Received: 10 February 2022 | Accepted: 27 July 2022

DOI: 10.1002/ccr3.6223

CASE REPORT

Clinical Case Reports Open Access WILEY

Primary hypothyroidism resolves after switching from L-thyroxine solid tablets to liquid oral substitution. A rare case without evidence of an underlying gastrointestinal malabsorption syndrome

Sophie Stupperich[1,2] | **Jessica Kotliarevskaia**[1] | **Reinhold Nies**[3] | **Maria Paparoupa**[4] | **Andreas Wittig**[1] | **Frank Schuppert**[1]

[1]Department of Gastroenterology, Endocrinology, Diabetology and General Medicine, Kassel, Germany

[2]Department of Obstetrics and Gynecology, Elisabeth Hospital Essen, Essen, Germany

[3]General Practitioner's Private Practice, Hofgeismar, Germany

[4]Department of Intensive Care Medicine, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

Correspondence
Maria Paparoupa, Department of Intensive Care Medicine, University Medical Center Hamburg-Eppendorf, Martinistr.52, D-20246 Hamburg, Germany.
Emails: m.paparoupa@uke.de; maria.paparoupa@yahoo.com

Abstract

A case of refractory primary hypothyroidism is presented. Despite laboratory-guided hormonal substitution, the patient remained hypothyroid. Multiple diagnostic tests ruled out all known causes of levothyroxine malabsorption. Interestingly, clinical and laboratory responding was promptly achieved, after switching the application format from solid tablets to liquid formula.

KEYWORDS

levothyroxine, L-thyroxine, malabsorption, thyroid hormones

1 | INTRODUCTION

Hypothyroidism is one of the most common endocrinological disorders observed in adulthood and is more prevalent in females than in males.[1] Primary hypothyroidism is linked to thyroid gland failure, causing low serum levels of free thyroxine hormone (FT4) and high levels of thyroid-stimulating hormone (TSH), produced by the pituitary gland via a negative feedback loop involving the hypothalamic–pituitary–thyroid axis. Secondary hypothyroidism is caused by a central (hypothalamic or pituitary) insufficiency and is rare, as described by Biondi et al.[2] Symptoms of hypothyroidism may range from fatigue, hoarse voice, hair loss, obstipation, weight gain to mood disorders, infertility, and dyslipidemia.[1,2] As clinical manifestations of hypothyroidism may become severe (myxedema and coma) timely diagnosis and treatment are crucial.[3]

The diagnosis of hypothyroidism is usually based on the TSH level. In the clinical setting, serum TSH concentration is the most sensitive marker and can be easily performed.[3] In the case of primary hypothyroidism, an increase in TSH can be observed either with FT4 being within the normal range (subclinical hypothyroidism) or being decreased (overt hypothyroidism).[2] The normal

range of serum TSH in our assay is between 0.40 and 4.0 mU/L. Mild hypothyroidism is defined by a TSH concentration between 4.5 and 9.9 mU/L and severe hypothyroidism by a TSH concentration above 10 mU/L. Although TSH testing seems to be fairly easy, particular factors may influence the hormone levels and increase the diagnostic complexity. The NHANES study reported, for example, a physiological increase in serum TSH levels in the elderly (upper limit set at 7.9 mU/L for >80-year-old patients).[4]

Once the diagnosis of primary hypothyroidism is established, treatment should be initiated timely. The standard replacement therapy constitutes oral levothyroxine sodium application. The main therapeutic goal is to establish a state of clinical symptoms' control, normalization of serum TSH and FT4 levels, and improvement of hypothyroidism-dependent cardiovascular risk factors. Overtreatment should be avoided.[2] Although the indication of pharmacological treatment of subclinical hypothyroidism remains debatable, overt hypothyroidism in adults consists of an absolute indication to start a substitution.[2,5]

The active hormonal components used in various formulations may be either of synthetic or natural origin. Nowadays, the most commonly used agents are synthetically derived.[6] Most commonly solid tablets are prescribed, but liquid formulations or soft gel capsules are also available.[7] As the half-life of oral levothyroxine is rather long, the administration once daily is usually sufficient. The treatment is generally well tolerated and an overall high rate of patient compliance has been reported.[6]

2 | CASE PRESENTATION

A 76-year-old female with known primary hypothyroidism due to Hashimoto immunogenic thyroiditis was referred to our department with progressive clinical manifestations. She presented herself with persistent tiredness, general weakness, dry skin, hair loss, and constipation. She reported a weight gain of approximately 6 kg in 36 months, leading to class III obesity (formerly known as morbid obesity: 116 kg/168 cm, BMI 41). She also described a feeling of tightness in her throat and had a hoarse voice.

