesis or thyroid-stimulating hormone secretion. Without early treatment, newborns with CH have irreversible neurological deficits and long-term metabolic complications. Therefore, several countries have implemented widespread newborn screening to identify and treat CH in newborns. Although newborn screening has improved diagnosis and treatment outcomes for CH, several questions remain concerning the etiology and increased incidence of CH in different populations. Moreover, the increase in the number of preterm, low-birth-weight newborns and of newborns admitted to the neonatal intensive care unit presenting with CH requires additional research to detect and treat all forms of CH.

KEYWORDS Congenital hypothyroidism; hypothyroidism; newborn screening

Congenital hypothyroidism (CH) is a thyroid hormone deficiency syndrome in newborns resulting from incomplete thyroid development and decreased thyroid hormone biosynthesis or thyroid-stimulating hormone (TSH) secretion.^{1,2} From the ancient world to the modern day, CH has been a common problem for children and adults in nations with poor nutrition and lack of prenatal care.³ In most cases, the diagnosis of CH has been delayed until the infant's second or third month, hampering cognitive and physical development.⁴ In the 1970s, Dr. Jean Dussault conducted the first newborn screening (NBS) for CH using neonatal filter paper on heel prick samples similar to previous phenylketonuria and tyrosinemia NBS methods.⁴ With modern NBS programs and levothyroxine therapy, most children with congenital hypothyroidism have normal or near-normal neurodevelopment outcomes.⁵

Congenital hypothyroidism can be permanent or transient depending on the etiology and duration of hypothyroidism.^{1,2} Anatomical abnormalities in thyroid gland development or hormone synthesis cause most cases of CH. Despite advances in genetic analysis, the etiology underlying thyroid dysgenesis remains elusive.^{1,2} However, several mutations in genes encoding thyroid peroxidase, thyroglobulin, and the sodium-iodide symporter are associated with CH.^{1,2} As shown in

Table 1, there are five primary types of congenital hypothyroidism: thyroid dysgenesis, thyroid dyshormonogenesis, TSH receptor insensitivity, central CH, and transient CH.

Currently, CH is reported to affect 1 in 3000 to 4000 of all newborns, with higher incidence rates among Asian, Native American, and Hispanic populations.^{1,2} In the USA, female newborns have a twofold increased risk of developing CH, which increases with higher maternal age, prematurity, and twin births.² In most instances, the clinical symptoms of CH do not appear until 3 months of age due to the presence of maternal thyroid hormones and partially developed newborn thyroid tissue.^{1,2,6} Most newborns with CH present with increased sleep, feeding difficulty, constipation, prolonged jaundice, and neurocognitive decline.^{1,2} Furthermore, newborns with CH show myxedematous facies, large fontanelles, macroglossia, a distended abdomen with umbilical hernia, and hypotonia.^{1,2}

Without early treatment, newborns with CH have irreversible neurological deficits and long-term metabolic complications.^{1,6} Therefore, several countries, including the USA, Canada, and Japan, have implemented widespread NBS to identify and treat CH.¹ NBS for CH currently involves blood collected from a heel prick, which is placed on special filter paper to detect elevated serum TSH and low thyroxine (T4) or free T4 levels.¹ Once CH is confirmed,

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Table 1. Etiology of congenital hypothyroidism

Etiology	Examples
Thyroid dysgenesis	Aplasia, hypoplasia, and ectopic gland
Thyroid dyshormonogenesis	Thyroid peroxidase defect, sodium-iodide symporter defect, and thyroglobulin defect
TSH receptor	TSH and G protein receptor defect
Central congenital hypothyroidism	Defects in thyroid hormone production, metabolism, or transport; congenital hypopituitarism and isolated congenital hypothyroidism
Transient congenital hypothyroidism	Excess maternal iodine or antithyroid drug exposure, maternal TSH receptor antibodies, and <i>THOX2</i> or <i>DUOX2</i> mutations

TSH indicates thyroid-stimulating hormone.

additional laboratory tests, such as thyroid radionuclide uptake and scan, thyroid sonography, or serum thyroglobulin, are used to identify the etiology and treatment course for CH in newborns.¹ However, NBS for CH is performed only on one-third of all newborns worldwide, resulting in \$40 billion annually for untreated CH cases.^{1,6,7} Therefore, NBS for CH remains a public health crisis requiring a reexamination of global NBS policies.⁷

