Malays J Pathol 2024; 46(1) : 109 – 113

CASE REPORT

Refractory hypothyroidism

Yin Ye LAI[1,2], Subashini C. THAMBIAH[2]*, Normaizuwana MOHAMED MOKHTAR[1], Intan Nureslyna SAMSUDIN[2]

[1]Department of Pathology, Hospital Kuala Lumpur, Ministry of Health Malaysia; [2]Department of Pathology, Faculty of Medicine & Health Sciences, Universiti Putra Malaysia.

Abstract

Introduction: Persistently elevated thyroid stimulating hormone (TSH) despite levothyroxine (LT4) treatment that exceeds the standard weight-adjusted dose is a common clinical presentation. This may lead to additional testing for LT4 malabsorption or poor LT4 adherence, the latter of which is challenging to confirm because it is predicated on accurate patient accountability. *Case report:* A 35-year-old lady, post-radioactive iodine therapy for Graves' disease remained euthyroid for a year on oral LT4. Two years later, she was clinically and biochemically hypothyroid despite claiming LT4 compliance. As all laboratory investigations were within the reference range, pseudomalabsorption was suspected and a LT4 absorption test was done. During the test, her free thyroxine increased significantly at 4 hours, reaching a peak of more than 50% from baseline while TSH decreased appropriately from 0 minute to 360 minutes. This was followed by normalisation of TSH with LT4 treatment under direct observation. *Discussion:* The LT4 absorption test is a prompt and economical means to rule out true malabsorption, decrease unwarranted subspecialty referrals and validate the weight-adjusted LT4 dose reduction.

Keywords: malabsorption, non-compliance, refractory hypothyroidism, levothyroxine, thyroid stimulating hormone

INTRODUCTION

Hypothyroidism affects women more than men, and its incidence increases with age.[1] Primary hypothyroidism accounts for more than 90% of hypothyroid cases and oral levothyroxine (LT4) substitute of 1.6-1.8 μg/kg daily restores euthyroidism in most patients.[2] Refractory hypothyroidism is a clinical condition where thyroid stimulating hormone (TSH) levels are not sustained within an optimal range even with large daily doses of LT4 therapy.[3] We report a case of refractory hypothyroidism in a 35-year-old lady who was diagnosed with pseudomalabsorption following a LT4 absorption test after excluding digestive, liver and kidney disease.

CASE REPORT

A 35-year-old Malay lady with underlying non-ischaemic valvular disease, hypertension and bronchial asthma was diagnosed with Graves' disease in 2018. She underwent radioactive iodine therapy and was subsequently prescribed 100 μg LT4 which was appropriate for her weight of 64 kg (LT4 1.6 μg/kg daily). This patient remained clinically and biochemically euthyroid for the next one year. However, at a clinic review in October 2020, she complained of fatigue, increasing weight, constipation, and irregular menstruation. Her condition worsened during the next review in March 2021. Despite an increase in LT4 dose of 125 μg which was higher than her calculated daily requirement (LT4 2.0 μg/kg daily), she continued to be hypothyroid during her follow up in June 2021 (Table 1). She claimed that she took her LT4 daily at 9 am in a fasting state an hour before breakfast. Apart from her oral anti-hypertensive medications (verapamil 80 mg and valsartan 40 mg), she denied taking over-the-counter medications which could potentially alter the absorption of LT4.

All laboratory tests performed to evaluate malabsorption were within the reference range.

**Address for correspondence*: Associate Professor Dr. Subashini Chellappah Thambiah, Department of Pathology, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, 43400 Serdang, Selangor, Malaysia. Tel: +60123923709, Fax: 03-97692373, Email: *subashini@upm.edu.my*

TABLE 1: Serial thyroid function test results

Date	5/5/18	9/8/18	5/9/18	29/11/18	16/11/19	3/10/20 *on oral LT4 100µg daily*	20/3/21 *on oral LT4 125µg daily*	11/6/21 *proceeded to LTA absorption test*	Reference interval
		Radioactive iodine therapy							
TSH mU/L	<0.01		<0.01	11.3	1.42	15	41.2	50.7	0.27-4.2
FT4 pmol/L	>100		22	3.6	21.9	20.3	10.9	6.4	12-22
FT3 pmol/L	-		3.6	0.8	-	-	-	-	3.1-6.8

