INSUFFICIENCY OF LEVOTHYROXINE THERAPY IN AUTOIMMUNE HYPOTHYROIDISM: EFFECT OF GLUCOCORTICOID ADMINISTRATION

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Abstract

Objective. The non-effectiveness of levothyroxine administration in hypothyroidism depends on many factors and mechanisms influencing its absorption in small intestines or bounding of circulating hormone with different active molecules.

Methods. Thyroid hormones, TSH, rT3, TGI, TPO-Ab, TG-Ab, were measured using commercially available assays. For anti-T4ab, radioiodine-labeled T4 was added to the patient's serum and the IgG fraction subsequently precipitated by addition of 15% polyethylene glycol. Background was determined by testing 100 control sera from individuals without autoimmune thyroid disease.

Results. A 42-year old woman (71.5 kg) with Hashimoto thyroiditis receiving levothyroxine (L-T4) 150 µg and liothyronine (L-T3) 37.5 µg was admitted to the hospital with clinical data of hypothyroidism, TSH-23.8 mU/L, FT4-6.18 pmol/L (n.range 9-19 pmol/L), TPO-Ab 696 IU/mL, TG-Ab 818 IU/mL, circulating T4- antibodies positive. She has a good adherence to medication, malabsorption or administration of other drugs were excluded. L-T4 absorption test revealed 44% increase of serum FT4 at 120 min after ingestion of 150 mcg L-T4 (2.1 mcg/kg). Methylprednisolone pulses of 500 mg i.v. administered in three consecutive days at equal doses of L-T4/L-T3 resulted in a rapid increase of FT4 to 14.5 pmol/L, fall of TSH to 0.18 mU/L and decrease of anti-T4 antibodies to referent range; TPO-Ab and TG-Ab also decreased significantly. Monotherapy by 150 mcg L-T4 was continued in the next three months. A recurrence of hypothyroidism with increase of circulating T4-Ab was observed 100 days later. New administrations of methylprednisolone two pulses of 500 mg revealed a similar normalization of thyroid hormones and anti-T4 antibodies.

Conclusion. The data showed that T4-antibodies might be a cause of insufficient effects of levothyroxine therapy in autoimmune hypothyroidism. This could be overcome by glucocorticoid administration probably resulting in FT4 release from circulating immune complexes.

Key words: Hypothyroidism, Levothyroxine therapy, Anti-thyroxine antibodies, Methylprednisolone pulse.

INTRODUCTION

Hormone replacement therapy for hypothyroidism is performed with levothyroxine (L-T4) at doses adjusted to the severity of hormone deficiency and the presence or absence of immune stimulation of thyroid gland activity (1). In the absence of endogenous thyroid hormone following surgical or radioiodide ablation of the thyroid gland or atrophy of the gland by autoimmune or inflammatory processes, the required daily dose of L-T4 in adults is 1.5 – 2.0 µg/kg body weight. However, achievement of full hormonal compensation in some patients is possible at much higher doses and the combination of L-T4 with liothyronine (L-T3) is still debatable (2, 3). Difficulties with hormone replacement depend on a variety of endogenous and exogenous factors. Many compounds and drugs might affect thyroid function and ongoing replacement therapy by different mechanisms (4, 5). This communication addresses glucocorticoids (GC) which might interfere with L-T4 at the different levels influencing T4-replacement. The patient described here addressed a number of issues concerning the insufficiency of combination of high doses of L-T4/L-T3 supplementation therapy and the effect of intravenous pulses of methylprednisolone.

CASE REPORT

We observed a 42 year-old woman with hypothyroidism 4 years after radioiodine therapy (5 mCi ¹³¹I) who was treated with gradually increasing doses of levothyroxine.

The patient was admitted to the hospital while on combined therapy with L-T4 (Euthyrox tablets, "Merck") 150 µg and L-T3 (Liothyronine sodium tablets, "Uni-Pharma") 37.5 µg given for the last two years with insufficient effectiveness TSH levels

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varied between 57 and 130 mIU/L). On admission she complained of general weakness, fatigue, insomnia, hairloss and weight gain of 17 kg over the last 12 months. Physical examination revealed body weight 71.5 kg (BMI – 28 kg/m²), mild edema of the face, dry skin, pulse rate of 85/min and blood pressure of 135/80 mmHg. There was no evidence of effusions of the pericardium, pleura and peritoneum, pretibial myxedema and thyroid associated orbitopathy. The ultrasound of thyroid gland showed a reduced size of both lobes and a patchy hypoechoic structure. Laboratory results showed TSH=23.8 mU/L (0.35 – 4.94), FT4=6.18 pmol/L (9-19), FT3=4.79 pmol/L (2.5 – 5.3), TG-Ab=818 IU/mL (0 – 5); TPO-Ab=696 IU/mL (0 – 5.6). Serum lipids (LDL, HDL, APO-B, Lp-a) and other basal metabolic parameters were in normal range.

