PEDIATRIC THYROIDOLOGY

Congenital Hypothyroidism: A Review of 2020 European Society for Pediatric Endocrinology and the European Society for Endocrinology Consensus Guidelines

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SUMMARY

Background

Newborn screening for congenital hypothyroidism (CH) identifies one affected infant from every 2000–3000 live births. Effective screening programs facilitate early recognition and treatment that have almost eliminated developmental delay and have optimized outcomes. Unfortunately, 70% of infants worldwide are born in areas without access to newborn screening programs. The most sensitive test for the detection of primary CH is measurement of the serum thyrotropin (TSH) level. Early treatment and close monitoring to normalize TSH throughout infancy and childhood are essential.

This publication by the European Paediatric Endocrine Society and the European Society for Endocrinology (1) is an updated version of the CH guidelines published by the European Society for Paediatric Endocrinology in 2014 (2). Other professional organizations have also published guidelines, including the Japanese Society for Pediatric Endocrinology (3) and the American Academy of Pediatrics (4).

Methods

Twenty-two panelists were selected from ENDO-ERN representing the European Paediatric Endocrine Society and the European Society for Endocrinology. They were divided into five working groups: neonatal screening, diagnosis and criteria for treatment, treatment and monitoring, outcomes, and genetics of CH and antenatal management. Starting in 2017, panelists spent 24 months reviewing articles published in English after 2013 and ranked their recommendations according to the GRADE system (grading of recommendations, assessment, development, and evaluation) (5). Both the strength of the recommendation (strong = applies to most patients; weak = depends on patient circumstances) and the quality of the evidence (low = case series; moderate = indirect evidence or studies with methodologic flaws; high = low risk for bias) were provided for all recommendations.

Recommendations

The main points of the guidelines include that abnormal CH screening results should be confirmed

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by measures of serum free thyroxine (FT₄) and TSH. CH is stratified into mild (FT₄, 10–15 pmol/L), moderate (FT₄, 5–10 pmol/L), and severe (FT₄, <5 pmol/L) categories and is treated with 10–15 µg of levothyroxine per kilogram of body weight per day. The FT₄ should be normalized as soon as possible and the TSH within 4 weeks of life.

Treatment with levothyroxine (L-T₄; usually 10–15 µg/kg/day) should begin if the FT₄ is low and the TSH is greater than the age-adjusted range or if the serum TSH is >20 mU/L (beyond 1 week of age) even if FT₄ is normal; or if the serum TSH remains above 6 mU/L beyond 21 days of age. The first aim of treatment is to achieve TSH in the normal range for age. The second goal is to maintain FT₄ in the upper half of the normal range for age. Treatment for central hypothyroidism (CH of pituitary or hypothalamic origin) should begin after finding evidence of normal adrenal function or after glucocorticoid replacement. Diagnostic isotope scanning and ultrasonography (dual imaging) should be performed prior to the 5th day of L-T₄ treatment, but should not delay treatment.

Genetic testing facilitates diagnosis and focused genetic counseling. All newborns with CH should be screened for birth defects (especially cardiac) and hearing loss. Many babies have an increased risk for false-negative CH screening results, including preterm, low-birth-weight (LBW) and very low-birth-weight (VLBW) infants, same-sex twin of an affected proband, and patients with Down syndrome. For these newborns, a second screening at approximately 10 to 14 days of age is recommended. Developmental progress and hearing should be regularly assessed, and eventual transition to adult care should be organized.

Conclusions

Early diagnosis and treatment of CH optimize developmental outcomes. Important questions remain regarding genetic etiology, the increasing incidence of CH, possible harm from untreated subclinical hypothyroidism (normal FT₄ with elevated TSH), and optimal screening for babies in intensive care.

COMMENTARY

This newest guideline (1) expands previous recommendations regarding CH screening, rapid treatment, and judicious monitoring (2–4). The new recommendations inform best practices and illuminate areas in need of additional study, including:

1. For infants without access to serum FT₄ measurement, L-T₄ should be started if TSH is >40 mU/L on filter paper testing.
2. During treatment, an FT₄ above normal may be acceptable if the TSH is in the age-adjusted normal range and no symptoms occur.
3. L-T₄ can be administered with food as long as the time and relation to food are consistent from one day to the next.
4. Liquid L-T₄ is an acceptable alternative to crushed tablets, as opposed to L-T₄ suspensions.
5. Thyroid nodules and cancers may develop in patients with CH caused by dysmorphogenesis. They should maintain a low-normal TSH and undergo periodic ultrasound.

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6. Genetic testing by comparative genomic hybridization, next-generation sequencing, or whole-exome sequencing should be performed to better inform the diagnosis and future management. This guideline (1) provides an excellent summary of known mutations resulting in CH, and recommendations for genetic counseling.
7. Treatment of pregnant women with hypothyroidism should include an increase of the L-T₄ dose, monitoring of FT₄ and TSH every 4 to 6 weeks, and maintenance of TSH <2.5 mU/L. In women with central hypothyroidism, the goal of therapy should be to maintain the FT₄ above the mean or median trimester-specific value.
8. Fetal goiter should prompt consideration for NKX2-1 mutations associated with increased mortality.

However, several issues lack harmonization and remain to be addressed, including the following:

- **Persistent mild CH.** In a 2018 survey of newborn screening programs in the United States, vastly different screening protocols were reported.

Of the 51 programs surveyed, 14 included a routine second screen, and 28 included a repeat filter paper test of the TSH if the initial screen returned a result of “borderline increased TSH” (6). Furthermore, almost half of the programs (24 of 51) did not use age-adjusted TSH reference values, including 8 programs that performed routine second screening and 16 programs that performed a second screen for a borderline initial test. This practice results in more false-negatives, and mild persistent CH could be missed. However, the neurodevelopmental consequences of untreated mild persistent CH are unknown.

- **Screening for CH in LBW and VLBW infants in the neonatal intensive care unit (NICU).** In 2016, a Japanese survey found that 65% of NICUs commonly performed simultaneous serum FT₄ and TSH measurements for infants <1500 grams (7). Only 29% used criteria to begin L-T₄ treatment, and those criteria varied from 15-30 mU/L for TSH and <0.5 to <0.7 ng/dl for FT₄. Additional work is needed to define appropriate screening strategies, outcomes, and goals for this population.

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PEDIATRIC THYROIDOLOGY Congenital Hypothyroidism: A Review of 2020 European Society for Pediatric Endocrinology and the European Society for Endocrinology Consensus Guidelines

Catherine E. Kerr and
Gary L. Francis

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