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ORIGINAL PAPER

Refractory depression in a patient with peripheral resistance to thyroid hormone (RTH) and the effect of triiodothyronine treatment

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Abstract We here described a 39-year-old woman with a severe chronic mood disorder, refractory to antidepressive therapy who showed a significant improvement after a self-prescription of high doses of liothyronine (T_3). A modified Refetoff protocol was carried out to study the role of thyroid hormones on her clinical and biochemical responses. Depression severity was assessed by the HAM-D and MADRS Depression Rating Scales. Sequencing of Thyroid Receptors (TR) α1 and β1 genes was done. At the final stage of the study, plasma T_3 and free T_3 were >800 ng/dl (80–180) and 1409 pg/dl (230–420), respectively. No changes in the cardiovascular parameters, alkaline phosphatase isoenzymes, creatinine kinase, or ferritin were observed. However, an improvement in mood was detected by specific scores (HAM-D 24 to 8; MADRS 40 to 11). No mutations in DNA- and hormone-binding-domains of TRβ1 and TRα1 genes were found in proband, suggesting that the defect could be due to an unknown mutation in either the TR gene or a post receptor abnormality. These results support the existence of a peripheral RTH manifestation as a refractory chronic depression reverted by high doses of T_3. Screening for RTH in refractory chronic depression may provide an alternative treatment for this psychiatric condition.

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Introduction

Thyroid hormones have been linked to mood disorders for more than 40 years, due to their therapeutic effects observed in some depressive patients, as well as the negative effects when they discontinue their use. Up to date it is known that hypo- and hyper-thyroid patients may share similar symptoms with those observed in psychiatric pathologies [1–3].

The mechanisms for the action of thyroid hormones in depression still remain unclear. Based on human thyroid hormone receptor expression and in experimental animal studies, three hypotheses related to the central neural system (CNS) have been postulated. Triiodothyronine (T_3) receptors would be very abundant in the amygdala and the hippocampus, positively regulating the expression of myelin, neurothrophins and their receptors, transcription factors, and splicing regulators and proteins; all of which are involved in intracellular neuronal signaling [4–8]. On the other hand, thyroid hormones would modulate expression of α- and β-adrenergic postsynaptic receptors in the brain cortex and cerebellum, having an important role in the regulation of mood and behavior [9].

A novel action mechanism of T3 has recently been postulated. This would be expressed through the regulation of intracerebral serotonin concentration. Animal studies had demonstrated that the acute or chronic administration of T3 induces an increase in the serotoninergic neurotransmission, reducing the sensibility of autorreceptors 5-HT1A and raising the sensibility of the 5-HT2 receptor. In human beings there is a positive correlation between

plasmatic levels of serotonin and T3 circulating concentrations. According to this idea, it has been shown that cerebral serotonin decreases in hypothyroidism and increases in hyperthyroidism. Furthermore, this fall in intracellular serotonin levels causes a rise in thyroid releasing hormone (TRH) concentrations completing a feedback loop between thyroid and SNC [9–12].

Resistance to thyroid hormones (RTH) is a syndrome with variable clinical presentation, characterized by reduced responsiveness of target tissues to thyroid hormone, despite the elevated levels of circulating hormones found in affected patients. At the present time, more than 1,000 cases that appear to fit with RTH, have been described. Three subtypes have been identified: generalized, which is presented in the majority of the cases, pituitary with a lower frequency than the former and peripheral in isolated cases. Patients with generalized RTH have high levels of T_3, thyroxin (T_4), and an increased thyroid stimulating hormone (TSH) level, which responds to the hypothalamic TRH. Patients with pituitary RTH have unsuppressed TSH, which responds to TRH, despite the elevated serum thyroid hormone levels. Patients with peripheral resistance have normal TSH and thyroid hormone levels, and are expected to be hypometabolic and manifest symptoms and signs of hypothyroidism [13, 14].

The biological effects of thyroid hormones are mediated by genomic and non-genomic actions. The former occurs within the nucleus [15] and the others on membrane bound receptors [16, 17]. RTH is inherited as an autosomal dominant disease and most of the reported cases have been linked to mutations in the TRβ gene [18]. Nowadays, it is known that generalized or pituitary RTH are caused by identical mutation, suggesting that the diagnosis is established by clinical rather than by genetic criteria. Most of the mutations are located in the hormone-binding and hinge domains, suggesting that mutations in this region might explain the decreased responsiveness of thyroid receptors to circulating thyroid hormones. The human TRβ gene is located in chromosome 3p24.3 and encodes β1 and β2 N-terminal variants. The region containing common exons 5–10 has been characterized in detail [15]. Specific exons encoding TRβ1 and β2 N-terminal domains have been identified [15] and the TRα gene has also been implicated in the origin of RTH, especially in TRα1 dominant organs, such as the heart, bone, and the brain, where the TH action is mediated through TRα1, raising the possibility that the RTH of the psychiatric disease may involve this gene [19]. The human TRα gene is located in chromosome 17q11.2 and contains 10 exons spanning 27 kb of DNA.

