Chapter 10
Central Hypothyroidism

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Objectives

To discuss the difficulties encountered in the diagnosis and management of patients with central hypothyroidism.

Case Presentation

In 1999, a 33-year-old woman obtains a consultation with an endocrinologist because of menstrual irregularity since 4 months (delays of 10–15 days) accompanied by an increased frequency of headache, sleep disorder, morning fatigue and dizziness. The woman was a semi-professional basketball player that recently decided to stop this sport because she was unable to follow the training program. Her gynecologist did not find any abnormality but prescribed some blood tests showing mild hyperprolactinemia on a single determination (31 ng/ml), a slight LDL-cholesterol elevation (always normal on previous determinations) and normal serum TSH (Table 10.1). Her physical examination revealed a normal blood pressure (110/70 mmHg) and heart rate (66 beats/min), the body mass index was 25 kg/m^2, and the thyroid appeared normal for volume and soft at palpation. The consultant diagnosed a mild hypercholesterolemia, stress-dependent hyperprolactinemia and normal thyroid function, and gave dietary recommendations, rest and a short course of an anti-anxiety drug. Two years later, the woman asked a new consultation due

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Table 10.1 Biochemical values on the different blood tests

	June 2008	April 2010	June 2010	August 2010, LT4 1.0 μg/kg bw/day	December 2010, LT4 1.4 μg/kg bw/day
PRL, ng/ml (n.v. 3–20)	31	Basal: 41 +60': 34	PRL recovery after IgG precipitation: 98 %	–	–
TSH, mU/l (n.v.: 0.4–4.0)	2.4	1.8	1.5	0.9	0.1
Free T4, pM (n.v.: 9–20)	–	9.0	8.6	11.4	16.3
Free T3, pM (n.v.: 4–8)	–	5.7	–	6.4	6.6
Anti-TPO Ab, kU/l (<20)	–	–	12	–	–
LDL-Cho, mg/dl (<150)	188	178	–	189	134
Hemochrome	Normal	–	Normal	Normal	–

to the persistence of the manifestations. The blood test then confirmed a normal TSH but with a FT4 value at the lower limit of normal, her PRL was above the normal range even after 1 h of rest (Table 10.1). The Endocrinologist then asked for a confirmatory test, a thyroid ultrasound, and a magnetic resonance study of the brain. The new blood test (Table 10.1) confirmed low FT4 and normal TSH, absence of macro-prolactin and normal results of the other tests for pituitary function, including ACTH/cortisol, IGF1 and urinary values; ultrasound revealed a thyroid of normal volume (9.6 ml) and structure, magnetic resonance of the pituitary sella region was normal. Central hypothyroidism accompanied by mild hyperprolactinemia of idiopathic origin was diagnosed. Subsequently, a more careful collection of the personal history revealed a traumatic head injury during a basketball match 5 years before that did not however require hospitalization.

The consultant started LT4 treatment for central hypothyroidism up to 1.0 μg/kg bw/day. On July 2010, the patient reported poor subjective improvement and mood depression. The TSH and free thyroid hormone values were in the normal range, the LDL-cholesterol levels were still elevated despite the dietary restrictions. The consultant confirmed the LT4 regimen explaining that other factors accounted for the persistence of the manifestations. After another 3 months without any improvement, the woman asked the advice of another consultant, who augmented the daily dose of LT4 up to 1.4 μg/kg on the basis of the symptoms and biochemical testing. Few weeks later, the patient observed the normalization of menses and the recovery of mood and physical performance, and she expressed the intention to restart the basketball training. The biochemical tests of December 2010 revealed a TSH value below but the FT4/FT3 levels at the mid of their normal range, the LDL-cholesterol was normal. The new consultant confirmed the current LT4 replacement.

