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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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 relating to the screening, diagnosis and management of peripheral 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 worldwide neonatal screening approaches to assess the cause (including genetics) of both peripheral and central (CH). The expert panel recommended the immediate initiation of appropriate L-thyroxine supplementation and the frequent monitoring to ensure dose adjustments to keep thyroid hormone levels in the target ranges, regular assessments of the need for treatment and of developmental and neurosensory functions, consulting health professionals as appropriate and education of the child and the family about CH. The harmonisation of diagnosis, management and routine health surveillance should optimise patient outcomes. All individuals with CH require continuous monitoring throughout their lives and a planned transition of care from the pediatric to the adult system of care.

Conclusions:
This consensus statement on CH should be used widely to detect and treat children affected by all forms of congenital hypothyroidism in light of the most recent evidences. It should help convince the health authorities of the benefit of neonatal screening to avoid this treatable cause of mental retardation. Further epidemiological and experimental studies should be implemented to understand the increased incidence of this condition.
INTRODUCTION

Congenital Hypothyroidism (CH) can be defined as a state in which congenital impairment of the hypothalamic–pituitary–thyroid axis results in a failure, or a risk of failure, to produce sufficient thyroid hormone. CH may be caused by abnormal development of the thyroid gland or axis, or to impaired thyroid hormone generation or action.

An international consensus on CH was published six years ago with literature that encompasses up to year 2011 (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, and from the two scientific societies, European Society for Pediatric Endocrinology and the European Society for Endocrinology participated. Email exchanges and 2 face to face meetings were organized in 2019. The participants were assigned to one of five groups to which topics 1 to 5 were allocated to prepare an updated summary of the literature. Each group revised the summaries, which were then discussed and agreed upon at the face to face meetings.

A detailed description of the grading scheme has been published elsewhere (2).

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).

Evidence: +00: low (case series or non-systematic clinical observations); ++0 moderate (studies with methodological flaws, inconsistent or indirect evidence); +++ high quality (low risk bias).
Neonatal screening

1.1 The benefits of CH screening
• Early detection and treatment of congenital hypothyroidism (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 3000 and 1 in 2000; the highest reported incidence of central CH is around 1 in 16,000.
• 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, the guideline committee supports adding measurement of total or free thyroxine (FT4) to TSH, to screen for central CH (1/++0).
• T4 measurement may also turn out to be useful for detecting certain forms of reduced sensitivity to thyroid hormone, like resistance to thyroid hormone or impaired thyroid hormone transport (due to mutations in the THRα and MCT8 genes, respectively); however, further research is needed to find out how an early detection and treatment could become possible (2/+00).
• Screening laboratories should be aware of possible factors disturbing biochemical measurement; in particular, the T4 or FT4 measurement may be affected by abnormal TH binding proteins or autoantibodies (1/+00).

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 born children and children with Down syndrome; for these groups a post-screening strategy may be considered (1/+00).
• The non-affected part of twins should be followed-up for possible TSH elevation later in life (1/+00).
• Specific attention should be paid to babies born in families with primary or central CH (1/+00).

• Clinical suspicion of hypothyroidism despite normal TSH in TSH-based screening programs should prompt further evaluation for central CH, particularly in cases 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 (2/++0).

• An abnormal screening result should be followed by confirmatory testing consisting of measurement of serum FT4 and TSH (if available in the country or region) (1/++0).

• If the serum FT4 concentration is below, and TSH clearly above the age-specific reference interval, then treatment should be started immediately (1/+++).

• If the serum TSH concentration is >20 mU/l, treatment should be started, even if FT4 is normal (arbitrary threshold, expert opinion) (2/+00).

• If the serum TSH concentration is ≥ 6 to 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 initiate thyroxine treatment immediately and retest, off-treatment, at a later stage, or to withhold treatment but retest one to two weeks later and re-evaluate the need for treatment; the evolution of the TSH and FT4 concentrations will be 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 (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, thyroxine treatment should be started if filter paper TSH concentration is >40 mU/L (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 thyroxine treatment only after evidence of intact adrenal function; if coexistent central adrenal insufficiency can not be ruled out, thyroxine 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 of screening laboratory staff or paediatric endocrine team) either by telephone or face to face, and supplemented by written information for the family (2/+00).
• A confirmed CH diagnosis should be communicated face to face by a medical specialist (2/+00).

2.3 Imaging techniques in CH

• Imaging studies should never delay the start of treatment (1/++0).
• The thyroid gland should be imaged using either radioisotope scanning (scintigraphy) with or without the perchlorate discharge test, or ultrasound (US), or both (1/++0).
• Occasionally, an X-ray of the knee may be performed to assess the severity of intrauterine tissue 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/+++).
• Down syndrome is associated with a higher incidence of CH (10-12%) and highly prevalent mild TSH elevation/subclinical hypothyroidism in the first months to years of life; since pituitary TSH production may be impaired early in life, remeasuring TSH at the end of the neonatal period should be considered (1/++0).

Treatment and monitoring of CH

3.1 Starting treatment for primary CH

• Thyroxine alone is recommended as the medication of choice for the treatment of CH (1/++0).
• Thyroxine 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 thyroxine 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, should be treated with the highest starting dose (10-15 μg/kg per day)
However, infants with mild CH (FT4 >15 pmol/L) should be treated with the lowest initial dose; in infants with pretreatment FT4 concentrations within the age-specific reference interval an even lower starting dose than 10 μg/kg may be considered (from 5 to 10 μg/kg) (1/++0).

If a starting dose of 50 μg per day or an even higher dose is chosen, clinical and biochemical follow-up should be scheduled no later than one week later (rather than the usual evaluation after two weeks) (1/+00).

Thyroxine should be administered orally; if intravenous treatment is necessary, the (starting) dose should be no more than 80% of the oral dose; subsequently, the dose adjusted guided by FT4 and TSH measurements (1/++0).

Thyroxine tablets should be crushed and administered via a small spoon, in a few milliliters of water or breast milk; the expert panel recognizes that crushing tablets is an off-label procedure, but that it has been done this way successfully for many years (2/+00).

Brand rather than generic thyroxine tablets should be used, particularly in severe CH and in infants (2/++0).

Liquid thyroxine for oral administration should only be used if pharmaceutically produced; the expert panel is against the use of “home-made” solutions or suspensions (1/++0).

Clinical experience suggests that the bioavailability of liquid thyroxine is higher than tablets, with a possible risk of overtreatment if the tablet doses are used (2/+00).

Parents should be provided with written instructions about thyroxine treatment (1/+00).

### 3.2 Monitoring treatment in primary CH

Serum FT4 and TSH concentrations should be measured before, or at least four hours after the last (daily) thyroxine administration (1/++0).

FT4 and TSH should always be judged 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 (1/++0).

Any reduction of the thyroxine 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)
• The first clinical and biochemical follow-up evaluation should take place one to two weeks after the start of thyroxine treatment (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 12 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 thyroxine dose or formulation, an extra evaluation should be carried out after four to six weeks (2/+00).

• Throughout childhood adequate treatment 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 thyroxine can be administered together with food; more important, thyroxine should be administered at the same time every day, also in relation to food intake, to achieve as constant as possible absorption of thyroxine; this approach may allow for dose adjustment for possible food-induced reduced thyroxine absorption (2/+00).

• In case of an unexpected need for thyroxine dose increase, reduced absorption or increased metabolization of thyroxine by other disease (e.g. gastrointestinal), medication or food should be considered (2/+00); NB incompliance may be the most frequent cause, especially in teenagers and adolescents.

3.3 Treatment for, and monitoring of central CH

• In severe forms of central CH (FT4 <5 pmol/L), we also recommend to start thyroxine 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/+00).

• 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/+00).

• 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).

