Macro-Thyrotropin: A Case Report and Review of Literature

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Context: Isolated elevation of TSH in the absence of thyroid symptoms can be very rarely caused by a macromolecule formed between TSH and Ig (macro-TSH), confounding the interpretation of thyroid function test results.

Objective: We described the use of several commonly available laboratory-based approaches to investigate an isolated TSH elevation [232 mIU/liter; free T_4, 10 pmol/liter (reference interval, 10.0–23.0 pmol/liter), Vitros platform] in a clinically euthyroid elderly gentleman, which led to the diagnosis of macro-TSH.

Methods and Results: TSH concentration of the patient was significantly lower (122 mIU/liter) when measured on the Advia Centaur platform. Serial dilution of the patient's sample showed a nonlinear increase in TSH recovery at increasing dilution (nonlinearity). Polyethylene glycol precipitation and mixing the patient's sample with a hypothyroid patient sample showed reduced TSH recovery, suggesting the presence of a high molecular weight interfering substance and excess TSH binding capacity, respectively. Heterophile blocking tube studies and rheumatoid factors were negative. Gel filtration chromatography demonstrated a TSH peak fraction that approximated the molecular size of IgG; together with the excess TSH binding capacity, this indicated the presence of TSH-IgG macro-TSH. A review of 12 macro-TSH case reports showed that samples with macro-TSH produce over-recovery with dilution, return negative results on anti-animal and anti-heterophile blocking studies, and commonly have recovery of less than 20% when subjected to polyethylene glycol precipitation.

Conclusion: Macro-TSH is an underrecognized laboratory interference. Routine laboratory techniques described above can help diagnose this rare entity. A close dialogue between the physician and the laboratory is important in approaching such cases. **(*J Clin Endocrinol Metab* 97: 1823–1828, 2012)**

An elevated TSH concentration in the presence of normal free T_4 (fT4) concentration is most commonly encountered in the setting of subclinical hypothyroidism. Other less common causes include TSH resistance syndromes, biologically inactive TSH, and laboratory interferences (1). The interpretation of such biochemical results can present as clinical conundrums, especially when the clinical symptoms are subtle or absent.

Macro-TSH is a rare laboratory interference that can interfere with laboratory measurement of TSH, leading to spuriously high results (1). It is a macromolecule that is formed between autoimmune anti-TSH Ig and TSH mol-

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in U.S.A.
Copyright © 2012 by The Endocrine Society
doi: 10.1210/jc.2011-3490 Received December 29, 2011. Accepted March 5, 2012.
First Published Online March 30, 2012

Abbreviations: fT4, Free T_4; PEG, polyethylene glycol.

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ecule. The diagnosis of macro-TSH is confirmed by gel filtration chromatography, which can be used to identify an Ig-TSH complex by dissociation or recovery studies. However, this is expensive and not routinely available in most clinical laboratories. Here, we describe the use of several commonly available laboratory techniques to investigate a case of isolated TSH elevation in a clinically euthyroid patient that led to the diagnosis of macro-TSH. An algorithm to guide the laboratory investigation of cases suspected of laboratory interference, including macro-TSH, is proposed.

Case Report

A 60-yr-old gentleman was admitted to the hospital for a left intertrochanteric fracture after an episode of syncope. His past medical history included hypertension, ischemic heart disease, and dyslipidemia. His oral medications were aspirin, atenolol, enalapril, lovastatin, and sublingual glyceryl trinitrate. During admission, he was noted to have sinus bradycardia (55–60 beats per minute). Although the bradycardia could have been attributed to the atenolol treatment, thyroid function tests were performed to exclude hypothyroidism. The thyroid function tests showed a markedly elevated TSH (232 mIU/liter; reference interval, 0.45–5.0 mIU/liter) with a low-normal fT4 (10 pmol/liter; reference interval, 10.0–23.0 pmol/liter). The thyroid function test was performed on the Vitros 5600 platform (Ortho Clinical Diagnostics, Rochester, NY).

Further history from this patient revealed no symptoms of hypothyroidism. There was no personal or family history of thyroid or autoimmune disorders. On physical examination, apart from sinus bradycardia, he was clinically euthyroid. There was no thyromegaly. The antithyroid peroxidase antibodies were raised at 496 IU/ml (reference interval, 0–50 IU/ml). Antithyroglobulin and anti-TSH receptor antibodies were not elevated. The lipid profile and SHBG concentration were within reference limits.

