Update on congenital hypothyroidism

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Purpose of review
The present review summarizes recent advances in the diagnosis and management of patients with congenital hypothyroidism.

Recent findings
Although most newborn screening strategies are designed to detect severe primary hypothyroidism that presents shortly after birth, some infants display a pattern of delayed TSH rise despite normal initial newborn screening. Recent studies suggest that delayed TSH rise may be more common and more severe than previously recognized. Although much less common than primary hypothyroidism, central congenital hypothyroidism is as likely to be of moderate or severe degree, which has implications for its detection and treatment. The discovery of new genetic causes of central congenital hypothyroidism, including the X-linked genes *IGSF1*, *TBL1X*, and *IRS4*, has begun to expand our understanding of thyroid axis regulation. Recent long-term data indicate that current treatment recommendations for congenital hypothyroidism result in grossly normal neurocognitive outcomes even in severely affected patients, and that overtreatment may not be as harmful as previously suspected. Liquid levothyroxine is now commercially available in the United States, but more studies are needed to determine optimal dosing using this formulation.

Summary
Prompt identification and adequate treatment of patients with congenital hypothyroidism is critical to optimize outcomes. New information continues to accumulate about how to improve detection of congenital hypothyroidism in specific subgroups of infants (particularly those with delayed TSH rise and central hypothyroidism) and about treatment of patients with this disorder.

Keywords
central hypothyroidism, congenital hypothyroidism, delayed TSH rise, levothyroxine, low birth weight, prematurity, preterm

INTRODUCTION

Thyroid hormone is crucial for normal physical and neurological development, and congenital hypothyroidism can result in intellectual impairment if not diagnosed and treated promptly. This update will discuss significant new developments in the diagnosis and treatment of congenital hypothyroidism since the topic was last reviewed in October 2015, focusing on the past three years [1].

Since its introduction over forty years ago, universal screening of newborns for congenital hypothyroidism has been implemented in many countries around the world. Because most cases of congenital hypothyroidism are caused by abnormalities of thyroid gland formation or thyroid hormone synthesis, newborn screening strategies are designed to detect elevated levels of thyroid-stimulating hormone (TSH) and/or decreased concentrations of thyroxine (T4). Strategies employing primary-TSH testing (with reflex T4) or primary-T4 testing (with reflex TSH) have similar accuracy in detecting severe primary hypothyroidism, which poses the greatest neurodevelopmental risk [2,3]. However, these strategies may be less sensitive for diagnosing congenital hypothyroidism in specific subgroups of infants, particularly those born preterm or with low birth weight (LBW), and those with central hypothyroidism. The present review focuses on new data regarding congenital hypothyroidism in these special populations and on recent developments in the treatment of congenital hypothyroidism.

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KEY POINTS

- Congenital hypothyroidism with delayed TSH rise is common among very low-birth weight infants and normal-weight infants admitted to neonatal intensive care units.
- Newly discovered genetic causes of central congenital hypothyroidism illuminate the regulation of the hypothalamic–pituitary–thyroid axis.
- Current treatment guidelines for congenital hypothyroidism result in normal long-term neurocognitive outcomes.
- Whether overtreatment of congenital hypothyroidism is associated with adverse outcomes remains uncertain.

CONGENITAL HYPOTHYROIDISM WITH DELAYED THYROID-STIMULATING HORMONE RISE

Some infants develop TSH elevation within the first few weeks of life despite normal initial newborn screening. This pattern of delayed TSH rise is particularly common in infants who are preterm, LBW, or acutely ill, and proposed mechanisms include immaturity of the hypothalamic–pituitary–thyroid axis, nonthyroidal illness, and exposure to medications that may suppress TSH secretion (e.g., dopamine or glucocorticoids) [4–6]. Recent studies of at-risk infants have expanded our understanding of the incidence and natural history of delayed TSH rise (Table 1). A study from Wisconsin of 3137 preterm infants (gestational age 22–31 weeks) documented a 1.8% incidence of delayed TSH rise in infants born with very low birth weight (VLBW, <1500 g) [7▪▪]. A similar incidence (1.9%) was observed in a Japanese cohort of 911 infants with birth weight less than 2000g admitted to a neonatal intensive care unit (NICU) [8]. These rates were somewhat higher than the incidence of 1.05% reported in a 2011 population-based study of the Rhode Island newborn screening program [5]. In the Wisconsin cohort, the incidence of delayed TSH rise among infants of extremely low birth weight (ELBW, <1000 g) was 3.7% [7▪▪], more than twice that previously reported in ELBW infants (1.7%) by Woo *et al.* [5].

