Chapter 12
Drug-Induced Central Hypothyroidism

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Objectives

1. Diagnose central hypothyroidism from compatible symptoms, signs, and thyroid function tests, and describe principles of management.
2. Review the etiologies and pathophysiology of central hypothyroidism, with a focus on drug-induced central hypothyroidism.

Case

A 72-year-old man was referred for evaluation of a persistently low TSH despite reduction in levothyroxine dosage. He had a long history of hypothyroidism due to Hashimoto's thyroiditis and was clinically and biochemically euthyroid on 150 mcg daily levothyroxine (weight 88.4 kg, ~1.7 mcg/kg) for several years. Six months prior to referral, he was diagnosed with cutaneous T-cell lymphoma (CTCL) and started on oral bexarotene. After 1 month of therapy, he developed progressive fatigue, dry skin, cold intolerance, constipation, and both myalgias and muscle weakness. TSH was <0.01 with a normal FT4, so his levothyroxine was reduced to 137mcg. His symptoms worsened, and TSH remained <0.01 2 months later, so he was referred to endocrinology. Notable examination findings included mild bradycardia, isolated diastolic hypertension, slowed but appropriate responses to questioning, dry skin, and delayed relaxation of deep tendon reflexes. TSH was 0.01 with a FT4 of 0.7 and T3 of 41. Levothyroxine was increased to 175mcg daily, but symptoms persisted and FT4 remained low. Over the next 5 months, his levothyroxine was steadily increased to 300mcg daily despite careful adherence,

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Table 12.1 Thyroid function tests after initiation of bexarotene, titration of levothyroxine, and addition of liothyronine

Months after initiation of bexarotene	Levothyroxine-T4, mcg	Liothyronine, mcg	TSH (mIU/L), 0.4–5.0	FT4 (ng/mL), 0.9–1.7	T3 (ng/dL), 80–200
3 months prior	150		3.25	–	–
1 month	150		<0.01	–	–
3	137		<0.01	–	–
4 (referral)	137		0.01	0.7	41
6	175		<0.01	0.8	43
8	250		<0.01	0.8	54
11	300	5 BID	<0.01	0.9	63
13	400	10 BID	<0.01	1.3	99
15	400	10 BID	<0.01	1.4	114

All labs were drawn between 2 and 4 pm, prior to his second daily dose of liothyronine

administration >60 minutes before meals, and avoidance of interfering medications and supplements. Symptoms persisted, and his T3 remained low, so liothyronine was cautiously added. After titration to a final dose of 400mcg levothyroxine and 10mcg BID liothyronine, his symptoms improved which correlated with resolution of abnormal physical exam findings and normalization of FT4 and T3 levels (Table 12.1).

Review of How the Diagnosis Was Made

The presence of an unequivocally low serum FT4 level with a suppressed TSH (while already on levothyroxine therapy) and signs and symptoms of hypothyroidism in a bexarotene-treated patient was consistent with drug-induced central hypothyroidism. Failure for the abnormal symptoms and biochemistry to normalize despite levothyroxine titration was concerning for nonadherence or malabsorption, but persistence despite optimal administration suggested increased hormone metabolism, which responded to use of supraphysiologic levothyroxine and the addition of liothyronine.

Lessons Learned

Central hypothyroidism is a rare disease of deficient thyroid hormone production by an otherwise functional gland due to inadequate stimulation by pituitary TSH [1]. Under normal circumstances, hypothalamic TRH regulates TSH synthesis, glycosylation (which influences bioactivity), and release, which itself stimulates nearly every step in thyroid hormone production. Pituitary mass lesions are the most

common cause of central hypothyroidism and lead to suppression of TSH through compression or ischemia of pituitary thyrotrophs or interruption of hypothalamic stimuli. Other causes of central hypothyroidism include infiltrative disorders (e.g., deposition diseases, infections, central nervous system malignancies) of the hypothalamus or pituitary, traumatic brain injury, pituitary ischemia/apoplexy, disorders of development, or a medication adverse effect. The diagnosis requires measuring total or free T4 since TSH may be low, normal, or even slightly high since quantitative detection does not necessarily correlate with biological activity, especially when an interruption in TRH-mediated glycosylation is present. Central hypothyroidism is treated with exogenous levothyroxine. Thyroid hormone should be titrated to a goal mid-normal range free T4 value since TSH is unreliable; TSH levels usually drop to <0.01 after initiation of levothyroxine due to loss of what little TSH production was present from decreased negative feedback.