The suspicion of a spuriously elevated TSH was raised because the patient was clinically euthyroid despite the markedly elevated TSH concentration. To screen for the presence of laboratory interference that may cause the markedly elevated TSH, TSH measurement was repeated on the same patient sample using another analytical platform (Advia Centaur; Siemens Healthcare Diagnostics, Deerfield, IL). An interfering substance (*e.g.* heterophile antibodies) may react variably to the different antibodies employed by different immunoassays, giving rise to grossly discrepant results between different assays. The TSH concentration measured by the Advia Centaur analyzer remained elevated (122 mIU/liter), although significantly lower than the results of the Vitros platform. The large difference could not be accounted for by the analytical bias between the assays alone, suggesting a high likelihood of assay interference. The fT4 concentration remained within the reference limits on the Advia Centaur platform. All subsequent TSH measurements were performed on the Advia Centaur platform.

In the linearity study, the serum of the patient was diluted with the TSH assay diluent provided by the manufacturer at 1:2 to 1:10 dilutions. The TSH recovery of the diluted samples showed increasing concentration (increasing recovery) at increasing dilution factor, showing nonlinearity. Ten times dilution of the patient's serum yielded a recovery of 135% (neat, 122 mIU/liter; 10× dilution, 165 mIU/liter). Nonlinearity can be caused by heterophile antibodies, rheumatoid factor, and macro-TSH. Rheumatoid factor, which can behave like heterophile antibodies, was undetectable in this patient.

The serum of the patient was then subjected to polyethylene glycol (PEG) precipitation (2) to remove high molecular weight proteins, including interfering antibodies and macro-TSH. The post-PEG TSH recovery for this patient was 3.2% (pre-PEG, 122 mIU/liter; post-PEG, 3.9 mIU/liter), indicating the presence of a high molecular weight interfering substance. When a euthyroid patient serum was subjected to the same PEG treatment in the same run, the recovery was 40% (pre-PEG, 2.42 mIU/liter; post-PEG, 0.96 mIU/liter). Incubation of the patient's serum with heterophile blocking tube (Scantibodies, Santee, CA) returned 95% recovery and was considered a negative study. However, heterophile blocking tube is a specific but insensitive test for heterophile antibodies interference.

From the results obtained up to this point, heterophile antibodies and macro-TSH remained possible causes of the interference. Patients with macro-TSH can contain excess free anti-TSH antibody that can sequester TSH and lower the TSH measurement. To examine this, the sample of the patient (122 mIU/liter, Advia Centaur; 217 mIU/liter, Vitros) was incubated with a sample from a patient known to have hypothyroidism (165 mIU/liter, Advia Centaur; 142 mIU/liter, Vitros) at 1:1 ratio for 4 h. The recovery of TSH after the incubation was 85% (expected concentration, 144 mIU/liter; measured concentration, 123 mIU/liter) when measured using the Advia Centaur platform and 97% (expected concentration, 180 mIU/liter; measured concentration, 174 mIU/liter) on the Vitros analyzer. The reduced TSH recovery after the incubation suggested the presence of excess TSH binding capacity, which occurs in macro-TSH but not in heterophile antibody interference.

The biological activity of the TSH molecule of the patient was assessed by thyroid stimulating Ig bioassay, as previously described (3). Briefly, the sample of the patient was treated with PEG. The precipitate was then incubated with

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TABLE 1. Summary of the results of the procedures to identify the false-positive TSH result due to macro-TSH

Procedures on patient's serum	TSH results	Conclusion
Untreated		
Advia Centaur	122 mIU/liter	Inappropriately elevated TSH levels despite clinical euthyroidism, suggestive of assay interference
Vitros	232 mIU/liter	
Dilutions in Advia Centaur diluent, 10-fold	165 mIU/liter; 135% recovery	Increasing recoveries for patient sample suggest interference from heterophile antibodies, rheumatoid factor, or macro-TSH
Precipitation with PEG and reassay supernatant	3.9 mIU/liter; 3.2% recovery	Presence of a high molecular weight interfering substance
Heterophile-blocking tube	116 mIU/liter; 95% recovery	Considered a negative study, although heterophile antibodies interference cannot be ruled out because this test is specific but nonsensitive for heterophile antibodies interference
Incubation with hypothyroid patient sample	Expected, 144 mIU/liter; measured, 123 mIU/liter; 85% recovery	Presence of excess TSH binding capacity, likely macro-TSH interference
Gel filtration chromatography analysis (Perkin-Elmer DELFIA assay)	Presence of high molecular weight TSH fraction, which increased after incubation with hypothyroid patient sample	Confirmed the presence of macro-TSH

TSH concentrations were reassayed using Advia Centaur assay for all the procedures, except for gel filtration chromatography analysis.

the cell line of the bioassay, and the cAMP generated was measured. The bioactivity of the sample of the patient was 120% compared with pooled serum control (reference interval, 50–179%), suggesting that the presence of biologically active interfering substance was unlikely. The result of this experiment was consistent with the euthyroid state and the absence of thyromegaly on clinical examination.

