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Refractory hypothyroidism: True malabsorption or pseudo-malabsorption?

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Abstract

Hypothyroidism is one of the most common endocrinopathies. Its treatment consists of hormonal supplementation with levothyroxine. Despite the simplicity and accessibility of this treatment, cases of refractory hypothyroidism have been reported despite high doses. Our case is a new observation exposing this problem while discussing the modalities of its management.

Patient aged 34, followed for 6 months for hypothyroidism post total thyroidectomy. She was taking 300 µg/day of levothyroxine. The patient reported compliance with her treatment. She did not report taking any other medications. Clinical examination revealed that the patient was profoundly hypothyroid. Biological tests showed TSH > 100 µUI/mL (0.35-4.94), FT4 less than 0.40 (0.7-1.48) and FT3< 1.07 pg/mL (1.71-3.71). After eliminating all obvious causes, an oral thyroid hormone absorption test was performed in hospital, with FT4 measurements at H0, H2, H4 and H6 after levothyroxine intake. The results showed increasing FT4 elevation, eliminating the diagnosis of malabsorption and testifying to our patient's poor compliance with treatment. We report on a case that highlights the value of the thyroid hormone absorption test, which can help distinguish between true malabsorption and pseudo-malabsorption, in which case re- education on proper compliance and possible psychological follow-up are required.

Keywords: Profound hypothyroidism; Thyroid hormone absorption test; Chronic disease; Diagnostic strategy; Therapeutic compliance

1. Introduction

Peripheral hypothyroidism is a common endocrinopathy with a clear female predominance. It is characterized by low FT4 levels and elevated TSH us. Treatment is simple and well codified, based on levothyroxine replacement therapy. We report a case of persistent hypothyroidism despite high doses of levothyroxine, detailing how to deal with this rare but disturbing entity. Our case highlights the value of the levothyroxine loading test in this context.

2. Case

Patient aged 34, married with 3 children, followed for asthma on treatment (poorly controlled on treatment given the frequency of attacks reported by the patient). In addition, the patient had been followed for 6 months for peripheral hypothyroidism following total thyroidectomy for multi-nodular goiter. The anatomopathological study was in favor of benignity. She was put on levothyroxine replacement therapy at an initial dose of 1.6 ug/kg/day. During her follow-up,

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check-ups were always in favor of profound hypothyroidism, which prompted the dose to be increased each time. At a dose of 300 ug/day, i.e. 3.75ug /kg/day of levothyroxine (weight: 80 kg) deemed too high, an etiological investigation was initiated (table 1).

Clinical examination revealed a patient with mucocutaneous pallor, soft tissue infiltration, psychomotor retardation and bradycardia. Examination of the cervical region was normal, apart from the thyroidectomy scar. The rest of the clinical examination, particularly respiratory, was without abnormalities.

Table 1 History of the patient's laboratory tests during follow-up, showing persistent Hypothyroidism

Date	T SH US µUI/mL (0,35–4,94)	Levothyroxine dose ug/kg/ day
September 2022	TSH > 100	1.6 (125 ug/d)
December 2022	TSH > 100	2.5 (200 ug/d)
April 2023	TSH > 100	3.75 (300 ug/d)

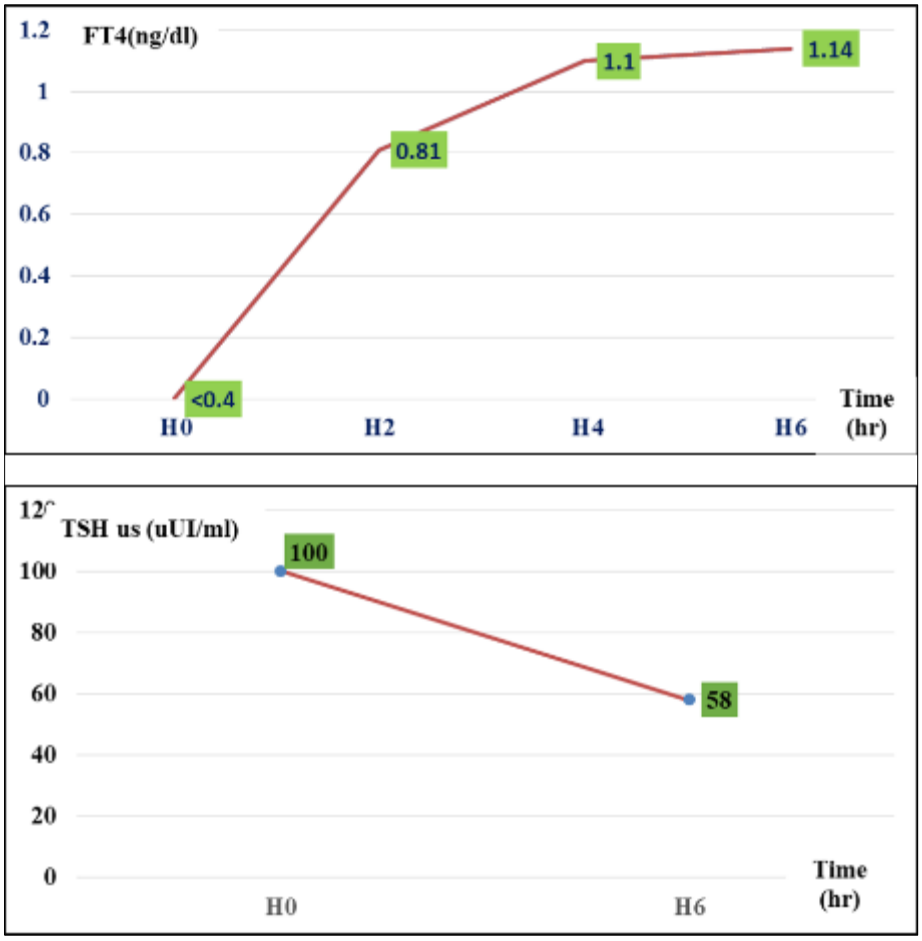

Figure 1 Results of levothyroxine loading test showing good absorption of treatment (rise in FT4 and fall in TSH us)