Drugs directly or indirectly affect thyroid function through a variety of mechanisms, including effects on thyroid hormone production, binding, activation, or metabolism; they can also interfere with thyroid hormone therapy and/or laboratory testing [2]. A small subset of drugs can negatively impact the hypothalamic-pituitary-thyroid axis, including glucocorticoids, dopamine, bromocriptine, somatostatin analogs, metformin, immune checkpoint inhibitors, and rexinoids. Other drugs, such as carbamazepine, oxcarbazepine, phenytoin, and salsalate, can spuriously mimic central hypothyroidism by inducing a low free T4, and to a lesser extent T3, through interference with thyroid hormone assays [3].

Glucocorticoids lower serum TSH levels at commonly used doses (e.g., ≥ 0.5 mg dexamethasone, ≥ 30 mg prednisone) through direct inhibition of TRH in the hypothalamus, which leads to reduced TSH production. Dopamine and bromocriptine (owing to their action as dopamine agonists) bind to pituitary D2 receptors and reduce TSH production. Somatostatin analogs bind to inhibitory pituitary somatostatin receptors which decrease adenylate cyclase signaling and ultimately cell polarization, which reduces TSH secretion. Metformin appears to reduce TSH in patients with hypothyroidism and type 2 diabetes although the exact mechanism is not known. Importantly, none of the aforementioned drugs has been shown to cause clinically significant central hypothyroidism at typical doses, although dopamine is admittedly difficult to study given concomitant nonthyroidal illness in critically ill patients. In contrast, immune checkpoint inhibitor therapy is an increasingly recognized cause of clinically significant hypopituitarism (in which central hypothyroidism may result) which results due to stimulation of pituitary autoimmunity and inflammatory hypophysitis.

Rexinoids are vitamin A derivatives that interact with the retinoid X nuclear hormone receptor (RXR). RXR functions as a heterodimer with other critical intranuclear receptors such as the thyroid hormone receptor, vitamin D receptor, and peroxisome proliferator-activated receptor. Bexarotene is the most clinically relevant rexinoid since topical and oral formulations are approved by the FDA treatment of cutaneous T-cell lymphoma. Clinically significant hypothyroidism is common and affects the majority of bexarotene-treated patients with cutaneous T-cell lymphoma [4]. Bexarotene rapidly and specifically suppresses TSH without

affecting other pituitary hormones, and the effect is observable in healthy controls as well as patients with cancer [3]. Mechanistic studies have demonstrated a direct suppression of the TSHβ subunit gene transcription which suggests the pituitary is the primary target, although a failure of hypothalamic TRH mRNA to rise in the presence of low T4 suggests the hypothalamus may be affected as well. Interestingly, bexarotene has also been shown to increase thyroid hormone metabolism, even in patients who are athyreotic, although the dominant mechanism (e.g., deiodination, sulfation, glucuronidation) remains unclear [5].

In the present case, the patient had clear evidence of central hypothyroidism due to bexarotene, which is an uncommon but well-characterized cause. His signs and symptoms of hypothyroidism, along with his low FT4, required very high doses of levothyroxine and the eventual addition of liothyronine to normalize. It is important to note that failure to respond to thyroid hormone replacement, especially in excess of weight-based doses (1.6 mcg/kg), should raise suspicion for nonadherence and/or malabsorption, even in patients who report optimal adherence and timing of therapy. This is a fairly common occurrence in clinical practice, and algorithms have been proposed to guide a thoughtful evaluation of the underlying cause(s): a thorough history and medication/supplement review, judicious use of levothyroxine absorption testing and/or workup for specific malabsorption syndromes, and optimization of timing, co-administered agents, and thyroxine formulation are clinically impactful [6]. In this patient's case, we did not definitely exclude malabsorption or nonadherence. However, his consistency in follow up, self-report of optimal administration, and stability in TFTs after achieving normal T4/T3 levels with titration in the presence of a drug known to increase thyroid hormone metabolism suggests hypermetabolism was the root cause.