Several factors may explain the higher incidence of delayed TSH rise observed in these newer studies compared to prior reports. In addition to differences in study population (preterm/LBW infants vs. all screened newborns), the primary-TSH strategy used in Wisconsin and Japan may detect more cases of delayed TSH elevation than the primary-T4 strategy used in Rhode Island, particularly milder cases in which T4 levels are not low. Moreover, although all three screening programs re-tested patients at 2 weeks of life, additional re-screening was performed at 4 weeks of life in Wisconsin and Japan, but not until 6 weeks in Rhode Island. This may have increased the detection of delayed TSH rise in the former two studies, particularly considering that the most severe TSH elevations (>100 mIU/l) occurred at a mean of 20.5 days of life [7▪▪]. These findings emphasize that the strategy and frequency of screening among preterm/LBW newborns may have a significant effect on the detection rate of delayed TSH rise.

In contrast to preterm and LBW infants, term infants have been thought to have a low incidence of delayed TSH rise (about 1 in 30 000) [5]. Therefore, it is notable that in a large Israeli study of 13 201 infants admitted to NICUs, most cases of delayed TSH rise (66%) occurred in infants of normal birth weight and of gestational age 37–39 weeks [9]. In fact, in this cohort, delayed TSH rise was as common among infants of normal bright weight (4.0%) as in ELBW infants (3.8%), and significantly more common than among VLBW infants (1.8%). This result likely reflects that—unlike the healthy, term infants in the population-based study of Woo

Table 1. Incidence of delayed TSH rise presented in recent publications

	Study population	Total *n*	Delayed TSH rise, *n* (%)	Incidence by birth weight		
				ELBW <1000 g	VLBW <1500 g	NBW
Woo *et al.* 2011 [5]	Population-based (Rhode Island, USA)	92800	22 (0.02%)	1.7%	1.1%	>1500 g: 0.003%
Zung *et al.* 2016 [9]	Infants in NICU (Israel)	13201	333 (2.5%)	3.9%	2.5%	>2500 g: 4.0%
Kaluarachchi *et al.* 2019 [7▪▪]	Preterm infants (Wisconsin, USA)	3137	45 (1.4%)	3.7%	1.8%	–
Uchiyama *et al.* 2018 [8]	LBW in NICU (Japan)	911	17 (1.9%)	All study patients <2000 g		–

ELBW, extremely low birth weight; LBW, low birth weight; NBW, normal birth weight; NICU, neonatal intensive care unit; VLBW, very low birth weight.

et al. [5]—full-term, normal-birth weight infants who require admission to a NICU are almost certain to have significant acute illness that may result in delayed TSH rise.

Indeed, in a follow-up case–control study examining a subset of this same Israeli NICU cohort consisting predominantly of term infants not of VLBW, a multivariate analysis showed that of 46 prenatal, perinatal, and postnatal clinical factors, the only four factors associated with delayed TSH rise (the presence of patent ductus arteriosus and administration of vancomycin, insulin, or furosemide) were related to the general severity of illness rather than to thyroid-specific physiology [10▪]. In contrast, among the LBW infants studied by Uchiyama *et al.* [8], a multivariate analysis demonstrated that small for gestational age birth (<10th percentile) was an independent risk factor for delayed TSH rise (odds ratio = 9.0; $P = 0.0001$), whereas the markers of illness severity reported by Zung *et al.* [10▪] were not. Although the study by Uchiyama *et al.* had a smaller sample size, and therefore less to power to detect potential associations, this discrepancy suggests that the laboratory pattern of delayed TSH rise in the NICU setting may reflect distinct underlying pathophysiologies in term infants as compared to preterm/LBW infants.