Three major strategies have been implemented worldwide for NBS of CH: blood T4 assay followed by TSH assay if blood T4 value is <10th percentile, initial blood TSH assay, and simultaneous T4 and TSH assays.⁸ Since the 1990s, most countries, except the USA, Israel, The Netherlands, and Japan, have adopted a primary TSH or simultaneous measurement of T4 and TSH screening strategy for CH.⁹ Unlike measuring initial blood TSH levels, the simultaneous measurement of T4 and TSH screening detects both subclinical and mild cases of CH.⁸ As a result, the increased sensitivity of the screening has increased the global incidence of CH.¹⁰ In recent years, several countries have adopted NBS for CH in preterm, low-birth-weight newborns; newborns exposed to TSH suppression from drugs; newborns from multiple pregnancies; or newborns admitted to the neonatal intensive care unit.⁸ Many international organizations also recommend frequent retesting of TSH or T4 to ensure proper diagnosis and treatment of CH in high-risk newborns.^{8,11,12} Furthermore, several countries have established nationwide CH databases for collecting data on screening, diagnosis, and follow-up of CH in newborns.¹³ The centralized CH databases have improved clinical outcomes and improved our understanding of the etiology of CH.¹³ Despite NBS reductions in CH complications, more investigation is needed to improve the specificity, cost, and TSH cutoff points for CH screening.⁹

Overall, NBS programs have effectively detected CH and prevented high-risk newborns from developing the neurological and metabolic complications associated with it.⁹ However, mass NBS for CH has increased false-positive results and recall rates, which reflects the percentage of tests for which the physician contacts the parents to arrange

another test.¹⁴ According to the American Academy of Pediatrics, the recall rate after administering a primary TSH screening is approximately 0.05%.¹⁴ However, the recall rates across the world range from 0.01% to 13.3%.¹⁴ The discrepancy probably reflects differences in screening protocols, laboratory techniques, site of sample collection, and recall criteria.¹⁴ Higher recall ratios confuse communication between physicians and parents, cause unwarranted anxiety, and increase the workload for families and medical staff.¹⁴ Therefore, additional investigation into effective screening methods and policies to lower recall rates would reduce unnecessary laboratory tests, costs, and psychological stress on families and medical staff.¹⁴

Current studies suggest that increasing ethnic diversity, changes in maternal iodine levels, and a lower TSH threshold have contributed to the rise in recall rates.^{15,16} The better sensitivity of TSH screening has also increased the number of CH cases detected and the infants treated for mild hypothyroidism despite the lack of clinical data.¹⁷ Furthermore, a recent study examining male and female newborns showed that male newborns were more likely than female newborns to have a false-positive result with TSH screening.¹⁸ Specifically, the study found that male infants were more likely to be triaged for TSH testing, repeat requests, and referrals, with only 49% of them having confirmed CH.¹⁸ Therefore, gender differences may contribute to the rising levels of recall rates with TSH screening.¹⁸ The increased survival in preterm or low-birth-weight infants has also increased the use of TSH screening and confirmed cases of CH.¹⁶ Despite these challenges, a recent study in China examining 437,342 newborns using TSH screening methods with molecular profile was able to detect several mutations, including *DUOX2*, *TG*, and *TSHR*, involved in CH in the Chinese population.¹⁹ The combination of molecular techniques may help clinicians identify high-risk infants for CH based upon specific molecular profiles associated with different ethnic groups.¹⁹ Furthermore, the incorporation of readily available molecular techniques may provide an additional method for confirming and assessing the course of treatment for premature infants or infants presenting with subclinical

hypothyroidism.¹⁹ Overall, further research is required to determine which methods or technologies may provide insight into reducing or eliminating factors to differentiate patients based on ethnicity, gender, and medical history.

TSH cutoffs for CH screening differ among local, national, and international regions across the globe.⁹ For example, the US NBS programs for CH showed variation across states in the frequency of TSH sample repeats depending on TSH cutoff values, institutional policies, and the use of age-adjusted TSH cutoffs.²⁰ Overall, the variation in TSH cutoffs between states focused on treating older CH infants with borderline results while ignoring CH infants with persistently mild TSH elevations.²⁰ Furthermore, lowering TSH cutoffs in Greece and Quebec increased recall rates, costs, and workload for medical staff with little observable change in clinical outcomes.^{20–22} Nevertheless, these examples are only part of the larger debate surrounding TSH cutoff limits and their effects on cost and long-term outcomes for infants with CH.^{20–22}

The challenge remains balancing NBS program efficiency while eliminating false-negatives and false-positives and reducing costs from unnecessary laboratory testing.^{20–22} Lowering the TSH cutoff has successfully increased the number of newborns treated for CH, which has improved health and developmental outcomes.²¹ However, lowering TSH cutoffs increases recall rates, overtreatment of newborns, and costs for frequent laboratory tests.²¹ In general, alterations in TSH cutoffs produce contradictory clinical outcomes in newborns with CH due to confounding variables, such as iodine insufficiency.²¹ Therefore, more investigation is needed to determine the relationship between TSH cutoffs and improved clinical outcomes in newborns with CH.²¹ Although NBS has improved the diagnosis and treatment outcomes for newborns with CH, several questions remain concerning the etiology and increased incidence of CH in different populations.⁹ Moreover, the increase in preterm, low-birth-weight newborns and neonatal intensive care unit admissions presenting with CH requires further research to detect and treat all forms of CH as a matter of public health importance.

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