Central Hypothyroidism

9

Luca Persani and Marco Bonomi

9.1 Definition and Epidemiology

Central hypothyroidism (CeH) is a disease characterized by a defective thyroid hormone production originating from an insufficient stimulation of an otherwise normal thyroid gland. This condition is the consequence of anatomic or functional disorders of the pituitary gland or the hypothalamus causing a defective TSH secretion [1, 2].

Though an isolated failure of thyrotrope cells is possible, the TSH defect is more frequently part of *combined pituitary hormone deficiencies* (CPHDs), which indeed complicate both diagnosis and clinical management of CeH. Diagnosis is usually made biochemically with low circulating free T4 (FT4) concentrations associated with low/normal serum TSH levels. Therefore, CeH represents the major false-negative result of the "reflex TSH strategy," a worldwide diffuse method to screen thyroid function by the first-line TSH test [3]. CeH can affect patients of all ages and severely affect their quality of life. Therefore, the existence of mild forms of CeH should always be suspected in patients with *hypothalamic-pituitary disorders* or in those with suggestive clinical manifestations after the exclusion of a primary thyroid disease.

CeH most frequently occurs as a sporadic form of hypothyroidism, and differently from primary hypothyroidism, there is no female prevalence. It apparently accounts for about 1 out of 1,000 hypothyroid patients as its prevalence was estimated to range from 1:16,000 to about 1:100,000 in the general adult or neonatal populations [3–5]. Such variable prevalence is probably depending upon several factors, including ethnicity and diagnostic strategies.

L. Persani, MD, PhD (✉) • M. Bonomi
Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy

Division of Endocrine and Metabolic Diseases, San Luca Hospital, IRCCS Istituto Auxologico Italiano, Piazzale Brescia 20, Milan 20149, Italy
e-mail: luca.persani@unimi.it

G. Bona et al. (eds.), *Thyroid Diseases in Childhood: Recent Advances from Basic Science to Clinical Practice*, DOI 10.1007/978-3-319-19213-0_9

Table 9.1 Known causes of central hypothyroidism (CeH) in children

Main causes	
Inheritable defects	CPHDs Pituitary transcription factor defects *LEPR* or *PROKR2* mutations Isolated CH *TSHβ*, *TRHR* or *IGSF1* mutations
Invasive or compressive lesions	Craniopharyngiomas Pituitary macroadenomas Meningiomas or gliomas Rathke cleft cysts Empty sella
Iatrogenic causes	Cranial surgery or irradiation Drugs (anti-cancer treatments, RXR agonists, dopamine)
Injuries	Head traumas Traumatic delivery
Unusual causes	
Vascular accidents	Pituitary infarction Subarachnoid haemorrhage
Autoimmune diseases	Lymphocytic hypophysitis Polyglandular autoimmune diseases
Infiltrative lesions	Iron overload Sarcoidosis or Histiocytosis X
Infective diseases	Tuberculosis or Mycoses

The mechanisms underlying CeH pathogenesis variably involve both hypothalamic and pituitary cells but are still undetermined in several cases. The major causes of CeH are listed in Table 9.1.

9.2 CeH Diagnosis in Children

9.2.1 Inheritable CeH Forms

The various genes so far linked to CeH are illustrated in Fig. 9.1.

In the neonates, CeH can be identified only by screening programs based on concomitant TSH and total T4 measurements in the dry blood spot [4–8]. CeH confirmation by serum FT4 and abnormal TSH response to TRH testing may reveal the risk of CPHDs and impending adrenal crisis [8]. CPHDs represent the more frequent forms of neonatal CeH. They can be the consequence of mutations in genes encoding for various *pituitary transcription factors*, such as *PROP1*, *POU1F1* (or PIT1), *HESX1*, *LHX3,* or *LHX4*, or for hormone receptors relevant for several hypothalamic functions, such as *LEPR* or *PROKR2* [1, 2, 9, 10]. In pituitary transcription factor defects, CeH can also have a delayed onset and be associated with hypoglycemia, craniofacial or pituitary abnormalities, and severity of growth retardation [1, 2, 9, 10]. The complex phenotypes associated with these defects are summarized in Table 9.2.

