

REVIEW

The diagnosis and management of central hypothyroidism in 2018

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Abstract

Central hypothyroidism (CeH) is a hypothyroid state caused by an insufficient stimulation by thyrotropin (TSH) of an otherwise normal thyroid gland. Several advancements, including the recent publication of expert guidelines for CeH diagnosis and management, have been made in recent years thus increasing the clinical awareness on this condition. Here, we reviewed the recent advancements and give expert opinions on critical issues. Indeed, CeH can be the consequence of various disorders affecting either the pituitary gland or the hypothalamus. Recent data enlarged the list of candidate genes for heritable CeH and a genetic origin may be the underlying cause for CeH discovered in pediatric or even adult patients without apparent pituitary lesions. This raises the doubt that the frequency of CeH may be underestimated. CeH is most frequently diagnosed as a consequence of the biochemical assessments in patients with hypothalamic/pituitary lesions. In contrast with primary hypothyroidism, low FT4 with low/normal TSH levels are the biochemical hallmark of CeH, and adequate thyroid hormone replacement leads to the suppression of residual TSH secretion. Thus, CeH often represents a clinical challenge because physicians cannot rely on the use of the 'reflex TSH strategy' for screening or therapy monitoring. Nevertheless, in contrast with general assumption, the finding of normal TSH levels may indicate thyroxine under-replacement in CeH patients. The clinical management of CeH is further complicated by the combination with multiple pituitary deficiencies, as the introduction of sex steroids or GH replacements may uncover latent forms of CeH or increase the thyroxine requirements.

Key Words

- ▶ thyroxine
- ▶ thyrotropin
- ▶ pituitary
- ▶ thyroid
- ▶ hormone replacement

Endocrine Connections
(2019) **8**, R44–R54

Introduction

Central hypothyroidism (CeH) is a rare and heterogeneous hypothyroid condition resulting from an insufficient stimulation of an otherwise normal thyroid gland by the hypophyseal thyrotropin hormone (TSH). This loss of central thyroid stimulation can result from a functional or an anatomical disorder of the hypothalamus and/or the pituitary, causing variable TSH secretion modifications (1, 2).

Epidemiology

CeH most frequently occurs as a sporadic form of hypothyroidism and can affect patients of all ages. There is no evidence of male gender prevalence despite the

recent finding of X-linked forms (3). CeH incidence was estimated to range from 1:16,000 to about 1:100,000 in different adult or neonatal populations hypothyroid patients (4, 5, 6, 7, 8). This variability in the CeH prevalence seems to be dependent upon several factors, such as the ethnicity and the differences in diagnostic strategy sensitivity. Indeed, the diagnostic strategy used by the Dutch national health system, based on the combined evaluation of total T4 (TT4), thyroxine-binding globulin and TSH (6), has proven to be more sensitive and to uncover milder forms of neonatal CeH that are not detected by the diagnostic strategy used in Japan and USA, based on the combination of low TT4 and

normal/low TSH (5, 7). Despite the possible association with life-threatening adrenal crisis in congenital multiple pituitary hormone deficiencies (MPHDs), CeH is not a direct cause of death. The addition of acquired forms of CeH on top of the incidence reported among Dutch newborns raises the suspicion that the prevalence of CeH in the general population is underestimated.

Pathogenesis

The pathogenic mechanisms underlying CeH are still undetermined in several cases although they variably involve both hypothalamic and pituitary cells. CeH can be either congenital or acquired. Congenital CeH is usually manifest in infancy, but has sometimes a delayed onset during childhood or adulthood. Genes causative for CeH can be divided into those leading to isolated form or to combined forms with an MPHD and are listed in Table 1. Nevertheless, more recently, other genes and syndromes have been variably associated with thyrotropin defects (see also Table 1).

On the other hand, the acquired forms of CeH are mainly related to expansive lesions of the hypothalamic/pituitary region, although head trauma, vascular accidents, autoimmunity, hemochromatosis or iron overload and several iatrogenic causes are also accountable for several CeH cases. Acquired CeH is definitely more common in the adulthood and is prevalently caused by macroadenomas of the pituitary and their treatments. Craniopharyngiomas represent the most prevalent expansive lesion associated with CeH in pediatric patients. The causes of acquired CeH are listed in Table 2 (see also comments in Fig. 1).

