Central hypothyroidism

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Hypothyroidism is a common clinical entity, occurring in 2% to 3% of the Canadian population.[1] Primary hypothyroidism is most common, with dysfunction occurring at the level of the thyroid gland.[2] In secondary or tertiary hypothyroidism (central hypothyroidism), the defect is at the pituitary, hypothalamus, or hypothalamic portal circulation level.[3]

Most hypothyroid patients are treated with levothyroxine; thyroid-stimulating hormone (TSH) levels are checked to monitor correct treatment doses. However, the role of TSH in central hypothyroidism is more limited, and primary reliance on its measurement might result in incorrect diagnosis or treatment. The following case illustrates this key concept.

Case description

A 43-year-old man presented with a 1-year history of horizontal diplopia and headaches. He also complained of memory impairment, erectile dysfunction, and constipation. He had a history of hypertension and hyperlipidemia, and a 40-pack-year history of smoking. He was not taking any medications.

Physical examination revealed abducent nerve palsy on the left side and dry skin. Magnetic resonance imaging of the head demonstrated a uniform enhancing lesion with a diameter of 4 cm involving the left medial sphenoidal wing, temporal lobe, cavernous sinuses, brainstem, and sella turcica. A transsphenoidal biopsy was performed, and a mesenchymal chondrosarcoma was diagnosed.

To evaluate the patient's pituitary function, laboratory testing was completed. This revealed a TSH level of 0.1 mU/L (normal 0.27 to 4.2 mU/L), a free thyroxine (T4) level of 13 pmol/L (normal 10 to 24 pmol/L), and a free triiodothyronine (T3) level of 3.8 pmol/L (normal 3 to 6.5 pmol/L). His morning cortisol level was low, at 95 nmol/L; other values included a serum testosterone level of 0.3 nmol/L (normal 6.3 to 26 nmol/L), a luteinizing hormone level of 0.2 IU/L (normal 1.5 to 9 IU/L), and a follicle-stimulating hormone level of 1.3 IU/L (normal 1 to 18 IU/L). As these results indicated anterior hypothyroidism, hydrocortisone (initially 50 mg twice daily) and levothyroxine (starting at 50 µg daily) were initiated.

Because of progressive cranial neuropathy and right hemiparesis, the patient underwent radiotherapy (45 Gy over 7 weeks). He was discharged to a rehabilitation unit where thyroid hormone replacement therapy was monitored. Based on a low (or suppressed) TSH level (0.06 mU/L), his levothyroxine dose was decreased in an attempt to maintain a TSH level in the normal range.

Four months later, he complained of constipation, cold intolerance, and increasing weight. Only TSH measurement was being used to monitor his thyroid function. Therefore, free T4 and T3 levels and TSH levels were checked once more. Free T4 levels were found to be low at 8 pmol/L, free T3 levels were low at 2.3 pmol/L, and TSH levels were normal at 1.96 mU/L, suggesting an insufficient thyroid hormone dose. His levothyroxine dose was increased to 100 µg daily. Because his serum testosterone level was low at less than 0.3 nmol/L, with low luteinizing hormone (0.1 IU/L) and follicle-stimulating

EDITOR'S KEY POINTS

- To diagnose central hypothyroidism, look for findings of lower free triiodothyronine and thyroxine levels together with low or inappropriately normal thyroid-stimulating hormone levels in a clinical situation suggestive of the disease.
- The role of thyroid-stimulating hormone alone in monitoring treatment of patients with central hypothyroidism is limited; aim for the maintenance of free triiodothyronine and thyroxine levels in the upper half of the normal range, with adjustment of treatment based on the patient's symptoms

POINTS DE REPÈRE DU RÉDACTEUR

- Pour diagnostiquer l'hypothyroïdie centrale, il faut constater des niveaux de triiodothyronine et de thyroxine libres plus bas, combinés à des niveaux faibles ou inopportunément normaux de thyréostimuline dans une situation clinique qui suggère la maladie.
- Le rôle de la thyréostimuline à elle seule dans la surveillance des patients atteints d'hypothyroïdie centrale est limité; il faut se fixer comme objectif de maintenir les niveaux de triiodothyronine et de thyroxine libres dans la moitié supérieure de l'échelle des valeurs normales et ajuster le traitement en se fondant sur les symptômes du patient.

This article has been peer reviewed.
Cet article a fait l'objet d'une révision par des pairs.
Can Fam Physician 2011;57:677-80

hormone (1.7 IU/L) levels, testosterone replacement therapy was initiated, with 150-mg testosterone enanthate injections administered intramuscularly every 2 weeks.

