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Views and Practice

A rare cause of central hypothyroidism: oral isotretinoin treatment

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Introduction

Oral isotretinoin (13-cis retinoic acid) is a natural, physiological compound formed as a result of vitamin A metabolism, and has been approved for the use in the treatment of severe nodular acne in 1982.[1] Isotretinoin has a 70-89% remission rate in treatment of acne vulgaris. Complete or near-complete healing is achieved in the lesions.[2] Isotretinoin can be used in the treatment of acne vulgaris with different dosing regimens and the most commonly used regimen is to use 0.5-2.0 mg/kg/day dose for 16-24 weeks. Cumulative dose is usually achieved with the use of isotretinoin at a dose of 1 mg/kg/day for 4-5 months on average.[1,2] Due to the presence of retinoic acid receptors in almost all parts of the body, isotretinoin has a broad side effect profile. The incidence and severity of side effects other than teratogenicity are predominantly dependent on dose and usually disappear when the drug is stopped. The most common side effects are those associated with skin and mucous membranes. More than half of the cases show dryness, xerosis and pruritus in the mucous membranes. Other side effects include xerophthalmia, night blindness, conjunctivitis, keratitis, optic neuritis, temporary and permanent hearing loss, pseudotumour cerebri, depression, suicide, nausea, vomiting, oesophagitis, gastritis, myalgia, arthralgia, arthritis, and osteoporosis with varying frequencies.[1,2] It is known that isotretinoin use may affect thyroid function tests. There are studies in the literature reporting that drug use causes hypothyroidism in some patients and hyperthyroidism in others.[3,4] In this case report, central hypothyroidism due to isotretinoin use is discussed based on data in the literature.

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Case

An 18-year-old female patient on isotretinoin treatment was admitted to our centre due to abnormal thyroid function tests. There were no symptoms of hypothyroidism other than weakness and fatigue and there was no family history of hypothyroidism. The only medication that patient was taking 20 mg/day isotretinoin for acne vulgaris and there was no history of drug or alcohol use or smoking. Physical examination of the patient revealed no evidence of hypothyroidism.

Re-examination of thyroid function tests revealed a free thyroxine (fT4) value of 0.74 ng/dL (0.89-1.37) and TSH value of 0.023 µIU/mL (0.47-3.41), being lower than the reference values. The aspartate aminotransferase (AST), alanine aminotransferase (ALT), urea, creatinine and electrolytes were normal. The patient was diagnosed as central hypothyroidism. Sella MRI and pituitary hormones were performed to exclude pathologies that would suggest central hypothyroidism in the patient. The pituitary hormones of the patient were normal (Table 1), and there was no pathology in the sella MRI examination (Figure 1). Clinical and laboratory findings indicated central hypothyroidism and levothyroxine treatment was initiated. Isotretinoin was discontinued and after two weeks of levothyroxine, blood hormone levels were determined as ft3: 2.95 ng/dL, ft4: 0.95 ng/dL and TSH:1.133 µIU/mL. The patient's symptoms improved after the levothyroxine treatment. These tests were repeated again after six months and the results were within normal limits.

Table 1. Pituitary hormone levels of the patient

	Patient results	Reference values
TSH (µIU/mL)	14.004	0.47-3.41
fT3 (pg/mL)	1.92	2.25-3.85
fT4 (ng/dL)	0.61	0.89-1.37
FSH (mIU/mL)	5.99	1.80-11.78
LH (mIU/mL)	5.37	1.80-11.78
Estradiol (pg/mL)	38	21-251
Prolactin (ng/mL)	47.93	1.20-29.93
ACTH (pg/mL)	24.5	5.0-46
Cortisol (µg/dL)	20.2	3.52-18.33
IGF-I (ng/mL)	267.0	141.0-483.0

TSH: Thyroid stimulating hormone, fT3: Free triodothyronine, fT4: Free thyroxine FSH: Follicle stimulating hormone, LH: Luteinizing hormone, ACTH: Adrenocorticotropic hormone, IGF-I: insulin-like growth factor-I.