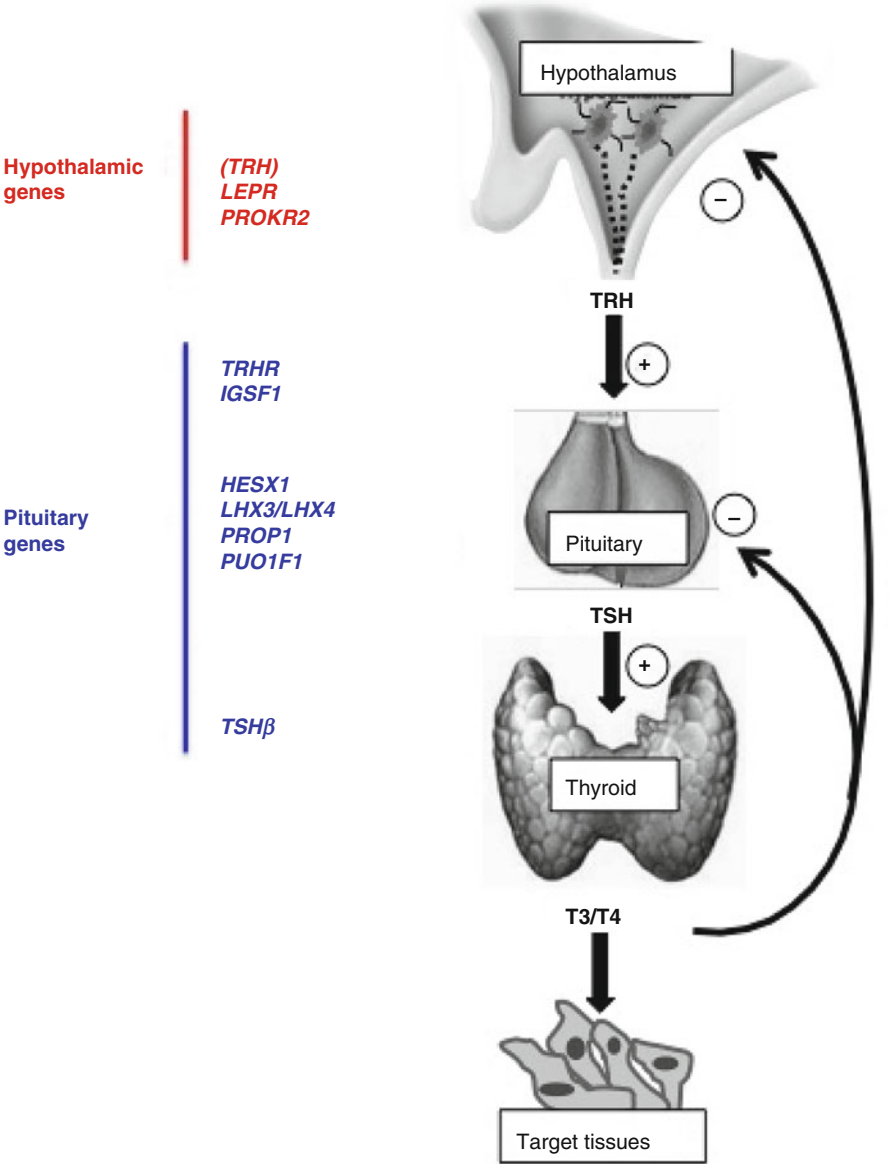

Fig. 9.1 Schematic illustration of the hypothalamic and pituitary genes so far associated with the pathogenesis of CeH. Though the involvement of TRH gene seems obvious, no variants have been so far detected in humans with CeH

Inheritable forms of CeH due to biallelic *TSHβ mutations* are frequently associated with severe neonatal onset and characterized by the typical manifestations of congenital hypothyroidism (macroglossia, coarse cry, jaundice, failure to thrive and retarded growth, umbilical hernia, hypotonia, etc.). If untreated with l-thyroxine

