Detection and treatment of congenital hypothyroidism

Annette Grüters and Heiko Krude

Abstract | Congenital hypothyroidism is the most frequent endocrine disorder in neonates. Controversy exists regarding the necessity to adjust current screening programs to also diagnose patients with central hypothyroidism or those with mild forms of congenital hypothyroidism, who have high TSH levels but normal T₄ and normal T₃ levels (also known as ‘subclinical hypothyroidism’). Thyroid hormone replacement should start as soon as the diagnosis is confirmed by measurement of elevated TSH and low serum thyroid hormone levels. Further diagnostic approaches, such as ultrasonography, scintigraphy and measurement of thyroglobulin levels, to determine the subtype of congenital hypothyroidism, should not delay initiation of treatment. Recommendations regarding the initial dosage of levothyroxine vary considerably, and no general accepted guideline exists with regards to initial dosage or optimal time point for dose adjustment according to biochemical parameters. More than 30 years after the introduction of the first neonatal screening programs, mental retardation can be prevented in the majority of children (>90%) with congenital hypothyroidism if therapy is commenced within the first 2 weeks of life, making neonate screening for this disorder the most successful population-based screening test in pediatrics.

Introduction

The term ‘congenital hypothyroidism’ was introduced more than 60 years ago when Radwin et al. first described children with hypothyroid-associated features of severe intellectual disability and growth retardation. Today, this definition of congenital hypothyroidism has to be revisited, as the diagnosis of the disease is made before the onset of severe clinical symptoms, on the basis of biochemical measurement of TSH and thyroid hormone levels alone.

Primary congenital hypothyroidism, the most common form of congenital hypothyroidism, occurs as a result of developmental defects of the thyroid gland, known as thyroid agenesis or dysgenesis, or is due to disruptions in thyroid hormone biosynthesis, also known as thyroid dyshormonogenesis. In the majority (80%) of cases, a structural defect of the thyroid gland is present: an ectopic gland in a cranial, sometimes lingual, position; thyroid gland hypoplasia; or the complete absence of thyroid tissue. Minor variants of thyroid dysgenesis include the absence of the thyroid isthmus or a lack of one—in most cases the left—lobe of the thyroid. This thyroid hemiagenesis can be found with a frequency of 1 in 1,000–2,000 individuals without a pre-existing diagnosis of hypothyroidism; its finding in children with neonatally elevated levels of TSH, therefore, does not confirm the diagnosis of congenital hypothyroidism. In the remaining 20% of children with congenital hypothyroidism, a normal or enlarged thyroid can be identified. These children are affected by a defect of thyroid hormone synthesis, which occurs in most cases as an autosomal recessive trait of inheritance. Secondary congenital hypothyroidism, also termed central congenital hypothyroidism, is caused by deficiencies in TSH, for example, in patients with pituitary insufficiency or structural abnormalities of the pituitary gland or hypothalamus.

Over time, TSH cut-off levels used in confirmatory diagnoses have been lowered, leading to the diagnosis of congenital hypothyroidism in patients who exhibit elevated TSH levels without decreased peripheral thyroid hormone concentrations or clinical symptoms. This mild form of congenital hypothyroidism occurs as the result of either a transient or permanent rise in TSH levels and has been named ‘subclinical hypothyroidism’. However, given that this condition does not reflect a true state of hypothyroidism, nor causes an obvious developmental defect, this form would be more accurately labeled as ‘hyperthyrotropinemia’.

The purpose of this Review is to summarize the current knowledge on the etiology underlying thyroid dygenesis and dyshormogenesis and to provide an update on the evidence concerning the diagnosis and treatment of patients with congenital hypothyroidism.

Neonatal screening

Klein and co-workers first showed that the IQ of a child with congenital hypothyroidism dramatically depends on the time of clinical diagnosis and initiation of replacement therapy. Only diagnosis and treatment before the age of 3 months enables normal mental development, an
Neonatal screening for primary congenital hypothyroidism is an efficient tool for the secondary prevention of severe mental retardation.

Diagnosis of primary congenital hypothyroidism is based on detection of an increased TSH concentration in the presence of low T4 levels in serum.

