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(CASE REPORT)

Treatment-resistant hypothyroidism due to storage of levothyroxine at cold temperature

Rodrigo Palazzo de Almeida Barros * and Leila Warszawski

R. Moncorvo Filho, 90 - Centro, Rio de Janeiro - RJ, 20211-340, Brazil.

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Abstract

We present a case of a 37-year-old woman who was referred to the Endocrinology Department of the State Institute for Diabetes and Endocrinology Luiz Capriglione, Rio de Janeiro, Brazil, with persistent hypothyroidism following a total thyroidectomy for multinodular goiter 6 months before the appointment. After the surgery, the patient was prescribed levothyroxine 100µg/day. Initial blood tests showed increased thyroid stimulating hormone and normal free thyroxine levels. Over the next 2 years, in spite of the patient's adherence to the treatment and progressive increments in levothyroxine doses, thyroid stimulating hormone levels remained elevated and she developed clinical hypothyroidism. She was then admitted to the hospital for clinical and hormonal stabilization. Upon further investigation, the patient informed that at the beginning of her levothyroxine treatment, she was instructed to store the drug in the refrigerator, at 4°C. Seven days after impatient treatment, thyroid stimulating hormone levels returned to normal and the subject was asymptomatic. After discharge, she was instructed to store the medication properly, at room temperature, and away from heat and light. Two years after discharge, she was still euthyroid and asymptomatic.

Keywords: Hypothyroidism; Levothyroxine; Cold temperature; Malabsorption; Drug resistance

1. Introduction

Hypothyroidism, diagnosed by increased thyroid-stimulating hormone (TSH) and low free thyroxine (fT4) levels, is managed with hormone replacement and invariably 100% of patients will require levothyroxine (LVT) therapy. According to the American Thyroid Association (ATA), LVT is the drug of choice and recommended doses range from 1,6 µg/Kg/day to 1,8 µg/Kg/day. If untreated, clinical manifestations range from no signs or symptoms to cardiovascular complications. The most common complaints are fatigue, lethargy, cold intolerance, weight gain, constipation, change in voice, and dry skin [1]. Contrary, excessive LVT may lead to several systemic symptoms [2,3].

Therapeutic failure with LVT is not uncommon and may be caused by a variety of conditions that either increase the bodily need of LVT or decrease its bioavailability (Table 1). In these situations, titration of LVT to high doses is necessary to reach euthyroidism, what could lead to inadequate or even supratherapeutic doses and cause unwanted side effects. Also, frequent adjustments of LVT increase the cost of treatment, office visits, and laboratory measurements [4].

* Corresponding author: Rodrigo Palazzo de Almeida Barros; E-mail:rpabarros@yahoo.com
R. Moncorvo Filho, 90 - Centro, Rio de Janeiro - RJ, 20211-340, Brazil.

Table 1 Causes of refractory hypothyroidism

	Causes of Refractory Hypothyroidism
1	Increased need of thyroxine:
	• Obesity
	• Gestation
	• Deiodinase polymorphisms
	• Autoimmune thyroiditis
2.	Decreased bioavailability:
a	Increased CYP450 activity:
	• Anticonvulsants: phenobarbital, phenytoin, carbamazepine
	• Antineoplastic agents: tyrosine kinase inhibitors, RAR/RXR modulators
	• Antibiotics: rifampicin
b	Malabsorption:
	• Infections: H. pylori and giardiasis
	• Drugs: proton pump inhibitors, antacids, aluminium hydroxide, calcium supplements, iron, sevelamer, cholestyramine, colestipol, raloxifene, ciprofloxacin, chromium picolinate, lanthanum carbonate, and orlistate
	• Diseases: celiac disease, chronic and atrophic gastritis, lactose intolerance, pancreatic insufficiency, cystic fibrosis, liver cirrhosis, and short-bowel syndrome
	• Food: grapefruit, orange, fibers, papaya, soya, milk, and coffee
	• Bariatric surgery
c	Pseudomalabsorption
d	Increased degradation of the active pharmaceutical ingredient (API): • Humidity • Light • Temperature • Formulation • Packing

The pharmacokinetics of LVT is complex and many factors influence the optimal dosing of the drug, such as exposure to light and moisture, air oxygen, formulation pH, and temperature.

The role of temperature on LVT tablets stability has been known for a long time and several researchers have already demonstrated that high temperatures increase the degradation and instability of the drug [5]. For this reason, several regulatory agencies recommend storage from 15°C to 25°C or 30°C. Oppositely, the effects of lower temperatures on the pharmacokinetics of LVT and their clinical consequences have never been studied.

