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Case Report Open Access

A Case of Pituitary Resistant Free Triiodothyronine Toxicosis Following Hepatitis B Immunization

J. Kelly Smith*

Departments of Academic Affairs and Biomedical Sciences, James H. Quillen College of Medicine, East Tennessee State University, Johnson City, Tennessee, USA

Abstract

A 16-year-old woman presented with clinical manifestations of hyperthyroidism several weeks after receiving her third hepatitis B immunization. An endocrine assessment revealed persistently elevated free triodothyronine (FT3) levels and multiple small nodules on thyroid ultrasound. A MRI of the brain, TSH response to thyrotropin releasing hormone, blood levels of TSH, T3, T4, FT4, and assays for thyroid autoantibodies were normal. She responded to Sertraline, which blocks the conversion of T4 to T3 and FT3 in peripheral tissues. She was shown to be genetically prone to developing autoimmune disease, raising the prospect that her illness was caused by pituitary thyrotroph T3 receptor autoantibody produced in response to hepatitis B immunization.

Keywords: Free-T3; Free-triiodothyronine; Free-T3 toxicosis; Reverse T3; Thyrotoxicosis; Thyroid stimulating hormone; Thyroid stimulating hormone receptors; Pituitary resistance to thyroid hormone; PRTH; Hypothalamic-pituitary-thyroid axis; Autoimmunity; Autoantibody; Hepatitis B vaccine; Sertraline hydrochloride; Iodinases

Case Report

The patient, a caucasian woman, was healthy and energetic until the age of 16 when, several weeks following her third hepatitis B virus (HBV) immunization, she noted the abrupt onset of palpitations, faintness, generalized weakness, difficulty in concentrating, and disabling fatigue unresponsive to rest. Within one month her fatigue was such that she became wheelchair bound. An extensive workup, which included neurology, cardiology, and endocrinology consultations, was non-diagnostic, and she was referred to our service for assessment. Despite the frigid weather, she was dressed in a T shirt and shorts. Her physical examination was notable for a resting tachycardia, brisk deep tendon reflexes, a fine hand tremor, and 4/5 muscle strength in her legs. She was unable to assume an upright position without assistance.

Her family history was notable for systemic lupus erythematosus in her sister and maternal cousin and euthyroid Grave's disease in her mother.

Routine blood tests, and an immune assessment, which included a lupus panel and measurements of serum antibodies to cholinergic receptors and herpes viruses, were unremarkable. Her leukocytes expressed three autoimmune-associated HLA haplotypes (A1, Cw7, and DR3).

A comprehensive thyroid panel revealed persistently elevated free triiodothyronine (FT3) levels, but was otherwise normal (Table 1). A thyroid ultrasound showed multiple small nodules with normal uptake on a Tc99 nuclear scan. A brain MRI and TSH, prolactin, and growth hormone production following administration of thyroid releasing hormone (TRH) were normal with the exception that peak prolactin levels were elevated (Table 2).

Blood was drawn at four 15 minute intervals following the intravenous administration of 7 mcg/kg thyrotropin releasing hormone. At 60 minutes T3 and FT3 levels rose by 22 and 13% over baseline, respectively, confirming biologic activity of newly generated TSH.

Because of its ability to inhibit conversion of T4 to T3 in peripheral tissues [1] she was treated with sertraline hydrochloride. During recovery, which occurred over several months, her level of disease activity [2] correlated with her FT3 levels ($p<0.001$) (Figure 1). Although TSH levels did not change, FT3 levels fell in proportion to the dose of sertraline, and reverse T3 (rT3), an inactive form of T3, rose in proportion to dosage ($p<0.001$) (Figure 2). Modest dose-related decreases in T3 also occurred ($p=0.0075$). She relapsed when sertraline was discontinued several years later, and improved on reinstitution of therapy.

Hormone Assays	Patient	Normal Range
TSH (mciu/ml)	1.7	0.5-4.7
TSH-alpha (ng/ml)	0.4	<2.6
T3 (ng/dL)	139	60-181
FT3 (pg/dL)	537	235-293
rT3 (ng/dL)	8.0	2.6-18.9
T4 (mcg/dL)	8.7	4.5-12.5
FT4 (ng/dL)	1.3	0.8-1.5
T3RU (%)	29	22-35
TG (ng/ml)	20	0-60
TBG (mcg/ml)	28	16-34
SHBG (nmol/L)	75	20-106
ANTIBODY ASSAYS		
T3	Negative	negative
TSIG (UIU TE/ml)	<2	<2
TBII (%)	< 8	<11
TG (U/ml)	<0.3	<1
Thyroid peroxidase (U/ml)	<0.3	<1

Table 1: Baseline thyroid studies. TSH: Thyroid-Stimulating Hormone; T3: Triiodothyronine; FT3: Free Triiodothyronine; rT3: Reverse Triiodothyronine; T4: Thyroxine, FT4: Free Thyroxine; T3RU: Triiodothyronine Resin Uptake; TG: Thyroglobulin; TBG: Thyroxine Binding Globulin; SHBG: Sex Hormone Binding Globulin; TSIG: Thyroid-Stimulating Immunoglobulin; TBII: Thyroid-Stimulating Hormone Binding Inhibitor Immunoglobulin.

