

Congenital hypothyroidism: a 2020 consensus guidelines update

An ENDO-EUROPEAN REFERENCE NETWORK (ERN) initiative endorsed by the European Society for Pediatric Endocrinology and the European Society for Endocrinology

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ABSTRACT

Background

An ENDO-ERN initiative was launched which was endorsed by the European Society for Pediatric Endocrinology and the European Society for Endocrinology with 22 participants from the ENDO-ERN and the two societies. The aim was to update the practice guidelines for the diagnosis and management of congenital hypothyroidism (CH). A systematic literature search was conducted to identify key articles on neonatal screening, diagnosis and management of primary and central congenital hypothyroidism. The evidence-based guidelines were graded with the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system, describing both the strength of recommendations and the quality of evidence. In the absence of sufficient evidence, conclusions were based on expert opinion.

Summary

The recommendations include the various neonatal screening approaches for CH as well as the etiology (also genetics), diagnostics, treatment and prognosis of both primary and central CH. When CH is diagnosed, the expert panel recommends the immediate start of correctly dosed levothyroxine treatment and frequent follow-up including laboratory testing to keep thyroid hormone levels in their target ranges, timely assessment of the need to continue treatment, attention for neurodevelopment and neurosensory functions and, if necessary, consulting other health professionals, and education of the child and family about CH. Harmonisation of diagnostics, treatment and follow-up will optimise patient outcomes. Lastly, all individuals with CH are entitled to a well-planned transition of care from pediatrics to adult medicine.

Conclusions

This consensus guidelines update should be used to further optimize detection, diagnosis, treatment and follow-up of children with all forms of CH in the light of the most recent evidence. It should be helpful in convincing health authorities of the benefits of neonatal

screening for CH. Further epidemiological and experimental studies are needed to understand the increased incidence of this condition.

Thyroid

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INTRODUCTION

Congenital Hypothyroidism (CH) can be defined as (variable) dysfunction of the hypothalamic–pituitary–thyroid (HPT) axis present at birth, resulting in insufficient thyroid hormone production and, with that, severe to mild thyroid hormone deficiency. CH may be caused by abnormal development or function of the thyroid gland, or of the hypothalamus and pituitary, but also to impaired thyroid hormone action.

In 2014, an international consensus guideline on CH was published that encompassed the scientific literature up to 2013 (1). An ENDO-ERN initiative was launched, which was endorsed by the European Society for Pediatric Endocrinology and the European Society for Endocrinology, with the aim to update the practice guidelines for the diagnosis and management of congenital hypothyroidism.

METHODS

Twenty-two participants from the ENDO-ERN network, Main Thematic Group 8 - Thyroid, including an ENDO-ERN patient association representative, and from the two scientific societies, the European Society for Pediatric Endocrinology and the European Society for Endocrinology participated. Preparation for the consensus took nearly 24 months, starting late 2017 including email exchanges and two preparatory face to face meetings organized in 2019. All co-authors performed a comprehensive literature research using PubMed including articles published from 01/01/2013 to present (early 2020) concerning the five different subthemes presented in the consensus. Publications before 2013 have already been considered in the previous CH consensus published in 2014. Only publications in English were considered. A comprehensive review of all selected articles formed the basis of discussion and writing for the five working groups: working group (WG)1: Neonatal screening, WG2: Diagnosis and criteria for treatment, WG3: Treatment and monitoring, WG4: Outcomes of neonatal screening and early treatment, WG5: Genetics of CH and antenatal management. A preliminary document summarizing the questions addressed in the preparatory meetings was prepared by each WG and shared for review with all the experts before the final meeting. At the final consensus meeting, propositions and recommendations were reconsidered by participants and discussed in plenary sessions,

enabling any reformulation of the recommendations. Recommendations were based on best available research evidence. Best practice statements were considered when necessary and if evidence is mixed, based on expert opinion.

A detailed description of the grading scheme GRADE (Grading of Recommendations Assessment, Development and Evaluation) has been published elsewhere (2). Factors that influence the strength of the recommendation (strong vs. weak) include the quality of evidence, the balance between benefits and risks, the burden of interventions, and the cost.

For each point, recommendations and evidence are described, with a modification in the grading evidence, as follows: 1 = strong recommendation (applies to most patients in most circumstances, benefits clearly outweigh the risk); 2 = weak recommendation (suggested by us or should be considered; the best action may depend on circumstances or patient values, benefits and risks closely balanced or uncertain). Quality of evidence is indicated as follows: +00: low (case series or non-systematic clinical observations, inconsistent and unprecise estimates or with indirect evidence); ++0 moderate (studies with methodological flaws, inconsistent or indirect evidence); +++ high quality (low risk bias).

Summary of the CH consensus guidelines update

Neonatal screening

1.1 The benefits of CH screening

- Early detection and treatment of CH through neonatal screening prevents irreversible neurodevelopmental delay and optimizes its developmental outcome (1/+++).
- Screening for CH should be introduced worldwide (1/+++).

1.2 Analytical methodology and effectiveness of CH screening strategies

- The incidence of CH partly depends on the screening strategy; based on data from a number of screening programs the incidence of primary CH lies between 1 in 3,000 and 1 in 2,000; the highest reported incidence of central CH is around 1 in 16,000 (1/+++).

- The initial priority of neonatal screening for CH should be the detection of all forms of primary CH - mild, moderate and severe; the most sensitive test for detecting primary CH is measurement of thyroid-stimulating hormone (TSH) (1/+++).
- When financial resources are available, we recommend adding measurement of total or free thyroxine (FT4) to TSH, to screen for central CH (2/++0).

1.3 Post-screening strategies in special categories of neonates at risk of CH

- Some groups of children may have a false negative neonatal screening result or have a high risk of mild CH not detected by neonatal screening, for instance premature, low birthweight and sick babies; for these groups a post-screening strategy including collection of a second specimen around 10 to 14 days of age may be considered (1/+00).
- In patients with Down syndrome, we recommend measuring TSH at the end of the neonatal period (1/++0).
- The initial screening in an affected twin may be normal; a second screening in same sex twins should be considered. The non-affected sibling of twins should be followed-up for possible TSH elevation later in life (2/+00).
- Clinical suspicion of hypothyroidism, despite normal TSH in TSH-based screening programs, should prompt further evaluation for primary (rare cases of false negative neonatal screening results) and central CH, particularly in children with a family history of central CH (2/+00).

Diagnostics and criteria for treatment

2.1 Biochemical criteria used in the decision to start treatment for CH

- A newborn with an abnormal neonatal screening result should be referred to an expert center (1/++0).
- An abnormal screening result should be followed by confirmatory testing consisting of measurement of serum FT4 and TSH (1/++0).

- If the serum FT4 concentration is below, and TSH clearly above the age-specific reference interval, then levothyroxine (LT4) treatment should be started immediately (1/+++).
- If the serum TSH concentration is >20 mU/L at confirmatory testing (approximately in the second week of life), treatment should be started, even if FT4 is normal (arbitrary threshold, expert opinion) (2/+00).
- If the serum TSH concentration is 6-20 mU/L beyond the age of 21 days in a healthy neonate with a FT4 concentration within the age-specific reference interval, we suggest to either start LT4 treatment immediately and retest, off-treatment, at a later stage, or to withhold treatment but retest one to two weeks later and to re-evaluate the need for treatment (lack of evidence in favour or against treatment, this is an area of further investigation) (2/++0).
- In countries or regions where thyroid function tests are not readily available, LT4 treatment should be started if filter paper TSH concentration is >40 mU/L (at the moment of neonatal screening; arbitrary threshold, expert opinion) (2/+00).
- If the serum FT4 is low, and TSH is low, normal or slightly elevated, the diagnosis central CH should be considered (1/++0).
- In neonates with central CH, we recommend to start LT4 treatment only after evidence of intact adrenal function; if coexistent central adrenal insufficiency cannot be ruled out, LT4 treatment must be preceded by glucocorticoid treatment in order to prevent possible induction of an adrenal crisis (2/+00).

2.2 Communication of abnormal screening and confirmatory results

- An abnormal neonatal screening result should be communicated by an experienced professional (e.g. member pediatric endocrine team, pediatrician or general physician) either by telephone or face to face, and supplemented with written information for the family (2/+00).

2.3 Imaging techniques in CH

- In patients with a recent CH diagnosis, we strongly recommend starting LT4 treatment before conducting thyroid gland imaging studies (1/++0).
- We recommend imaging of the thyroid gland using either radioisotope scanning (scintigraphy) with or without the perchlorate discharge test, or ultrasonography (US), or both (1/++0).
- Knee X-ray may be performed to assess the severity of intrauterine hypothyroidism (2/+00).

2.4 Associated malformations and syndromes

- All neonates with a high TSH concentration should be examined carefully for dysmorphic features suggestive for syndromic CH, and for congenital malformations (particularly cardiac) (1/+++).

Treatment and monitoring of CH

3.1 Starting treatment for primary CH

- LT4 alone is recommended as the medication of choice for the treatment of CH (1/++0).
- LT4 treatment should be started as soon as possible, not later than two weeks after birth or immediately after confirmatory (serum) thyroid function testing in neonates in whom CH is detected by a second routine screening test (1/++0).
- The LT4 starting dose should be up to 15 µg/kg per day, taking into account the whole spectrum of CH, ranging from mild to severe (1/++0).
- Infants with severe CH, defined by a very low pretreatment serum FT4 (<5 pmol/L) or total T4 concentration in combination with elevated TSH (above the normal range based on time since birth and gestational age, should be treated with the highest starting dose (10-15 µg/kg per day) (1/++0).

- Infants with mild CH (FT4 >10 pmol/L in combination with elevated TSH), should be treated with the lowest initial dose (around 10 µg/kg per day); in infants with pretreatment FT4 concentrations within the age-specific reference interval an even lower starting dose may be considered (from 5-10 µg/kg) (1/++0).
- LT4 should be administered orally, once a day (1/++0).
- The evidence favoring brand vs generic LT4 is mixed but based on personal experience/expert opinion we recommend brand rather than generic (2/++0).

3.2 Monitoring treatment in primary CH

- We recommend measurement of serum FT4 and TSH concentrations before, or at least four hours after the last (daily) LT4 administration (1/++0).
- We recommend evaluation of FT4 and TSH according to age-specific reference intervals (1/++0).
- The first treatment goal in neonates with primary CH is to rapidly increase the circulating amount of thyroid hormone, reflected by normalization of serum TSH; thereafter, TSH should be kept within the reference interval.
- If TSH is in the age-specific reference interval, FT4 concentrations above the upper limit of the reference interval can be accepted and recommend maintaining the same LT4 dose (1/++0).
- Any reduction of the LT4 dose should not be based on a single higher than normal FT4 concentration, unless TSH is suppressed (i.e. below the lower limit of the reference interval) or there are signs of overtreatment (e.g. jitteriness or tachycardia) (1/++0).
- The first clinical and biochemical follow-up evaluation should take place one to two weeks after the start of LT4 treatment (one week at the latest in case of a starting dose of 50 µg per day or an even higher dose) (1/+00).

- Subsequent (clinical and biochemical) evaluation should take place every two weeks until complete normalization of serum TSH is achieved; thereafter, the evaluation frequency can be lowered to once every one to three months until the age of 12 months (1/+00).
- Between the ages of 12 months and three years, the evaluation frequency can be lowered to every two to four months; thereafter, evaluations should be carried out every three to six months until growth is completed (1/+00).
- If abnormal FT4 or TSH values are found, or if compliance is questioned, the evaluation frequency should be increased (2/+00).
- After a change of LT4 dose or formulation, an extra evaluation should be carried out after four to six weeks (2/+00).
- We recommend physicians to avoid long-term under- or overtreatment during childhood (1/++0).
- In contrast to adults, in neonates, infants and children LT4 can be administered together with food (but with avoidance of soy protein and vegetable fiber); more important, LT4 should be administered at the same time every day, also in relation to food intake; while this approach can improve compliance, it ensures as constant as possible LT4 absorption and, with that, as good as possible LT4 dose titration (2/+00).
- In case of an unexpected need for LT4 dose increase, reduced absorption or increased metabolization of thyroxine by other disease (e.g. gastrointestinal), food or medication should be considered (2/+00); incompliance may be the most frequent cause, especially in teenagers and adolescents.

3.3 Treatment and monitoring of central CH

- In severe forms of central CH (FT4 <5 pmol/L), we also recommend to start LT4 treatment as soon as possible after birth at doses like in primary CH (10-15 µg/kg per day, see 3.1), in order to bring FT4 rapidly within the normal range (1/++0).
- In milder forms of central CH, we suggest starting treatment at a lower LT4 dose (5-10 µg/kg per day), to avoid the risk of overtreatment (1/++0).

