

TRH stimulation test in patients with repeatedly elevated TSH and normal FT₄

Teste de estímulo com TRH em pacientes com TSH repetidamente elevado e T₄L normal

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ABSTRACT

Subclinical hypothyroidism (SCH) is defined by elevated thyroid-stimulating hormone (TSH) with normal free thyroxine (FT₄). We aimed to evaluate the thyrotropin-releasing hormone (TRH) stimulation test in patients with repeatedly elevated TSH (up to 10 mIU/l) and normal FT₄, but without apparent thyroid disease. Women with TSH > 4.5 and ≤ 10 mIU/l (in two measurements) and normal FT₄ were selected. Women with a known non-thyroid cause of TSH elevation, those treated with anti-thyroid drugs, amiodarone, lithium, and those with a history of thyroidectomy, neck radiotherapy and ¹³¹I treatment were excluded. Seventy women had negative antithyroperoxidase antibodies. Ultrasonography revealed a eutopic thyroid, usual echogenicity, and a volume ≤ 15 ml, and they underwent the TRH stimulation test during initial evaluation. After stimulation with TRH, TSH > 30 mIU/l was observed in 38 women (expected response), while 32 women had TSH < 20 mIU/l (inadequate response). Age, basal TSH or thyroid volume did not differ between both groups, but FT₄ concentrations were significantly lower in the first group. Follow-up was available for 66/70 women. Seven women developed a need for levothyroxine, all of them in the group with an adequate response to TRH [7/36 (19.4%) versus 0/30]. The results suggest that some cases of TSH elevation (even persistent) do not represent the early stage of thyroid insufficiency.

Key words: subclinical hypothyroidism; thyrotropin-releasing hormone; thyroid function tests.

RESUMO

O hipotireoidismo subclínico (HSC) é definido pela elevação dos níveis de hormônio tireoestimulante (TSH) com os níveis de tiroxina livre dentro da normalidade (T₄L). O objetivo deste relato foi avaliar o teste de estímulo com hormônio liberador de tirotrófina (TRH) em pacientes com TSH repetidamente elevado (até 10 mUI/l) e T₄L normal, mas sem doença tireoidiana aparente. Mulheres com TSH > 4,5 e ≤ 10 mUI/l (em duas medidas) e T₄L normal foram selecionadas. Foram excluídas aquelas com causa não tireoidiana conhecida de elevação do TSH, além das tratadas com medicamentos antitireoidianos, amiodarona, lítio e com histórico de tireoidectomia, radioterapia cervical e tratamento com ¹³¹I. Setenta mulheres apresentaram anticorpos antitireoperoxidase negativos. A ultrassonografia revelou tireoide eutópica, ecogenicidade usual e volume ≤ 15 ml; todas foram submetidas ao teste de estímulo com TRH na avaliação inicial. Após estímulo com TRH, TSH > 30 mUI/l foi observado em 38 mulheres (resposta esperada), enquanto 32 mulheres apresentaram TSH < 20 mUI/l (resposta inadequada). Idade, TSH basal ou volume da tireoide não diferiram entre os dois grupos, mas as concentrações de T₄L foram significativamente menores no primeiro grupo. O acompanhamento foi disponível para 66/70 mulheres. Sete pacientes evoluíram com necessidade de levotiroxina, todas elas no grupo com resposta adequada ao TRH [7/36 (19,4%) versus 0/30]. Os resultados sugerem que alguns casos de elevação do TSH (mesmo persistente) não representam a fase inicial de uma insuficiência tireoidiana.

Unitermos: hipotireoidismo subclínico; hormônio liberador de tireotropina; testes de função da tireoide.

RESUMEN

El hipotiroidismo subclínico (HSC) es definido por la elevación de los niveles de hormona tiroestimulante (TSH) con los niveles de tiroxina libre (T4L) dentro de rangos de normalidad. El objetivo de este reporte fue evaluar la prueba de estímulo con hormona liberadora de tirotropina (TRH) en pacientes con TSH persistentemente elevado (hasta 10 mIU/l) y T4L normal, pero sin enfermedad tiroidea aparente. Se eligieron mujeres con TSH > 4,5 y ≤ 10 mIU/l (en dos medidas) y T4L normal. Se excluyeron aquellas con causa no tiroidea conocida de alza de TSH además de las tratadas con medicamentos antitiroideos, amiodarona, litio y con historia de tiroidectomía, radioterapia cervical y tratamiento con ¹³¹I. Setenta mujeres presentaron anticuerpos antitiroperoxidasa negativos. La ecografía mostró tiroides eutópica, ecogenicidad usual y volumen ≤ 15 ml; todas se sometieron a la prueba de estímulo con TRH en la evaluación inicial. Tras estímulo con TRH, TSH > 30 mIU/l se observó en 38 mujeres (respuesta esperada), mientras 32 mujeres presentaron TSH < 20 mIU/l (respuesta inadecuada). El seguimiento estuvo disponible para 66/70 mujeres. Siete pacientes evolucionaron con necesidad de levotiroxina, todas ellas en el grupo con respuesta adecuada al TRH [7/36 (19,4%) versus 0/30]. Los resultados sugieren que algunos casos de alza de TSH (aunque persistente) no representan la fase inicial de una insuficiencia tiroidea.