• In central CH, a low TSH concentration point to adequate thyroxine treatment (1/+00).
• When under- or overtreatment is suspected in a patient with central CH, then TSH and/or free or total triiodothyronine T3 (FT3, total T3) should be measured (1/+00).
• When serum FT4 is below or close to the lower limit of the reference interval, then thyroxine undertreatment should be considered, particularly if TSH >1.0 mU/L (1/+00).
• In patients with central CH, an increase of the thyroxine dose after the start of growth hormone treatment should be considered, guided by FT4 and TSH measurement (1/+00).
• When serum FT4 is above or close to the upper limit of the reference interval, then thyroxine overtreatment should be considered (assuming that thyroxine has not been administered 20-40 minutes before blood withdrawal), particularly if associated with clinical signs of thyrotoxicosis, or a high (F)T3 concentration (1/+00).

3.4 Diagnostic re-evaluation 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 (hypothalamus-pituitary-)thyroid axis after the age of two years is indicated, particularly in children with gland-in-situ (GIS) and in those with presumed isolated central CH (1/++0).
• For a precise diagnosis, thyroxine treatment should be phased out over a four to six weeks period or just stopped, and full re-evaluation should be carried out after three to four weeks, consisting of (at least) FT4 and TSH measurement and, if hypothyroidism is confirmed (primary CH: TSH ≥10 mU/L; central CH: FT4 below the lower limit of the reference interval in combination with a low, normal of only mildly elevated TSH), thyroid imaging; 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, 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 thyroxine dose of less than 3 mcg/kg per day at the age of six months, then re-evaluation can be anticipated (1/++0).
• In retrospect, specific attention should be paid to newborns exposed to iodine; iodine antiseptic use should be avoided (1/++0).

3.5 Treatment and monitoring of pregnant women with CH

• In women with CH who are planning pregnancy thyroxine treatment should be optimized;
based on TSH measurement(s) the preconception thyroxine dose should be adjusted to achieve a TSH value between the lower reference interval and 2.5 mU/L; in addition, these women should be counseled regarding the higher need for thyroxine during pregnancy, and to contact their caregiver immediately upon confirmed or suspected pregnancy to increase their thyroxine dose by 25%–30% (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 mIU/L in the first trimester and <3 mIU/L later in pregnancy (1/+00).

• In pregnant women with central CH, the thyroxine doses should be increased aiming at a FT4 concentration above the mean/median value of the trimester specific reference interval (1/+00).

• Following delivery, the thyroxine dose should be reduced to preconception dose; additional thyroid function testing should be performed at approximately six weeks post partum (1/++0).

• In countries with mild to severe iodine deficiency, treatment with iodine (100-200 µg/day) is recommended in all women with CH trying to become pregnant until the end of lactation (1/++0).

Outcomes of neonatal screening and early treatment

4.1 Neurodevelopmental outcomes

• Nowadays, the vast majority of early and adequately treated children with CH have a normal developmental outcome (1/+++).

• 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 mental retardation than CH (1/+00).

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

4.2 Development of goiter in thyroid dyshormonogenesis

• Children and adolescents with primary CH due to dyshomonogenesis may develop goiter
and nodules; in these cases, serum TSH should be carefully targeted in the lower part of normal range (2/++0).

- Since a few cases of thyroid cancer have been reported, periodical ultrasound of the thyroid gland is recommended (1/+00).

4.3 Growth, puberty and fertility
- Adequately treated children with 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 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 both parents, starting at the time of the diagnosis, and later on the patients 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 to optimise continuity of care and, with that, clinical outcomes and quality of life, and to increase understanding of CH and promote self-management (1/+++).

Genetics of CH, genetic counseling and antenatal management

5.1 Criteria for genetic counselling
- Genetic counselling should be targeted, rather than generally advised to all CH patients, and done by an experienced professional (2/++0).
- The counselling should include explaining the 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 (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).
• See Tables 1 to 3 for CH due to thyroid dysgenesis and syndromic forms, dyshormonogenesis, and central CH, respectively.

5.3 Antenatal diagnostics, evaluation of fetal thyroid function and management of fetal hypothyroidism
• If a (large) fetal goiter is diagnosed, prenatal care should be provided in a specialized center of prenatal care (1/+++).
• In a euthyroid pregnant woman, a large fetal goiter with progressive hydramnios, and risk of premature or concerns about tracheal occlusion are conditions that may be a reason for fetal treatment by intra-amniotic thyroxine injections (1/++0); in a hypothyroid pregnant woman, the preferred approach is to treat the woman (rather than the fetus) with thyroxine (1/++0).
1. NEONATAL SCREENING

1.1 The benefits of CH screening

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

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 1:16,000.
- 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).
- When financial resources are available, the guideline committee supports adding measurement of total or free thyroxine (FT4) to TSH, to screen for central CH.
• T4 measurement may also turn out to be useful for detecting certain forms of reduced sensitivity to thyroid hormone, like resistance to thyroid hormone or impaired thyroid hormone transport (due to mutations in the \textit{THR\alpha} and \textit{MCT8} genes, respectively); however, further research is needed to find out whether affected neonates benefit from an early detection and treatment.

• Screening laboratories should be aware of possible factors disturbing biochemical measurement; in particular, the T4 or FT4 measurement may be affected by abnormal TH binding proteins or autoantibodies.

\textbf{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 who would have been missed (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 \textit{DUOX2/DUOXA2} varies widely between individuals and over time, with some patients requiring no treatment, and some having transient CH. However, justification for screening and detecting biochemically less severe, eventually transient CH cases requires assessment of neurodevelopmental sequelae, but this has proved difficult (19). Long-term outcome studies of the effect of thyroxine 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. However, also measuring T4 \pm TBG provides the potential to diagnose central CH. Although slightly more than 50% of neonates with central CH has moderate to severe CH, i.e. a first diagnostic FT4 concentration of 5 to 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 it a potential candidate for neonatal screening.

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

**Summary**

- 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 born children and children with Down syndrome; for these groups a post-screening strategy may be considered.
- The non-affected part of twins should be followed-up for possible TSH elevation later in life.
- Specific attention should be paid to babies born in families with primary or central CH.
- Clinical suspicion of hypothyroidism despite normal TSH in TSH-based screening programs should prompt further evaluation for central CH, particularly in cases with a family history of central CH.

**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).

Although the concordance rate for CH in twins is low, they are overrepresented in the CH population (32). Because of fetal blood mixing, the TSH concentration of the affected part of the twins may be lower than expected and may escape detection in TSH-based screening (32, 33). Therefore, a low threshold for repeat TSH measurement is suggested. In addition, the non-affected part of twins should be followed-up for possible TSH elevation later in life (34).

Down syndrome is associated with a higher than expected incidence of CH, and highly prevalent mild TSH elevation/subclinical hypothyroidism, especially in the first months to years of life (35-37). The probable cause of both phenomena is variable thyroid dysgenesis, probably related to the extra chromosome 21 and possibly to overexpression of the DYRK1A gene (38-41). Because many neonates with Down syndrome have non-thyroidal illness due to (surgery for) cardiac or intestinal disease (42), 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 seems warranted.

In babies born in families affected with primary or central CH, FT4 and TSH measurement is advised, even if TSH was normal in TSH-based screening programs. 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 (25,43). 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 (25,43,44). 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.

• An abnormal screening result should be followed by confirmatory testing consisting of measurement of serum FT4 and TSH (if available in the country or region).

• If the serum FT4 concentration is below, and TSH clearly above the age-specific reference interval, then treatment should be started immediately.

• If the serum TSH concentration is >20 mU/l, treatment should be started, even if FT4 is normal (arbitrary threshold, expert opinion).

