Case Report

An Anti-Idiotype Antibody to T3: A Misleading Cause of Inappropriate TSH Secretion - Case Report

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A 67-year-old woman presented with a one-week history of generalized muscle weakness. On physical examination, she had a left facial palsy, dysarthria, grade 1 strength in lower extremities and grade 3 in upper extremities, diminished deep tendon reflexes, and peripheral sensation in a glove and stocking pattern. Anal sphincter tone and perianal sensation were normal. She was being treated with atenolol for hypertension. She was clinically euthyroid. The provisional clinical diagnosis was Guillain-Barre syndrome. Her laboratories profile showed hyponatremia so that thyroid function test was investigated. TSH 7.090 mIU/L (0.27 to 4.20), FT3 13.33 pg/ml (2.00 to 4.40), FT4 1.37 ng/dl (0.93 to 1.70) tested by one-step electrochemiluminescent immunoassay (Cobas® platform). Negative results of anti-thyroid peroxidase antibody (16.25 IU/ml) and anti-thyroglobulin antibody (<10 IU/ml). Serum morning cortisol concentration was normal. The sample was repeated at the same lab to exclude laboratory error. The results confirmed mildly elevated TSH with a high FT3 concentration but a FT4 level in the reference range. Thus, the authors assessed FT3, FT4, and TSH in a different laboratory (Architect® platform). This revealed FT3, FT4, and TSH within reference ranges. Confirming the assay interference, the sample was sent to Roche for further analysis as well. The results showed that she had antibodies to anti-idiotype of T3 and FT3 assay.

Keywords: Free T3, Assay interference, Human anti-mouse antibodies, Anti-idiotype antibodies

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Measurements of thyrotropin (TSH), total and free thyroxine (TT4, FT4), and total and free triiodothyronine (TT3, FT3) are widely used diagnostic methods for the evaluation of thyroid function. However, some serum samples will demonstrate a non-specific binding with assay reagents that can interfere with the measurement of these hormones. Recently, there have been numerous reports of interferences in thyroid hormone immunoassays. In highly sensitive single- or double-antibody immunoassays, the presence of circulating endogenous antibodies directed against different antigens may cause either falsely depressed or falsely increased values of thyroid hormones[1]. They can be heterophile antibodies, human anti-animal antibodies or autoantibodies to TSH, T4, or T3. Discrepancies between assay values and previous results obtained with the same assay, as well as other biochemical parameters or clinical setting are paramount in the suspicion and detecting process of interference[2,3]. Here, the authors reported a case of a spurious elevation of FT3 in a Thai patient caused by human anti-animal antibodies (anti-idiotype specificity).

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Case Report

A 67-year-old woman presented with generalized muscle weakness for one week. Physical examination revealed a blood pressure of 144 over 85 mmHg, body temperature of 37.7°C, pulse rate at 70 per minute, and respiratory rate of 16 per minute. Neurological examination showed left facial palsy, dysarthria, grade 1 strength at lower extremities, and grade 3 at upper extremities, deep tendon reflex diminished, peripheral sensation decreased in a glove and stocking pattern, normal anal sphincter tone, and perianal sensation. Thyroid gland was normal in size. Examination findings were normal. She had

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Table 1. Patient's thyroid function tests

	TSH (mIU/L)	FT3 (pg/ml)	FT4 (ng/dl)	TT3 (ng/ml)	TT4 (ug/dl)
9/4/2018					
Cobas e610 (Roche)*	7.09	13.33	1.37	-	-
11/4/2018					
Cobas e610 (Roche)*	6.41	11.54	1.59	0.93	6.34
18/4/2018					
Cobas e610 (Roche)*	2.63	7.26	1.22	0.68	5.37
Architect i2000 (Abbott)**	2.16	2.11	0.97	0.59	5.00
Modular E170 (Roche)***	2.65	7.04	1.24	-	-

TSH=thyroid stimulating hormone; FT3=free triiodothyronine; TT3=total triiodothyronine; FT4=free thyroxine; TT4=total thyroxine

Reference ranges

* Cobas: TSH 0.27 to 4.20 mIU/L, FT3 2.00 to 4.40 pg/ml, FT4 0.93 to 1.70 ng/dl, TT3 0.80 to 2.00 ng/ml, TT4 4.60 to 12.00 ug/dl

** Architect: TSH 0.35 to 4.94 uIU/ml, FT3 1.88 to 3.18 pg/ml, FT4 0.70 to 1.48 ng/dl, TT3 0.64 to 1.52 ng/ml, TT4 4.87 to 11.72 ug/dl

