SUBCLINICAL CENTRAL HYPOTHYROIDISM

J. Ilany*, O. Cohen

Institute of Endocrinology, Sheba Medical Center, Tel-Hashomer, Israel

Abstract

A case of a young woman with cold intolerance is presented. Her thyroid function tests were all within the normal range although both TSH and free T4 were in the low normal range. The possibility of subclinical central hypothyroidism was raised and tests to confirm it were performed. The results could be consistent with the diagnosis and treatment with thyroid hormone was started with clinical improvement. However, with treatment, her TSH level decreased below the normal reference range. We discuss the question of having hypothyroid symptoms with normal thyroid function tests, should we treat it and how to evaluate the clinical and laboratory response to treatment in this patient.

INTRODUCTION

The issue of subclinical thyroid abnormalities has been widely discussed in the medical literature recently (1-3). The definitions of these conditions are based upon laboratory results, namely, abnormal TSH level in the presence of normal free T4 (FT4) (1). The association of clinical symptoms and routine treatment of subclinical abnormalities is debated (1-6). The common causes of subclinical thyroid disease (STD) are similar to those that cause overt thyroid disease (3), primary thyroid abnormalities being by far the leading cause.

We present a patient that was suspected to be hypothyroid because of complaints of cold intolerance. However, all her thyroid function tests (TFTs) were within the normal reference range. Dynamic tests could be consistent with central hypothyroidism and she started treatment with thyroid hormone replacement. The treatment improved her symptoms but suppressed her TSH to be abnormally low. We discuss the questions whether this patient has normal or abnormal thyroid function, can "within normal range TFTs" be abnormal? Could her symptoms be related to thyroid problem despite normal TFTs? And, is it justified to continue thyroxine treatment even though we suppress her TSH to abnormal level?

*Correspondence to: Jacob Ilany, Institute of Endocrinology, Sheba Medical Center, Tel-Hashomer, 52621, Israel, Tel.: 972-3-5305382, 972-5-23852461, Fax: 972-3-6357018

E-mail: jacob.ilani@sheba.health.gov.il

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MATERIALS AND METHODS

TSH, FT4, TT3, cortisol, FSH, LH, IGF-1 and prolactin (PRL) were measured by a chemiluminescent immunometric method (Immulite 2000, Diagnostic Products Corporation, Los Angeles, CA). The sensitivity of the TSH assay was <0.01 mIU/L (3rd generation). Thyroglobulin Ab and thyroid peroxidase Ab (Anti TPO) were measured using an immunometric chemiluminescent assay (Immulite, Diagnostic Products Corporation, Los Angeles, CA).

For TRH test, 200 microgram of TRH (Protirelin, Ferring, Israel) were intravenously administered. Plasma samples were obtained at baseline and after 15, 30, 60, and 90 minutes for TSH and PRL. For the examination of the nocturnal surge of serum TSH level, blood samples were drawn at $13.^{00}$, $14.^{00}$ and $15.^{00}$ h and again at $01.^{00}$, $02.^{00}$ and $03.^{00}$ h.

TRH receptor (TRH-R) gene was sequenced as follows: DNA was extracted using a commercial kit (Gentra System Inc., Minneapolis, MN). The two exons of TRH-R were amplified with the primers (Ex1a-F: ttg tga ttg gga ctt gat cag aaa, Ex1a-R: atc ttt ttg gct ctg gaa aat gtg, Ex1b-F: cta tgt tgg atg cct ctg cat tac, Ex1b-R: cac tgt gaa aca ttt gca tga ttg, Ex2-F: gga act aaa ggt ttg ggt gag aga, Ex2-R: gct att tca cag atc tgc tcc att t). PCR was carried out in a 25-ml reaction containing 50 ng of DNA, 10 uM of each primer, 1.5 mM dNTPs in 1.5 mM $MgCl_2$ PCR buffer with 1.2U *Taq* polymerase (Bio-Line, London, UK). After an initial denaturation of 5 minutes at 95°C, 30 cycles were performed (94 °C for 30 seconds, 56 °C for 45 seconds and 72°C for 45 seconds), followed by a final extension of 10 minutes at 72 °C. PCR products were sequenced using an automated ABI Prism 310 Genetic Analyzer (Perkin-Elmer).