In this report, we present for the first time a case of an athyreotic patient who developed persistent hypothyroidism resistant to LVT therapy because of storage of LVT tablets at low temperature.

2. Case Presentation

A 37-year-old African American woman attended this institute in September 2016 for hypothyroidism following a total thyroidectomy (TT) 6 months before for multinodular thyroid goiter. After the surgery, she was regularly taking LVT tablets 100 μg/day without medical follow-up.

She presented with recently diagnosed hypertension, insomnia, hair loss, and weight loss. In addition to LVT, she was taking losartan 50 mg twice a day, hydrochlorothiazide 25 mg and fluoxetine 20 mg once a day. She used to take the LVT tablets daily at least 30 minutes before breakfast and denied the intake of soya-derived products, espresso coffee, papaya, and vitamins. Also, the patient had no history of epigastric pain or stomach disorders. The TT histopathological report confirmed multinodular goiter without evidences of malignancy or autoimmunity.

She was instructed to maintain the LVT dose and return one month later. She returned complaining of headaches, drowsiness and weight gain. Hormonal evaluation showed normal fT4 and elevated TSH levels, and LVT was increased to 150µg/day (1.2 µg/Kg/day).

Following the diagnosis of hypothyroidism, the patient came for follow-ups regularly for 2 years. Thyroid stimulating hormone and fT4 levels were evaluated every visit and LVT was adjusted according to the results and symptoms, up to 2.54 µg/Kg/day (Table 2). During this period, despite the patient's adherence to the treatment and progressive increments in LVT doses, she still complained of weight gain, hair loss, fatigue, cramps, and drowsiness. Thyroid stimulating hormone levels remained well above the reference value and even with high doses of LVT, TSH levels never returned to the normal range (Figure 1). Free thyroxine levels remained most of the time within the normal range during the whole treatment.

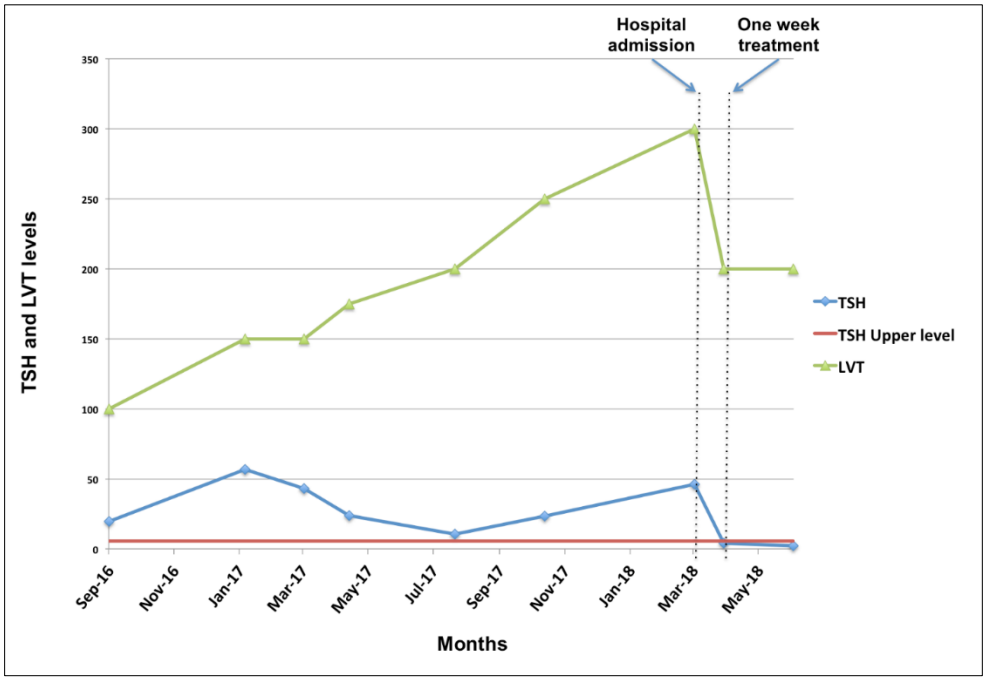

Figure 1 Progression of TSH (blue line) and LVT (green line) levels during 2 years of follow up after diagnosis. TSH = thyroid stimulating hormone (µUI/mL); LVT = levothyroxine (µg). Red line = upper TSH value. TSH normal rage values: 0.34 µUI/mL - 5.40 µUI/mL