• If the serum TSH concentration is ranging 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 initiate thyroxine treatment immediately and retest, off-treatment, at a later stage, or to withhold treatment but retest one to two weeks later and re-evaluate the need for treatment; the evolution of the TSH and FT4 concentrations will be 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 (lack of evidence in favour or against treatment, this is an area of further investigation).

• In countries or regions where thyroid function tests are not readily available, thyroxine treatment should be started if filter paper TSH concentration is >40 mU/L (arbitrary threshold, expert opinion).

• If the serum FT4 is low, and TSH is low, normal or slightly elevated, the diagnosis central CH should be considered.

• In neonates with central CH, we recommend starting thyroxine treatment only after evidence of intact adrenal function; if coexistent central adrenal insufficiency cannot be ruled out, thyroxine treatment must be preceded by glucocorticoid treatment in order to prevent possible induction of an adrenal crisis.

**Evidence**

Early detection of 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 (45). 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 (46). 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 (dbsTSH concentrations between 6-20 mU/L, but a normal FT4 concentration) benefit from thyroxine treatment is still unclear (47,48). Randomised controlled trials addressing this question have not been performed. In a large cohort study, Lein et al found a worse neurocognitive outcome in neonates with neonatal screening TSH concentrations between the 75th and 99.9th percentiles (49) while neonates with TSH values above the 99.9th percentile (12-14 mIU/L) had better cognitive development, possibly due to thyroxine treatment. In contrast, in a Belgian cohort of children there was no relation mild TSH elevation and (impaired) neurodevelopment (50-52).

In healthy neonates, it is generally suggested to evaluate thyroid function (TSH and FT4 measurement) every one to two weeks, and consider thyroxine treatment when TSH increases or FT4 decreases (46). Mild CH can be a permanent or transient condition. The family history, thyroid imaging and genetic testing may be helpful to shed light on the etiology, and to determine the necessity of (long-term) treatment (48).

In some countries or regions confirmatory thyroid function testing may not be readily available. In this scenario thyroxine 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 (53).

Central hypothyroidism is characterised by a low serum FT4 on combination with a low, normal or slightly elevated TSH concentration. Other causes of the FT4-TSH combination are non-thyroidal illness and certain forms of reduced sensitivity to thyroid hormone (25). Central CH can be isolated or part of multiple pituitary hormone deficiency (MPHD) (54). In case of untreated adrenal insufficiency, thyroxine treatment may provoke an adrenal crisis. So, thyroxine treatment can only be started after a normal adrenal function test result or (already started) glucocorticoid treatment (43).

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 of screening laboratory staff or paediatric endocrine team) either by telephone or face to face and supplemented by written information for the family.
• A confirmed CH diagnosis should be communicated face to face by a medical specialist.

Evidence

In the organization of a (neonatal) screening program, both in industrialized and developing countries, communicating abnormal results is a key task 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, the quality of information 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 for with maternity units, 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 may be helpful. Taking time and using simple language to explain the managing and implications of the diagnosis, and the importance of early detection and adequate thyroxine treatment are essential. Written materials can be helpful but should not replace this face-to-face discussion (55-57).

2.3 Imaging techniques in CH

Summary
• Imaging studies should never delay the start of treatment.
• The thyroid gland should be imaged using either radioisotope scanning (scintigraphy) with or without the perchlorate discharge test, or ultrasound (US), or both.
• Occasionally, an X-ray of the knee may be performed to assess the severity of intrauterine tissue hypothyroidism.

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 ultrasound

Ultrasound is an important diagnostic tool for determining the presence of the thyroid gland and, when present, its location, size and echotexture. It is a non-invasive, non-irradiating, cost-effective imaging technique, but highly observer dependent. Thyroid volume in newborns varies from $0.84\pm0.38\ mL$ to $1.62\pm0.41\ mL$ (58-60), without significant changes during the first three weeks of life (61). Thyroid size can be influenced by (long-term) TSH suppression during thyroxine 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 ($^{99m}\text{Tc}$) and iodine-123 ($^{123}\text{I}$) are both captured by NIS at the basal side of thyrocytes and are both suitable for imaging. $^{99m}\text{Tc}$ is more widely available, less expensive, faster in use (image acquisition 15 minutes after administration) and has a shorter half-live than $^{123}\text{I}$. However, images are of lower quality than with $^{123}\text{I}$. 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 (62,63). Furthermore, it exposes infants to a lower dose of whole-body irradiation compared with $^{99m}\text{Tc}$ (3-10 $\mu$Ci/kg vs. 50-250 $\mu$Ci/kg body weight) (64,65).

When the thyroid is present and normally located, 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 $^{123}\text{I}$ 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 thyroxine treatment), previous iodine exposure, maternal blocking TSH-receptor antibodies, and mutations in genes affecting iodine uptake (NIS) or TSH receptor function (TSHR) defects. In these cases, thyroid ultrasound 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 scan and perchlorate discharge testing can also be performed after recombinant human TSH administration (66).

**Dual imaging**

Combining thyroid ultrasound and scintigraphy provides high-resolution anatomical (ultrasound) and functional (scintigraphy) information, allowing to distinguish between permanent and possible transient CH (62,65,67). 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 (63, 65).

**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, has been shown to correlate with neurodevelopmental outcome (68), and can be assessed by performing a x-ray of the knee (presence of absence of the femoral and tibial epiphyses). Thyroxine treatment normalizes bone maturation within the first year of life (68). More recent data of the value of bone maturation are not available. However, a knee X-ray can be performed as an additional parameter reflecting severity of intrauterine hypothyroidism (ref).

### 2.4 Associated malformations and syndromes

**Summary**

- All neonates with a high TSH concentration should be examined carefully for dysmorphic features suggestive for syndromic CH, and for congenital malformations (particularly cardiac).
- Down syndrome is associated with a higher incidence of CH (10-12%) and highly prevalent mild TSH elevation/subclinical hypothyroidism in the first months to years of life; since
pituitary TSH production may be impaired early in life, remeasuring TSH at the end of the neonatal period should be considered.

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 athyrosis 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 (70). 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) (71,72).

Other examples of syndromic CH are Alagille syndrome type 1 (OMIM #118450) with thyroid in situ and cardiac malformations (207), Williams–Beuren (OMIM #194050) and DiGeorge syndromes (OMIM #188400) with a high prevalence of thyroid hypoplasia (50–70%) and subclinical hypothyroidism (25–30%) (73,74, and Kabuki (75) and Johanson-Blizzard syndromes (76) 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 (77) is higher in individuals with CH than in the general population, with differences in prevalence between studies (78-84); 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.

3. TREATMENT AND MONITORING OF CH

3.1 Starting treatment for primary CH

3.2 Monitoring of treatment in primary CH

3.3 Treatment and monitoring of central CH

3.4 Diagnostic re-evaluation 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

- Thyroxine alone is recommended as the medication of choice for the treatment of CH.
- Thyroxine 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.
- The thyroxine starting dose should be up to 15 μg/kg per day, taking into account the whole spectrum of CH, ranging from mild to severe.
- Infants with severe CH, defined by a very low pretreatment serum FT4 (<5 pmol/L) or total T4 concentration, should be treated with the highest starting dose (10-15 μg/kg per day).
- However, infants with mild CH (FT4 >15 pmol/L) should be treated with the lowest initial dose; in infants with pretreatment FT4 concentrations within the age-specific reference interval an even lower starting dose than 10 mcg/kg may be considered (5-10 μg/kg).
- If a starting dose of 50 μg per day or an even higher dose is chosen, clinical and biochemical follow-up should be scheduled no later than one week later (rather than the usual evaluation after two weeks).
- Thyroxine should be administered orally; if intravenous treatment is necessary the (starting) dose should be no more than 80% of the recommended oral dose; subsequently, the dose adjusted guided by FT4 and TSH measurements.
- Thyroxine tablets should be crushed and administered via a small spoon, in a few milliliters of water or breast milk; the expert panel recognizes that crushing tablets is an off-label procedure, but that it has been done this way successfully for many years.
- Brand rather than generic thyroxine tablets should be used, particularly in severe CH and in infants. However, once started, treatment should be continued using the same preparation in order to avoid supplemental examinations.
- Liquid thyroxine for oral administration should only be used if pharmaceutically produced; the expert panel is against the use of “home-made” solutions or suspensions.
- Clinical experience suggests that the bioavailability of liquid thyroxine is higher than tablets, with a possible risk of overtreatment.
- Parents should be provided with written instructions about thyroxine treatment.

