Congenital Hypothyroidism – Monitoring Thyroid Function in Infants

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Abstract

Guidelines for monitoring thyroid function in congenital hypothyroidism (CH) are published by the American Academy of Pediatrics, the European Society for Paediatric Endocrinology and the UK Newborn Screening Programme Centre. The fact that the recommendations are not uniform reflects management uncertainty. In addition, clinical care may not always be informed by these guidelines. Recent studies suggest that more frequent monitoring is indicated in some infants. Monitoring to identify delayed thyroid stimulating hormone (TSH) rise is indicated in pre-term, low birth weight and sick full-term newborns. Monitoring thyroid function in infants with CH monthly after normalisation of TSH until six months of age, and every one to two months between six and 12 months of age, will decrease exposure to suboptimal thyroid hormone levels. Assessment for permanency of hypothyroidism should be done only in children in which there is likelihood of resolution and not earlier than three years of age. In some instances, when TSH elevations persist after normalisation of the free thyroxine, it may be reasonable to try combined therapy with triiodothyronine.

Keywords

Congenital hypothyroidism, thyroid function, delayed thyroid stimulating hormone (TSH) rise, thyroid hormone therapy, persistent TSH elevation

Disclosure: The authors have no conflicts of interest to declare.
Received: 3 August 2011 **Accepted:** 26 September 2011 **Citation:** *European Endocrinology*, 2012;8(1):53–6 *DOI:10.17925/EE.2012.08.01.53*
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Congenital hypothyroidism (CH) screening was introduced in 1974 and has become common practice, preventing the devastating neurological and developmental outcomes of untreated CH. Thyroid hormones are essential for normal brain development during early years. It is uniformly agreed that screening programmes are essential for early identification and treatment, and that adequate thyroxine (T4) dosing both initially and during the first three years of life correlates with good outcomes.[1–3] There is, however, controversy regarding the timing of repeat thyroid function tests (TFTs) after the initial screen, as well as the frequency of monitoring required to optimise the outcomes of children diagnosed with CH who are being treated. This paper discusses current monitoring guidelines and reviews recent studies suggesting the need for changing these guidelines.

Incidence of Congenital Hypothyroidism

Before the use of newborn screening programmes was widespread, the reported incidence of CH was 1:7,000–1:10,000. As expected, the CH incidence rate increased significantly – to approximately 1:4000 – after the introduction of screening programmes.[4] Another significant increase in reported incidence has occurred during the last two decades. It is unclear whether this increase is the result of increased detection or a true increase in incidence due to a change in unidentified risk factors.

One possible reason for the higher reported incidence of CH is the change in screening methods and cut-offs used for its diagnosis. The use of a thyroid stimulating hormone (TSH) assay for initial screening is associated with a reported CH incidence higher by 24 % than that reported by laboratories using a T4 assay.[5] During the 1990s, many laboratories switched to an initial TSH testing method, possibly contributing to the higher current measured incidence of CH. A recent paper by Hertzberg and colleagues, however, concluded that there was indeed an increased incidence rate, even after adjusting for the screening methodologies and parameters.[5]

To further characterise this recent increased incidence, a cohort of children in Massachusetts during the low incidence period (1991–1994, incidence of 1:3010) was compared with a cohort of children during the high incidence period (2001–2004, incidence of 1:1660). Screening was performed with T4 and subsequent TSH on selected specimens. The severity of CH was determined as follows: initial TSH level ≥100 milliunits per litre (mU/l) = severe CH; and initial TSH level <100 mU/l but ≥20 mU/l = mild CH. Initial TSH level <20 mU/l with subsequent abnormal TSH was termed 'delayed TSH rise'. Clinical and laboratory follow-up determined whether CH was permanent or transient. The increased incidence of CH was attributed to an increase in mild cases and delayed cases, with no increase in severe hypothyroidism. There was no difference in the proportion of transient cases. The conclusion was that the rising incidence of CH in Massachusetts was attributable to enhanced detection, rather than to an absolute increase in numbers.[6]

Many clinicians question the need for treatment in children with mild CH and delayed TSH rise. In the Massachusetts study, none of the

severe CH cases were transient in the older cohort and only 4 % of the severe cases were transient in the younger cohort; 43 % of the mild CH cases were transient in the older cohort and 36 % of the mild cases were transient in the younger cohort. Unfortunately, there are no criteria to discriminate between children who will have transient and those who will have persistent hypothyroidism. Because there are no long-term follow-up studies on outcomes with and without treatment, it is unclear whether patients benefit from treatment. In the absence of essential long-term follow-up data, patients with mild CH and delayed TSH rise are managed similarly to those with severe CH, with the same treatment and monitoring plan.