Here we report the case of a patient with a peripheral RTH manifested as refractory chronic depression that improved with the use of supraphysiological doses of L-T_3. In order to confirm the RTH, she underwent a study protocol with challenging doses of L-T_3, evaluating her biochemical and psychiatric state. We also screened for the presence of mutations in TRβ and TRα genes to identify the molecular basis of the clinical RTH observed in this patient. Furthermore, we screened for the presence of anti-T_3 autoantibodies in sera from proband and from her relatives.

Subjects and methods

Case report

Our patient was a 39-year-old female (weight 68 kg, height 1.63 m; body mass index (BMI) 25.6 kg/m^2), who has had depressive episodes, since she was 8-year-old. Clinical records report three suicide attempts, and different antidepressive treatments, presenting low to partial response to different combined therapies with the following classes of drugs: antidepressives (amitriptiline, fluoxetine, paroxetine, sertraline, citalopram, escitalopram, and bupropion), benzodiazepines (clonazepam, clordiazepoxide, and diazepam), neuroleptics (tioridazine, risperidone, and zisapridona) and mood stabilizers (lithium carbonate, and carbamazepine). She also received 14 electroconvulsive therapy sessions. For the last 10 years she was under the care and continuous pharmachologic treatment by a single psychiatrist (SG); she complied with the prescribed doses of antidepressants. Doses were pushed to the upper limits of the accepted dose ranges looking for clinical response. Since the patient was resistant to the antidepressant pharmacologic schedules used, potentiation strategies with mood stabilizers and atypical neuroleptics were added. Doses and time treatment periods were consistent with clinical conventions for good response in most depressive patients. She also received psychotherapy on a regular basis. Nevertheless, her mood never improved enough to reach euthymia, which caused marked and continuous disability in most areas of social and labor functioning, including the interruption of university studies, inability to sustain a job for more than several weeks and to maintain a stable relationship with a partner.

In 1997 (31-years-old), her medical evaluation showed several physical symptoms (e.g. fatigue, somnolence, constipation, psychomotor lethargy and accentuated asthenia) and signs (dry skin, weight gain, thinning of the eyebrows, cold hands, dry hair) compatible with primary hypothyroidism (TSH = 10.5 μUI/ml and Free T4 = 0.8 ng/dl). The anti-TPO antibody was negative and the ultrasonography showed a small thyroid gland. Clinical symptoms decreased partially after 3 months of treatment with 100 μg/day L-thyroxin (L-T_4), but the depressive disorder persisted in spite of normal TSH

values (TSH = 1.5 μUI/ml). Thus, we recommended the use of a combined therapy: 100 μg/day T_4 + 25 μg/day liothyronine (L-T_3). She noticed an improvement in the above-mentioned symptoms, so she decided to increase the L-T_3 dose up to 225 μg/day, with evident mood improvement and without signs of hyperthyroidism. Biochemical analyses showed an elevation of T_3 (>800 ng/dl) and TSH suppression (<0.01 μUI/ml). It should be noted that drugs, such as lithium, among others, can affect the thyroid function [10]. Hypothyroidism is an adverse effect associated with lithium, probably impairing thyroid hormone release, organic binding reaction and also triggering autoimmune thyroiditis [10, 20]. However, the clinical and biochemical picture of our patient was compatible with a RTH, but it has not been described, as a side effect of psychiatric drugs [10].

The father's thyroid function values were consistent with subclinical hypothyroidism (TSH: 7.59 μUI/ml, F-T_3: 380 pg/dl, F-T_4: 1.41 ng/dl) and her mother and sister showed normal thyroid hormone values (TSH: 0.65 μUI/ml, F-T_3: 360 pg/dl, F-T_4: 1.38 ng/dl, and TSH: 1.85 μUI/ml, F-T_3: 420 pg/dl, F-T_4: 1.47 ng/dl, respectively). The father was in treatment for depression, but he could not be evaluated with the Refetoff test, because he was affected by coronary heart disease. The aim and design of our study was explained to the patient, who signed a written informed consent, according to the guidelines of the Declaration of Helsinki. This study protocol was also approved by the Research Committee, Facultad de Medicina, Pontificia Universidad Católica de Chile.