3.2 Monitoring treatment in primary CH

Summary
• Serum FT4 and TSH concentrations should be measured before, or at least four hours after the last daily thyroxine administration.

• FT4 and TSH should always be judged according to age-specific reference intervals.

• 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; therafter, 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.

• Any reduction of the thyroxine dose should not be based on a single higher that normal FT4 concentration, unless TSH is suppressed (i.e. below the lower limit of the reference interval).

• The first clinical and biochemical follow-up evaluation should take place one to two weeks after the start of thyroxine treatment.

• Subsequent (clinical and biochemical) evaluation should take place every two weeks until complete normalization of serum TSH is achieved; therafter, the evaluation frequency can be lowered to once every one to three months until the age of 12 months.

• Between the ages of 12 months and three years, the evaluation frequency can be lowered to every two to four months; therafter, evaluations should be carried out every three to 12 months until growth is completed.

• If abnormal FT4 or TSH values are found, or if compliance is questioned, the evaluation frequency should be increased.

• After a change of thyroxine dose or formulation, an extra evaluation should be carried out after four to six weeks.

• Throughout childhood adequate treatment is essential, and long-term under- or overtreatment, i.e. TSH concentrations above or below the reference interval, should be avoided.

• In contrast to adults, in neonates, infants and children thyroxine can be administered together with food (but soy and vegetable fibers should be avoided); more important, thyroxine should be administered at the same time every day, also in relation to food intake, to achieve as constant as possible absorption of thyroxine; this approach may allow for dose adjustment for possible food-induced reduced thyroxine absorption.

• In case of an unexpected need for thyroxine dose increase, reduced absorption or increased metabolism of thyroxine by other disease (e.g. gastrointestinal), medication or food should
be considered; NB incompliance may be the most frequent cause, especially in teenagers and adolescents.

3.3 Treatment for, and monitoring of central CH

Summary

• In severe forms of central CH (FT4 < 5 pmol/L), we also recommend starting thyroxine 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.
• 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.
• In newborns with central CH, we recommend monitoring treatment by FT4 and TSH determinations according to the same schedule as for primary CH; TSH determination can be omitted if low at baseline; serum FT4 should be kept above the mean/median value of the age-specific reference interval.
• In central CH, a low TSH concentration point to adequate thyroxine treatment.
• When under- or overtreatment is suspected in a patient with central CH, then TSH and/or free or total triiodothyronine T3 (FT3, total T3) should be measured.
• When serum FT4 is below or close to the lower limit of the reference interval, then thyroxine undertreatment should be considered, particularly if TSH > 1.0 mU/L.
• In patients with central CH, an increase of the thyroxine dose should be considered after the start of growth hormone treatment, guided by FT4 and TSH measurement.
• When serum FT4 is above or close to the upper limit of the reference interval, then thyroxine overtreatment should be considered (assuming that thyroxine has not been administered just after blood withdrawal), particularly if associated with clinical signs of thyrotoxicosis, or a high (F)T3 concentration.

3.4 Diagnostic re-evaluation 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 (hypothalamus-pituitary-) thyroid axis after the age of two years is indicated, particularly in children with gland-in-situ (GIS) and in those with presumed isolated central CH.
• For a precise diagnosis, thyroxine treatment should be phased out over a four to six weeks period or just stopped, and full re-evaluation should be carried out after three to four weeks, consisting of (at least) FT4 and TSH measurement and, if hypothyroidism is confirmed (primary CH: TSH ≥10 mU/L; central CH: FT4 below the lower limit of the reference interval in combination with a low, normal of only mildly elevated TSH) thyroid imaging; 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, then continue withdrawal and re-test in another three to four weeks.

• If a child with no permanent CH diagnosis and a GIS requires a thyroxine dose of less than 3 mcg/kg per day at the age of six months, then re-evaluation can be done already at that time.

• In retrospect, specific attention should be paid to newborns exposed to iodine; iodine antiseptic use should be avoided.

3.5 Treatment and monitoring of pregnant women with CH

Summary

• In women with CH who are planning pregnancy thyroxine treatment should be optimized; based on TSH measurement(s) the preconceptual thyroxine dose should be adjusted to achieve a TSH value between the lower reference interval and 2.5 mU/L; in addition, these women should be counseled regarding the higher need for thyroxine during pregnancy, and to contact their caregiver immediately upon confirmed or suspected pregnancy to increase their thyroxine dose by 25%–30%.

• 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 mIU/L in the first trimester and <3 mIU/L later in pregnancy.

• In pregnant women with central CH, the thyroxine doses should be increased aiming at a FT4 concentration above the mean/median value of the trimester specific reference interval.

• Following delivery, the thyroxine dose should be reduced to preconception dose; additional thyroid function testing should be performed at approximately six weeks post partum.

• In countries with mild to severe to iodine deficiency, treatment with iodine (100-200 µg/day) is recommended in all women with CH planning pregnancy and then until the end of lactation.
Evidence

3.1 Starting treatment for primary CH

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 adoptions 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 thyroxine treatment, and the thyroxine 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 thyroxine treatment and the optimal starting dose are deduced from reasonable 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 and average thyroxine dose dose lower than 10µg/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 (85). Patients were treated with thyroxine from a mean age of nine days with a starting dose between 10-15 µg/kg depending on CH severity. Neonates with athyrosis were treated with 15µg/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 (86). The treatment approach resembled the New Zealand approach with a median age at diagnosis of eight days, a mean thyroxine starting dose of 13.5µg/kg, 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 child with severe CH can reach a normal IQ that does not differ from unaffected siblings, if thyroxine treatment starts before the age of ten days and the starting dose is greater than 10 µg/kg, with 15 µg/kg in the most severe forms. More precise values for the optimal age at start of thyroxine 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 more then 10 µg/kg, but not lower than that. We thus recommend that a term, normal weight baby with severe CH (e.g. athyreosis) should start with 50µg thyroxine per day, and a term, normal weight baby with mild CH (e.g. due to thyroid hypoplasia) with 37.5 µg per day.

Hormone preparations and administration

Since there are no 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 crushed thyroxine tablets dissolved in water or breast milk administered via a spoon, or liquid thyroxine preparations. In none of the studies T3 was administered. Because the cognitive outcomes in these studies were favorable, using only thyroxine and administering as just described is recommended. It should be stressed that only pharmaceutically produced medication should be prescribed. In addition, it seems possible that liquid thyroxine
preparations have a greater bioavailability with consequences for changing medication from tablets to liquid, and the other way around.

3.2. Monitoring treatment in primary CH

3.2.1. Shortly after the start of thyroxine treatment

Repeated measurement of serum FT4 and TSH are the backbone of monitoring thyroxine treatment in patients with primary CH (87-89). 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 (90). 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 (91). Rapid normalization of TSH and keeping FT4 in the upper half of the age-specific reference interval has been shown to normalize the neurodevelopmental outcome (85, 92-94).

3.2.2. Follow-up after the first weeks of thyroxine treatment

There is no evidence for a one optimal follow-up scheme. Recent studies focussing on optimization of biochemical control suggest frequent controls 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 (95,96), 2) the highest doses within the recommended range of 10-15 μg/kg per day resulted in more dose adjustments because of hyperthyroxinemia (97-99), and 3) monthly controls 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) (89). 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 (85,86). Thereafter, in New Zealand blood tests were done monthly during the first year and bi-monthly during the second year, and three-monthly in the Berlin study. Obviously, follow-up schemes have to be personalized according to parents’ capabilities and compliance.

