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Central hypothyroidism

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Abstract Central hypothyroidism (CH) is a rare cause of hypothyroidism due to an insufficient stimulation of an otherwise normal thyroid gland and it is caused by either pituitary (secondary hypothyroidism) or hypothalamic (tertiary hypothyroidism) defects. The diagnosis of CH is usually suggested by the finding of lowered thyroid hormone concentrations, associated with inappropriately low/normal TSH levels. Restoration and maintenance of euthyroidism represent the therapeutic goals in all forms of CH. On these basis, the vast majority of patients with CH is treated with standard levo-thyroxine (L-T4) therapy which is tailored according to FT4 circulating levels that should be maintained in the normal range.

Keywords Hypothyroidism · Hypopituitarism · FT4 · TSH

Introduction

Central hypothyroidism (CH) is a rare cause of hypothyroidism characterized by a defect of thyroid hormone production due to an insufficient stimulation by thyrotropin (TSH) of an otherwise normal thyroid gland. The prevalence of CH in the general population is estimated around 1:80,000–1:120,000 individuals. CH is a heterogeneous disease mainly due to the wide spectrum of pathogenetic mechanisms involved. Indeed, CH can be congenital in the case of genetic defects or acquired in the case of lesions affecting either the pituitary (secondary hypothyroidism) or the hypothalamus (tertiary hypothyroidism). In some cases, CH is an isolated defect of pituitary function, but in most cases it is combined with other pituitary hormone deficiencies (CPHDs). In the majority of the patients, the hypothyroid state is not severe and the onset can be progressive, therefore manifestations are frequently masked by CPHDs. Diagnosis is usually made on a biochemical basis showing defective thyroid hormone circulating levels associated to inappropriately low TSH levels. Treatment of CH takes advantage of thyroid hormone replacement even though treatment cannot be is easily tuned as in primary hypothyroidism (PH) because the evaluation of circulating TSH has a very limited value in central defects.

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Etiopathogenesis

A quantitative defect in the amount of functional pituitary thyrotroph cells (the so-called thyrotropin reserve) is probably the pathogenic mechanism at the base of most CH cases, including those with immunoreactive TSH concentrations within the reference range [1, 2]. This quantitative defect in TSH producing cells is associated with a qualitative defect in the secreted TSH isoforms, that conserve immunoreactivity but display a severe impairment in intrinsic biological activity and ability to stimulate thyroid TSH receptors [3, 4]. The acquired forms of CH may result from different conditions (Table 1). Pituitary mass lesions, especially pituitary adenomas, are the most common cause of central hypothyroidism. In particular, pituitary adenomas can cause hypothyroidism by

Table 1 Causes of acquired central hypothyroidism (CH). Isolated CH is congenital in most of the cases

1. *Invasive lesions*: pituitary macroadenomas, craniopharyngiomas, meningiomas, gliomas, metastases, carotid aneurysms
2. *Iatrogenic causes*: cranial surgery or irradiation, drugs (e.g. bexarotene)
3. *Injury*: head traumas, traumatic delivery
4. *Immunologic lesions*: lymphocytic hypophysitis
5. *Infarction*: post-partum necrosis (Sheehan), pituitary apoplexy
6. *Infiltrative lesions*: sarcoidosis, hemochromatosis, histiocytosis X
7. *Infectious lesions*: tuberculosis, syphilis, mycoses
8. *Idiopathic*: alteration of transcription factors, other unknown causes
9. *Isolated*: TSH beta gene mutations
10. *Malformations*: primary empty sella syndrome