Psychological assessments

Two depression-rating scales were assayed in the patient, the HAM-D (Hamilton Rating Scale for Depression) and MADRS (Montgomery-Asberg Depression Rating Scale). The 17-item HAM-D test is a screening instrument designed to measure the severity of illness in adults already diagnosed as having an episode of major depression. A score ≥20 is considered severe depression [21]. The MADRS is a 10-items rating scale that assesses sadness, tension, appetite and suicidal thoughts. It is commonly used to detect changes in antidepressant trials, where a score ≥16 is considered a clinically significant depressive severity [22].

Modified Refetoff protocol and biochemical measurements

In order to certify RTH, the patient was hospitalized for 11 days in the Clinical Hospital at the Pontificia Universidad Católica de Chile, to perform a modified Refetoff protocol (see below), and secondarily for molecular studies. The patient discontinued oral L-T_3 administration 1 week before the modified Refetoff study onset, just maintaining 100 μg/day of T_4 to prevent previous hypothyroidism and to avoid worsening her psychiatric disorder. At the hospital, after T3 withdraw, she presented normal T_3 and T_4 values. She underwent a modified Refetoff protocol receiving sodium L-triiodothyronine orally [Liothyronine (L-T_3), Merck Laboratory] as follows: 1–3rd day 75 μg/day (25 μg every 8 h); 4–6th day 150 μg/day (50 μg every 8 h); 7–10th day 225 μg/day (75 μg every 8 h). These doses were chosen based on her previous T_3 intake, self-administrated by the patient. During the study she maintained her conventional antidepressive treatment (escitalopram 30 mg/day, ziprasidone 120 mg/day and clonazepam 4 mg/day). Her heart rate and blood pressure were evaluated every 4 h with a mercury sphygmomanometer; and body weight was controlled daily by a health care professional. Blood samples were drawn every 3 days at the conclusion of each incremental L-T_3 dose to determine thyroid hormone levels (T_3, Free T_3, T_4, and Free T_4 and TSH), ferritin, alkaline phosphatases and isoenzymes, cholesterol, total creatinine kinase (CK), calcium, phosphorus, total protein, and albumin). We did not measure the sex-hormone-binding-globulin (SHBG), because the patient was undergoing estrogen treatment and it was withdrawn only 1 month before the study. When the patient stayed at home she was evaluated once a week. Her heart rate and blood pressure were recorded by an ambulatory blood pressure monitor (Rozinn, Model-RZ250 ABP Recorder, Glendale NY, USA) during 24 hours, and her body weight was controlled by a health care professional.

DNA amplification and sequencing analysis of TRβ and TRα genes

Genomic DNA was isolated from leukocytes from the patient, using a commercially available DNAzol reagent (Invitrogen Corp., San Diego, CA). DNA sequence analysis of the DNA- and hormone-binding domains of TRβ and TRα genes were performed. PCR amplification was carried out using oligonucleotide primers (Table 1). Amplified gene products were purified by Qiaquick gel extraction purification kit (Qiagen, USA). Sequence analysis of both genes was performed in the ABI Prism 377 DNA genetic analyzer (Applied Biosystem, USA). TRβ nucleotide sequences were matched with the complementary region spanning from 24104197 to 24476278 nt of chromosome 3 sequence (gi: 51464027), and for TRα, the nucleotide sequences were matched with the complementary region spanning from 35472686 to 35503644 nt of chromosome 17 sequence. This analysis was performed with BLAST and secondarily with CLUSTAL W looking for genetic alterations.