Collectively, the results suggested the presence of a high molecular weight interfering substance. This substance has excess capacity to sequester TSH and low biological activity (Table 1). Assay interference by heterophile antibodies or rheumatoid factors were less likely based on the above investigations. The presence of a high molecular mass TSH immunoreactivity was confirmed using gel filtration chromatography as previously described (4). The TSH concentrations were measured by the Perkin-Elmer DELFIA assay, which was employed by the reference laboratory performing the gel filtration chromatography. A TSH peak fraction that approximated the molecular size of IgG was found, suggesting the presence of macro-TSH or a cross-linking heterophile (Fig. 1). When the serum of the patient was incubated with a sample from a patient with hypothyroidism and reanalyzed, the immunoreactivity of the high molecular weight species increased, confirming the presence of excess TSH binding capacity in the patient serum and the presence of macro-TSH.

Discussion

Assay interference in the measurement of TSH is relatively common. Analytically suspicious TSH results have been reported to be present in 0.5–5% of patient samples (5, 6), and up to 38.2 and 55.6% when samples of healthy subjects were screened for interference by a stringent serial dilution protocol and heterophile-blocking tube tests, respectively (7). As such, spurious elevation of TSH should be considered and investigated when isolated elevations of TSH are incongruent with the patient's clinical presentation, particularly when these elevations are extreme.

Substances that commonly interfere with TSH assays include heterophile antibodies, human antimouse/animal antibodies, and rheumatoid factors (8). Monoclonal Ig has also

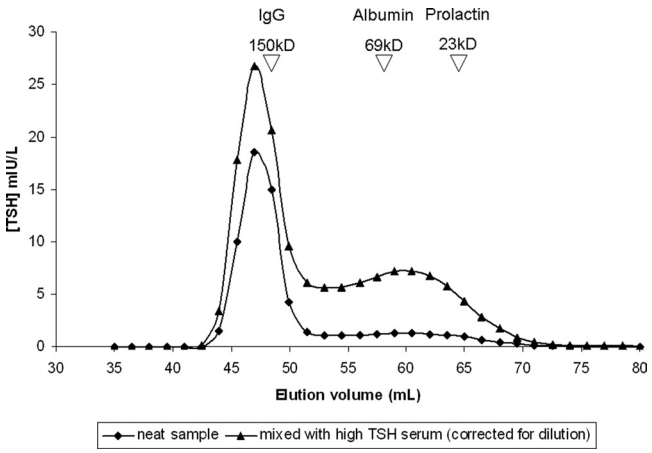

FIG. 1. Gel-filtration chromatogram of the patient sample showing a TSH peak fraction that approximated the molecular size of IgG (*solid dots*). The high molecular weight TSH peak fraction became higher (*solid triangles*) after mixing with a hypothyroid TSH sample, showing excess TSH binding capacity in the patient sample. The low molecular weight TSH fraction (near the albumin fraction) increased as a result of the excess TSH from the hypothyroid sample that is not bound by the excess TSH binding capacity of the patient.

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been shown to positively (9) and negatively (10) interfere with TSH assays. With the advent of the use of therapeutic immunological agents, spuriously high TSH results arising from monoclonal mouse antibody and anti-idiotypic antibody are also recognized (11, 12). A common mechanism for positive assay interference is the cross-linking of capture and signal antibodies of sandwich immunoassay, thereby falsely generating assay signal and spuriously elevating the TSH result. Interference from antibodies has been reviewed in detail elsewhere (13, 14). Highly discrepant TSH measurements on different TSH assays and the finding of nonlinearity on serial dilution provide early indication of the presence of assay interference.

Circulating autoimmune antithyroid hormone antibodies that affect thyroid hormone assays have been documented (15, 16). Similarly, circulating autoimmune anti-TSH antibody that interferes with TSH measurement has been reported in patients receiving bovine TSH as well as those with autoimmune thyroid diseases (17). Macro-TSH molecule is a rare entity and has only been demonstrated more recently. TSH is a small molecule that is excreted via the kidneys. When TSH forms a macromolecule complex with an antibody, the renal clearance of TSH is markedly reduced. However, the immunoreactivity of the TSH complex may be retained. The accumulated macro-TSH is therefore reflected as spuriously elevated TSH concentrations. Crucially, macro-TSH can occur in patients with TSH concentration that is within reference limits (18). However, the biological activity of macro-TSH may be reduced, and the patient remains clinically euthyroid.