The main 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 that needs to be compensated by a higher FT4 concentration. Data on the effects of clearly increased serum (F)T4 concentrations are scarce. In one study, 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 (100,101). Earlier studies suggested adverse effects on attention span (102). However, Aleksander et al showed no differences between patients and siblings despite comparable periods of overtreatment (86). As long as there is no extra 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 or T3 is elevated. 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 (103,24). Persistence of such mild hypothalamus-pituitary resistance has been reported in adult CH patients compared to patients with acquired hypothyroidism (104).

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, the most severe forms of CH and the highest range of the recommended thyroxine 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 is 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 (105). 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 (106).

3.2.3. Adverse effects of thyroxine

Adverse effects of long-term thyroxine treatment are rare or null if adequately prescribed. Cases of pseudotumor cerebri or craniosynostosis have been described (107,108). However, 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 (109). 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 (82).

### 3.2.4. Cardiac insufficiency

Thyroxine has clear positive ino- and chronotropic effects on L-T4 on the heart. In newly diagnosed CH in newborns with congenital heart disease and impending heart failure, we therefore recommend to apply a lower thyroxine 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.

### 3.2.5. Impaired bioavailability by diseases, drugs or food

Thyroxine is mainly absorbed in the proximal small intestine. Undiagnosed or untreated celiac disease will reduce thyroxine absorption. Children with short bowel syndrome will also have reduced absorption (110). Recently, rectal administration of thyroxine was been shown to be effective in a child with this condition (111). Increased type 3 deiodinase activity in large hemangiomas can cause increased metabolic clearance of administered thyroxine and, with that, necessitate a higher thyroxine dose (112-114). Bioavailability of thyroxine 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 (115,116).

While in adults the recommended thyroxine intake moment is 60 minutes before intake of food intake (117), such a recommendation is difficult to realize in infants (115). Pragmatically, thyroxine should be administered at a fixed time with an equal interval to food intake everly day to have a constant as possible, enabling optimal as possible thyroxine dose adaptation. Soy containing food products have been repeatedly shown to inhibit thyroxine absorption in children with CH (118, 119).

### 3.3 Treatment and monitoring of central CH

Just like primary CH, treatment of central CH consists of daily administration of thyroxine (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 thyroxine starting dose.
The (biochemical) thyroxine 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 (120, 121). 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 to 15 pmol/L) (20, 122). Although studies investigating the optimal starting dose in central CH are lacking, clinical experience has taught that a thyroxine starting dose of 10-15 $\mu$g/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 $\mu$g per kg is advisable.

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

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

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) (123, 124), low birth weight (125, 126), neonatal morbidity requiring intensive care (4), ethnicity (more of the in non-white patients) (8), less severe CH at diagnosis (assessed by screening TSH, or diagnostic TSH or FT4) (8,123,124,127-132). In contrast, factors like prematurity (11,133,134), other congenital abnormalities (132), a family history of thyroid disease (133), abnormal thyroid morphology (thyroid hypoplasia at diagnosis) (133) and a higher thyroxine dose requirement at one to three years of age are associated permanent CH (with conflicting results between studies for the factor dose requirement)(123, 124, 127-131, 134, 136-138). Recent studies have shown that early treatment withdrawal to assess the necessissity of furhter 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 tyroxine dose. Saba et al (139) investigated 92 patients with CH and a GIS and found 49 of them (54%) to have transient CH. In this study, the optimal thyroxine dose cutoff values for predicting transient CH at the ages of six and 12 months were 3.2 $\mu$g/kg and 2.5 $\mu$g/kg per day, respectively, with a sensitivity of 71% at both time points, and a specificity of 79% and 78% six and 12 months, respectively (with values below these thresholds considered predictive of transient CH). In the study by Oron et al (140), 17 out of 84 patients with a GIS (20%) turned out to have transient CH. The optimal thyroxine dose cutoff 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 (141). 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, 142, 143). This may be more profound in premature born babies, as 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 (144).

### 3.5 Treatment and monitoring of pregnant women with CH

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. 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 (145, 146). TSH ≥10 mIU/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 mIU/L. Yet, these women did have a higher risk of induced labor for vaginal delivery (145). 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, motricity and language skills. However, children born to mothers with TSH ≥10 mIU/l were more likely to have low motricity or communication skills scores. Yet, it remains unclear whether these adverse effects modify subsequent neurodevelopment (147). During pregnancy, thyroid hormone requirement increases and most thyroxine treated women require a dose increase up to 30%. Women with athyreosis, the most severe form of CH, require the highest doses (up to 200 µg per day) (145, 146,148). Therefore, careful
monitoring of thyroxine treatment of pregnant women with hypothyroidism is extremely important.

4. OUTCOMES OF NEONATAL SCREENING AND EARLY TREATMENT

4.1 Neurodevelopmental outcome

Summary

• Nowadays, the vast majority of early and adequately treated children with CH have a normal developmental outcome.
• 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.
• 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 mental retardation than CH.
• 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.
• Since a few cases of thyroid cancer have been reported, periodical ultrasound of the thyroid gland is recommended.

4.3 Growth, puberty and fertility

• Adequately treated children with CH have normal growth and puberty, and their fertility does not differ from individuals who do not have CH.

4.4 Bone, metabolic and cardiovascular health
• Adequately treated children with CH also have normal bone, metabolic and cardiovascular health.

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

Summary
• Medical education about CH should be improved at all levels, with regular updates.
• Education of both parents, starting at the time of the diagnosis, and later on the patients is essential; not only throughout childhood, but also during transition to adult care and in females during pregnancy.
• Since adherence to treatment may influence the outcomes, it should be promoted throughout life.

4.6 Transition to adult care
• When patients are transferred from paediatric to adult care, the main aims are to optimise continuity of care and, with that, clinical outcomes and quality of life, and to increase understanding of CH and promote self-management.

Evidence
4.1 Neurodevelopment outcome
In the vast majority of early and adequately treated children with CH neurodevelopmental and school outcomes level are normal (85, 86, 149-151), and intellectual disability - defined as an IQ <70 - has virtually disappeared (152). In the past, patients with severe CH treated with a low initial thyroxine dose had lower IQ scores (although within normal range), and subtle neurological deficits in cognitive and motor development (153-155) when compared to control populations including healthy siblings (155, 156). In the last two decades, early treatment with a high initial thyroxine (≥10 μg/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 (85,86).
However, despite early and adequate treatment patients with severe CH may still have subtle cognitive and motor deficits, and lower educational attainment (151, 157, 158). 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 (159). Children with it may also display reduced hippocampal volume (160) and abnormal cortical morphology among brain
regions (thinning or thickening) (161), that may explain subtle and specific deficits in memory, language, sensorimotor and visuospatial function. (160, 161). 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 (101). Overtreatment during the first months of life, a critical period for brain development, may be associated with attention deficit at the school age (101, 162, 163), and lower IQ scores (100). Finally, other factors such as socio-educational status (165, 157) and poor adherence to the treatment (157, 165, 151) 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 (56). 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 mental retardation than CH. Undiagnosed hearing impairment can adversely impair speech development, school performance and quality-of-life (151, 167). Thyroid hormone plays a role in cochlear and auditory function development (151, 168-170). Despite early and adequate thyroxine 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 (167, 170). Young adults with CH reported hearing impairment more frequently (9.5%) as compared to the general population (2.5%) (151). 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 (167). 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

Children and adolescents with primary CH due to dyshormonogenesis (mainly *TPO* gene, but also *SLC5A5/NIS* 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 thyroxine treatment. In other cases, poor compliance to treatment, with persistently high TSH levels during adolescence, was the probable cause (171-174). Therefore, TSH should be targeted in the lower part of normal range during treatment of dyshormogenic 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 CH due to dyshormonogenesis (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

If early and adequately treated, children with CH will have normal growth and pubertal development (175-179). Adult height is normal and comparable to siblings (86) with no effects of severity of CH at diagnosis, CH etiology or the thyroxine starting dose (175, 176, 45); moreover, in the majority of children adult height is above the target height in both sexes (175, 176, 45). Onset of puberty occurs at the normal age in the vast majority of CH patients and progresses normally in both sexes (175, 106, 45). The same applies to age at menarche and menstrual cycles (106,175). In adults, fertility is generally normal CH (180). However, women with CH have an increased risk of having adverse pregnancy outcomes. In addition, their offspring is at risk for poorer motor coordination (see also paragraph 3.5) (145,147).