Case Report

A 20 year old otherwise healthy woman consulted an endocrinologist because of cold intolerance. She said that she needed to put on a sweater even in a hot summer day and this was ongoing already for a few years. She denied recent change of weight or constipation and had regular periods. No family history of thyroid problem was known. Her physical examination was normal with weight of 72 kg (BMI 26.4), pulse of 76/min and blood pressure of 110/60mmHg. Her extremities

Table 1. Baseline hormonal evaluation of the patient

Test	Results	Normal reference range	Units
TSH	0.45	0.35-4.94	mIU/L
FT4	11.7	9-19	pmol/L
TT3	1.6	0.9-2.4	nmol/L
Anti-TPO	<10	<35	IU/ml
Anti-Tg	<20	<40	IU/ml
Cortisol	433	138-690	nmol/L
Prolactin	368	25-628	mIU/L
IGF-1	411	191-529	ng/ml
LH	2.8	2.57-26.53	mIU/ml
FSH	4.5	3.35-21.5	mIU/ml

Table 2. Results of TRH test and test for nocturnal TSH surge

	Time (min)	TSH (mIU/L)	Prolactin (µg/L)
TRH test*	0	0.46	8.4
	15	3.68	55.2
	30	4.6	46.4
	60	2.91	21.3
	90	1.9	13.8
TSH surge	$13.^{00}$	0.45	-
	$14.^{00}$	0.39	-
	$15.^{00}$	0.37	-
	$01.^{00}$	0.92	-
	$02.^{00}$	0.62	-
	$03.^{00}$	0.55	-

* The normal response for women is net increase of at least 6-22 mIU/L at any time point.

were warm and no cyanosis was noticed. Three previous TSH measurements were found in her medical records and all were in the low normal range (0.49 to 0.66 mlU/L). Free T4 was not checked up to this point. Thyroid function tests were repeated and were found to be low-normal both for TSH and for FT4 (Table 1). Other pituitary axis hormones were normal and anti-TPO antibodies were negative. Anti-pituitary antibodies were not measured. To evaluate the possibility of central hypothyroidism, a TRH test and test of nocturnal TSH surge were performed. The results of the TRH test (table 2) showed sub-normal response of TSH with normal response of prolactin. There was a small nocturnal surge of TSH (Table 2). A brain CT scan was interpreted as normal. At this point treatment with 50 micrograms of thyroxine (Eltroxin, GmbH&Co., Germany) was started.

After 3 to 4 months on treatment she reported an improvement of her long standing cold intolerance and weight loss of 10 kg without any specific dietary change. She did not have palpitations or any other complaints consistent with hyperthyroidism and her pulse was 84/min. Her thyroid functions on treatment are illustrated in Fig. 1. TSH level was suppressed by the treatment to below normal range. Since then she is being treated with thyroxine and had 2 normal pregnancies. During a short period when thyroxine treatment was withheld, she re-complained of cold intolerance. In an attempt to further search for a cause for her central hypothyroidism, DNA analysis of her TRH-receptor gene was performed and was found to be normal.

DISCUSSION

Does this patient have thyroid problem and is well treated, or that her thyroid function is normal and she is being over treated with thyroxine to the point of being hyperthyroid? If she needs treatment, how should we follow her response to treatment and decide the right dose of thyroid replacement therapy?