Altogether these pathological mechanisms can lead to CeH through variable mechanisms:

- impaired thyrotrope stimulation by the hypothalamic factors or modifications in the thyroid hormone feedback set-point (e.g. TRH resistance or *IGSF1* or *TBL1X* or *IRS4* mutations or hypothalamic lesions) (9, 10, 11, 12);
- reduced pituitary TSH reserve (e.g. *TSH β* mutations or a deficient number of thyrotrope cells or pituitary lesions causing the loss of the thyrotrope population);
- impaired intrinsic bioactivity of the secreted TSH molecules (13, 14, 15, 16, 17).

The three mechanisms are frequently coexisting as a consequence of the expansive lesions of the sella region (16, 17). The impaired bioactivity of circulating TSH has been prevalently demonstrated by *in vitro* bioassays (15),

but this phenomenon can also be supported *in vivo* by the impaired increment of circulating free T4 and/or T3 following the TSH response upon TRH stimulation test (18, 19).

Clinical presentation

CeH represents a challenging condition in clinical practice as it is characterized by suboptimal accuracy of clinical and biochemical parameters for diagnosis and management. Clinical presentation of CeH may vary depending on the cause. It is worth noting that the typical manifestations of severe congenital hypothyroidism are rarely present at birth in most of the CeH patients since the chorionic gonadotropin could be effective in stimulating the fetal thyroid, differently from a primary thyroid defect, and thyrotrope function is not completely defective in particular when the hypothalamic stimulation is principally affected. Mental retardation can be particularly severe in case of delay in the diagnosis of isolated congenital CeH associated with biallelic *TSH β* mutations, due to the false-negative results of the neonatal TSH screening for primary thyroid defects (3, 20, 21, 22, 23, 24, 25). However, when CeH diagnosis is reached in newborns, treatment should be given as soon as possible (Fig. 1).

Genetic CeH can more frequently be part of an MPHD and can be associated with growth retardation, delayed pubertal development and/or variable neurological defects that can be a direct effect of the genetic lesion (Table 1) (1, 26, 27, 28, 29). *IGSF1* followed by *PROPI* are the genes most frequently accounting for the inheritable forms of CeH. However, a progressive onset of the thyrotrope defect beyond the critical neonatal period can be not infrequently seen in several of these genetic CeH cases (3, 9, 28, 30). On the other hand, some peculiar clinical stigmata illustrated in Table 1 can suggest specific gene defects such as the macorchidism for *IGSF1* or hearing defects for *TBL1X* (10, 11, 31, 32).

Acquired forms of CeH are usually sporadic and in most cases due to large pituitary macroadenomas with a suprasellar extensions, craniopharyngiomas and suprasellar tumors, head trauma, vascular accident or cranial irradiation (1, 28, 33). In these cases, the tumor size might cause either a defective functionality of the neurohypophysis with an associated diabetes insipidus and/or a compression of the optic chiasm with a direct consequence in the quality of the visual field. Moreover, these lesions usually affect both pituitary

Table 1 Candidate genes for inherited CeH forms and related phenotypes.