The differential diagnosis of congenital hypothyroidism includes defects of thyroid hormone synthesis in patients with a normal thyroid gland or goiter and several diseases arising from thyroid transcription factor defects in patients with thyroid dysgenesis.

Although evidence for particular treatment modalities was not generated in prospective controlled studies, an initial daily dose of >10 μg levothyroxine per kg of body weight is recommended to treat congenital hypothyroidism.

Owing to the transient rise of TSH in the first 48 h after birth,12 either cord blood samples or dried blood spots taken from heel pricks after the third day of life were used to measure either TSH alone (Europe and Japan) or T4, followed by TSH in neonates with a T4 concentration below the 10th percentile (North America).2 Both strategies aimed to identify children with primary congenital hypothyroidism but not those with central congenital hypothyroidism. The results of these first screening programs were encouraging and confirmed that early diagnosis and treatment can offer a normal intellectual outcome in a disease that was historically thought to result in severe mental retardation.2,3

The incidence of congenital hypothyroidism that was observed in the first screening programs was similar, with a rate of 1 in 3,000–4,000, which was twofold higher than the incidence calculated by clinical diagnosis in the prescreening era.18–20 Further neonatal screening programs have confirmed an incidence of 1 in 3,500 in a wide range of different geographic and ethnic populations.19 Two exceptions in US screening programs refer to Hispanic neonates, who exhibit an increased incidence of 1 in 2,000, and to neonates of African American origin, who show a reduced incidence of 1 in 10,000.19 Interestingly, a female preponderance was observed in all screening cohorts, similar to that seen in cohorts studied before the introduction of screening.20

Over the past four decades, increasing overall incidence rates have been observed in the USA, without an obvious identifiable reason. Several factors have been proposed to underlie this increase: the diagnosis of more subtle cases of congenital hypothyroidism due to lower TSH cut-off levels; the increasing number of preterm children, who can be affected by a transient rise in TSH levels; and a change in study populations, with a higher proportion of neonates with a Hispanic background.21

Etiology

Insights into the pathogenesis of congenital hypothyroidism have revealed that genetic causes are detectable not only in patients with dyshormonogenesis, but also in individual patients with developmental defects of the thyroid, which were previously regarded to have a noninherited sporadic disorder.22 However, although molecular genetic testing can clarify the cause of dyshormonogenesis in the majority of patients, the molecular basis of congenital hypothyroidism in those with thyroid dysgenesis remains predominantly unknown. Only few familial cases of thyroid dysgenesis have been reported to date,23 and discordance is found even between monozygotic twins.24 Nevertheless, in single cases of thyroid dysgenesis, inactivating mutations in transcription-factor-encoding genes expressed during thyroid organogenesis have been identified (Figure 1).22 In addition, congenital hypothyroidism with normal localization of the thyroid gland or a goiter can reflect a recessively inherited defect of thyroid hormone synthesis (Figure 2). These rare mutations have clinical relevance, as they enable clinicians to provide genetic counseling, as well as adequate treatment and follow-up, for example because affected patients

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**Key points**

- Neonatal screening for primary congenital hypothyroidism is an efficient tool for the secondary prevention of severe mental retardation.
- Diagnosis of primary congenital hypothyroidism is based on detection of an increased TSH concentration in the presence of low T4 levels in serum.
- The differential diagnosis of congenital hypothyroidism includes defects of thyroid hormone synthesis in patients with a normal thyroid gland or goiter and several diseases arising from thyroid transcription factor defects in patients with thyroid dysgenesis.
- Although evidence for particular treatment modalities was not generated in prospective controlled studies, an initial daily dose of >10 μg levothyroxine per kg of body weight is recommended to treat congenital hypothyroidism.