Laboratory tests

Measurements carried out in Tokuda Hospital were performed on Architect 8200 SI Integrated system (“Abbot Diagnostics”). Whole blood samples were drawn in the morning after an overnight fasting for the measurement of thyroid stimulating hormone, free thyroxine and free triiodothyronine by indirect chemiluminescent-microparticle immunoassay (CMIA), TPO-Ab and Thyroglobulin antibodies (TG-Ab) by immune-turbidimetric two-step enzymatic method.

Measurements carried out at the University of Chicago: Total T4 (TT4), Total T3 (TT3), and TSH were measured by chemiluminescence immunometric assays using the Elecsys Automated System (Roche Molecular Biochemicals GmbH and Hitachi, Ltd., both located in Indianapolis, IN). Total rT3 (TrT3) was measured by a commercial RIA (Adaltis Italia S.p.A, Bologna, Italy) and Thyroglobulin (TG) by an in-house RIA. The serum FT4 and FT4 index (FT4I)

was calculated as the product of the total serum concentrations of T4 and the normalized resin T4 uptake ratio. Antibodies to thyroglobulin (TG-Ab) and thyroperoxidase (TPO-Ab) were measured by Kronus radioimmunoassay and reported as IU/mL, calibrated using the WHO reference 65/93 for TG-Ab and the WHO reference 66/387 for TPO-Ab. To demonstrate the presence of antibodies to T4 (Thyroxine Antibodies - T4-Ab), radioiodine-labeled T4 was added to the patient’s serum and the IgG fraction subsequently precipitated by addition of 15% polyethylene glycol. Background was determined by testing 100 control sera from individuals without autoimmune thyroid disease. In all percent of precipitable level was <2.5%.

RESULTS

Compromised intestinal absorption of L-T4 was excluded by T4-Absorption test with the measurement of serum FT4 before and 120 min after the ingestion of crushed L-T4 (a tablet 150 µg L-T4, “Merck”). The latter showed an increase of FT4 from 6.18 up to 8.94 pmol/L.

The management was carried out with Methylprednisolone (MPS) pulse doses of 500 mg i.v. administered for three consecutive days while maintaining the same doses of L-T4 and L-T3. The administered doses of MPS were similar to these recommended for the management of Graves’ orbitopathy. There were no contraindications for the use of MPS and no cardiovascular or gastrointestinal side effects were observed. The results on the 14th day showed an increase of FT4 up to 14.5 pmol/L, fall of TSH to 0.18 mU/L and significant decrease of thyroid antibodies TG-Ab, TPO-Ab on the 30th day (Figs 1-3). All symptoms and signs of hypothyroidism disappeared and L-T3 was stopped. Monotherapy with L-T4 was continued 3 months later when additional 2 pulses MPS

Table 1. Results of thyroid function after methylprednisolone (The data obtained at the Endocrinology Laboratory to The University of Chicago Medical Center, IL, USA)

TESTS	Reference range	Days after 3 pulses of 500 mg MPS		
		30 days	60 days	100 days
TT4 (nmol/L)	64.3 – 154.4	128.7	79.8	70.0
FT4 Index	6.0 – 10.5	12.2	6.9	5.0
TT3 (mmol/L)	1.23 – 3.00	2.80	1.61	1.04
TrT3 (mmol/L)	0.25 – 0.55	0.28	0.26	0.14
TSH (mIU/L)	0.4 – 3.6	0.37	0.17	120
TG (ng/mL)	2 – 38	6	6	7
TG -Ab (IU/mL)	< 4	4500	3500	4000
TPO -Ab (IU/mL)	< 2	570	445	400
T4-Ab (%)	< 2.5	3.0	2.0	2.6

TT4 - total thyroxine; TT3 - total triiodothyronine; TrT3 - total reverse triiodothyronine; TSH - thyroid-stimulating hormone; TG - thyroglobulin; TG-Ab - thyroglobulin antibodies; TPO-Ab - thyroperoxidase antibodies; T4-Ab - thyroxine antibodies.

Figure 1. Changes in serum TSH concentrations following MPS administration. Arrows indicate i.v. pulses of 500 mg MPS. Measurements were carried out in Tokuda Hospital. Normal ranges of TSH 0.35 – 4.94 mU/L.

