Scientific Research Publishing

Open Journal of Endocrine and Metabolic Diseases, 2022, 12, 177-183
https://www.scirp.org/journal/ojemd
ISSN Online: 2165-7432
ISSN Print: 2165-7424

Selective Pituitary Resistance to Thyroid Hormone: Clinical Hyperthyroidism with High TSH on Levothyroxine Administration in I-131 Ablated "Graves Disease"

Ravi Moghe[1], Sarah Exley[2], Udaya M. Kabadi[1,2,3*]

[1]Des Moines University, Des Moines, USA
[2]Broadlawns Medical Center, Des Moines, USA
[3]University of Iowa, Iowa City, USA
Email: *ukabadi@gmail.com

How to cite this paper: Moghe, R., Exley, S. and Kabadi, U.M. (2022) Selective Pituitary Resistance to Thyroid Hormone: Clinical Hyperthyroidism with High TSH on Levothyroxine Administration in I-131 Ablated "Graves Disease". *Open Journal of Endocrine and Metabolic Diseases*, **12**, 177-183.
https://doi.org/10.4236/ojemd.2022.128013

Received: July 1, 2022
Accepted: August 13, 2022
Published: August 16, 2022

Abstract

Resistance to Thyroid Hormone (RTH) is a rare form of hormone resistance secondary to changes in the genes encoding thyroid hormone receptors. The two subtypes, Pituitary RTH (PRTH) and Generalized RTH (GRTH), cause clinically distinguishable patient presentations. In PRTH, typically only the pituitary gland is resistant to thyroid hormone (TH) while the rest of the body maintains sensitivity. Selective pituitary resistance to thyroid hormone results in dysregulation of thyroid hormone homeostasis with clinical presentation as either euthyroid or hyperthyroidism. PRTH is characterized by elevated thyroid hormone levels with an elevated or inappropriately normal TSH concentration. Herein we describe a case report of a 70-year-old woman who complained of weight loss of over 35 lbs., palpitations, jitters, hair loss, diarrhea, fatigue, muscle weakness, etc. over 6 months, thus, indicating the presence of iatrogenic hyperthyroidism while receiving levothyroxine 175 ug daily prescribed by her primary care provider because of a reported history of "Graves disease" treated by radioactive iodine ablation of the thyroid several years ago. The daily dose of levothyroxine had been increased gradually at an interval of 3 months over a year because of persistent elevation of serum TSH level. Laboratory tests revealed markedly elevated Free T4, Free T3 and TSH levels, along with low concentrations of all lipid fractions, serum creatinine and urea nitrogen levels, indicating TSH induced hyperthyroidism or PRTH. Further testing documented a mutation of thyroid hormone receptor beta gene 2 confirming presence of PRTH. We believe that the initial diagnosis of Graves Disease was erroneous and I-131 ablation further confounded and missed the diagnosis of PRTH. Thus, the purpose of this report is to report a

patient with PRTH and describe potential pitfalls in diagnosis and management of this rare disorder.

Keywords

Pituitary, Thyroid Hormone Resistance, Iatrogenic Hyperthyroidism, Graves' Disease

1. Introduction

First described in 1967 by Dr. Refetoff [1], the syndrome of resistance to thyroid hormone (RTH) bearing his name is a rare and complex disorder. Initial descriptions narrated universal resistance of all the tissues responsive to thyroid hormone (1 - 7). Further investigations led to the recognition of distinct clinical presentations arising due to mutations in three of six physiologic steps involved in expression of thyroid hormone effect on target sites (4 - 7). Since the initial documentation of RTH induced by a mutation in the TH receptor Beta (TRB) gene 2, over 137 different mutations leading to 40,000 cases of RTH have been identified [2]-[14]. The other two affected steps in RTH involve mutations in genes responsible for TH membrane transport and TH metabolism [3].

RTH syndromes are further subdivided into two clinical presentations, generalized RTH (GRTH) and pituitary RTH (PRTH). Both subtypes are due to defects in different isoforms of TRB genes with GRTH affecting TRB-1 and PRTH affecting TRB-2. The TRB-2 isoform, found on cells in the hypothalamus, pituitary gland, cochlea, and retina, is involved in the negative feedback loop for regulation of thyroid hormone. Inactive TRB-2 weakly activates its target genes, while T3-bound TRB-2 strongly activates target genes to a much greater effect than TRB-1 does. As a result of this increased sensitivity, TRB-2 can activate a given target gene 5-10-fold more than TRB-1 can, at the same concentration of T3. Because the negative feedback loop is more sensitive than the activation loop, surges of T3/T4 can suppress the hypothalamus and pituitary before the less sensitive TRB-1 is saturated, providing a mechanism for maintaining homeostasis [4]. When a mutation is present that selectively alters TRB-2, negative feedback between T3 and TSH is diminished or often lost.

