DIAGNOSING A PROBABLE CASE OF THYROID HORMONE RESISTANCE IN A RESOURCE-POOR SETTING

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ABSTRACT

Resistance to Thyroid Hormone (RTH) is a rare inherited condition usually caused by mutations of the thyroid hormone receptor beta (THRB), thyroid hormone cell membrane transporters, or thyroid hormone metabolism which can present as asymptomatic, hypothyroidism, or hyperthyroidism. The objective is to report a probable case of RTH presenting with hypothyroidism and to demonstrate the resilience in the diagnosis of endocrine disorders in resource-poor settings. A 23-year old University undergraduate presented with clinical features of hypothyroidism but elevated thyroid hormones and thyroid stimulating hormone (TSH): free T4=38 [normal range 10-24] pmol/L, free T3=11 [normal range 3-8] pmol/L, TSH=3.8 [normal range 0.5-5.0] mU/L; and normal brain MRI. A working diagnosis of RTH was made. Though there was no facility to test for THRB gene mutation, the positive family history of a similar pattern of thyroid function tests, made for a probable diagnosis of RTH, and she was empirically placed on a gradually increased dose of levothyroxine from 50 µg till resolution of symptoms was achieved and maintained 6 months later at 600 µg daily. At 10 months follow-up, the patient felt well with the resolution of symptoms and improved academic performance despite elevated thyroid hormones and unsuppressed TSH. The diagnosis of RTH requires a high index of suspicion, to enable early diagnosis, and prevent unnecessary invasive treatments. The treatment target should be the resolution of symptoms and signs and not normalization of thyroid hormone levels. This report also underscores the resilience that can be adopted in diagnosing and treating endocrine cases in resource-poor settings.

Keywords: Thyroid hormone resistance, Hypothyroidism, Levothyroxine, Impaired sensitivity to thyroid hormone

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INTRODUCTION

Thyroid hormone resistance or Resistance to Thyroid Hormone (RTH) or impaired sensitivity to thyroid hormone (ISTH), also known as Refetoff syndrome is a rare inherited condition with an incidence of about 1 in 40,000 live births (Rivas et al. 2016) usually caused by germline mutations of the thyroid hormone receptor beta (THRB) gene resulting in lower binding affinity for thyroid hormones; impaired suppression of thyroid stimulating hormone (TSH) i.e., normal or elevated TSH; and elevated thyroid hormones (Rivas et al. 2016). However, mutations in thyroid hormone cell membrane transporters and thyroid hormone metabolism have been identified in about 15% of cases reported. (Lee et al. 2022) The clinical presentation, phenotypes, and severity of RTH vary implying variance in genetic expressivity and penetrance which may be linked to heterogeneity of coactivators and corepressors of other genes. (Singh et al. 2017; Moran et al. 2017) It can present as asymptomatic, hypothyroidism, hyperthyroidism, or a combination of symptoms of hypothyroidism and hyperthyroidism depending on the level of expression of THRβ and THRA genes in target tissues, (Neamțu et al., 2016) thus very confusing to clinicians not familiar with the condition, leading to misdiagnosis, unnecessary invasive treatments like radioactive iodine ablation due to refractory goiters, and frustrating to patients. (Pattan et al., 2021) Two forms of RTH have been described i.e., Pituitary Resistance to Thyroid Hormone (PRTH) which presents predominantly with clinical hyperthyroidism; and Generalized Resistance to Thyroid Hormone (GRTH) which tends to present with clinical hypothyroidism. (Neamțu et al., 2016) The symptoms tend to wane with age, and patients may eventually become clinically euthyroid. (Neamțu et al., 2016)

CASE REPORT

A 23-year old University undergraduate presented with a 3-year history of mild anterior neck swelling, cold intolerance, recurrent constipation, insomnia, and a 1-year history of weakness, poor self-care, and episodes of unprovoked crying. The parents complained that her academic performance had been declining since the onset of her illness. Her menstrual cycle though remained regular, and no galactorrhoea. She was evaluated several times in different hospitals with no definite diagnosis. On physical examination, she was conscious but lethargic, afebrile with a temperature of 35.6 ºC (below normal), dry scaly skin, obese with a body mass index of 33 Kg/ square meter, no pitting pedal oedema, and no myxedema noted. Anterior neck examination revealed a diffuse thyroid swelling 6cm x 4cm, firm and non-tender; pulse rate 84 bpm, blood pressure 120/70 mmHg, jugular venous pressure not raised, and heart sounds were normal S1 and S2, neurological examination was normal except for delayed relaxation phase of knee jerk reflex; chest and abdominal examinations were essentially normal. Her elder sister and maternal aunt were diagnosed with goitreous hypothyroidism and are currently on treatment. The thyroid function test of the maternal aunt showed similar findings of elevated thyroid hormones and unsuppressed TSH. However, the elder sister had findings that showed primary hypothyroidism i.e., low thyroid hormones and elevated TSH. The mother of the index patient also had elevated thyroid hormones and TSH, however, she was healthy and had no symptoms or thyroid illness. A clinical diagnosis of “hypothyroidism” was made for the index patient.