Biological tests showed TSH > 100 µUI/mL (0.35-4.94), FT4 less than 0.40 ng/dl (0.7-1.48) and FT3< 1.07 pg/mL (1.71-3.71), hypocalcemia with corrected calcemia at 77 mg/l. The patient reported compliance with her treatment. She did not report taking any other drugs or foods that might interfere with treatment. Malabsorption tests, celiac serology and oeso gastro duodenal fibroscopy all came back normal. After eliminating all obvious causes, an oral thyroid hormone absorption test was performed in hospital, with FT4 measurements at H0, H2, H4 and H6 after levothyroxine administration. The results of the test showed increasing FT4 elevation, ruling out the diagnosis of malabsorption and testifying to our patient's poor compliance with treatment (figure 1).

3. Discussion

Peripheral hypothyroidism is common. Its treatment, which is simple and accessible, is based on hormone replacement therapy with levothyroxine. The usual dose of levothyroxine is 1.6 ug/kg/day taken once a day, preferably in the morning on an empty stomach 30 minutes to an hour before breakfast, to ensure better absorption [1,2]. Absorption may be incomplete and variable, due to a number of physiological and pathological factors. In fact, it can be modified by numerous factors which should be eliminated before considering a malabsorption test [3].

3.1. Drug interference

- Cholestyramine, antacids (aluminum hydroxide),
- Cimetidine, ion exchange resins, laxatives, activated charcoal,
- Calcium carbonate, iron salts, propranolol, lovastatin, simvastatin, amiodarone, estrogen therapy,
- Raloxifene, rifampicin, phenobarbital, phenytoin,
- Carbamazepine, imatinib, sertraline, anti-angiogenic agents.

3.2. Digestive pathologies

- Celiac disease, Biermer's disease, lactose intolerance.
- Giardiasis or amoebiasis, Helicobacter pylori gastritis, gastrointestinal surgery.
- Cholestatic hepatopathy, type 3 desiodase-producing hepatic angiomas
- Exocrine pancreatic insufficiency.

3.3. Nutritional interference: soy, plums, nuts, phytotherapy**.**

3.4. **Physiological conditions requiring higher doses:** Pregnancy (increase dose by almost 30% as soon as diagnosis is made), weight gain.

3.5. Tissue resistance to thyroid hormones.

3.6. Cardiac: congestive heart failure**.**

The difference in pharmacokinetics between different levothyroxine preparations influences the degree of absorption, since the latter depends on the excipient used in the preparation. A change of dosage form should be considered in order to optimize absorption (in our patient, even a change of dosage form did not influence the persistence of hypothyroidism).

After eliminating the above-mentioned causes, the diagnosis of pseudo-malabsorption of thyroid hormones due to lack of compliance and adherence to treatment is strongly suspected. This concept was first described by Ain et al. in 1991, describing a factitious disorder related to a lack of patient compliance, making it difficult to balance the thyroid balance [4]. A levothyroxine load test is useful in these cases, but the modalities vary from one center to another. The modalities adopted by our center are as follows:

- Principle: 60 to 100% of the administered dose is normally absorbed in the jejunum, with a serum peak at the second hour.
- Modalities: after a loading dose of oral levothyroxine and under good conditions:
    - In hospital
    - Fasting patient, no vomiting and no other medication taken.
    - Loading dose delivered under medical supervision.
- Advantages: enables definitive differentiation between true malabsorption and Pseudo-malabsorption, where a marked rise or even normalization of FT4 eliminates organic malabsorption.
- Dose: 10 ug / kg / day according to the literature (between 1000 and 2000 ug according to other authors). Our patient received 800 ug of levothyroxine.
- Biological tests: TSH and FT4 at H0, FT4 at H2 and H4, TSHus and FT4 at H6. The significant rise in FT4 and the marked drop in TSH (58 uIU/ml in our patient at the end of the test) led us to adopt the diagnosis of pseudo-malabsorption.

Questioning with the patient's husband confirmed the irregularity of our patient's levothyroxine intake, as is the case with her asthma treatment, which also explains her iterative asthma attacks and poorly controlled respiratory pathology.

We repeated the education, insisting on the need for therapeutic compliance and clearly explaining the possible risks of stopping or irregularly taking the treatment. We made her family (her husband) aware of the problem and of the need for him to take levothyroxine regularly and under the right conditions as previously explained. A psychological follow-up was proposed to the patient.

4. Conclusion

Our case joins the few rare observations already reported in the literature:

- To illustrate the difficulty of managing chronic pathologies requiring lifelong treatment.
- Demonstrate the difficulty of etiological investigation due to the entanglement of the psychic and the organic.
- Emphasize the value of the thyroid hormone absorption test to distinguish between true malabsorption and pseudo-malabsorption, in which case re-education in proper compliance should be carried out in conjunction with psychological support.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare that the research was conducted without any commercial or financial relationships that could be construed as potential of interest.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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