Gene	OMIM	Inheritance	Phenotype
Isolated CeH			
<i>TSHβ</i>	188540	AR	Neonatal onset with low TSH, high aGSU and normal PRL circulating levels, pituitary hyperplasia reversible on L-T4
<i>TRHR</i>	188545	AR	Normal TSH and low PRL circulating levels, blunted TSH/PRL responses to TRH, male index cases with growth retardation and overweight during childhood; one female proband with prolonged neonatal jaundice
<i>TBL1X</i>	300196	X-linked	Mild isolated CeH in males with normal TSH circulating levels and normal response to TRH stimulation test (only 1 out of 11 female carriers have CeH); hearing defects
<i>IRS4</i>	300904	X-linked	Mild isolated CeH in males with normal TSH circulating levels, blunted TSH response to TRH
Multiple pituitary hormone deficiencies			
<i>IGSF1</i>	300137	X-linked	Mild CeH with normal TSH circulating levels and blunted response to TRH stimulation; males are preferentially affected but low FT4 can be found also in a minority of the 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
<i>PUO1F1</i>	173110	AR, AD	Variable age of onset, associated with GH and PRL deficiency, prominent forehead, midface hypoplasia, depressed nose
<i>PROP1</i>	601538	AR	Variable age of onset, combined with GH, PRL LH/FSH deficiencies and delayed ACTH defects, small to large pituitary volume
<i>HESX1</i>	601802	AR, AD	Hypopituitarism associated with septo-optic dysplasia
<i>SOX3</i>	313430	X-linked	Anterior pituitary hypoplasia with ectopic posterior pituitary, persistent cranio-pharyngeal canal and learning difficulties
<i>OTX2</i>	600037	AD	Anterior pituitary hypoplasia with ectopic posterior pituitary and ocular defects (ano-/micro-ophthalmia/retinal dystrophy)
<i>LHX3</i>	600577	AR	Hypopituitarism with inconstant ACTH defect, small to large pituitary, short and rigid cervical spine and variable hearing defect
<i>LHX4</i>	602146	AR, AD	Variable hypopituitarism, anterior pituitary hypoplasia with ectopic posterior pituitary, Arnold–Chiari syndrome, hypoplasia of the corpus callosum
<i>LEPR</i>	601007	AR	CeH with hyperphagia, obesity and combined with central hypogonadism
Genetic defects inconstantly associated with CeH			
<i>SOX2</i>	184429	AD	Variable hypopituitarism, pituitary hypoplasia, microphthalmia, variable learning difficulties
<i>NFKB2</i>	164012	AD	Deficient anterior pituitary with variable immune deficiency (DAVID) syndrome associated with ACTH deficiency and variable GH and TSH defects
<i>CHD7</i>	608892	AD	CHARGE syndrome (Coloboma, Heart anomaly, choanal Atresia, Retardation, Genital and Ear anomalies) with ectopic posterior pituitary and variable LH/FSH, TSH and GH defects
<i>FGFR1</i>	136350	AD	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
<i>FGF8</i>	600483	AR	KS and nCHH, variable associations with defects of other pituitary hormones including TSH, holoprosencephaly and corpus callosum agenesis
<i>FOXA2</i>	600288	AD	Hypopituitarism with craniofacial and endoderm-derived organ abnormalities and hyperinsulinism
<i>PROKR2</i>	607123	AR, AD	Variable hypopituitarism associated with septo-optic dysplasia or pituitary stalk interruption syndrome

AD, autosomal dominant; AR, autosomal recessive; OMIM, online mendelian inheritance in men (<https://www.ncbi.nlm.nih.gov/omim/>).

and hypothalamus function with a resulting MPHDS clinical picture and hyperprolactinemia secondary to the pituitary stalk resection or compression. Thus, signs and symptoms due to this MHPD condition, such as menstrual disorders, decreased libido, hair loss, galactorrhea, pallor, altered lipid metabolism, visual defect,

headache and others might overlap and cover the specific manifestations due to the hypothyroidism. All these manifestations can severely compromise the performance and wellbeing of the patients and generate negative effects on various tissues. Therefore, evaluation for CeH should always be included among the hormone

Table 2 Causes of acquired CeH forms.