Management of delayed TSH rise is complicated by the lack of high-quality evidence regarding its natural history and clinical significance. One study reported a possible association of delayed TSH rise with small head circumference, but no differences in neurodevelopmental outcomes were observed [5]. Nevertheless, identifying delayed TSH rise may be clinically important. Among 193 infants with delayed TSH rise, Zung *et al.* [9] demonstrated a strong inverse correlation between concentrations of TSH and T4 ($R^2 = 0.505$; $P < 0.001$). Many of these patients had T4 concentrations below the normal range, and 58% were treated with levothyroxine. Kaluarachchi *et al.* [7▪▪] found that 33% (15/45) of preterm infants with delayed TSH rise had TSH concentrations above 100 mIU/l at diagnosis, and all infants with confirmatory serum TSH concentrations more than 20 mIU/l had concurrent low serum concentrations of free T4. These studies indicate that although delayed TSH rise is usually transient, it may be associated with overt hypothyroidism for which prudence may indicate treatment despite the lack of available outcome data. Moreover, because the majority of these severe cases manifest TSH elevation between 2 and 4 weeks of age [7▪▪], it is possible that 2–4 weeks of age may be more appropriate than later time points for routine re-screening of preterm, LBW, and acutely ill neonates to optimize detection of clinically significant delayed TSH rise.

CENTRAL CONGENITAL HYPOTHYROIDISM

Central congenital hypothyroidism is caused by decreased production and/or bioactivity of TSH as a result of hypothalamic or pituitary dysfunction. The reported incidence of central congenital hypothyroidism is between 1 in 16 000 and 1 in 50 000 newborns [11], and most cases are associated with additional pituitary hormone deficits [12]. Traditionally, isolated central congenital hypothyroidism has been attributed primarily to rare genetic defects in the TRH receptor (*TRHR*) [13] or the beta-subunit of TSH (*TSHB*) [14]. However, modern genetic techniques such as next-generation sequencing have identified new genetic causes of central congenital hypothyroidism, providing new insights into the regulation of the thyroid axis (Table 2).

Table 2. Genetic causes of isolated central congenital hypothyroidism

Affected gene	Year described	Inheritance	Mechanism	Response to TRH		Associated abnormalities
				TSH	PRL	
TSHB [14]	1989	AR	Inability to make β-subunit of TSH	Low	Normal	High α-GSU levels
TRHR [13]	1997	AR	Inactivation of TRH receptor	Low	Low	
IGSF1 [15]	2012	XLR	TRH receptor expression and/or signaling	Low	Low	Macro-orchidism, decreased prolactin, variable transient growth hormone deficiency
TBL1X [22]	2016	XLR	Uncertain (defect in thyroid hormone receptor co-repressor signaling)	Normal	N/A	Sensorineural hearing loss
IRS4 [24]	2018	XLR	Uncertain	Low	N/A	

α-GSU, glycoprotein hormone alpha-subunit; AR, autosomal recessive; N/A, data not available; PRL, prolactin; TRH, thyrotropin releasing hormone; TSH, thyroid-stimulating hormone; XLR, X-linked recessive.

IGSF1 was identified in 2012 as the causative gene of an X-linked syndrome of central congenital hypothyroidism and macro-orchidism [15]. In the ensuing years, IGSF1 deficiency has been established as the most common genetic cause of isolated central congenital hypothyroidism, accounting for 38% of cases (5 of 13) in a recent report from Japan [16]. Additional (but variable) clinical features of the IGSF1 deficiency syndrome include hypoprolactinemia, mildly delayed puberty, and transient childhood growth hormone deficiency [17,18▪▪].

The precise function of the IGSF1 protein has only recently begun to be elucidated. Turgeon *et al.* [19] demonstrated that in male mice lacking Igsf1, the pituitary thyrotropes have reduced expression of the TRH receptor and impaired release of TSH in response to TRH, whereas hypothalamic levels of TRH are increased, consistent with a state of TRH resistance. In human cells, IGSF1 stimulates TRH receptor activity, possibly by blocking tonic inhibition of TRHR expression by TGF-β [20]. Together these findings suggest that loss of IGSF1 leads to central hypothyroidism by blunting TRH receptor signaling. Interestingly, IGSF1 also inhibits the pituitary activin receptor that stimulates FSH secretion, implying that excessive FSH production may underlie the macro-orchidism observed in IGSF1 deficiency [20]. More research is needed to better understand the function of IGSF1, its potential roles in other signaling pathways, and the reasons for the phenotypic heterogeneity among patients with IGSF1 deficiency [21].

