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Normal Thyroid-Stimulating Hormone and Elevated Free Thyroxine in a Patient Presenting with Self-Reported Heart Palpitations

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Guest: Dr. William Butler from the Hospital of the University of Pennsylvania and Children's Hospital of Philadelphia.

Bob Barrett: This is a podcast from *Clinical Chemistry*, a production of the Association for Diagnostics & Laboratory Medicine. I'm Bob Barrett. Thyroid hormones are responsible for modulating the metabolic rate, linear growth in childhood, cognitive development, reproductive function, and other essential biological processes. When thyroid dysfunction is suspected, measurement of thyroid stimulating hormone, or TSH, is typically performed as frontline testing. Most of the time, a normal TSH rules out thyroid dysfunction but in some cases, physicians and laboratorians need to dig a little deeper.

When TSH is within the reference interval and free thyroid hormone concentrations are elevated, it could be a TSH secreting pituitary tumor, antibodies binding to TSH and preventing its removal from circulation, interference with TSH measurement methods, or rare genetic variants affecting free T4 [thyroxine] concentrations. Quickly solving this puzzle is of utmost importance and provides a prime opportunity for clinical care teams and laboratorians to work together for the good of the patient.

A new clinical case study, appearing in the April 2025 issue of *Clinical Chemistry*, describes an unusual case of inappropriately normal TSH coupled with elevated concentrations of free thyroid hormones, and highlights the role of the clinical laboratory in establishing the diagnosis of a rare condition. In this podcast, we welcome the case study's lead author. Dr. William Butler is the senior clinical chemistry fellow at the Hospital of the University of Pennsylvania and Children's Hospital of Philadelphia. His special interests include tumor markers, endocrinology, and maternal-fetal laboratory medicine. So Dr. Butler, let's get into this case. What led the clinical team to consult the clinical laboratory for assistance?

William Butler: Yeah. So, we actually got involved on this case somewhat late in the game. So, the patient presented to his PCP about four months prior to the case sort of crossing my desk, with the chief complaint of heart palpitations and by the time he talked to us, the endocrinologist that was assigned to his case actually did a very thorough workup on this patient. So, you know, this included testing the free T4 concentration by an

alternative methodology, equilibrium dialysis just to confirm that it was a true elevation.

They tested other thyroid hormones such as total and free T3, they did a pituitary workup which included both imaging and laboratory testing, some basic interference workup. So, by the time they got to us, both the patient and his endocrinologist were both, you know, understandably frustrated and looking for answers as to why this patient has this abnormally elevated free T4 but normal TSH and were just hoping that the clinical laboratory could provide some further steps and guidance on this.

Bob Barrett: You mentioned that the patient had a pituitary adenoma on imaging, which could theoretically explain an inappropriately normal TSH in the presence of an elevated FT4. What led the team to continue working up the case for other analytical or pathological causes?

William Butler: So, I think this is actually one of the best teaching points of this case. Pituitary adenomas, particularly microadenomas, are really prevalent in the population. About 20% of the general population would be found to have an incidental pituitary adenoma if they had imaging. Functional adenomas on the other hand, particularly TSH-secreting adenomas, are not as common. So naturally, TSH-secreting adenomas only comprise about 1% of all pituitary adenomas and they're most frequently a macroadenoma.

Given the presence of both the pituitary adenoma and a normal TSH with an elevated free T4, it was appropriate to consider secondary hyperthyroidism in this case. So, the way the workup was – at first was they did imaging but and then they measured analytes such as alpha subunit, which is elevated in at least over about 50% to 85% of patients with a TSH-secreting adenoma. Furthermore, since about 25% of TSH-secreting adenomas also secrete other pituitary hormones, most frequently growth hormone or prolactin, testing for these analytes was performed. So, it really was a collective decision.

So, given that the lesion was only 4.5 mm, the patient had normal alpha subunit concentration, and normal concentrations of growth hormone and prolactin, the clinical team believed that this adenoma discovered on the imaging was probably an incidental finding and they wanted to pursue other potential etiologies for this.

Bob Barrett: You mentioned that you considered macro-TSH in your differential to explain the inappropriately normal TSH concentration, so let's get into that. Can you briefly describe what this is and how this typically presents biochemically?

William Butler: Yeah, so macro-TSH has been described in the literature more recently over the last few years. Rarely, a patient may produce autoantibodies against the TSH hormone itself, resulting in immune complexes that are not freely filtered by the glomerulus and then accumulate in the blood.

And this is most well-known to occur with prolactin. So, in fact, macroprolactin accounts for about 20% of hyperprolactinemia cases and occurs in about 4% to 5% of the general population. Macro-TSH on the other hand is reportedly less common affecting about -- thought to affect about 1% of the population, and in most cases, at least described in the literature, the TSH is usually very high, often greater than 100 but not exclusively so. However, to be thorough, we wanted to exclude the possibility that macro-TSH was potentially masking a case of primary hyperthyroidism, as that is a diagnosis we would not want to miss.

