

Selective Peripheral Resistance to Thyroid Hormone – A Case Report

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ABSTRACT

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Thyroid hormone resistance syndrome is a very rare disorder characterized by partial resistance of the target tissue to thyroid hormone. We present a case of a 52 year old male with hypothyroidism and selective peripheral resistance to thyroid hormone. who required very high doses of thyroid hormone to relieve his symptoms. TSH remained very low suggesting normal pituitary response.

Keywords: Thyroid function, Resistance to thyroid hormone, RTH syndrome.

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INTRODUCTION

Thyroid hormone resistance syndrome is a very rare disorder characterized by partial resistance of the target tissue to thyroid hormone. Most of these cases are often misdiagnosed and inappropriately treated. Resistance to Thyroid Hormone (RTH) is classified into 3 types – general, selective pituitary and selective peripheral resistance. General RTH (pituitary and peripheral combined) is the commonest. We report here a case of selective peripheral RTH.

CASE

A 52 year old male presented to thyroid clinic of SUT Hospital on 9/2004. He was born out of non- consanguineous marriage. There was no family history of thyroid disease. He was diagnosed to have diabetes and dyslipidemia in 1996 and was started on Glibenclamide, and Simvastatin. In 1999, he noticed weight gain, fatigue, cold intolerance and somnolence. Blood examination revealed low T_3 and T_4 and increased TSH and was started on LT_4 (Eltroxin) 100mg/day. LT_4 was gradually increased since the patient continued to gain weight and had worsening symptoms including somnolence. When we saw him on 9/2004 he was on a massive dose of LT_4 - 800mg/day. There was neither any history of GI surgery or malabsorption nor history of intake of drugs that interfere with throxine absorption or metabolism.

On examination the patient was obese, height-170 cms, weight-91kgs with a BMI of 31.4. He had coarse

dry skin and hoarseness of voice. His pulse rate was 72/minute and BP 140/80mm Hg. He had no goiter. Neurological examination was normal. His initial thyroid function results and follow-up values are given in Table 1.

Table 1. Thyroid function values

Date	T3 ng/dl N=(62-179)	T4 µg/dl N=(4.5-12.5)	TSH µIU/ml N=(0.4-5)	Tt (mcg)
6/1999	70	5067	34	100
1/2000	163	13.5	.005	200
9/2000	216	17	<.002	300
10/2002	160	14	<.01	400
9/2003	173	17.7	<.01	600
6/2004	260	19.7	<.01	800

He also had elevated anti-microsomal antibody of 79 IU/ml (normal is <34 IU/ml). Thus, based on the initial values of a low T_3 , T_4 and elevated TSH in 1999, the patient was diagnosed to have hypothyroidism and was started on LT_4 . The patient complained of continued weight gain and somnolence even when the patient had an elevated T_3 , T_4 and very low TSH and that probably was the reason for increasing the LT_4 dosage to 800mg/day. The patient's FT_3 , FT_4 values during the our examination on 9/2004 were very much above normal values and TSH was very low (see table 2). Fasting lipids were normal. For clinical confirmation we reduced the dose of LT_4 from 800 to 700mg/day and observed for weight gain, bradycardia and delayed relaxation of ankle jerks.

During follow-up 2 months later, the patient developed worsening of symptoms. He had gained 4 kgs weight,

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developed bradycardia with pulse rate 52/min and had delayed relaxation of ankle-jerks when the dose of LT_4 was reduced by 100mg, even though the TH levels were high with very low TSH (see Table 2). When the LT_4 dose was again increased to 800mg/day and followed up after 1 month, his day time somnolence subsided, weight reduced by 2kgs, heart rate increased to 70/minute. Thus this patient required supra-physiological doses of TH to overcome the resistance at the peripheral tissues and to remain euthyroid clinically. The pituitary gland being normally sensitive to TH responded to elevated levels of TH and hence TSH production is very much suppressed, clearly indicating that the patient had normal pituitary response and selective peripheral tissue resistance to TH. This patient also had underlying autoimmune- hypothyroidism which makes this case unique.

Table 2. Follow up Thyroid Values

Date	Eltroxin (μ g)	Wt(kg)	Pulse rate	FT4 pg/ml (2.5-4.5)	FT3 ng/ml (0.8t)	TSH μ IU/ml(0.4-5)
9/2004	800	91	74/min	6.4	4.2	0.01
11/2004	700	95	52/min	5.4	3.8	0.02
12/2004	800	93	70/min	6.2		<0.01

During subsequent follow-up in December 2007, he was asymptomatic on 800 μ g of LT_4 per day.