- In newborns with central CH, we recommend monitoring treatment by measuring FT4 and TSH according to the same schedule as for primary CH; serum FT4 should be kept above the mean/median value of the age-specific reference interval; if TSH low prior to treatment, subsequent TSH determinations can be omitted (1/+00).
- When under- or overtreatment is suspected in a patient with central CH, then TSH, or free or total triiodothyronine (FT3, T3) can be measured (1/+00).
- When FT4 is around the lower limit of the reference interval, then undertreatment should be considered, particularly if TSH >1.0 mU/L (1/+00).
- When serum FT4 is around or above the upper limit of the reference interval, then overtreatment should be considered (assuming that LT4 has not been administered just before before blood withdrawal), particularly if associated with clinical signs of thyrotoxicosis, or a high (F)T3 concentration (1/+00).

3.4 Diagnostic re-evaluation of thyroid function beyond the first six months of life

- When no definitive diagnosis of permanent CH was made in the first weeks or months of life, then re-evaluation of the HPT axis after the age of two to three years is indicated, particularly in children with a gland-in-situ (GIS), and in those with presumed isolated central CH (1/++0).
- For a precise diagnosis, LT4 treatment should be phased out over a four to six weeks period or just stopped, and full re-evaluation should be carried out after four weeks, consisting of (at least) FT4 and TSH measurement.
- If primary hypothyroidism is confirmed (TSH \geq 10 mU/L) consider thyroid imaging and, if possible, genetic testing; if central CH is likely (FT4 below the lower limit of the reference interval in combination with a low, normal or only mildly elevated TSH) consider evaluating the other anterior pituitary functions and genetic testing.
- If TSH is above the upper limit of the reference interval but <10 mU/L (primary CH) or FT4 just above the lower limit of the reference interval (central CH), then continue withdrawal and re-test in another three to four weeks (1/++0).

- If a child with no permanent CH diagnosis and a GIS requires a LT4 dose less than 3 mcg/kg per day at the age of six months, then re-evaluation can be done already at that time (1/++0).
- We recommend avoiding iodine as an antiseptic during peri- and neonatal period, as it can cause transient CH (1/++0).

3.5 Treatment and monitoring of pregnant women with CH

- In women with CH who are planning pregnancy we strongly recommend optimization of LT4 treatment; in addition, these women should be counseled regarding the higher need for LT4 during pregnancy (1/++0).
- FT4 (or total T4) and TSH levels should be monitored every four to six weeks during pregnancy, aiming at TSH concentrations in accordance with current guidelines on treatment of hypothyroidism during pregnancy, i.e. <2.5 mU/L throughout gestation in patients treated with levothyroxine (1/+00).
- In pregnant women with central CH, the LT4 doses should be increased aiming at a FT4 concentration above the mean/median value of the trimester specific reference interval (1/+00).
- Following delivery, we recommend lowering LT4 dose to preconception dose; additional thyroid function testing should be performed at approximately six weeks post partum (1/++0).
- All pregnant women should ingest approximately 250 µg iodine per day (1/++0).

Outcomes of neonatal screening and early treatment

4.1 Neurodevelopmental outcomes

- Psychomotor development and school progression should be periodically evaluated in all children with CH; speech delay, attention and memory problems, and behavioral problems are reasons for additional evaluation (1/++0).
- In the small proportion of children with CH who do display significant psychomotor developmental delay and syndromic CH with brain abnormalities, it is crucial to rule out other causes of intellectual impairment than CH (1/+00).

- Not just neonatal, but repeated hearing tests should be carried out before school age and, if required, during further follow-up (2/++0).

4.2 Development of goiter in thyroid dyshormonogenesis

- Children and adolescents with primary CH due to dyshormonogenesis may develop goiter and nodules; in these cases, serum TSH should be carefully targeted in the lower part of normal range and periodical ultrasound investigation is recommended to monitor thyroid volume (2/++0).
- Since a few cases of thyroid cancer have been reported, fine needle aspiration biopsy for cytology should be performed in case of suspicious nodules on ultrasound investigation (1/+00).

4.3 Growth, puberty and fertility

- Adequately treated children with non-syndromic CH have normal growth and puberty, and their fertility does not differ from individuals who do not have CH (1/+++).

4.4 Bone, metabolic and cardiovascular health

- Adequately treated children with non-syndromic CH also have normal bone, metabolic and cardiovascular health (1/++0).

4.4 Patient and professional education, and health related quality of life

- Medical education about CH should be improved at all levels, with regular updates (1/+++).
- Education of parents, starting at the time of the diagnosis, and later on of the patient is essential; not only throughout childhood, but also during transition to adult care and in women during pregnancy (1/+++).
- Since adherence to treatment may influence the outcomes, it should be promoted throughout life (1/++0).

4.5 Transition to adult care

- When patients are transferred from paediatric to adult care, the main aims are continuity of care and, with that, optimal clinical outcomes and quality of life, and to increase understanding of CH and promote self-management (1/+++).

Genetics of CH, genetic counselling and antenatal management

5.1 Criteria for genetic counselling

- Genetic counselling should be targeted rather than general (to all CH patients) and done by an experienced professional (2/++0).
- Counselling should include explaining inheritance and the risk of recurrence of the patient's primary or central form of CH, based on the CH subtype, the family history and, if known, the (genetic) cause (1/++0).
- Parents with a child, or families with a member with CH should have access to information about the two major forms of primary CH – thyroid dysgenesis and dyshormonogenesis – and, if included in the neonatal screening, about central CH (1/+++).

5.2 Genetics of CH

- If genetic testing is performed, its aim should be improving diagnosis, treatment or prognosis (1/++0).
- Before doing so, possibilities and limits of genetic testing should be discussed with parents or families (1/++0).
- When available, genetic testing should be performed by means of new techniques, like comparative genomic hybridization (CGH) array, next-generation sequencing of gene panels (targeted NGS) or whole exome sequencing (WES) (1/++0).
- Preferably, genetic testing or studies should be preceded by careful phenotypic description of the patient's CH, including morphology of the thyroid gland (2/++0).
- Not only thyroid dyshormonogenesis, but also familial occurrence of dysgenesis and central hypothyroidism should lead to further genetic testing (1/++0).
- Any syndromic association should be studied genetically, not only to improve genetic counselling, but also to identify new candidate genes explaining the association (1/++0).

- Further research is needed to better define patients or patient groups that will benefit most from these new diagnostic possibilities (2/++0).

5.3 Antenatal diagnostics, evaluation of fetal thyroid function and management of fetal hypothyroidism

- We recommend antenatal diagnosis in cases of goiter fortuitously discovered during systematic ultrasound examination of the fetus, in relation to thyroid dysmorphogenesis (1|+++); a familial recurrence of CH due to dysmorphogenesis (25% recurrence rate) (1|+++); and known defects of genes involved in thyroid function or development with potential germline transmission (1|++0). Special issues should be considered for syndromic cases with potential mortality and possible germline mosaicism (as for *NKX2-1* gene mutation/deletion and severe pulmonary dysfunction with possible transmission via germline mosaicism). In such circumstances, the discussion of the prenatal diagnosis should be open. The therapeutic management of affected foetuses should comply with the laws in force in the country concerned (1|++0). The familial recurrence of CH due to dysgenesis (2% of familial occurrences) requires further study to determine the feasibility and clinical relevance for antenatal detection.

- For the evaluation of fetal thyroid volume, we recommend ultrasound scans at 20 to 22 weeks gestation to detect fetal thyroid hypertrophy and potential thyroid dysfunction in the fetus. Goiter or an absence of thyroid tissue can also be documented by this technique. Measurements should be made as a function of GA, and thyroid perimeter and diameter should be measured to document goiter (1/+++).

- If a (large) fetal goiter is diagnosed, prenatal care should be provided in a specialized center of prenatal care (1/+++).

- We recommend cordocentesis, rather than amniocentesis, as the reference method for assessing fetal thyroid function. Norms have been established as a function of GA. This examination should be carried out only if prenatal intervention is considered (see below) (1|+++).

- In most cases, fetal thyroid function can be inferred from context and ultrasound criteria, and fetal blood sampling is, therefore, only exceptionally required (2|++0).

- We strongly recommend fetal treatment by intra-amniotic thyroxine injections in a euthyroid pregnant woman with a large fetal goiter associated with hydramnios and/or tracheal occlusion; in a hypothyroid pregnant woman, we recommend to treat the woman (rather the fetus) with thyroxine (1/++0).
- For goitrous nonimmune fetal hypothyroidism leading to hydramnios, we recommend intra-amniotic injections of L-T4 to decrease the size of the fetal thyroid gland. The injections should be performed by multidisciplinary specialist teams (1|+++).
- The expert panel proposes the use of 10 microg/kg estimated fetal weight/15 days in the form of intra-amniotic injections. The risks to the fetus and the psychological burden on the parents should be factored into the risk/benefit evaluation (2|+00).

1. NEONATAL SCREENING

- 1.1 The benefits of CH screening
- 1.2 Analytical methodology and effectiveness of CH screening strategies
- 1.3 Post-screening strategies in special categories of neonates at risk of CH

1.1 The benefits of CH screening

Summary

- Early detection and treatment of CH through neonatal screening prevents irreversible neurodevelopmental delay and optimizes its developmental outcome (1/+++).
- Screening for CH should be introduced worldwide (1/+++).

Evidence

Neonatal screening for CH has almost eliminated the profound negative effects of thyroid hormone deficiency on growth and neurodevelopment (cretinism) in those countries where it has been established. Improved developmental outcomes were already reported a few years after the start of neonatal screening (3,4), and justified its economic costs by

clearly outweighing the costs of providing health and educational care for individuals with neurodevelopmental damage due to CH (5).

Despite the benefits of neonatal screening, 70% of infants worldwide are born in areas that do not have access to neonatal screening (6). In addition, many of these infants are born in areas of endemic iodine deficiency, placing them at increased risk of thyroid hormone deficiency.

1.2 Analytical methodology and effectiveness of CH screening strategies

Summary

- The incidence of CH partly depends on the screening strategy; based on data from a number of screening programs the incidence of primary CH lies between 1 in 3,000 and 1 in 2,000; the highest reported incidence of central CH is around 1 in 16,000 (1/+++).
- The initial priority of neonatal screening for CH should be the detection of all forms of primary CH – mild, moderate and severe; the most sensitive test for detecting primary CH is measurement of thyroid-stimulating hormone (TSH) (1/+++).
- When financial resources are available, we recommend adding measurement of total or free thyroxine (FT4) to TSH, to screen for central CH (2/++0).

Evidence

Since the introduction of neonatal screening for CH in the late 1970s, using total T4 plus, or followed by TSH, gradually evolving into TSH only, its incidence and yield have also changed. An initial estimated incidence was revised from 1 in 7,000 to around 1 in 4,000 soon after the introduction of screening in the UK (7), probably reflecting more accurate data with detection of CH cases that were previously undiagnosed. Since then, the CH incidence has increased to between 1 in 3,000 and 1 in 2,000.

This can be partly explained by the lowering of neonatal screening TSH cut-off values, resulting in the detection of newborns who would have been missed otherwise (false negatives) (8), but also in finding children with biochemically milder forms of CH (mostly with thyroid gland in situ) (9-11). However, the overall increase in the incidence of CH

cannot be attributed solely to lower screening TSH cut-off values (12), and thus environmental, ethnic and genetic factors should be considered, and all require further evaluation (13-18). For instance, the clinical expression of mutations in genes like *DUOX2/DUOXA2* varies widely between individuals and over time, with some patients requiring no treatment, and some having transient CH. On the other hand, *DUOX* gene mutations can be associated with worsening of thyroid functions in the first weeks of life (16). However, justification for screening and detecting biochemically less severe, eventually transient CH cases requires assessment of neurodevelopmental sequelae, but this has been proved difficult (19). Long-term outcome studies of the effect of LT4 treatment on prevention of neurodevelopmental delay in these patients will also be required.

Neonatal screening programmes were originally designed to detect primary CH by total T4 plus, or followed TSH measurement, and later by measurement of only TSH, with optimal timing of samples at least 48 hours after birth. However, also measuring T4 \pm thyroxine-binding globulin provides the potential to diagnose central CH. Although slightly more than 50% of neonates with central CH have moderate to severe CH, i.e. a first diagnostic FT4 concentration of 5-10 pmol/L or lower, and central CH is likely to be associated with other pituitary abnormalities, this diagnosis is often delayed (20,21). Therefore, detection of central CH by neonatal screening has the potential to prevent the neurodevelopmental sequelae of TH deficiency and associated morbidities. The reported incidence of central CH detected through neonatal screening lies between 1 in 30,000 and 1 in 16,000, depending on the screening strategy (22-26). Although additional data on the true clinical benefits and false-positive rates are required, central CH is a potential candidate for neonatal screening.

Until 2019 only supportive therapy was available for patients with MCT8 deficiency. This changed when a clinical trial demonstrated that treatment with triiodothyroacetic acid (Triac) ameliorates key features of the peripheral thyrotoxicosis and might benefit brain development once treatment is commenced early in life (27). Therefore, early recognition of MCT8 affected children becomes of utmost importance through T4 and TSH neonatal

screening eventhough the part of the fetal component of the disease that can be alleviated by Triac treatment remains to be determined.

Pitfalls in the newborn screening do exist and can be due to abnormal thyroid hormone binding globulin, severe concomitant illnesses as well as several drugs and autoantibodies (24,28).