Table 1 Oligonucleotide primers (5′→3′) for TRβ1 and TRα1 gene amplification

Exon	Primer sense	Primer anti-sense	T° ann. (°C)	Size (bp)
5β	CCT CTT CCT GGC AAG CCA ATT	CCA GAC ACC TGG ATG ATC A	56	352
6β	GGA GCT AGA GGC CTA GAA AC	GGA GGT GGT ATG ACA GGG TA	57	503
7β	GGA GAG AAA CTG TCC CAG TGT	AGC CTC TCA GAG CTA CGG TTT	59	493
8β	ACC AGC ATG TGC AGT GCT CT	GGC CTT ACA CGG ACA AGC TAA	58	702
9β	GTC GAA AGT CTG CAG CCA AGT	GTC CAC TGG CAA ACC TGC AAT	59	583
10β	GAG GCA TCA CCT TTC ACA CTC	TGG TAG TGC TTG GTG CTG GT	58	806
5α	TAA ACT GCA TGG TTG GTT C	GTG GGC TCT GAG GGT AC	52	148
6α	CCC AAC TGC TAG GTG ATT TG	GCT CAC TCT CTT CTC CCT	54	206
7α	GGA GCC TCA GTG AGA GGC TGA AA	CCT CCA GCA CAG CAT CAC AT	58	147
8α	GGA CAC TCT AGG GGA GAC TCA A	GCT TCT GAG CCC TCC CGA CTA AT	60	259
9α	CCC CTC TAG TCC TTT CTT CC	CAT GTG GAG GAA GCG GCT GGC G	61	128
10α	CCA GAG GCT CAT CTT GGA AT	GGT GCT TGT CTC TGC AGG TAG GT	58	846

Anti-T_3 autoantibody detection assays

Sera obtained from this patient on three different opportunities, without treatment and under thyroid hormone treatment (first with 100 μg/day T_4 + 75 μg/day T_3 and 2 months later receiving 100 μg/day T_4 + 225 μg/day T_3), were screened for the presence of anti-T_3 autoantibodies. Simultaneously, we screened sera from healthy volunteers (controls), and from two hyperthyroid subjects with similar plasma T_3 concentrations to the index case. The assay was performed, as previously described [23].

Results

Effects of exogenous thyroid hormone administration on peripheral tissues

The effects of supraphysiological amounts of L-T_3 were studied by monitoring thyroid hormones, metabolic and cardiac functions for a 40-day period in a chronic depressive patient. The patient's responses to the oral thyroid hormone administration during the modified Refetoff protocol (100 μg/day T_4 + increasing doses of T_3) are shown in Table 2. T_3 and free T_3 concentrations progressively increased from 83 ng/dl to a maximum of >800 ng/dl and from 164 pg/dl to a maximum of 1409 pg/dl respectively at 10 days of exogenous thyroid hormone administration (100 μg/day T_4 + 225 μg/day T_3). At day 11, the patient returned to her home with the indication of oral thyroid hormone administration (100 μg/day T_4 + 225 μg/day T_3) and she was evaluated 4 weeks later. TSH levels remained suppressed during the entire study and T_4 and free T_4 concentrations showed small changes. Despite the high concentration of T_3 and free T_3 reached at the end of the modified Refetoff protocol, the mean blood pressure (MBP) and heart rate did not show significant changes. In order to test thyroid hormone action on peripheral tissues, we analyzed the time course of the changes in alkaline phosphatases, its bone, and hepatic isoenzyme levels and creatinine kinase, which were within the normal range. We also analyzed the time course of the total protein and albumin that showed minimal changes and were either low or in the lower portion of the normal range (Table 2). Only the plasma ferritin levels remained below the normal range showing a slight rise with 150 μg of T_3 intake, which was not maintained when the T_3 dose increased (Table 2).

After 4 weeks receiving 100 μg/day T_4 + 225 μg/day T_3 we observed that the biochemical parameters were still within normal ranges, although bone fraction of alkaline phosphatases concentrations experienced a slight increase, and cholesterol concentrations decreased after the fourth week of this treatment (Table 2). The 24-h ambulatory blood pressure monitor revealed that medium blood pressure (MBP), as well as the heart rate remained within the normal range. The body weight control did not report variations.

Effects of supraphysiological amounts of L-T_3 on psychopathological aspects

At the initial stage of the modified Refetoff protocol our patient presented a severe mood disorder confirmed by a score of 24 in the HAM-D test. In contrast, at the end of the protocol, when T_3 concentration was >800 ng/dl and free T_3 concentration was 1409 pg/dl, the HAM-D score dropped to 8 points, concomitant with an evident mood improvement. In addition, MADRS score reduction (40–11) confirmed that she had responded positively to T_3 administration. We also observed a significant improvement in the physical and clinical symptoms of hypothyroidism. Serial rating scales

Table 2 Patient's response to oral administration of 100 μg/day T_4 and increasing the L-T_3 doses during the modified Refetoff protocol