Several patients with acquired CH previously classified as *idiopathic* are nowadays attributable to defects in pituitary transcription factors

compression of pituitary thyrotrophs, interruption of the hypothalamic-pituitary portal blood flow, or rarely by acute hemorrhage or infarction resulting in pituitary apoplexy. In addition, surgery or radiation therapy for pituitary adenomas or other mass lesions can cause central hypothyroidism. Other causes of acquired CH are infiltrative disorders affecting the pituitary or the hypothalamus (e.g. hemochromatosis, tuberculosis, syphilis, sarcoidosis,fungal infections, toxoplasmosis, and histiocytosis), autoimmune lymphocytic hypophysitis, head trauma with injury of the stalk. Finally, it has been observed that breech delivery accounts for most of the idiopathic cases, probably by disrupting either hypothalamic-pituitary connections (partial or total stalk interruption) or TRH secretion from the hypothalamic nuclei (trauma? hypoxia?). In this condition, TSH secretion is not suppressed and TSH circulating levels are normal or even elevated. Characteristic of these forms of tertiary hypothyroidism is the secretion of TSH molecules with reduced biological activity [2–4]. Same situation may be also found in the rare condition of post-partum pituitary apoplexy (Sheehan's syndrome). A iatrogenic form of acquired and isolated CH has been recently documented by Sherman et al. [5] who showed that the treatment of some neoplastic diseases with RXR ligands, such as bexarotene, might induce a clinical and biochemical picture of CH.

Congenital forms of CH can be isolated, if the defect is limited to thyrotroph function (isolated TSH deficiency), or associated with combined pituitary hormone deficiency (CPHD), if the defect involves other pituitary cell lineages (combined pituitary hormone deficiencies, CPHDs) (Table 2). In the case of isolated TSH deficiency, thyrotroph-specific genes, such as TSHβ or TRH receptor (TRH-R), are involved. TSHβ gene mutations were found in several families [6–8], while TRH-R mutations have so far been reported in only one case [9]. In all these cases, the inheritance is recessive with homozygous (all TSHβ cases) or compound heterozygous (in the case of TRH-R) mutations. In patients with mutations in the pituitary transcription factor genes, CH is due to the defect of hypothalamic/pituitary differentiation [10–13]. Defects in factors inducing pituitary commitment, such as HESX1, give rise to panhypopituitarism. Alternatively, defects in factors involved in cellular specification, such as PROP-1 or PIT-1, give rise to more

Table 2 Genetic forms of central hypothyroidism (CH)

Gene (Locus)	Endocrine phenotype	Associated features	Inheritance	Biochemical tests
TSHβ	Severe isolated CH with neonatal onset		Recessive	TSH: low/normal α-GSU: high
TRH-R	Isolated CH with neonatal onset		Recessive	TSH: low/normal TRH test: blunted TSH and PRL response
PIT1 (POU1F1)	Moderate/severe CH with combined GH and PRL defects and neonatal/infantile onset		Dominant or recessive	TSH: low/normal
PROP1	Moderate/severe CH with combined GH, PRL, LH/FSH, ACTH defects and neonatal/infantile onset		Recessive	TSH: low/normal
HESX1	Severe CH with GH, PRL, LH/FSH, ACTH combined defects	Septo-optical dysplasia (SOD)	Dominant or recessive	TSH: undetectable
LHX3	Severe CH with GH, PRL, LH/FSH combined defects	Rigid cervical spine	Recessive	TSH: low/normal

Table 3 Characteristic findings in patients with central hypothyroidism

1 Clinical features
• Hypothyroid manifestations
• Manifestations of concomitant or pre-existing hypothalamic/ pituitary disease
• Altered imaging of hypothalamic-pituitary region
2. Biochemical findings
• Low/normal TSH concentrations (no interference in TSH assay)
• Low bioactivity of circulating TSH
• Lack of nocturnal TSH surge
• Low free T4 levels
3. Findings against a primary thyroid defect
• Absent anti-thyroid auto-antibodies
• Homogenous thyroid structure at ultrasound

restricted tropin deficiencies (Table 2). In several PROP1 or PIT1 mutations, CH may have a delayed onset suggesting that the defect may also affect thyrotroph cell survival beyond differentiation Table 3.