The clinical picture of RTH therefore often varies, but the common features that are a hallmark of RTH are elevated serum Free T4 to a higher degree than T3, normal to increased TSH level that responds to TRH, and a goiter [1]-[8]. A fourth feature, an absence of the usual signs and symptoms of an excess of circulating thyroid hormone is associated with GRTH, but not with PRTH, as the negative feedback loop is the primary disturbance in the latter. In both PRTH and GRTH, the pituitary has resistance to TH, thus negative feedback is lost and the HPT axis produces excess amounts of T4. In GRTH, the peripheral tissue is also resistant to TH, thus promoting clinical manifestations of hypothyroidism

with elevated T4 and TSH levels or euthyroid state with supernormal T4, and normal TSH concentrations [1]-[8]. In PRTH, the sensitivity of thyroid hormones to peripheral tissues is maintained while the resistance to pituitary thyrotrophs remains. Thus, these patients present clinically as either hyperthyroid, frequently with a goiter akin to Graves Disease with thyrotoxicosis, though with elevated or non-suppressed TSH. Failure to differentiate PRTH from Graves with thyrotoxicosis has been cited to result in inappropriate treatment of nearly one-third of patients with RTH [15] [16] [17] [18].

2. Case Report

67-year-old Caucasian female claimed to have received RAI ablation to her thyroid gland for "Graves disease" at another institution roughly 30 years ago. Her medical records were not able to be acquired to confirm true diagnosis of Graves' disease. The patient reported long-standing COPD secondary to smoking for over 50 years. Present medications included levothyroxine 175 mcg for "RAI ablation induced hypothyroidism" and multiple inhalers for treatment of COPD. She also reported intermittent oral or parenteral steroid and antibiotic therapy for acute exacerbations of COPD. At the time of presentation, patient also reported extensive weight loss, almost 40 pounds despite a good appetite, palpitations, fatigue, and proximal muscle weakness requiring use of a wheelchair for ambulation, profuse sweating and insomnia during the previous year or two. Physical examination documented a thin cachectic woman with extensive generalized muscle wasting and mild respiratory distress. She was afebrile. Pulse was regular with a rate of 120 beats/minute. Blood pressure was 170/90 mmHg and respiratory rate was 22/minute. She weighed 35 kg with a BMI 15 kg/m^2. Eye examination showed no proptosis, lid lag and intact extraocular movements as well as pupillary response. Neck examination showed neither palpable thyroid gland nor cervical lymphadenopathy and pulsating carotids without bruits. Lung auscultation revealed prolonged expiration with diffuse wheezing but no rales. Heart sounds were distant with regular sinus rhythm without murmur. Abdomen was soft, non-tender without organomegaly or ascites and normal bowel sounds. Neurological assessment documented fine tremor of outstretched fingers, exaggerated deep tendon reflexes and proximal muscle weakness in the lower extremities. Her laboratory tests showed normal complete blood counts, lowered serum urea nitrogen, creatinine and lipids, elevated creatinine kinase, Free T4, Free T3 and TSH levels (**Table 1**). Other blood chemistries, including liver enzymes, were normal. Ultrasound examination of neck demonstrated no functional thyroid tissue, and MRI of pituitary gland did not show any changes indicative of a pituitary adenoma. Clinical manifestations as well as free T4 and free T3 levels and other laboratory test abnormalities associated with hyperthyroidism progressively became worse on increasing daily dose of L Thyroxine although without normalization of serum TSH concentration (**Table 1** and **Table 2**). Moreover, reduction of LT4 daily dose improved clinical manifestations and

Table 1. Daily LT4 Dose (mcg), Body weight (kg), pulse rate per minute and blood pressure (mm Hg) recordings during 1 year following initial consultation

	Initial Visit	3 Months	6 Months	9 Months	12 Months
Daily LT4 Dose	175	200	225	175	125
Body Weight	41	39	36	40	44
Pulse Rate	102	100	110 Atrial Fibrillation	102	90
Blood Pressure	132/65	136/62	132/60	130/66	130/68

Table 2. Daily LT4 dose, Free T4, Free T3, TSH and other pertinent laboratory data during 1 year following initial consultation.

