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ORIGINAL ARTICLE

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Levothyroxine absorption test results in patients with TSH elevation resistant to treatment

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Abstract

Introduction Persistent elevation of thyroid-stimulating hormone (TSH) is common in endocrinology practice in patients undergoing replacement or suppression therapy with levothyroxine sodium (LT4). After examining the causes of this condition, LT4 absorption test is recommended. In this report, we wanted to share our results of LT4 absorption test in patients with elevated TSH levels.

Materials–methods The files of patients who presented to our clinic between 2015 and 2018, whose TSH elevation continued despite high-dose LT4 therapy, and who underwent absorption test were reviewed retrospectively.

Results Levothyroxine sodium absorption test was applied to five patients. Absorption test revealed LT4 malabsorption in two patients and pseudomalabsorption in the other three patients.

Discussion When all published pseudomalabsorption cases were considered, it has been stated that at least 2.5 times increase in basal fT4 level may exclude malabsorption. The formula we used has been implemented by Cleveland Clinic since 2014.

Conclusion In cases where TSH normalization is not achieved despite high doses of LT4 therapy, LT4 absorption test is an easy test for administration and interpretation and prevents unnecessary medical treatments and examinations.

Keywords Levothyroxine · Malabsorption · Pseudomalabsorption

Introduction

Persistent elevation of thyroid-stimulating hormone (TSH) is common in endocrinology practice in patients undergoing replacement or suppression therapy with levothyroxine sodium (LT4). The daily LT4 dose is dependent on lean body mass [1]. There is consistent evidence that lean body mass, TSH goal, etiology of hypothyroidism, degree of serum TSH elevation, pregnancy, and age can influence dose requirement. As accepted generally in the literature, hypothyroid patients require LT4 doses of 1.6–2.7 mcg/kg [1].

The most common cause of the TSH elevation is the incompliance of patient with the correct use of medication. After the correct use of medication is checked, it is necessary to examine the drugs that decrease LT4 absorption or increase its degradation. If there is no finding in drug examination, nephrotic syndrome is dismissed; liothyronine (LT3) therapy and LT4 with vitamin C can be used to decrease the stomach pH. If TSH elevation continues despite all these measures, separation of malabsorption–pseudomalabsorption should be performed with LT4 absorption test. Our treatment will be psychological support and administration of total weekly dose in 1 day under supervision in order to improve patient compliance in case of pseudomalabsorption [2]. But our treatment alternatives will be liquid, suppository, intravenous, or intramuscular (im) LT4 application in case of malabsorption [3–7]. There are number of papers dealing with gastrointestinal malabsorption of thyroxine. Gastrointestinal malabsorption of oral thyroxine is also more frequent than previously reputed and may account for a significant fraction of refractory hypothyroidism [8]. The gastrointestinal disorders (*Helicobacter pylori* infection, lactose intolerance, parasites, celiac disease, atrophic, and superficial gastritis) are widespread to be considered as a major issue in patients with thyroxine refractoriness. In particular, *H. pylori* infection affects 30–50% of population in the world and it is known to affect the absorption of further drugs [9]. On the other hand, some of these disorders are occult and should be

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screened. The presence of iron-deficiency anemia and thyroxine malabsorption combination may represent an alert signal for the presence of a gastric disorder in patients with thyroid autoimmunity [10]. When there is a diagnosis of lactose intolerance, both a low lactose diet and a lactose-free LT4 preparation should be administered to restore euthyroidism or make it possible to decrease the dose of the LT4 preparation [11]. The algorithm for patients with TSH elevation resistant to treatment is presented in Fig. 1.

The aim of this report is to share LT4 absorption test results of patients with TSH elevation resistant to treatment.

Materials–methods

The files of patients who presented to our clinic between 2015 and 2018, whose TSH elevation continued despite high-dose LT4 therapy, and who underwent absorption test were reviewed retrospectively. High-dose thyroxine is identified as ≥2.7 mcg/kg thyroxine but with this dose can not to be provided euthyroidism.