Mutations in *TBL1X* and *IRS4* are newly described genetic causes of central congenital hypothyroidism. *TBL1X* is expressed in the pituitary and hypothalamus and encodes a protein that is an essential component of the NCoR-SMRT co-repressor complex, which interacts with thyroid hormone receptors to mediate gene regulation by thyroid hormone. Patients with TBL1X deficiency manifest X-linked central congenital hypothyroidism, often accompanied by hearing loss [22,23]. Mutations in *IRS4* (involved in intracellular signaling, including by leptin) also have been associated with X-linked central congenital hypothyroidism in several males, some of whom were shown to have a blunted TSH response to TRH stimulation [24]. The precise mechanisms by which defects in *TBL1X* and *IRS4* cause central hypothyroidism remain to be elucidated, but their discovery has sparked new interest in hypothalamic–pituitary regulation of the thyroid, and we likely can look forward to more such discoveries as genetic investigations of central congenital hypothyroidism continue.

Most newborn screening programs worldwide employ a primary-TSH screening strategy that does not detect central hypothyroidism [25]. A prospective study from Argentina demonstrated that adding routine T4 testing to a primary-TSH screening strategy can successfully diagnose central congenital hypothyroidism that would otherwise have escaped detection [26▪]. In this study, central congenital hypothyroidism was diagnosed in 1 in 22 573 newborns—accounting for 11% of all cases of congenital hypothyroidism—at a cost of $49 661 US dollars per case of central hypothyroidism detected. Of note, this figure did not include the costs associated with detecting and further evaluating more common but less dangerous disorders like thyroxine-binding globulin deficiency and transient hypothyroxinemia.

These added costs must be evaluated with respect to the risks of failing to detect central congenital hypothyroidism. One important risk relates to the close association of central hypothyroidism with potentially life-threatening pituitary hormone deficits (adrenal insufficiency and growth hormone deficiency). Another potential risk is the adverse effect on neurodevelopment of untreated central hypothyroidism, but few data are available to assess how clinically significant this risk is. Some studies have reported developmental delays in children with untreated central congenital hypothyroidism, but these findings could be caused by associated problems such as brain malformations or neonatal hypoglycemia rather than by a direct effect of central hypothyroidism on neurodevelopment [27]. Nevertheless, Zwaveling-Soonawalla *et al.* [28] have shown that central congenital hypothyroidism is as likely as primary congenital hypothyroidism to be of moderate or severe degree. This is significant because studies of primary congenital hypothyroidism have suggested that free T4 levels at diagnosis are directly correlated with developmental outcomes [29–31]. Although Zwaveling-Soonawalla *et al.* did not assess developmental outcomes, 55% of subjects with central congenital hypothyroidism had free T4 concentrations less than 10 pmol/l (0.78 ng/dl) that have been associated with impaired development in other studies [29–31] and that warrant treatment according to current guidelines [32,33]. Studies demonstrating that early treatment of central hypothyroidism results in improved neurodevelopment will be difficult to perform because of the rarity of the condition, but these new data documenting the severity of central hypothyroidism are relevant to the cost–benefit analysis of detecting central hypothyroidism by newborn screening.

TREATMENT OF CONGENITAL HYPOTHYROIDISM

Current guidelines for the treatment of congenital hypothyroidism recommend prompt initiation of

levothyroxine at an adequate dose (10–15 mcg/kg daily) [32]. Although this approach prevents severe neurodevelopmental effects, several studies have observed milder adverse outcomes even after early and adequate treatment, particularly in infants with the most severe hypothyroidism [34,35]. However, many of these studies have evaluated developmental outcomes at relatively young ages, and few data are available on the long-term outcomes of infants managed under the current treatment paradigm.