After his dose of levothyroxine was increased, his constipation and fatigue improved and he was able to increase his physical activity, aiding in his rehabilitation. Results of repeat bloodwork 2 months later showed a TSH level of 0.15 mU/L and both free T4 and free T3 levels in the reference range (11 pmol/L and 3.1 pmol/L, respectively).

The patient's levothyroxine dose was subsequently adjusted to keep his free T4 and T3 levels in the reference range. Additionally, it was recommended that levothyroxine not be administered simultaneously with calcium supplementation, as concomitant calcium administration can reduce the intestinal absorption of levothyroxine.[4]

Discussion

This case illustrates the importance of the accurate diagnosis, treatment, and monitoring of central hypothyroidism.

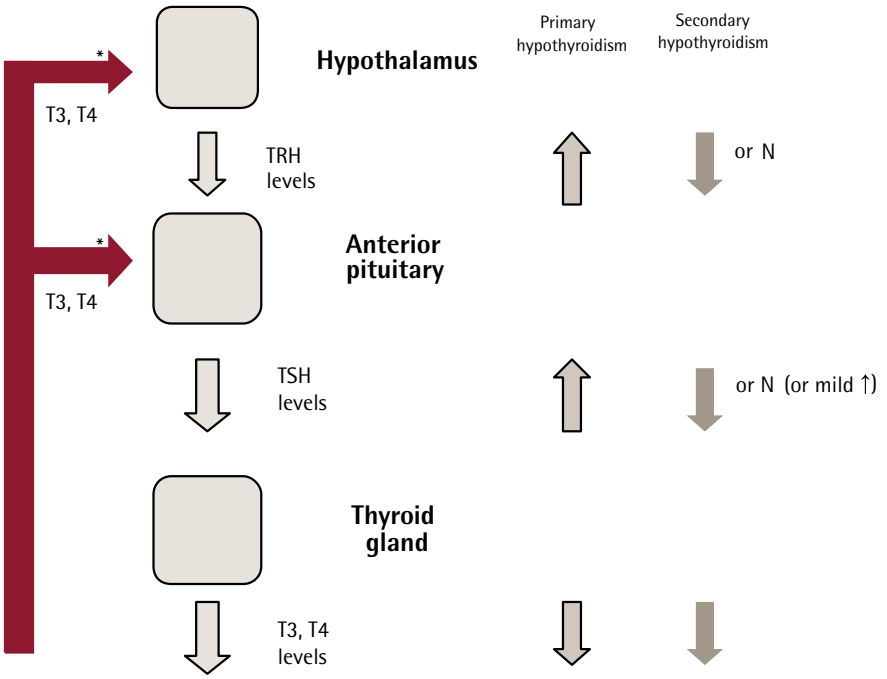
Diagnosis of central hypothyroidism. As in primary hypothyroidism, a detailed history and physical examination are important to diagnosis. Cold intolerance and weight gain are common complaints (**Box 1**).[5] Compared with primary hypothyroidism, however, clinical manifestations of central hypothyroidism might be masked by symptoms of coexisting hormone deficiencies such as hypoadrenalism

Box 1. Signs and symptoms of hypothyroidism

- Weakness, fatigue
- Dry skin
- Cool extremities
- Puffy face, hands
- Difficulty hearing
- Alopecia
- Paresthesia
- Bradycardia
- Menorrhagia
- Poor concentration
- Peripheral edema
- Poor memory
- Delayed tendon reflex relaxation
- Constipation
- Carpal tunnel syndrome
- Weight gain
- Serous cavity effusions
- Dyspnea
- Hoarse voice

Data from Garber et al, 2006.[5]

Figure 1. Hypothalamic-pituitary-thyroid axis activity in hypothyroidism



*Red arrows represent negative feedback inhibition.
N—normal, T3—triiodothyronine, T4—thyroxine, TRH—thyrotropin-releasing hormone, TSH—thyroid-stimulating hormone.

and hypogonadism.[2] Thus, biochemical diagnosis is critical in this group.

Primary hypothyroidism is usually diagnosed based on an elevated TSH level. In this situation, the failure of the thyroid gland to secrete sufficient thyroid hormone results in decreased levels of T3 and T4. In turn, there is less negative feedback inhibition at the hypothalamus and pituitary, causing TSH levels to increase (**Figure 1**). Increased TSH levels are therefore indicative of the diagnosis, and normalization is seen during adequate treatment.

