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CASE REPORT

Macro-TSH Interference in Thyroid Function Testing: a Case Report and Literature Review

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SUMMARY

Background: **TSH (Thyroid-Stimulating Hormone) is a key hormone secreted by the pituitary gland, which controls the production and release of thyroid hormones (T4) and triiodothyronine (T3) through a negative feedback mechanism. TSH plays a crucial role in the diagnosis and treatment of various thyroid diseases; however, TSH testing may be affected by a variety of factors, leading to inaccurate test results. The main interferents include heterophilic antibodies, thyroid hormone autoantibodies (THAb), and macro-TSH. These interferents may cause TSH test results to be falsely elevated or reduced.**

Methods: **In thyroid function testing, chemiluminescence immunoassay (CLIA) is a commonly used technique that uses chemiluminescence-labeled antibodies to detect specific levels of thyroid hormones and TSH. In this case, the patient had no history of thyroid disease. When thyroid test results do not match clinical symptoms, and the changes in TSH, free triiodothyronine (FT3), and free thyroxine (FT4) do not conform to the rules, it is necessary to exclude the presence of test interferents. The patient had no history of rodent contact, so interference from heterophilic antibodies was temporarily not considered. Our laboratory's preferred method for excluding interference from large molecular substances is PEG6000 treatment.**

Results: **Routine thyroid function tests showed a TSH level of 16.1751 μIU/mL, higher than the normal reference range (0.3500 - 4.9400 μIU/mL). FT3 was 3.47 pmol/L (reference range 2.43 - 6.01 pmol/L), FT4 was 13.10 pmol/L (reference range 9.01 - 19.05 pmol/L), TT3 was 0.96 nmol/L (reference range 0.88 - 2.33 nmol/L), and TT4 was 74.12 nmol/L (reference range 62.68 - 150.84 nmol/L). After treatment with the PEG6000 precipitation method, the TSH test result in the patient's serum dropped to 0.98 μIU/mL, within the normal range.**

Conclusions: **TSH testing is crucial for the diagnosis and treatment of thyroid diseases. Accurate TSH levels are essential for determining thyroid function status, guiding treatment plans, and monitoring disease progression; this case emphasizes the importance of identifying and excluding the influence of interfering factors in thyroid function testing. Interfering factors, such as the presence of macro-TSH, can lead to clinical misdiagnosis and mistreatment. The mechanism and clinical significance of macro-TSH formation are not yet fully elucidated, and the combination of anti-TSH antibodies with TSH may be the main cause of macro-TSH formation. All macro-TSH patients show positive anti-TSH antibodies, but not all patients with positive anti-TSH antibodies will form macro-TSH. When thyroid function test results do not match clinical symptoms or the changes in TSH, FT3, and FT4 do not conform to the rules, it is necessary to exclude the presence of test interferents such as macro-TSH. In this case, the normalization of TSH levels after treatment with the PEG6000 precipitation method confirmed the presence of macro-TSH in the patient's serum, thus avoiding unnecessary treatment.**

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KEYWORDS

thyroid function testing, macro-TSH, PEG6000 precipitation method

INTRODUCTION

TSH (Thyroid-Stimulating Hormone) is a key hormone in regulating thyroid function, secreted by the pituitary gland, and controls the production and release of thyroid hormones (T4) and triiodothyronine (T3) through a negative feedback mechanism. TSH plays several crucial roles, including:

Diagnosis of thyroid diseases
Measurement of TSH levels is the most common screening method for thyroid dysfunction. Decreased or increased TSH levels can confirm the presence of thyroid function abnormalities, but further examinations are needed to determine the specific cause [1].

Treatment of thyroid nodules and goiter
TSH plays a significant role in the formation of thyroid nodules and goiter. Using thyroid hormones to suppress TSH secretion may help reduce nodules or goiter, or at least prevent further enlargement [2].

Adjuvant treatment of thyroid cancer
TSH is an important clinical drug for the adjuvant treatment of thyroid cancer, reducing TSH secretion to shrink thyroid swelling. For patients with autonomous thyroid hormone production resulting in serum TSH concentrations already below normal, suppression therapy is expected to be ineffective [3].

Autoimmune thyroid diseases
The TSH receptor (TSHR) plays a significant role in the occurrence and development of thyroid-related diseases. Autoimmune thyroid diseases, such as Graves' disease and Hashimoto's disease, are related to the activation or inhibition of TSHR [4].