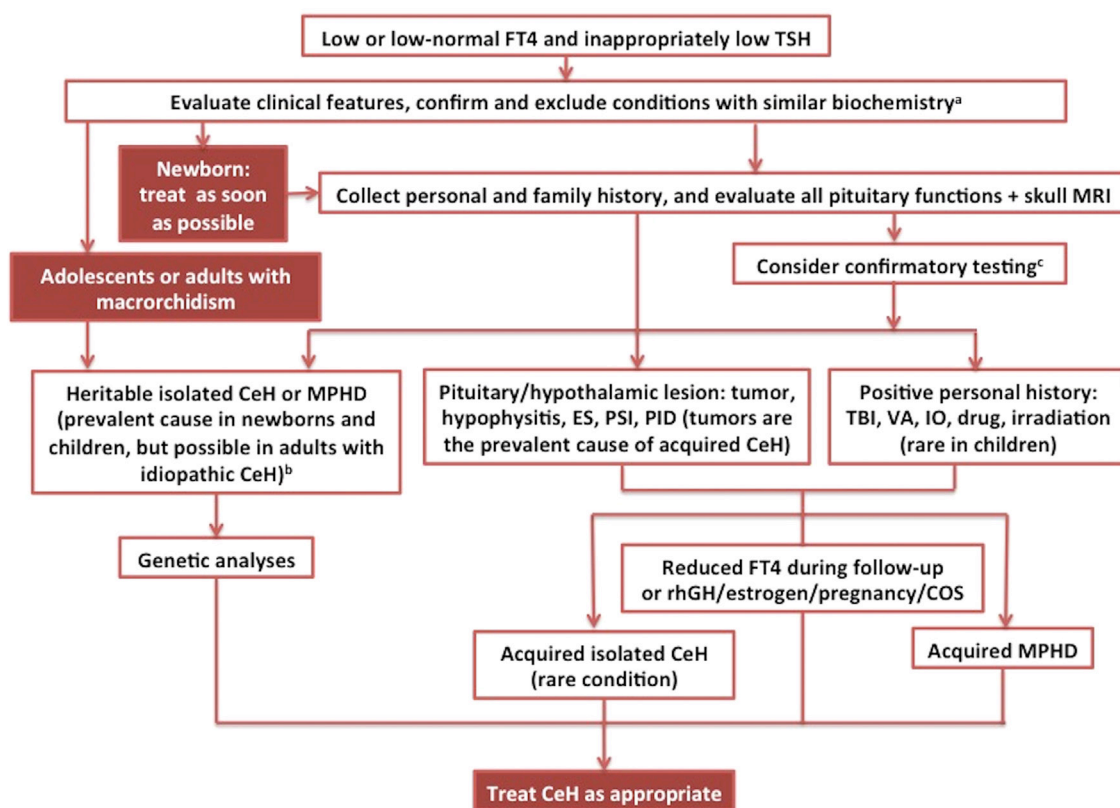
Invasive and/or compressive lesion of the sella turcica region	Pituitary macroadenomas Craniopharyngiomas Meningiomas and gliomas Rathke cleft cysts Metastatic seeding Carotid aneurysm
Iatrogenic causes	Cranial surgery or irradiation Drugs (e.g., rexinoids or mitotane)
Injuries	Head trauma Traumatic delivery
Vascular accidents	Pituitary infarction Sheehan syndrome Subarachnoid hemorrhage
Autoimmune disease	Lymphocytic hypophysitis (including the forms induced in post-partum or during therapy with check-point inhibitors)
Infiltrative lesions	Iron overload Sarcoidosis Histiocytosis X
Infective diseases	Tuberculosis Mycoses Syphilis

determinations of the patients with diseases of the hypothalamic–pituitary region (34).

Diagnosis

The diagnosis of CeH can be reached by three different means:

- clinical manifestations (hypothyroid symptoms) – this is a rare event; a typical example is the poor growth associated with jaundice and muscle hypotonia in infants with congenital CeH;
- biochemical findings (low, or even low–normal, free T4 with inappropriately low/normal TSH) – this is the most frequent case possibly occurring at birth because of a positive neonatal screening or during the biochemical workup of patients with known lesions of the hypothalamic–pituitary region or during their follow-up;



^a Confirm low or low-normal FT4 and inappropriately low TSH, and exclude conditions reported in Table 3

^b see Table 1 for details; ^c see text for details

Figure 1

Flowchart for the diagnosis of CeH. CeH, central hypothyroidism; COS, controlled ovarian stimulation; ES, empty sella; IO, iron overload or hemochromatosis; MPHD, multiple pituitary hormone defect; MRI, magnetic resonance imaging; PID, pituitary stalk interruption; rhGH, recombinant human growth hormone; TBI, traumatic brain injury; VA, vascular accident.

- c. genetic investigations following one proband diagnosis – several patients diagnosed with isolated mild CeH in adulthood do not have the perception of being hypothyroid and only the treatment experience can uncover the beneficial effects of thyroid replacement on their wellbeing. The experience with CeH patients diagnosed by genetic testing tells us that gene defects can be a likely cause for mild idiopathic CeH discovered during adolescence or adulthood following an incidental biochemical finding of low free T₄ (FT₄).