These tests included full blood count, liver function test, renal profile, and other electrolytes (Table 2). Upon exclusion of digestive, liver and kidney disease, the endocrinologist decided to proceed with a LT4 absorption test. The patient fasted for 8 hours and omitted her usual dose of LT4 on the morning of evaluation. She was then administered 800 µg LT4 orally under direct supervision, and serum free thyroxine (FT4) and TSH were taken at different intervals. FT4 increased substantially during the test, attaining a peak of >50% from baseline at 4 hours while TSH, normal at baseline, decreased appropriately from 0 minute to 360 minutes (Table 3).

Since previous counselling had no effect on this patient's treatment compliance, she was scheduled for 'direct observation' of weekly LT4 dose at the outpatient clinic. On weekly supervised LT4 dosing, the patient was able to maintain normal thyroid function (Table 4) and reported resolution of prior hypothyroid symptoms.

TABLE 2: Baseline routine blood investigation results

Parameters	Result	Reference interval
Haemoglobin, g/dL	15.2	13.0-17.0
White cell count, 10^9 /L	7.18	4.0-10.0
Platelet, 10^9 /L	288	150-450
Urea, mmo/L	3.5	2.8-8.1
Sodium, mmol/L	138	135-145
Potassium, mmol/L	3.8	3.4-4.5
Chloride, mmol/L	103	98-107
Creatinine, µmol/L	56	27-87
Calcium, mmol/L	2.43	2.15-2.5
Magnesium, mmol/L	0.87	0.66-1.07
Phosphate, mmol/L	0.97	0.81-1.45
Total protein, g/L	76	64-83
Albumin, g/L	44	35-52
Globulin, g/L	32	20-36
Albumin/globulin ratio	1.4	0.8-2.0
Alkaline phosphatase, IU/L	83	35-105
Alanine transaminase, IU/L	10	<34
Total bilirubin, µmol/L	8	2-17

TABLE 3: LT4 absorption test results

Time (minutes)	0	30	45	60	90	120	240	360	Reference interval
TSH mU/L	0.94	0.76	0.70	0.68	0.59	0.53	0.46	0.45	0.27-4.2
FT4 pmol/L	29.7	37.9	42.7	47.6	51.5	54.3	60.2	55.6	12-22

DISCUSSION

In refractory hypothyroidism, optimal TSH levels are not maintained despite large daily LT4 doses.[4] Non-compliance remains the most common cause for this discordant finding.[4] Omitting even a day's LT4 dose can affect TSH levels for several days due to its long half-life.[4] Ingesting LT4 less than 30 minutes prior to food consumption also contributes to suboptimal drug absorption.[4] Other non-pathologic causes of refractory hypothyroidism include generic substitution of LT4 products with different bioavailability, dietary interference with fiber-rich food or concomitant use of medications (histamine-receptor blockers, proton-pump inhibitors) which may impede LT4 absorption.[4] Less common causes of refractory hypothyroidism that are more challenging to identify are dysfunctional hypothalamic-pituitary-thyroid axis (resistance to thyroid hormone), poor conversion of thyroxine (T4) to triiodothyronine (T3) and cystic fibrosis.[4]

Refractory hypothyroidism may be the only presenting feature of an occult gastrointestinal disorder such as *Helicobacter pylori* infection, atrophic gastritis and coeliac disease.[5] In these conditions, it would be ideal to first exclude gastrointestinal diseases via immunological (anti-parietal cell and anti-gliadin antibodies) and histopathological (endoscopy and duodenal biopsy) tests.[6] In this setting however, the endocrinologist proceeded with a LT4 absorption test due to a few reasons. Firstly, the seroprevalence of coeliac disease antibodies is low in the Malaysian population, more so in the Malay race.[7] Secondly, anti-parietal cell and anti-gliadin antibody testing were not available in this hospital and outsourcing the test is costly with prolonged turnaround time. Furthermore, gastric/duodenal biopsy is an invasive procedure hence performed only if other tests are equivocal.

