Title

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CLINICAL VIGNETTE

An Unusual Case of Abnormal Thyroid Function Test: Resistance to Thyroid Hormone

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Case Presentation

A 54-year-old female presented with a 3-year history of fatigue, cold intolerance, weight gain, and intermittent palpitations, which began after hysterectomy. Initially symptoms were thought to be due to menopause, but did not improve after estradiol and progesterone replacement. Subsequently, thyroid function testing showed an elevated free T4 level with normal thyroid-stimulating hormone (TSH). Table 1 includes thyroid function testing over time. She diagnosed with hyperthyroidism and started on methimazole. On methimazole, her T3 and T4 levels remained elevated with inappropriately normal TSH. Radioactive iodine uptake scan showed diffusely increased uptake suggesting endogenous thyroid hormone production. Ultrasound of thyroid showed an enlarged thyroid gland. Pituitary MRI showed a 5mm pituitary adenoma and she underwent trans-sphenoidal resection for presumed TSH-secreting pituitary adenoma. However, no TSH producing tumor was found on pathology, and her T3 and T4 remained elevated postoperatively. She eventually underwent genetic testing which revealed a heterozygous mutation in thyroid hormone receptor ß on locus p.Arg320Leu. This replaced arginine by leucine at position 320 of the THRB protein. She was diagnosed with thyroid hormone resistance. Other family members also underwent genetic testing, and her father tested positive for the same mutation. Her son did not have formal genetic testing but showed elevated thyroid hormone levels, suggesting that he inherited the same mutation. She did not receive any treatment for thyroid hormone resistance for the first 2 years after the diagnosis as she had no overt clinical manifestation of thyroid dysfunction. However, she continued to note fatigue and was initiated on low dose levothyroxine, with improvement of her fatigue.

Discussion

Resistance to thyroid hormone (RTH) is a rare disease with prevalence estimated at 1 in 40,000 live births based on neonatal screening.[1] Since the initial report of RTH by Refetoff in 1967, more than 3000 cases have been reported along with with additional mutations.[2] The majority of RTH cases have mutations in Thyroid hormone receptor-beta (TR-ß), which affects the T3-binding-domain of thyroid hormone receptor ß gene, altering transcription of genes containing a thyroid hormone response element. Ultimately, RTH leads to resistance of thyroid hormone on tissue level, leading to loss of feedback suppression of TSH leading to elevation in T3 and T4 with a non-suppressed TSH, which is the biochemical hallmark of disease.[3]

The clinical manifestations of RTH are highly variable, from euthyroid/hypothyroidism to hyperthyroidism. This is attributed to variable compensation for the insensitivity to thyroid hormone in different tissues. Because of varying sensitivity, thyroid hormone excess and thyroid hormone deficiency can co-exist in different tissues and the treatment needs to be assessed on individual basis.[3] Affected patients may have delayed growth and bone maturation from hypothyroidism, along with tachycardia from thyrotoxicosis.[3] However, most have normal growth and development and normal metabolic state at the expense of compensatory high thyroid hormone level and a small goiter, and do not require any treatment.[4]

For patient with sinus tachycardia, beta blockers may control tachycardia and palpitations.[3] Ablative treatment should be avoided, either surgical or radioactive iodine ablation because it can complicate thyroid hormone replacement therapy. There is no accurate way to assess tissue thyroid level and degree of thyroid hormone resistance is variable between individuals.[4]

Because patients have elevated T4 and T3 with goiter, many patients with RTH may be misdiagnosed as having primary hyperthyroidism and receive either anti-thyroid medication or ablative treatment for hyperthyroidism, which can lead to clinical hypothyroidism and worsening of goiter.[5] TSH producing pituitary adenoma may also present with similar laboratory findings with elevated T3, T4, and non-suppressed TSH with clinical goiter plus thyrotoxicosis and may mimic RTH. It is prudent to rule out TSH-producing pituitary adenoma with MRI of pituitary and measuring serum alpha-subunit, which will be disproportionally elevated with TSH-producing adenoma. Our patient had incidentally found pituitary micro-adenoma as well as menopause which further compounded her clinical picture and led to unnecessary surgery and delayed diagnosis. While genetic testing is the most accurate way to establish diagnosis, presence of similar abnormal thyroid function tests in first-degree relatives also suggests diagnosis as approximately 80% of TRβ RTH cases are dominantly inherited.[6]