1.3 Post-Screening strategies in special categories of neonates at risk of CH

Summary

- Some groups of children, such as preterm or low birth weight and sick babies, pass their initial screening test but are at high risk for later development of mild CH. For these groups a post-screening strategy may be considered (1/+00).
- In patients with Down syndrome, we recommend measuring TSH at the end of the neonatal period (1/++0).
- The initial screening in an affected twin may be normal; a strategy of a second screening should be considered. The non-affected sibling of twins should be followed-up for possible TSH elevation later in life (2/+00).
- Clinical suspicion of hypothyroidism, despite normal TSH in TSH-based screening programs, should prompt further evaluation for primary (rare cases of false negative neonatal screening results) and central CH, particularly in children with a family history of central CH (2/+00).

Evidence

Babies with primary CH who are born premature or with low birthweight, or who are sick in the neonatal period may not be able to generate an adequate TSH response in the first weeks of life. Therefore, in TSH-based neonatal screening programs their screening result may be false negative (29,30). Maturation or recovery of the hypothalamic-pituitary-thyroid axis with an increase in TSH occurs between the ages of two to six weeks of life, and many neonatal screening programs have revised recommendations for this group of infants (29,31). In preterm newborns, the TSH surge and the blood levels of T4 and T3 are

lower compared to term neonates. The immature hypothalamic–pituitary–thyroid axis in the extreme preterm neonates is characterized by 1) a markedly attenuated TSH surge, 2) a T4 decrease instead of an increase, and 3) a clearly lower and shorter T3 increase within the first 24 hours of life. Interestingly, the T3 surge is observed as early as 1 hour postnatally, while the T4 surge only appeared at 7 hours after birth in infants born 28 to 30 gestational weeks and 31 to 34 gestational weeks (32). This observation may be explained by three factors: decreased T3 metabolism in the placenta, increased outer ring deiodination of T4, and increased thyroïdal T3 release in response to the TSH surge. However, because the T3 increase at 1 hour after birth was independent of the TSH surge, and T4 peak values were reached only at 7 hours after birth in more mature infants, an abrupt loss of placental D3 activity is the most probable physiologic explanation for the observed rapid T3 increase followed by a slightly delayed T4 increase. Transient hypothyroxinemia of the preterm neonate is a frequent finding, often aggravated by general illness of the preterm neonate and it is due to an immature hypothalamic–pituitary–thyroid function. So far, LT4 therapy of preterm hypothyroxinemia remains controversial and large-scale randomized trials are necessary to provide more clarity on its potential impact or absence thereof. Even after diagnosis of CH in preterm infants, one needs to be aware of the high incidence of postnatal transient forms of CH, emphasizing the need of diagnostic reevaluation beyond infancy. The Wolff–Chaikoff effect is only mature at the end of the third trimester. Premature neonates cannot protect themselves from excessive exposure to iodine overdose. Thus, the use of iodine-containing disinfectants is contraindicated in preterm babies, since exposure to topical iodine may cause transient neonatal hypo- or hyperthyroidism as summarized in a systematic review (33).

Although the concordance rate for CH in twins is low, twins are overrepresented in the CH population (34). Because of fetal blood mixing, the TSH concentration of an affected twin may be lower than expected and may escape detection in TSH-based screening (34, 35). Therefore, a low threshold for repeat TSH measurement is suggested, or a second screening should be considered in same-sex twins. In addition, the non-affected twin should be followed-up for possible TSH elevation later in life (36).

Down syndrome is associated with a 14 to 21 times higher than expected incidence of CH, and highly prevalent mild TSH elevation/subclinical hypothyroidism, especially in the first months to years of life (37-39). The probable cause of both phenomena is thyroid dysgenesis, probably related to the extra chromosome 21 and possibly to overexpression of the DYRK1A gene (40-43). Because many neonates with Down syndrome have non-thyroidal illness due to (surgery for) cardiac or intestinal disease (44), TSH generation may be impaired resulting in a false-negative neonatal screening result (in TSH-based screening programs). Therefore, additional measurement of TSH and FT4 around the age of three to four weeks should be considered.

In babies born into families affected with primary or central CH, FT4 and TSH measurement is advised, even if TSH was normal in TSH-based screening programs. A delayed rise of TSH has been reported in newborns affected with defects in the DUOXs system (16). In central CH, TSH is usually normal, but can be lower than normal or mildly elevated; only FT4 will contribute to the diagnosis (25,45). In case of a known genetic cause, (even prenatal) genetic testing can prevent diagnostic delay.

Central CH should be considered in neonates with clinical manifestations of CH or congenital hypopituitarism, but a low, normal or slightly elevated TSH concentration (25,45,46). In addition, we recommend endocrine testing all neonates with a familial history of central CH, or signs or symptoms of congenital hypopituitarism eg, micropenis with undescended testes, hypoglycaemia, prolonged jaundice, or unexplained failure to thrive.

2. DIAGNOSTICS AND CRITERIA FOR TREATMENT

2.1 Biochemical criteria used in the decision to start treatment for CH

2.2 Communication of abnormal neonatal screening and confirmatory results

2.3 Imaging techniques in CH

2.4 Associated malformations and syndromes

2.1 Biochemical criteria used in the decision to start treatment for CH

Summary

- A newborn with an abnormal neonatal screening result should be referred to an expert center (1/++0).
- An abnormal screening result should be followed by confirmatory testing consisting of measurement of serum FT4 and TSH (1/++0).
- If the serum FT4 concentration is below, and TSH clearly above the age-specific reference interval, then levothyroxine (LT4) treatment should be started immediately (1/+++).
- If the serum TSH concentration is >20 mU/L at confirmatory testing (approximately in the second week of life), treatment should be started, even if FT4 is normal (arbitrary threshold, expert opinion) (2/+00).
- If the serum TSH concentration 6-20 mU/L beyond the age of 21 days in a healthy neonate with a FT4 concentration within the age-specific reference interval, we suggest to either start LT4 treatment immediately and retest, off-treatment, at a later stage, or to withhold treatment but retest one to two weeks later and to re-evaluate the need for treatment (lack of evidence in favour or against treatment, this is an area of further investigation) (2/++0).
- In countries or regions where thyroid function tests are not readily available, LT4 treatment should be started if filter paper TSH concentration is >40 mU/L (at the moment of neonatal screening; arbitrary threshold, expert opinion) (2/+00).
- If the serum FT4 is low, and TSH is low, normal or slightly elevated, the diagnosis central CH should be considered (1/++0).
- In neonates with central CH, we recommend to start LT4 treatment only after evidence of intact adrenal function; if coexistent central adrenal insufficiency cannot be ruled out, LT4 treatment must be preceded by glucocorticoid treatment in order to prevent possible induction of an adrenal crisis (2/+00).

Evidence

Early detection and prompt treatment of CH (within the first two weeks of life) are essential to optimize the neurocognitive outcome, linear growth, the onset and progression of puberty, pubertal growth and final height of affected neonates (47). All newborns with an abnormal neonatal screening result must be referred to an expert center for immediate thyroid function testing (TSH and FT4) to confirm the diagnosis of CH.

Treatment is indicated if the serum TSH concentration is >20 mU/L or FT4 is below the age-specific reference interval (48). In the latter case severe, moderate and mild forms can be classified according to FT4 concentrations, <5 pmol/L, 5-10 pmol/L and 10-15 pmol/L, respectively (1).

Whether neonates with mild hypothyroidism/hyperthyrotropinemia (i.e. diagnostic TSH concentrations between 6-20 mU/L, but a normal FT4 concentration) benefit from LT4 treatment is still unclear (49,50). Randomised controlled trials addressing this question have not been performed. The evolution of the TSH and FT4 concentrations and trend is instrumental in deciding whether to treat or not; the family history, thyroid imaging and, if available, genetic analysis may be helpful in predicting the course of the thyroid function. In a large cohort study, Lain et al found a worse neurocognitive outcome in children of school age with neonatal screening TSH concentrations between the 75th and 99.9th percentiles (51), while those with neonatal TSH values above the 99.9th percentile (12-14 mU/L) had better cognitive development, possibly due to LT4 treatment. In contrast, in a Belgian cohort of children there was no relation between mild neonatal TSH elevation and neurodevelopment at the preschool age (52-54).

In healthy neonates, it is generally suggested to evaluate thyroid function (TSH and FT4 measurement) every one to two weeks, and consider LT4 treatment when TSH is above, or FT4 is below the age-specific reference interval (48). Mild CH can be a permanent or transient condition. The family history, thyroid imaging and genetic testing may be helpful to clarify the etiology and the need of (long-term) treatment (50).

In some countries or regions confirmatory thyroid function testing may not be readily available. In this scenario LT4 treatment can be started when the neonatal screening TSH concentration is ≥ 40 mU/L, without awaiting the confirmatory thyroid function test result. Such a value is highly suggestive of moderate to severe primary CH (55).

Central hypothyroidism is characterised by a low serum FT4 on combination with a low, normal or slightly elevated TSH concentration. Other causes of this FT4-TSH combination are non-thyroidal illness, premature birth (with a correlation between severity and gestational age/ birth weight), and certain forms of reduced sensitivity to thyroid hormone (25). Central CH can be isolated or part of multiple pituitary hormone deficiency (MPHD) (56). In case of untreated adrenal insufficiency, LT4 treatment may cause an adrenal crisis. Therefore, LT4 treatment should be started only after a normal adrenal function test result or after glucocorticoid treatment has been started (45).

2.2 Communication of abnormal neonatal screening and confirmatory results

Summary

- An abnormal neonatal screening result should be communicated by an experienced professional (e.g. member pediatric endocrine team, paediatrician or general physician) either by telephone or face to face, and supplemented with written information for the family (2/+00).
- A confirmed CH diagnosis should be communicated face to face by a medical specialist (2/+00).

Evidence

In the organization of a (neonatal) screening program, both in industrialized and developing countries, communicating abnormal results is a key responsibility that should be carefully managed by trained personal. Accurate pre-screening information for families about the screening test and possible outcomes (e.g. false positives) improves participation and reduces possible parental anxiety. An abnormal neonatal screening result should be communicated quickly, but the way this should be done may differ, depending on biochemical severity and local circumstances (e.g. phone call directly to the family, web-based tool if available, etc.). The communication of a confirmed CH diagnosis should

be carried out face to face by a medical specialist with sufficient knowledge of CH; in case of language or cultural differences, deployment of a translator or (cultural) mediator is recommended. Taking time and using simple language to explain the implications and management of the diagnosis, and the importance of early detection and adequate LT4 treatment is essential. Written materials can be helpful but should not replace this face-to-face discussion (57-59).

2.3 Imaging techniques in CH

Summary

- In patients with a recent CH diagnosis, we strongly recommend starting LT4 treatment before conducting thyroid gland imaging studies (1/++0).
- We recommend imaging of the thyroid gland using either radioisotope scanning (scintigraphy) with or without the perchlorate discharge test, or ultrasonography (US), or both (1/++0).
- Knee X-ray of the knee may be performed to assess the severity of intrauterine hypothyroidism (2/+00).

Evidence

Although it doesn't change initial treatment, it is recommended to determine the etiology of CH at the time of diagnosis. However, this approach should never delay the start of treatment in newborns with CH. Early determination of the cause of CH provides the family with a precise diagnosis (including visual evidence) and, with that, strong arguments that their child has a congenital disorder necessitating lifelong daily treatment. Furthermore, an early accurate diagnosis – in most cases achievable by dual imaging – abolishes the need for further diagnostic testing and re-evaluation of the cause later on. Finally, (dual) imaging can give direction to genetic counseling and testing, providing information about the risk of recurrence and a possible early diagnosis in future siblings.

Thyroid ultrasonography

Ultrasonography (US) is an important diagnostic tool for determining the presence of the thyroid gland and, when present, its location, size and echotexture. US however is less accurate than radionuclide scan for detection of an ectopic thyroid gland. It is a non-invasive, non-irradiating, cost-effective imaging technique, but highly observer dependent. Thyroid volume in newborns varies from 0.84 ± 0.38 mL to 1.62 ± 0.41 mL (60-62), without significant changes during the first three weeks of life (63). Thyroid size can be influenced by (long-term) TSH suppression during LT4 treatment. In that case, TSH should be measured at the time of the US so that thyroid size can be correctly interpreted. Thyroid US should be performed by an expert.

Thyroid scintigraphy

Scintigraphy is the most accurate diagnostic test for determining the etiology of CH, especially in case of thyroid dysgenesis. Technetium-99m (^{99m}Tc) and iodine-123 (^{123}I) are both captured by NIS at the basal side of thyrocytes and are both suitable for imaging. ^{99m}Tc is more widely available, less expensive, faster in use (image acquisition 15 minutes after administration) and has a shorter half-life than ^{123}I . ^{99m}Tc is not organified, it is therefore difficult to provide quantification of the radionuclide uptake using ^{99m}Tc . Images are of lower quality than with ^{123}I . The latter isotope needs later image acquisitions (at two to three, and 24 hours), but provides more contrast and adds information about organification process, allowing perchlorate discharge testing when the thyroid is eutopic (64,65). Furthermore, it exposes infants to a lower dose of whole-body irradiation compared with ^{99m}Tc (3-10 $\mu\text{Ci}/\text{kg}$ vs. 50-250 $\mu\text{Ci}/\text{kg}$ body weight) (66,67).