In the LT4 absorption test protocol, fT4 is given in the morning after fasting for at least 8 h on empty stomach and under supervision to check patient compliance. After 1000 mcg LT4 is given peroral with half-full glass of water, venous blood samples are collected for TSH measurement. Free T4 levels are measured in venous blood at 1, 2, 3, 4, 5, and 6 h after drug intake. The following formula is used to calculate the absorption rate.

$$\%\text{LT4 absorption} = [(\text{peak } \Delta\text{T4} \times \text{volume distribution(dL)} \div \text{administered dose of LT4}(\mu\text{g})] \times 100$$

$$\text{Volume distribution(dL)} : 4.42 \times \text{body mass index}(\text{kg/m}^2)$$

More than 60–80% absorption indicates normal absorption [12].

It is a routine procedure to take written informed consent before LT4 absorption test after procedural risks are explained in detail.

Results

LT4 absorption test was applied to five patients. All patients underwent total thyroidectomy due to multinodular goitre and two patients had micropapillary carcinoma. Treatment incompliance, interacting drug intake, and nephrotic syndrome were excluded before test. Vitamin C and LT3 treatment were tried in all patients but TSH was not normalized. Absorption test revealed LT4 malabsorption in two patients and pseudomalabsorption in the other three patients. Lactose intolerance was the underlying etiology in two cases with malabsorption. LT4 preparations without lactose were tried to be obtained from abroad for these two cases, but it could not be achieved. A low lactose diet was administered for these patients. Therefore, the patients were given im 500 mcg LT4 weekly as a single dose and TSH normalization was achieved. The patients with pseudomalabsorption were consulted with psychiatry for drug incompliances and secondary gain. TSH normalization was achieved in two patients with pseudomalabsorption. A weekly dose in one time was started to be administered orally in one patient under supervision and TSH normalization was achieved in this patient. There was no side effect due to high-dose LT4 use during the test. The test results of the patients are summarized in Table 1.

Discussion

The main factors affecting levothyroxine need are age and fat-free mass. Mother's need for LT4 increases physiologically during pregnancy. The influences on LT4 absorption combined with potential patient nonadherence can often cloud the clinical picture. The supervision of the patient for thyroxine tablet swallowing is an easy step to avoid further tests or false comments. Psychiatric evaluation should be considered if noncompliance is suspected [13, 14].

In hypothyroid patients, fT4 increases 1 h after LT4 intake and peaks at 2–3 h in average [15, 16]. How much fT4 increase can exclude malabsorption in the LT4 absorption test? There has been no threshold value in the literature on this issue. Some emphasize that at least 50–100% increase should be achieved at fT4 level [17, 18], while some argue that normal fT4 level will be sufficient to exclude malabsorption [19]. When all published pseudomalabsorption cases were considered, it has been stated that at least 2.5 times increase in basal fT4 level may exclude malabsorption [20]. The formula we used has been implemented by Cleveland Clinic since 2014 [12]. When we reevaluate the absorption test results of our patients in the light of the other tests mentioned above, our diagnoses remain accurate. The small size of our patient group is the biggest handicap of our study. As the number of patients increases, our results will be stronger.

Hypothyroidism requires life-long thyroid hormone replacement therapy within a narrow therapeutic range. Our study can be an easy guide to control the correct absorption of this important drug. It should also be studied in larger patient groups.