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**Figure 1** | Congenital hypothyroidism due to thyroid dysgenesis. **a** | The three different forms of thyroid dysgenesis are shown: complete absence of the thyroid gland, ectopic gland and thyroid hypoplasia. The first and second images were obtained by scintigraphy, the third by ultrasonography. **b** | Different steps of the embryonic development of the thyroid gland in mice embryos, as shown in 3D reconstructions. Green marks the endodermal pharynx from which the thyroid primordium (in gray) is budding at day 10 of mouse development. The thyroid bud keeps in contact with the arteries of the heart outflow tract (in red) until later stages, when the aortic arch develops further caudally into the mediastinum. The thyroid migrates back cranially and by lateralization builds the final lateral functional lobes of the gland at day 15, which corresponds to week 12 of human development. During these different steps of embryogenesis, several transcription-factor-encoding genes are continuously expressed, whereas the TSHR gene, as the other functional genes important for thyroid hormone synthesis, is only expressed during late stages of fetal development.

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with thyroid dysgenesis can manifest with more complex comorbidities. Nevertheless, in some patients with well-defined genetic defects, such as Down syndrome or Williams–Beuren syndrome, the molecular basis of the usually mild forms of congenital hypothyroidism or hyperthryotropinemia remains to be identified.

**Mutations causing thyroid dysgenesis**

Due to the low frequency of mutations in patients with thyroid dysgenesis, genetic testing should be initiated only in those patients with either a suggestive clinical manifestation (FOXE1, NKX2-1 and NKX2-5 gene mutations) or with a familial occurrence of thyroid dysgenesis (PAX8 and TSHR gene mutations).

**FOXE1**

At birth, the clinical diagnosis of a child with congenital hypothyroidism and thyroid dysgenesis associated with cleft palate and striking spiky hairs should suggest the diagnosis of the Bamforth–Lazarus syndrome, which is caused by a mutation in the transcription-factor-encoding gene FOXE1. These children have an unfavorable cognitive outcome despite adequate treatment of congenital hypothyroidism owing to the additional role of FOXE1 in the development of the central nervous system (CNS). This prognosis, as well as the autosomal recessive mode of inheritance, should be addressed in genetic counseling.

**NKX2-1**

The majority of patients with mutations of the NKX2-1 gene present with either mild or severe congenital hypothyroidism in association with variable pulmonary symptoms, as well as neurological alterations, such as severe choreoathetosis, ataxia and other movement disorders. This particular association of symptoms results from the multiple roles of the NKX2-1 transcription factor in the development and function of different organ systems, that is, the CNS, lung and thyroid. The phenotype of NKX2-1-deficient patients is variable, with no direct correlation of disease severity between these organ systems. Neonates and infants have died due to severe pulmonary insufficiency despite only mild hypothyroidism, whereas other patients have severe motor defects but completely normal thyroid function and no pulmonary symptoms. Sequencing of the NKX2-1 gene is recommended in neonates with elevated TSH levels and severe pulmonary complications or in children with congenital hypothyroidism and unfavorable motor development despite adequate treatment. In the first year of life, muscular hypotonia occurs, which is followed by the more specific movement defect of chorea (involuntary, irregular migrating contractions of the limbs) or athetosis (involuntary, convoluted writhing and twisting movements of the fingers, arms, legs and neck) during further motor development. During adolescence, the movement disorder does not deteriorate, and an improvement of chorea was observed in some adult patients. Genetic counseling is based on the autosomal dominant inheritance; however, the relevance of counseling is very limited due to the variable penetrance of NKX2-1 gene mutations within the three affected organ systems.

**NKX2-5**

A very rare variant of congenital hypothyroidism due to mutations in the NKX2-5 gene was described in four patients, of whom one was affected by an associated heart defect. Although heart defects account for 50% of all associated malformations in congenital hypothyroidism, only this one NKX2-5 mutation has been reported to date.

**PAX8**

Another example of a thyroid transcription factor defect that affects thyroid function and development is the PAX8 gene mutation. This defect in thyroid dysgenesis leads to a variable and potentially asymmetric hypoplasia of the thyroid gland. Hypothyroidism can be mild, and some patients manifest an elevation of TSH levels only later during childhood, thereby escaping the diagnosis by neonatal screening. In addition to thyroid dysgenesis, PAX8 gene mutations can also lead to unilateral kidney agenesis. Patients with a PAX8 mutation should, therefore, undergo renal ultrasound investigation. Although PAX8 is also expressed in the brain and the ear anlage, no further defect or clinical symptom of the CNS has been described in PAX8-deficient patients.