Diagnosis

Clinical features of CH may vary greatly depending on etiology, severity of the thyroid impairment, number of associated hormone deficiencies and age of the patient at the time of disease onset. In general, acquired CH is less severe than the congenital form. Symptoms and signs of thyroid insufficiency are usually the same but milder than those of primary hypothyroidism and goiter is always absent.

The diagnosis of CH cannot be made with the sole TSH determination [14] since in these patients TSH may be in the normal range. For this reason, neonatal screening programs for congenital hypothyroidism based on the sole TSH examination fail to recognize patients with congenital CH, such as those with TSHβ mutations, and these cases are frequently diagnosed when irreversible neurological damages have already been produced [7]. Early neonatal diagnosis of CH can instead be reached in Centers where blood T4 measurement is part of the screening parameters [15]. In these conditions, the incidence of permanent congenital CH was reported to be about 1:20,000 alive neonates, accounting for 13% of congenital hypothyroidism cases. Indeed, CH diagnosis requires the contemporary evaluation of TSH and thyroid hormone and is usually suggested by the finding of lowered thyroid hormone concentrations, associated with inappropriately low/normal TSH levels. It is worth noting that some CH patients with a prevalent hypothalamic defect have high circulating TSH levels, a finding potentially leading to misdiagnosis.

Among the parameters of thyroid function [14, 16] the one that is provided with the highest accuracy for the diagnosis of CH is free thyroxine (FT4) [17]. The other parameters lack the sufficient sensitivity or specificity for diagnosis of hypothyroidism, in particular in patients that frequently present combined pituitary defects which may also affect the levels of tissue parameters of thyroid hormone action or thyroid hormone metabolism [17–19].

Recently, Alexopoulou et al. [20] suggested a diagnostic value to decreases of circulating T4 concentrations >20% of the initial T4 determination in patients with different pituitary diseases followed-up for several years. This cut-off value was set on the basis of a 10% variation over-time of T4 levels observed in normal individuals [21]. These approaches would allow the early diagnosis and treatment of mild hypothyroid states of central origin, in analogy with the mild forms of primary hypothyroidism revealed by high TSH levels. Lack of nocturnal TSH rise may be useful in the diagnosis of CH patients and elevations of circulating TSH levels [22, 23], but can be evaluated only in hospitalised patients.

Finally, patients with non thyroidal illness (NTI) have values of thyroid function testing that largely overlap with those of CH patients [14]. Nevertheless, the presence of concomitant diseases at the time of blood withdrawal should always be excluded before suspecting CH. A clue to distinguish true CH from NTI is the evaluation of serum FT3, which is always reduced in NTI and normal in mild to moderate forms of CH.

TRH test

TRH testing may be of help in the differential diagnosis between tertiary (hypothalamic) and secondary (pituitary) origin of the central defect [24, 25]. TRH is usually injected intravenously as a bolus and blood is withdrawn at −30, 0, 20, 60, 120 and 180 min for the measurement of TSH, FT4 and FT3, the latter at the time 0, 120 and 180 min [3, 25]. The information taken from the test is twofold, as TSH response may give an idea of the levels of hypothalamic-pituitary alteration, while the response of FT4 and FT3 to endogenous TRH-stimulated TSH may give an idea of the biological activity of the secreted TSH molecules. As far as the first point is concerned, TSH response may be absent or impaired in the pituitary lesion (total lack of functioning pituitary thyrotropes), whereas in the case of normal, exaggerated, delayed or prolonged responses the lesion appears to be at the hypothalamic level. Nonetheless, some recent works indicate that a clear distinction between the two forms of CH may be just theoretical, as both sites are affected in most patients [2], so that this distinction may be in particular cases useless [26].

Finally, as far as FT4 and FT3 responses to endogenous TRH-stimulated TSH are concerned, a absent or impaired FT4 and FT3 responses indirectly indicate the secretion of TSH devoid of the normal biological activity. In conclusion, the diagnosis of the various form of CH may benefit of the TRH test, in particular in order to explain why, in the presence of normal, but biologically inactive, TSH circulating levels, the thyroid is unable to produce normal amounts of FT4 and FT3.