Thyroid function test was then, ordered which showed: free T4=38.2 (normal range 10-24) pmol/L, free T3=11.0 (normal range 3-8) pmol/L, TSH=3.8 (normal range 0.5-5.0) mU/L; and serum prolactin was 27 (normal < 25) ug/L.
The results were cross-checked in a private-owned and a government-owned laboratory. Thyroid ultrasound showed uniformly diffuse swelling of the thyroid glands bilaterally. Magnetic Resonance Imaging (MRI) of the brain showed no pituitary gland or hypothalamic abnormality, and audiometry examination showed no abnormality. A working diagnosis of “probable thyroid hormone Resistance” was made. Since there was no facility to test for mutations or defects in the Thyroid Hormone Receptor B (THRB) gene (the most common type of mutation reported), she was empirically placed on levothyroxine 50 µg daily with initial improvement in symptoms but relapsed one (1) week later. The dose was then, increased to 100 µg daily, leading to improvement in symptoms again with relapse reported during a follow-up visit four (4) weeks later. She was compliant with the medications as reported by her mother since she was earlier instructed to supervise the administration of levothyroxine. She was not taking medications that could interfere with levothyroxine like biotin-containing vitamins, or supplements containing iron, magnesium, or calcium. Levothyroxine was stored as per instructions in product insert at 20–25°C (68–77°F), and protected from light and moisture. The dose of levothyroxine was subsequently increased by 100 µg every 4 weeks following relapse after initial improvement until steady improvement of symptoms was sustained at a dose of 600 µg daily in divided doses. Due to complaints of palpitation and sustained tachycardia of 96-100 bpm, she was also placed on a cardioselective beta-blocker (atenolol 50 mg daily) with cessation of palpitation and normalization of pulse rate to 82 bpm.

At 6 monthly follow-up visits, the patient felt well, and happy with the resolution of symptoms and signs of hypothyroidism despite increased thyroid hormone levels and unsuppressed TSH (Table 1). Her academic performance at the University had since improved. However, at the 8th-month follow-up, she began to exhibit a few toxic symptoms such as heat intolerance, and excessive sweating; the dose of levothyroxine was reduced in a graded fashion of 100 µg per 4 weeks until clinical stability and maintenance were achieved at 400 µg per day. This may mean that with treatment, there may be some intrinsic recovery from thyroid hormone resistance. Therefore, monitoring of the index patient will continue with the hope that intrinsic recovery of the thyroid hormone resistance continues, possibly manifesting with the appearance of toxic symptoms that will a further reduction in the daily dose of levothyroxine. However, the patient is presently maintained on 400 µg daily with clinical stability.

Table 1: Serial Thyroid Hormone Levels of the Patient

<table>
<thead>
<tr>
<th>Thyroid Hormone</th>
<th>Normal range</th>
<th>Day 0 (before LT4)</th>
<th>1/12 on LT4</th>
<th>3/12 on LT4</th>
<th>6/12 on LT4</th>
<th>8/12 on LT4</th>
<th>10/12 on LT4</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH (mU/mL)</td>
<td>0.5-5.0</td>
<td>3.8</td>
<td>3.7</td>
<td>3.5</td>
<td>3.5</td>
<td>3.3</td>
<td>3.6</td>
</tr>
<tr>
<td>Free T3 (pmol/L)</td>
<td>3.0-8.0</td>
<td>11.0</td>
<td>13.1</td>
<td>14.6</td>
<td>17.2</td>
<td>22.9</td>
<td>16.7</td>
</tr>
<tr>
<td>Free T4 (pmol/L)</td>
<td>10-24</td>
<td>38.2</td>
<td>40.3</td>
<td>42.7</td>
<td>44.1</td>
<td>52.7</td>
<td>43.4</td>
</tr>
</tbody>
</table>

LT4=levothyroxine, x/12= x months, TSH= thyroid stimulating hormone, T3=liothyronine, T4=thyroxine; between 1/12 and 6/12 on LT4: LT4 was gradually increased from 100 µg to 600 µg; between 8/12 to 10/12: LT4 was reduced from 600 µg to 400 µg.
DISCUSSION

