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Drug Induced Central Hypothyroidism – A Case Report

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Abstract

Drug induced Central Hypothyroidismis a well-recognized entity. Failure to recognize this condition may result in unnecessary investigation and inappropriate management. Here we describe a patient who developed Central Hypothyroidism secondary to short term treatment with high dose steroid. Early recognition of this condition helped to diagnose and appropriate management of the patient.

Introduction

Thyroid axis is particularly prone to interaction with a wide range of medicines. It is therefore important to consider this diagnosis to avoid unnecessary investigations and therapeutic failure.

Thyroid function is affected by various drugs. Majority of these drugs act at thyroid level in the patients whose thyroid functions are normal, or at the level of thyroid hormone absorption or metabolism in patients who need exogenous levothyroxine. Glucocorticoids, dopamine agonists, somatostatin analogs, and rexinoids are among those few drugs that affect thyroid function by suppressing TSH in the thyrotrope or hypothalamus. However, majority of these drugs do not induce clinically evident central hypothyroidism. Rexinoids which belongs to a newer group of nuclear hormone receptor antagonists cause clinically significant central hypothyroidism in many of the patients whereas, dopamine agonists can intensify 'hypothyroidsm' in those patients with nonthyroidal illness. In this article, we review mechanisms governing TSH suppression of these drugs as well as the clinical implication of these effects.

Keywords

Central hypothyroidism, Thyroid axis.

Case Report

A 43 year old patient attended our clinic with the report of thyroid functions done in another hospital. Thyroid functions were advised by the gastroenterologist for fatigue and generalized weakness. He was recently treated by the gastroenterologist for Upper Gastrointestinal bleeding secondary to esophageal varices. He has no history of thyroid disease or was not on any antithyroid medication. No history of thyroid surgery or radiation treatment to thyroid. The Physician who saw the thyroid function result suspected central hypothyroidism. He advised MRI of the brain and pituitary hormones for further evaluation of central hypothyroidism.During his initial examination in our clinic, we elicited the history that he was recently started on high dose of methyl prednisolone for Sudden Sensory Hearing Loss by the ENT Specialist. This prompted us to consider the possibility of Steroid induced Central Hypothyroidism. We decided to withhold the MRI and other investigations. We repeated the thyroid functions which confirmed low T3, T4 and TSH. Patient was explained the possibility of Steroid Induced Central Hypothyroidism. He was advised to repeat thyroid functions after one month. Repeat thyroid functions after one month showed normal T3, T4, and TSH confirming our provisional diagnosis of Steroid Induced Central hypothyroidism.

Thyroid function Reports

Initial Reports

T3: 0. 69 ng/ml (normal: 0.6 to 1.8)

T4: 2.71 Microgram/dl (normal: 4.6 to 11.5)

TSH: 0.010mIU/L (normal: 0.35 to 5.5)

Repeat Thyroid functions after one month

T3: 101.0ng/dl (normal: 60-180)

T4: 5.1 Mcg/dl(normal: 4.5 to 12.5)

TSH: 1.83mIU/L (normal: 0.35 to 5.5)

Discussion

The most common side effect of drug-induced thyroid dysfunction is hypothyroidism. Several drugs can cause interactions with the thyroid axis. Many aspects of thyroid hormone pharmacology is affected by these medications. It is therefore necessary to understand these interactions to prevent unnecessary treatment or misdiagnosis. These drug interactions can cause different forms of thyroid disorders, the most common being hypothyroidism. Drug induced hypothyroidism can be caused due to several mechanisms.

1. Inhibition of synthesis and / or release of thyroid hormones.
2. Immune mechanisms
3. Drug induced thyroiditis
4. Inhibition of TSH synthesis

Drugs that cause Hypothyroidsm

Primary hypothyroidism

Inhibition of synthesis and/or release of thyroid hormones

Thionamides

Iodine and iodine-containing drugs (amiodarone, contrast agents, etc.)

Lithium

Minocycline and other tetracyclines

Immune Mechanisms

Interferon-alpha

Other cytokines (IFN β, IL-2)