Her relevant past medical history included depression, hepatic steatosis grade 3 with evidence of hepatomegaly on ultrasound, asthma, previous cholecystectomy, and secondary hyperparathyroidism due to a chronic renal impairment.

She was already diagnosed with hypothyroidism at the first presentation by her primary care physician and was on 325 μg oral L-thyroxine tablets daily. Regardless of the high oral dose of L-thyroxine, she developed progressive symptoms of hypothyroidism as outlined above. The initial laboratory workup revealed TSH levels being elevated to 85.0 mlU/L (normal range: 0.35–4.94 mlU/L), FT3 < 1 ng/L (normal range: 1.7–3.7 ng/L) and FT4 0.64 ng/dL (normal range: 0.7–1.48 ng/dL). Thus, she was admitted with suspected L-thyroxine malabsorption.

Several hydrogen breath tests with glucose, lactose, fructose, and xylose were performed to exclude abnormal bacterial colonization of the gastrointestinal (GI) tract or an intolerance to lactose and fructose, as these might constitute a possible cause of L-thyroxine malabsorption. The tests showed a fructose intolerance, whereas abnormal bacterial colonization of the GI tract and lactose intolerance were excluded.

Tissue transglutaminase antibodies type IgG were not detectable, but type IgA and anti-gliadin IgG antibodies were positive with 85.1 U/mL (normal range: 1:<10) and 34.2 U/mL (normal range: 1:<10), respectively. Her direct renin blood levels were elevated to 794 ng/L (reference range: 1.7–23.9 ng/L). This could be explained by spironolactone and candesartan intake, both medications known to influence serum renin levels. Parietal cell autoantibodies were found weakly elevated on one occasion, but a control blood sampling showed normal results. Further blood and urine tests excluded pheochromocytoma, Cushing's syndrome, anterior pituitary insufficiency, congenital adrenal hyperplasia, hereditary or acquired angioedema, gastrinoma, chronic inflammatory diseases of the GI tract, and any autoimmune causes of intestinal malabsorption, which are all potential causes of L-thyroxine malabsorption.

Additionally, several endoscopic controls were performed over time and revealed the histological picture of chronic duodenitis with lymph follicle hyperplasia and an erosive corpus gastritis type B. The patient was started on pantoprazole 40 mg once daily. No mucosal changes typical for coeliac disease or ulcerations were identified. There was no evidence of lambliasis or malignancy. An initially detected helicobacter pylori infection was successfully eradicated, without improvement of the subsequent L-thyroxine absorption tests. Additionally, a colonoscopy was performed showing no abnormalities. Cervical sonography showed a mildly enlarged thyroid gland correlating to a Hashimoto immunogenic thyroiditis and a computed tomography scan (CT-scan) of the neck revealed no further abnormalities.

During the time course, several oral L-thyroxine resorption tests were performed as described by Simsir et al.[8] Therefore, the patient was kept nil by mouth before the test and omitted the oral L-thyroxine tablet on the morning of the test. Blood was drawn at time point 0 testing for TSH, FT3, and FT4 serum levels. Then, the patient received 1000 μg oral L-thyroxine (10 tablets à 100 μg). TSH, FT3, and FT4 serum levels were defined 1 h after ingestion and every hour

TABLE 1 Blood results of the performed L-Thyroxine absorption tests between 02/2020 and 02/2021

