



## CASE REPORT

# Two Cases of Pseudomalabsorption Treated Successfully with Parenteral Levothyroxine

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### Abstract

Hypothyroidism is a frequently seen endocrine disorder which may be managed by levothyroxine (LT4) replacement in most of the patients. Some patients with hypothyroidism do not respond and are refractory to oral LT4 therapy. The most encountered causes of unresponsiveness to oral LT4 replacement comprise non-compliance with therapy and malabsorption. We report two cases who were totally thyroidectomized (one for multinodular goiter, one for papillary thyroid cancer) and having symptoms of hypothyroidism and high TSH levels despite high doses of LT4 (800-1100 mcg/day). The patients were searched for malabsorption and no causal relationships were found. Hypothyroidism was corrected in clinical and laboratory manner, after parenteral LT4 was administrated. In the follow-up of the patients in outpatient clinics, they were clinically stable. Hence, we diagnosed the patients as hypothyroidism resistant to therapy due to pseudomalabsorption. As a conclusion, we should consider pseudomalabsorption of levothyroxine, resulted by non-compliance with treatment, in patients who persistent hypothyroidism occurred despite high dose LT4 replacement.

### Keywords

Parenteral levothyroxine, Pseudomalabsorption of levothyroxine

tolerance, concentration difficulties, fatigue, constipation, and hair loss. Levothyroxine sodium (LT4) is the most commonly used form of thyroid hormone for the treatment of hypothyroidism. Hypothyroid patients are supplemented with oral synthetic thyroxine in doses to achieve physiological serum levels of fT4. The average daily dosage of LT4 is 1.6 mcg / kg, and absorption of LT4 from the gastrointestinal tract is approximately 81% after an oral dose [2,3]. The mean dosage is generally adequate, and results with this dose may be reproducible. Together with this, if higher dosage of LT4 is required, we should search the cause. Several causes of malabsorption of LT4 were defined and discussed in the literature. Some of the common causes are diseases of gastrointestinal tract, liver, pancreas, surgery of gastrointestinal tract, some drugs (cholestyramine, aluminum hydroxide-containing antacids, ferrous sulphate, phenobarbital, carbamazepine, rifampin, amiodarone), dietary ingredients (e.g.; herbal medicines), congestive heart failure, pregnancy, lactose intolerance. However, by far the most common cause of malabsorption is poor compliance or noncompliance with oral LT4 in the patients with hypothyroidism [4-7].

## Introduction

Primary hypothyroidism is one of the common endocrine disorders, and may cause significant morbidity if it is not treated properly. Hypothyroidism is determined in approximately 16 out of 1000 adult subjects [1]. The patients may be debilitated with some symptoms of hypothyroidism such as weight gain, cold in-

Sriniva, et al. evaluated four patients with hypothyroidism resistant to therapy despite very high doses (up to eight times higher the mean daily dose of LT4), and their study revealed that all the four patients had normal gastrointestinal absorption of oral LT4. Thus, their findings suggested that the persistent condition could be resulted from non-compliance with LT4. This clinical situation is called by some authors as "pseudoma-

labsorption of thyroxine” [8]. Our article will highlight the factors interfering with LT4 treatment and causing malabsorption, the consequences of untreated hypothyroidism and the management of patients with pseudomalabsorption of levothyroxine.