When the thyroid is present and normally located, and if sodium perchlorate is available, perchlorate discharge testing can be performed to study the iodine retention capacity of the thyroid gland. Sodium perchlorate is administered and thyroid activity is measured before and one hour afterwards. The perchlorate discharge test is considered positive when discharge of ^{123}I is more than 10% of the administered dose. Together with serum thyroglobulin measurement, the perchlorate discharge test provides useful information for targeted genetic testing to diagnose the various forms of CH caused by

dyshormonogenesis (1). One pitfall of scintigraphy is lack of isotope uptake despite the presence of thyroid tissue. This can be due to TSH suppression at the time of the scintigraphy (when performed beyond five to seven days after the start of LT4 treatment), previous iodine exposure, maternal blocking TSH-receptor antibodies, and mutations in genes affecting iodine uptake (*NIS*) or TSH receptor (*TSHR*) defects. In these cases, thyroid US should be performed to demonstrate the presence or absence of thyroid tissue. When treatment related TSH suppression is the cause, and treatment can not be interrupted, thyroid scintigraphy and perchlorate discharge testing can also be performed after recombinant human TSH administration (68).

Dual imaging

The combination of thyroid US and scintigraphy provides high-resolution anatomical (US) and functional (scintigraphy) information, allowing to distinguish between permanent and possible transient CH (64,67,69). Each technique compensates for limitations and pitfalls of the other. Dual imaging is particularly effective in confirming athyreosis (when scintigraphy shows absence of isotope uptake) and detecting thyroid ectopy (65, 67).

X-ray of the knee

At birth bone maturation is delayed in the majority of patients with severe CH and is considered a disease severity parameter. It has been shown to correlate with neurodevelopmental outcome (70), educational level (71), hearing impairment (72) and can be assessed by performing a x-ray of the knee (presence or absence of the femoral and tibial epiphyses). LT4 treatment normalizes bone maturation within the first year of life (70,73). Although disease severity can be derived from the first diagnostic FT4 and TSH concentrations, a knee X-ray can be performed as an additional parameter reflecting the severity of intrauterine hypothyroidism.

2.4 Associated malformations and syndromes

Summary

- All neonates with CH should be examined carefully for dysmorphic features suggestive for syndromic CH, and for congenital malformations (particularly cardiac) (1/+++).

Evidence

Permanent CH can be isolated or syndromic. Careful clinical examination during the first days of life is therefore necessary to detect dysmorphic features suggestive of a syndrome. Syndromic CH is mostly caused by mutations in genes encoding transcription factors or involved in early thyroid development. The Bamforth-Lazarus syndrome (OMIM #241850) is characterized by thyroid dysgenesis (mainly athyreosis or severe hypoplasia), cleft palate, and spiky hair with or without bilateral choanal atresia or bifid epiglottis, and is due to biallelic mutations in the *FOXE1* gene (74). Another example of syndromic CH that can be recognized during neonatal period or early infancy is the Brain-Lung-Thyroid syndrome (OMIM #610978) due to *NKX2-1* haploinsufficiency, characterized by various types of CH, infant respiratory distress syndrome (IRDS), and benign hereditary chorea (BHC) (75,76). Other examples of syndromic CH are Alagille syndrome type 1 (OMIM #118450) with thyroid in situ, liver (bile duct hypoplasia) and cardiac malformations (77), Williams–Beuren (OMIM #194050) and DiGeorge syndromes (OMIM #188400) with a high prevalence of thyroid hypoplasia (50–70%) and subclinical hypothyroidism (25–30%) (78,79), and Kabuki (80) and Johanson-Blizzard syndromes (81) with a eutopic thyroid gland. Pendred syndrome due to mutations in the *SLC5A5* gene (OMIM #274600), with or without goiter, should be considered in case of congenital sensorineural hearing loss. Finally, the prevalence of congenital malformations, particularly cardiac defects, including septal defects, and renal abnormalities (82) is higher in individuals with CH than in the general population, with differences in prevalence between studies (83-89); indeed, the reported frequency of cardiac defects in CH is between three and 11%, compared to 0.5 to 0.8% in all live births. For Down syndrome, see 1.3.

3. TREATMENT AND MONITORING OF CH

- 3.1 Starting treatment for primary CH
- 3.2 Monitoring treatment in primary CH
- 3.3 Treatment and monitoring of central CH
- 3.4 Diagnostic re-evaluation of thyroid function beyond the first six months of life
- 3.5 Treatment and monitoring of pregnant women with CH

3.1 Starting treatment for primary CH

Summary

- LT4 alone is recommended as the medication of choice for the treatment of CH (1/++0).
- LT4 treatment should be started as soon as possible, not later than two weeks after birth or immediately after confirmatory (serum) thyroid function testing in neonates in whom CH is detected by a second routine screening test (1/++0).
- The LT4 starting dose should be up to 15 µg/kg per day, taking into account the whole spectrum of CH, ranging from mild to severe (1/++0).
- Infants with severe CH, defined by a very low pretreatment serum FT4 (<5 pmol/L) or total T4 concentration in combination with elevated TSH (above the normal range based on time since birth and gestational age), should be treated with the highest starting dose (10-15 µg/kg per day) (1/++0).
- Infants with mild CH (FT4 >10 pmol/L in combination with elevated TSH), should be treated with the lowest initial dose (around 10 µg/kg per day); in infants with pretreatment FT4 concentrations within the age-specific reference interval an even lower starting dose may be considered (from 5-10 µg/kg) (1/++0).
- LT4 should be administered orally, once a day (1/++0).
- The evidence favoring brand vs generic LT4 is mixed, but based on personal experience/expert opinion we recommend brand rather than generic (2/++0).

Evidence

There are no randomized clinical trials that support a specific treatment approach in CH with high quality evidence. Since the first enthusiastic reports on the successful treatment of “sporadic cretinism” with thyroid extracts derived from animal thyroid glands, all further adaptations and improvements have been based on retrospective or prospective observational studies only. However, today a large series of such cohort studies is available that were undertaken to correlate final outcome to different treatment strategies. Initially

somatic development in terms of growth and puberty was studied, but later on cognitive outcome - the most precious, but also vulnerable developmental outcome - became the focus of such studies. The highest level of evidence was gained by those studies that assessed the cognitive outcome (IQ) in individuals with CH and unaffected sibling controls. Together, the available data allow for reliable conclusions and recommendations. One such conclusion is that one can expect a favorable outcome in most children with CH who were given the “right” treatment. In this respect, numerous outcome studies point to a strong impact of two (main) factors that influence cognitive outcome: the age at start of LT4 treatment, and the LT4 starting dose.

Age at start of treatment and starting dose

Bearing in mind that these factors were not studied systematically, one can only deduce conclusions and recommendations from observational studies. Therefore, the recommendations on the optimal age at start of LT4 treatment and the optimal starting dose are deduced from reasonably powered studies that eventually demonstrated no difference in cognitive outcome between individuals with CH and unaffected siblings. So far only two such studies are available. Initially, two outcome studies in young adult CH patients and sibling controls showed an IQ gap of eight points. In these observational studies, treatment was started at an average age of 24 days and with average LT4 dose lower than 10 µg/kg per day. The first study that reported no gap comparing 44 CH and 53 unaffected sibling controls with a median age at time of testing of nine years was from New Zealand and published in 2013 (90). Patients were treated with LT4 from a mean age of nine days with a starting dose between 10-15 µg/kg depending on CH severity. Neonates with athyreosis were treated with 15 µg/kg per day. TSH normalized within a median of 14 days after diagnosis. Power calculation predicted that the number of patients and siblings would be sufficient to detect a difference of 5.2 IQ point. There was no significant difference between the tested patients and siblings.

The second study reporting no gap comparing 76 CH patients and 40 sibling controls was from Berlin and was published in 2018 (91). The treatment approach resembled the New Zealand approach with a median age at diagnosis of eight days, a mean LT4 starting dose

of 13.5 µg/kg per day, and TSH normalizing within a median time of 15 days. In contrast to the New Zealand study, the mean ages of the patients and controls were 18.1 and 19.8 years, respectively. There was no significant difference in overall IQ (102.5 vs 102.5), nor were there differences in other (cognitive) tests of attention, memory, fine motor skills, quality of life scores, and in anthropometric measurements. In addition, there was no negative effect of episodes of overtreatment in terms of a suppressed TSH. Even in the children with the highest number of episodes of TSH suppression, IQ and other outcome parameters did not differ.

Based on the evidence from four studies reporting sibling controlled cognitive outcome data, one can deduce and conclude that a even a child with severe CH can reach a normal IQ that does not differ from unaffected siblings, if LT4 treatment is started before the age of ten days and the starting dose is at least 10 µg/kg, with 15 µg/kg in the most severe forms. More precise values for the optimal age at start of LT4 treatment or the starting dose leading to such a favorable outcome cannot be given since this has not been systematically studied. However, in a meta-analysis included in the Berlin study comparing IQ differences between severe and mild CH cases with respect to the starting dose revealed that this difference can only be overcome with a starting dose of at least 10 µg/kg, but not lower than that.

Hormone preparations and administration

Since there are only a few studies on the effect of different hormone preparations or methods of administration available, recommendations are based on the results of the previously mentioned studies. Those studies that reported a normal cognitive outcome did either use crunched LT4 tablets dissolved in water or breast milk administered via a spoon, or liquid LT4 preparations (both administered orally). In none of the studies T3 was administered. Because the cognitive outcomes in these studies were favorable, it is recommended to use only LT4, administered as just described. The expert panel recognizes that crushing tablets is an off-label procedure, but that it has been done this way successfully for many years. Clinical experience suggests that the bioavailability of liquid LT4 preparations is higher than tablets, with a possible risk of overtreatment if tablet doses are used. The higher bioavailability may also have dosing consequences for changing

medication from tablets to liquid, and the other way around. In addition, CH patients treated with liquid LT4 may need more frequent FT4 and TSH measurements, and dose adjustments during their first months of life (92,93). If intravenous treatment is necessary, the (starting) dose should be no more than 80% of the oral dose; subsequently, the dose should be adjusted guided by FT4 and TSH measurements. It should be stressed that only pharmaceutically produced medication should be prescribed. This applies to both tablets and liquid LT4 preparations. Brand rather than generic LT4 tablets should be used, particularly in severe CH and in infants (94). The expert panel is against the use of compounded solutions or suspensions. Finally, parents should be provided with written instructions about LT4 treatment.

3.2. Monitoring treatment in primary CH

Summary

- We recommend measurement of serum FT4 and TSH concentrations before, or at least four hours after the last (daily) LT4 administration (1/++0).
- We recommend evaluation of FT4 and TSH according to age-specific reference intervals (1/++0).
- The first treatment goal in neonates with primary CH is to rapidly increase the circulating amount of thyroid hormone, reflected by normalization of serum TSH; thereafter, TSH should be kept within the reference interval.
- If TSH is in the age-specific reference interval, FT4 concentrations above the upper limit of the reference interval can be accepted and recommend maintaining the same LT4 dose (1/++0).
- Any reduction of the LT4 dose should not be based on a single higher than normal FT4 concentration, unless TSH is suppressed (i.e. below the lower limit of the reference interval) or there are signs of overtreatment (e.g. jitteriness or tachycardia) (1/++0).

- The first clinical and biochemical follow-up evaluation should take place one to two weeks after the start of LT4 treatment (one week at the latest in case of a starting dose close to 15 µg/kg per day or an even higher dose) (1/+00).
- Subsequent (clinical and biochemical) evaluation should take place every two weeks until complete normalization of serum TSH is achieved; thereafter, the evaluation frequency can be lowered to once every one to three months until the age of 12 months (1/+00).
- Between the ages of 12 months and three years, the evaluation frequency can be lowered to every two to four months; thereafter, evaluations should be carried out every three to six months until growth is completed (1/+00).
- If abnormal FT4 or TSH values are found, or if compliance is questioned, the evaluation frequency should be increased (2/+00).
- After a change of LT4 dose or formulation, an extra evaluation should be carried out after four to six weeks (2/+00).
- Adequate treatment throughout childhood is essential, and long-term under- or overtreatment, i.e. TSH concentrations above or below the reference interval, should be avoided (1/++0).
- In contrast to adults, in neonates, infants and children LT4 can be administered together with food (but with avoidance of soy protein and vegetable fiber); more important, LT4 should be administered at the same time every day, also in relation to food intake. This approach can improve compliance, ensures as consistent as possible LT4 absorption and as good as possible LT4 dose titration (2/+00).
- In case of an unexpected need for LT4 dose increase, reduced absorption or increased metabolization of thyroxine by other disease (e.g. gastrointestinal), food or medication should be considered (2/+00); non-compliance may be the most frequent cause, especially in teenagers and adolescents.

