Neuroendocrinology Letters Volume 38 No. 4 2017
ISSN: 0172-780X; ISSN-L: 0172-780X; Electronic/Online ISSN: 2354-4716
Web of Knowledge / Web of Science: Neuroendocrinol Lett
Pub Med / Medline: Neuro Endocrinol Lett

Pituitary hyperplasia mimicking macroadenoma associated with primary hypothyroidism in a patient with selective L-thyroxine malabsorption

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Submitted: 2017-02-28 Accepted: 2017-05-02 Published online: 2017-08-28

Key words: **L-Thyroxine; malabsorption; hyperplasia; adenoma; thyroid gland; pituitary gland**

Neuroendocrinol Lett 2017; **38**(4):243–247 **PMID:** 28871708 NEL380417C01

Abstract

We present the case of a 29-year-old woman who developed a severe hypothyroidism induced by a thyroxine malabsorption and a secondary pituitary hyperplasia. We performed thyroxine absorption tests to diagnose the malabsorption and to evaluate the best therapeutic intervention. Once assessed a correct therapy lowering TSH, we observed the regression of pituitary mass confirming our diagnosis of secondary pituitary hyperplasia. We suggest to evaluate any possible reason for thyroxine malabsorption and to consider the hypothesis of pituitary hyperplasia in the presence of pituitary mass together with overt hypothyroidism.

Abbreviations:

TRT	- thyroid hormone therapy
TSH	- thyroid stimulating gland
TRH	- thyroid releasing hormone
FT4	- free L-thyroxine
FT3	- free L-triiodothyronine
MRI	- magnetic resonance imaging
L-T4	- L-thyroxine
L-T3	- L-triiodothyronine
EGDS	- esophagogastroduodenoscopy

INTRODUCTION

In the endocrine practice hypothyroidism resulting from different pathological conditions is highly prevalent (Jonklaas *et al.* 2014). In most patients, administration of thyroid hormone therapy (TRT) completely resolves hypothyroidism in few weeks. Replacement dose of 1.6 μg/kg/die L-T4 represents an adequate replacement for most adults, whereas higher dose are necessary in newborns and in children (Vaidya & Pearce 2008; Leger *et al.* 2014; Wiersinga 2001). Recent guidelines recommend the use of L-T4 for TRT, even if combination of L-T4 and L-T3 represents an option in patients who remain symptomatic despite the normalization of TSH, FT4 and FT3 and in those patients

CASE REPORT

with metabolic dysfunction, such as impaired function of deiodinase 1 and 2 (Okosieme *et al.* 2016). Rarely, physicians may have to face the failure of TRT due to a malabsorption leading to overt hypothyroidism. A severe hypothyroidism may cause a marked TSH elevation due to an increase in TRH secretion. The absence of thyroxine feedback inhibition on hypothalamus and on pituitary gland may induce a process of pituitary hyperplasia mimicking macroadenoma (Namburi *et al.* 2014; Agrawal & Diwan 2011; Rajput *et al.* 2012). Even the most advanced imaging techniques (i.e. CT and MR scan) may not distinguish between adenoma and hyperplasia of pituitary thyrotrophic cells; definitive diagnosis is established following TRT, as pituitary hyperplasia responds to TRT whereas adenoma does not.

CASE REPORT

A 29-year-old woman presented to our attention with complaint of severe asthenia, weight gain, hypercholesterolemia and oligoamenorrhea.

Her medical history was unremarkable except for chronic autoimmune thyroiditis (TPO Ab 334 IU/ml, normal 0–50 IU/ml) and hypothyroidism (FT4 0.32 ng/dL, normal 0.61–1.12 ng/dL; TSH 150 µIU/mL, normal 0.34–5.6 µIU/mL) diagnosed at age of 19. The patient was then started on 50 µg/d of L-T4 in tablet form, on empty stomach in the morning. On follow up after 12 weeks, TSH was not yet in normal range and L-T4 was gradually raised to 150 µg/d (2.9 µg/kg/die) over the course of 20 weeks. After 5 weeks of treatment with 150 µg/d, thyroid function test revealed TSH 0.65 mU/ml (normal 0.5–4.0 mU/ml), FT3 4.14 pg/ml (normal 1.5–4.5 pg/ml) FT4 1.7 ng/dl (normal 0.75–1.95 ng/dl). Her weight was stable at 50 kg and a regular menstrual cycle was observed. Yearly follow-up was then performed.