Liothyronine Days	Basal	75 μg 1–3	150 μg 4–6	225 μg 7–10	225 μg 40	Reference range
Clinical parameters						
MBP (mmHg)	97	88	91	93	94	[75–108]
Heart rate (min^{-1})	82	84	104	88	70	[60–100]
Thyroid hormones						
T_3 (ng/dl)	83	338	766	>800	>800	[80–180]
Free T_3 (pg/dl)	164	519	901	1409	1028	[230–420]
T_4 (μg/dl)	6.7	5.9	6.5	5.7	7.4	[4.3–12.5]
Free T_4 (ng/dl)	0.7	0.7	1.1	1.0	0.9	[0.9–1.8]
TSH (μUI/ml)	0.03	0.01	0.02	<0.01	<0.01	[0.4–4.2]
Biochemical profile						
Cholesterol (mg/dl)	203	256	250	204	115	<200
Creatinine kinase (U/l)	Nd	Nd	Nd	31	29	[24–195]
Alk Phosphatase (U/l)	76	88	113	112	90	[30–100]
Bone fraction (U/l)	35	37	39.5	44.8	48.6	[15–62.4]
Hepatic fraction (U/l)	39	43.1	68.9	61.6	37.8	[12.3–66]
Serum calcium (mg/dl)	8.9	9.5	9.9	9.5	9.0	[8.5–10.5]
Serum phosphorus (mg/dl)	3.7	4.1	4.6	4.8	3.9	[2.6–4.5]
Total protein (g/dl)	5.7	6.3	6.2	6.0	5.5	[6.0–8.0]
Albumin (g/dl)	3.4	3.9	3.8	3.9	3.6	[3.5–5.0]
Ferritin (ng/ml)	6.5	6.1	9.3	7.6	6.7	[12.8–215]

MBP: Medium blood pressure. Plasma concentrations of these parameters were measured a day before and on the 4th, 7th and 10th days of the modified Refetoff protocol (before the first doses of T_3 were given). In addition, they were measured 4 weeks after the modified Refetoff protocol during treatment with 100 μg/day T_4 + 225 μg/day T_3. Nd = Not determined

are not available for a follow-up period because the patient retired her consent and looked for further clinical care with a new clinician. The available clinical information is that in the following years, the frequencies of depressive episodes, maintaining high T_3 treatment and the same psychiatric drugs she used in the past, have been very infrequent, no more than 1 or 2 per year, shorter and less severe. Moreover, her social and work level of functioning improved noticeably, based on the fact that she has been in a stable relationship for a longer period than ever and lately she has been working continuously for several months.

Molecular analysis of TRβ and TRα genes

PCR amplification and sequencing of hot-spot regions of the TRβ gene was performed with human genomic DNA isolated from lymphocytes from the patients. In the index case's TRβ gene, we did not find any alteration (mutation) either in the DNA- (exons 5–6) or in the ligand-binding domains (exons 7–10), although the genetic analysis revealed the existence of the following novel variants: (1) Interventor Sequences (IVS)5–26 A/T Heterozygous (Het); (2) exon 7 C/T Het (Phe245Phe); (3) IVS9-63 T/A Het. Furthermore, no mutations were found in DNA- (exon 5–7) and ligand binding domain (exon 8–10) of the TRα gene in our patient.

Screening of autoantibodies to T_3

Since the presence of autoantibodies to T_3 can prevent the interaction of T_3 with its receptor, as well as overestimating the real serum T_3 concentrations, we investigated for the presence of anti-T_3 autoantibodies in all the samples from the patient, in her family's members, in sera samples of healthy subjects and in sera samples from two hyperthyroid patients with similar T_3 concentrations to the index case. None of the assayed sera demonstrated the presence of anti T_3 autoantibodies.

Discussion

This study documents a case of peripheral RTH manifested, as a refractory chronic depression clinically reverted with the use of supraphysiological doses of T_3 and suppressed levels of TSH in the absence of hyperthyroid symptoms. The cardiovascular parameters were always within the normal range; even though we observed that the

heart rate decreased at the end of the modified Refetoff test. Moreover, no significant differences were observed in either bone tissue remodeling or protein metabolism markers (i.e. alkaline phosphatase and bone fraction, creatinine kinase, albumin, serum calcium and phosphorus as is shown in Table 2). The low-ferritin level should be explained by excessive menstrual bleeding, because other causes were ruled out. The ferritin response to T_3 administration was as expected in patients with RTH, with a slight increase in sera ferritin concentration in spite of an 8-fold increase in serum concentration of free T_3 [24]. In contrast, we reported a reduction of cholesterol levels, which is concomitant with the increase of thyroid hormone, suggesting that the cellular response to T_3 may vary even within the same tissue. In fact, it has been demonstrated that the promoter region of the LDL receptor gene has a thyroid response element (TRE) that triggers the upregulation of this gene in the presence of T_3 [25, 26].