However, diagnostic and clinical management of CeH is still nowadays a challenging condition due to the lack of accurate clinical and biochemical parameters. Very recently, a group of pediatric and adult endocrinologists have produced the 2018 Guidelines European Thyroid Association on the diagnosis and management of CeH (35). In their recommendations, experts agreed that diagnosis of overt CeH should be considered in every subject with low serum concentrations of FT₄, measured by reliable immunoassay and low or normal immunoreactive TSH concentration, confirmed on two independent determination (35). A schematic illustration of the diagnostic workup for CeH based on the ETA guidelines is reported in Fig. 1.

Indeed, evidences in a series of CeH patients clearly established that diagnosis of this condition cannot be achieved by the single measurement of TSH. In this respect, the missed diagnosis of CeH represents the most important false-negative result of the ‘reflex TSH’ strategy that is frequently applied for the screening of thyroid function either in newborns or in adults (1, 36). Therefore, the FT₄ determination, more than the TT₄, which is influenced by the serum-binding protein variation (37, 38) or the FT₃, which might be low in some nonthyroidal illness or deiodinase defect rather than in CeH, represents the parameter with the highest diagnostic sensitivity and specificity in this hormone defect (1, 39, 40, 41, 42). As an additional complication, one should remember that slight elevations of serum TSH concentrations can also be found in some CeH patients with a predominant hypothalamic defect. In this subgroup of patients, TSH levels are superimposable to those generally found in subclinical or mild primary hypothyroidism, although the molecule is devoid of full biological activity and the FT₄ is already in the hypothyroid range (13, 14, 16, 17). Conditions that can lead to low/normal TSH and low FT₄ levels listed in Table 3 should also be ruled out in a correct differential diagnosis. Moreover, the presence of a possible interference in FT₄ or TSH measurement should

Table 3 Conditions associated with low/normal TSH and/or low, or even low-normal, free FT₄ levels that could lead to erroneous CeH diagnosis or to transient CeH.

Severe form of nonthyroidal illness or sick euthyroid syndrome
Drugs inhibiting TSH secretion: (a) glucocorticoids; (b) dopamine; (c) cocaine; (d) anti-epileptics; (e) anti-psychotics; (f) metformin
Thyrotoxicosis-related conditions: Levothyroxine withdrawal syndrome, prolonged TSH suppression after recovery from thyrotoxicosis
Pregnancy related conditions: (a) Isolated maternal hypothyroxinemia (to be interpreted in the context of trimester-specific FT ₄ reference ranges for pregnant women). (b) Premature birth (delayed TSH rise in hypothyroid infants)
Genetic conditions: (a) Allen-Herndon-Dudley syndrome (<i>MCT8</i> gene pathogenic allelic variants); (b) RTH α due to <i>THRA</i> heterozygous mutations; (c) <i>TSHβ</i> allelic variants with conserved bioactivity but lost immunoreactivity of circulating TSH

also be considered and excluded (1, 37, 38). Indeed, the FT₄ absolute value is related to the assay applied. Although the equilibrium dialysis is the most accurate method for the determination of the FT₄ levels, this is not compatible with the routine lab work out, and the automated FT₄ assays are commonly used (38). Among these immunoassays, the so-called ‘one-step’ assays are surely less reliable than the ‘two-step’ methods. In these latter methods, an immunoextraction (back-titration) allows the removal of the interfering factors of the serum (e.g., T₄/T₃-binding auto-antibodies or abnormal-binding proteins). In case of a suspected FT₄ assay interference, a ‘two-step’ method or a mass spectrometry should be considered to solve the question. Heterophile antibodies, such as anti-animal antibodies, which might be present in the patient sera, can interfere TSH measurements by immunometric assays, when they are directed against the same species as the assay antibodies. In particular, a heterophile antibody able to block the TSH binding to either capture or detection antibodies will lead to a negative immunoassay interference and a falsely low TSH level determination. This might cause the misdiagnosis of a primary hypothyroidism as a CeH. Due to the frequency of heterophile antibodies, most of the commercial TSH assays contain the pre-immune serum from the source animal in the reagents. Another cause of interference may be represented by the ‘macro-TSH’, which may lead to falsely elevated TSH concentrations. In this case, CeH patients might be interpreted as being affected by primary hypothyroidism. In the real life, a good advise to render less likely a suspected interference is the use of

alternative immunoassays including different antibody pairs or the measurement of TSH levels after removal of the interfering immunoglobulins by treating the serum with polyethylene glycol or protein G or by dilution and recovery test (1, 38).

