



Macro-TSH Can be a Rare Cause of Elevated Serum Thyroid Stimulating Hormone Concentration: A Case Report

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Abstract

In this case report, an 18 years old female subject with incidentally detected thyroid stimulating hormon (TSH) elevation due to macro-TSH without clinical findings of thyroid disorder was defined. Initially, the laboratory investigations revealed high TSH [11.45 μ IU/mL; normal reference interval (NRI: 0.50-5.50 μ IU/mL)] with electrochemiluminescence immunoassay (ECLIA) method. When L-thyroxine and L-triiodothyronine treatments were found to be ineffective for lowering TSH, polyethylene glycol (PEG) method for TSH measurement was planned to rule out the possibility of macro-TSH. TSH level upon using the PEG method was found to be within normal ranges as 1.96 μ IU/mL. In conclusion, normal free thyroxine level accompanied by elevated TSH is mostly encountered in cases of subclinical hypothyroidism. Such a laboratory finding can also be caused by macro-TSH which is a rare condition. To avoid unnecessary investigations and treatment, macro-TSH should be kept in mind in patients with high TSH levels without symptoms of hypothyroidism in the differential diagnosis.

Key words: Subclinical hypothyroidism, macro-TSH, polyethylene glycol

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Introduction

Thyroid stimulating hormone (TSH) is an essential parameter for evaluating thyroidal dysfunctions. Normal free thyroxine (FT4) level accompanied by elevated TSH is mostly due to subclinical hypothyroidism. This situation can also be seen in some TSH producing pituitary adenomas, thyroid hormone resistance (Refetoff syndrome) syndromes and laboratory interferences due to inactive TSH and heterophile antibodies. Macro-TSH is a macromolecule formed by anti TSH immunoglobulin G (a TSH- Ig G) molecule and TSH molecule which leads to elevation in TSH levels in laboratory measurements [1]. The presence of macro-TSH which is a rare entity can be confirmed by polyethylene glycol (PEG) precipitation method [2].

In this case report, we aimed to emphasize the importance of clinical and laboratory evaluations in determining macro-TSH for avoiding unnecessary investigations and treatment.

Case Report

An 18 years old female subject was referred to our clinic in February 2013 with elevated levels of TSH detected incidentally. In her clinical evaluation she had no symptoms of hypothyroidism or any other thyroid disorder. In her personal and family histories, both the patient and the family members had no previously diagnosed thyroid disorder. The patient had no medication usage. In her physical examination, no thyroid nodule was detected. The laboratory investigations revealed high TSH [11.45 μ IU/mL; normal reference interval (NRI: 0.5-5.5 μ IU/mL)], normal FT4 [13.85 pmol/L; (NRI: 12-22 pmol/L)] and low free triiodothyronine (FT3) [1.94 pmol/L; (NRI: 3.9-6.8 pmol/L)] levels. Except the high levels of anti-thyroglobulin antibody (aTGB-Ab) [290.9 IU/ml; (NRI: 0-115 IU/ml)], other antibodies; anti-thyroid peroxidase antibody (aTPO-Ab) [24.48 IU/ml; (NRI: < 34 IU/ml)] and anti-TSH receptor antibody [<2.40 IU/ml; (NRI: 0-10 IU/ml)] were within the normal ranges. Ultrasonographic (USG) evaluation revealed that the right thyroid lobe had the dimensions of 13x18x52 mm, the left lobe 13x13x50 mm and the isthmus was 3 mm in diameter. In the doppler USG the thyroid gland was normovascular. L-thyroxine (L-T4) replacement treatment 50 μ g daily was started who was thought to have early stage of Hashimoto's disease. After 3 months of treatment, the control level of FT4 was found to be elevated (25.3 pmol/L) due to the treatment and the elevated levels of TSH (8.79 μ IU/mL) remained stable. FT3 level was

found to be within normal ranges (4.42 pmol/L) (Table 1). The dosage of L-thyroxine was decreased and L-triiodothyronine (L-T₃) (12.5µg/day) was added to the treatment because of the fact that T₃ level is more effective in suppressing TSH release from the hypophysis. After 6 weeks, despite the high level of FT₃ (8.40 pmol/L), TSH level was still found to be high (7.57µIU/mL) (Table 1).