Ten years later an increase in body weight of eight kilograms was observed despite no change in lifestyle; a blood test revealed TSH 665.5 mU/ml (normal 0.5–4.0 mU/ml), FT3 1.0 pg/ml (normal 1.5–4.5 pg/ml) and FT4 0.1 ng/dl (normal 0.75–1.95 ng/dl). L-T4 therapy was substituted with combination therapy consisting in L-T4 50 µg/die in liquid form and L-T3 20 µg bid in liquid form(Biondi & Wartofsky 2012). At the same time, eye fundus examination and brain MRI were performed at the request of a neurologist following a perceived loss of peripheral vision and frequent headaches, unresponsive to pharmacological treatment. Eye fundus examination showed papilledema and a significant impairment of visual field limited to the left eye. MRI showed a pituitary enlargement and revealed in left pituitary lobe 11×8×7 mm mass, intensely enhanced following gadolinium injection, without any elevation of the optic chiasm and of the pituitary stalk. This mass was reported to be suggestive of a pituitary macroadenoma by radiologists (Figure 1).

In the suspect of a pituitary adenoma we performed further blood analysis of pituitary function including: prolactin, GH, IGF-1, FSH, LH, ACTH and cortisol. Blood test results showed a slight increase of prolactin (30.0 ng/ml, normal 5–27 ng/ml) ascribed to either TRH increase or to stress reaction to blood draw. On the