	Normal Range	Initial Visit	3 Months	6 Months	9 months	12 months
LT4 Dose (mcg)	-	175	200	225	175	125
Free T4 (ug/dl)	0.89 - 1.71	1.89	2.16	2.7	1.96	1.56
Free T3 (ng/dl)	2.3 - 4.2	4.8	5.6	5.9	4.4	3.6
TSH (uU/ml)	0.55 - 5.12	75	64	60	66	68
Cholesterol [C (mg/dl)]	<130	145	128	116	148	170
Triglyceride (mg/dl)	<200	84	84	81	89	88
LDLC (mg/dl)	<130	98	79	76	94	102
HDLC (mg/dl)	<160	28	30	25	32	46
Urea Nitrogen (mg/dl)	9 - 23	12	9	9	13	16
Creatinine (mg/dl)	0.6 - 1.3	0.5	0.5	0.4	0.6	1.0

laboratory tests including free T4 and free T3 concentrations (Table 1 and Table 2).

Clinical manifestations with marked elevated serum Free T4 and Free T3 concentrations indicated the presence of iatrogenic hyperthyroidism. However, simultaneous markedly elevated serum TSH level also suggested either TSH secreting pituitary disorder, including adenoma, or PTRH. Absence of pituitary abnormality on Sella MRI, normal TSH alpha subunit and total absence of thyroid tissue excluded TSH secreting pituitary adenoma and narrowed the diagnosis of PRTH. Genetic testing documented a mutation in TRH beta gene 2 and confirmed the diagnosis of PTRH.

3. Discussion

RTH is a rare disorder affecting thyroid hormone sensitivity (1 - 14). Clinical presentations of this syndrome vary but commonly present with elevated T4 and T3, a goiter and increased TSH. Pituitary resistance to TH is present in both subtypes, with GRTH also exhibiting peripheral insensitivity to TH, as well as

with manifestations of hypothyroidism. Due to the variable presentation of RTH and its subtypes having similar presentations to other thyroid diseases, misdiagnosis of RTH patients is not too infrequent [15]. Occasionally, RTH with concurrent presence of Graves' disease has also been reported [16] [17] [18]. PRTH presenting with goiter and elevated T4 and T3 levels consistent with hyperthyroidism may be misdiagnosed as Graves' disease if the serum TSH and Thyroid stimulating immunoglobulin concentrations are not determined. However, RTH should not be treated like Graves disease and RTH patients should receive supraphysiologic doses of LT3 and/or LT4 and avoid ablation [15]. Misdiagnosis of Graves disease may lead to a thyroidectomy as well as radioactive iodine ablation.

Initial management of this patient was focused on normalization of TSH level by increasing daily LT4 dose at 6 - 8 weeks' intervals as recommended in the majority of case reports [1]-[14]. However, our patient experienced worsening clinical manifestations of hyperthyroidism, including extensive weight loss of over 15 lbs, despite improved appetite, palpitations due to sinus tachycardia, tremors, anxiety, multiple bowel movements, fatigue, lack of sleep, etc. with TSH 30 - 40 miu/l and elevated Free T4 and free T3 levels while receiving increasing daily dose of levothyroxine denoted the diagnosis of PRTH [2] [4] [5] [6] [7] [8] [12] [13] [14]. Finally, improved clinical manifestations of hyperthyroidism on lowering the daily dose of L T4 established the diagnosis of PRTH.

Treatment of GRTH involves upward titration of a daily dose of LT4 to attain and maintain normal TSH concentration. However, the same therapeutic approach leads to onset of clinical hyperthyroidism, severe at times in subjects with PRTH even before normalization of serum TSH level as illustrated in our subject. Moreover, recent advancements in knowledge of molecular mechanisms of thyroid hormone action on hypothalamus, pituitary thyrotrophs and peripheral tissues [19] [20] have prompted other therapeutic options including administration of thyroid hormone analogs and thyroid hormone metabolites [21] [22] [23]. TRIAC (triiodothyroacetic acid) has been shown to be as or more effective in attaining and maintaining clinical euthyroid status in comparison to either LT4 and LT3 individually or in combination [24].

Therefore, this case report illustrates occasional confusion with initial diagnosis of "Graves Disease" with confirmation of PRTH several years later.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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