A MEDLINE search revealed 12 cases of laboratory-confirmed macro-TSH from recently published case reports (2, 3, 18–22). Among these patients, the majority were females and displayed no symptoms of thyroid disorders, except one with clinical features of hyperthyroidism (19). Some of these patients had elevated concentrations of antithyroglobulin antibodies (2) and anti-TSH receptor antibodies (18). In contrast, our patient had an elevated concentration of antithyroid peroxidase antibodies, which was not previously reported. In all the cases but one (21), macro-TSH is formed between anti-TSH IgG and TSH molecule.

Vertical transfer of anti-TSH antibody from mother to fetus has been described in two reports. In these reports,

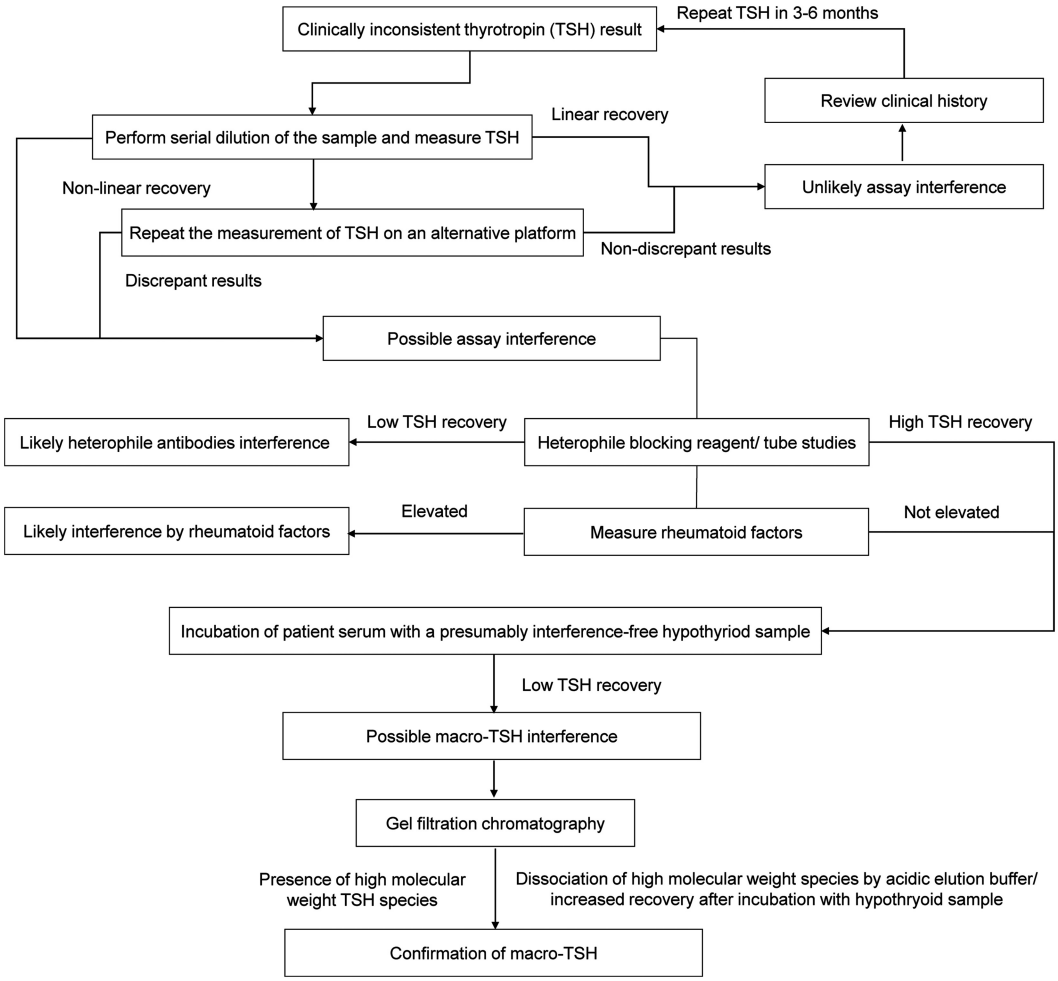

FIG. 2. A proposed diagnostic strategy for the investigation of macro-TSH.