Monitoring Thyroid Function in Newborns at Risk of Developing Delayed Thyroid Stimulating Hormone Rise

Delayed TSH rise is defined as a normal TSH level with low T4 level on a newborn's initial screening, with detection of elevated TSH and persistent low T4 on subsequent screening. Since newborn screening programmes differ in their screening methods and indications for repeat screening, some programmes will miss this pattern. Screening programmes using a primary TSH test that do not routinely obtain a second sample will miss this pattern of abnormal TFTs.

The current American Academy of Pediatrics (AAP) guidelines include measurement of TFTs at two weeks if the initial screening has shown low T4 and normal TSH in pre-term infants, low birth weight infants and sick full-term newborns.[2] There are no recommendations regarding the initial method and timing of screening to ensure that those 'delayed TSH rise' babies will be identified. Data from the Massachusetts Newborn Screening Program in 2000 suggested that delayed TSH rise is more common in low birth weight babies.[7] A few possible aetiologies have been suggested to explain delayed TSH rise in sick premature infants. One possible explanation is an attenuated response of the hypothalamic–pituitary–thyroid axis secondary to its immaturity. Another possible cause is an increased incidence of sick euthyroid syndrome. Some premature and sick babies are exposed to iodine and receive dopamine, both known to suppress TSH secretion. There are insufficient data to distinguish between the different possible aetiologies.

Recent reports from screening programmes in New South Wales in Australia[8] and Rhode Island in the US[9] confirm that delayed TSH rise is more common in low birth weight babies.

In 2006–2008, the newborn screening programme in Australia monitored TSH levels in 2,117 very low birth weight (VLBW) babies (weight ≤1,500 g) during the first days of life and at one month of age. A spot TSH level was considered positive if ≥20 mIU/l during week one or ≥7 mIU/l at one month. Forty-three babies had transient hypothyroidism, with TFTs normalising before two months of age, usually without treatment. Eighteen babies required treatment beyond two months of age (1:128 of surviving babies). Sixteen had normal TSH results on initial testing, and 12 had TSH levels <6 mIU/l, a finding supporting the delayed TSH rise phenomenon as well as indicating the need for secondary screening at one month of age.[8]

The Rhode Island study looked at the incidence of CH with a delayed TSH rise in VLBW and extremely low birth weight (ELBW) infants as well as at their developmental, growth and endocrine outcomes at a corrected age of 18 months. It included a retrospective analysis of the TFTs of 92,800 newborns. CH with a delayed TSH rise occurred in 1 in 58 ELBW infants, 1 in 95 VLBW infants, and 1 in 30,329 infants weighing >1,500 g. The incidence found in the >1,500 g group in this study was probably an underestimation, because, in that group, repeat TFTs were not systematically carried out but only undertaken if medically indicated. The outcomes of VLBW and ELBW infants with CH and delayed TSH rise were comparable with matched controls without CH or delayed TSH rise in terms of mean head circumference, weight, length and developmental score. A higher incidence of head circumference measurements below the 10th percentile was found in the VLBW infants with delayed TSH elevation.[9]

The long-term outcomes of subclinical hypothyroidism with mildly elevated TSH and normal T4 remains unclear. The finding that, in patients with delayed TSH rise, TFTs may normalise without treatment raises the question of whether or not treatment is indicated.

With increasing numbers of premature infants surviving, larger numbers of children with delayed TSH rise can be expected. Additional studies are required to determine the need for treatment and establish appropriate guidelines for the monitoring of TFTs in at-risk newborns.

Monitoring Thyroid Function in Newborns Diagnosed with Congenital Hypothyroidism During the First Three Years of Life

The current AAP guidelines include measurement of T4 and TSH two to four weeks after starting treatment, every one to two months during the first six months of life, every three to four months between six months and three years of age, and every six to 12 months until growth is complete. More frequent testing is suggested when non-adherence to treatment is suspected or when TFTs are abnormal. Furthermore, TFTs should be repeated four weeks after any change in levothyroxine (L-T4) dose.[2] The European Society for Paediatric Endocrinology (ESPE) recommends monitoring TFTs every one to two weeks after initiation of treatment until T4 and TSH have normalised, but does not give guidelines for long-term monitoring.[10]