Table 2 TSH and fT4 levels and prescribed daily doses of LVT. TSH = thyroid stimulating hormone (µUI/mL); fT4 = free T4 (ng/dL); LVT = levothyroxine (µg). Normal range values: TSH, 0.34 µUI/mL - 5.40 µUI/mL; fT4: 0.54 ng/dL - 1.48 ng/dL

Date	Sep 2016	Oct 2016	Jan 2017	Mar 2017	Apr 2017	Aug 2017	Oct 2017	Mar 2018
TSH (mU/L)	-	19.61	56.62	42.89	23.56	10.32	23.52	45.97
T4L (ng/dL)	-	1.20	0.58	0.52	0.75	1.03	0.80	0.50
LVT (µg)	100	150	150	175	200	225	250	300
LVT (µg/Kg)	0.85	1.20	1.26	1.28	1.48	1.66	1.84	2.54

In April 2018, she returned to our service complaining of worsening of symptoms and weight gain. At this point, she was taking high doses of LVT (2.54 µg/Kg/day). She was diagnosed with uncompensated hypothyroidism and admitted to the hospital for stabilization and investigation of malabsorption. Upon admission, she informed that after TT she was instructed to keep LVT tablets in the original blister in the fridge, at 4°C. In hospital, she was given LVT stored at room temperature. Seven days later, she was clinically stable, asymptomatic, and TSH level (4.06 mU/L) was normal (figure 1). Evaluation of malabsorption was not performed because the patient was euthyroid and clinically stable. After discharge, the patient was prescribed LVT 200 µg/day (1.67 µg/kg/day) and instructed to store LVT tablets properly. Since then, the patient has been asymptomatic with normal TSH and fT4 levels. The evaluation of LVT refractory followed the algorithm presented in Figure 2.