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the neonates presented with hyperthyrotropinemia on routine neonatal screening (3, 20). Misdiagnosis of this benign assay interference can have detrimental consequences to the newborn. Elevated TSH results in a euthyroid newborn should be investigated initially by measuring the TSH and the fT4 of the mother (23). If the maternal TSH is elevated in isolation, macro-TSH should be considered and investigated appropriately. If macro-TSH is present, the TSH concentration of the newborn should fall gradually and normalize by 8 months, mirroring the natural elimination of maternal antibodies in a newborn (20).

From the case reports, all macro-TSH patients' samples produced over-recovery when they were diluted above a factor of five. Treating the samples with anti-animal and anti-heterophile blocking reagents always produced negative results. With PEG precipitation, the TSH recoveries were less than 20%, except for two cases where the recoveries were about 50% (19, 21). In comparison, 10 presumably normal samples produced TSH recovery of 58–79% after treatment with PEG precipitation (19). However, it is important to note that these values are assay dependent, and individual laboratories should derive local reference values for PEG-treated TSH measurement.

Macro-TSH appears to affect most commercially available TSH assays. It is less detectable compared with native TSH because the presence of the attached Ig on the TSH molecule may compromise the antigen-antibody binding of the TSH assays. Furthermore, the affinity of the antibodies used in the assays influences their ability to detect macro-TSH. The Roche and Perkin-Elmer DELFIA assays are more sensitive to macro-TSH interference (reporting higher spuriously elevated TSH results) (19–22), whereas the Advia Centaur assay is least sensitive to such interference (reporting lower spuriously elevated TSH results) (2, 4, 21, 22).

When a macro-TSH sample is mixed and incubated with an interference-free hypothyroid sample, the excess anti-TSH antibody from the macro-TSH sample will bind to the excess native TSH of the hypothyroid sample, forming macro-TSH. The TSH recovery of the mixture is reduced because some of the native TSH has been converted to the less detectable macro-TSH. However, the reduction of TSH recovery occurs to a lesser extent in TSH assays that are sensitive to macro-TSH because these assays can still detect considerable amounts of the newly formed macro-TSH. Hence, assays that are less sensitive to macro-TSH are better suited for this investigation because the magnitude of fall in TSH recovery will be more noticeable.

Macro-TSH is suggested when a macro-TSH/hypothyroid mixture returns lower TSH measurement after the incubation, and the TSH result of the mixture is lower in assays known to be less sensitive to macro-TSH. However, these methods are not sensitive for the diagnosis of macro-TSH interference because it is possible that a high-affinity, low-concentration anti-TSH antibody may not present with excess serum TSH binding capacity. These methods are in routine use in the laboratory of one of the authors (D.J.H.). From his personal experience, a recovery of less than 20% is usually associated with macro-TSH, confirmed on subsequent gel filtration chromatography analysis.

A definitive test for macro-TSH is the dissociation experiment by gel filtration chromatography. This technique involves using an acidic elution buffer (pH 3.0) to dissociate the antigen-antibody complex during gel filtration chromatography (2). Under such conditions, the peak fraction of the high molecular weight (Ig-associated) TSH species would diminish, whereas the peak fraction of the low molecular weight (monomer) TSH species would increase. This finding was not observed in our patient because the acidic nature of the eluent has interfered with the immunoassay (*i.e.* Perkin-Elmer DELFIA assay) used to measure the TSH concentration.

The clinical significance and prevalence of macro-TSH is currently not clear. Nevertheless, early recognition of this assay interference can avoid misdiagnosis and unnecessary investigation and/or treatment. Patients with macro-TSH should probably be followed up, especially those with elevated antithyroid antibodies and newborns (23). Because TSH measurements are no longer reliable in this clinical scenario, these patients should be monitored clinically and with fT4 measurements. In this situation, fT4 should be measured by equilibrium dialysis or ultrafiltration followed by HPLC-tandem mass spectrometry. These methods have better inverse log-linear correlation coefficient between TSH and fT4 than the direct analog immunoassays (24–26).

In conclusion, this report highlights the importance of close dialogue between the physician and the laboratory in approaching such cases. Macro-TSH can be strongly suspected when a sample shows under-recovery after being subjected to PEG precipitation and incubation with normal hypothyroid sample and over-recovery on serial dilution. Anti-animal and anti-heterophile antibodies should be absent. When these criteria are met, the diagnosis of macro-TSH can be confirmed by gel filtration chromatography. A diagnostic strategy for macro-TSH is proposed in Fig. 2.

Acknowledgments

We are indebted to Dr. Lee Lee Wong for her technical help.

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This report was partly supported by the Department of Medicine Fund, National University Hospital, Singapore.

Disclosure Summary: None of the authors has any conflict of interest to declare.

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