Beyond interference, the conditions that can give rise to biochemical results similar to those found in CeH include different groups of conditions listed in Table 3 (see also Fig. 1). In a hospital setting or in the elderly the non-thyroidal illnesses or euthyroid sick syndrome are the most frequent possibility and they are obviously hallmarked by a prevalent and often isolated fall of T3 or free T3 (FT3) levels and by the concomitance of severe or chronic disease states.

Treatments with drugs able to inhibit the TSH secretion or the recovery from a thyrotoxic state can sometimes be confused with a CeH. A careful collection of the personal history, the repetition of the biochemical examination and exclusion of an underlying primary thyroid disease are key to uncover such possibilities. Gestational hypothyroxinemia can come into differential diagnosis with CeH, but this risk may be greatly reduced by the definition of trimester-specific FT4 reference levels. The delayed TSH rise in premature babies can be associated with a transient CeH that is generally of short duration and does not require treatment in most cases. Furthermore, patients with rare inheritable defects of thyroid hormone action can have low FT4 and normal or slightly elevated TSH. However, patients affected with MCT8 or THRA mutations leading to Allan–Herndon–Dudley syndrome or resistance to thyroid hormone α (RTH α) have distinct and typical clinical features and T3 levels at the upper limit of normal range (43). A peculiar confounding condition may be represented by *TSH β* allelic variants with conserved bioactivity but lost immunoreactivity of circulating TSH (44). This condition should be suspected when undetectable or low TSH is repeatedly associated with clearly normal and stable thyroid hormone levels and confirmed by an absent TSH rise after TRH stimulation.

In familial, congenital or syndromic CeH cases, genetic analyses should be accomplished (35). The discovery of pathogenic variant(s) in one candidate gene can lead to uncover possible carriers and early diagnosis in the affected families and support the CeH diagnosis in uncertain cases, including those with a delayed evidence or onset of the biochemical abnormalities without an apparent cause. Genetic analysis can be done either with an automated direct sequencing of specific genes, following a phenotype-driven approach or by using a

targeted next-generation sequencing technique and thus running in the same time a panel of multiple candidate genes (3, 35).

A still controversial issue is the diagnosis of the hidden or mild forms of CeH usually characterized by FT4 in the lower part of the normal range. Studies performed in patients with primary thyroid disease indicate that replacement therapy of mild or subclinical hypothyroidism may improve the wellbeing and physical or mental performances or prevent cardiovascular morbidities. The same should be true also for mild/hidden forms of CeH, but the lack of a sufficiently sensitive parameter hampers their recognition. In patients at risk, such as those on follow-up for hypothalamic/pituitary lesions or brain cancer survivors, or the carriers of pathogenic variants in novel candidate genes, the diagnosis of CeH can be supported by several investigations or findings (35).

These tests include:

- abnormal TSH response to TRH stimulation (17, 45, 46, 47, 48, 49, 50);
- blunted nocturnal TSH rise (47);
- impaired circulating TSH bioactivity (15, 16, 18, 51);
- low TSH index (52);
- progressive decrease of FT4 in patients on follow-up (>20% of the initial value) (1, 35, 41);
- abnormal findings of parameters of thyroid hormone action (41, 42, 53).

The interpretation of these tests may be controversial and their application depends upon the resources and availability in the different clinical and laboratory settings (1, 35) (Fig. 1).