While the AAP recommends repeat TFTs to be carried out two to four weeks after initiation of therapy, the UK guidelines recommend that the first follow-up should be within 14 days, and the ESPE guidelines recommend follow-up within 7–14 days of treatment initiation. The shorter interval in the ESPE guidelines is based on a study showing that 7.4 % of infants started on a dose of 25 µg of L-T4 had subnormal free T4 (fT4) seven days after treatment initiation. The percentage was lower with higher initial doses (5.1 % with a 37.5 µg dose and 0 % with a 50 µg dose).[11] The shorter interval is important for monitoring adherence to treatment and verifying the adequacy of the dose and delivery method, but it is less important if the AAP recommendation of a high initial dose of 10–15 µg/kg of body weight is followed.

A recent paper published by our group suggests monthly monitoring during the first year of life is needed to maintain fT4 levels in the upper half of the normal range and TSH in the normal range.[12] This retrospective study evaluated 70 children with CH for initial TSH levels, frequency of follow-up, changes in dose and TFTs during the first year of life. Age-appropriate normal ranges for TFT levels were used until three months of age, after which adult normal ranges were used. TFTs were regarded as abnormal if total T4 (tT4) or fT4 were not in the upper half of the normal range, or if TSH was not in the normal range.

Subjects had TFTs carried out monthly for the first six months of life and every one to two months between six and 12 months of age. Criteria indicating the need for monthly monitoring included:

- change in dose within one month of a previous visit;
- total T4 or fT4 levels not in upper half of normal range within one month of a previous visit;
- TSH level of 5–10 µU/ml (less than twice the upper limit of normal) within one month of a previous visit associated with tT4/fT4 not in the upper half of normal range (to avoid inclusion of subjects with transient resistance to TSH sometimes reported in the first year of life in children with CH);
- TSH >10 µU/ml (more than twice the upper limit of normal) within one month of a previous visit, regardless of tT4/fT4 levels; and
- TSH <0.1 µU/ml.

When monitoring was conducted every other month, a TSH level of more than twice the upper limit of normal was regarded as an indicator of the need for more frequent monitoring – assuming that monthly monitoring would have picked up minor elevations in TSH, allowing earlier changes in L-T4 doses. Monthly monitoring appeared to be necessary in 74 % of children in the first six months of life and 36 % of children aged 6–12 months. These percentages would probably have been even higher if the goal of maintaining the TSH levels between 0.5 and 2.0 mU/l during the first three years of life had been used, as suggested by Baloch et al.[13]

Predictors of the need for monthly monitoring in the second six months of life included higher TSH and lower tT4 at diagnosis. Unfortunately, the overlap between the groups was such that monthly monitoring during the first year of life would seem to be necessary for all children diagnosed with CH, until further studies are available. These recommendations are closer to the previous AAP guidelines, published in 1993, which stated that TFTs should be monitored every one to two months during the first year of life, every two to three months between one and three years of age, and every three to 12 months until growth is complete.[14]

The frequency of monitoring of TFTs after three years of age has not been well studied, as fewer data are available regarding long-term outcomes of children with CH with suboptimal treatment after the age of three. The current AAP guidelines recommend monitoring TFTs every six to 12 months until growth is complete.

Assessing Permanency of Hypothyroidism

Given the deleterious effect of under-treatment of CH during the first years of life, over-diagnosis is the inevitable price to pay for treating patients with transient hypothyroidism. To identify this subpopulation, children should be taken off thyroid replacement therapy for a trial period as soon as it is thought that a short period of untreated hypothyroidism will not have a significant effect on the developing brain.

The AAP recommends assessing the permanency of CH in children in whom an initial thyroid scan did not show an ectopic or absent gland, if the initial TSH was <50 mU/l and if there was no increase in TSH after the newborn period. Assessment of the permanency of CH should not be performed earlier than three years of age. Two options are suggested: either a trial off therapy for 30 days, or a reduction of the replacement dose by 50 % for 30 days, with subsequent TFTs to assess the effects. A permanent diagnosis of CH is established if those TFTs are compatible with hypothyroidism. If they are normal after a 50 % dose reduction, medication should be discontinued for 30 days and new TFTs carried out at the end of the period. Any child given a diagnosis of transient hypothyroidism should be followed closely by the paediatrician, with TFTs carried out at any clinical suspicion of hypothyroidism. There are no established guidelines for the frequency of follow-up after withdrawal of thyroid hormone therapy.

Determining the aetiology of the child's hypothyroidism may be helpful in deciding whether or not to temporarily withdraw replacement therapy.