Treatment

Restoration and maintenance of euthyroidism represent the therapeutic goals in all forms of CH. Specific therapies, such as oral TRH administration [3] have been abandoned because of their cost and their restricted applicability to few patients with hypothalamic hypothyroidism. Though Bunevicius et al. [27] claimed that combined treatment with thyroxine plus triiodothyronine could be more beneficial than thyroxine alone in hypothyroid patients, more recent study failed to show such superior efficacy of combined treatment [28]. On these basis, the vast majority of patients with CH is presently treated with standard levothyroxine (L-T4) therapy.

Unfortunately, no consensus has been found yet concerning the evaluation of the adequacy of L-T4 replacement dose, as, unlike for primary hypothyroidism, serum TSH levels cannot be used in either the diagnosis or the monitoring of L-T4 therapy [29, 30]. Indeed, we reported that low doses of thyroid hormone are sufficient to suppress TSH secretion in the large majority of CH patients though FT4 levels were still in the hypothyroid range in 73% of the patients [17]. Similarly, Carrozza et al. [31] reported that the large majority of 135 CH patients had subnormal TSH during L-T4 treatment. These data have been subsequently confirmed by Shimon et al. [32] who suggested that TSH levels above 1.0 mU/l may reflect insufficient replacement, this finding possibly reflecting an abnormal sensitivity in the negative feedback mechanism.

The evaluation of free thyroid hormones acquires a major role in the monitoring of L-T4 treatment in such clinical condition [17, 20, 31]. The accuracy of free thyroid hormone measurement is superior to that of total hormone measurement provided that FT4 and FT3 are evaluated by direct two-step methods, which are known to be rarely interfered by drugs or abnormal binding proteins [14, 33]. In primary thyroid diseases, FT4 measurement has a superior accuracy in hypothyroid conditions whereas FT3 is more accurate in hyperthyroidism. Accordingly, if blood is withdrawn before the morning L-T4 administration, low FT4 values may reveal under-treatment and high FT3 values are more sensitive to disclose over-treatment [17].

Clinical examination and the evaluation of clinical and biochemical indexes of thyroid hormone action at the tissue level [16] may give additional useful information for tailoring L-T4 treatment of CH patients. It is worth noting that these parameters could be misinterpreted due to the concomitant presence of other pituitary defects [17, 24]. This is particularly true for bone parameters (such as bone Gla protein, BGP, and carboxyterminal telopeptide of type 1 collagen, ICTP), cholesterol and other parameters of lipid metabolism, as well as sex hormone binding globulin (SHBG). Therefore parameters, such as soluble receptor of interleukin-2 (sIL2R), that are not known to be interfered by other pituitary functions should be preferred [17]. These findings suggest that longitudinal evaluation of these parameters in CH patients may be potentially helpful to reveal possible over- or under-treatment. As these parameters generally exhibit larger variations in the thyrotoxic state [33, 34], their sensitivity should be superior in revealing over- than under-treatment. Accordingly, overtreatment in CH patients was associated to elevated levels of sIL2R in a previous study [17].

L-T4 treatment should be started at low daily dosage and then increased by 25 μg every 2–3 weeks in order to reach full replacement dose. It is worth noting that L-T4 therapy should be started only after having excluded a concomitant central adrenal insufficiency. In case adrenal function cannot be assessed prior to the start of L-T4, a prophylactic treatment with steroids is advised and assessment of corticotrope function can be postponed.