Review of the Management of This Case

Diagnosis

This case describes a young woman with a central hypothyroidism and mild hyperprolactinemia. In this condition, the serum TSH screening alone cannot reveal the dysfunction of the hypothalamic–pituitary–thyroid axis, as TSH levels are most frequently normal [1–3]. Central hypothyroidism is presently known to account for about 1:1,000 hypothyroid patients, but is still probably underestimated and the Endocrinologists should always consider this possibility when hypothyroid manifestations coexist with biochemical alterations or clinical manifestations pointing to a pituitary origin. In this case, the first consultant initially gave little attention to the mild hyperprolactinemia and considered to check more appropriately and extensively thyroid function tests and PRL levels only 2 years after the start of symptoms. Indeed, the correct diagnosis could be suggested by the presence of a pituitary mass or history of pituitary disease, but a more careful recording of the personal history of this woman reporting the head trauma could have helped to anticipate the diagnosis. Indeed traumatic head injury or vascular accidents even of minor entity can account for several cases of central hypothyroidism previously classified as idiopathic. Most frequently, central hypothyroidism is combined with other pituitary hormone deficiencies that may mask the manifestations of a mild hypothyroid state, but their presence would support the central origin of thyroid dysfunction. In this case, the mild hypercholesterolemia was a finding supporting the recent onset of hypothyroidism, while the hyperprolactinemia, the absence of antithyroid autoantibodies and the normal findings at thyroid ultrasound were indeed pointing to the central origin.

Treatment

LT4 replacement therapy was correctly started. The initial daily dose was mistakenly judged sufficient by the consultant based on normal values of all thyroid function tests. Indeed, TSH determination is not a reliable marker of thyroid hormone action at the hypothalamic–pituitary level in patients with central hypothyroidism but the finding of unsuppressed TSH levels during thyroxine therapy is strongly suggestive of an insufficient regimen [1, 4–6]. Accordingly, LDL-cholesterol was still abnormal despite the dietary restriction. Due to the persistence of hypothyroid manifestations, the patients went to another consultant that correctly interpreted the biochemical results and augmented the daily dose of thyroxine. The regimen of 1.4 μg/kg bw was effective in restoring the wellbeing, normal menstrual activity, and physical performance in this sportswoman. The finding of suppressed TSH accompanied by thyroid hormone levels in the central part of normal range and the normalization of LDL-cholesterol were supporting the correct replacement.

Lessons Learned

Isolated central hypothyroidism can occur in a young sportswoman as a likely consequence of a mild head trauma. The diagnosis of central hypothyroidism should always be considered when hypothyroid-like manifestations coexist with low/normal TSH concentrations in the serum, but it should not completely discarded also in the presence of slightly elevated TSH, as in the cases with prevalent hypothalamic defect [1, 3]. Hyperprolactinemia, combined pituitary hormone deficiencies, or nonhormonal manifestations of a pituitary or hypothalamic mass should raise the suspect of a defective TSH secretion. However, nontumoral causes of pituitary dysfunction, including traumatic injuries, ictus, lymphocytic hypophysitis, other inflammatory diseases or genetic forms, should be kept in mind [1–3]. The finding of FT4 values below or at the lower limit of normal should then be correctly interpreted, particularly when these data are accompanied by an unexplained and persistent rise of cholesterol levels. The normal findings at thyroid ultrasound and the absence thyroid autoimmunity are also supporting the central origin of the disease.

As in primary hypothyroidism, treatment of central hypothyroidism should restore appropriate serum concentrations of thyroid hormones. Thyroxine treatment should be given to the same doses used in primary hypothyroidism, but this is frequently not the case mainly because this corresponds in most of central hypothyroid patients to the suppression of their circulating TSH levels [1, 4–6]. This phenomenon is most likely due to the reduced pituitary TSH reserve [7, 8]. Therefore, the finding of normal TSH concentrations should raise the suspect that the thyroxine regimen is not sufficient for that particular central hypothyroid patient. Other conditions that can cause the need to adjust the daily thyroxine doses are illustrated in Table 10.2 and include the treatment of combined pituitary hormone deficiencies,

