

propylthiouracyl.¹ In the case reported, an early diagnosis could not have been made because the patient had no clinical signs and was being treated with methimazole, with the resultant potential implications. It should be noted that the prevalence of liver parameter changes with the other two thioamides is so low that in a case such as the one reported, if the liver profile is not tested, this side effect may be overlooked. On the other hand, this has little practical relevance because the proportion of cases with asymptomatic elevations showing a poor course is probably very low.

Because of the frequency and severity of the consequences, the measurement of liver function parameters, either at regular intervals or for any clinical suspicion, is clearly needed in subjects treated with propylthiouracyl.

The question is whether routine liver profiles in patients treated with methimazole or carbimazole would be cost-effective since, as already noted, liver iatrogeny with such drugs is uncommon and results in cholestatic patterns which may be diagnosed clinically. The prevalence of liver abnormalities with these drugs is very likely to be higher, but they possibly run an indolent course and resolve spontaneously.

Conflicts of interest

The authors state that they have no conflicts of interest.

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A case of biochemical assay discrepancy: Interference with measurement of thyroid-stimulating hormone due to rheumatoid factor[☆]

Quando la analítica desconcierta: interferencia en la determinación de tirotrópina debido a factor reumatoide

Measurement of thyroid-stimulating hormone (TSH) is the most helpful test for the diagnosis and monitoring of primary hypothyroidism.¹ However, it may sometimes provide conflicting and confusing results.

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We report the case of a 45-year-old woman who underwent work-up for elevated TSH levels. Tests performed for asthenia and mild fatigue for the previous few months found a TSH level (chemoluminescence assay [IMA], AccessDXI 800 BECKMAN COULTER® [Fast hTSH]) of 142 μ IU/mL (0.34–5.6) and a free thyroxine (FT4) level of 7.76 pg/mL (5.8–16.4). Subclinical primary hypothyroidism was suspected, and replacement therapy was started with levothyroxine (L-T4) 50 μ g/day. Repeat tests at six months showed a TSH level of 129 μ IU/mL and a FT4 level of 9.89 pg/mL, with no changes in subjective symptoms reported by the patient. The dose of L-T4 was increased to 100 μ g/day, and three weeks later, TSH and FT4 levels were 115 μ IU/mL and 14.09 pg/mL respectively.

No significant findings were made in the physical examination. The patient had a weight of 62 kg and a height of 163 cm, and thyroid palpation was normal. Neck ultrasound examination showed two non-suspicious nodules less than 1 cm in size, and antithyroid autoantibodies were negative. Results of all other routine laboratory tests were normal,

Table 1A Measurement of TSH and FT4 by different procedures on the same day.

| | Chemoluminescence immunoassay (IMA) | Radioimmunoassay (RIA) |
|-------------------------------------|-------------------------------------|------------------------|
| TSH ($\mu\text{U/mL}$) [0.3–5] | 60.98 | 1.1 |
| FT4 (pg/mL) [6–16] | 7.34 | 10 |

except for cholesterol levels: total cholesterol 268 mg/dL, HDL-C 38 mg/dL, and LDL-C 201 mg/dL.

Based on an initial suspicion of L-T4 underdosage, the dose was increased to 125 $\mu\text{g/day}$. Six weeks later, TSH and FT4 levels were above the normal reference limit: 72 $\mu\text{IU/mL}$ and 17.0 pg/mL respectively. When asked about treatment compliance, both the patient and her family reported adequate intake and adherence.

Since FT4 had gradually increased, while TSH levels continued to be much higher than normal, the differential diagnosis was expanded. Complete tests of hypothalamic-pituitary function were requested, and TSH was measured by radioimmunoassay (RIA), a procedure different from the one previously used. Test results included: TSH, 0.08 $\mu\text{IU/mL}$ (0.4–5); FT4, 18 pg/mL (6–17); total T3, 106 ng/dL (90–175); prolactin, 368 $\mu\text{U/mL}$ (100–410); LH, 20 mU/L; FSH, 38 mU/L; estradiol, 34 pg/mL; ACTH, 27 pg/mL (9–54); and basal cortisol, 87 ng/mL (65–210). The discrepancy in TSH measurement was confirmed when a sample taken on the same day was processed using both procedures, IMA and RIA (Table 1A).