It has been demonstrated that the large majority of CH patients had circulating levels of FT4 and FT3 within the normal range with a mean (±SD) L-T4 daily dose of 1.5 ± 0.3 and 1.6 ± 0.5 μg/kg b.w. [17, 24]. These optimal doses are similar to those reported for primary hypothyroidism [29, 30]. Among CH patients, significant differences in L-T4 doses are seen depending on the age or concomitant treatments. We showed that younger patients require higher doses than the older ones [17], as also seen in primary hypothyroidism [29, 35]. Concomitant estrogens or GH replacement therapies require significantly higher L-T4 doses [24, 36]. Moreover, GH deficiency may mask subclinical forms of CH that reach a biochemical evidence only after institution of GH replacement therapy [36]. As far as estrogens are concerned, an increased L-T4 requirement has been demonstrated also in primary hypothyroidism during estrogens treatment [37], this phenomenon being likely the consequence of the transient increase of thyroxine-binding globulin levels [38]. Conversely, it has been showed that GH administration enhance peripheral deiodination of T4 to T3 [18, 19, 39, 40]. This positive effect of GH on T4 metabolism is not transient, but it is biologically relevant only in patients with CPHDs who already have a partial impairment of thyrotroph function and not in those with isolated CH [41].

Treatment strategies are different in CH with neonatal to childhood onset. Normal infants and children have higher free thyroid hormone levels [14]. Therefore, higher L-T4 doses are recommended in hypothyroid pediatric patients [42] and treatment should be started at full-replacement doses at least in cases with neonatal onset in order to promptly protect neurological development [43]. Recent evidences recommend to initiate treatment of neonatal disorders with 12–17 μg/kg of L-T4 and to adequate doses on the basis of FT4/FT3 measurement every 2–4 weeks. The target range should be that observed in normal children [14]. Progressively lower doses are required in infancy and childhood.

