



CASE REPORT

Navigating Diagnostic Challenges in Endocrinology: A Case Report of Macro-TSH

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Abstract

Introduction: "Macro-hormones often artefactually elevate biochemical tests" [1]. There are numerous factors that may lead to elevated TSH and corresponding normal thyroid hormones; however Macro-TSH should always be considered as an analytical interference if the biochemical and clinical findings are incongruent.

Case presentation: A 47-year-old female was referred with elevated plasma thyroid stimulating hormone (TSH) levels. The patient reported increased hair loss and infrequent menstrual periods which is likely related to her recent significant weight loss and perimenopausal symptoms respectively. No other stigmata of thyroid disease were noted, and the patient appeared euthyroid clinically. The reported plasma levels of free T3 and T4 and Thyroxine Binding globulin were normal, and the Thyroid Peroxidase antibody was negative. The TSH levels were analyzed by different immunoassay platforms (Roche, Abbott, Delfia, Centaur) all producing significantly raised results. Further analysis confirmed the presence of Macro-TSH.

Conclusion: This patient presents with a rare condition known as Macro-TSH. Macro-TSH is a complex molecule, consisting of a TSH molecule and an immunoglobulin, which causes spuriously elevated plasma TSH levels despite the biologically active TSH levels being normal. This rare condition leads to a conflicting physiological picture in that patients with Macro-TSH have isolated elevated TSH levels with a clinically euthyroid presentation.

however other less common causes include biologically inactive TSH, TSH resistance and laboratory interferences [2]. The interpretation of such biochemical results can be puzzling; especially when the clinical symptoms are minor or absent.

Case Presentation

A 47-year-old female was referred to the Endocrine Clinic for elevated plasma TSH and subsequent normal free T3 and T4 values. These diagnostic findings suggest subclinical hypothyroidism; however, suspicions are raised because the patient clinically presents as euthyroid. This patient also has a complex endocrine history that reveals itself due to incidental findings on previous diagnostic exams. Of note her history includes gestational diabetes, borderline NIDDM, colloid cysts of the right thyroid lobe and a paraganglioma on the vagus nerve in her neck. A blood sample was taken as per the endocrine clinic. The same blood sample was analyzed on four platforms and the TSH was significantly raised and varied (Roche TSH 11.5 mU/L, Abbott TSH 7.59 mU/L, Delfia TSH 6.76 mU/L and Centaur TSH 11.49 mU/L). All other thyroid function tests were reported as normal. Further analysis confirmed the presence of Macro-TSH. Following thorough investigations, the endocrine specialists confirm that the patient TSH levels will be unreliable to monitor thyroid function in the future due to the presence of Macro-TSH. Additionally regular monitoring of thyroid function is not recommended. However, if suspicions of thyroid disease arise her free T4 levels would be a reliable blood test with a referral

Introduction

An elevated plasma TSH with corresponding normal free T3 and T4 levels warrants thorough investigation. These biochemical plasma concentrations most commonly represent subclinical hypothyroidism;



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to the endocrine specialist for further management and care.

Discussion

Thyroid hormone production is under the control of the Hypothalamus-Pituitary-Thyroid (HPT) Axis. The thyroid gland is responsible for producing thyroid hormones, Triiodothyronine (T3) and thyroxine [1]. The majority of thyroid hormone produced by the thyroid gland is T4; despite T3 being the most active in the body. T3 has critical effects on the HPT axis by providing negative feedback to the hypothalamus and anterior pituitary gland to control TRH and TSH secretion and ultimately maintain physiological levels of circulating thyroid hormones [3].

Thyroid hormones are essential for maintaining metabolic homeostasis and have an important role in growth, development, cardiovascular function, and energy metabolism [4,5]. The primary role of TSH is regulation of the thyroid gland and therefore it is an important variable used to evaluate thyroid function [4]. TSH screening for thyroid function is common and clinically meaningful when the hypothalamic-pituitary-thyroid axis is intact [4]. TSH screening becomes unreliable if central hypo- or hyperthyroidism or drug effects exist and laboratory interferences must also be considered [4].

Macro-hormones are circulating conjugates of hormone bound to other plasma proteins [1,4]. Macro-TSH occurs when monomeric TSH is bound with anti-TSH antibodies; most commonly immunoglobulin G (IgG) [1]. Macro-TSH is biologically inactive, but its presence results in spuriously elevated plasma TSH levels [1]. Importantly the total amount of free TSH in the plasma is biologically active and if measured within normal range.

Immunoassays are used to evaluate thyroid function. Laboratory interferences of TSH are common and can impede the accurate measurement of plasma TSH [6]. Macro-TSH is a rare laboratory interference that leads to false high measurements [2]. Currently there is not a routine immunoassay that can detect the presence of Macro-TSH in a serum sample. However, there is evidence that Macro-TSH affects commercially available TSH immunoassays [6]. Macro-TSH detection is related to the antibodies used in the immunoassays and their sensitivity to Macro-TSH [6]. This varying sensitivity to Macro-TSH produces the inconsistent spuriously elevated TSH results [6]. Crucially these methods are not diagnostic of Macro-TSH and the only definitive test for Macro-TSH is by gel filtration chromatography [6].

As per Larsen, et al. [1] Macro-TSH is a rare condition that is present in less than 1% of most populations. Currently the etiology of anti-human TSH autoantibody development is unknown; as is the timeline that Macro-TSH can persist in the blood [1,7]. Patients with Macro-TSH present euthyroid clinically and laboratory

results include elevated TSH with normal levels of thyroid hormones T3 and T4 [1]. Recognition of this immunoassay interference is important as Macro-TSH can easily be misdiagnosed and lead to inappropriate treatment of subclinical hypothyroidism with exogenous thyroid hormones.

Conclusion

In summary we describe a female patient who presents euthyroid clinically with elevated serum TSH and normal T3 and T4 thyroid hormones. Macro-TSH is a complex molecule, composed of TSH and immunoglobulin. In the presence of Macro-TSH molecules, spuriously elevated serum TSH levels are measured in laboratory assays despite the biologically active TSH levels being normal. Ultimately, this rare condition creates a conflicting physiological picture in that laboratory results will report an isolated elevated TSH level with a clinically euthyroid patient presentation. Importantly, Macro-TSH is a rare laboratory interference that should be considered in patients with conflicting biochemical results compared to the clinical presentation.

Conflict of Interests

The authors of this article have no conflict of interests to declare.

Author Contribution

All authors contributed equally in the preparation of this manuscript.

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