*** Modular: TSH 0.27 to 4.20 mIU/L, FT3 2.00 to 4.40 pg/ml, FT4 0.93 to 1.70 ng/dl

no symptoms of thyrotoxicosis, hypothyroidism, or history of neck surgery or neck radiation. She had no family history of thyroid disease. She had had long-standing hypertension currently treated with atenolol. The admitting diagnosis was Guillain-Barre syndrome (GBS) based on clinical grounds and the following laboratory features, elevated cerebrospinal protein levels with normal white blood cell count and liver function tests. Additional Laboratory included Na 129 mEq/L (135 to 145), K 3.7 mEq/L (3.5 to 5), Cl 96 mEq/L (96 to 106), CO_2 16 mEq/L (23 to 30), creatine phosphokinase (CPK) 1662 U/L (22 to 198). It was assumed that the high CPK level likely was secondary to axonal degeneration from the GBS itself. Intravenous immune globulin (IVIG) was given for GBS treatment. Because of the hyponatremia, increased urine sodium, decreased serum osmolality with increased urine osmolality, she was diagnosed as having the syndrome of inappropriate antidiuretic hormone (SIADH). Treatment with fluid restriction corrected her low serum sodium. Next, the cause of the SIADH was assessed. Both a malignancy workup and a review of potential drugs were negative. Since either hypothyroidism or adrenal insufficiency can cause hyponatremia, thyroid function tests and serum morning cortisol were determined. TSH, FT3, and FT4 were measured with a one-step electrochemiluminescent immunoassay (Cobas®, Roche Diagnostic, Basel, Switzerland). The result revealed TSH 7.090 mIU/L (0.27 to 4.20), FT3 13.33 pg/ml (2.00 to 4.40), and FT4 1.37 ng/dl (0.93 to 1.70). Other investigations revealed negative results of anti-thyroid peroxidase antibody (16.25 IU/ml) and anti-thyroglobulin antibody (<10 IU/ml). Serum morning cortisol concentration was 14.8 µg/dl.

Since our patient was clinically euthyroid and had a normal-sized thyroid gland, the thyroid function tests were repeated (Table 1) with the same kit in our lab department. The results confirmed mildly elevated TSH with high FT3 concentration but FT4 was in the reference range (Table 1). Then, FT3, FT4, and TSH were measured in a different laboratory (Architect®, Abbott Diagnostics, Illinois, United States). This revealed FT3, FT4, and TSH within reference ranges. The sample was sent to Roche for further analysis as well that confirmed that the patient had anti-idiotype antibodies interference in the assay resulting in a falsely elevated FT3.

Discussion

The authors reported a 67-year-old woman with high FT3 results, but not TT3, that was not associated with low TSH values. Differential diagnosis for increased level of FT3 with normal or high TSH are 1) assay interference from antibodies to thyroid hormone (THAAbs) or human anti-mouse antibodies (HAMAs), 2) TSH-secreting pituitary adenoma, 3) resistance to thyroid hormone (RTH), and 4) drugs (e.g., amiodarone, heparin)[4]. This patient was clinically euthyroid, with no family history of thyroid disease and had not taken medications that could interfere with thyroid hormone values. TSH-secreting

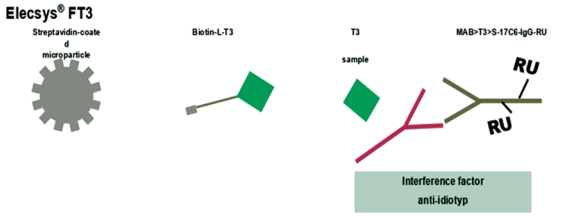

Figure 1. Anti-idiotype interference.

pituitary adenoma was less likely with no symptoms of thyroid hormone excess. Abnormal binding protein was less likely given the elevated FT3 and normal TT3. RTH is dominantly inherited condition. Although most patients with RTH are clinically euthyroid, the presence of goiter can range from 65% to 95% of known case[5]. Hence, assay interference is the most likely factor to investigate.

The discordance between high FT3 without a low TSH can be found in conditions where the serum contained an interfering substance such as heterophilic antibodies, anti-T3 antibodies[6], anti-ruthenium antibodies (involved in the Elecsys assay), or interfering drugs such as non-steroidal anti-inflammatory drugs[7]. Upon further analysis of the sample with a research toolbox, an interfering factor, specifically for the FT3 III assays (Elecsys), was detected. The interference factor was anti-idiotype, resulting in the falsely elevated FT3 value. The authors checked for anti-T3 antibodies. None were found.

The authors' lab used electrochemiluminescent immunoassay (Cobas®, Roche Diagnostic, Basel, Switzerland). The Elecsys FT3 assay is a competitive immunoassay involving a specific anti-T3 sheep monoclonal antibody labeled with a ruthenium complex, T3-biotin, and streptavidin-coated microparticles (Figure 1).

In the Elecsys FT3 competitive immunoassay, there are two types of antibodies, anti-ruthenium antibodies (RU) and T3 coated with biotin (Biotin-L-T3). In the report case, anti-idiotype antibodies bind to anti-RU preventing the binding of T3 to the assay antibodies, yielding falsely high FT3 results. The anti-idiotype antibody is directed against specific idiotypes[8]. To avoid interference from anti-ruthenium antibodies, a new blocking protein was developed and included in the Elecsys FT3 assay by Roche, starting from a lot number 174865[1], and the blocker can eliminate this interference. Unfortunately, interference due to anti-idiotype antibodies was not eliminated. The frequency of this interference is less than 0.05%[6].

The patient's mildly elevated TSH initially is not likely due to the same process interfering with the TSH assay as the FT3 because it was normal seven days later in the same system. As the patient was sick, it could be that she had mild hypothyroidism that cleared when she was treated. The lower TT3 present in the sample seven days after the normal level in the initial sample is likely related to changes in binding proteins induced by the primary illness or its treatment since the FT3 was normal.

Conclusion

When clinical and thyroid function test results diverge, the clinician should always consider that something may be interfering with the assay to avoid misdiagnosis and an inappropriate treatment decision.

What is already known on this topic?

Interference in immunoassay can affect thyroid function test.

What this study adds?

Interference in immunoassay due to anti-idiotype antibodies to T3 is less common than interactions with antibodies to thyroglobulin, microsomal thyroid peroxidase, TSH receptor, T3, and T4. The frequency of this interference is less than 0.05%. This report may be useful to avoid misdiagnosis and inappropriate management.

Conflicts of interest

The authors declare no conflict of interest.

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