Key Learning Points

1. Central hypothyroidism is rare, usually caused by pituitary mass lesions, and is diagnosed by signs and symptoms of hypothyroidism with a low free/total T4 level and an inappropriately low, normal, or slightly elevated TSH level.
2. Central hypothyroidism is treated with thyroid hormone replacement (levothyroxine in the vast majority of cases) and requires following free T4 rather than TSH levels for therapy titration; it is imperative that clinicians do not misinterpret the low TSH as a sign of overreplacement.
3. Bexarotene is a rare cause of central hypothyroidism and causes both inhibition of TSH release and increased thyroid hormone metabolism. High doses of thyroid hormone may be required to restore clinical and biochemical euthyroidism.
4. In patients who require higher than weight-based doses (1.6 mcg/kg) of thyroid hormone, nonadherence and/or malabsorption is the most common cause and should be strongly suspected and treated, unless a known cause of altered thyroid hormone metabolism is present.

Questions

1. A 84-year-old man is diagnosed with symptomatic overt hypothyroidism based on a TSH of 16 mIU/L, a free T4 of 0.7 ng/dL, and compatible symptoms. PMH is significant for mild cognitive impairment, performance anxiety (he is a pianist) HTN, HLD, diet-controlled DM2, GERD, iron deficiency, and obesity.

Medications include lisinopril, atorvastatin, omeprazole, ferrous sulfate, a daily multivitamin, and propranolol PRN. Levothyroxine is initiated and increased to 200mcg (82 kg, ~2.4 mcg/kg) over several months with ongoing symptoms and persistently elevated TSH. The most likely explanation for his persistently elevated TSH is:

(a) A drug-induced increase in levothyroxine clearance/metabolism
(b) Levothyroxine nonadherence and/or malabsorption
(c) Nephrotic syndrome
(d) TSH assay interference

2. A 48-year-old woman is referred for evaluation of a suppressed TSH <0.01 with palpitations, heat intolerance, and weight loss. A FT4 is 1.2 ng/dL and T3 is 150 ng/dL. PMH is significant for GERD. She takes 81 mg aspirin and 20 mg omeprazole. The most appropriate diagnosis is:

(a) Central hypothyroidism
(b) Subclinical hypothyroidism
(c) Subclinical hyperthyroidism
(d) Overt hyperthyroidism

3. All of the following are causes of drug-induced hypothyroidism, *except*:

(a) Lithium
(b) Amiodarone
(c) Anti-CTLA4 and anti-PD1/PDL1 immunotherapy
(d) Metoprolol

Answers

1. (b) Most patients who apparently fail to respond to levothyroxine therapy demonstrate therapy nonadherence and/or malabsorption. This patient has a risk factor for nonadherence (mild cognitive impairment) and is on several medications known to interfere with levothyroxine absorption (iron, MVI, omeprazole). Propranolol can affect thyroid hormone metabolism but only at very high doses; none of the other medications have a known effect on metabolism. Nephrotic syndrome is a rare cause of hypothyroidism due to urinary loss of TBG and thyroid hormone. TSH assay interference is unlikely if the elevated TSH continues to fit the clinical picture (e.g., hypothyroid symptoms persist), and a more likely explanation is present.
2. (c) A fully suppressed TSH with normal FT4/T3 is most consistent with subclinical hyperthyroidism; an elevation in FT4 and/or T3 would qualify as "overt" hyperthyroidism. Despite the confusing nomenclature, "subclinical" thyroid disease is purely a biochemical diagnosis, and presence or absence of symptoms is not included in the definition. TSH is almost never fully suppressed in central hypothyroidism unless measured after thyroid hormone initiation, and this patient has no risk factors for it.
3. (d) Lithium, amiodarone, and checkpoint inhibitor immunotherapy are all associated with drug-induced hypothyroidism. Metoprolol can cause bradycardia and fatigue, but does not have significant effects on thyroid function.

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