4.4 Bone, metabolic and cardiovascular health

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 (68); however, within the first months of life thyroxine treatment rapidly normalizes bone maturation (69). Since thyroid hormones have major effects on bone remodeling, thyroxine overtreatment may increase bone turnover with higher bone resorption than formation, resulting in progressive bone loss (181). Yet, long-term studies in children and young adults with CH have shown normal bone mineral density (182-185) suggesting early started, adequate thyroxine treatment is not harmful to bone health. Given the importance of sufficient calcium intake patients with CH, in addition to adequate thyroxine treatment, should consume 800 to 1200 mg calcium daily; if dietary calcium intake is low, supplements should be added (1, 182).
Body mass index and composition are generally normal in children and adult with CH (85,86 179) and comparable to that of the general population. However, earlier adiposity rebound 186-188 and increased risks of being overweight or obese has been reported in up to 37% of young adults with CH (151, 45, 106). Therefore, lifestyle interventions, including diet and exercise, should be encouraged to avoid metabolic abnormalities (1).

In addition to an increased risk of congenital heart disease (80-82) neonates with untreated CH may have increased aortic intima media thickness (IMT), serum cholesterol levels (189) and impaired cardiac function (190, 191) reversed by early thyroxine treatment (192).

Young adults with CH have normal, blood pressure, glucose and lipid metabolism, and carotid IMT (192, 86) 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 (192, 193). 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

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 selfesteem 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 (194). Most (151, 195,196), but not all (194,197) 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 (196), which was already present in childhood (195). 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 (151).

4.6 Transition to adult care

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 (198,199). 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 (145,147).

5. GENETICS OF CH, GENETIC COUNSELLING AND ANTENATAL MANAGEMENT

5.1 Criteria for genetic counseling

Summary

• Genetic counselling should be targeted rather than generally advised to all CH cases, and done by an experienced professional.

• The counselling should include explaining the 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.

• 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.

5.2 Genetics of CH

Summary
If genetic testing is performed, its aim should be improving diagnosis, treatment or prognosis.

Before doing so, possibilities and limits of genetic testing should be discussed with parents or families.

When available, genetic testing should be performed by means of new techniques, like comparative genomic hybridization (CGH) array, next-generation sequencing of a gene panel (targeted NGS) or whole exome sequencing (WES).

Preferably, genetic testing or studies should be preceded by careful phenotypic description of the patient’s CH - including morphology of the thyroid gland.

Not only thyroid dyshormonogenesis, but also familial occurrence of dysgenesis and central hypothyroidism should lead to further genetic testing.

Any syndromic association should be studied genetically, not only to improve genetic counselling, but also to identify new candidate genes explaining the association.

Further research is needed to better define patients or patient groups that will benefit most from these new diagnostic possibilities.

See Tables 1 to 3 for CH due to thyroid dysgenesis and syndromic forms, dyshormonogenes, and central CH, respectively.

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

Summary

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

In a euthyroid pregnant woman, a large fetal goiter with progressive hydramnios, and risk of premature or concerns about tracheal occlusion are conditions that may be a reason for fetal treatment by intra-amniotic thyroxine injections; in a hypothyroid pregnant woman, the preferred approach is to treat the woman (rather than the fetus) with thyroxine.

Evidence

5.1 Criteria for genetic counseling

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 \textit{NKX2-1} gene mutations who are at risk of life-threatening respiratory disease (200); 4) enable “personalized” thyroxine treatment to prevent goiter formation, which may occur in CH due to \textit{TPO} or \textit{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 thyroxine treatment may be non-beneficial (48).

5.2 Genetics of CH

Primary CH

Thyroid dysgenesis (TD) due to thyroid maldevelopment, is the most frequent cause of permanent primary CH, explaining approximately 65% of cases (12,201). 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 (dyshormonogenesis). Thyroid dysgenesis is considered a sporadic disease. However, the familial component cannot be ignored, suggesting a genetic predisposition and a probably complex inheritance mode (202,203). In only 10% of TD cases a genetic cause is identified with mutations in like \textit{TSHR} (204) or genes encoding transcription factors involved in thyroid development (\textit{TTF1/NKX2.1, PAX8, FOXE1, NKX2-5, GLIS3}) (205,206). 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 \textit{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) (207, 208). By whole exome sequencing (WES) in familial TD cases, Carré et al found borealin (encoded by \textit{BOREALIN}), a major component of chromosomal passenger complex be also involved in thyrocyte migration and adhesion, explaining cases of thyroid ectopy (209). Mutations or deletion in the \textit{NTNI} 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 (210). Finally, mutations in *TUBB1* (Tubulin, Beta 1 class VI) gene have recently been identified in three families with thyroid dysgenesis (mostly ectopy) and abnormal platelet physiology in patients harboring the mutations (basal activation and exaggerated platelet aggregation) (211). 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 (40). How overexpression of this gene causes thyroid abnormalities remains to be elucidated. Another 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 (212). Table 2 resumes genes associated with TD.

In contrast to TD, thyroid dyshormonogenesis 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*, *DUOXA2* 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 extended the assumed thyroid phenotype resulting from mutations in genes responsible thyroid hormone synthesis, causing dyshormonogenesis. For instance, mutations in *SLC26A4/PDS* (213) and *DUOX2* (214) have been unexpectedly found in patients with non-goitrous CH and thyroid hypoplasia, narrowing the gap between TD and dyshormonogenesis. Recently, *DUOX2* mutations have also been reported in patients with thyroid ectopy; however, further studies are needed to confirm and explain this striking finding (215). Moreover, the first CH patients with both *DUOX1* as well as *DUOX2* mutations have been reported, suggesting that CH can have a digenic cause (216). *DUOX2* mutations have also been found in patients with early-onset inflammatory bowel disease, suggesting an extrathyroidal role for *DUOX2* (217). Biochemically, carriers of variations in the *DUOX* genes, may have a delayed rise of TSH after birth (218, 16). Table 3 shows genes implicated in thyroid dyshormonogenesis. 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.
(84, 219, 220). 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 (84). These
novel data may also provide an explanation for the frequent sporadic presentation of CH and
observed complex modes of inheritance. In such context, \textit{JAG1} may act as gene modifier in a
multifactorial architecture of CH (208).

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
3). Isolated central CH due to bi-allelic \textit{TSH\beta} 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 (221-223). Therefore, central CH
must be ruled out in all infants with signs or symptoms of CH and low, normal or only
slightly elevated TSH concentration.

To date, defective TRH action due to bi-allelic mutations in the \textit{TRHR} gene has been
described in only a few families (43). 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 \textit{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 (224). Immunoglobulin superfamily member 1 gene (\textit{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 (225, 226). Some female carriers
can also manifest central CH. Recent data indicate IGSF1 as the most frequently implicated
gene in congenital central CH (226).