Only a few cases of peripheral RTH have been reported [14, 27, 28], but no linkage to mood disorder has been mentioned. In one of these reports, the authors performed a study protocol using increasing doses of T_3 (50–500 μg/day) in a 33-year-old woman with a history of partial thyroidectomy, who achieved clinical euthyroidism associated to a maximum dose. Analysis of DNA- and ligand binding domain of TRβ gene performed on that patient failed to show sequence differences compared with a normal wild type TRβ gene [27]. It is known that these domains are mutational hot spots of the TRβ gene, but in our patient we were unsuccessful in finding any mutation that alters the TRβ1 activity directly. However, we know that 15% of the RTH reports did not find TRβ mutations, suggesting that other factors may be responsible for peripheral RTH phenotype [14]. Since our patient did not show change neither in blood pressure or in heart rate, in spite of the high serum T_3 concentration reached, we analyzed the sequence of the TRα gene, which is expressed in heart and predominates in vascular endothelial cells [17]. On the other hand increasing evidence has been accumulated indicating that mood disorders are related to TRα-mediated T_3 action using animal models [29]. TRα knocked out mice studies have shown evidences of damage in hipocampal structure and function, these findings open the possibility of a linkage between human TRα alterations and psychiatric syndromes [19]. However, we were unable to demonstrate mutations in the TRα gene from this patient. The only coding regions that have not been sequenced yet, are the ones including exons 2, 3, and 4 in TRα, and exons 3 and 4 in the TRβ gene, but these zones are not linked to DNA- or ligand-binding domain [15]. However, we have not evaluated the possibility of an abnormal splicing secondary to the described substitutions in the interventor sequences (introns).

The absence of mutations in the coding regions of both genes raise the possibility that polymorphisms in other regions of TR isoforms, mutations in cofactors (NCoA-1, NCoA-2, NCoA-3) or dysregulation of its expression [30] may be involved in the peripheral RTH phenotype. Most thyroid hormone receptor isoforms, in presence of thyroid hormone, associate a coactivator protein, forming a complex that mediates the transcriptional activation. In 1999, knockout mice that lacked the coactivator SRC-1 showed a mild RTH, however this or other 'post-receptor' defects have never been described in RTH patients [31].

Anti-T_3 autoantibodies were screened because they interfere in the T_3 conventional measurements, giving overestimated T_3 values [32]. There is evidence regarding this, suggesting the presence of an underlying autoimmune disorder in cases of unipolar depression, with the possible involvement of the thyroid gland [33]. However, in our study we did not detect anti-T_3 autoantibodies in the index case.

The T_3 effect observed in this patient can be analyzed taking a reference from other patients with refractory depression who improved their mood with macrodoses of thyroid hormones. This is known in psychiatry as "potentiation therapy" [34]. In a subgroup of those patients, mood improvement is achieved only with supraphysiological doses with low or almost inexistent peripheral effects, which suggests the existence of a RTH [35]. There are several reports which document that the use of supraphysiological doses are effective, and display good tolerance when they are included in the anti-depressive treatment, or as mood stabilizers. It is interesting to focus our attention on the low or almost inexistent adverse effects observed in patients affected by unipolar depression with the use of these doses compared to the effects observed in hyperthyroid patients. There are few reports about cardiovascular risk in these patients, and there is no evidence of hyperthyroidism, even in cases of long-term use [36]. Furthermore, loss of bone mass has not been verified and there are some studies demonstrating a gain in mineral bone density [37]. The reason for this unexpected response remains unclear, but it is possible that some of these patients, who associate a partial RTH, could revert with the use of macrodoses of thyroid hormones.

In summary, we report a case of a peripheral RTH, first manifested as a hypothyroidism and secondarily as a chronic refractory depression reverted with the use of very high doses of T_3. This is one of the first reports to associate a peripheral thyroid hormone resistance with a depressive disorder, emphasizing the importance of a screening and evaluation for similar patients. Diagnosis of peripheral resistance is difficult because thyroid hormone and TSH values are normal, and some depressive patients carrying a peripheral resistance remain non-diagnosed. Furthermore, our study may contribute to explain the

benefits of potentiation therapy with thyroid hormones in euthyroid depressive patients widely reported in the psychiatric literature.

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