Persistent Elevated Levels of Thyroid Stimulating Hormone

Levels of TSH remain elevated in some children with CH despite appropriate L-T4 treatment and normalisation of serum fT4 and tT4 levels. In this subpopulation, supraphysiologic T4 levels are required to suppress TSH levels. The precise mechanism is unclear but, in cases where adherence to treatment is not in question, it is thought that the setting of T4 negative feedback control on pituitary TSH secretion is abnormal. The treatment goal in this population is controversial. Maintaining normal T4 levels with an elevated TSH may be associated with an increased risk of thyroid nodules and cancer, but over-treatment may have a deleterious effect on growth and development and may affect school performance. In adults, combined L-T4 and triiodothyronine (T3) treatment protocols have lead to lower TSH levels.[15] A combined regimen of L-T4 and T3 was thought to be a possible strategy for overcoming persistent TSH elevation, based on the postulate that non-suppressed TSH was secondary to lower T3 levels in the central nervous system, because approximately 20 % of T3 is secreted directly by the thyroid gland.

Combined L-T4 and T3 treatment was studied in a group of 10 children aged over five years with confirmed good adherence to treatment. All patients had a persistently high TSH level (>6.4 µIU/ml), which could only be normalised by supraphysiological L-T4 treatment, resulting in hyperthyroidism (fT4 above upper normal range). Patients were switched to a combined protocol, with half their L-T4 dose substituted with T3, in a 4:1 ratio. TFTs were monitored during a one-year follow-up period, and the doses of T3 and L-T4 were titrated to achieve normal TSH levels. All patients achieved normalisation of TSH without hyperthyroidism at a mean of seven months. Patients on the combined regimen had lower serum fT4 and tT4 levels and higher serum T3 levels compared with patients on L-T4 treatment alone.[16]

Genetic Causes of Congenital Hypothyroidism

Eighty-five per cent of cases of CH are attributable to thyroid dysgenesis and 2 % of these are familial. Most of the genes implicated in thyroid dysgenesis are associated with phenotypic syndromes and would typically be diagnosed as a result of the associated anomalies. Examples are mutations in *TTF-2*, *NKX2.1* and *NKX2.5*. Mutations in paired box gene eight (*PAX8*) were shown to cause thyroid dysgenesis, with no other congenital anomalies.[4]

Inborn errors of thyroid hormone biosynthesis account for 10–15 % of cases of congenital hypothyroidism. Mutations associated with dyshormonogenesis include sodium iodide symporter defects and thyroid peroxidase defects. Multiple causes of defects in thyroid peroxidase function have been described, including hydrogen peroxide

generation defects (due to mutations in *DUOX2* or *DUOXA2*), Pendred syndrome, thyroglobulin defects and defects in iodotyrosine deiodinase (as a result of mutations in *DEHAL1* or *SECISBP2*).

Mutations in the genes that encode the TSH receptor or G-protein may cause resistance to TSH binding or signalling, and this is another subtype of genetic CH.

There are no specific guidelines for monitoring the genetic conditions associated with hypothyroidism, but establishing the diagnosis would allow to classify the child as having persistent hypothyroidism, which in turn would avoid unnecessary trial periods off treatment and testing. It is also important to identify children with these gene mutations so that families can receive genetic counselling and siblings can be tested.

From Guidelines to Practice

A recent study in the UK compared the national practice of early management of CH with the latest available European and UK guidelines.[17] The current clinical practice of 143 members of the British Society for Paediatric Endocrinology and Diabetes was assessed using a questionnaire. The survey investigated the timing of the initial and first post-treatment visits, L-T4 preparation, initial dose, and clinical aims in terms of biochemical outcomes. The study found gaps between the practice and guidelines in key aspects of the management of CH. For example, 26 % of responders chose an initial L-T4 dose of <10 µg/kg/day, and 20 % of respondents scheduled the first post-treatment visit more than 14 days after initiation of treatment – both in contradiction with the recommendations in the guidelines. These numbers emphasise the importance of promulgating guidelines among providers to ensure optimal patient care.

Summary

Adequate and timely follow-up of CH is critical for optimising outcomes. Guidelines for follow-up should be revised frequently to accommodate new information. Presently, there are differences between the guidelines of the AAP, ESPE and UK thyroid study groups. Further differences arise in practice due to a lack of adherence to the recommendations. For optimum patient care, it would be important to ensure that uniform evidence-based guidelines are developed and that they are followed in practice. ■

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