Therapeutical management

The first-line treatment of central hypothyroidism remains the replacement therapy using levothyroxine (L-T4) (35). Treatment is recommended in all patients receiving the diagnosis once a concomitant cortisol deficit has been excluded. In those presenting adrenal insufficiency or when its presence cannot be excluded, L-T4 supplementation should follow an adequate treatment with glucocorticoid in order to prevent the induction of an adrenal crisis. On the contrary, thyroid hormones enhance GH sensitivity and rise both IGF1 levels and ALS, thus also increasing GH metabolic effect during therapies (54) and allowing a correct evaluation of the somatotrope function.

In adult patients with central diseases, it is recommended to tailor the replacement L-T4 therapy according to the weight and the age of each patient (35). In patients older than 60 years of age and in those with cardiovascular comorbidities, the starting dose should be ranging 1.0–1.2 µg/kg/day. Furthermore, treatment of milder CeH forms (FT4 values within the lower limit of normal range) can be avoided in subjects older than 75 years, as suggested by findings indicating a protective effect of mild or subclinical primary hypothyroidism on cardiovascular mortality risk in the elderly (55). Moreover, in elderly patients, as well as in those with long standing disease and higher cardiovascular risk, the ETA task force advised to start with lower doses of L-T4 and then gradually uptitrate the dosage in subsequent weeks or months (35). It is important to evaluate the adequacy of the replacement after 6–8 weeks measuring FT4 and targeting this parameter above the median values of the reference range. During LT4 replacement, the concomitant determination of TSH is useless in CeH patients with low levels at diagnosis, whereas the lack of TSH secretion suppression in CeH patients with normal TSH concentrations at diagnosis may indicate under replacement. Indeed, all these considerations are valid only if the hormonal examinations are performed before or at least 4 h after the daily intake of LT4 and are carried out in the same laboratory (1, 35).

Once the therapy has been judged adequate, it should be reevaluated annually measuring serum FT4. Measurement of TSH and T3 could be useful only to exclude the suspect of undertreatment and overtreatment, respectively. An insufficient replacement therapy should be suspected whenever FT4 concentrations are found below or at the lower limit of the normal range, especially when manifestations of hypothyroidism are present or TSH is still within the normal range. In contrast, an excessive LT4 intake should be considered whenever FT4 concentrations are above or at the upper limit of the normal range, in particular when clinical manifestations of thyrotoxicosis and/or high FT3 levels are present (1, 35).

Moreover, an adjustment in levothyroxine dosage may be required in many conditions (listed in Table 4) and FT4 and TSH should be reassessed 4–6 weeks after any change of the regimen.

Since the thyroid hormone levels are higher during childhood, higher doses of LT4 are required in children (56). In severe congenital CeH, it is mandatory to quickly reach adequate serum FT4 concentrations, and L-T4 treatment should be initiated within 2 weeks from birth

Table 4 Conditions requiring a reevaluation and possible adjustment of the replacement therapy.

Conditions at risk of an uptitration of L-T4 therapy
Delay in psychomotor and cognitive development in infants and children
Introduction of GH replacement therapy
Introduction of estrogen replacement therapy or oral contraceptive
Pubertal development
Controlled ovarian stimulation
Pregnancy
Weight gain
Introduction of therapies affecting levothyroxine metabolism or absorption
Conditions at risk of a downtitration of L-T4 therapy
Cardiovascular comorbidities
Delivery
Menopause
Weight loss
Discontinuation of GH or estrogen therapies or treatments affecting levothyroxine metabolism or absorption

at the daily doses commonly used for primary congenital hypothyroidism (10–12 µg/kg/day) (35). In milder congenital forms, the starting doses of the replacement therapy could be lower (L-T4 5–10 µg/kg/day) to avoid an overtreatment and the same holds for diagnoses reached during childhood and adolescence (3.0–5.0 or 2.0–2.4 µg/kg/day, respectively). Once the replacement therapy is started, pediatric patients should be monitored in order to maintain FT4 levels in the reference ranges for age, and their follow-up should be similar to what is done for primary hypothyroidism. In CeH children, LT4 therapy was accompanied by an acceleration of growth velocity thus allowing the attainment of target height (9, 30, 47). A gradual downtitration is obviously required in transition to adulthood (57).