In contrast, owing to hypothalamic or pituitary failure, TSH levels might not increase in response to low T3 and T4 levels.[6] Thyroid-stimulating hormone levels can, in fact, be in the low, normal, or elevated range.[3] This is because TSH pulse frequency and amplitude might be maintained, and additionally, its biologic activity might be reduced with its immunoactivity still retained.[2] Furthermore, other hormone deficiencies can affect its measure.[7] Therefore, for the diagnosis of central hypothyroidism, one needs findings of low free T3 and T4 levels together with low or "inappropriately" normal TSH concentration in the context of hypothalamic-pituitary disease.[3]

Central hypothyroidism is most often caused by pituitary mass lesions. Radiation is another culprit, with hypothyroidism occurring in 3% to 9% of patients who undergo pituitary radiation[8] and in up to 5% of patients who receive radiation for extracranial head and neck tumours.[2] The main causes of central hypothyroidism are listed in **Box 2.**[7]

Monitoring therapy. The treatment of choice for hypothyroidism is levothyroxine. The average dose is 1.6 µg per kilogram of body weight, but there is considerable variation among individuals. The adequacy of the replacement dose must be checked frequently (every 4 to 8 weeks), especially at the beginning of therapy. Once the correct dose has been established, thyroid hormone levels should be measured once or twice per year. For the reasons cited above, TSH levels cannot be used to monitor therapy in central hypothyroidism. The most reliable marker is serum free T4 levels (**Figure 2**).[9] Free T3 levels should also be measured; however, they tend to remain in the normal range and are less useful. It is also advisable to concomitantly measure levels of TSH.

A common treatment target is maintenance of free T4 and T3 levels in the upper half of the normal range, with some adjustment based on the patient's clinical symptoms. In addition, treatment of other pituitary hormone deficiencies might affect dosing[9] and should prompt reevaluation of thyroid hormone test results 2 to 4 months later. Most important, a low TSH level should not be seen as an indicator of a suprathera-peutic dose of levothyroxine.

Box 2. Causes of central hypothyroidism

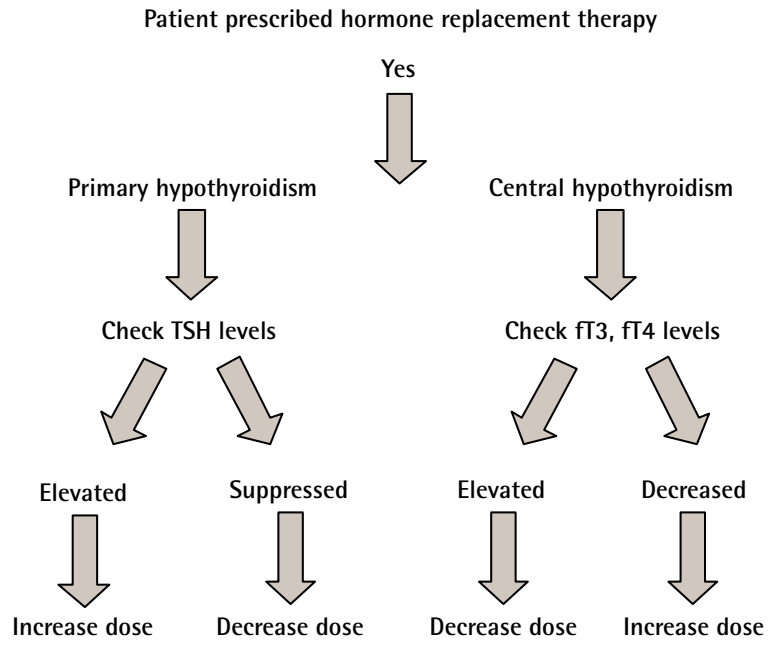
- Certain drugs, such as opioids, glucocorticoids (in pharmacologic doses), dobutamine, dopamine, octreotide, and bexarotene
- Space-occupying lesions of the brain or pituitary
- Radiation
- Vascular disease, including Sheehan syndrome
- Traumatic brain injury
- Growth-hormone therapy
- Certain infections, such as lymphocytic adenohypophysitis
- Genetic mutations
- Idiopathic causes

Data from Yamada and Mori, 2008.[7]

Conclusion

Accurate diagnosis and surveillance of patients being treated for central hypothyroidism is of great importance. Measuring only TSH levels is not sufficient, and

Figure 2. Monitoring therapy in hypothyroidism



fT3—free triiodothyronine, fT4—free thyroxine, TSH—thyroid-stimulating hormone.

can lead to incorrect treatment decisions. One must also monitor free T3 and T4 levels, and pay special attention to clinical signs and symptoms of hypothyroidism or hyperthyroidism.

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Competing interests
None declared

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