Many variations of the LT4 absorption test such as: short (6 hours), long (5 weeks) and modified version (5 days) have been published in the literature.[2] Although all three versions report good utility in distinguishing between malabsorption versus non-compliance, the absence of a universal protocol or standardised methodology have resulted in limitations of its implementation in clinical practice.[2] In this patient, the short version of LT4 absorption test was performed due to its simplified protocol. This procedure involved 8 hours overnight fasting with subsequent administration of LT4 the next morning with blood sampling at baseline and hourly for 6 hours post LT4.[5]

In 1981, Greenstadt and colleagues developed the following formula to calculate the percentage of LT4 absorption: peak total thyroxine (TT4) (μg/dL) X volume of distribution of LT4 / administered dose of LT4 X 100%. The calculation of the volume of distribution has been suggested to estimate the amount of drug absorbed whereby a value more than 60% indicates normal absorption.[8] One limitation of this historical formula is the utilisation of TT4 instead of FT4. In the present day, many laboratories including ours measure FT4 because this non-protein bound, biologically active form of T4 is less affected by physiological

TABLE 4: Weekly thyroid function test results under 'direct observation' of LT4 administration

Date	9/7/21	16/7/21	1/8/21	Reference interval
TSH mU/L	0.24	0.61	1.71	0.27-4.2
FT4 pmol/L	24.0	18.4	18.9	12-22

and pathological changes in plasma protein binding capabilities.[9] Although a study in 2014 demonstrated a strong correlation between FT4 and TT4 in LT4 absorption test[10], more comparison studies are needed to suggest that FT4 can replace TT4 in Greenstadt's formula.

FT4 classically rises one hour after LT4 intake and peaks on average at 2 to 3 hours in hypothyroid patients.[5] Although elevation of FT4 makes LT4 malabsorption unlikely, the lack of a harmonised threshold value on how much FT4 elevation would be enough to exclude malabsorption is debatable. Some authors suggest that a normal FT4 level obtained during LT4 absorption test is sufficient to conclude pseudomalabsorption[5], whilst others argue that a FT4 surge, ranging from 50-100% of baseline, or at least 2.5 times increment in patients with baseline FT4 below the lower limit of normal should be achieved.[11]

In this patient, the normal baseline TSH seen in the LT4 absorption test suggested that the patient was compliant to LT4 in the weeks preceding the testing. The decision to perform the LT4 absorption test may have perhaps motivated the patient to comply with treatment. The objective finding of substantial increase in FT4 during the test, attaining a peak of >50% from baseline at 4 hours while TSH, decreased appropriately from 0 minute to 360 minutes strongly suggested that the refractory hypothyroidism in this lady was due to poor LT4 compliance.

Severe hypothyroidism may impair absorption. This is a possible outcome from small bowel mucosal oedema. However, this was unlikely in this patient as studies have noted that in severe hypothyroidism (TSH >150 mU/L), patients had the lowest actual rise in FT4 at 120 minutes.[3]

In this case, pseudomalabsorption was considered but denied by the patient. This could lead to a strain in the therapeutic relationship between the physician and the patient.[2] Hence, by furnishing objective evidence of LT4 malabsorption under controlled conditions with the LT4 absorption test, physicians can identify non-adherent patients without perturbing this therapeutic relationship.[2] LT4 absorption test is not only a prompt and economical means to rule out true malabsorption but also decreases unwarranted subspecialty referrals and validates the weight-adjusted LT4 dose reduction.[2] Additionally, a positive test refutes the necessity to perform further investigations.[3] The objective finding of a significant increase in FT4 while TSH decreases appropriately during the test strongly supports poor LT4 compliance as a cause for the refractory hypothyroidism.