**TSHR**

Even before the description of thyroid dysgenesis caused by transcription factor defects, inactivating mutations of the
TSH receptor were found to result in congenital hypothyroidism and thyroid dysgenesis with autosomal recessive inheritance. Because the encoding gene, TSHR, is expressed only late during fetal development, homozygous or compound heterozygous inactivating mutations lead to hypoplasia and not to an ectopic gland or agenesis of the gland. A less severe inactivation of the TSH receptor can also result in mildly elevated TSH levels with normal T<sub>3</sub> levels.<sup>42</sup>

**Mutations causing thyroid dyshormonogenesis**

Each step of the complex process of thyroid hormone synthesis, including iodine transport into the thyroid follicle (via the sodium-iodide symporter NIS and the sodium-independent chloride/iodide transporter pendrin<sup>43</sup>) and iodine incorporation into the nascent thyroid hormone (via the enzymes thyroid peroxidase [TPO],<sup>44</sup> dual oxidases [DUOX]<sup>15</sup> and the matrix protein thyroglobulin<sup>45</sup>) can be affected (Figure 2).

**TPO and TG**

Since the first description of an inactivating mutation in the TPO gene in 1992,<sup>47</sup> it was shown that in most children with thyroid dyshormogenesis, a molecular inherited defect of thyroid hormone synthesis can be diagnosed. The partial or complete loss of activity of TPO or thyroglobulin (encoded by the TG gene) leads to severe hypothyroidism with a large goiter.

**SLC26A4**

The SLC26A4 gene encodes pendrin, a protein expressed in follicular cells and in cells of the inner ear that transports iodine into the thyroid follicle. In children with mutations in this gene, an associated hearing loss can be present and might help to focus the molecular genetic diagnosis.<sup>48</sup>

**DUOX**

In contrast to the effects of insufficient or absent TPO or thyroglobulin activity, defects in the H<sub>2</sub>O<sub>2</sub>-generating oxidase system (DUOX2, DUOX2a) are more subtle and can appear as a transient, mild TSH elevation,<sup>49</sup> possibly due to the redundancy of different proteins in the oxidase system.

**GNAS**

Combined central and primary congenital hypothyroidism can result from mutations in the GNAS gene, which cause pseudohypoparathyroidism type 1a.<sup>50</sup> The underlying gene defect affects the function of the G-protein α, which is crucial for TRH as well as TSH receptor signaling, leading to only mildly elevated TSH levels.<sup>51</sup> Features that are clinically suggestive of this form of congenital hyperthyroidism are the associated findings of short digits and short stature and mental retardation despite adequate levothyroxine treatment.

**Clinical diagnosis**

**Signs and symptoms**

Clinical symptoms of congenital hypothyroidism detected by screening in neonates are usually subtle and nonspecific. They include long-term jaundice, feeding difficulty, lethargy, constipation, macroglossia, hypothermia, edema, wide posterior fontanel, umbilical hernia and the so-called ‘hypothyroid facial appearance’.<sup>52</sup> If congenital hypothyroidism remains untreated, the clinical symptoms become evident in the second half of the first year of life, with growth retardation and a delay in motor development. In addition to the delay in the development of motor skills, intellectual disability is the most important and devastating clinical symptom of congenital hypothyroidism, as it is not reversible.

Almost 10% of neonates with congenital hypothyroidism are affected by additional congenital malformations.<sup>52</sup> Congenital heart defects are the most common, affecting 50% of patients. Congenital hypothyroidism can also occur as one obligatory feature of rare genetic syndromes, such as the Bamforth–Lazarus syndrome,<sup>29</sup> and is more frequent in children with Down syndrome<sup>53</sup> and pseudohypoparathyroidism type 1a.<sup>54</sup> Clinical symptoms of an underlying syndrome can precede the diagnosis of congenital hypothyroidism, especially in patients with the Bamforth–Lazarus syndrome, in whom cleft palate and spiky hairs are present at birth. Mild congenital hypothyroidism or elevated TSH levels are more frequent in patients with Williams–Beuren syndrome<sup>26</sup> and in those with pseudohypoparathyroidism type 1a.<sup>54</sup>