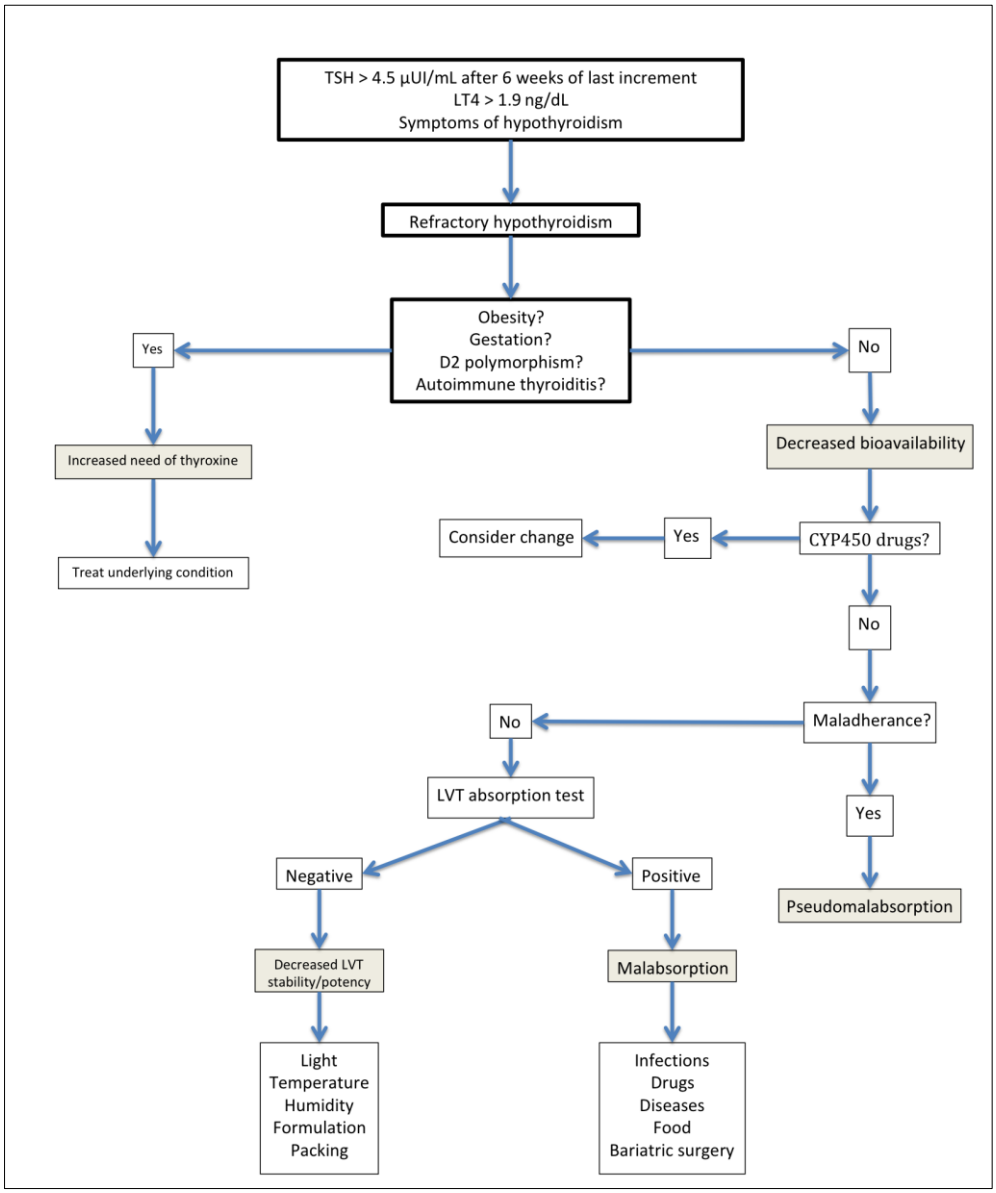

Figure 2 Diagnostic flowchart of refractory hypothyroidism

3. Discussion

Hypothyroidism following TT is an expected outcome and LVT is the mainstream treatment. Although straightforward, clinicians must adjust LVT doses over the years according to TSH levels and symptomatology.

Resistance to treatment is not uncommon and some patients will require high doses of LVT to achieve euthyroidism. By definition, refractory hypothyroidism is characterized by: 1) TSH levels above the upper target level, usually 4.5 mU/L, following a 6-week interval after the dosage was last increased; 2) high doses of LVT (> 1.9 µg/kg/day), and 3)

persistence of hypothyroidism symptoms [6]. Our patient had TSH level (45.97 mU/L) well above the upper limit 3 months after the last LVT increase, was taking 2.54 μg/kg/day, and had clear symptoms of severe hypothyroidism.

The causes of refractory hypothyroidism are multiple, but most of them are caused by situations that increase the need of thyroxine or that decrease its bioavailability (Table 1). The precise identification of this situation is arduous and there is no consensus in the literature about which strategy is best, but Centanni and collaborators have proposed an algorithm to spot the source of the problem [7]. Based on this, we have investigated our patient following the algorithm shown in Figure 2.

The initial goal was to exclude situations that could be increasing the need of thyroxine: gestation, obesity, D2 polymorphism, and autoimmune thyroiditis. In these situations, the need of thyroxine is increased to adjust the body to new metabolic states and maintain homeostasis.

During gestation, estradiol and thyroid binding globulin (TBG) levels and plasma volume are increased, which increase the need of thyroxine by 40% [8]. During 2 years of follow-up, nevertheless, our patient never got pregnant.

In obesity, sarcopenia decreases deiodinase type 2 expression, plasma volume increases, and LVT absorption decreases, increasing the need of thyroxine [9]. Our patient was clearly obese and this could be a factor interfering with hormonal action. However, as observed during impatient treatment, hypothyroidism was completely reversed with LVT stored properly.

Researchers have also described that polymorphisms of type 2 deiodinase may cause hypothyroidism [10]. Evaluation of our patient's medical history, however, did not show any evidence of deiodinases mutations.

Recently, Lozanov and collaborators have also described that, in rare cases, autoimmune thyroiditis may lead to increased need of thyroxine. They speculate that autoantibodies directed to thyroxine decrease hormonal action [11]. The histopathological report of our patient, however, did not show any evidence of autoimmune thyroiditis.

The following step was to identify situations that could decrease LVT bioavailability. In these situations, the extent of LVT that becomes available to its intended biological destinations decreases and higher doses of the drug are needed to maintain euthyroidism [12]. The most common causes are the use of drugs that increase hepatic CYP450 activity, pseudomalabsorption, LVT malabsorption, and situations that decrease the stability and potency of LVT (Table 1). First of all, we investigated the use of drugs that could be interfering with CYP450 activity. Our patient was taking losartan, hydrochlorothiazide, and fluoxetine. The first two do not interfere with CYP450 activity, but fluoxetine may decrease its activity. Nonetheless, we believe that this was not the case because the use of regularly stored LVT reversed hypothyroidism completely and the patient used to take LVT at 30 minutes before fluoxetine. We speculate that the dose used by the patient (20 mg/day) was not enough to modulate CYP450 activity.