## Case Report

### Case 1

40-year-old female was referred to endocrinology clinics with resistant hypothyroidism. She underwent total thyroidectomy for multinodular goiter 4 years ago, and was carrier for HCV. She did not have remarkable findings in her family history. She had been taking oral LT4 with a daily dose of 900 mcg, and she complained severe asthenia and fatigue. On physical examination; blood pressure was 110/80 mmHg, pulse 65/min, respiratory rate 14/min. She had pallor, periorbital edema, surgical scar about 3 cm in diameter on her neck. Cardiovascular examination revealed that heart sounds were normal and rhythmic, and there was bilateral 2+ pretibial edema. On admission, TSH was 91 (0.38-5.63 mIU/L), fT4 0.37 (0.61-1.12 pg/mL), fT3 < 0.14 (2.3-4.2 ng/dL). Autoantibodies (anti-microsomal and anti-thyroglobulin) were negative. Although we increased the dosage of LT4 up to 1200 mcg/day, levels of TSH was not decreased (123 and 68 mIU/L, respectively). We questioned about the patient compliance with the drug, whether she took the drug on an empty stomach or with other drugs or not. She had no personal history as regards to pregnancy or intestinal surgery. Then, the patient was admitted to endocrinology outpatient clinics to examine the cause of elevated TSH level. Endoscopic evaluation of gastrointestinal tract was performed to detect malabsorption; upper gastrointestinal endoscopy revealed atrophic gastritis and colonoscopy was normal. Gastric biopsy revealed the presence of chronic active gastritis and *Helicobacter pylori* (*H. pylori*). Eradication treatment for *H. pylori* was given and eradication was controlled by stool antigen test. Anti-gliadin, anti-tissue transglutaminase and anti-endomysium an-

tibodies, and anti-HCV were negative. Echocardiography revealed slight pericardial effusion and mild aortic insufficiency. Biochemical findings did not show any clues about absorption disorder. We considered that the diagnosis could be pseudomalabsorption, and administered intramuscular 200 mcg every other day for 5 days. After thyroid function tests of the patient came into normal limits with the therapy, she was discharged from the hospital. Clinical and laboratory findings were stable after discharge. Laboratory results were shown in Table 1.

### Case 2

44-year-old female, who was totally thyroidectomized for papillary thyroid cancer one year ago and then LT4 and radioactive iodine (RAI) were given, was referred to our clinics. She had been taking sulfasalazine and methotrexate for ankylosing spondylitis. We progressively increased LT4 dosage of the patient taking initially 150 mcg, due to inadequate TSH suppression. On physical examination of the patient complaining asthenia; blood pressure was 100/75 mmHg, pulse 75/min, and respiratory rate 16/min. Systemic examinations were unremarkable with the exception of periorbital edema and surgical scar about 4 cm in diameter on her neck. Laboratory results revealed that TSH was 149 mIU/L, fT4 0.15 ng/dL, and anti-microsomal and anti-thyroglobulin antibodies were negative. The patient was admitted to endocrinology inpatient clinics due to very high TSH and low fT4 levels despite 1100 mcg LT4 daily. Upper gastrointestinal endoscopy performed to search malabsorption showed pangastritis and duodenitis. Biopsy revealed villus atrophy and crypt hyperplasia; and *Giardia lamblia* and *H. pylori* were negative. We found that autoantibodies for celiac disease were negative. We questioned also this patient about compliance with the therapy, usage of drug, or additional drugs. We found that there were no interactions of absorption of levothyroxine with the other drugs which the patient had been taking. She had no history of intestinal surgery or pregnancy. We did not detect any findings of malabsorption; and with the

**Table 1:** The results of thyroid function tests of the first patient.

Days after parenteral LT4 administration	TSH (0.38-5.633 mIU/L)	fT4 (0.48-0.951 ng/dL)	fT3 (2.3-4.2 ng/dL)
0 <sup>th</sup> day	51.051	0.38	2.91
3 <sup>rd</sup> day	46.792	0.55	3.15
5 <sup>th</sup> day	46.926	0.82	3.15
9 <sup>th</sup> day	9.489	0.82	3
12 <sup>th</sup> day	1.344	2.28	4.21
30 <sup>th</sup> day	0.772	0.59	3.6
60 <sup>th</sup> day	0.882	0.6	3.2

**Table 2:** The results of thyroid function tests of the second patient.

Days after parenteral LT4 administration	TSH (0.38-5.633 mIU/L)	fT4 (0.48-0.951 ng/dL)	fT3 (2.3-4.2 ng/dL)
0 <sup>th</sup> day	111.94	0.31	2.42
3 <sup>rd</sup> day	2.584	2.72	3.53
9 <sup>th</sup> day	0.283	3.05	6.57
30 <sup>th</sup> day	0.813	0.57	3.42
60 <sup>th</sup> day	0.618	0.8	3.5

diagnosis of pseudomalabsorption we administered 200 mcg intravenous LT4 every other day. In the follow-up of the patient, TSH was normalized; we maintained these normal values in outpatient clinics (Table 2).