Table 10.2 Conditions associated with the risk of a revision of L-T4 regimen

Possible undertreatment
• Serum TSH above 0.5 mU/l, in particular if associated with serum FT4 values below the lower tertile of normal range
• Decrease of serum FT4 values below the lower tertile of normal range
• Start of oral contraceptives or estrogen replacement therapy
• Start of GH replacement therapy in patients with combined pituitary hormone deficiencies
• Start of treatments affecting LT4 absorption or thyroid hormone metabolism
• Unexplained increases of serum cholesterol
• Manifestations suggestive of hypothyroidism, in particular when associated with one of the above conditions
Possible overtreatment
• Values of FT4 and/or FT3 above the upper tertile of normal range
• Stop of oral contraceptives
• Stop of GH or estrogen replacement therapy
• Stop of treatments affecting LT4 absorption or thyroid hormone metabolism
• Unexplained increases of sex hormone binding globulin in the hyperthyroid range
• Clinical manifestations suggestive of thyrotoxicosis, in particular when associated with one of the above conditions

such as GH or estradiol replacement [1, 3, 9]. Several studies (reviewed in [1, 3]) compared the levels of FT4 in primary and central hypothyroid subjects with those found in controls matched for age and sex; these data indicate that central hypothyroids are frequently underreplaced [6]. Thyroxine treatment should therefore aim to bring the FT4 values in the central part of the normal range, underreplacement should be suspected when FT4 is in the lowest tertile and overreplacement when the free thyroid hormone is in the highest tertile. The suspect may be confirmed by the contemporary determination of clinical and/or biochemical parameters of thyroid hormone action, such as heart rate, cholesterol levels, and sex hormone-binding globulin.

Questions

1. Which of the following thyroid function tests pattern is most suggestive of central hypothyroidism?

   (a) Low TSH, normal FT4, low T3
   (b) Normal TSH, low FT4, low T3
   (c) Normal TSH, low FT4, normal T3
   (d) High TSH with normal FT4, normal T3

2. A 27 y/o woman with hypercholesterolemia, fatigue, hair loss, and amenorrhea, who has undergone external beam radiation to the head 10 years earlier, has the following test results: Low FSH, low estradiol, normal TSH, normal prolactin, low IGF-1, and normal ACTH stimulation test. Besides starting hormone replacement therapy with estradiol and progesterone, you:

   (a) Reassure the patient that only yearly adrenal and thyroid function tests will be needed
   (b) Order a TRH stimulation test
   (c) Order a FT4
   (d) Order glycoprotein hormone alpha-subunit levels

3. A 35 y/o man who has undergone a hypophysectomy 6 years ago because of craniopharyngioma is evaluated. He is currently on transdermal testosterone, oral hydrocortisone, and oral levothyroxine. His tests show low testosterone and prolactin and suppressed TSH. Besides increasing the testosterone dose, you:

   (a) Decrease the levothyroxine dose.
   (b) Order FT4
   (c) Ask him to repeat the TSH 3 months after the increase in testosterone dose
   (d) Decrease the hydrocortisone dose

Answers to Questions

1. (b) In central hypothyroidism, TSH is often normal, while FT4 is low. Central hypothyroidism results from direct damage to the pituitary thyrotrophs, as the theory is that the few remaining exhausted thyrotrophs, while maximally stimulated by TRH and lack of thyroxine, produce a TSH molecule that is quantitavely adequate, but not as bioactive in stimulating thyroid hormone production as normal TSH. As a result, TSH levels are "inappropriately normal" in relation to the low thyroxine level. As a compensatory mechanism, peripheral conversion of T4 to T3 is enhanced, maintaining low normal T3 level in all but the most extreme forms of the condition.
2. (c) While in most situations a normal TSH level predicts normal thyroid function, when there is significant clinical suspicion of central hypothyroidism, measuring FT4 levels is necessary to rule out the condition.
3. (b) In central hypothyroidism, adequate replacement with levothyroxine in physiologic doses rapidly and thoroughly suppresses TSH levels. Therefore, overtreatment with levothyroxine can only be ruled out or ruled in with FT4 levels.

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