So -- And essentially, we're trying to rule out the possibility that the TSH is actually suppressed and that macro-TSH is making this result look normal. Similar to macroprolactin, PEG precipitation or size exclusion chromatography are the methods of choice, with PEG being performed by most laboratories, mostly for convenience and cost. The caveat here is that the cutoffs for determining the presence of macro-TSH are less well-defined as they are for macroprolactin, so that's an important item to consider when interpreting the results of this testing.

We send to Mayo Clinic which uses the mean ± 2 standard deviations of healthy controls to define what they consider normal for a macro-TSH test. So based on the report, the range of TSH precipitated in controls is 5% to 57%. So, you can imagine there's quite a lot of variability there and more work is needed to better define those cutoffs. However, based on their interpretation, we did not see much evidence to support that macro-TSH was causal to the normal TSH concentration that we were seeing in this patient.

Bob Barrett: So, it seems that you exhausted all options before considering *THRB* gene sequencing on this patient. Why was that?

William Butler: RTH syndrome, resistance to thyroid hormone syndrome, is a rare condition. So, it only affects about 1 in 40,000 live births and although this condition should be on the differential for a patient presenting with these biochemical findings, an elevated free T4 and normal TSH, it's far less likely to occur compared to other etiologies.

Furthermore, testing for this condition involves next-generation sequencing of the thyroid hormone receptor gene, which -- and that is an expensive test and it's close to $3,000.

So, we wanted to exclude all other possibilities before proceeding with this testing as we didn't want to create any additional financial burden for this patient.

Bob Barrett: Doctor, what is resistance to thyroid hormone syndrome and when should a clinician or laboratorian suspect this condition?

William Butler: Resistance to thyroid hormone syndrome is an inherited condition and it can be autosomal-dominant, inherited in an autosomal-dominant or recessive fashion, depending on the specific mutations involved. So essentially, a mutation in either thyroid hormone receptor gene, so there's two. They're kind of two different chromosomes, *THRA* and *THRB*, which encode the thyroid hormone receptor alpha and beta, respectively.

A mutation in either of those genes causes reduced sensitivity or signaling in response to stimulation by thyroid hormone. So, many patients are actually asymptomatic. However, some patients experience neurodevelopmental symptoms such as growth or mental retardation, hyperactivity, or heart palpitations to varying degrees. But in most cases, it's usually a mild presentation and that's because the reduced sensitivity to thyroid hormone is usually compensated by an increase in free thyroxine.

However, what makes this condition interesting is that since *THRA* and *THRB* are differentially expressed to various levels in different tissues, the increased free thyroxine concentration may actually cause a tissue-specific hyperthyroidism in tissues that express more of the normal receptor. To break that down, for example, the THR alpha receptor is more abundant in the heart. So, it increased free T4 concentration, which might compensate for the reduced sensitivity in the THR beta receptor.

It might cause excess stimulation of the TH alpha receptor, which might lead to symptoms such as heart palpitations. Now, it's important to distinguish this condition from primary or secondary hyperthyroidism as they -- these patients are clinically considered euthyroid and treatment is based on symptom management. So, a patient with hyperactivity might be treated with ADH medications, a patient with heart palpitations might be treated with beta blockers, et cetera.

The real exception to this rule is with pregnant patients carrying a fetus that is lacking the mutation, as excess thyroid hormone can cause a fetal thyrotoxicosis secondary to the high maternal thyroid hormone levels. So, if the mom has the condition and the fetus doesn't, then that patient might be treated with antithyroid medications, although this obviously carries the risk of then inducing hypothyroidism in the mom.

Bob Barrett: Well finally, Dr. Butler, as this workup initially started when a patient did present with heart palpitations, does RTH syndrome explain the initial clinical presentation, and how is the condition treated?

William Butler: Yeah, this is a tricky question to answer and my answer is this -- resistance to thyroid hormone syndrome would be a reasonable explanation for the heart palpitations, assuming cardiac pathology has been ruled out, because we don't want to miss any of that as a possible cause.

So, our patient was informed by his clinical team to still seek out a cardiologist during this workup. It's unclear if he did. Assuming he did and the workup, you know, for any cardiac pathology was unrevealing, then it is reasonable to assume that the heart palpitations present here is due to resistance thyroid hormone syndrome, which would then be treated by the use of medications such as beta blockers.

Bob Barrett: That was Dr. William Butler from the University of Pennsylvania in Philadelphia, Pennsylvania. He authored a clinical case study in the April 2025 issue of *Clinical Chemistry,* describing a challenging case of thyroid hormone resistance, and he's been our guest in this podcast on that topic. I'm Bob Barrett. Thanks for listening.