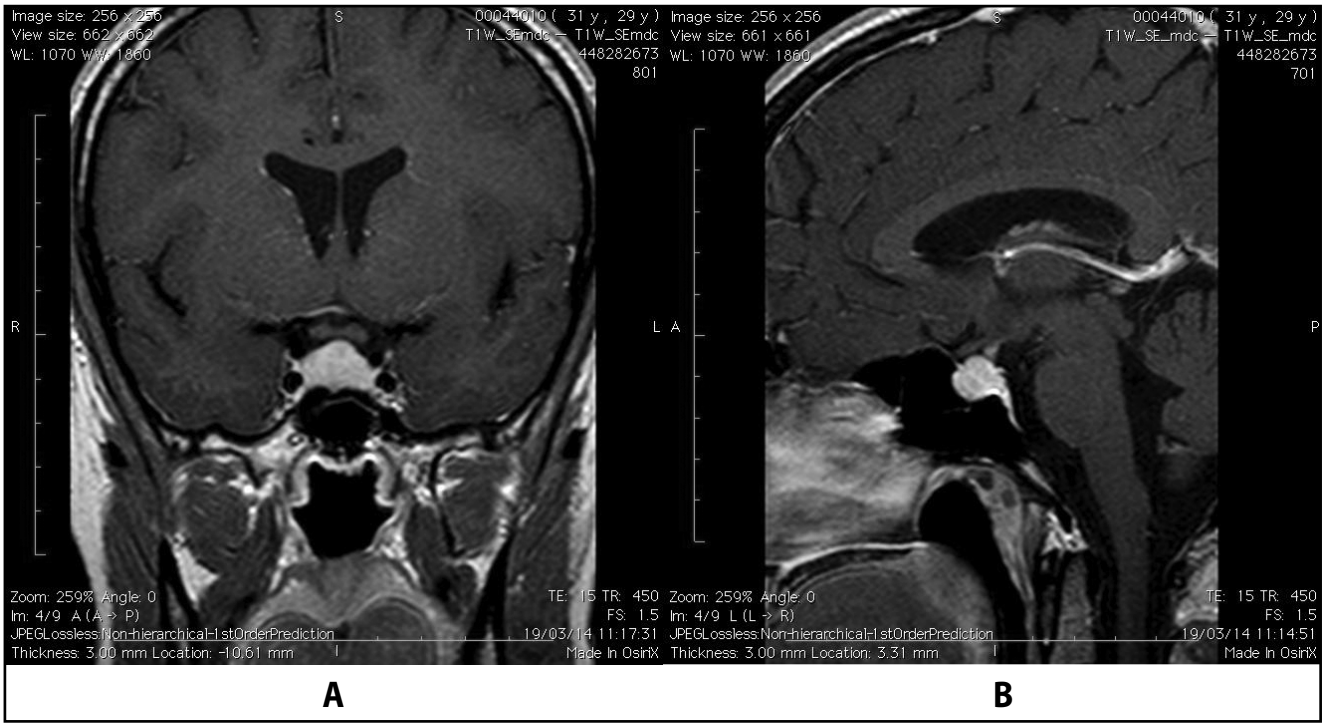

Fig. 1. Initial pituitary Gd-DTPA enhanced MRI revealing pituitary left lobe enlargement. (**A**) Enhanced coronal image. (**B**) Enhanced sagittal image.

base of the clinical features and of the blood test results it was possible to rule out the pituitary TSH adenoma, suggesting a case of thyreotropic cell hyperplasia as the secondary etiology of the pituitary mass. Meanwhile oligoamenorrhea occurred, and complete recovery of menstrual function was observed in about six months with menstrual cycle length of about 32 days.

Since the patient was not responsive to a high dosage combination therapy, a gastrointestinal origin of malabsorption was suspected. An EGDS with multiple biopsies, a fecal parasitological test and urea breath test for lactose intolerance were performed with negative results. Urea breath test for helicobacter pylori was positive and triple therapy was started. Two months later the follow-up urea breath test was negative. On follow up after 8 weeks, the blood test showed overt hypothyroidism (TSH 542.83 mU/ml, FT3 1.28 pg/ml and FT4 0.1 ng/dl).

Being a selective L-T4 malabsorption suspected, a three hours LT4 oral loading test was performed, showing a continuous increase of FT4 in the bloodstream (Figure 2). A six hours L-T4 oral load was subsequently performed, revealing a peak absorption time at fourth hour (Figure 3).

Both oral L-T4 load tests revealed a low and delayed serum peak concentration of free thyroid hormones. Consequently therapy was gradually raised to L-T4 400 µg/die in soft gel capsule administered five hours before any food intake and thyroid test showed TSH 2.53 mU/ml (0.35–4.95 mU/ml), FT4 1.19 ng/dl (0.70–1.50 ng/dl), FT3 3.03 pg/ml (1.7–3.7 pg/ml).

A follow-up MRI scan was performed revealing a significant shrinkage of pituitary gland to 6 mm, homogeneously enhanced without any circumscribed lesion, confirming our diagnostic hypothesis of thyrotropic pituitary hyperplasia (Figure 4).

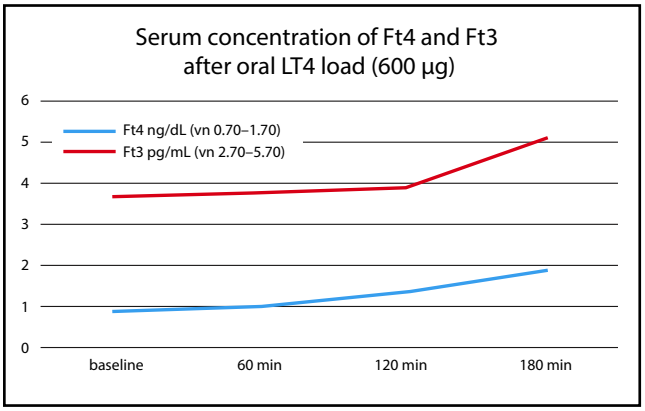

Fig. 2. Graph shows a delayed but continuous increase of both serum Ft4 and Ft3 after 180 minutes.