Evidence

Shortly after the start of LT4 treatment

Repeated measurement of serum FT4 and TSH, and clinical assessment (especially for signs of overtreatment when using the highest starting dose) are the backbone of monitoring LT4 treatment in patients with primary CH (95-97). TSH normalizes slower than FT4. Therefore, the first treatment goal is as rapid as possible normalization of FT4. Since FT4 reflects the unbound, biologically active form of thyroxine, measurement of FT4 preferred to total T4 (98). The second treatment goal is normalization of TSH within four weeks. Consequently, FT4 (or total T4) should guide dosing until TSH reaches the age-specific reference interval (99). Rapid normalization of TSH and keeping FT4 in the upper half of the age-specific reference interval has been shown to optimize the neurodevelopmental outcome (90, 100-102).

Follow-up after the first weeks of LT4 treatment

There is no evidence for a one optimal follow-up scheme. Recent studies focusing on optimization of biochemical thyroid function testing suggest the importance of frequent laboratory monitoring and dose adjustment during the first year of life. Findings in these studies were that 1) patients with severe CH (athyreosis and dysgenesis vs. dyshormonogenesis, with high TSH values at diagnosis) need more dose adjustments during the first year of life (103,104); 2) the highest doses within the recommended range of 10-15 µg/kg per day resulted in more dose adjustments because of hyperthyroxinemia (105-107); and 3) monthly thyroid function testing led to frequent dose adjustments during the first year of life (75% at 0-6 months of age, and 36% at 7-12 months of age) (97). However, in none of these studies neurodevelopmental outcome data were available, the most important long-term treatment goal in CH. With this in mind, the follow-up schemes that were chosen in the studies that reported normal IQ outcomes can be used as recommendation. In the New Zealand and the Berlin studies treatment effectiveness in terms of normalization of serum parameters was tested weekly after the start of treatment until they normalized (90,91). Thereafter, in New Zealand blood tests were done monthly during the first year and bi-monthly during the second year, and every three

months in the Berlin study. Obviously, follow-up schemes have to be personalized according to parents' capabilities and compliance.

The main biochemical target parameter in primary CH is TSH. The Berlin study reported on all obtained serum parameters during the first two years of life in all treated children. This revealed that when TSH was within the reference interval, T4 was often elevated but T3 was normal. Noteworthy, also in adult patients with severe acquired hypothyroidism a higher serum FT4 is necessary to reach normal TSH concentrations. This may be due to lack of thyroidal production of T3 that needs to be compensated by a higher FT4 concentration.

Data on the effects of clearly increased serum (F)T4 concentrations are scarce. In two studies, long-term follow-up after periods of overtreatment during the first two years of life suggested a decreased IQ at the age of 11 years, and an increased rate of ADHD (108,109). Earlier studies suggested adverse effects on attention span (110). However, Aleksander et al showed no IQ differences between patients and siblings despite comparable periods of overtreatment (91). As long as there is no evidence for a possible negative effect of periods of overtreatment, dose reduction in case of an elevated FT4 should only be done after a second FT4 measurement, unless TSH is suppressed. Besides overtreatment, "resetting" of the hypothalamus-pituitary-thyroid feedback axis after intrauterine hypothyroidism has been proposed as a possible mechanism, especially in patients younger than 12 months (111,24). Persistence of such mild hypothalamus-pituitary resistance has been reported in adult CH patients compared to patients with acquired hypothyroidism (112).

In summary, there is no definitive evidence for one optimal follow-up scheme based on studies with cognitive outcome as main parameter. However, a normal cognitive outcome has been achieved with monthly and bi-monthly, and with three-monthly controls during the first two to three years of life, after TSH normalization in the first weeks after diagnosis. Furthermore, patients with the most severe forms of CH and the highest range of the recommended LT4 starting dose are at an increased risk for frequent dose adjustments in the first year of life because of elevated FT4 levels. Since the long-term neurological consequences of hyperthyroxinemia/periods of overtreatment are still not

clarified, the follow-up frequency should be individualized with more controls in case of suboptimal FT4 or TSH values. After dose adjustment a next control is recommended four to six weeks later (113). Finally, adolescence and the period of transition to adult care are critical periods. Individualized follow-up schemes should be drawn up to assure normal growth and puberty in the adolescent, and fertility in the young adult (114).

Adverse effects of LT4

Adverse effects of long-term LT4 treatment are rare or absent if adequately prescribed. Cases of pseudotumor cerebri or craniosynostosis have been described (115,116). However, relative macrocrania at the age of 18 months, but without any case of craniosynostosis, was reported in a cohort of 45 CH patients with documented FT4 concentrations above the reference interval during their first six to nine months of life (117). In one cohort of young adults with CH cardiovascular abnormalities were reported (impaired diastolic dysfunction and exercise capacity, and increased intima-media thickness); however, the clinical relevance of these findings remains unknown. Moreover, in a large nationwide study standardized mortality ratio in patients with CH was not increased for diseases of the circulatory system (87).

Cardiac insufficiency

LT4 has clear positive ino- and chronotropic effects on the heart. In newly diagnosed CH in newborns with congenital heart disease and impending heart failure, we therefore recommend to apply a lower LT4 starting dose - approximately 50% of the recommended dose -, and to increase it guided by serum FT4 and TSH measurement, and the infant's clinical condition.

Impaired bioavailability by diseases, drugs or food

LT4 is mainly absorbed in the proximal small intestine. Undiagnosed or untreated celiac disease will reduce LT4 absorption. Children with short bowel syndrome will also have reduced absorption (118). Recently, rectal administration of LT4 was been shown to be effective in a child with this condition (119). Increased type 3 deiodinase activity in large hemangiomas can cause increased metabolic clearance of administered LT4 and, with that,

necessitate a higher LT4 dose (120-121). Bioavailability of LT4 can also be reduced by concomitant use of other medication. E.g. proton pump inhibitors, calcium or iron will decrease absorption, while anti-epileptic medication (phenobarbital, phenytoin, carbamazepine) and rifampicin will increase its metabolic clearance. Interactions need to be considered and can sometimes be overcome by avoiding concomitant ingestion (123,124).

While in adults the recommended LT4 intake moment is 30-60 minutes before intake of food intake (125,126), such a recommendation is difficult to realize in infants (123). Pragmatically, LT4 should be administered at a fixed time with an equal interval to food intake every day to have a constant as possible LT4 absorption and, with that, as good as possible LT4 dose titration. Soy containing food products have been repeatedly shown to inhibit LT4 absorption in children with CH (127,128).

3.3 Treatment and monitoring of central CH

- In severe forms of central CH (FT4 <5 pmol/L), we also recommend to start LT4 treatment as soon as possible after birth at doses like in primary CH (at least 10 µg/kg per day, see 3.1), in order to bring FT4 rapidly within the normal range (1/++0).
- In milder forms of central CH, we suggest starting treatment at a lower LT4 dose (5-10 µg/kg per day), to reduce the risk of overtreatment (1/++0).
- In newborns with central CH, we recommend monitoring treatment by measuring FT4 and TSH according to the same schedule as for primary CH; serum FT4 should be kept above the mean/median value of the age-specific reference interval; if TSH low prior to treatment, subsequent TSH determinations can be omitted (1/+00).
- When under- or overtreatment is suspected in a patient with central CH, then TSH, or free or total triiodothyronine (FT3, T3) can be measured (1/+00).
- When FT4 is around the lower limit of the reference interval, then undertreatment should be considered, particularly if TSH >1.0 mU/L (1/+00).
- When serum FT4 is around or above the upper limit of the reference interval, then overtreatment should be considered (assuming that LT4 has not been administered just

before blood withdrawal), particularly if associated with clinical signs of thyrotoxicosis, or a high (F)T3 concentration (1/+00).

Evidence

Just like primary CH, treatment of central CH consists of daily administration of LT4 (orally; tablets or liquid dosage form). The biggest differences between the treatment of primary and central CH are in the monitoring of treatment - with serum FT4 (instead of TSH) being the most important parameter -, and in the LT4 starting dose. Important to realize is that in central CH a low TSH concentration does not point to overtreatment.

The (biochemical) LT4 treatment aim is bringing and keeping the FT4 concentration in the upper half of the age-specific FT4 reference interval. Although randomized clinical trials testing this approach in children are lacking, studies in adults give some support (129,130).

Central CH can be a severe condition (FT4 at diagnosis <5 pmol/L), but most cases can be classified as mild to moderate (FT4 at diagnosis 5-15 pmol/L) (20, 131). Although studies investigating the optimal starting dose in central CH are lacking, clinical experience has taught that a LT4 starting dose of 10-15 µg/kg in mild to moderate cases quickly results in supraphysiological FT4 concentrations. So, with exception of severe cases a lower starting dose. i.e. 5-10 µg per kg is advisable.

With regard to the treatment monitoring frequency, the schedule for primary CH should be followed.

3.4 Diagnostic re-evaluation of thyroid function beyond the first six months of life

Summary

- When no definitive diagnosis of permanent CH was made in the first weeks or months of life, then re-evaluation of the HPT axis after the age of two to three years is indicated, particularly in children with a gland-in-situ (GIS), and in those with presumed isolated central CH (1/++0).
- For a precise diagnosis, LT4 treatment should be phased out over a four to six weeks period or just stopped, and full re-evaluation should be carried out after four weeks, consisting of (at least) FT4 and TSH measurement.

- If primary hypothyroidism is confirmed (TSH ≥ 10 mU/L) consider thyroid imaging and, if possible, genetic testing; if central CH is likely (FT4 below the lower limit of the reference interval in combination with a low, normal or only mildly elevated TSH) consider evaluating the other anterior pituitary functions and genetic testing.
- If TSH is above the upper limit of the reference interval but < 10 mU/L (primary CH) or FT4 just above the lower limit of the reference interval (central CH), then continue withdrawal and re-test in another three to four weeks (1/++0).
- If a child with no permanent CH diagnosis and a GIS requires a LT4 dose less than 3 $\mu\text{g}/\text{kg}$ per day at the age of six months, then re-evaluation can be done already at that time (1/++0).
- We recommend avoiding iodine as an antiseptic during peri- and neonatal period, as it can cause transient CH (1/++0).

Evidence

In recent years, the prevalence of transient CH has steadily increased. In a number of studies factors have been identified that increase the likelihood of transient disease, such as sex (more often in boys) (132,133), low birth weight (134,135), neonatal morbidity requiring intensive care (135), ethnicity (more often in non-white patients) (14), less severe CH at diagnosis (assessed by screening TSH, or diagnostic TSH or FT4) (8,132,133,136-141). In contrast, factors like prematurity (11,142,143), other congenital abnormalities (141), a family history of thyroid disease (142), abnormal thyroid morphology (thyroid hypoplasia at diagnosis) (142), TSH elevation > 10 mU/L after the age of 1 year (when infants outgrow the LT4 dose) and a higher LT4 dose requirement at one to three years of age are associated permanent CH (with conflicting results between studies for the factor dose requirement) (132, 133, 136-140, 143 -147). Recent studies have shown that early treatment withdrawal to assess the necessity of further treatment can be considered and done from the age of six months onwards, particularly in patients with a GIS, a negative first-degree family history of CH, or in those requiring a low LT4 dose. Saba et al (148) investigated 92 patients with CH and a GIS and found 49 of them (54%) to have transient CH. In this study, the optimal LT4 dose cut-off values for predicting transient CH at the ages of six and 12 months were 3.2 $\mu\text{g}/\text{kg}$ and 2.5 $\mu\text{g}/\text{kg}$ per day,

respectively, with a sensitivity of 71% at both time points, and a specificity of 79% and 78% at the ages of six and 12 months, respectively (with values below these thresholds considered predictive of transient CH). In the study by Oron et al (149), 17 out of 84 patients with a GIS (20%) turned out to have transient CH. The optimal LT4 dose cut-off values at the age of six months was 2.2 µg/kg per day, with a sensitivity of 90% and a specificity of 57%. Both studies highlight the need for careful clinical and biological monitoring to identify children who do not require long-term treatment.

Medication that interferes with thyroid function, in particular iodine and iodo-mimetics, may result in transient but profound hypothyroidism (150). The use of iodine as a skin antiseptic, such as povidone-iodine (PVP-1), is therefore not recommended in obstetrics and neonatology, since it reaches the fetal or neonatal thyroid gland easily, causing transient hypothyroidism (via skin and placenta in mothers, and skin in neonates) (29, 151,152). This may be more profound in premature born babies, as escape from the Wolff Chaikoff effect does not mature until term. Mothers should be asked about consumption of iodine-rich nutritional food or supplements, which can also induce transient congenital hypothyroidism (153).

3.5 Treatment and monitoring of pregnant women with CH

Summary

- In women with CH who are planning pregnancy we strongly recommend optimization of LT4 treatment; in addition, these women should be counseled regarding the higher need for LT4 during pregnancy (1/++0).
- FT4 (or total T4) and TSH levels should be monitored every four to six weeks during pregnancy, aiming at TSH concentrations in accordance with current guidelines on treatment of hypothyroidism during pregnancy, i.e. <2.5 mU/L throughout gestation in patients treated with levothyroxine (1/+00).
- In pregnant women with central CH, the LT4 doses should be increased aiming at a FT4 concentration above the mean/median value of the trimester specific reference interval (1/+00).

