Pseudomalabsorption of thyroid hormones: case report and review of the literature

Pseudomalabsorption des hormones thyroïdiennes : cas clinique et données de la littérature

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Abstract

Many causes of thyroxine malabsorption are described in the literature, but the most common cause of failure of thyroxine therapy is poor patient compliance, or pseudomalabsorption. We describe the case of a female patient who underwent total thyroidectomy for Basedow-Graves disease. Post-operatively, several treatment regimens were employed to achieve euthyroidism, but only injectable thyroxine was found to be effective. To exclude levothyroxine malabsorption, the patient was hospitalized in a hypothyroid state while a single oral test dose of levothyroxine (1000 μg) was administered. Within 4 hours a decrease of TSH level (from 59.7 to 55.6 μUI/ml) and a significant increase in free T4 levels (from 0.8 to 15.5 pg/ml) was observed, eliminating a malabsorption problem. The cause of resistance to thyroid hormone therapy was poor patient compliance, leading to the designation of this as a case of pseudomalabsorption.

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Keywords: Pseudomalabsorption; Hypothyroidism; Thyroxine; Oral test
1. Introduction

In 1891, Murray discovered the beneficial effects of sheep thyroid extract in treating a patient with myxedema [1]. Thereafter, in 1926 Harrington synthesized thyroxine (T₄), which was recognized as the main hormone in desiccated thyroid in the early 1950’s [1]. Nowadays thyroxine is available for oral and intravenous administration, the latter being used particularly in patients with severe hypothyroidism and myxedematous coma but also in cases of persistent hypothyroidism despite high oral doses of thyroid hormones. Synthetic thyroxine (levothyroxine, LT₄) is the main drug used in the clinical setting to achieve normal serum free T₄ (fT₄) levels. The usual replacement dose is 1.6 μg/kg body weight per day and is most frequently administered orally in the fasting state [2]. When euthyroidism is not achievable despite large doses of oral levothyroxine, poor compliance to oral therapy or deficient gastrointestinal absorption may be suspected.

The most common cause of supposed malabsorption is, however, poor compliance with oral thyroxine therapy [2,3], which is termed pseudomalabsorption. The concept of pseudomalabsorption of thyroid hormones was first outlined in 1991 to describe a factitious disorder due to patient non-compliance with the intention to deceive [4]. The diagnosis is made after excluding all causes of malabsorption and demonstrating normal thyroid hormone absorption following a single large test dose of thyroxine [3,5].

2. Case presentation

A 69-year-old female patient was referred for endocrinological evaluation to our unit because of persistent hypothyroidism despite oral treatment with large doses of thyroid hormones. The patient had a personal history of gastric ulcer, which was repeatedly treated with antisecretory therapy and she had previously received Helicobacter pylori eradication treatment. In the last several years she had not required any ulcer treatment.

Two of her daughters were known to have autoimmune thyroiditis with hypothyroidism for which they received oral thyroid hormone therapy.

A diagnosis of Graves’-Basedow’s hyperthyroidism had been made in 1997 and a complete thyroidectomy was performed in 1998. After surgery, oral thyroid hormone therapy was instituted, but despite a variety of treatment regimens a euthyroid state was not achieved. In March 2006, treatment with intramuscular levothyroxine was initiated (200 μg/day) and the patient became euthyroid for the first time. In October 2006 intramuscular levothyroxine was withdrawn from availability and so oral treatment was reinitiated. Because of persistent hypothyroidism the patient was referred to the University Hospital of Liège in 2007.

The patient denied poor compliance, claiming that she took her thyroid hormone treatment daily. At referral, her treatment was liothyronine (Cytomel®) 150 μg/day (normal daily dose: 25–50 μg/day [2]). On examination the patient had a rough voice and dry, pale skin. On questioning she demonstrated bradycardia. She weighed 59 kg (body mass index 23 kg/m²), her blood pressure was 130/80 mmHg and her temperature 36 °C. Her heart rate was 65 beats per minute and of regular rhythm; cardiac auscultation was normal.

Thyroid function evaluation confirmed hypothyroidism (TSH: 59.7 μUI/ml, normal range: 0.2–4.2 μUI/ml; fT₄ 0.8 pg/ml, normal range: 7–17 pg/ml; fT₃ 0.3 pg/ml, normal range: 1.5–4.6 pg/ml).

In this context thyroid hormone malabsorption was considered and investigated. Anamnesis excluded drug and dietary interference, and also previous gastrointestinal surgery. Gastrointestinal diseases were eliminated through immunological and laboratory tests (anti-parietal cell antibodies and anti-gliadin antibodies were negative). No evidence of relevant liver, pancreatic and heart diseases were found. Considering the personal history of gastric ulcer, an upper gastrointestinal tract endoscopy and biopsy was performed, which revealed oesophagitis, antral gastritis and H. pylori infection. Her duodenal biopsy was normal. Impairment of gastric acid secretion (gastritis and H. pylori infection) is associated with a median increase in thyroxine dose requirement of 22–34% [6], but this was insufficient to explain persistent hypothyroidism despite high doses of thyroid hormones.