Table 9.2 Phenotypes associated with the inheritable forms of CeH

Genes (OMIM *gene number)	Associated phenotype and transmission (OMIM #disease number)
TSHβ (*188540)	Recessively inherited severe isolated CeH of neonatal onset with high α-GSU, pituitary hyperplasia (#275100)
TRH-R (*188545)	Recessively inherited isolated CeH with blunted TSH/PRL response to TRH and apparently uneventful infantile development, and with childhood (growth retardation) to adulthood onset
IGSF1 (*300137)	X-linked CeH associated with low PRL, variable partial GH deficiency, and macrorchidism
POU1F1 (*173110)	Moderate/severe CeH (dominant or recessive inheritance) of neonatal to infantile onset combined with GH and PRL defects, prominent forehead, mid face hypoplasia, depressed nose (#613038)
PROP1 (*601538)	Recessively inherited moderate/severe CeH of neonatal to infantile onset, combined with GH, PRL, LH/FSH defects, and delayed ACTH deficiency, pituitary hypo-/hyperplasia (#262600)
HESX1 (*601802)	Dominantly or recessively inherited panhypopituitarism associated with septo-optical dysplasia (SOD), supernumerary/hypoplastic digits (#182230)
LHX3 (*600577)	Recessively inherited hypopituitarism with conserved ACTH function and associated with pituitary hypo- or hyperplasia, short/rigid cervical spine and variable deafness (#221750)
LHX4 (*602146)	Dominantly inherited CPHD associated with abnormalities of cerebellum and small sella turcica (#262700)
PROKR2 (*607123)	Variable CPHD associated with SOD or pituitary stalk interruption (SIP) (variable inheritance)
LEPR (*601007)	Recessively inherited severe obesity and hyperphagia combined with delayed puberty and mild thyrotropin defect

within 6 weeks of life, these patients generally develop cretinism [1, 6, 11, 12]. The association of CeH with high α-GSU levels in an infant is invariably indicative of a TSHβ defect [11].

The TRH knockout mice have a typical CeH phenotype [6], but no *TRH* gene defect has been documented so far in humans. However, a defective TRH action due to natural mutations in the *TRHR* gene has been so far described in two families [13, 14]. We reported a family with a complete TRH receptor defect caused by an early stop codon potentially leading to the translation of a truncated protein lacking all the seven transmembrane and intracellular domains [14]. The probands of this family represent a natural *TRHR* knockout model: a unique opportunity to understand the role of *TRHR* in humans. The early development of patients with *complete TRH resistance* appeared uneventful. The diagnosis in the male proband with homozygous TRHR mutations was reached because of delayed growth accompanied by

fatigue at 11 years of age. The presence of this defect can be suggested by the blunted responses of TSH and PRL to TRH stimulation [13, 14] (Table 9.2). Unexpectedly, the same diagnosis was reached in the 33-year-old sister by genetic testing, during her second pregnancy. This woman with complete TRH resistance had reached her target height and normal IQ and has presently delivered three heterozygous babies with normal pre- and postnatal growth. In none of these cases, she experienced any lactating defect. Interestingly, when a hypothyroid questionnaire was administered to this woman before the start of l-thyroxine during the second gestation, she responded positively to only 1 question out of 12. Nevertheless, when the therapy was withdrawn for 6 weeks during her puerperium, the number of positive responses rose up to 10/12, thus indicating that thyroid hormone replacement had certain subjective beneficial effects that were unexpected a priori. Therefore, this study showed that the hypothalamic hormone is required to set the *pituitary feedback mechanism* at a level adequate to maintain free thyroxine levels in the normal range. In addition, the conservation of a significant *nocturnal TSH surge* in this condition indicates that TRH action influences the amplitude, but additional sleep-related factors account for the determination of the circadian oscillation. Interestingly, though *TRH* is also expressed in the pancreatic islets, we could not demonstrate any defect of glucose homeostasis in these patients [14].

Very recently, several familial cases of *X-linked* CeH from the Netherlands, the UK, and Italy have been reported to be associated with genetic defects in *IGSF1* [15, 16]. This gene encodes a membrane protein containing immunoglobulin-like motifs but of still unclear biological functions that is expressed in the pituitary and testes. IGSF1 defects are associated with a novel syndrome including CeH and *macroorchidism* and seldom GH deficiency. CeH in these cases is associated with blunted TSH and PRL responses to TRH testing consistent with the finding of a reduced Trh-r expression in the pituitaries of IGSF1 knockout mice. Accordingly, IGSF1 transcripts were found in Pit1-dependent lineages (thyrotrope, lactotrope, and somatotrope). Igsf1-deficient male mice show low pituitary and serum TSH concentrations, decreased thyroxine and triiodothyronine concentrations, and increased body mass [15].