- Following delivery, we recommend lowering the LT4 dose to preconception dose; additional thyroid function testing should be performed at approximately six weeks post partum (1/++0).
- All pregnant women should ingest approximately 250 µg iodine per day (1/++0).

Evidence

Optimal management of pregnant women with CH requires knowledge and understanding of the normal physiological changes. In early pregnancy, before and during the development of the functioning fetal thyroid gland, the fetus depends on thyroid hormone supply by the mother, requiring an optimal iodine status. Indeed, since the fetal thyroid gland is not functionally matured before week 18–20 of pregnancy, the fetus largely depends on the supply of maternal thyroxine during the early stages of intrauterine brain development making FT4 the most important hormone for the fetus. During the second half of pregnancy, fetal thyroid hormones are both from maternal and fetal origin. Overt and subclinical maternal hypothyroidism have been associated with adverse pregnancy outcomes as well as with neurodevelopmental deficits in the offspring, particularly if the dysfunction occurs early in pregnancy. With respect to adverse pregnancy outcomes, maternal CH is associated with an increased risk of gestational hypertension, emergency cesarean section, induced labor for vaginal delivery and preterm delivery (154,155). TSH ≥ 10 mU/L during the first three to six months of pregnancy is associated with a higher risk of preterm delivery and fetal macrosomia. These associations were not found in women with satisfactory control of hypothyroidism, i.e. TSH < 10 mU/L. Yet, these women did have a higher risk of induced labor for vaginal delivery (154). Children born to mothers with CH were found to have a higher risk of poor motor coordination, but not of other developmental domains like mobility, communication, and motor and language skills. However, children born to mothers with TSH ≥ 10 mU/L were more likely to have low motor or communication skills scores. Yet, it remains unclear whether these adverse effects modify subsequent neurodevelopment (156, 157). During pregnancy, thyroid hormone requirement increases and most LT4 treated women require a dose increase up to 30%. Women with athyreosis, the most severe form of CH, require the highest doses

and treatment should aim to keep TSH concentrations below 2.5 mU/L throughout pregnancy (154,155,158). Therefore, careful monitoring of LT4 treatment of pregnant women with hypothyroidism is extremely important.

4. OUTCOMES OF NEONATAL SCREENING AND EARLY TREATMENT

4.1 Neurodevelopmental outcomes

4.2 Development of goiter in thyroid dysmorphogenesis

4.3 Growth, puberty and fertility

4.4 Bone, metabolic and cardiovascular health

4.5 Patient and professional education, and health-related quality of life

4.6 Transition to adult care

4.1 Neurodevelopmental outcomes

Summary

- Psychomotor development and school progression should be periodically evaluated in all children with CH; speech delay, attention and memory problems, and behavioral problems are reasons for additional evaluation (1/++0).
- In the small proportion of children with CH who do display significant psychomotor developmental delay and syndromic CH with brain abnormalities, it is crucial to rule out other causes of intellectual impairment than CH (1/+00).
- Not just neonatal, but repeated hearing tests should be carried out before school age and, if required, during further follow-up (2/++0).

Evidence

In the vast majority of early and adequately treated children with CH neurodevelopmental and school outcomes level are normal (90,91,159-161), and intellectual disability - defined as an IQ <70 - has virtually disappeared (162). In the past, patients with severe CH treated

with a low initial LT4 dose had lower IQ scores (although within normal range), and subtle neurological deficits in cognitive and motor development (163-164) when compared to control populations including healthy siblings (164,165). In the last two decades, early treatment with a high initial LT4 (≥ 10 $\mu\text{g}/\text{kg}$ per day and improvement in the management of CH patients has resulted in better cognitive and motor developmental outcomes, comparable to those of sibling controls (90,91).

However, despite early and adequate treatment patients with severe CH may still have subtle cognitive and motor deficits, and lower educational attainment (161, 167, 168). These deficits may reflect prenatal brain damage due to thyroid hormone insufficiency in utero, not completely reverted by postnatal treatment. Even though trans-placental supply of maternal thyroxine may protect the fetal brain from severe neurological impairment, it may not be sufficient to protect from severe fetal hypothyroidism (168). Children with CH may also display reduced hippocampal volume (169) and abnormal cortical morphology among brain regions (thinning or thickening) (170), that may explain subtle and specific deficits in memory, language, sensorimotor and visuospatial function (169,170). In addition, early episodes of both under- and overtreatment may be associated with permanent behavioral problems in a limited number of preadolescent children with CH (109). Overtreatment during the first months of life (with the exception of FT4 above the normal range with not suppressed TSH and/or without signs or symptoms of hyperthyroidism), a critical period for brain development, may be associated with attention deficit at the school age (109, 171,172), and lower IQ scores (108,173,174). Finally, other factors such as socio-educational status (71) and poor adherence to the treatment (71, 167,174) may also negatively affect cognitive outcome and educational attainment. Therefore, psychomotor development and school progression should be periodically evaluated in all children with CH. In case of doubt, evaluation by a specialized team is indicated at specific ages (12,18, 24 and 36 months, 5, 8 and 14 years) in order to monitor progression of specific developmental skills (58). Speech delay, attention and memory problems, and behavioral problems are reasons for additional evaluation. In the small proportion of children with CH who do display significant delay in psychomotor development, it is necessary to rule out other causes of intellectual impairment than CH.

Undiagnosed hearing impairment can adversely impair speech development, school performance and quality-of-life (71,72, 175). Thyroid hormone plays a role in cochlear and auditory function development (71, 176,177). Despite early and adequate LT4 treatment, mild and subclinical hearing impairment has been reported in about 20 to 25% of adolescent with CH. The risk of hearing loss was higher than in healthy controls (3%), and closely associated with the severity of CH (72, 178). Young adults with CH reported hearing impairment more frequently (9.5%) as compared to the general population (2.5%) (71). Hearing loss was mostly bilateral, mild to moderate, of the sensorineural type, concerned high or very high frequencies and in some cases required hearing aids. Even after exclusion of patients with Pendred Syndrome the risk of developing a hearing impairment seems to be more than three times higher in CH subjects than in general population (72). Not just neonatal, but repeated hearing tests should be carried out before school age and, if required, during follow-up.

4.2 Development of goiter in thyroid dyshormonogenesis

Summary

- Children and adolescents with primary CH due to dyshormonogenesis may develop goiter and nodules; in these cases, serum TSH should be carefully targeted in the lower part of normal range and periodical ultrasound investigation is recommended to monitor thyroid volume (2/++0).
- Since a few cases of thyroid cancer have been reported, fine needle aspiration biopsy for cytology should be performed in case of suspicious nodules on ultrasound investigation (1/+00).

Evidence

Children and adolescents with primary CH due to dyshormonogenesis (mainly *TPO* gene, but also *SLC5A5/NIS*, *SLC26A4/PDS*, *DUOX* and *TG* gene mutations) may have an increased risk of developing goiter and thyroid nodules, and may even have an increased risk of malignancy. However, to date only a few cases of thyroid cancer (either papillary or follicular) have been reported in patients with long-standing CH. In some cases, goiter was

already present and thyroid nodules (isolated or multiple) developed despite apparently adequate LT4 treatment. In other cases, poor compliance to treatment, with persistently high TSH levels during adolescence, was the probable cause (179-182). Therefore, TSH should be targeted in the lower part of normal range during treatment of dysmaturational CH. Despite the rare occurrence of thyroid carcinoma in CH patients we recommend periodical neck US - e.g., every two to three years – in children and adolescents with goitrous CH due to dysmaturationalogenesis (including *NIS* gene mutations), to identify nodules that may require fine needle aspiration biopsy to rule out thyroid carcinoma.

4.3 Growth, puberty and fertility

Summary

- Adequately treated children with non-syndromic CH have normal growth and puberty, and their fertility does not differ from individuals who do not have CH (1/+++).

Evidence

Early and adequately treated, children with non-syndromic CH have normal growth and pubertal development (183-187). Adult height is normal and comparable to siblings, with no effects of severity of CH at diagnosis, CH etiology or LT4 starting dose (47,183-185); moreover, in the majority of children adult height is above the target height in both sexes (47,183,184). Onset of puberty occurs at the normal age in the vast majority of CH patients and progresses normally in both sexes (47,183,114). The same applies to age at menarche and menstrual cycles (114,183). In adults, fertility is generally normal (188). However, women with CH may have an increased risk of adverse pregnancy outcomes. In addition, their offspring is at risk for poorer motor coordination (see also paragraph 3.5) (154,156).

4.4 Bone, metabolic and cardiovascular health

Summary

- Adequately treated children with non-syndromic CH also have normal bone, metabolic and cardiovascular health (1/++0).

Evidence

Thyroid hormones play an important role in skeletal growth and bone mineral homeostasis. At birth skeletal maturation is delayed in the majority of CH patients with severe hypothyroidism (70); however, within the first months of life LT4 treatment rapidly normalizes bone maturation (71). Since thyroid hormones have major effects on bone remodeling, LT4 overtreatment may increase bone turnover with higher bone resorption than formation, resulting in progressive bone loss (189). Yet, long-term studies in children and young adults with CH have shown normal bone mineral density (190-193) suggesting that early started and adequate LT4 treatment is not harmful to bone health. Given the importance of sufficient calcium intake patients with CH, in addition to adequate LT4 treatment, should consume 800 to 1200 mg calcium daily; if dietary calcium intake is low, supplements should be added (1, 190).

Body mass index and composition are generally normal in children and adult with CH (90,91, 187) and comparable to that of the general population. However, earlier adiposity rebound (194-196) and increased risks of being overweight or obese has been reported in up to 37% of young adults with CH (47,71,114). Therefore, lifestyle interventions, including diet and physical exercise, should be encouraged to avoid metabolic abnormalities (1).

In addition to an increased risk of congenital heart disease (86-88) neonates with untreated CH may have increased aortic intima media thickness (IMT), serum cholesterol levels (197) and impaired cardiac function (198,199) reversed by early LT4 treatment (200).

Young adults with CH have normal, blood pressure, glucose and lipid metabolism, and carotid IMT (90,200). However, repeated episodes of inadequate treatment may place them at risk of subtle cardiovascular dysfunction like low exercise capacity, impaired diastolic function, increased IMT and mild endothelial dysfunction (201). Whether these subtle abnormalities result in impaired quality of life or in an increased risk of cardiovascular disease need to be further clarified. Anyway, good adherence to treatment in adolescents and young adults with CH is mandatory for optimal metabolic and cardiovascular health.

4.5 Patient and professional education, adherence and health-related quality of life

Summary

- Medical education about CH should be improved at all levels, with regular updates (1/+++).
- Education of parents, starting at the time of the diagnosis, and later on of the patient is essential; not only throughout childhood, but also during transition to adult care and in women during pregnancy (1/+++).
- Since adherence to treatment may influence the outcomes, it should be promoted throughout life (1/++0).

Evidence

It's very clear, and it shouldn't have to be stated here, that medical professionals should have basic knowledge about CH. The education of parents, starting at diagnosis and updated regularly, and of CH patients throughout childhood is mandatory. Good understanding of CH is essential to manage parental anxiety attitude, and to promote treatment adherence throughout life. Both are important conditions to assure optimal outcomes in CH. Adequate education of patients is also important to improve self-esteem and health-related quality of life (HRQoL), and to assure treatment adherence particularly during adolescence and pregnancy. The perception of the impact of CH on behavior varies with age and differs between children and their parents (202). Most (71,203,204), but not all (202,205) studies suggest that children and young adults with CH have an increased risk for lower HRQoL. Young adults with CH do not report problems concerning autonomy and sexual functioning. However, compared with the general population they experience lower HRQoL with respect to cognitive and social functioning, daily activities, aggressiveness and self-worth (204), which was already present in childhood (203). Moreover, young adults with CH are more likely to report associated chronic diseases, hearing impairment, visual problems and overweight than their peers. Fewer attain the highest socioeconomic category and full-time employment, and more are still living with their parents. CH severity at diagnosis, long-term treatment adequacy, and the presence of other chronic health conditions (see above) seem to be the main determinants of educational achievement and

HRQoL scores. Yet, despite these subtle disadvantages most patients well-integrated into society (71).

4.6 Transition to adult care

Summary

- When patients are transferred from paediatric to adult care, the main aims are continuity of care and, with that, optimal clinical outcomes and quality of life, and to increase understanding of CH and promote self-management (1/+++).

Evidence

The period of transition from paediatric to adult care can be challenging since it is associated with an increased risk of poor treatment compliance and inadequate follow-up that may have repercussions, in terms of increased morbidity, and poor educational and social outcomes (206,207). Family structure and parental involvement are important for preventing and tackling this problem. Finally, given the female preponderance in all thyroid diseases and the finding that (subclinical) hypothyroidism may be associated with subfertility and adverse pregnancy and offspring outcomes, improvement and maintenance of disease control in young women is crucial (154,156).