This issue is addressed by a recent German cohort study of 76 patients with congenital hypothyroidism who received optimal treatment (mean initial levothyroxine dose 13.5 mcg/kg/day, initiated at a median of 8 days of age) and were followed to adolescence or adulthood (mean age 18.1 years) [36▪▪]. In multivariate analysis, the subjects showed no differences in intelligence quotient (IQ), quality of life, or other neurocognitive or motor outcomes compared to their unaffected sibling controls. This appears to indicate that current recommendations for the initial treatment of congenital hypothyroidism result in grossly normal cognitive outcomes in the long term, although they do not exclude the possibility of more subtle deficits that might be detected with more refined neurocognitive testing.

In addition, Aleksander *et al.* [36▪▪] performed a meta-analysis evaluating the effect of initial levothyroxine dose on cognitive development. In this meta-analysis of 10 studies (including 438 patients), the IQ of patients with severe congenital hypothyroidism was 6–9 points lower on average than that of mildly/moderately affected patients when an initial levothyroxine dose less than 10 mcg/kg/day was used, but no difference in IQ was observed with initial doses above 10 mcg/kg/day. This finding appears to provide support for the currently recommended dose of 10–15 mcg/kg/day, at least for severely affected patients.

However, concern has been raised about the danger of overtreatment, which occurs frequently (in up to 60% of patients) at this high initial levothyroxine dose [37]. An influential study by Bongers-Schokking *et al.* [38] found reduced IQ at age 11 years in children with congenital hypothyroidism exposed to overtreatment, and the same researchers recently demonstrated higher caregiver-reported scores for Attention, Delinquency, and Aggression at ages 6 and 11 years in children exposed to early overtreatment [39]. These and similar findings have contributed to current consensus recommendations to avoid overtreatment of congenital hypothyroidism [32]. However, a limitation of these studies is that they define overtreatment as free T4 elevation above a calculated individual free T4 steady state concentration that is not commonly used in clinical practice. This may have some relation to the somewhat unexpected finding in these studies that adverse outcomes were associated with elevated free T4 concentrations but not with low TSH concentrations, which would also be expected to result from overtreatment.

The recent study of Aleksander *et al.* provides a counterpoint to prior findings of the adverse effects of overtreatment. In their cohort, overtreatment during infancy was strikingly frequent, with elevated T4 levels or low TSH levels present at 58 and 45%, respectively, of laboratory assessments over the first 2 years of life [36▪▪]. Nevertheless, no association was observed between neurocognitive outcomes and overtreatment defined by a variety of methods (mean TSH or T4, proportion of overtreated lab values, or duration of exposure to overtreatment). These data, in contrast to those of Bongers-Schokking *et al.*, suggest that overtreatment may not have clinically significant long-term neurocognitive sequelae. Until more data are available to resolve this controversy, it would appear prudent to avoid overtreatment as much as possible, but not so assiduously as to increase the risk of undertreatment.

In addition to specifying the initial dose of levothyroxine, current recommendations favor the administration of levothyroxine in tablet form, noting that liquid formulations should be used only if they are 'pharmaceutically produced and licensed' [32]. Although such commercial liquid formulations have been available in Europe for some time, none has been available in the United States until the recent approval of Tirosint-SOL levothyroxine solution by the US Food and Drug Administration. Still, published data on the use of liquid levothyroxine for congenital hypothyroidism remain limited. Some theoretical advantages of liquid formulations include the ability to deliver more precisely individualized doses for infants, unaltered absorption when administered with milk [40], and possible increased patient satisfaction over tablets [41]. However, two European studies found increased rates of TSH suppression in infants with congenital hypothyroidism treated with liquid levothyroxine compared to tablet form, despite equivalent weight-based dosing [42,43]. Although it remains uncertain whether such overtreatment is associated with clinically significant adverse effects (as discussed above), at minimum these findings suggest that the optimal initial dose of levothyroxine may differ between liquid and tablet formulations. Therefore, additional studies of liquid formulations to determine optimal dosing appear warranted before the widespread introduction of these formulations into clinical practice.

CONCLUSION

Current regimes for the detection and treatment of congenital hypothyroidism have resulted in normal neurocognitive outcomes for the majority of patients. However, uncertainty remains about the significance and ideal management of specific forms of congenital hypothyroidism, including delayed TSH rise and central hypothyroidism. Additional, ideally outcome-based studies of these issues may lead to further optimization of care for infants with these disorders.

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Conflicts of interest

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- ■ of special interest
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