DISCUSSION

Thyroid hormone resistance syndrome was first described by Refetoff et al., in 1967.¹ Incidence of RTH is very low about 1 in 50,000 live births. In 80-90% of patients, it is inherited as autosomal dominant trait and the remaining is either autosomal recessive or sporadic. Men and women are affected equally. The disorder is caused by mutations in TH receptor b (TRb) gene. Three types have been described- Generalized resistance, selective peripheral and selective pituitary resistance, peripheral resistance being the rarest. The resistance is usually partial and hence overcome by high doses of thyroid hormone.

Thyroid hormone acts by binding to TRa and TRb receptors which are inside the nucleus of the cells in the target tissues. TRa gene is located in chromosome 17 and TRb gene in chromosome 3.² Major portion of T_4 is converted into T_3 which traverses through the cell cytoplasm to the nucleus. where it binds with thyroid receptor (TR) which in turn helps in binding with co-activator proteins resulting in gene transcription. RTH is due to mutation in the ligand binding domain of TRb receptors. T_3 do not bind with mutant

TR and in the absence of T_3 , TR binds with co-repressor proteins and gene transcription does not take place. The mutant receptor inhibits activity of normal TRa and TRb receptors, a phenomenon known as “dominant negative inhibition.”³

General resistance is the commonest type of resistance and usually presents during childhood. In general resistance, appropriate levels of TH is not able to overcome the pituitary resistance and hence pituitary continues to secrete more TSH resulting in goiter. In this type initially circulating TH hormone finds peripheral tissues resistant but when thyroid gland releases more amount of TH secondary to increased TSH stimulation it is able to overcome the partial resistance and patient may remain euthyroid during this period. Patients exhibit features of hyperkinetic behaviour, hyperactive attention deficit disorder, learning disability, mental retardation, hearing loss, short stature, tachycardia. The pituitary may finally respond to increased TH by reducing its secretion of TSH to the normal range. The laboratory abnormality that is seen is high T_3 and T_4 and high or high normal TSH. Differential diagnosis include dysalbuminemic hyperthyroxinemia where thyroid binding globulin has increased affinity to TH resulting in elevated total T_3 and T_4 . But FT $_3$ and FT $_4$ will be normal which will help to differentiate. Another important condition to be differentiated is TSH secreting pituitary adenomas and imaging of pituitary gland will be of help. If the patient is euthyroid, no treatment is required. If the patient has elevated TSH and hypothyroid symptoms, then high doses of LT_4 in the range of 1000mg will be required to suppress the TSH and to overcome peripheral resistance.

In isolated pituitary resistance, the pituitary gland does not respond normally to TH and continues to secrete TSH resulting in goiter and increased T_3 and T_4 presenting as hyperthyroidism. At one point, high levels of circulating TH may overcome the resistance and able to suppress the TSH to near normal levels. Again it is important to differentiate this type of RTH from TSH secreting pituitary tumours. Treatment with LT_4 analogues like dextro-rotatory T_4 or Triiodo-thyroacetic acid (TRIAC) which has got more potent inhibitory effects on pituitary are used.

In selective peripheral resistance cases, pituitary responds normally to TH and hence TSH levels remains low or normal. But the normal TH levels are unable to overcome the tissue resistance resulting in subnormal tissue metabolism and may present as hypothyroid. During treatment they require very

high doses of T₄ to override the resistance in the peripheral tissues. But the effect of these large doses on the normally responsive pituitary is suppression of TSH to extremely low levels.

This patient is unique in view of the initial TFT values (low T₃, low T₄ and high TSH) suggestive of hypothyroidism and subsequently developing features of peripheral resistance (high T₃, T₄ and low TSH).

CONCLUSION

Awareness about RTH syndrome will help clinicians to interpret the odd results of thyroid function tests and to make proper decision regarding management. Patients with peripheral resistance must take large doses of T₄ to prevent long-term cardiovascular morbidity. The first case report on partial peripheral resistance to thyroid hormone was published in 1981.⁴ There are 2 case reports on RTH from India, both had general RTH.^{5,6}

END NOTE

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