Palabras clave: hipotiroidismo subclínico; hormona liberadora de tirotropina; pruebas de función de la tiroides.

INTRODUCTION

Subclinical hypothyroidism (SCH) is traditionally defined as serum thyroid-stimulating hormone (TSH) elevation in the presence of circulating thyroid hormone concentrations within the reference range⁽¹⁻⁴⁾. It is known that not all cases of hyperthyrotropinemia are related to thyroid insufficiency. Some conditions that can elevate serum TSH are easily recognized: untreated adrenal insufficiency, chronic renal failure, antidopaminergic drugs, and recovery from severe acute disease. Additionally, slight TSH elevation is seen in older adults (> 70 years) when the normal range obtained for adults is used. Obese individuals may also exhibit slightly elevated TSH. Elevation of TSH can, likewise, be the result of a predominance of TSH isoforms with low biological activity or analytical interferences from macro TSH and human anti-mouse antibodies. Finally, even within the population reference interval, the concentrations of free thyroxine (T4) above and below which TSH secretion is inhibited and stimulated, respectively, show wide individual variation and are genetically determined.

According to current recommendations, individuals with SCH younger than 65-70 years who have symptoms of hypothyroidism and high cardiovascular risk, including dyslipidemia or diabetes mellitus, are candidates for levothyroxine (L-T4) therapy⁽¹⁻⁴⁾. Even if the clinical history does not reveal a cause of thyroid dysfunction and goiter is absent, positive antithyroperoxidase antibodies (TPOAb) and ultrasonographic (US) abnormalities are not necessary for diagnosis or for the decision to treat⁽¹⁻⁴⁾. It is possible that some patients who meet the current diagnostic criteria of SCH

and who are potential candidates for L-T4 therapy have in fact hyperthyrotropinemia unrelated to thyroid insufficiency and may be treated erroneously⁽⁵⁾. We previously showed that this applies to a significant number of patients⁽⁶⁾. Even after confirmation of the result and exclusion of known non-thyroid causes of TSH elevation, clinical history, TPOAb measurement and US did not disclose thyroid disease in approximately 20% of women with elevated TSH ≤ 10 mIU/l and normal free T4⁽⁶⁾. However, currently no recommendation exists regarding additional tests in patients without apparent thyroid disease designed to distinguish individuals without thyroid dysfunction and with elevated TSH due to other reasons, such as those mentioned above, from individuals who actually have initial thyroid dysfunction⁽¹⁻⁴⁾. Individuals with TSH ≤ 10 mIU/l deserve greater attention because they account for approximately 80% of SCH cases^(1,3,4).

In patients with hyperthyrotropinemia due to thyroid insufficiency, a TSH hyper-response upon stimulation with thyrotropin-releasing hormone (TRH) is expected⁽⁷⁻⁹⁾. Indeed, this response can be seen early even when TSH is still within the normal range⁽¹⁰⁾. We evaluated the TRH stimulation test in women with repeatedly elevated TSH (up to 10 mIU/l) without a known cause of hyperthyrotropinemia and with normal free T4 concentrations, who could be diagnosed with SCH⁽¹⁻⁴⁾, but who did not exhibit apparent thyroid disease (based on clinical history, TPOAb, and US).

The aim of this study was to evaluate the usefulness of this test as a tool to distinguish patients without thyroid dysfunction and with elevated TSH due to other reasons from those who actually have initial thyroid dysfunction.

METHODS

Women not treated with L-T₄ and with TSH > 4.5 and ≤ 10 mIU/l were initially selected. Women treated with anti-thyroid drugs, amiodarone, lithium and alpha-interferon and those with a history of thyroidectomy, neck radiotherapy or ¹³¹I treatment for hyperthyroidism, or with a known non-thyroid cause of TSH elevation (untreated adrenal insufficiency, chronic renal failure, antidopaminergic drugs, recovery from severe acute disease) were excluded. The remaining patients were reevaluated by measurement of TSH and free T₄ after 8-12 weeks. Finally, among patients with persistently elevated TSH ranging from 4.5 to 10 mIU/l and normal free T₄, 70 had negative TPOAb and US revealed a eutopic thyroid, usual echogenicity, and a volume ≤ 15 ml (group of interest)⁽⁶⁾. All of these women were ≤ 70 years and had a body mass index < 35 kg/m²⁽⁶⁾.