Figure 3. Changes in serum TPO and TG antibodies following MPS administration. Arrows indicate i.v. pulses of 500 mg MPS. Measurements were carried out in Tokuda Hospital. Normal ranges of TPO-Ab < 5.61 mU/L and TG-Ab < 4.11 mU/L.

were carried out. The control blood samples within the next few weeks were assessed simultaneously in Tokuda Hospital Sofia and in University of Chicago (USA). The results of both laboratories were consistent and showed a gradual decline of circulating thyroid hormones into the third month when hypothyroidism was expressed again (TSH 98.0 mU/L) (Table 1, Fig. 1). The presence of circulating anti-T4 antibodies (3% of serum T4 bound to IgG) established on the 14th day after initial MPS administration decreased to the range (2%) in a few weeks. Serum TSH and thyroid hormones sustained in the normal range about 100 days when rebounded to initial values in parallel to T4-antibodies (2.6%). Pulses of MPS 500 mg repeated for 2 days revealed the similar effect on all laboratory and clinical data. No side effects of MPS administrations have been observed.

Figure 2. Changes in serum FT4 concentrations following MPS administration. Arrows indicate i.v. pulses of 500 mg MPS. Measurements were carried out in Tokuda Hospital. Normal ranges of FT4 9.0 – 19.0 pmol/L.

All procedures were made according to a protocol approved by the Ethic Committee of Tokuda Hospital with the written consent of the patient.

DISCUSSION

This case addressed several questions: (1) What is the reason for the inadequate effect of combined therapy with T4/T3 given in relatively high doses? (2) What might be the explanation for the prompt beneficial effect of MPS? (3) What is a suitable scheme for the long-term replacement therapy in the case?

There might be several reasons for the insufficient effect of replacement therapy in hypothyroidism. The most common one is noncompliance in medication but it was not suspected. Other causes as uncontrolled ingestion of drugs, dietary factors or gastrointestinal diseases were excluded in the case. The intestinal L-T4 absorption was assessed with the levothyroxine-Absorption test, recommended by JH Walker *et al.* (6). The measuring of serum FT4 before and 120 min after oral administration of a weight-related dose of crushed L-T4 150 µg (2.1 µg/kg), revealed an increase of serum FT4 of more than 44% from baseline level. A disturbed T4 transport or impaired conversion of T4 to T3 as a cause can be also considered (7). The parallel decrease of serum FT4, FT4-index, FT3 and reverse T3 in the case do not support these possibilities. Third, a compromised action of thyroid hormone at the level of the nuclear T3-receptor β1 could be a possible reason too. Syndromes of resistance to thyroid hormone have been described with different forms and characteristics (8). However, in such an event, as demonstrated in the syndrome

of resistance to thyroid hormone beta-receptor, the elevated serum TSH levels are associated with high serum FT4 and FT3.

On the other hand, autoimmune mechanism could also be taken into consideration, which might be realized by production of the specific anti-thyroxine antibodies blocking the circulating thyroxine. Data in this respect are available in some studies (9-12). In a representative series of 627 subjects the thyroid hormone antibodies among hypothyroid, hyperthyroid and non-thyroid autoimmune conditions were found in 7.0%, 1.5% and 7.5% respectively with correlation coefficient of 0.79 between antibody activities and percentage fall in FT4 in serum (13). Our patient revealed a too high immunological activity despite the lack of active thyroid tissue after ablation and the low thyroglobulin in serum. Very high levels of TPO-Ab and TG-Ab were found together with specific anti-thyroxine antibodies all of which significantly decreased after MPS pulse therapy. It is known that high doses of glucocorticoids affect the thyroid immunological activity and production of TSH-receptor antibodies in Graves' disease induces clinical outcome without administration of antithyroid drugs (14, 15). In our case there were significant immunosuppressive effects of methylprednisolone applied in high pulse doses which decrease the specific anti-T4 antibodies probably resulting in FT4 release from the circulating immune complexes. It is known that high doses of glucocorticoids suppress serum TSH levels. The data obtained show two-fold increase of serum FT4/TT4 which is not compatible with MPS-induced suppression of TSH. Rebound of hypothyroidism three months after MPS treatment might be due to the escape from the glucocorticoid effect.

In conclusion, the data presented illustrate that glucocorticoids administered in high doses could be considered in some hypothyroid patients requiring excessive doses of thyroid hormones. In these patients a number of authors recommend a combined therapy with levothyroxine and liothyronine but there are conflicting data on this issue. In the case described the combination of L-T4 and L-T3 has been insufficient to achieve full compensation of hypothyroidism. Additional clinical and experimental studies are needed.

Conflict of interest

The authors declare that they have no conflict of interest.

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