9.2.2 Acquired CeH Forms

The hypothyroid state is mild to moderate in most patients with acquired CeH, as the pituitary TSH reserve is infrequently depleted. Although manifestations of CeH are similar to those of primary hypothyroidism, they can be masked by symptoms of CPHDs [1, 2]. CeH represents a major false-negative result of the "*reflex TSH strategy*" for the diagnosis of thyroid dysfunction [1, 5–7]. Therefore, acquired CeH should be suspected in all subjects with known hypothalamic/pituitary lesions (e.g., *craniopharyngiomas*, pituitary macroadenomas) or in those with clinical and biochemical manifestations (e.g., growth retardation, fatigue, cholesterol elevation) suggestive of hypothyroidism despite normal/low circulating TSH. On serum samples, the diagnosis of CeH is usually suggested by the finding of low FT4

Table 9.3 Conditions that can be associated with diminished FT4 serum levels and aberrantly low/normal TSH

Central hypothyroidism (hypothalamic hypothyroidism may seldom be associated with TSH values above the upper normal limit)
Severe non-thyroidal illness (e.g., anorexia)
L-T4 withdrawal syndrome
Recovery from thyrotoxicosis
Drugs inhibiting TSH secretion
Allan-Herndon-Dudley syndrome (MCT8 mutations)
TRα1 mutations

concentrations, associated with low/normal TSH levels [1, 2, 17, 18]. Nevertheless, some CeH patients with a predominant hypothalamic defect have high serum immunoreactive TSH levels but devoid of full biological activity. In these cases, TSH elevations are similar to those generally found in subclinical or mild primary hypothyroidism and may lead to the misdiagnosis [1, 2]. In Table 9.3, the conditions associated with low/normal TSH and low FT4 levels and that could come into differential diagnosis with CeH are listed.

When a low FT4 is combined with a normal TSH value, the diagnostic workup for the confirmation of CeH should include the exclusion of interference in FT4 or TSH measurements [1, 2]. In general, automated FT4 assays are less reliable than the equilibrium dialysis, which is however not compatible with the routine work. If interference is suspected, this should be explored by using a "two-step" assay or by mass spectrometry. If the problem persists, hormone measurement following equilibrium dialysis remains the gold standard for eliminating FT4 assay interference. Less frequently, TSH immunometric measurement can be interfered by the presence of heterophile antibodies in a patient's serum, if directed against the same species as the assay antibodies: thus, a heterophile antibody that blocks TSH binding to either capture or detection antibodies will cause a falsely low TSH readout potentially indicating a central instead of a primary hypothyroidism. Though most of the manufacturers are nowadays providing reagents including the preimmune serum from the source animal, heterophile antibodies may still interfere in the TSH determination on some instances. If interference is suspected, the discordant TSH concentration should be checked (a) by means of an immunoassay using a different antibody pair, (b) after immunosubtraction by treatment with polyethylene glycol (PEG) or protein G, or (c) by dilution or recovery tests [1, 2].

Once the interference is excluded, the finding of "low FT4" combined with an abnormally "low TSH" outlines the diagnosis of overt forms of CeH, but the diagnosis of milder defects, characterized by FT4 levels still within the normal range, remains unsolved. An indication on how these cases can be disclosed comes from studies on children surviving cancer disease [19–21]. Cranial irradiation can indeed cause hypothalamic defects with TRH secretory abnormalities resulting in either *hidden CeH* (CeH with FT4 values included in the normal range that can be recognized only by the demonstration of abnormal circadian or stimulated TSH secretory kinetics) or *manifest CeH* (most frequently associated with low TSH and FT4).

Since mild CeH may be associated with a decreased growth velocity in children surviving cancer disease, several groups investigated the possible solutions for the diagnosis of mild or hidden CeH [19–21]. Though abnormalities in *circadian TSH secretion* may not correlate with FT4 levels, the lack of a nocturnal TSH rise can be useful in the diagnosis of CeH but can be evaluated only in hospitalized patients [19–21]. TRH is not available in the USA, but *TRH test* may confirm the suspect of mild CeH and may be of help in the differential diagnosis between tertiary (hypothalamic) and secondary (pituitary) hypothyroidism as the two defects may be associated with exaggerated/delayed/prolonged or blunted TSH responses, respectively [1, 2, 19–23]. However, it must be underscored that a significant portion of patients with CeH may still have a normal TSH increase after TRH stimulation, and a clear distinction between the two forms of CeH may be difficult, as both sites are affected in most patients. The practical utility of TRH testing is therefore to be limited to the patients with uncertain diagnosis, in whom the abnormal TSH response to TRH may confirm the CeH [22, 23].