Conclusion

In cases where TSH normalization is not achieved despite high doses of LT4 therapy, LT4 absorption test is an easy

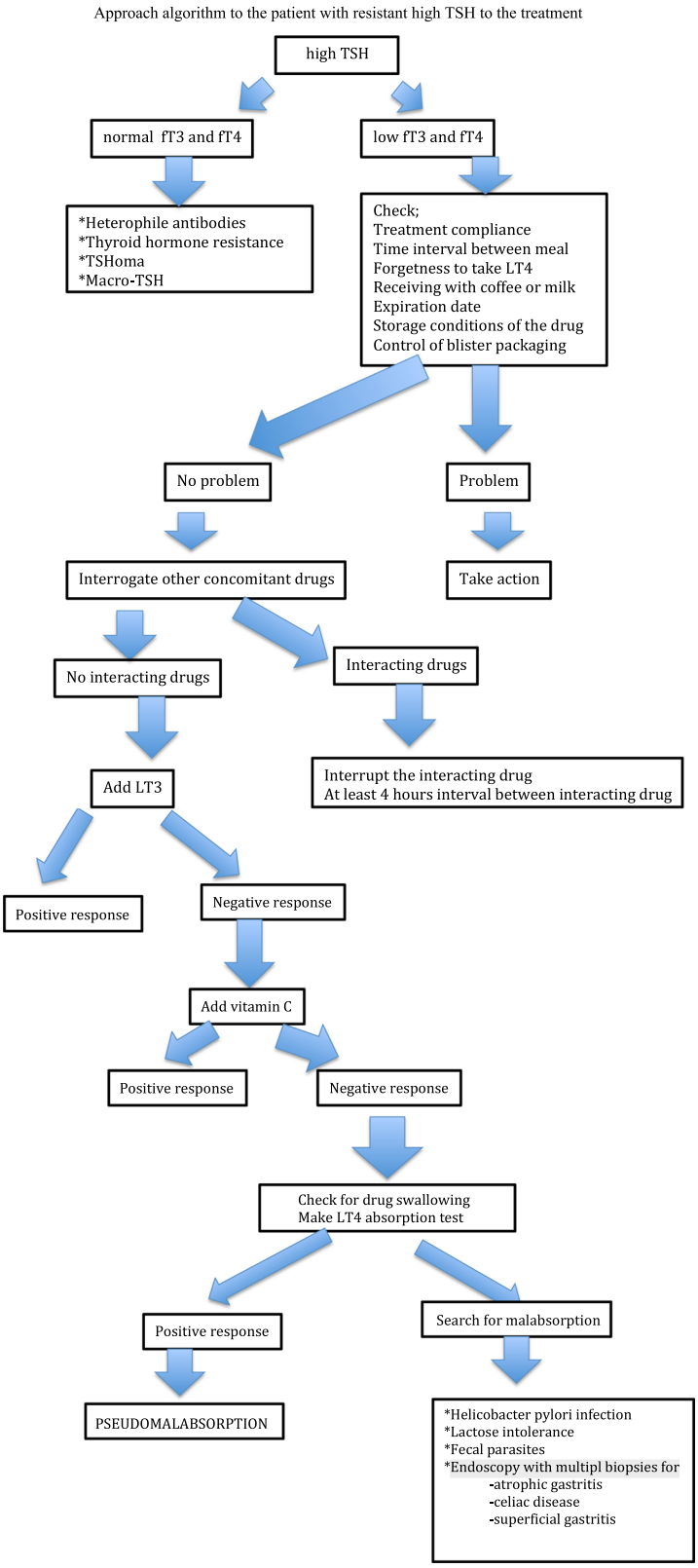

Fig. 1 Approach algorithm to the patient with resistant high thyroid-stimulating hormone to the treatment

Table 1 LT4 Absorption test results

Patient	Basal fT4[a]	Peak fT4	BMI (kg/m^2)	Absorption (%)
1	0.636	0.639	27	6
2	0.290	0.440	27	40
3	0.400	2.000	47	166
4	0.200	1.300	26	97
5	0.530	1.980	30	90

[a]Reference range of normal fT4 level is 0.89–1.76 ng/dL

test for administration and interpretation and prevents unnecessary medical treatments and examinations. It can be used safely for differential diagnosis and treatment.

Author contributions I.Y.S. and U.E.S. wrote the manuscript. I.Y.S. and A.G.O. reviewed/edited the manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethics statement All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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