5. GENETICS OF CH, GENETIC COUNSELLING AND ANTENATAL MANAGEMENT

5.1 Criteria for genetic counseling

5.2 Genetics of CH

5.3 Antenatal diagnostics, evaluation of fetal thyroid function and management of fetal hypothyroidism

5.1 Criteria for genetic counseling

Summary

- Genetic counselling should be targeted rather than general (to all CH patients), and done by an experienced professional (2/++0).

- Counselling should include explaining inheritance and the risk of recurrence of the patient's primary or central form of CH, based on the CH subtype, the family history and, if known, the (genetic) cause (1/++0).
- Parents with a child, or families with a member with CH should have access to information about the two major forms of primary CH - thyroid dysgenesis and dysmorphogenesis - and, if included in the neonatal screening, about central CH (1/+++).

Evidence

Genetic counselling is highly recommended for patients and families with one or more affected member(s) with CH. Precise criteria were already established for the CH consensus guideline published in 2014 (1). Table 1 describes proposed criteria for genetic counseling.

Detailed phenotypic description of the index patient's CH form is essential and should include the presence or absence of associated malformations (syndromic vs. isolated CH), guiding genetic counselling and, if possible and necessary, genetic testing. Patients and family members should be informed about the inheritance and the risk of recurrence, and the presence of associated disorders in case of syndromic CH.

Accurate genotyping/genetic testing of patients with CH by mutation analysis of candidate genes can or may 1) explain the disease, 2) predict the risk of CH and extra-thyroidal defects in family members (to be performed in all cases of syndromic primary CH, and in central CH); 3) identify carriers of *NKX2-1* gene mutations who are at risk of life-threatening respiratory disease (208); 4) enable "personalized" LT4 treatment to prevent goiter formation, which may occur in CH due to *TPO* or *TG* gene mutations if TSH concentrations are not carefully kept in the lower part of the reference interval; and 5) identify patients with mild TSH resistance in whom long-term LT4 treatment may be non-beneficial (50).

5.2 Genetics of CH

Summary

- If genetic testing is performed, its aim should be improving diagnosis, treatment or prognosis (1/++0).
- Before doing so, possibilities and limits of genetic testing should be discussed with parents or families (1/++0).
- When available, genetic testing should be performed by means of new techniques, like comparative genomic hybridization (CGH) array, next-generation sequencing of gene panels (targeted NGS) or whole exome sequencing (WES) (1/++0).
- Preferably, genetic testing or studies should be preceded by careful phenotypic description of the patient's CH, including morphology of the thyroid gland (2/++0).
- Not only thyroid dysmorphogenesis, but also familial occurrence of dysgenesis and central hypothyroidism should lead to further genetic testing (1/++0).
- Any syndromic association should be studied genetically, not only to improve genetic counselling, but also to identify new candidate genes explaining the association (1/++0).
- Further research is needed to better define patients or patient groups that will benefit most from these new diagnostic possibilities (2/++0).

Evidence

Primary CH

Thyroid dysgenesis (TD) due to thyroid maldevelopment, is the most frequent cause of permanent primary CH, explaining approximately 65% of cases (12,209). In contrast to TD with conditions like athyreosis or thyroid ectopy, the other 35% is best described as GIS of which less than 50% is due to inherited defects of thyroid hormone synthesis (dysmorphogenesis). Thyroid dysgenesis is considered a sporadic disease. However, the familial component cannot be ignored, suggesting a genetic predisposition and a probably complex inheritance mode (210,211). In only 10% of TD cases a genetic cause is identified with mutations in *TSHR* (212), or in genes encoding transcription factors involved in thyroid development (*TTF1/NKX2.1*, *PAX8*, *FOXE1*, *NKX2-5*, *GLIS3*) (213,214). During the past years, novel and faster genetic and molecular tests, and the availability of large, well-

phenotyped cohorts of patients have led to the discovery of new genetic causes of CH. Heterozygous mutations in the *JAG1* gene, responsible for Alagille syndrome and encoding the jagged protein in the Notch pathway, have been identified in TD patients (mainly with orthotopic thyroid hypoplasia) (77, 215). By whole exome sequencing (WES) in familial TD cases, Carré et al found borealin (encoded by *BOREALIN*), a major component of chromosomal passenger complex, to be also involved in thyrocyte migration and adhesion, explaining cases of thyroid ectopy (216). Mutations or deletion in the *NTN1* gene have been found in patients with TD. Netrin is part of a family of laminin-related proteins, involved in cell migration and possibly in the development of pharyngeal vessels (217). Finally, mutations in the *TUBB1* (Tubulin, Beta 1 class VI) gene have recently been identified in patients from three families with thyroid dysgenesis (mostly ectopy) and abnormal platelet physiology (basal activation and exaggerated platelet aggregation) (218). Functional studies in knock-out mice validated the role of Tubb1 in thyroid development, function and disease.

With respect to the cause of the mild, non-autoimmune subclinical hypothyroidism in neonates and infants with Down syndrome, new insights were provided by a study in *Dyrk1A(+ / +)* mice showing abnormal thyroid development and function (42). How overexpression of this gene causes thyroid abnormalities remains to be elucidated. Another more frequent form of syndromic CH is Brain-Lung-Thyroid (BLT) syndrome due to *NKX2-1* haploinsufficiency. Extensive genetic analysis of a large group of affected patients revealed novel variants, expanding BLT syndrome phenotype (219). Table 2 summarizes genes associated with TD.

In contrast to TD, thyroid dysmorphogenesis is inherited in an autosomal recessive pattern and, except for Pendred syndrome, CH is isolated in most cases. Genes involved in thyroid hormone synthesis are *SLC5A5* (*NIS*), *SLC26A4* (*PDS*), *TPO*, *TG*, *DUOX2*, *DUOX2* and *IYD* (*DEHAL1*). These seven genes encode proteins for the various steps in this process. The use of modern genetic techniques, like single nucleotide polymorphisms (SNP) arrays and next-generation sequencing (NGS; whole exome and genome sequencing, WES/WGS) has provided new insights into the genetics of CH. First, NGS has identified new genes and/or extended the assumed thyroid phenotype resulting from mutations in genes

responsible thyroid hormone synthesis, causing dysmorphogenesis. For instance, biallelic mutations in *SLC26A7* cause goitrous CH (220,221). *SLC26A7* is a member of the same transporter family as *SLC26A4* (pendrin), an anion exchanger with affinity for iodide and chloride (among others). However, in contrast to pendrin, *SLC26A7* does not mediate cellular iodide efflux and affected individuals have normal hearing (220,221). Mutations in *SLC26A4/PDS* (222) and *DUOX2* (223) have been unexpectedly found in patients with non-goitrous CH and thyroid hypoplasia, narrowing the gap between TD and dysmorphogenesis. Recently, *DUOX2* mutations have also been reported in patients with thyroid ectopy; however, further studies are needed to confirm and explain this striking finding (224). Moreover, the first CH patients with both *DUOX1* as well as *DUOX2* mutations have been reported, suggesting that CH can have a digenic cause (225). *DUOX2* mutations have also been found in patients with early-onset inflammatory bowel disease, suggesting an extrathyroidal role for *DUOX2* (226,227). Table 3 shows genes implicated in thyroid dysmorphogenesis. Also, recently, NGS studies in cohorts of CH patients screened for mutations in sets of CH genes revealed that a significant proportion of these patients has multiple variations in more than one thyroid specific gene (89, 228, 229). Strikingly, these variations were found in genes encoding both thyroid transcription factors as well as proteins involved in thyroid hormone synthesis, independently of the thyroid phenotype. These variations in more than one gene (oligogenicity) should therefore be considered as a plausible hypothesis for the genetic aetiology of CH (89). These novel data may also provide an explanation for the sporadic presentation of CH and observed complex modes of inheritance. In such context, *JAG1* may act as gene modifier in a multifactorial architecture of CH (215).

Central CH

Thanks to NGS, the number of probable genetic causes of isolated central CH and central CH within the framework of multiple pituitary hormone deficiency (MPHD) has increased (Table 4). Isolated central CH due to bi-allelic *TSHB* gene mutations is associated with severe hypothyroidism and characterized by the typical manifestations of CH (eg. hypotonia, jaundice, umbilical hernia, macroglossia, etc.). If left untreated, these patients develop cretinism comparable to patients with severe primary CH (230-232). Therefore,

central CH must be ruled out in all infants with signs or symptoms of CH and a low, normal or only slightly elevated TSH concentration.

To date, defective TRH action due to bi-allelic mutations in the *TRHR* gene has been described in only a few families (45). Though prolonged neonatal jaundice was reported in one female, even complete TRH resistance does not cause severe neonatal hypothyroidism. The diagnosis in three of the four probands with bi-allelic *TRHR* mutations was made during childhood because of delayed growth accompanied by lethargy and fatigue or by overweight. However, complete TRH resistance diagnosed by genetic testing has been diagnosed in a pregnant woman (233). Immunoglobulin superfamily member 1 gene (*IGSF1*) mutations are the molecular cause of a recently described X-linked syndrome including mild to moderate central CH. In this syndrome, central CH is associated with abnormal testicular growth leading to adult macro-orchidism (+2.0 SDS), a tendency towards pubertal delay, low prolactin and, rarely, reversible growth hormone deficiency (234,235). Some female carriers can also manifest central CH. Recent data indicate *IGSF1* as the most frequently implicated gene in congenital central CH (235).

Mutations in the *TBL1X* gene are a second cause of X-linked cause of central CH. *TBL1X*, transducin-like protein 1, is an essential subunit of the nuclear receptor corepressor (NCoR)-silencing mediator for retinoid and thyroid hormone receptors (SMRT) complex, the major TH receptor (TR) CoR involved in T3-regulated gene expression. In addition to Central CH, many patients exhibit hearing loss (236). Finally, mutations in *IRS4* are another cause of X-linked mild Central CH. Since *IRS4* is involved in leptin signalling, the cause of the central CH may be disrupted leptin signalling (237). Central CH is more frequently part of MPPHD and can be associated with one or more other pituitary hormone deficiencies. In addition, a certain percentage of affected patients has morphological abnormalities of the pituitary gland or hypothalamus, or other neurological defects (25,45). Table 4 shows genes implicated in central hypothyroidism.

5.3 Antenatal diagnostics, evaluation of fetal thyroid function, and management of fetal hypothyroidism

Summary

- We recommend antenatal diagnosis in cases of goiter fortuitously discovered during systematic ultrasound examination of the fetus, in relation to thyroid dyshormonogenesis (1|+++); a familial recurrence of CH due to dyshormonogenesis (25% recurrence rate) (1|+++); and known defects of genes involved in thyroid function or development with potential germline transmission (1|++0). Special issues should be considered for syndromic cases with potential mortality and possible germline mosaicism (as for *NKX2-1* gene mutation/deletion and severe pulmonary dysfunction with possible transmission via germline mosaicism). In such circumstances, the discussion of the prenatal diagnosis should be open. The therapeutic management of affected foetuses should comply with the laws in force in the country concerned (1|++0). The familial recurrence of CH due to dysgenesis (2% of familial occurrences) requires further study to determine the feasibility and clinical relevance for antenatal detection.
- For the evaluation of fetal thyroid volume, we recommend ultrasound scans at 20 to 22 weeks gestation to detect fetal thyroid hypertrophy and potential thyroid dysfunction in the fetus. Goiter or an absence of thyroid tissue can also be documented by this technique. Measurements should be made as a function of GA, and thyroid perimeter and diameter should be measured to document goiter (1/+++).
- If a (large) fetal goiter is diagnosed, prenatal care should be provided in a specialized center of prenatal care (1/+++).
- We recommend cordocentesis, rather than amniocentesis, as the reference method for assessing fetal thyroid function. Norms have been established as a function of GA. This examination should be carried out only if prenatal intervention is considered (see below) (1|+++).
- In most cases, fetal thyroid function can be inferred from context and ultrasound criteria, and fetal blood sampling is, therefore, only exceptionally required (2|++0).

- We strongly recommend fetal treatment by intra-amniotic thyroxine injections in a euthyroid pregnant woman with a large fetal goiter associated with hydramnios and/or tracheal occlusion; in a hypothyroid pregnant woman, we recommend to treat the woman (rather the fetus) with thyroxine (1/++0).
- For goitrous nonimmune fetal hypothyroidism leading to hydramnios, we recommend intra-amniotic injections of L-T4 to decrease the size of the fetal thyroid gland. The injections should be performed by multidisciplinary specialist teams (1|+++).
- The expert panel proposes the use of 10 microg/kg estimated fetal weight/15 days in the form of intra-amniotic injections. The risks to the fetus and the psychological burden on the parents should be factored into the risk/benefit evaluation (2|+00).