Interestingly, time-related decreases in circulating FT4 concentrations larger than 20 % *versus* the initial FT4 determination were reported to support the diagnosis of CeH in patients with different pituitary diseases followed up for several years [1, 18]. This cutoff value was set on the basis of a 10 % variation over time of T4 levels in normal individuals [24]. Provided that FT4 determination is repeatedly performed in the same laboratory, this approach would then allow the diagnosis and treatment of mild or hidden hypothyroid states of central origin.

The indexes of peripheral thyroid hormone action, such as sex hormone-binding globulin (SHBG), bone markers, serum lipids, and others, lack sufficient sensitivity and specificity for the diagnosis of mild or subclinical hypothyroidism, especially in patients who present with CPHDs, which may *per se* affect the levels of these indexes.

In the presence of low thyroid hormone levels, the exclusion of a primary thyroid defect may be required either because CeH may sometimes result from an *intermittent thyrotoxic state* (Table 9.3) or because hypothalamic hypothyroidism may be associated with slightly raised TSH concentrations at immunoassay. Indeed, the exclusion of primary thyroid disease by biochemical testing and/or ultrasound examination is the main objective in this differential diagnosis. Conversely, a family history of CeH or the clinical history (e.g., *head trauma*) or manifestations (e.g., headaches or visual field defects) may be suggestive of the presence of hypothalamic-pituitary defects, and the MRI imaging generally confirms the central origin of hypothyroidism. It is worth to note that some drugs have been associated with an increased risk of CeH [25], including the use of dopamine in dystocic delivery.

Severe and chronic *nonthyroidal illness* (NTI) are associated with values of thyroid function tests that largely overlap with those of CeH patients [1, 2]; therefore, the presence of concomitant diseases at the time of blood sampling should always be excluded before suspecting "true" CeH.

Allan-Herndon-Dudley syndrome, an X-linked form of mental retardation associated with tissue-specific resistance to thyroid hormones, can be associated with low FT4 and normal or slightly elevated TSH levels [26]. This disease is caused by mutations in the *MCT8* gene encoding a membrane thyroid hormone transporter.

These patients can be distinguished from those with CeH by the severe clinical phenotype, including cognitive and psychomotor retardation, and the typical elevation of T3 circulating levels that are usually two- to threefold higher than in normal subjects. Similar biochemical findings can be found also in patients with *thyroid hormone action defects* (THAD) [27] due to heterozygous mutations in *THRA gene*, encoding the thyroid hormone receptor α1 (TRα1). Severe constipation, defective and disharmonic growth, mental retardation, and delayed bone development appear as distinct features of this disease [28, 29].

9.3 CeH Replacement Therapy

As in primary hypothyroidism, treatment of CeH should restore appropriate serum concentrations of thyroid hormones. As for other forms of hypothyroidism, the daily administration of l-thyroxine is the preferred treatment of CeH [1, 2, 30, 31]. Several studies in children and adult primary hypothyroid patients did not find a superiority of combined LT4 plus triiodothyronine (LT3) treatment [31]; therefore, the LT4 + LT3 combinations should still be considered as an experimental treatment modality for patients that do not reach well-being on an adequate l-thyroxine regimen.

Because of the risk to induce an *adrenal crisis*, if a combined corticotrope deficiency has not been excluded, a prophylactic steroid treatment should be administered before the start of thyroxine therapy.

In normal infants and children, the thyroid hormone levels are higher than in adults [1, 2, 32]. Therefore, higher l-thyroxine doses are recommended in hypothyroid pediatric patients, and treatment should be started at full replacement doses, especially in patients with neonatal onset due to TSHß mutations in order to rapidly reach adequate circulating FT4 levels and promptly support neurological development [11, 33]. Guidelines recommend to initiate treatment of neonatal disorders with 10–15 μg/kg of l-thyroxine and to adjust doses on the basis of FT4 measurements every 2–4 weeks [34]. *L-T4 treatment* has been reported to promote an acceleration of growth velocity allowing reaching the target height [1, 14, 34]. Progressively lower doses are required in childhood and in *transition to adulthood* [35].