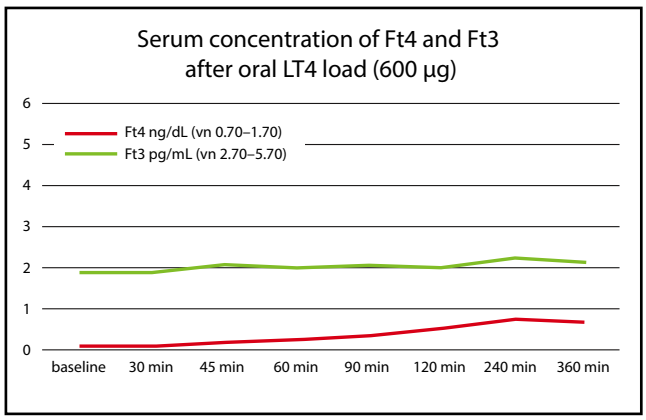

Fig. 3. Graph shows a limited and delayed absorption of L-T4, with a peak serum concentrations of both FT3 and FT4 at 240 minutes after the oral load.

DISCUSSION

The majority of hypothyroid patients responds well to TRT; nevertheless, malabsorption of L-thyroxine is one of the most common issue during TRT, as many drugs may interfere with its absorption such as: calcium carbonate, cholestyramine, colesevelam, ferrous sulfate, proton pump inhibitors, aluminum-containing antacid, cation-exchange resin, sucralfate, raloxifene, orlistat, phosphate binders, coffee, soy, dietary fiber, grapefruit juice (Singh *et al.* 2000; Liwanpo & Hershman 2009; Campbell *et al.* 1992; Sachmechi *et al.* 2007; McLean *et al.* 1993; Campbell *et al.* 1994; Siraj *et al.* 2003; Madhava & Hartley 2005; Benvenga *et al.* 2008; Bell & Ovalle 2001; McMillan *et al.* 2016; Lilja *et al.* 2005).

Furthermore, adequate gastric acid secretion is required for tablet TRT. Indeed, tablet L-T4 is administered on empty stomach, 30–60 minutes before any food, as assumption of food increases gastric pH decreasing L-T4 tablet dissolution(Sachmechi *et al.* 2007). Absorption of L-T4 may be negatively affected by different pathological conditions such as autoimmune atrophic gastritis, Helicobacter pylori infection, lactose intolerance, celiac disease, inflammatory bowel disease, bowel resection, Giardia infection (McMillan *et al.* 2016; Centanni *et al.* 2006; Cellini *et al.* 2014; Zubarik *et al.* 2015; Seppel *et al.* 1996; Vinagre & Souza 2011).

Recently, the introduction of L-T4 in liquid form and in soft gel decreased the cases of L-T4 malabsorption as these pharmacological preparations do not require an acidic gastric environment and do not contain lactose (Virili *et al.* 2016; Vita *et al.* 2013).

However, despite using high doses of L-T4 in soft gel, our patient remained hypothyroid with high levels of TSH. We excluded poor adherence to therapy, all the pathological causes of LT-4 malabsorption and all the possible drug interactions. Oral L-T4 load test performed twice showed a delayed and reduced increase in serum FT4 and FT3 levels, suggesting a selective malabsorption. We opted for increasing daily dose of L-T4 in soft gel till 400 µg/die administered on empty stomach at 6.00 a.m. five hours before consuming the first meal. In such a way, we observed a gradual rise in