Finally, during pregnancy, it is recommended to increase the hormonal supplementation by 20–50% of the initial dose and to maintain the FT4 levels in the upper quartile of the reference range to compensate the expanding extracellular T4 pool and avoid hypothyroidism in the fetus (58).

Unlike the treatment of primary hypothyroidism, in which TSH is an excellent marker of an adequate replacement, the CeH management is more complex. Even low doses of L-T4 are able to suppress TSH secretion (42, 59). In a comparison between patients with adequately treated primary thyroid disease and other patients presenting hypothalamic–pituitary lesions performed by Koulouri *et al.* in 2011, it was shown that FT4 levels were significantly lower in central hypothyroidism, suggesting a frequent undertreatment (39). Indeed, in acquired

forms of CeH as those following surgery or radiotherapy for pituitary lesions or the start of treatments with an intrinsic risk of CeH, it could prove useful to assess FT4 concentrations before the intervention and LT4 replacement could eventually be targeted to reach prior FT4 levels, but this is impossible in all the other forms of CeH.

The evaluation of biochemical indexes of thyroid hormone metabolism and action at the tissue level, such as SHBG, bone GLA protein for thyrotoxicosis or cholesterol for undertreatment, could sometimes be useful but are too frequently interfered by other hormonal alterations.

Importantly, in MPHDS other major confounders must be taken into account. Both estrogens and GH influence thyroid hormone transport and/or metabolism and consequently interfere CeH management (33, 60). Sex steroid and GH deficiencies can mask an underlying CeH while the introduction of these replacement therapies often requires an uptitration of L-T4; particular attention should also be given to the ovarian stimulation for assisted reproduction procedures because of the associated estrogen rise (61). Controversial is instead the potential influence of glucocorticoid replacement in uncovering a hidden CeH (62). According to these evidences, particular attention should be given to patients with MPHDS whenever new replacement therapies are added or modified.

Other treatments potentially leading to CeH include mitotane, which decreases viability of thyrotrope cells, and the rexinoids (e.g. bexarotene), directly repressing *TSH β* expression, as well as novel biological drugs inducing hypophysitis such as ipilimumab or other checkpoint inhibitors (63). Therefore, TSH and FT4 should be checked before and repeatedly during these treatments. At variance, dopamine agonists and somatostatin analogs exert milder and transient inhibition on thyrotropes.

Interestingly, a prospective study (64), performed on a small number of patients, uncovered a negative metabolic effect of an insufficient treatment of CeH, by evaluating lipid profile and the body fat mass by DEXA scan. These data, besides supporting the necessity of an adequate therapy maintaining FT4 values in the upper range of normality, suggest a negative effect even in the hidden forms of CeH, often undiagnosed.

Whenever there is an insufficient increment of serum FT4 or its decrement during treatment with a given dose of L-T4, malabsorption should be suspected (65).

As for the use of a combined therapy with L-T4 and L-T3 in CeH, it raises the same issues discussed for primary disease. In fact, there is no evidence from the many studies

performed both in adults and in children to support a superiority of this treatment over the sole levothyroxine (66, 67, 68). However, it has been demonstrated in the Watts study that patients having a particular polymorphism in *DIO₂*, Thr92Ala, the combined L-T4 and L-T3 therapy leads to a more favorable clinical outcome (69). This suggests that the subjects presenting particular SNPs in genes important for the peripheral regulation of hormones activity (such as deiodinases and thyroid hormone transporters) could benefit from the combined therapy with triiodothyronine according to their genetic background (70). Actually, the above mentioned studies, which failed to find any difference between the two approaches, could lack the power to underline such changes, since the *DIO₂* polymorphism is relatively infrequent (71). In particular, the combined therapy should be considered in patients lamenting symptoms despite an adequate supplementation with L-T4 alone, following the ETA guidelines (67). However, the lack of a highly reliable parameter to check overtreatment as TSH in primary disease, the combined L-T4/L-T3 replacement may be at a higher risk of thyrotoxicosis in CeH (68).

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

Funding

This work was partially funded by the Ricerca Corrente funds of the Istituto Auxologico Italiano IRCCS, Milan, Italy (code: 05C303_2013).

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Received in final form 10 January 2019

Accepted 15 January 2019

Accepted Preprint published online 15 January 2019