The target range should be that observed in normal children. Since TSH values do not correlate with thyroid function in CeH, the decision to modify the replacement regimen should be primarily taken on the basis of the clinical manifestations. In addition, several evidences, reviewed in ref. 1, indicate that *TSH determination* is not completely devoid of significance during L-T4 treatment in CeH. In summary, one should suspect undertreatment in all the conditions listed here below:

- Serum TSH above 0.5 mU/L, in particular if associated with serum FT4 values below the lower tertile of normal range
- Fall of serum FT4 values below the lower tertile of normal range
- Introduction of *GH replacement therapy*
- Introduction of *estrogen replacement* therapy or oral contraceptives
- Introduction of treatments impacting LT4 absorption or thyroid hormone metabolism

Conversely, one should suspect overtreatment in the presence of clinical manifestations suggestive of thyrotoxicosis, when associated with one of the following conditions:

- Serum values of FT4 and/or FT3 above the upper tertile of normal range
- Withdrawal of GH or estrogen replacement therapy
- Withdrawal of oral contraceptives or estrogen
- Withdrawal of treatments impacting LT4 absorption or thyroid hormone metabolism

References

1. Persani L (2012) Central hypothyroidism: pathogenic, diagnostic and therapeutic challenges. J Clin Endocrinol Metab 97:3068–3078
2. Persani L, Beck-Peccoz P (2012) Chapter 38: Central hypothyroidism. In: Braverman LE, Cooper D (eds) Werner & Ingbar's the thyroid: a fundamental and clinical text, 10th edn. Lippincott Williams & Wilkins/Wolters Kluwer Health, Philadelphia, pp 560–568
3. Price A, Weetman AP (2001) Screening for central hypothyroidism is unjustified. Br Med J 322:798
4. Nebesio TD, McKenna MP, Nabhan ZM et al (2010) Newborn screening results in children with central hypothyroidism. J Pediatr 156:990–993
5. Kempers MJ, Lanting CI, van Heijst AF et al (2006) Neonatal screening for congenital hypothyroidism based on thyroxine, thyrotropin, and thyroxine-binding globulin measurement: potentials and pitfalls. J Clin Endocrinol Metab 91:3370–3376
6. Miyai K (2007) Congenital thyrotropin deficiency–from discovery to molecular biology, postgenome and preventive medicine. Endocr J 54:191–203
7. LaFranchi SH (2010) Newborn screening strategies for congenital hypothyroidism: an update. J Inherit Metab Dis 33(Suppl 2):S225–S233
8. van Tijn DA, de Vijlder JJ, Vulsma T (2008) Role of the thyrotropin-releasing hormone stimulation test in diagnosis of congenital central hypothyroidism in infants. J Clin Endocrinol Metab 93:410–419
9. Pfäffle R, Klammt J (2011) Pituitary transcription factors in the aetiology of combined pituitary hormone deficiency. Best Pract Res Clin Endocrinol Metab 25:43–60
10. Raivio T, Avbelj M, McCabe MJ et al (2012) Genetic overlap in Kallmann syndrome, combined pituitary hormone deficiency, and septo-optic dysplasia. J Clin Endocrinol Metab 97:E694–E699
11. Bonomi M, Proverbio MC, Weber G et al (2001) Hyperplastic pituitary gland, high serum glycoprotein hormone α-subunit, and variable circulating thyrotropin (TSH) levels as hallmark of central hypothyroidism due to mutations of the TSHβ gene. J Clin Endocrinol Metab 86:1600–1604
12. Ramos HE, Labedan I, Carré A et al (2010) New cases of isolated congenital central hypothyroidism due to homozygous thyrotropin beta gene mutations: a pitfall to neonatal screening. Thyroid 20:639–645
13. Collu R, Tang J, Castagnè J et al (1997) A novel mechanism for isolated central hypothyroidism: inactivating mutations in the thyrotropin-releasing hormone receptor gene. J Clin Endocrinol Metab 82:1561–1565
14. Bonomi M, Busnelli M, Beck-Peccoz P et al (2009) A family with complete resistance to thyrotropin-releasing hormone. N Engl J Med 360:731–734
15. Sun Y, Bak B, Schoenmakers N et al (2012) Loss-of-function mutations in IGSF1 cause an X-linked syndrome of central hypothyroidism and testicular enlargement. Nat Genet 44: 1375–1381