Other mechanisms

Drug-induced thyroiditis

Tyrosine kinase inhibitors

Secondary hypothyroidism

Inhibition of TSH synthesis

Bexarotene

Somatostatin analogues

Glucocorticoids and dopamine

Immune mechanisms

Anti-CTLA4

Interactions in the treatment of hypothyroidism

Decrease in levothyroxine absorption

Alteration in transport and metabolism of thyroid hormones

Mechanisms of secondary/central drug-induced hypothyroidism

A. Inhibition of TSH synthesis

1. **Bexarotene:** Bexarotene is a synthetic compound that belongs to a new subclass of retinoid that activates retinoid X receptors (RXRs), which is termed as a rexinoid agent. It can be used in the management of cutaneous T-cell lymphoma and it causes central hypothyroidism by suppressing TSH.[1]Bexarotene, like T3 and 9-cis-retinoic acid, produces about 50% in vitro suppression of the gene promoter of TSH beta-subunit. It also promotes the peripheral metabolism of thyroid hormones by inducing glucuronyl transferases and sulfotransferases.[2]As a result, patients with bexarotene-induced hypothyroidism need higher hormone replacement doses (upto two times higher).[3]Hypothyroidism develops few days after the initiation of the treatment and all the patients regain thyroid axis function once it is discontinued. This effect is not seen with 13-cis-retinoic acid (isotretinoin), which is used for treating severe acne.
2. **Somatostatin analogues:** Somatostatin analogues have shown therapeutic efficacy in patients with the syndrome of pituitary resistance to thyroid hormones and with thyrotropinomas.[4]Somatostatin reduces both TSH pulse frequency and amplitude when administered in healthy individuals. [5]According to Colao et al., long term use of somatostatin analogues lowers the TSH and its reaction to thyrotropin-releasing hormone stimulus without any effect on the serum levels of thyroid hormone.[6] An occurrence of 2% of central hypothyroidism was reported in a study of somatostatin analogues in acromegaly.[7] Even though, somatostatin analogues suppress TSH by acting directly on thyrotopes, it is estimated that these effects are only transient and do not promote the development of central hypothyroidism.[8]
3. **Glucocorticoids and dopamine:** The effect of glucocorticoids on TSH secretion has long been acknowledged. [9]Hydrocortisone plays a significant role in the diurnal variation of TSH at physiological levels, with lower levels in the morning and higher levels at night. This explains the reason for elevated TSH levels in patients with untreated adrenal insufficiency. TSH is suppressed by high doses of glucocorticoids in both normal and in hypothyroid patients. The use of glucocorticoids for a long period of time does not normally cause central hypothyroidism. Recent research suggests that patients with corticotroph microadenomas might have central hypothyroidism caused by an excess of cortisol suppressing the hypothalamic-pituitary-thyroid axis.

TSH secretion is suppressed by dopamine and its agonists, such as bromocriptine, which activate the D2 receptors.[8]The administration of dopamine or its derivatives, dobutamine and dopexamine, can make it difficult to interpret TSH serum levels, but it does not trigger central hypothyroidism.TSH values during treatment with these medicines normally falls between 0.08 and 0.4 mUI/l if ultrasensitive methods detecting TSH levels within the range of 0.01 mUI/ml are used. These levels are different

from those usually seen in hyperthyroidism (TSH less than 0.01nUI/ml).[10]

B. Immune mechanisms

1. **Anti-Cytotoxic T lymphocyte associated antigen 4 (anti-CTLA-4) antibodies:** Monoclonal anti-CTLA-4 antibodies are used to manage various neoplasias, like metastatic renal carcinoma and melanoma.Ipilimumab or tremelimumab administration may cause acute lymphocytic hypophysitis and panhypopituitarism, with central hypothyroidism being the more common deficiency (90% of cases).[11]Hypophysitis is seen in 7-13 % of patients treated with Ipilimumab, with headache being the most common symptom.[12]It is more commonly observed in males with an average age of 60 years and generally starts 2-4 months post-treatment, usually after the third cycle. Metastatic melanoma and other pituitary tumors are the various differential diagnosis. Nuclear magnetic resonance imaging may exhibit pituitary enlargement with increased longitudinal diameter, thickening of the stalk, suprasellar convexity, and a hyperintense heterogeneous signal, which can aid in the diagnosis of hypophysitis.[13]Unlike postpartum or gestational autoimmune hypophysitis, ipilimumab-induced hypophysitis is not associated with diabetes insipidus.[15]Ipilimumab has also been seen to impair thyroid function (less frequently) and even cause primary adrenal insufficiency.
2. **Anti-Programmed cell death-1 receptor (anti-PD-1) antibodies:** Anti-PD-1 drugs like pembrolizumab and nivolumab can cause hypophysitis, but only a few cases have been documented.Anti-PD-1-induced thyroid disorders, particularly silent thyroiditis, more commonly seen and affects 5-10% of patients.

Conclusion

While several drugs and medications may affect thyroid function, only a small number of them (glucocorticoids, dopamine agonists, somatostatin analogs, and rexinoids) suppress TSH at the hypothalamic or pituitary levels.Fortunately, even after excessive high dose use, glucocorticoids and somatostatin analogs do not cause clinically noticeable central hypothyroidism. Dopamine agonists does not cause clinically evident central hypothyroidism, but they can have additive effect of suppressing TSH in patients with non-thyroid illness, potentially leading to iatrogenic central hypothyroidism. Rexinoids can cause severe central hypothyroidism in majority of the patients, who require levothyroxine replacement and monitoring of serum free T4 levels. Clinicians must be mindful of this rare and treatable side-effect since this newer group of medications could be used in more patients (advanced cancer, metabolic disorders, dermatologic disorders).

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