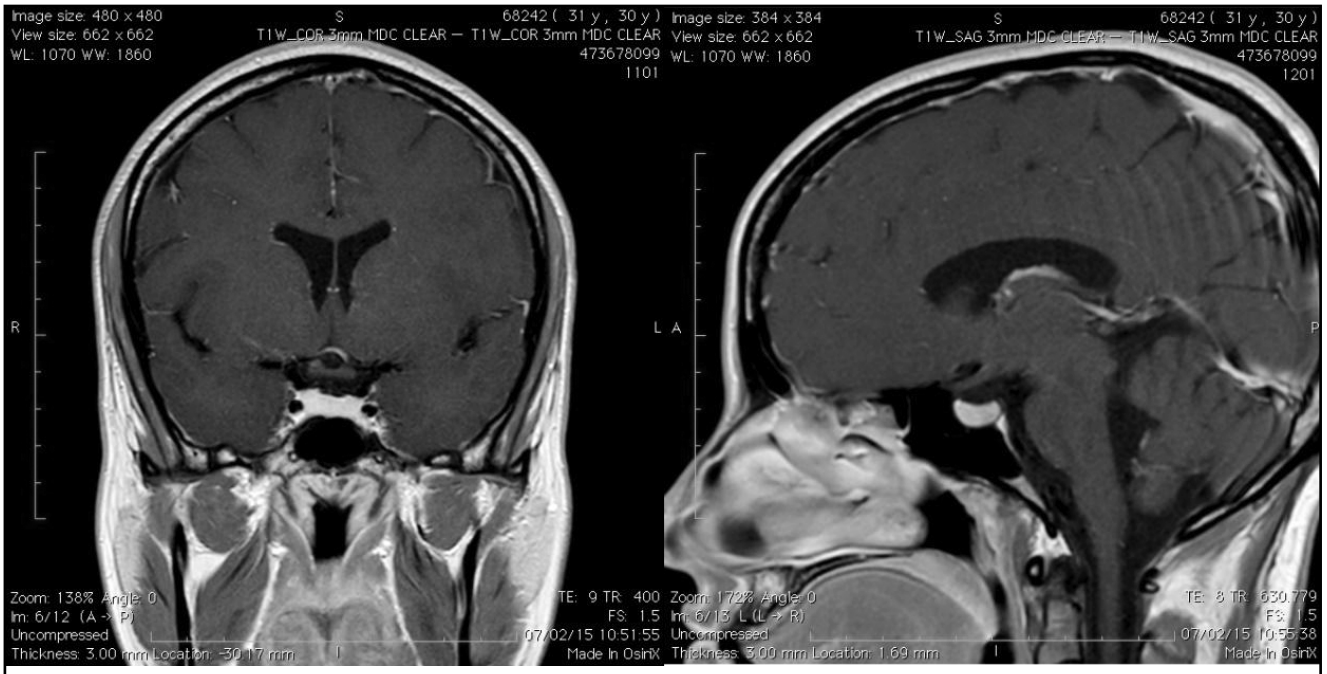

Fig. 4. Pituitary Gd-DTPA enhanced MRI 6 months after the modification of thyroid hormone replacement showing significant reduction of pituitary size. (**A**) enhanced coronal image. (**B**) enhanced sagittal image.

serum level FT4 and FT3 and a decrease in TSH levels till the definitive normalization of each parameter.

In our patient severe hypothyroidism resulted in hyperplasia of thyrotroph cells due to the lack of negative feedback of thyroid hormones on hypothalamus with subsequent increase of TRH and of TSH values. Hyperplasia represents a reversible process occurring in response to a physiological increase in pituitary stimulation (Ashley *et al.* 2005; Lee *et al.* 2008). However, despite the significant improvements in cerebral imaging it's not possible to distinguish pituitary macroadenoma from hyperplasia; nevertheless, we excluded the hypothesis of TSH-adenoma considering the clinical and biochemical signs of hypothyroidism. The diagnosis of secondary pituitary hyperplasia was then confirmed by the regression of the pituitary mass after the normalization of TSH values.

The normalization of TSH caused also a decrease of serum prolactin level and in few months normal menstrual cycle occurred.

CONCLUSION

We advised to evaluate any pituitary mass accompanied by high serum TSH values and low thyroid hormones considering the diagnosis of thyrotrophic pituitary hyperplasia. Adequate TRT may solve the problem even in the case of selective L-T4 malabsorption. In such a case a L-T4 absorption test is recommended to evaluate the pathology leading to the best treatment option.

Informed consent: *Informed consent was obtained from the patient included in the study*

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

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