***Corresponding author:** J. Kelly Smith, Departments of Academic Affairs & Biomedical Science, James H. Quillen College of Medicine, East Tennessee State University, Johnson City, TN, USA, Tel: 423-794-7425; E-mail: smithj@etsu.edu

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	TSH (mciu/ml)	PROLACTIN (ng/ml)	GROWTH HORMONE (ng/ml)
BASAL LEVELS	2.3 (normal 0.5-4.7)	14 (normal 3-30)	<0.5 (normal <8)
PEAK LEVELS	19 (normal >7 <30)	112 (normal 14-70)	7.7 (normal >7)

Table 2: Hypothalamic-pituitary-thyroid axis.

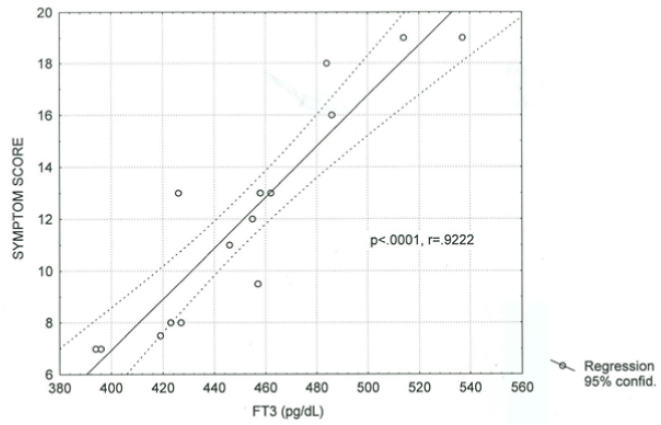

Figure 1: Correlation of free triiodothyronine (FT3) levels with Klein's hyperthyroid symptom scale. Normal FT3 level = 264 ± 29 pg/dL (s.d.).

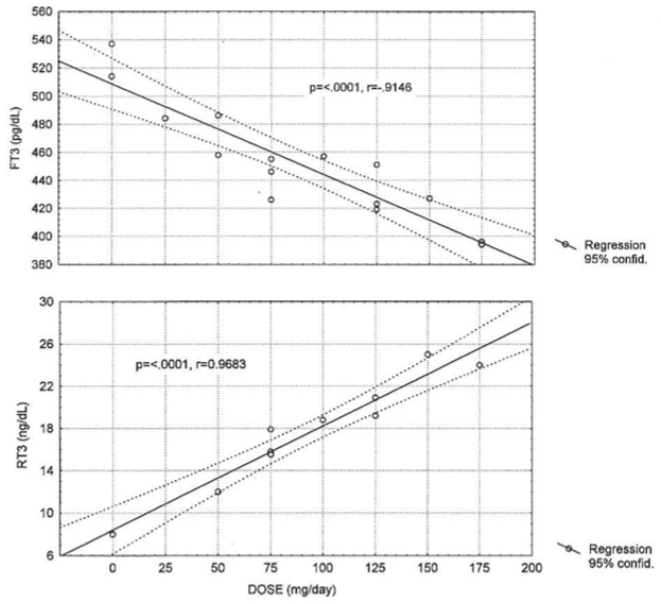

Figure 2: Correlation of free triiodothyronine (FT3) and reverse triiodothyronine (rT3) levels with sertraline dose. The response is compatible with sertraline-induced impairment of deionization of T4 to FT3 and of rT3 to T2 by type 1 and type 2 deiodinases. Type 3 deiodinase activity, which generates rT3 from T4, appears to have been unaffected.

Discussion

Our patient is an example of a difficult diagnostic problem in which the hoof beats were those of zebras, not horses. Her presentation was most compatible with a diagnosis of thyrotoxicosis and yet assays for TSH, T3, T4, FT4, thyroid autoantibodies, and thyroid-stimulating immunoglobulins were normal. Paying homage to the importance of her clinical findings, we ordered FT3 levels and established a diagnosis of pituitary resistant FT3 toxicosis.

Pituitary resistance to thyroid hormone (PRTH) should be suspected whenever TSH levels are inappropriately high (non-suppressed) in patients with elevated levels of thyroid hormones [3]. FT3 and FT4 down-regulate the expression of genes coding for α and β subunits of TSH by binding to TRβ2 receptors in the nuclei of thyrotrophs, thereby providing a necessary thyroid-pituitary feedback. FT3 has a 10- to 15-fold greater affinity for TRβ2 receptors than FT4, and thus is the main arbiter of TSH regulation [4]. PRTH usually results from inherited or spontaneous mutations in genes coding for TRβ2 binding domains, but any process that disrupts access to or the functionality of TRβ2 can cause the disorder [3]. Of note is the fact that our patient's TSH, prolactin, and growth hormone responses to TRH stimulation are similar to those described in PRTH [5-8].

Our patient responded to treatment with sertraline hydrochloride, a serotonin reuptake inhibitor. Her response was compatible with sertraline-induced impairment of deionization of T4 to T3 and of rT3 to T2 by type 1 and type 2 deiodinases present in peripheral tissues [4]. Type 3 deiodinase activity, which generates rT3 from T4, appears to have been unaffected. It is of note that her FT3 was being replaced by the metabolically inactive rT3.

Because the pituitary gland is open to the general circulation, it is possible that HBV triggered the production of anti-TRβ2 autoantibodies with the capability of blocking access of FT3 and FT4 to TRβ2 binding domains. Adults receiving HBV have been reported to have increased odds-ratios of developing autoimmune disease, including systemic lupus erythematosus, rheumatoid arthritis, optic neuritis, multiple sclerosis, and immune thrombocytopenia [9,10], and our patient was particularly predisposed to developing autoimmune thyroid disease, which is associated with HLA-DR3 haplotypes in Caucasians [11].

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