This case illustrates a rare mutation that can present with abnormal thyroid function tests with atypical clinical

presentation. Resistance to thyroid hormone should be considered when a patient presents with elevated T4 without a suppressed TSH especially if the patient is relatively asymptomatic. This also highlights the importance of genetic testing to assist with prompt diagnosis with appropriate treatment and counselling.

Date	TSH [0.3-4.7mIU/mL]	FT4 [0.8-1.6ng/dL]	FT3 [222-383pg/dL]	Total T4 [4.9-11.4mcg/dL]	Comment
Aug-11	2.44[0.55-4.78mIU/L]*	2.71[0.89-1.7ng/dL]*	6.2[2.3-4.2pg/mL]*		On no meds
Oct-12		3.2 [0.9-1.7ng/dL]*	7.7 [2.0-4.4pg/mL]*		on MMI**
Jan-13	2.16 [0.40-4.5mIU/mL]*	3 [0.8-1.8ng/dL]*	6.5[2.3-4.2 pg/mL]*		off MMI
Jul-13	2.1	3.1	710	15	on MMI
Aug-13	1.7	3.2	674	15.1	On MMI 1 month before TNTS***
Oct-13	1.9	4.5	798		off meds, 1 month after TNTS
Mar-15	1.8	3.3		15.2	off meds
Aug-16	1.8	3.2	746		Off meds, start LT4
Oct-16	1.8	3.1	633		LT4 50mcg daily
Jan-17	0.9	3.1	542		LT4 75mcg daily
Jul-17	2.1	3.3	735		LT4 75mcg daily
Dec-17	1.1	3	560		LT4 75mcg 6days a week
June-19	1.7	3.1	617		LT4 75mcg 6days a week

Table 1. Thyroid function tests though her clinical course
*Reference lab ranges are listed for outside laboratory tests with different reference values.
**MMI= methimazole
***TNTS= trans-sphenoidal pituitary surgery
****LT4= levothyroxine

REFERENCES

1. **Lafranchi SH, Snyder DB, Sesser DE, Skeels MR, Singh N, Brent GA, Nelson JC**. Follow-up of newborns with elevated screening T4 concentrations. *J Pediatr*. 2003 Sep;143(3):296-301. PubMed PMID: 14517508.
2. **Weiss RE, Dumitrescu AM, Refetoff S**. Syndromes of impaired sensitivity to thyroid hormone. In: Weiss RE, Refetoff S, editors. *Genetic Diagnosis of Endocrine Disorders*, 2nd ed. Elsevier Inc; 2016.
3. **Dumitrescu AM, Refetoff S**. The syndromes of reduced sensitivity to thyroid hormone. *Biochim Biophys Acta*. 2013 Jul;1830(7):3987-4003. doi: 10.1016/j.bbagen.2012.08.005. Epub 2012 Aug 16. Review. PubMed PMID: 22986150; PubMed Central PMCID: PMC3528849.
4. **Refetoff S, Dumitrescu AM**. Syndromes of reduced sensitivity to thyroid hormone: genetic defects in hormone receptors, cell transporters and deiodination. *Best Pract Res Clin Endocrinol Metab*. 2007 Jun;21(2):277-305. Review. PubMed PMID: 17574009.
5. **Refetoff S, Weiss RE, Usala SJ**. The syndromes of resistance to thyroid hormone. **Endocr Rev**. 1993 Jun;14(3):348-99. Review. PubMed PMID: 8319599.
6. **Gurnell M, Chatterjee VK**. Thyroid hormone resistance syndrome. In: Wass JAH, Stewart PM, Amiel SA, Davies MJ, editors. *Oxford Textbook of Endocrinology and Diabetes*, 2nd ed. New York: Oxford University Press; 2011.