Evidence

Antenatal diagnostics is advised in case of fortuitously discovered fetal goiter during fetal US examination in an anti-TSH receptor antibodies negative mother, an earlier child with primary CH due to dys hormonogenesis (and a 25% risk of recurrence), and in an earlier child with (severe) syndromic CH. How to evaluate fetal thyroid function and to manage (non-autoimmune) fetal hypothyroidism has been described in the 2014 CH consensus guidelines (1). In short, fetal thyroid size can be assessed by US at 20 to 22, and at 32 weeks gestation. When thyroid measurement values based on diameter or perimeter are above the 95th percentile (238), the mother and fetus should be referred to a specialized center for prenatal care. If prenatal intervention is considered, cordocentesis can be performed to assess fetal thyroid function. Conditions that may be a reason for fetal treatment are a large fetal goiter with progressive hydramnios, and risk of premature delivery or concerns about tracheal occlusion. If fetal treatment is considered in a euthyroid pregnant woman, one way is to administer intra-amniotic thyroxine injections in a dosage of 10 µg/kg estimated fetal weight per 15 days. Studies have confirmed the feasibility and safety of intra-amniotic L-T4 injection and strongly suggest that this treatment is effective for decreasing goiter size. However, none of the many L-T4 regimens used ensures euthyroidism at birth. It is therefore not possible to formulate guidelines from current data. These further diagnostics and intervention should only be done by an

experienced multidisciplinary team in a specialized center of prenatal care after a careful benefit/risk evaluation. Determination of the indications and optimal modes of prenatal treatment for nonimmune fetal goitrous hypothyroidism will require larger, well-designed studies that would be best conducted via international co-operation between multidisciplinary medical teams. Alternative ways of treating the fetus by administering drugs to the mother should also be investigated. In a hypothyroid pregnant woman, the preferred approach is to treat the woman with (rather than the fetus) with LT4. Finally, adequate iodine intake should be ensured for all pregnant women (250 µg per day).

CONCLUSIONS

This update of the consensus guidelines on CH recommends worldwide neonatal screening and appropriate diagnostics - including genetics - to assess the cause of both primary and central hypothyroidism. The expert panel recommends the immediate start of correctly dosed LT4 treatment, and frequent follow-up including laboratory testing and dose adjustments to keep thyroid hormone levels in their target ranges, timely assessments of the need to continue treatment, attention for neurodevelopmental and neurosensory functions and, if necessary, consulting other health professionals, and education of the child and family about CH. Harmonisation of diagnostics, treatment and follow-up will optimise patient outcomes. Lastly, all individuals with CH are entitled to a well-planned transition of care from pediatrics to adult medicine. This consensus guidelines update should be used to further optimize detection, diagnosis, treatment and follow-up of children with all forms of CH in the light of the most recent evidence. It should be helpful in convincing health authorities of the benefits of neonatal screening for CH. Despite almost 50 years of neonatal screening for CH, some important questions remain, like the genetic etiology of thyroid dysgenesis, the assumed harm of subclinical CH, i.e. a normal FT4 in combination with an elevated TSH, and the cause of the gradually increased incidence of CH with GIS. Further epidemiological and experimental studies are needed to understand the increased incidence of this condition.

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TABLE 1. Situations in Which Genetic Counselling Should Be Proposed**I. Pregnant women**

Positive family history for non-syndromic CH

Dyshormonogenesis (previously affected child) (1|+++)

Dysgenesis (at least 1 member of the family) (2/++0)

Positive family history of syndromic CH with:

Neurological disorders, including unexplained intellectual impairment

Deafness

Congenital heart disease, surfactant deficiency syndrome

Cleft palate

Kidney malformations

Any sign of Albright hereditary osteodystrophy (*GNAS* mutation) (1|++0)

Unexplained abnormality of T4, T3, or TSH levels in family members (mild forms of CH) (2|++0)

II. Infant or child with CH (2|++0)

Subject with

Deafness

Neurological signs (hypotonia, choreoathetosis, intellectual disability)

Lung disorders (surfactant deficiency syndrome, interstitial lung disease)

Congenital heart disease

Cleft palate

Thyroid

Congenital hypothyroidism: a 2020 consensus guidelines update An ENDO-EUROPEAN REFERENCE NETWORK (ERN) initiative endorsed by the European Society for Pediatric Endocrinology and the European Society for Endocrinology (DOI: 10.1089/thy.2020.0333)

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Kidney malformations

Any sign of Albright hereditary osteodystrophy (*GNAS* mutation)

Family history

Consanguinity

Kidney malformations

Deafness

Specific malformations (as listed above)

Unexplained intellectual impairment despite adequate treatment of CH in family members

Any sign of Albright hereditary osteodystrophy (*GNAS* mutation)

TABLE 2: Genes associated with thyroid dysgenesis or syndromic primary CH.

Gene (OMIM)	Protein role	Typical thyroid phenotype	Mode of inheritance	Associated conditions
NKX2-1 (600635)	NF	Variable	AD	Respiratory distress, choreoathetosis, variable expressivity
FOXE1 (602617)	NF	Athyreosis, severe hypoplasia	AR	Cleft palate, choanal atresia, and spiky hair
PAX8 (167415)	NF	Variable	AD	Urogenital tract defects (horseshoe kidney, renal agenesis, ureter and testes anomalies), variable expressivity
NKX2-5 (600584)	NF	Thyroid <i>in situ</i> , variable hypothyroidism	Unclear	Congenital heart malformations
GLIS3 (610192)	NF	Variable	AR	Neonatal diabetes, polycystic kidneys, and cholestasis
JAG1 (601920)	Jagged 1: Notch receptor ligand	Variable orthotopic hypoplasia	AD	Heart malformations, variable expressivity
TBX1 (602054)	NF	Thyroid <i>in situ</i>	AD	Di George syndrome with congenital heart malformations, variable

				expressivity
NTN1 (601614)	Laminin-related secreted protein	Thyroid ectopy	unknown	Arthrogryposis
CDCA8 (609977)	Cell Division Cycle Associated protein 8 or Borealin: component of the chromosomal passenger complex	Thyroid ectopy, hemiagenesis, thyroid asymmetry	Variable (AD, AR)	None in sporadic cases
TUBB1 (612901)	member of the β -tubulin protein family	Thyroid dysgenesis	Variable (AD, AR with second hit)	Formation of macroplatelets and hyperaggregation of platelets

NF: nuclear factor, AD: autosomal dominant, AR: autosomal recessive

TABLE 3: Genes associated with thyroid dysmorphogenesis.

Gene (OMIM)	Protein role	Typical thyroid phenotype	Mode of inheritance	Associated conditions
TSHR (603372)	G-protein coupled receptor (GPCR)	Complete or partial TSH resistance: athyreosis → thyroid in situ and severe → mild hypothyroidism	AD, AR	
GNAS (139320)	alpha subunit of the stimulatory guanine nucleotide-binding protein (G protein)	Partial TSH resistance, mild hypothyroidism	Maternal inheritance, parental imprinting of gene locus	PseudoHypo Parathyroidism (PHP, multiple hormone resistances)
SLC5A5 (601843)	NIS: Sodium-Iodide symporter	Absent or low iodide uptake at scintiscan, variable hypothyroidism and goiter	AR	

<i>SLC26A4/PDS</i> (605646)	Pendrin: Anion transporter	Partial iodide organification defect, mild to moderate hypothyroidism, goiter, high serum Tg	AR	Pendred syndrome: sensorineural deafness with enlarged vestibular aqueduct (EVA), predisposition to alkalosis,
<i>DUOX1/DUOX2</i> (606758/606759)	Dual oxydases: peroxide generating system	Partial or complete iodide organification defect, goiter, transient or permanent hypothyroidism of variable severity, high serum Tg	AD, AR	
<i>DUOXA2</i> (612772)	Dual Oxydase Associated protein: a endoplasmic reticulum chaperone protein	Partial or complete iodide organification defect, goiter, transient or permanent hypothyroidism of variable severity, high serum Tg	AR	
<i>TPO</i> (606765)	Thyroid peroxidase:	Complete iodide	AR	

	iodide organification and thyronine coupling	organification defect, severe hypothyroidism, goiter, high serum Tg		
TG (188450)	Thyroglobulin: glycoprotein precursor to the thyroid hormones	High iodide uptake, variable hypothyroidism, congenital or rapidly growing goiter, low serum Tg	AR	
IYD/DEHAL (612025)	Dehalogenase providing iodide salvage in thyroid)	Conserved iodide uptake, negative perchlorate discharge test, goiter, variable hypothyroidism, high serum Tg and MIT/DIT concentrations in serum and urine	AR or AD with incomplete penetrance	

<p>SLC26A7 (608479)</p>	<p>Anion transporter</p>	<p>Goiter, variable hypothyroidism, conserved iodide uptake, partial defect at perchlorate discharge, high serum Tg,</p>	<p>AR</p>	
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Tg: thyroglobulin, AD: autosomal dominant, AR: autosomal recessive

Thyroid

TABLE 4. Genes associated with central CH and related phenotypes.

	Gene (OMIM*)	Protein function	Thyroid phenotype	Mode of inheritance	Associated conditions
Isolated Central CH	<i>TSHβ</i> (188540)	Hormone subunit	Neonatal onset with low TSH	AR	High α GSU and normal PRL serum levels, pituitary hyperplasia reversible on L-T4
	<i>TRHR</i> (188545)	GPCR	Normal TSH and low PRL serum levels, blunted TSH/PRL responses to TRH	AR	Male index cases with growth retardation and overweight during childhood; one female proband with prolonged neonatal jaundice
	<i>TBL1X</i> (300196)	NF	Mild isolated central CH in males with normal TSH serum levels and normal response to TRH stimulation test	X-linked	Hearing defects
	<i>IRS4</i> (300904)	NF	Mild isolated central CH in males with normal TSH serum levels, blunted TSH response to	X-linked	

			TRH		
Multiple Pituitary Hormone Deficiencies	<i>IGSF1</i> (300137)	Plasma membrane protein of unknown function	Normal TSH serum levels and blunted response to TRH test; males are preferentially affected	X-linked	Low PRL levels, variable GH deficiency, possible transient mild hypocortisolism and metabolic syndrome; late adrenarche and delayed rise of testosterone in males, dissociated from testicular growth ending in post-pubertal macrorchidism
	<i>PROP1</i> (601538)	NF	Variable age of onset	AR	GH, PRL LH/FSH deficiencies and delayed ACTH defects, small to large pituitary volume
	<i>POU1F1</i> (173110)	NF	Variable age of onset	AR, AD	GH and PRL deficiency, prominent forehead, midface hypoplasia, depressed nose
	<i>HESX1</i> (601802)	NF	Central CH	AR, AD	Hypopituitarism associated with septo-optic dysplasia
	<i>SOX3</i> (313430)	NF	Central CH	X-linked	Anterior-pituitary hypoplasia with ectopic posterior pituitary, persistent cranio-pharyngeal canal and learning difficulties

variably associated	OTX2 (600037)	NF	Central CH	AD	Anterior pituitary hypoplasia with ectopic posterior pituitary and ocular defects (anophthalmia/microphthalmia/retinal dystrophy)
	LHX3 (600577)	NF	Central CH	AR	Hypopituitarism with inconstant ACTH defect, small to large pituitary, short and rigid cervical spine and variable hearing defect
	LHX4 (602146)	NF	Central CH	AR, AD	Variable hypopituitarism, anterior pituitary hypoplasia with ectopic posterior pituitary, Arnold-Chiari syndrome, hypoplasia of the corpus callosum
	LEPR (601007)	Cytokine receptor	Central CH	AR	Hyperphagia, obesity and combined with central hypogonadism
	SOX2 (184429)	NF	Central CH	AD	Variable hypopituitarism, pituitary hypoplasia, microphthalmia, variable learning difficulties
	PROKR2 (607123)	GPCR	Variable TSH defects	AR, AD	Variable hypopituitarism associated with septo-optic dysplasia or

					pituitary stalk interruption syndrome
	NFKB2 (164012)	NF	Variable TSH defects	AD	Deficient Anterior pituitary with Variable Immune Deficiency (DAVID) syndrome associated with ACTH deficiency and variable GH defects
	CHD7 (608892)	ATP- dependent helicase	Variable TSH defects	AD	CHARGE syndrome (Coloboma, Heart anomaly, choanal Atresia, Retardation, Genital and Ear anomalies) with ectopic posterior pituitary and variable LH/FSH and GH defects
	FGFR1 (136350)	Receptor tyrosine kinase	Variable TSH defects	AD	KS and nCHH, variable association with defects of other pituitary hormones including TSH, septo-optic dysplasia and ectopic posterior pituitary
	FGF8 (600483)	GF	Variable TSH defects	AR	KS and nCHH, variable associations with defects of other pituitary hormones including TSH, holoprosencephaly and

					corpus callosum agenesis
	FOXA2 (600288)	NF	TSH defects	AD	Hypopituitarism with craniofacial and endoderm-derived organ abnormalities and hyperinsulinism

NF: nuclear factor, GF: growth factor, AR: autosomal recessive; AD: autosomal dominant, KS: Kallman syndrome, nCHH: normosmic congenital hypogonadotropic hypogonadism, PRL: prolactin, aGSU: alpha glycoprotein subunit, GH: growth hormone, LH: luteinizing hormone, FSH: follicle-stimulating hormone, ACTH: adrenocorticotrophic hormone, TRH: thyrotropin releasing hormone, OMIM= online mendelian inheritance in men (<https://www.ncbi.nlm.nih.gov/omim/>)