The patient was hospitalized in order to evaluate thyroxine absorption. A 1000 μg dose of levothyroxine (Elthyrone®, Abbott) was administrated orally in fasting state at 8 a.m. Blood samples were collected at the beginning and after 2, 4, 6 and 24 h and TSH, fT₄ and fT₃ were measured (Fig. 1). Within 4 h a decrease of TSH level (from 59.7 to 55.6 μUI/ml) and a marked increase in fT₄ levels (from 0.8 to 15.5 pg/ml) were observed. After 24 h the TSH level decreased further to 45 μUI/ml, while the fT₄ value had dropped (9.8 pg/ml) as compared to the 4 h post-thyroxine value. Her fT₃ level gradually increased during the test, but without reaching the lower inferior limit of normal range (from 0.3 pg/ml to 0.8 pg/ml after 24 h). A diagnosis of thyroid hormone pseudo-malabsorption was made.

The patient continued to deny withholding her thyroid medication even after the results of the absorption test had been explained and insisted on her preference for intravenous therapy. Considering the age of the patient and the fact that she...
was living alone we decided that the most convenient and cost-effective option would be oral therapy under surveillance. To eliminate the possibility of impaired absorption due to H. pylori infection, specific eradication therapy was also prescribed.

3. Discussion

Normally 62–82% of the ingested oral thyroxine dose is absorbed through the intestinal mucosa, with a peak between the first and the third hour post-administration [7]. Gastric acid secretion seems to be important for subsequent intestinal absorption as those with impaired gastric acid secretion usually require higher doses of oral thyroxine [6]. Absorption is followed by hepatic metabolism with excretion of conjugated T4. Normally 62–82% of the ingested oral thyroxine dose is absorbed through the intestinal mucosa, with a peak between the first and the third hour post-administration [7]. Gastric acid secretion seems to be important for subsequent intestinal absorption as those with impaired gastric acid secretion usually require higher doses of oral thyroxine [6]. Absorption is followed by hepatic metabolism with excretion of conjugated T4. Fecal thyroxine appears and T3 in bile, which are afterwards deconjugated and partially reabsorbed in the intestinal tract [8]. Fecal thyroxine appears only in the unconjugated form [9]. Described causes of thyroxine malabsorption are presented in Table 1.

Ain et al. introduced the term of pseudomalabsorption in 1991 after evaluating four cases of persistent hypothyroidism despite high oral doses of thyroid replacement therapy [4]. The authors emphasized the psychiatric component leading to non-compliance with therapy and suggested that this disorder should be named “pseudomalabsorption of levothyroxine”. At present, to our knowledge, there are only 12 patients reported to have this condition (Table 2), all of whom were confirmed by an absorption test. The main characteristic of thyroxine pseudomalabsorption is patient’s denial of poor compliance, which leads to difficulties in diagnosis and management. Usually the diagnosis is made after excluding other causes of malabsorption and evaluating the intestinal absorption utilizing a test with a large single oral dose of thyroxine.

### Table 1

<table>
<thead>
<tr>
<th>Causes of levothyroxine malabsorption</th>
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<tbody>
<tr>
<td>Coeliac disease [10]; lactose intolerance [10]; intestinal Giardia lamblia infection [11]; Helicobacter pylori [6]; atrophic gastritis [6]; Surgery: jejunostomy; jejunoileal bypass; short bowel syndrome [2,12]</td>
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### Table 2

<table>
<thead>
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<th>Causes of thyroxine malabsorption</th>
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<tr>
<td>Gastrointestinal</td>
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<tr>
<td>Coeliac disease [10]; lactose intolerance [10]; intestinal Giardia lamblia infection [11]; Helicobacter pylori [6]; atrophic gastritis [6]; Surgery: jejunostomy; jejunoileal bypass; short bowel syndrome [2,12]</td>
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<tr>
<td>Liver</td>
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<tr>
<td>Obstructive liver disease [8]</td>
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<td>Pancreas</td>
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<td>Pancreatic insufficiency</td>
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<tr>
<td>Heart</td>
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<tr>
<td>Congestive heart failure</td>
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<tr>
<td>Physiological conditions which require increased doses</td>
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<tr>
<td>Pregnancy [13]</td>
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<tr>
<td>Drugs</td>
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<td>Cholestyramine, aluminum hydroxide, ferrous sulphate, sucralfate, phenitoin, calcium carbonate, raloxifene hydrochloride, colestipol, ciprofloxacin, laxatives, diphenylhydantoin, rifampicin, phenobarbital, carbamazepine and others [2,3]</td>
</tr>
<tr>
<td>Dietary interactions</td>
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<td>High-fiber diet, walnuts, soybean, herbal remedies</td>
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The side effects of a single high peroral dose of thyroxine are limited, none of the previous published cases presented with adverse events following ingestion. That is partially explained by the fact that T4 is tightly bound by circulating thyroxine-binding globulin and enters the tissues very slowly; also, T4 must be converted in T3 in order to be biologically active. Our patient tolerated the oral test with 1000 μg of oral levothyroxine very well. A rise in serum fT4 was observed as in our case, supervised oral thyroxine ingestion [3].

In such cases management is complicated. It has been suggested that informing the patient of the negative effects of poor compliance may improve the 5-year compliance with therapy [4]. Various protocols have been proposed for reaching euthyroidism: 500 μg of intravenous thyroxine every 3–4 days [5] or, as in our case, supervised oral thyroxine ingestion [3].

In summary, for patients with persistent hypothyroidism in spite of high substitutive doses of thyroid hormones, anamnesis should exclude drugs and dietary interactions and conditions that could impair thyroxine absorption should be investigated (for patients with a previous history or current symptoms of gastric ulcer, upper gastrointestinal endoscopy would appear highly advisable). If these investigations remain negative, pseudomalabsorption due to non-compliance becomes the main diagnostic likelihood and a thyroxine absorption test should be considered.

### References