Table 1. Thyroid hormone levels of the patient before and after treatment

Thyroid hormone levels before and after treatment	02/2013 (Initial, before treatment)	05/2013 (Under L-thyroxine treatment)	07/2013 (Under L-thyroxine and L-triiodothyronine treatments)
TSH (µIU/mL) (NRI: 0.5-5.5)	11.45	8.79	7.57
Free T ₄ (pmol/L) (NRI: 12-22)	13.85	25.30	23.00
Free T ₃ (pmol/L) (NRI: 3.9-6.8)	1.94	4.42	8.40

TSH: Thyroid stimulating hormone concentration, T₄: Thyroxine, T₃: Triiodothyronine

When L-T₃ and L-T₄ treatments were found to be ineffective for lowering TSH, polyethylene glycol (PEG) method for TSH measurement was planned to rule out the possibility of macro-TSH which is a rare condition. TSH was measured at the same time with electrochemiluminescence immunoassay (ECLIA) and PEG and compared. TSH was found to be 8.35 µIU/mL with ECLIA and after PEG procedure, the measured level of TSH was found to be 0.02 µIU/mL and %77 of it is was due to macro-TSH, so the treatment was stopped. After the cessation of treatment for 3 months, TSH level upon using the PEG method was found to be within normal ranges as 1.96 µIU/mL.

Discussion

In this case report, a rare condition of macro-TSH with elevated levels of TSH and without symptoms of hypothyroidism leading to diagnostic confusion was defined.

TSH is a glycoprotein composed of alpha and beta subunits that are noncovalently linked. It controls thyroid cell growth and hormone production by binding to a specific TSH receptor. Generally accepted normal level of TSH in circulating blood is 0.5-5.5 µIU/mL. TSH secretion is under the control of T₃ level and thyrotropin releasing hormone (TRH). In some situations the usual reciprocal relationship between serum TSH and free thyroid hormone

concentrations is disrupted. Assay interference like the presence of anti-TSH antibodies is one of these situations in which the patient is euthyroid clinically [3-5].

Macrohormones are high molecular weight complexes. In the literature, most of the data about macrohormones consists of prolactin. Macro-TSH is a rare entity which came into prominence in recent years. TSH weighs 30 kDA and is easily cleared by kidneys. When TSH binds with Ig G, its molecular weight increases and its clearance level decreases significantly. As a result macro-TSH accumulates in blood and its' level increases. Despite the high levels of macro-TSH, the thyroid hormones don't increase and the patients are often euthyroid showing that the biological effects of macro-TSH are either weak or not exist at all [6].

The TSH levels of such cases reported in the literature are often greater than 10 μ IU/mL. This was also the situation in our case. Our patient's TSH measured with ECLIA method was found to be 11.45 μ IU/mL initially. Unlike all the other reported cases in the literature, FT3 level was lower than normal in our case, although she is euthyroid clinically. It's obscure if this low level might have a role in the formation of macro-TSH. If the role of FT3 in the peripheral tissues and its' effect in the suppression of TSH are taken into account, this point should be clarified with advanced studies. On the other hand, this low level detected once can also be a laboratory error further confusing the diagnosis as far as our patient had no additional factor preventing peripheral conversion of FT4 to FT3, like drug usage.

Little is known about the prevalence and clinical importance of macro-TSH. In a study conducted in the serum samples of 495 patients with TSH levels greater than 10 μ IU/mL, macro-TSH was detected in only 3 and the prevalence was stated to be % 0.6 [2]. As far as the rarity of the publications about macro-TSH is considered, it is reasonable to think that this situation is not realized or does not come to mind in some unexplained high levels of TSH.

Thyroglobulin, TPO and the TSH receptor are three major thyroidal autoantigens. Circulating autoantibodies to these antigens are useful markers for thyroid autoimmunity. Increased incidence of autoimmune thyroid disease in postpubertal and premenopausal women, as well as the occurrence of postpartum thyroiditis, implies a role for female sex hormones in autoimmune thyroid disorders [3,4]. The previously reported 12 macro-TSH cases in the literature were mostly women like our patient. Eleven of them reported to have no symptom or evidence of thyroid disease, only one patient was reported to have symptoms of hyperthyroidism. Most of the cases reported had a high rate of aTGB-Ab and aTSH-R Ab

positivity. In one case high level of aTPO-Ab was reported [1,7]. In parallel with the literature, our patient had no clinical symptom suggesting thyroid disorder and only increased levels of aTGB-Ab was found.

Immunoglobulins such as aTGB-Ab, aTPO-Ab and aTSH-R Ab can cross the placenta and affect the fetus. There are neonates having congenital hypothyroidism due to antibodies with macro-TSH reported in the literature, in whom it was shown that the macro-TSH passed from the mother across the placenta [8,9]. This point may be important and should be kept in mind in women who are diagnosed with macro-TSH in their child-bearing age, like our patient. In the clinical follow-up of such patients, it wouldn't be accurate to trust only the TSH measurement. It is necessary to follow symptoms and FT4 levels as well as TSH [10,11].

In conclusion, macro-TSH is a TSH and anti-TSH IgG autoantibody complex. Its presence should be evaluated in cases with unexpectedly high TSH values especially with antibody positivity against thyroidal autoantigens. When a discrepant result is found, particularly an increased TSH together with normal FT4 and FT3 levels and clinical euthyroidism, then antibody interference should be suspected [5,12]. It's clear that detection of macro-TSH will prevent diagnostic confusions and unnecessary evaluations and treatments.

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