**Cases missed by screening**

Variants of congenital hypothyroidism that are characterized by an inappropriate low TSH level, such as central and preterm congenital hypothyroidism, cannot be diagnosed with TSH-based screening strategies. Because free T<sub>4</sub> measurement in dried blood spots has not been established with sufficient sensitivity and specificity so far, indirect strategies were developed to diagnose these disease variants. In the Netherlands, an elaborated approach combines the screening of total T<sub>4</sub> with measurement of TSH and thyroxine-binding globulin as a surrogate for the free T<sub>4</sub> fraction.<sup>55</sup> The results of this program clearly show that, in addition to primary congenital hypothyroidism, almost all cases of central congenital hypothyroidism can be detected, with an incidence rate of 1 in 21,000, which is close to the rate of 1 in 19,000 calculated based on the clinical diagnosis of central congenital hypothyroidism.<sup>56</sup>

Due to the immature hypothalamic–pituitary–thyroid axis in preterm neonates,<sup>57</sup> some preterm children with hypothyroidism exhibit a late rise of TSH levels and might, therefore, be missed with TSH-based screening programs. Moreover, dopamine, which is frequently used in the treatment of ill premature neonates, can attenuate TSH release.<sup>58</sup> Although these occurrences are rare,<sup>59</sup> single case reports of prematurely born patients with undiagnosed congenital hypothyroidism have led to the important recommendation to re-screen neonates born preterm before discharge from the hospital, especially those in intensive care units who received dopamine.<sup>60</sup>

**Confirmatory diagnosis**

**Biochemical measurements**

Once a child has a conspicuous result in the neonatal screening, the definite diagnosis of congenital hypothyroidism
depends on a so-called ‘confirmatory diagnosis’ (Figure 3). To avoid misdiagnosis owing to a transient TSH surge or a sample error, serum measurement of TSH, T4—either total or free T4—and T3 is necessary before treatment can be initiated. In neonates with elevated serum TSH and low thyroid hormone levels, the diagnosis of congenital hypothyroidism is considered to be confirmed; thyroid imaging and testing for maternal thyroid antibodies is then recommended to more precisely define subgroups of congenital hypothyroidism.61,62

In patients with confirmed severe congenital hypothyroidism, serum levels of TSH >50 mU/l and low T4 or free T4 levels are present, whereas T3 values are in the lower normal range in most cases. More difficult to interpret are those values that reflect mild congenital hypothyroidism, with TSH levels <50 mU/l and normal or borderline T4 (or free T4) concentration. Because signs and symptoms of congenital hypothyroidism are related to decreased thyroid hormone levels and not to elevated TSH levels, it is necessary to assess whether a child is deprived of thyroid hormone or not. Interindividual T4 levels vary enormously, and the normal range of T4, and free T4, can differ by 100% (Table 1).63 In addition, newborn T4 levels change rapidly in the first days of life, and the almost twofold higher levels in the first week of life need to be considered in the assessment.63 In a child with a functioning pituitary gland, an elevated but not further increasing TSH level is a good marker indicating an individual steady-state of sufficient T4. Treatment, therefore, does not need to be initiated as long as the serum T4 is within the normal, age-adjusted range and the TSH concentration does not further increase in repeated serum controls.

A stable, elevated TSH level with normal T4 concentration is present in at least 3% of the ‘healthy’ child population, given that the upper normal TSH level is defined by statistical means of +2 SD when measuring normal control populations. Longitudinal measurements in large cohorts revealed that a TSH level <7.5 mU/l will not further increase over time.64 This ‘normal’, elevated TSH level, therefore, probably reflects an inborn variant of the individual set-point of the hypothalamus–pituitary–thyroid axis and does not represent imminent pathology.