References

1. Horimoto M, Nishikawa M, Ishihara T, Yoshikawa N, Yoshimura M, Inada M (1995) Bioactivity of thyrotropin (TSH) in patients with central hypothyroidism: comparison between in vivo 3, 5, 3 -triiodothyronine response to TSH and in vitro bioactivity of TSH. J Clin Endocrinol Metab 80:1124–1128. doi:10.1210/jc.80.4.1124
2. Persani L, Ferretti E, Borgato S, Faglia G, Beck-Peccoz P (2000) Circulating TSH bioactivity in sporadic central hypothyroidism. J Clin Endocrinol Metab 85:3631–3635. doi:10.1210/jc.85.10.3631
3. Beck-Peccoz P, Amr S, Menezes-Ferreira MM, Faglia G, Weintraub BD (1985) Decreased receptor binding of biologically inactive thyrotropin in central hypothyroidism. Effect of treatment with thyrotropin-releasing hormone. N Engl J Med 312:1085–1090
4. Beck-Peccoz P, Persani L (1994) Variable biological activity of thyroid-stimulating hormone. Eur J Endocrinol 131:331–340
5. Sherman SI, Gopal J, Haugen BR et al (1999) Central hypothyroidism associated with retinoid X receptor-selective ligands. N Engl J Med 340:1075–1079. doi:10.1056/NEJM199904083401404
6. Medeiros-Neto G, Herodotou DT, Rajan S et al (1996) A circulating, biologically inactive thyrotropin caused by a mutation in the beta subunit gene. J Clin Invest 97:1250–1256. doi:10.1172/JCI118540
7. Bonomi M, Proverbio MC, Weber G, Chiumello G, Beck-Peccoz P, Persani L (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. doi:10.1210/jc.86.4.1600
8. Szkudlinski MW, Fremont V, Ronin C, Weintraub BD (2002) Thyroid-stimulating hormone and thyroid-stimulating hormone receptor structure-function relationships. Physiol Rev 82:473–502
9. Collu R, Tang J, Castagne 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. doi:10.1210/jc.82.5.1561
10. Dattani MT, Robison IC (2000) The molecular basis for developmental disorders of the pituitary gland. Clin Genet 57:337–346. doi:10.1034/j.1399-0004.2000.570503.x
11. Cohen LE, Radovick S (2002) Molecular basis of combined pituitary hormone deficiencies. Endocr Rev 23:431–442. doi:10.1210/er.2001-0030
12. Clement K, Vaisse C, Lahlou N et al (1998) A mutation in the human leptin receptor gene causes obesity and pituitary dysfunction. Nature 392:398–401. doi:10.1038/32911
13. Nillni EA, Vaslet C, Harris M, Hollenberg A, Bjorbak C, Flier JS (2000) Leptin regulates prothyrotropin-releasing hormone biosynthesis. Evidence for direct and indirect pathways. J Biol Chem 275:36124–36133. doi:10.1074/jbc.M003549200
14. Baloch Z, Carayon P, Conte-Devolx B et al (2003) Laboratory medicine practice guidelines. Laboratory support for the diagnosis and monitoring of thyroid disease. Thyroid 13:3–126
15. van Tijn DA, de Vijlder JJ, Verbeeten B Jr, Verkerk PH, Vulsma T (2005) Neonatal detection of congenital hypothyroidism of central origin. J Clin Endocrinol Metab 90:3350–3359. doi:10.1210/jc.2004-2444
16. Smallridge RC (1996) Metabolic, physiological, and clinical indexes of thyroid function. In: Braverman LE, Utiger RD (eds) The thyroid, 7th edn. Lippincott, Philadelphia, pp 397–405
17. Ferretti E, Persani L, Jaffrain-Rea ML, Giambona S, Tamburrano G, Beck-Peccoz P (1999) Evaluation of the adequacy of l-T4 replacement therapy in patients with central hypothyroidism. J Clin Endocrinol Metab 84:924–929. doi:10.1210/jc.84.3.924
18. Jorgensen JO, Moller J, Laursen T, Orskov H, Christiansen JS, Weeke J (1994) Growth hormone administration stimulates energy expenditure and extrathyroidal conversion of thyroxine to triiodothyronine in a dose-dependent manner and suppresses circadian thyrotrophin levels: studies in GH-deficient adults. Clin Endocrinol 41:609–614. doi:10.1111/j.1365–2265.1994.tb01826.x
19. Jorgensen JO, Pedersen SA, Laurberg P, Weeke J, Skakkebaek NE, Christiansen JS (1989) Effects of growth hormone therapy on thyroid function of growth hormone-deficient adults with and without concomitant thyroxine-substituted central hypothyroidism. J Clin Endocrinol Metab 69:1127–1132
20. Alexopoulou O, Beguin C, De Nayer P, Maiter D (2004) Clinical and hormonal characteristics of central hypothyroidism at diagnosis and during follow-up in adult patients. Eur J Endocrinol 150:1–8. doi:10.1530/eje.0.1500001
21. Andersen S, Pedersen KM, Bruun NH, Laurberg P (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. doi:10.1210/jc.87.3.1068
22. Rose SR, Lustig RH, Pitukcheewanont P et al (1999) Diagnosis of hidden central hypothyroidism in survivors of child cancer. J Clin Endocrinol Metab 84:4472–4479. doi:10.1210/jc.84.12.4472
23. Yamakita N, Komaki T, Takao T, Murai T, Hashimoto K, Yasuda K (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. doi:10.1210/jc.86.3.1054
24. Costom BH, Grumbach MM, Kaplan SL (1971) Effect of thyrotropin-releasing factor on serum thyroid-stimulating hormone. An approach to distinguishing hypothalamic from pituitary forms of idiopathic hypopituitary dwarfism. J Clin Invest 50:2219–2225. doi:10.1172/JCI106717
25. Faglia G, Beck-Peccoz P, Ferrari C et al (1973) Plasma thyrotropin response to thyrotropin-releasing hormone in patients with pituitary and hypothalamic disorders. J Clin Endocrinol Metab 37:595–601
26. Mehta A, Hindmarsh PC, Stanhope RG, Brain CE, Preece MA, Dattani MT (2003) Is the thyrotropin-releasing hormone test necessary in the diagnosis of central hypothyroidism in children. J Clin Endocrinol Metab 88:5696–5703. doi:10.1210/jc.2003-030943
27. Bunevicius R, Kazanavicius G, Zalinkevicius R, Prange AJ Jr (1999) Effects of thyroxine as compared with thyroxine plus triiodothyronine in patients with hypothyroidism. N Engl J Med 340:424–429. doi:10.1056/NEJM199902113400603
28. Clyde PW, Harari AE, Getka EJ, Shakir KMM (2003) Combined levothyroxine plus liothyronine compared with levothyroxine