Mutations in the \textit{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 (227). 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 (228). Central CH is more frequently part of MPHD 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 (25,43). Table 4 shows genes implicated in central hypothyroidism.

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

Antenatal diagnostics is advised in case of fortuitously discovered fetal goiter during fetal US examination in an anti-TSH receptor antibodies negative mother, and earlier child with primary CH due to dyshormonogenesis (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 guideline (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 (229) 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; 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; in a hypothyroid pregnant woman, the preferred approach is to treat the woman with (rather than the fetus) with thyroxine. Finally, adequate iodine intake should be ensured for all pregnant women (250 µg per day).

CONCLUSIONS

This update of the consensus on congenital hypothyroidism recommends worldwide neonatal screening, approaches to assess the cause (including genetics) of both peripheral and central hypothyroidism. The expert panel recommends the immediate initiation of appropriate L-thyroxine supplementation and the frequent monitoring to ensure dose adjustments to keep
thyroid hormone levels in the target ranges, regular assessments of the need for treatment and
of developmental and neurosensory functions and consulting health professionals as needed,
as well as education of the child and family about CH. The harmonisation of diagnosis,
management and routine health surveillance should optimise patient outcomes. All
individuals with CH require continuous monitoring throughout their lives and a planned
transition of care from the pediatric to the adult system of care. This consensus statement on
CH should be used widely to detect and treat in an optimal way children affected by all forms
of the disease. It should help convince the health authorities of the benefit of neonatal
screening to avoid this treatable cause of mental retardation. Further epidemiological and
experimental studies should be implemented to understand the increased incidence of this
condition.
I. Pregnant women

- Positive family history for nonsyndromic CH
- Dyshormonogenesis (previously affected child) (1|+++)
- Dysgenesis (at least 1 member of the family) (2/+++)

- Positive family history of syndromic CH with:
  - Neurological disorders, including unexplained mental retardation
  - 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
  - Kidney malformations
  - Any sign of Albright hereditary osteodystrophy (GNAS mutation)

- Family history
  - Consanguinity
  - Kidney malformations
  - Deafness
  - Specific malformations (as listed above)
  - Unexplained mental retardation despite adequate treatment of CH in family members
  - Any sign of Albright hereditary osteodystrophy (GNAS mutation)
<table>
<thead>
<tr>
<th>Gene (OMIM)</th>
<th>Protein role</th>
<th>Typical thyroid phenotype</th>
<th>Mode of inheritance</th>
<th>Associated conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>NKX2-1 (600635)</td>
<td>Nuclear factor</td>
<td>Variable</td>
<td>AD</td>
<td>Respiratory distress, choreoathetosis, variable expressivity</td>
</tr>
<tr>
<td>FOXE1 (602617)</td>
<td>Nuclear factor</td>
<td>Athyreosis</td>
<td>AR</td>
<td>Cleft palate, choanal atresia, and spiky hair</td>
</tr>
<tr>
<td>PAX8 (1674145)</td>
<td>Nuclear factor</td>
<td>Variable</td>
<td>AD</td>
<td>Urinary tract defects, variable expressivity</td>
</tr>
<tr>
<td>NKX2-5 (600584)</td>
<td>Nuclear factor</td>
<td>Thyroid in situ, variable hypothyroidism</td>
<td>Unclear</td>
<td>Congenital heart malformations</td>
</tr>
<tr>
<td>GLIS3 (610192)</td>
<td>Nuclear factor</td>
<td>Variable</td>
<td>AR</td>
<td>Neonatal diabetes, polycystic kidneys, and cholestasis</td>
</tr>
<tr>
<td>JAG1 (601920)</td>
<td>Jagged 1: Notch receptor ligand</td>
<td>Variable orthotopic hypoplasia</td>
<td>AD</td>
<td>Heart malformations, variable expressivity</td>
</tr>
<tr>
<td>TBX1 (602054)</td>
<td>Nuclear factor</td>
<td>Thyroid in situ</td>
<td>AD</td>
<td>Di George syndrome with congenital heart malformations, variable expressivity</td>
</tr>
<tr>
<td>NTN1 (601614)</td>
<td>Laminin-related secreted protein</td>
<td>Thyroid ectopy</td>
<td>unknown</td>
<td>Arthrogryposis</td>
</tr>
<tr>
<td>CDCA8 (609977)</td>
<td>Cell Division Cycle Associated protein 8 or Borealin:</td>
<td>Thyroid ectopy</td>
<td>AR</td>
<td>None in sporadic cases</td>
</tr>
</tbody>
</table>
| TUBB1  
(612901) | component of the chromosomal passenger complex | member of the β-tubulin protein family | Thyroid dysgenesis | Variable | Formation of macroplatelets and hyperaggregation of human platelets |
<table>
<thead>
<tr>
<th>Gene (OMIM)</th>
<th>Protein role</th>
<th>Typical thyroid phenotype</th>
<th>Associated conditions and mode of inheritance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TSHR</strong> (603372)</td>
<td>GPCR</td>
<td>Complete or partial TSH resistance: apparent athyreosis → thyroid in situ and severe → mild hypothyroidism</td>
<td>Dominant or recessive inheritance</td>
</tr>
<tr>
<td><strong>GNAS</strong> (139320)</td>
<td>alpha subunit of the stimulatory guanine nucleotide-binding protein (G protein)</td>
<td>Partial TSH resistance, mild hypothyroidism</td>
<td>PseudoHypo Parathyroidism (PHP, multiple hormone resistances) of maternal inheritance, parental imprinting of gene locus</td>
</tr>
<tr>
<td><strong>SLC5A5</strong> (601843)</td>
<td>NIS: Sodium-Iodide symporter</td>
<td>Absent or low iodide uptake at scintiscan, variable hypothyroidism and goiter</td>
<td>Recessive inheritance</td>
</tr>
<tr>
<td><strong>SLC26A4/PDS</strong> (605646)</td>
<td>Pendrin: Anion transporter</td>
<td>Partial iodide organification defect, mild to moderate hypothyroidism, goiter</td>
<td>Pendred syndrome: sensorineural deafness with enlarged vestibular aqueduct (EVA), high serum Tg, predisposition to alkalosis, recessive inheritance</td>
</tr>
<tr>
<td><strong>DUOX1/DUOX2</strong> (606758/606759)</td>
<td>Dual oxydases: peroxide generating system</td>
<td>Partial or complete iodide organification defect, goiter, transient or permanent hypothyroidism of variable severity</td>
<td>High serum Tg, dominant or recessive inheritance</td>
</tr>
<tr>
<td>Gene</td>
<td>Description</td>
<td>Symptoms</td>
<td>Inheritance</td>
</tr>
<tr>
<td>-----------</td>
<td>------------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------------------------</td>
<td>---------------------------------</td>
</tr>
<tr>
<td><strong>DUOX2</strong></td>
<td>Dual Oxydase Associated protein: an endoplasmic reticulum chaperone protein</td>
<td>Partial or complete iodide organification defect, goiter, transient or permanent hypothyroidism of variable severity</td>
<td>High serum Tg, recessive inheritance</td>
</tr>
<tr>
<td><strong>TPO</strong></td>
<td>Thyroid peroxidase: iodide organification and thyronine coupling</td>
<td>Complete iodide organification defect, severe hypothyroidism, goiter</td>
<td>High serum Tg, recessive inheritance</td>
</tr>
<tr>
<td><strong>TG</strong></td>
<td>Thyroglobulin: glycoprotein precursor to the thyroid hormones</td>
<td>High iodide uptake, variable hypothyroidism, congenital or rapidly growing goiter</td>
<td>Low serum Tg, recessive inheritance</td>
</tr>
<tr>
<td><strong>IYD/DEHAL</strong></td>
<td>Dehalogenase providing iodide salvage in thyroid)</td>
<td>Conserved iodide uptake, negative perchlorate discharge test, goiter, variable hypothyroidism</td>
<td>High serum Tg and MIT/DIT concentrations in serum and urine, recessive inheritance (dominant inheritance of goiter with incomplete penetrance)</td>
</tr>
<tr>
<td><strong>SLC26A7</strong></td>
<td>Anion transporter</td>
<td>Goiter, variable hypothyroidism, conserved iodide uptake, partial defect at perchlorate discharge</td>
<td>High serum Tg, recessive inheritance</td>
</tr>
</tbody>
</table>
### TABLE 4. Genes associated with central CH and related phenotypes.