**Imaging**

As part of the confirmatory diagnosis, imaging can be employed in neonates with biochemically proven congenital hypothyroidism to define the subgroup of hypothyroid pathology (thyroid dysgenesis versus dyshormonogenesis). The technique used for imaging differs between centers and depends mostly on local experience and availability. The less invasive ultrasonography technique is sufficient to separate a structural defect from a normal or enlarged gland, whereas only the more invasive scintigraphy—either with radioactive iodine or technetium, performed when TSH...
concentration is still high—enables an exact localization of an ectopic, lingual thyroid gland.\(^6\)

To further increase the specificity in discerning subgroups of congenital hypothyroidism, thyroglobulin can be measured as a thyroid-tissue-specific marker. The discrimination of goiter versus athyrosis (lack of the thyroid gland) can easily be achieved in children by combining measurement of thyroglobulin levels and ultrasonography. However, the more subtle differentiation of apparent athyrosis from an ectopic thyroid gland—although possible in most cases of complete absence of thyroglobulin—remains difficult in some children, owing to the individual overlap of thyroglobulin levels in these conditions.\(^6\) Nevertheless, as the demonstration of an ectopic gland versus athyrosis does not change the indication for or dose of levothyroxine, several pediatric centers regard ultrasonography combined with measurement of thyroglobulin levels to be sufficient and do not perform scintigraphy.

Imaging should not delay the initiation of therapy, which should start as early as possible. Scintigraphy can be combined with a perchlorate-based protocol to measure the amount of organified iodine to demonstrate a defect in thyroid hormone synthesis. However, this investigation, which is part of a scientific approach rather than clinical routine, can be postponed until a later age, when children will be off treatment for re-evaluation of the initial diagnosis in their third year of life.

### Thyroid antibodies and iodine

In children with confirmed biochemical hypothyroidism and a normal thyroid gland on imaging, a further diagnostic step should be performed to exclude either a maternal thyroid autoimmune disease or an iodine overload as a potential cause of transient congenital hypothyroidism. Typically, maternal antibodies that can cause fetal hypothyroidism block the TSH receptor, and after clearance from the infant’s circulation at an age of 6 months, thyroid function normalizes.\(^6\) The same transient course can be expected in those rare cases of iodine overload that can result from maternal disinfection with povidone iodine before or during delivery or from a direct application of this substance to the neonate during preoperative disinfection. The transdermal resorption of high amounts of iodine leads to an inactivation of the neonatal thyroid gland (Wolff–Chaikoff effect) and sometimes causes severe but short-lasting hypothyroidism.\(^6\) Treatment of the child is still necessary for several weeks until normal thyroid function is restored.

### Treatment

In principle, successful treatment is achieved by application of a single oral levothyroxine dose in the morning. The choice of levothyroxine rather than liothyronine or a combination of the two is reasonable, because the biologically active liothyronine is generated by local expression of deiodinases, especially in the brain and other target tissues.\(^7\) In addition, studies have shown that treatment with liothyronine is not superior in terms of final cognitive outcome.\(^7\) In most countries, levothyroxine for oral application is only licensed as a tablet. In Europe, liquid preparations with a concentration of 5 μg per drop are licensed, which allows smaller intervals of dose adjustment.\(^7\)

Resorption of oral levothyroxine is excellent, and differences in individual kinetics that might exist are overcome by dose adjustment according to actual TSH levels. However, soy milk has been shown to interfere markedly with the resorption of levothyroxine to the extent that the drug’s dose has to be increased after consumption of soy-rich foodstuffs.\(^7\)

Owing to the long half-life of levothyroxine in the circulation, several days of administration are needed to reach a steady-state. In addition, a preliminary report in adult patients documented an at least equal, if not better, effect of levothyroxine application in the evening rather than in the morning.\(^7\) The current recommendation to take levothyroxine in the morning might, therefore, need revisiting; in particular situations of low compliance, the time point of drug administration should be adapted to the individual.