	06/02/2020			26/05/2020			07/09/2020			09/03/2021		
hour	TSH (mlU/L)	T3 (ng/dl)	T4 (ng/dl)	TSH (mlU/L)	T3 (ng/dl)	T4 (ng/dl)	TSH (mlU/L)	T3 (ng/dl)	T4 (ng/dl)	TSH (mlU/L)	T3 (ng/dl)	T4 (ng/dl)
0	13.1		0.92	1.77	2.7	1.70	0.394	1.8	1.53	0.914	2.4	1.69
1	12.7		1.35	1.86	2.7	1.59	0.577	1.8	0.91	1.22	2.7	1.00
2	12.6		1.37	1.51	2.5	1.43	0.57	1.8	1.18	0.980	2.4	1.52
3	10.3		1.42	1.72	2.7	1.70	0.537	1.8	1.28	0.736	2.4	1.69
4	11.0		1.37	2.07	2.6	1.03	0.52	1.8	1.40	0.735	2.1	1.77
5	10.1		1.41	1.83	2.6	1.20	0.487	1.8	1.47	0.634	2.2	1.72
6	10.1		1.49	1.72	2.5	1.25	0.404	1.7	1.51	0.642	2.8	1.74

for a total of 6 h postingestion. Overall, four oral L-thyroxine absorption tests over a time course of 2 years revealed a maximum of oral L-thyroxine intake of 10% (Table 1).

Treatment with oral L-thyroxine was continued during the investigations and was adjusted from 225 μg to 250 μg once daily orally in tablet form to archive symptomatic control. Several months later, our patient presented with increased stool frequency (three to four mushy stools daily). At that point, she was on oral Levothyroxine replacement therapy of 300 μg once daily. After extensive inconclusive diagnostic measures, she was started probationary on 100 μg of oral L-thyroxine in liquid form. Surprisingly, TSH, FT3, and FT4 levels normalized rapidly under this treatment (Figure 1).

A recent control confirmed euthyroidism and the patient has no clinical symptoms under currently 100 μg of oral L-thyroxine substitution in liquid form. She lost 10 kg of weight since starting the liquid L-thyroxine substitution. Additionally, she was started on 500 mg of Vitamin C, once daily, in order to improve the Levothyroxine absorption.

3 | DISCUSSION

Therapy refractory hypothyroidism is a known problem in endocrinology and may have a great negative impact on patients' everyday life and symptoms' control. Primary hypothyroidism is considered to be refractory to oral thyroxine when there is biochemical or clinical evidence of hypothyroidism, despite increasing dosages of levothyroxine beyond 1.9 μg/kg daily.[9] If a treatment-refractory hypothyroidism is present, underlying causes need to be ruled out, as presented by Centanni et al. (Table 2).

The first cause to be excluded is the absence of adherence to the treatment. Then, different diagnostic tools may be used to address the problem of an underlying malabsorption syndrome. Many conditions, such as Helicobacter pylori infection, lactose intolerance, inflammatory bowel disease, gastrointestinal surgery, parasitic infections, and drug interactions have been already described to potentially influence the absorption of oral L-thyroxine.[9,10] Usually, those conditions can be identified with the appropriate tests and after being treated accordingly, TSH levels should be normalized under an adequate treatment. In cases of chronic malabsorption, L-thyroxine can be changed from solid tablets to liquid formulation. As described by Vita et al. liquid (drops) and soft gel formulations tend to have a better effect in patients with atrophic gastritis or those receiving proton pump inhibitors on a regular basis.[7] This is thought to be due to increased dissolution and absorption. In patients without malabsorption syndromes, the change of formulation has not shown any significant benefit.[11]