Pseudomalabsorption is the most common cause of refractory hypothyroidism, and clinicians should be aware of this condition to prevent unnecessary investigations and stressful situations to the patient. In order to evaluate this possibility, a meticulous anamnesis by the healthcare team was carried out. We did not find any evidence that the patient was noncompliant to the treatment. Also, the patient assured that she was taking the drug once daily, on an empty stomach, half to one hour before breakfast. Thus, pseudomalabsorption was not considered as well.

The next step would have been the LVT absorption test, which is the gold standard method to evaluate this condition and sometimes fundamental to differentiate malabsorption from pseudomalabsorption. In this report, however, before the test, the subject was admitted to the hospital with severe uncompensated hypothyroidism in need of high doses of LVT (2.54 μg/kg/day). Upon hospitalization, she informed the staff that she used to store unopened LVT tablets in their original blisters in the refrigerator. Over the following days, the patient received regularly stored LVT. Surprisingly, one week after impatient treatment, she was clinically stable, TSH was 4.06 mU/L and the dose of LVT diminished from 2.51 μg/kg/day to 1.67 μg/kg/day. We concluded that the main reason for her persistent refractory hypothyroidism was erroneous storage of LVT at lower temperature and not malabsorption.

The stability and potency of LVT is dependent on several factors, including light exposure, humidity, formulation, processing, packing and temperature. Any modification in these factors can cause the degradation of the active pharmaceutical ingredient (API). It is known that heating causes deamination and decomposition of the API, decreasing the stability and potency of the drug [13]. As far as we know, only one group has shown that storage of LVT at high temperatures causes refractory hypothyroidism [14]. In their report, several patients diagnosed with this condition

used to store their medications above the recommended temperature, and euthyroidism was restored after patients were educated about the importance of proper storage.

To our knowledge, this is the first report in the literature to show that storage of LVT tablets bellow the recommend temperature leads to refractory hypothyroidism. Interestingly, in 2004, Australian pharmacists were instructed to store LVT refrigerated, which lead to unexpected increase in TSH levels in previously compliant patients [15].

Most studies evaluating the degradation, potency and stability of LVT use standard ranges, from room to higher temperatures [5,16], and it is clear that higher temperatures interfere with LVT pharmacokinetics, which could lead to a LVT resistant state. Differently, the effect of lower temperature is unknown. In 2015, Nahata showed that liquid LVT is stable for only two weeks at 4°C [17], but the effects of longer storage on the drug pharmacokinetics and the clinical consequences were not evaluated.

According to the World Health Organization (WHO), the FDA, and the European Agency for the Evaluation of Medical Products, all drugs intended for medical use should be tested for stability under temperatures above 40°C, but not under lower ranges. Exceptions are made for those drugs intended for storage in a refrigerator, or when data from published literature provides evidence of drug stability under different temperatures. Unfortunately, these testing guidelines still leave a gap in the stability studies protocols and it is the researchers' responsibility to determine the adequate temperature range [18]. Regarding the stability of LVT at lower temperature, further research is needed.

In conclusion, we show for the first time evidence that improper storage of LVT tablets in the refrigerator can cause refractory hypothyroidism. The mechanisms behind this phenomenon are still unclear because stability studies do not evaluate the effect of low temperatures in APIs. Although information about this condition is absent, refractory hypothyroidism caused by lower temperatures is easily preventable by adequate communication with patients and constant education about proper storage of LVT tablets. The early diagnosis of this condition can prevent unnecessary LVT dose increments and testing and unwanted consequences to the patient.

4. Conclusion

Hypothyroidism is a common situation caused by a plethora of medical conditions. In the present case study, we have identified that inappropriate storage of levothyroxine at low temperature can cause persistent hypothyroidism with deleterious consequences to health. Education of healthcare providers and patients about proper storage of drug tablets can easily prevent the development of refractory hypothyroidism and ameliorate adherence and outcomes of treatment.

Compliance with ethical standards

Acknowledgments

This research was self-sponsored by authors.

Disclosure of conflict of interest

No conflict of interest.

Statement of ethical approval

The Research Ethics Committee of the State Institute of Diabetes and Endocrinology Luiz Capriglione - IEDE/SES has approved this work under the protocol number 5.242.333.

Statement of informed consent

Informed consent was obtained from the patient and is available upon request.

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