### Dose and start of treatment

Since the first introduction of screening, the optimal starting point and dose of levothyroxine have been discussed controversially. The initial doses for neonates in the first screening programs were chosen on the basis of practicability (availability of tablet preparations of levothyroxine for adults: 25.0 μg, 50.0 μg or 37.5 μg as half of a 75.0 μg tablet) and individual clinician’s experience. In North America, a daily dose of 25 μg was given,\(^2\) whereas in Europe several centers administered 50 μg per day,\(^3\) resulting in individual doses of levothyroxine of 5–10 μg/kg or 10–20 μg/kg body weight, respectively. Irrespective of the dose, the initial results were encouraging, given that a beneficial effect, with normal growth, motor development and IQ, was found in almost all treated children.\(^6\) However, in two studies of young adult patients diagnosed in the first screening programs
in Canada and Norway, who were treated with an initial dose of 25 μg per day, the final full-scale IQ was in the normal range, albeit consistently 6–8 points lower than that of an appropriate sibling control group.58,59 This gap was argued to potentially result from an insufficient effect of the 25 μg levothyroxine dose.60

Newer, retrospective comparisons and prospective, but nonrandomized, observations revealed an improved cognitive outcome with an increased dose of levothyroxine >10 μg/kg body weight daily.60–62 In addition, a randomized study comparing 37.5 μg and 50.0 μg of levothyroxine revealed a better full-scale IQ in the high-dose group compared with the low-dose group at an age of 2–8 years.63 Together, these data clearly favor high levothyroxine doses (>10 μg/kg per day) to improve IQ outcome in children with congenital hypothyroidism. However, in a cohort from Switzerland, a high dose of 14.9 μg/kg body weight still resulted in a 9-point lower full-scale IQ compared with that of a matched control group.64 To date, no significant adverse effects have been reported when children are treated with high doses of levothyroxine (37.5 μg or 50 μg per day) in all studies.

Closely linked with the effect of a high versus low initial treatment dose is the question whether an early start of treatment can further improve the IQ in patients with congenital hypothyroidism. Several studies compared an early versus late start of treatment, that is, 10 days versus 16 days65 and <15 days versus >21 days after birth,66 which revealed a consistently better IQ in the early-treatment group. Whether an even earlier start of treatment, before the age of 10 days, will close the gap of full-scale IQ points remains to be investigated. Based on currently available outcome data, which do not reach a high level of evidence, most guidelines now recommend a high dose of levothyroxine of 10–15 μg/kg body weight with the aim to start treatment within the first 2 weeks of life.62,66

Other potential explanations for the continuously observed gap in full-scale IQ outcome might be that the fetal period of severe hypothyroidism can induce neuronal damage that cannot be compensated for by postnatal treatment. On the other hand, the remaining IQ gap might be related to the still unknown molecular pathogenesis of congenital hypothyroidism. As shown for the mental retardation in patients with FOXE1 deficiency31 and for neurological defects in those with NKX2-1 deficiency,32 a molecular defect that results in thyroid dysgenesis might also interfere with normal brain development. In some cases, this mechanism might lead to an unfavorable cognitive or neurological outcome despite screening for and optimal treatment of congenital hypothyroidism. Further outcome studies need to take into account probable molecular mechanisms that might interfere with normal cognitive development.

Mild forms of congenital hypothyroidism

A current topic of discussion concerns the diagnosis and necessity for treatment of mild forms of congenital hypothyroidism in children with hyperthyrotopinemia. Several groups have now reported their experience with low TSH cut-off levels of 10 mU/L87,88 and even 6 mU/L.89 The incidence of congenital hypothyroidism increased to 1 in 1,44687 and to 1 in 1,556, respectively, using these thresholds.89 This increase was accompanied by a more than 10-fold higher rate of screening TSH reinvestigations, for example, a recall rate that is in the range of 0.1–0.3% of all screened neonates when the TSH cut-off level is 15 mU/L. The majority of children with supposed congenital hypothyroidism were shown to have permanent elevated TSH levels (>5 mU/L) at 2–3 years of age,89 which was argued to be proof of congenital hypothyroidism and support the need for continued treatment with levothyroxine. However, these children—who had hyperthyrotopinemia rather than ‘true’ congenital hypothyroidism—were treated without any evidence of a clinically significant benefit of treatment for their cognitive development. Nevertheless, given the devastating effect of hypothyroidism on the neonatal development of the CNS and because individual patients with mild TSH elevation might have borderline T4 values,87 the tendency to overtreat is easily comprehensible. Therefore, outcome studies that include a substantial number of untreated children with mild congenital hypothyroidism are urgently needed to better judge this particular treatment indication.