<table>
<thead>
<tr>
<th>Gene (OMIM*)</th>
<th>Protein function</th>
<th>Phenotype</th>
<th>Inheritance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TSHβ</strong> (188540)</td>
<td>Hormone subunit</td>
<td>Neonatal onset with low TSH, high αGSU and normal PRL serum levels, pituitary hyperplasia reversible on L-T4</td>
<td>AR</td>
</tr>
<tr>
<td><strong>TRHR</strong> (188545)</td>
<td>GPCR</td>
<td>Normal TSH and low PRL serum levels, blunted TSH/PRL responses to TRH, male index cases with growth retardation and overweight during childhood; one female proband with prolonged neonatal jaundice</td>
<td>AR</td>
</tr>
<tr>
<td><strong>TBL1X</strong> (300196)</td>
<td>Nuclear factor</td>
<td>Mild isolated central CH in males with normal TSH serum levels and normal response to TRH stimulation test; only 1 affected female carrier; associated hearing defects</td>
<td>X-linked</td>
</tr>
<tr>
<td><strong>IRS4</strong> (300904)</td>
<td>Nuclear factor</td>
<td>Mild isolated central CH in males with normal TSH serum levels, blunted TSH response to TRH</td>
<td>X-linked</td>
</tr>
<tr>
<td><strong>IGSF1</strong> (300137)</td>
<td>Plasma membrane protein of unresolved function</td>
<td>The most frequent cause of mild central CH with normal TSH serum levels and blunted response to TRH test; males are preferentially affected but low FT4 can be found also in female carriers, likely due to skewed X-chromosome inactivation; associated with low PRL levels, variable GH deficiency, transient mild hypocortisolism and metabolic syndrome; late adrenarche and delayed rise of testosterone in males, dissociated from testicular growth ending in post-pubertal macrorchidism</td>
<td>X-linked</td>
</tr>
<tr>
<td><strong>PROP1</strong> (601538)</td>
<td>Nuclear factor</td>
<td>Variable age of onset, combined with GH, PRL LH/FSH deficiencies and delayed ACTH defects, small to large pituitary volume</td>
<td>AR</td>
</tr>
<tr>
<td><strong>POU1F1</strong> (173110)</td>
<td>Nuclear factor</td>
<td>Variable age of onset, associated with GH and PRL deficiency, prominent forehead, midface hypoplasia, depressed nose</td>
<td>AR, AD</td>
</tr>
<tr>
<td>Gene</td>
<td>Type</td>
<td>Description</td>
<td>Phenotype</td>
</tr>
<tr>
<td>-------</td>
<td>---------------</td>
<td>-----------------------------------------------------------------------------</td>
<td>-------------------------------------------------------</td>
</tr>
<tr>
<td>HESX1</td>
<td>Nuclear factor</td>
<td>Hypopituitarism associated with septo-optic dysplasia</td>
<td>AR, AD</td>
</tr>
<tr>
<td>(601802)</td>
<td></td>
<td>Anterior-pituitary hypoplasia with ectopic posterior pituitary, persistent cranio-pharyngeal canal and learning difficulties</td>
<td>X-linked</td>
</tr>
<tr>
<td>SOX3</td>
<td>Nuclear factor</td>
<td>Anterior pituitary hypoplasia with ectopic posterior pituitary and ocular defects (ano-/micro-ophthalmia/retinal dystrophy)</td>
<td>AD</td>
</tr>
<tr>
<td>(313430)</td>
<td></td>
<td>Hypopituitarism with inconstant ACTH defect, small to large pituitary, short and rigid cervical spine and variable hearing defect</td>
<td>AR</td>
</tr>
<tr>
<td>OTX2</td>
<td>Nuclear factor</td>
<td>Variable hypopituitarism, anterior pituitary hypoplasia with ectopic posterior pituitary, Arnold-Chiari syndrome, hypoplasia of the corpus callosum</td>
<td>AR, AD</td>
</tr>
<tr>
<td>(600037)</td>
<td></td>
<td>Central CH with hyperphagia, obesity and combined with central hypogonadism</td>
<td>AR</td>
</tr>
<tr>
<td>LHX3</td>
<td>Nuclear factor</td>
<td>Variable hypopituitarism, pituitary hypoplasia, microphthalmia, variable learning difficulties</td>
<td>AD</td>
</tr>
<tr>
<td>(600577)</td>
<td></td>
<td>Variable hypopituitarism associated with septo-optic dysplasia or pituitary stalk interruption syndrome</td>
<td>AR, AD</td>
</tr>
<tr>
<td>LEPR</td>
<td>Cytokine receptor</td>
<td>Deficient Anterior pituitary with Variable Immune Deficiency (DAVID) syndrome associated with ACTH deficiency and variable GH and TSH defects</td>
<td>AD</td>
</tr>
<tr>
<td>(601007)</td>
<td></td>
<td>CHARGE syndrome (Coloboma, Heart anomaly, choanal Atresia, Retardation, Genital and Ear anomalies) with ectopic posterior pituitary and variable LH/FSH, TSH and GH defects</td>
<td>AD</td>
</tr>
<tr>
<td>PROKR2</td>
<td>GPCR</td>
<td>Kallmann’s syndrome (KS) and normosmic congenital hypogonadotropic hypogonadism (nCHH), variable association with defects of other pituitary hormones including TSH, septo-optic dysplasia and ectopic posterior pituitary</td>
<td>AD</td>
</tr>
<tr>
<td>(607123)</td>
<td></td>
<td>KS and nCHH, variable associations with defects of</td>
<td>AR</td>
</tr>
<tr>
<td>CHD7</td>
<td>ATP-depended helicase</td>
<td>Central CH with hyperphagia, obesity and combined with central hypogonadism</td>
<td>AR</td>
</tr>
<tr>
<td>(608892)</td>
<td></td>
<td>CHARGE syndrome (Coloboma, Heart anomaly, choanal Atresia, Retardation, Genital and Ear anomalies) with ectopic posterior pituitary and variable LH/FSH, TSH and GH defects</td>
<td>AD</td>
</tr>
<tr>
<td>FGFR1</td>
<td>Receptor tyrosine kinase</td>
<td>Deficient Anterior pituitary with Variable Immune Deficiency (DAVID) syndrome associated with ACTH deficiency and variable GH and TSH defects</td>
<td>AD</td>
</tr>
<tr>
<td>(136350)</td>
<td></td>
<td>Kallmann’s syndrome (KS) and normosmic congenital hypogonadotropic hypogonadism (nCHH), variable association with defects of other pituitary hormones including TSH, septo-optic dysplasia and ectopic posterior pituitary</td>
<td>AD</td>
</tr>
<tr>
<td>FGF8</td>
<td>Growth</td>
<td>KS and nCHH, variable associations with defects of</td>
<td>AR</td>
</tr>
<tr>
<td>(600483) factor</td>
<td>other pituitary hormones including TSH, holoprosencephaly and corpus callosum agenesis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FOXA2 (600288) Nuclear factor</td>
<td>Hypopituitarism with craniofacial and endoderm-derived organ abnormalities and hyperinsulinism AD</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AR= autosomal recessive; AD= autosomal dominant


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