alone in primary hypothyrodism. A randomized controlled trial. JAMA 290:2952–2958. doi:10.1001/jama.290.22.2952
29. Helfand M, Crapo LM (1990) Monitoring therapy in patients taking levothyroxine. Ann Intern Med 113:450–454
30. Oppenheimer JH, Braverman LE, Toft A, Jackson IM, Ladenson PW (1995) A therapeutic controversy. Thyroid hormone treatment: when and what? J Clin Endocrinol Metab 80:2873–2883. doi:10.1210/jc.80.10.2873
31. Carrozza V, Csako G, Yanovski JA et al (1999) Levothyroxine replacement therapy in central hypothyroidism: a practice report. Pharmacotherapy 19:349–355. doi:10.1592/phco.19.4.349.30940
32. Shimon I, Cohen O, Lubetsky A, Olchovsky D (2002) Thyrotropin suppression by thyroid hormone replacement is correlated with thyroxine level normalization in central hypothyroidism. Thyroid 12:823–827. doi:10.1089/105072502760339406
33. Beck-Peccoz P, Brucker-Davis F, Persani L, Smallridge RC, Weintraub BD (1996) Thyrotropin-secreting pituitary tumors. Endocr Rev 17:610–638. doi:10.1210/er.17.6.610
34. Beck-Peccoz P, Persani L (2001) TSH-producing adenomas. In: DeGroot LJ, Jameson JL (eds) Endocrinology, 4th edn, Chapter 24. WB Saunders, Philadelphia, pp 321–328
35. Griffin JE (1990) Hypothyroidism in the elderly. Am J Med Sci 299:334–345. doi:10.1097/00000441-199005000-00009
36. Porretti S, Giavoli C, Ronchi C et al (2002) Recombinant human GH replacement therapy and thyroid function in a large group of adult GH-deficient patients: when does L-T4 therapy become mandatory? J Clin Endocrinol Metab 87:2042–2045. doi:10.1210/jc.87.5.2042
37. Arafah BM (2001) Increased need for thyroxine in women with hypothyroidism during estrogen therapy. N Engl J Med 344:1743–1749. doi:10.1056/NEJM200106073442302
38. Ain KB, Mori Y, Refetoff S (1987) Reduced clearance rate of thyroxine-binding globulin (TBG) with increased sialylation: a mechanism for estrogen-induced elevation of serum TBG concentration. J Clin Endocrinol Metab 65:689–696
39. Grunfeld C, Sherman BM, Cavalieri RR (1988) The acute effects of human growth hormone administration on thyroid function in normal men. J Clin Endocrinol Metab 67:1111–1114
40. Portes ES, Oliveira JH, Maccagnan P, Abucham J (2000) Changes in serum thyroid hormones levels and their mechanisms during long-term growth hormone (GH) replacement therapy in GH deficient children. Clin Endocrinol 53:183–189. doi:10.1046/j.1365-2265.2000.01071.x
41. Giavoli C, Porretti S, Ferrante E et al (2003) Recombinant hGH replacement therapy and the hypothalamus-pituitary-thyroid axis in children with GH deficiency: when should we be concerned about the occurrence of central hypothyroidism? Clin Endocrinol 59(806):810. doi:10.1046/j.1365–2265.2003.01892.x
42. 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
43. Selva KA, Mandel SH, Rien L et al (2002) Initial treatment dose of L-thyroxine in congenital hypothyroidism. J Pediatr 141:786–792. doi:10.1067/mpd.2002.128887