## Discussion

First choice of therapy to be selected for the patients with hypothyroidism is oral LT4 replacement. Average daily dose of LT4, 1.6 mcg/kg, may enable to keep serum TSH in normal limits in the most of hypothyroid adult patients. It is well known that approximately 70 to 80 percent of an oral LT4 dose is absorbed from gastrointestinal tract [9]. Levothyroxine is absorbed mostly from the ileum under normal circumstances, and its absorption is increased with fasting state [2]. We aimed to present two cases who initially did not respond to high dose oral LT4 replacement and malabsorption was not detected, and then responded to parenteral LT4.

It is obvious that untreated hypothyroidism results with the persistence of the symptoms such as fatigue, weight gain, constipation, and also with morbidity regarding to these symptoms. Together with this, if left untreated, hypothyroidism may culminate in more severe and potentially life threatening complications of hypothyroidism. Specifically, myxedema coma, or sometimes called crisis, is a rare serious life-threatening medical emergency that represents the most severe complication of long-standing and decompensated hypothyroidism. Therefore, early diagnosis and treatment of hypothyroidism have a high importance [10]. The usage of very high dose LT4 for the findings of clinical and/or biochemical hypothyroidism is a rarely seen clinical picture. The situation is generally based on malabsorption or pseudomalabsorption of LT4.

Malabsorption of levothyroxine may be resulted from several diseases leading absorption disorder of the gastrointestinal tract (e.g.; celiac disease, lactose intolerance, deficiency of vitamin B12, intestinal infections, disorders of pancreas and liver, and drugs) [11-13]. It was also reported that several drugs (such as cholestyramine, colestipol, aluminum hydroxide-containing antacids, ferrous sulphate, sucralphate, laxatives, calcium carbonate, lovastatin, bile acid sequestrants, activated charcoal, anion exchange resins, phenytoin, rifampin, amiodarone, estrogen) were in interaction with thyroid hormones [6,7,14-20].

Treatment of pseudomalabsorption of LT4 is precluded due to poor compliance of the patient with therapy and not be able to recognize the patient. The poor compliance is generally based on psychiatric disorders of depressive nature which are not rare in severe hypothyroidism, although a small number of patients exhibit true psychopathology [19]. In some studies, measuring the thyroid hormone levels after an oral loading dose of LT4 in such patients showed that all patients were finally observed to have normal absorption of oral LT4. The patients may easily be distinguished from those with simple noncompliance in that they show the characteristics of factitious disorder

[2]. Besides the problems associated with the treatment, it should be kept in mind that hypothyroidism itself could also contribute to disorder of absorption from intestinal mucosa [21]. We did not know the factor initiating pseudomalabsorption in our both cases. The factor which is emphasized mostly is to be having lower compliance of the patients. It was also reported that due to advantage of longer half-life of LT4 (5-7days), total weekly dosage of LT4 could be given at once in young patients with compliance problems without cardiac diseases. Besides, the other method is to give LT4 by parenteral route or psychiatric management [22].

As a conclusion; we did not find any cause disrupting the absorption of LT4 in our patients. By considering hypothyroidism itself contributing to absorption disorder together with pseudomalabsorption, we administered parenteral LT4 to the patients. No complications or side effects associated with parenteral administration or dosage of LT4 were observed. That maintenance of thyroid hormones in normal limits and regression of symptoms of the patients suggested the diagnosis of pseudomalabsorption of LT4.

## Conflict of Interest

There is no any conflict of interest.

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