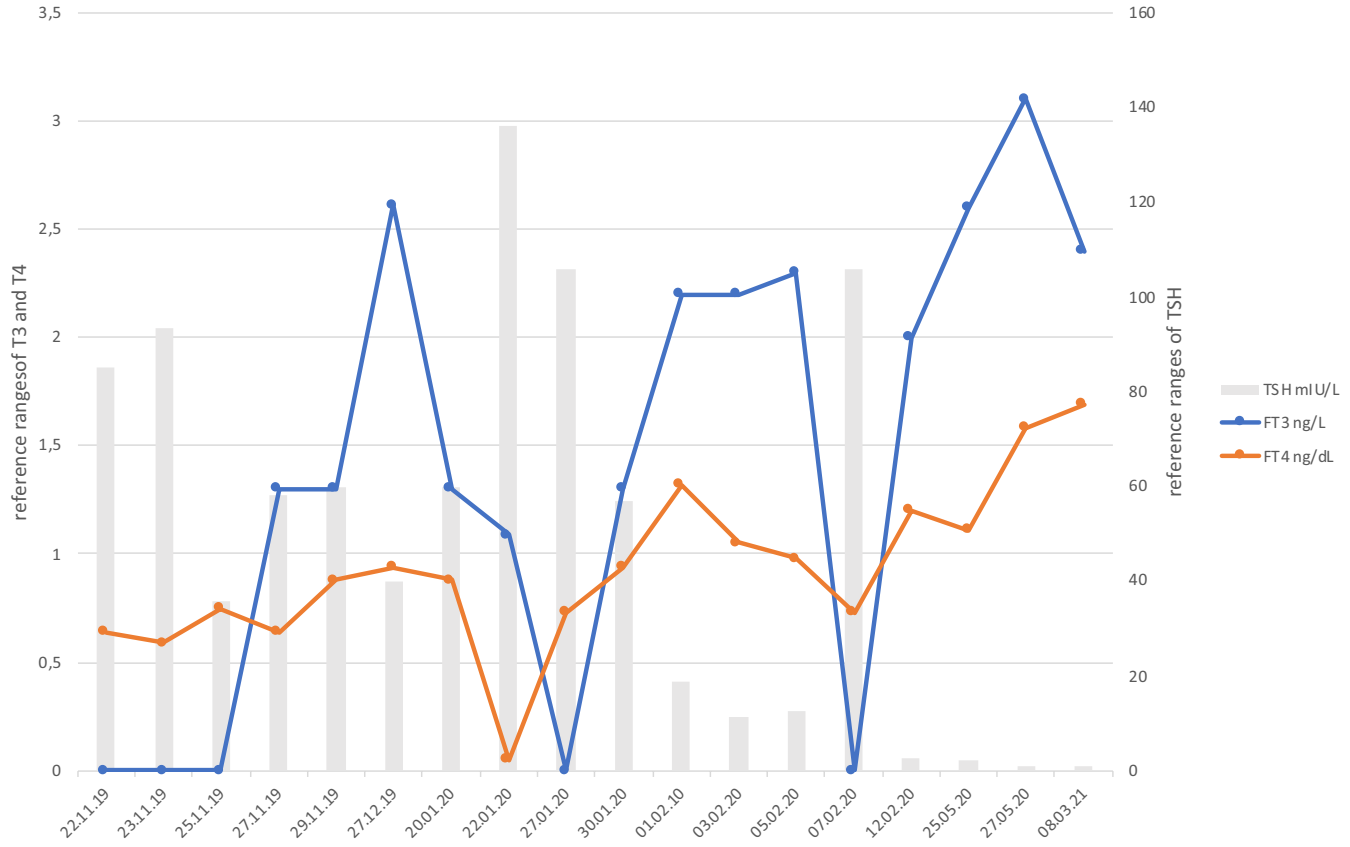

FIGURE 1 Graph showing the development of T3, T4, and TSH values over time

TABLE 2 Causes of treatment-refractory hypothyroidism by Centanni et al

Decreased bioavailability.
Poor adherence to, or tolerability of, drug therapy.
Maldigestion due to patient-related factors or behavior.
Proton pump inhibitor therapy.
Gastric infection with *Helicobacter pylori*.
Intestinal malabsorption of L-thyroxine.
Luminal factors (e.g., food, coffee, and medications).
Intramural factors (e.g., short bowel syndrome, lactose intolerance, gluten enteropathy, inflammatory bowel disease, infiltrative enteropathy, and infection with Giardia).
Increased need for levothyroxine.
Weight gain.
Pregnancy.
Increased metabolism of thyroxine.
Other factors that can alter serum levels of TSH.
Addison's disease.
Altered regulation of the hypothalamic–pituitary–thyroid axis.
TSH heterophile antibodies.
Inappropriate tablet storage.

Thus in our case, all known causes of malabsorption were either excluded or treated. Even after the treatment of Helicobacter pylori infection, which could have been considered to consist the only possible cause being identified, TSH levels did not normalize. Thus, we decided to empirically switch to a liquid formulation, which has immensely changed the course of the treatment. Serum TSH levels normalized and the patient's symptoms resolved. Under a significantly lower daily dose of L-thyroxine, the patient remains euthyroid.