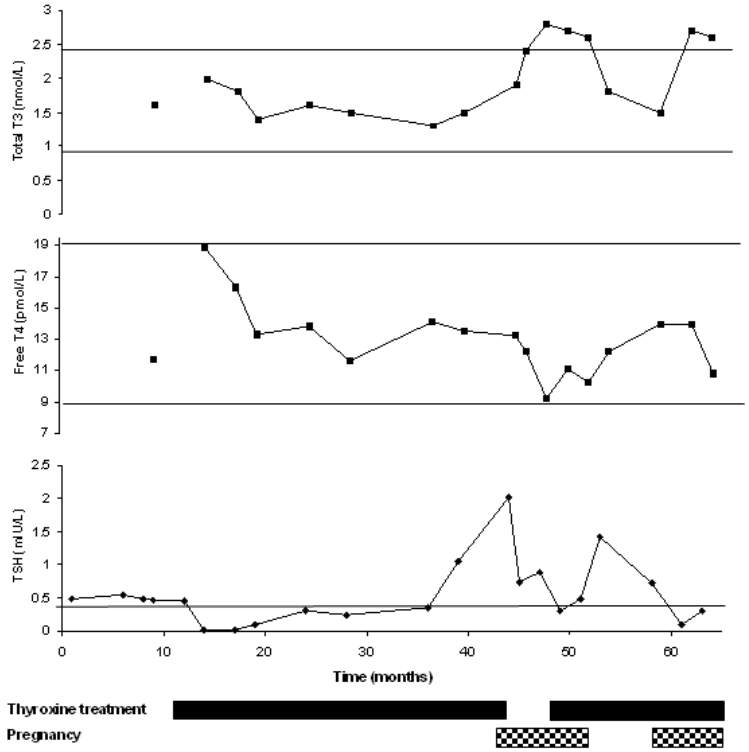

Figure 1. Time course of plasma TSH, FT4 and total T3 levels during follow up of more than 5 years. The horizontal lines denote the normal reference values for each test. The horizontal bars represent the time of thyroxine treatment (solid) and pregnancy (chequered). Note the increased level of total T3 with decreased level of free T4 and TSH during pregnancy.

Can "normal range" thyroid function be abnormal?

Our patient had "within normal range" baseline TFTs, both of FT4 and of TSH. Can her thyroid function be still abnormal? Looking at the value of FT4 alone, it was on the lower normal range. In case of elevated TSH we would treat it with thyroxine. In case of mildly elevated TSH we define it as "subclinical hypothyroidism". Andersen *et al.* (7) found that there is a narrow individual variation in serum T3 and T4 in normal subjects. Based on their findings they concluded that "a test results within the laboratory reference limits is not necessarily normal for the individual". The individual "set point" of thyroid functions was found by others as well and was shown to be genetically determined (8). So, "normal" FT4 can still be abnormal. If the FT4 level of our patient is low for her, her low-normal TSH level reflects central hypothyroidism (CH), even though we generally expect FT4 level to be abnormally low in CH patients (9). Normal TSH level is very common in CH patients (9). In survivors of childhood cancer, "hidden

central hypothyroidism", namely, normal baseline TFT with abnormal dynamic tests (TSH surge and TRH stimulation test), was shown to be fairly common (10). We may refer to this condition as "subclinical central hypothyroidism". It should be noted that many health insurance organizations allow only TSH as a first line test to assess thyroid function. This is the reason why our patient had only previous TSH measurements and not thyroid hormone levels. When only TSH is measured, central hypothyroidism is likely to be undiagnosed in many patients (11). However, in cases of "subclinical central hypothyroidism" the diagnosis can be missed even when TSH and FT4 are checked because they both can be in the normal range. Similar but not identical clinical presentation was described by Yamakita *et al.* (12) in 6 patients with isolated TSH deficiency. All their patients had low TSH levels with normal FT4 levels. Usually, we would consider such patients as having subclinical hyperthyroidism. However, they had symptoms more related to hypothyroidism, and, more important, had low iodine uptake with low basal metabolic rate. Thus, the spectrum of central hypothyroidism can be expended to include patients with normal FT4 constituting a subclinical central hypothyroid state.

Does our patient have CH?

To further evaluate our patient for CH we have conducted dynamic studies. In a TRH stimulation test her TSH level reached a peak of 4.6 mIU/L in 30 minutes (table 2). This response is subnormal but with normal timing. The normal response for woman is net increase of 6-22mIU/L (13). A similar pattern was found in some of the patients with "hidden central hypothyroidism" in the study by Rose et al (10). The TSH diurnal profile of our patient showed a midnight surge although it was attenuated (Table 2). This pattern is also consistent with the diagnosis of CH althought does not prove it (10, 12, 14). No abnormalities in other pituitary axis were demonstrated and pituitary imaging was normal, making our patient as an "isolated TSH deficiency" case. The prolactin response to TRH stimulation remains normal in our patient as was shown in other "isolated TSH deficiency" cases (12). One possibility to explain isolated TSH deficiency is a TRH receptor mutation. Cases of TRH receptor mutations were described by Collu *et al.* (15). Double heterozygote for the mutations has no response of TSH and prolactin to TRH administration. Heterozygote cases for a TRH receptor mutation have normal TFTs and normal TSH and prolactin response in TRH test, although one of them had borderline TSH response. Our patient was found to have normal TRH receptor sequence. Her normal prolactin response to TRH stimulation is also less consistent with TRH receptor mutation. To conclude, our patient has CH but no specific cause could be found.