Although theoretically the ingestion of a single high dose of LT4 may be correlated with side effects such as palpitations and angina especially in patients with lower weight[2], these adverse effects are rarely seen.[6] This is because T4 is bound by thyroxine-binding globulin, slowly enters the tissues, and needs to be converted to T3 first to be biologically active.[6]

Treatment of pseudomalabsorption includes parenteral infusion of LT4 or supervised oral ingestion.[12] Once weekly LT4 administration is effective and therefore a possible alternative to routine daily treatment.[12] This patient had normalisation of TSH with LT4 treatment under direct observation confirming non-compliance. Patients who are diagnosed with pseudomalabsorption should also be investigated for psychiatric conditions especially depression, which is possible in severe hypothyroidism.[12] Reassessment of these patients after successful treatment of hypothyroidism is pertinent to rule out factitious disorder, which may lead to unnecessary medical and surgical procedures.[12]

CONCLUSION

Poor compliance to medical treatment is a well-known issue in the management of chronic diseases.[12] Anamnesis should rule out dietary/drug interactions and diseases that could cause LT4 malabsorption in patients with persistent hypothyroidism despite increased substitutive dose of LT4. If the history and routine laboratory investigations are unremarkable, pseudomalabsorption becomes the key differential diagnosis, which prompts consideration of LT4 absorption test.[6] This case is of a non-compliant patient who was objectively proven to have normal LT4 absorption by the LT4 absorption test, which led to a reduction in LT4 dosage and euthyroid state without further invasive testing while maintaining the doctor-patient relationship.

Acknowledgements: The authors would like to thank the Director General of Health for his permission to publish this article.

Authors' contributions: Lai YY and C. Thambiah S drafted the manuscript. Lai YY, C. Thambiah S, Mohamed Mokhtar N and Samsudin IN contributed to reviewing and editing the manuscript. All the authors have read and approved the final manuscript.

Conflict of interest: The authors declared no conflict of interest.

REFERENCES

1. Nakano Y, Hashimoto K, Ohkiba N, *et al*. A case of refractory hypothyroidism due to poor compliance treated with the weekly intravenous levothyroxine administration. Case Rep Endocrinol. 2019;2019:5986014.
2. Aljenaee K, Cheah SK, McDermott JH, Ali S. Thyroxine absorption test. Biomed J Sci & Tech Res. 2018;3(2):3171-74.
3. Walker JN, Ibbotson V, Vincent A, *et al*. A thyroxine absorption test followed by weekly thyroxine administration: a method to assess non adherence to treatment. Eur J Endocrinol. 2013;168:913-17.
4. Centanni M, Benvenga S, Sschmechi I. Diagnosis and management of treatment refractory hypothyroidism: an expert consensus report. J Endocrinol Invest. 2017;40:1289-301.
5. Simsir IY, Soyaltin UE, Ozgen AG. Levothyroxine absorption test results in patients with TSH elevation resistant to treatment. Endocrine. 2018;64(1):118-121.
6. Livadariu E, Valdes-Socin H, Burlacu MC, Vulpoi C, Daly AF, Beckers A. Pseudomalabsorption of thyroid hormones: case report and review of literature. Ann Endocrinol. 2008;68(6):460-3.
7. Yap TW, Chan W, Leow AH, *et al*. Prevalence of serum celiac antibodies in a multiracial Asian population -a first study in the young Asian adult population of Malaysia. PLoS One. 2015;10(3):e0121908.
8. Greenstadt MA, Nicoloff JT, Spencer CA, Kaptein EM. Development of a Non-Isotopic Method for Determination of Oral T4 Absorption. Clin. Res. 1981; 29:A83-A83.
9. Soh SB, Aw TC. Laboratory Testing in Thyroid Conditions - Pitfalls and Clinical Utility. Ann Lab Med. 2019;39(1):3-14.
10. Sun GE, Pantalone KM, Faiman C, Gupta M, Olansky L, Hatipoglu B. The clinical utility of free thyroxine in oral levothyroxine absorption testing. Endocr Pract. 2014;20(9):925-9.
11. Soares RMV, Figueiredo RM, Dantas MMN, *et al*. Rapid levothyroxine absorption test for diagnosis of LT4 pseudomalabsorption: case report and proposal of a cutoff point. J Endocrinol Diabetes Obes. 2016;4(1):1083.
12. Wilder NV, Bravenboer B, Herremans S, Vanderbruggen N, Velkeniers B. Pseudomalabsorption of levothyroxine: a challenge for the endocrinologist in the treatment of hypothyroidism. Eur Thyroid J. 2017;6(1):52-6.