4 | CONCLUSION

Our case highlights that unknown mechanisms may be involved in the malabsorption of oral Levothyroxin in solid tablets format. An empirical switch to liquid formulation may resolve this therapy refractory issue.

AUTHOR CONTRIBUTIONS

Sophie Stupperich treated the patient, collected all needed data, and wrote the manuscript. Jessica Kotliarevskaia reviewed the patient case and wrote parts of the manuscript. Reinhold Nies contributed the data collected in his Private Practice. Andreas Wittig and Frank Schuppert treated the patient throughout the time. Frank Schuppert and Maria Paparoupa reviewed the manuscript and provided consultation, regarding intellectual argumentation. All authors have read and approved the submitted version of the manuscript.

ACKNOWLEDGMENT

Open Access funding enabled and organized by Projekt DEAL. WOA Institution: Universitatsklinikum Hamburg-Eppendorf Consortia Name : Projekt DEAL

CONFLICT OF INTEREST

The authors have disclosed that they have no significant relationship with, or financial interest in, any commercial companies pertaining to this article.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICAL APPROVAL

No ethical approval was needed, as all personal information was anonymized and the identification of our patient is not possible.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

ORCID

Sophie Stupperich https://orcid.org/0000-0001-7811-6546
Maria Paparoupa https://orcid.org/0000-0003-1713-6759

REFERENCES

1. Golden SH, Robinson KA, Saldanha I, Anton B, Ladenson PW. Clinical review: prevalence and incidence of endocrine and metabolic disorders in the United States: a comprehensive review. *J Clin Endocrinol Metab*. 2009;94:1853-1878.
2. Biondi B, Cooper DS. Thyroid hormone therapy for hypothyroidism. *Endocrine*. 2019;66:18-26.
3. Baskin HJ, Cobin RH, Duick DS, et al. American ASSOCIATION of clinical ENDOCRINOLOGISTS medical guidelines for clinical practice for the evaluation and treatment of hyperthyroidism and hypothyroidism. *Endocr Pract*. 2002;8:457-469.
4. Hollowell JG, Staehling NW, Flanders WD, et al. Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Health and nutrition examination survey (NHANES III). *J Clin Endocrinol Metab*. 2002;87:489-499.
5. Garber JR, Cobin RH, Gharib H, et al. Clinical practice guidelines for hypothyroidism in adults: cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association. *Thyroid*. 2012;22:1200-1235.
6. Biondi B, Wartofsky L. Treatment with thyroid hormone. *Endocr Rev*. 2014;35:433-512.
7. Vita R, Benvenga S. Tablet levothyroxine (L-T4) malabsorption induced by proton pump inhibitor; a problem that was solved by switching to L-T4 in soft gel capsule. *Endocr Pract*. 2014;20:e38-e41.
8. Yildirim Simsir I, Soyaltin UE, Ozgen AG. Levothyroxine absorption test results in patients with TSH elevation resistant to treatment. *Endocrine*. 2019;64:118-121.
9. Centanni M, Benvenga S, Sachmechi I. Diagnosis and management of treatment-refractory hypothyroidism: an expert consensus report. *J Endocrinol Invest*. 2017;40:1289-1301.
10. Virili C, Antonelli A, Santaguida MG, Benvenga S, Centanni M. Gastrointestinal malabsorption of thyroxine. *Endocr Rev*. 2019;40:118-136.
11. Laurent I, Tang S, Astère M, et al. Liquid L-thyroxine versus tablet L-thyroxine in patients on L- thyroxine replacement or suppressive therapy: a meta-analysis. *Endocrine*. 2018;61:28-35.

How to cite this article: Stupperich S, Kotliarevskaia J, Nies R, Paparoupa M, Wittig A, Schuppert F. Primary hypothyroidism resolves after switching from L-thyroxine solid tablets to liquid oral substitution. A rare case without evidence of an underlying gastrointestinal malabsorption syndrome. *Clin Case Rep*. 2022;10:e06223. doi: 10.1002/ccr3.6223