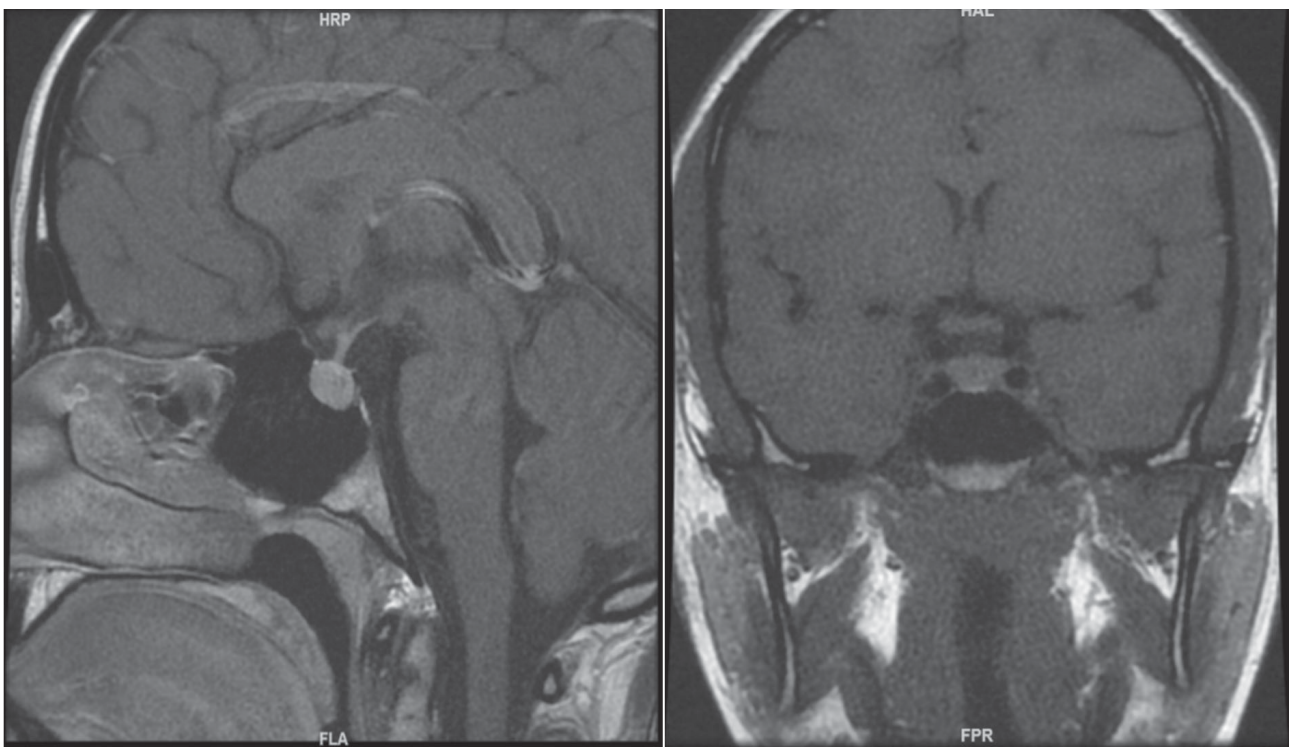

Figure 1. The magnetic resonance imaging of the pituitary gland was reported as normal.

Discussion

There are few studies in the literature examining the effect of isotretinoin on thyroid function tests. Isotretinoin was shown to be particularly effective on severe cystic acne in 1979 by Peck et al and approved by FDA for severe nodular acne in 1982.[5] Since then, it has been used successfully in the treatment of many dermatological diseases, especially acne vulgaris.[5] Although isotretinoin dose in acne treatment varies from 0.1 to 2.0 mg/kg/day, it is rarely used in doses above 1.0 mg/kg/day since due to an increase in the frequency of side effects. In order to increase bioavailability, daily dose should be divided into two and taken with meals.[6] The effect of isotretinoin therapy on thyroid function tests and autoantibodies has not yet been fully determined and several case reports and studies have shown that isotretinoin therapy may affect thyroid function.

Masood et al, reported a 25-year-old female patient treated with 20 mg/day isotretinoin for six months and thyroid function tests were performed four weeks before and six weeks after the treatment. An increase in TSH values and decrease in fT4 values were observed in the tests performed before the treatment, whereas these values were found to be normal in the tests performed six weeks after the treatment and patient's hypothyroidism-related complaints had improved. The authors noted that these changes in thyroid function tests could be associated with isotretinoin use.[4] In our case, TSH values were high before isotretinoin treatment and fT4 value was low and it was seen that these results were compatible with the literature. In a study conducted by Marsden et al, seven acne rosacea patients were treated with 1 mg/kg/day isotretinoin for 12 weeks. Significant decreases in fT3 and fT4 levels were observed after the treatment but TSH and TRH levels remained constant. An increase in liver enzyme levels was also observed. It was reported that changes in thyroid function tests could be partially explained by the induction of hepatic microsomal enzymes by isotretinoin treatment.[7] In our case, although central hypothyroidism was detected, hepatic function tests were normal. These results showed that the central hypothyroidism in our case was not related to microsomal enzymes.

It is known that bexarotene is a vitamin A derivative retinoid. There are case reports and studies of central hypothyroidism due to systemic bexarotene use in the literature. In a study conducted by Smith et al, 10 patients using bexarotene for six weeks showed no change in TSH values at the end of treatment, whereas tT4, fT4, and T3 values were decreased. The authors noted that the cause of this change was central hypothyroidism due to retinoids. Experimental studies have shown that retinoid LG268 causes suppression of TSH 'promoter' activity, TSH mRNA synthesis, and TSH secretion.[8] In another study by Karadağ et al, changes in the levels of hormones secreted from the pituitary gland of patients receiving isotretinoin treatment were investigated. fT4, fT3 and TSH values were significantly decreased in the tests performed three months after the start of treatment. It was reported that these observed changes could be due to RXR-mediated suppression of TSHβ gene expression similar to bexarotene use.[9]

Retinoids can affect cell growth, differentiation and metabolism through retinoic acid receptors and retinoid X receptors. These receptors also mediate the activity of steroids and thyroid hormones. Espacially, hypothalamic-pituitary-thyroid function is primarily affected by retinoid X receptor-selective retinoids.[10] However, isotretinoin affects the thyroid gland by mechanisms other than the retinoid X receptor. In the literature, the effects of isotretinoin use on thyroid function tests have been explained by induction of autoimmune events, retinoids affecting TSH synthesis and secretion, and induction of hepatic microsomal enzymes. We believe that monitoring thyroid function tests in addition to lipid profile and liver function tests, and initiating treatment when necessary may be useful in patients taking systemic isotretinoin, particularly in those with

hypothyroidism symptoms or findings suggestive of thyroid disease.

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