This is a rare probable case of thyroid hormone resistance presenting as clinical hypothyroidism. Some of the rare reports of this condition showed that they can also present asymptomatic or with hyperthyroidism. (Gnanapragasam et al., 2021; Del Prete et al., 2021; Ahmed et al., 2021; Akahori et al., 2021; Joshua et al., 2021) The index patient presented with a history of anterior neck swelling, cold intolerance, constipation, weakness, weight gain, and physical signs including dry, scaly skin and obesity, which were in keeping with hypothyroidism. However, there was tachycardia which did not conform with hypothyroidism. This can be explained by the varied distribution of thyroid hormone receptors (THR)-alpha and THR-beta in the various tissues of the body. THR-alpha predominates in the heart, thus not affected by the THR-beta defect in most thyroid hormone resistance phenotypes. (Neamțu et al., 2016) Therefore, the increased thyroid hormones stimulate the unaffected THR-alpha in the heart causing tachycardia. This necessitated the treatment of the index patient with a cardioselective beta blocker to ameliorate the chronotropic effect of the elevated endogenous thyroid hormones and the levothyroxine used to treat the patient.

In the same vein, the absence of menstrual irregularities may be explained by the presence of both THR-alpha and THR-beta in the uterus. Therefore, uterine THR-alpha activation maintained normal uterine physiology. (Sayem et al., 2017) Furthermore, considering the index patient’s presentation with hypothyroidism, coupled with elevated thyroid hormones and unsuppressed TSH, it is most likely a case of Generalized Resistance to Thyroid Hormone (GRTH), unlike Pituitary Resistance to Thyroid Hormone (PRTH) that tends to present with hyperthyroidism with similarly elevated T3, T4, and TSH. Another differential diagnosis of inappropriate TSH secretion is pituitary or hypothalamic neoplasm which is very unlikely due to lack of signs and symptoms of raised intracranial pressure, absence of cranial nerve palsies, absence of clinical features of excess or deficiencies of other hypothalamic-pituitary-target organ axes like the hypothalamic-pituitary-adrenal axis, hypothalamic-pituitary-gonadal axis; and normal brain MRI findings. Though audiometry examination was normal, only a proportion of persons with RTH were reported to have audiometric anomalies.

The index patient ingested an increasing dose of levothyroxine starting from 50 µg up to 600 µg 6 months later when symptom resolution was achieved and maintained. Anyfantakis et al. (2016) also reported the use of a high dose of levothyroxine to treat RTH. This is because a high dose of thyroid hormone was needed to overcome thyroid hormone resistance, and produce a target organ effect. However, after 2 months of stable clinical condition, the index patient began to exhibit a few symptoms of hyperthyroidism like heat intolerance, and excessive sweating; the dose of levothyroxine was reduced in a graded fashion of 100 µg per 4 weeks until clinical stability and maintenance were achieved at 400 µg per day. This may mean that with treatment, there may be some intrinsic recovery from thyroid hormone resistance as reported by some authors. (Rivas et al., 2016; Lee et al., 2022; Singh et al., 2017; Pattan et al., 2021) Therefore, monitoring of the index patient will continue with the hope that intrinsic recovery from the thyroid hormone resistance continues, possibly manifesting with the appearance of toxic symptoms again, that will necessitate a further reduction in the daily dose of levothyroxine. The patient has, however, remained clinically stable at a daily 400 µg levothyroxine dose, even with elevated thyroid hormones and unsuppressed TSH. Therefore, clinical symptoms and signs are a major part of the monitoring of persons with RTH. The index patient, however, is at best, a
probable case of RTH, since THRB gene testing was not available. This case is, however, still worthy of a report to alert or further enlighten physicians and endocrinologists to exhibit a high index of suspicion for RTH when thyroid-related symptoms and signs do not match thyroid function tests; to investigate the family history of a similar pattern of thyroid function tests with or without thyroid-related symptoms, and to highlight the resilience of managing endocrine cases in resource-poor settings. The limitations of this report include the non-availability of THRB gene testing and the radioactive iodine uptake (RAIU) test. The presence of ultrasound findings of bilateral diffuse enlargement of thyroid glands mostly correlates with diffuse high RAIU, which is in keeping with persistent stimulation of the thyroid gland due to unsuppressed TSH, as a result of end-organ resistance and negative feedback mechanisms. This is, therefore at best, a highly probable case of RTH.

CONCLUSION

Though this is a probable case of Resistance to Thyroid Hormone since genetic testing was not available, however, there was a resolution of hypothyroidism signs and symptoms with the maintenance of clinical recovery at supra-pharmacological doses of levothyroxine. Therefore, the diagnosis of RTH requires a high index of suspicion, to enable early diagnosis, and prevent unnecessary invasive treatments like radioactive iodine therapy, and surgery. The target of treatment should be the resolution of symptoms and signs and not the normalization of thyroid hormone levels. This case report also underscores the resilience that can be adopted in diagnosing and treating endocrine cases in resource-poor settings.

REFERENCES