Molecular mechanism research
The detailed pattern of interaction between TSH and its receptor TSHR, as well as the revelation of the molecular mechanism of TSH activation of TSHR, provides a structural basis for the development of antibodies or small molecule drugs for the treatment of thyroid-related diseases [5,6].
But sometimes TSH testing may be affected by various factors, leading to inaccurate test results. The main interferents include heterophilic antibodies, thyroid hormone autoantibodies (THAb) [7], and macro-TSH [8]. These interferents may cause TSH test results to be falsely elevated or reduced, affecting clinical decisions. Macro-TSH is a complex formed by the combination of immunoglobulins with TSH. Its molecular weight is about five times that of TSH monomers, hence the name "macro-TSH." Due to its large molecular weight, macro-TSH has a reduced renal clearance rate and tends to accumulate in the serum. Macro-TSH does not have biological activity but has immunological activity and can be detected, leading to falsely elevated TSH test results [8].
The presence of macro-TSH in thyroid function testing may lead to clinical decision errors, causing misdiagnosis and improper treatment. For example, in patients with subclinical hypothyroidism, about 0.6% to 1.62% have macro-TSH [9,10]. If individuals with normal TSH are misjudged as having subclinical hypothyroidism due to the presence of macro-TSH, unnecessary treatment may result. Therefore, it is crucial to accurately distinguish whether the increase in serum TSH in patients with subclinical hypothyroidism is caused by macro-TSH.
The mechanism and clinical significance of macro-TSH have not been fully elucidated. It is currently believed that the combination of anti-TSH antibodies with TSH is the main cause of macro-TSH. Studies have found that all patients with macro-TSH have positive anti-TSH antibodies, but it is not yet clear whether all patients with positive anti-TSH antibodies will form macro-TSH [11]. Therefore, when thyroid function test results do not match clinical symptoms or the changes in TSH, free triiodothyronine (FT3), and free thyroxine (FT4) do not conform to the rules, it is necessary to exclude the presence of test interferents such as macro-TSH.

CASE PRESENTATION

A 56-year-old female patient was admitted to the hospital due to abdominal pain. Routine thyroid function tests revealed that TSH was 16.1751 μIU/mL (reference range 0.3500 - 4.9400 μIU/mL), higher than the normal reference range. FT3 was 3.47 pmol/L (reference range 2.43 - 6.01 pmol/L), FT4 was 13.10 pmol/L (reference range 9.01 - 19.05 pmol/L), TT3 was 0.96 nmol/L (reference range 0.88 - 2.33 nmol/L), and TT4 was 74.12 nmol/L (reference range 62.68 - 150.84 nmol/L). The patient's serum was treated with PEG6000 precipitation method, and the TSH test result after treatment was 0.98 μIU/mL within the normal range.

DISCUSSION

In the detection of thyroid function, chemiluminescence immunoassay (CLIA) is a commonly used technology, which uses chemiluminescence labeled antibodies to detect specific thyroid hormone and TSH levels. It has the advantages of high degree of automation, short turnaround time, high specificity and sensitivity. The high sensitivity and specificity of this method make it an important tool for the diagnosis of thyroid dysfunction. However, false positive or false negative results may af-

fect clinical decision-making, leading to inappropriate treatment or delay in the diagnosis of the disease.
Upon inquiry, the patient had no history of thyroid disease. When thyroid test results do not match clinical symptoms, and the changes in TSH, free triiodothyronine (FT3), and free thyroxine (FT4) do not conform to the rules, it is necessary to exclude the presence of test interferents. The patient had no history of rodent contact, so interference from heterophilic antibodies was temporarily not considered. Our laboratory's preferred method for excluding interference from large molecular substances is PEG6000 treatment. PEG precipitation is an effective biomolecular separation technique, especially suitable for research that requires the separation of large molecules from complex samples [12]. After treatment, it was found that the patient's TSH returned to normal, suggesting the presence of macro-TSH in the patient's serum.

CONCLUSION

The accuracy of TSH testing is crucial for the diagnosis and treatment of thyroid diseases. The presence of interfering factors makes it particularly important to quickly and accurately identify and exclude these interferences to avoid clinical misdiagnosis and mistreatment.

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Declaration of Interest:
All authors declare that they have no conflict of interest.

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