Can a patient with "subclinical hypothyroidism" be symptomatic?

Although controversial, the answer is probably yes (3). In one double blind placebo controlled trial (5) symptoms consistent with hypothyroidism were more common in patients with subclinical hypothyroidism than in the control group. Treatment with thyroxine improved the symptoms significantly compared to

placebo. Cold intolerance was quite a common complaint among hypothyroid patients. Cold intolerance was the only complaint in our case. Symptomatic improvement with treatment and reappearance when treatment was withheld suggest that it is related to hypothyroidism. The weight loss that occurred with the relatively low dose thyroxine treatment may also imply that she had hypothyroidism related excess of weight prior to therapy. Recently, a study showed that even modest changes in serum TSH level within the normal reference range may be associated with weight gain (16). Because of this minor symptomatology, her pre-treatment Billewicz score for hypothyroidism was -34 and decreased to -45 with treatment (17). We think that for a symptomatic individual with laboratory results of subclinical thyroid disease, the causality should be considered. Response to a trial of thyroxine treatment can strengthen this possibility.

What do we expect when we treat a patient with normal TFT or CH with Thyroxine?

Because of the negative feedback in the pituitary-thyroid axis we can assume that treating a patient with thyroxine in a dose up to full replacement dose will not cause a below normal suppression of TSH level. In a study by Pollock *et al.* (18), people with normal TFTs were treated with 100 microgram of thyroxine daily for 12 weeks. In one group with "symptoms of hypothyroidism" and average weight of 84 kg the level of TSH decreased from 1.77 to 0.66mU/L. In the control group, the average weight was 66 kg and TSH decreased from 1.55 to 0.32mU/L while FT4 level increased from 14.3 to 20.2pmol/L. The difference between the groups is likely to be explained by the weight difference. The second group was probably over treated with thyroxine. Our patient weighted 72 kg and was treated with only 50 microgram daily, and still her TSH level was suppressed to below normal reference range while FT4 rose only to mid normal range level. We think that this response does not represent over treatment but it is rather expected in patient with CH. Shimon *et al.* (19) showed that in CH cases the pituitary-thyroid negative feedback remains active and the level of TSH suppression by thyroxine treatment is correlated with thyroxine level normalization. The response of our patient fits the expected response as they showed in their paper. During pregnancies, her TFT changed as expected. The total T3 levels were higher and free T4 levels were lower than before. These changes probably reflect the higher levels of binding proteins during pregnancy and the reduced ability to compensate for them.

The issue of treatment of patients with subclinical hypothyroidism is controversial. Studies that examined the effects of replacement therapy on symptoms in these patients yielded conflicting results (3). Most will probably treat symptomatic patients (2). Treatment of patients with symptoms that could be attributed to hypothyroidism, but with normal TFT, was not more effective than placebo in a randomized double blind trial (18). The 6 patients with isolated TSH deficiency described by Yamakita *et al.* (12) were treated with thyroxine with improvement of their symptoms despite having normal FT4 and FT3 before

treatment, including one case with cold intolerance. As expected, treatment reduced TSH level to even lower level than without treatment.

CONCLUSION

We present a patient with symptomatic "idiopathic isolated subclinical central hypothyroidism". Her baseline TFTs were within the normal range but dynamic tests were consistent with central hypothyroidism. She was put on thyroxine treatment with impressive clinical improvement but TSH level became abnormally low, as we would expect in such case. In an individual, normal range TFTs do not always rule out abnormal thyroid function, which can be symptomatic. Treatment should be guided by both FT4 and TSH level as well as by clinical response.

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