Follow-up and outcome

After initiation of therapy, the usual recommendation is to monitor TSH and T4 levels at weekly intervals for 1 month, at monthly intervals for 3 months, followed by a continuous follow-up every 3 months during the first 2 years of life and later every 6 months. Studies about treatment modalities during the maintenance phase and later every 6 months. Studies about treatment modalities during the maintenance phase have been surprisingly rare so far. One study from Brazil reported a clinically significant effect of the number of follow-up appointments on final IQ outcome.89

Congenital hypothyroidism is a chronic disease and the outcome of the affected children depends on optimal compliance of the parents and later in life of the patients themselves. As in other chronic, inherited diseases, treatment of congenital hypothyroidism and patient care is a balance of avoiding fear but maintaining a good compliance at the same time. However, congenital hypothyroidism seems to be easily treatable compared with other metabolic, inherited diseases, and a tendency to follow up children with congenital hypothyroidism in unspecialized pediatric endocrine centers exists. How these children will develop and how efficient the health-care service within this public medical domain actually is remains so far unknown. Published outcome studies of patients with congenital hypothyroidism are generated in highly specialized and closely interlinked research groups that have dedicated decades of work to the diagnosis and treatment of congenital hypothyroidism. So far, the general fate of children from a population-wide view is unknown, because only very few health-care service studies were undertaken with a focus on congenital hypothyroidism.89 This fact is surprising given that congenital hypothyroidism is one of the most frequent conditions among the spectrum of rare diseases. The population-based screening programs that are now established in a large number of countries generate a yearly cohort of approximately 3,000 patients...
with congenital hypothyroidism with the need for replacement therapy in the USA, Europe and Japan alone. The ongoing increase in screening sensitivity due to reductions in the TSH cut-off threshold will increase this number even further and will fuel the need to appropriately re-evaluate treatment indications in children with hypothyrotopinemina. Obviously, further studies will focus on these aspects of health-care research in the follow-up and outcome of children with congenital hypothyroidism.

Owing to the successful treatment of children with congenital hypothyroidism, these individuals now reach an adult age and are able to lead presumably normal lives. Thus a hitherto nonexistent group of adult patients now requires adult health-care services that are educated about outcome, long-term needs and related organ-specific effects in patients with developmental defects of the thyroid gland treated with thyroid hormone replacement. Adult patients with congenital hypothyroidism are at risk of obesity, and impaired diastolic function and increased intima-media thickness in young adult patients with congenital hypothyroidism diagnosed in screening programs were described in a study from Italy. Together, these data clearly demonstrate the need for ongoing specialized care of adult patients with congenital hypothyroidism.

Conclusions
Neonatal screening for congenital hypothyroidism represents the most efficient method to prevent mental retardation and ensure normal IQ levels in this patient population. Successful replacement therapy is easily achieved by a single, daily dose of oral levothyroxine. However, uncertainty and controversy remain regarding the appropriate starting dose. Despite several guidelines being in favor of a high dose (>10 μg/kg body weight per day), the evidence level supporting this recommendation is still low. Moreover, the implementation of screening programs harbors the risk of overdiagnosing and overtreating a large number of children, especially with the current tendency to lower TSH cut-off levels. The more sensitive the screening programs, the higher the risk of losing the balance between their burden and benefits. Further evidence is needed to justify treatment of neonates with mild hypothyrotopinemina as has now become routine in most programs with a reduced TSH cut-off level. In addition, the development of standardized follow-up programs for adult patients with congenital hypothyroidism, who can presumably live a normal life but are considered to be chronically ill, is a further task that needs to be addressed to optimize treatment of congenital hypothyroidism following detection by neonatal screening.

Review criteria
Articles cited in this Review were selected on the basis of a search of the PubMed database. Search terms were “congenital hypothyroidism” and “outcome”, “treatment”, “diagnosis” and “pathogenesis”. The literature search was not limited to certain years. Only full-text papers written in English were selected.


Author contributions
Both authors contributed equally to all aspects of the article.