16. Joustra SD, Schoenmakers N, Persani L et al (2013) The IGSF1 deficiency syndrome: characteristics of male and female patients. J Clin Endocrinol Metab 98:4942–5492
17. Ferretti E, Persani L, Jaffrain-Rea ML et al (1999) Evaluation of the adequacy of l-T4 replacement therapy in patients with central hypothyroidism. J Clin Endocrinol Metab 84:924–929
18. Alexopoulou O, Beguin C, De Nayer P et al (2004) Clinical and hormonal characteristics of central hypothyroidism at diagnosis and during follow-up in adult patients. Eur J Endocrinol 150:1–8
19. Rose SR, Lustig RH, Pitukcheewanont P et al (1999) Diagnosis of hidden central hypothyroidism in survivors of childhood cancer. J Clin Endocrinol Metab 84:4472–4479
20. Darzy KH, Shalet SM (2005) Circadian and stimulated thyrotropin secretion in cranially irradiated adult cancer survivors. J Clin Endocrinol Metab 90:6490–6497
21. Yamakita N, Komaki T, Takao T et al (2001) Usefulness of thyrotropin (TSH)-releasing hormone test and nocturnal surge of TSH for diagnosis of isolated deficit of TSH secretion. J Clin Endocrinol Metab 86:1054–1060
22. Faglia G (1998) The clinical impact of the thyrotropin-releasing hormone test. Thyroid 8:903–908
23. Mehta A, Hindmarsh PC, Stanhope RG et al (2003) Is the thyrotropin-releasing hormone test necessary in the diagnosis of central hypothyroidism in children? J Clin Endocrinol Metab 88:5696–5703
24. Andersen S, Pedersen KM, Bruun NH et al (2002) Narrow individual variations in serum T4 and T3 in normal subjects: a clue to understanding of subclinical thyroid disease. J Clin Endocrinol Metab 87:1068–1072
25. Haugen BR (2009) Drugs that suppress TSH or cause central hypothyroidism. Best Pract Res Clin Endocrinol Metab 23:793–800
26. Friesema EC, Visser WE, Visser TJ (2010) Genetics and phenomics of thyroid hormone transport by MCT8. Mol Cell Endocrinol 322:107–113
27. Refetoff S, Bassett JH, Beck-Peccoz P et al (2014) Classification and proposed nomenclature for inherited defects of thyroid hormone action, cell transport, and metabolism. Eur Thyroid J 3:7–9
28. Bochukova E, Schoenmakers N, Agostini M et al (2012) A mutation in the thyroid hormone receptor alpha gene. N Engl J Med 366:243–249
29. van Mullem A, van Heerebeek R, Chrysis D (2012) Clinical phenotype and mutant TRα1. N Engl J Med 366:1451–1453
30. Beck-Peccoz P (2011) Treatment of central hypothyroidism. Clin Endocrinol 74:671–672
31. Wiersinga WM, Duntas L, Fadeyev V et al (2012) 2012 ETA guidelines: the use of L-T4 + L-T3 in the treatment of hypothyroidism. Eur Thyroid J 1:55–71
32. Hollowell JG, Staehling NW, Flanders WD et al (2002) Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). J Clin Endocrinol Metab 87:489–499
33. Selva KA, Mandel SH, Rien L (2002) Initial treatment dose of L-thyroxine in congenital hypothyroidism. J Pediatrics 141:786–792
34. American Academy of Pediatrics, Rose SR; Section on Endocrinology and Committee on Genetics, American Thyroid Association, Brown RS; Public Health Committee, Lawson Wilkins Pediatric Endocrine Society, Foley T, Kaplowitz PB, Kaye CI, Sundararajan S, Varma SK (2006) Update of newborn screening and therapy for congenital hypothyroidism. Pediatrics 117:2290–2303
35. Koch CA, Sarlis NJ (2001) The spectrum of thyroid diseases in childhood and its evolution during transition to adulthood: natural history, diagnosis, differential diagnosis and management. J Endocrinol Invest 24:659–675