TSH, TPOAb and free T₄ were measured with a chemiluminescent assay (Immulite 2000, Diagnostic Products Corporation, Los Angeles, CA), with reference values of 0.4-4 mIU/l, up to 35 kIU/l and 10.3-23 pmol/l, respectively. TRH stimulation tests were performed in the fasting state (8-10 hours). All patients received 200 mg TRH intravenously as a bolus injection. Blood samples were obtained at baseline, and 30 and 60 minutes after TRH stimulation for TSH analysis^(7,10,11).

Statistical analysis was performed using Fisher's exact test. A *p*-value of < 0.05 was considered significant.

RESULTS

After stimulation with TRH, TSH > 30 mIU/l (31 to 52 mIU/l) was observed in 38 women. This was considered an expected response^(7, 10, 11). In contrast, 32 women exhibited peak TSH < 20 mIU/l (8 to 17 mIU/l), which was considered an inadequate response^(7, 10, 11). Age (*p* = 0.85), basal TSH (*p* = 0.2) or thyroid volume on US (*p* = 0.3) did not differ between the two groups. Although within the normal range in all women, free T₄ concentrations were significantly lower in those with an expected TSH response (*p* = 0.01).

Twenty women reported adverse reactions during the TRH test: nausea (*n* = 8), bad taste in the mouth (*n* = 8), urinary urgency (*n* = 4), and hot flashes (*n* = 5). All symptoms occurred immediately after the infusion and only lasted a few minutes.

Follow-up was available for 66 women⁽⁶⁾. After a follow-up of seven to 14 years (median 10 years), only seven women exhibited

progression of SCH (TSH > 10 mIU/l accompanied by reduced free T₄ or two TSH values > 10 mIU/l within an interval of eight weeks)⁽⁶⁾. Progression of SCH was only observed in women with an expected TSH response on initial evaluation [7/36 (19.4%) versus 0/30 with an inadequate response, *p* = 0.013].

DISCUSSION

We believe that the inadequate response to TRH stimulation itself already indicates hyperthyrotropinemia unrelated to primary thyroid insufficiency⁽⁷⁻⁹⁾. This hypothesis was supported by the difference in free T₄ concentrations and progression to hypothyroidism found between women with an "expected" response versus those with "inadequate" response.

When the study began, we considered the TRH stimulation test to be the best parameter for identifying cases of hyperthyrotropinemia not secondary to thyroid dysfunction. Although the response of serum TSH to TRH shows individual variation, the results of the present study confirm that the traditional peak TSH cut-off of 30 mIU/l^(7, 10, 11) identifies individuals with true thyroid dysfunction. Some years after the start of the study, polyethylene glycol (PEG) precipitation became the focus of the literature^(12, 13). It is reasonable to currently begin the investigation for hyperthyrotropinemia without apparent cause by PEG precipitation, a simple, noninvasive and low-cost method^(12, 13). However, this method does not detect all causes of elevated TSH not resulting from initial thyroid dysfunction. Indeed, we recently performed PEG precipitation following the protocol of Hattori *et al.* (2016)⁽¹²⁾ in 12 women with an inadequate response to TRH on initial evaluation and persistently elevated TSH, and precipitation was normal (< 70%) in nine of them (data not shown).

Regardless of the screening method, the study calls attention to the possibility that, in the absence of underlying thyroid disease, a considerable number of cases with repeatedly elevated TSH and normal free T₄ concentrations, even without a known non-thyroid cause of this alteration, do not represent the early stage of thyroid insufficiency but rather hyperthyrotropinemia of another nature. We therefore agree that much care should be taken when diagnosing SCH in the absence of apparent thyroid disease^(5, 6). Although we did not study this group, this concern certainly also applies to patients with TSH > 10 mIU/l^(12, 13). In the present study, age, basal TSH and thyroid volume were not useful for identifying these cases, reinforcing the need for specific investigation. If not for all, this investigation should at least be performed for patients who are candidates for L-T₄ therapy, so that they are not treated erroneously.

DECLARATION OF INTEREST

The author declares that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

COMPLIANCE WITH ETHICAL STANDARDS

The study was approved by the Research Ethics Committee of our institution (20085719.1.0000.5138).

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