Such apparently paradoxical results led to the tests recommended by the National Academy of Clinical Biochemistry (NACB) Laboratory Medicine Practice Guidelines being performed to assess the potential interference with immunochemical measurements.² Serial dilutions first showed a lack of parallelism with a control sample (Fig. 1A). A subsequent test on the same sample with a method from another manufacturer (Cemtauro BAYER®) reported a TSH level of 3.2 $\mu\text{IU/mL}$ (0.3–5), which represented a difference greater than 50% as compared to the previous result. Finally, a polyethylene glycol (PEG) precipitation test was done. This is a nonspecific procedure that allows for proteins to be separated by decreasing their solubility until they precipitate. When PEG is applied to serum, precipitation is quite specific for immunoglobulins and their complexes, and all forms of interference by antibodies may therefore be identified. Percent recovery after precipitation with PEG was only 7%, which suggested the existence of an interferent (Fig. 1B).

Based on these results and in order to identify the interferent, serologic and autoimmunity tests were performed in the patient (Table 1B). A rheumatoid factor level of 6690 IU/mL (normal, <20) was found, despite the fact that the patient had no sign or symptom suggesting a rheumatological condition.

The dose of L-T4 was adjusted to 50 $\mu\text{g/day}$, and one month later the patient showed an analytical euthyroid state (TSH 3.8 $\mu\text{IU/mL}$ by RIA, although the value found by IMA was

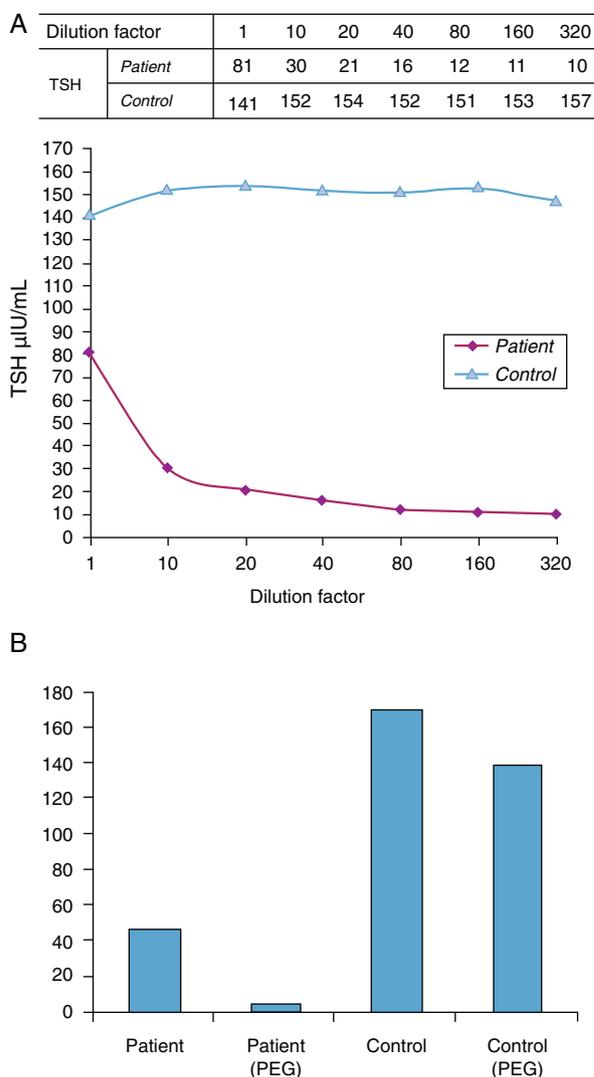


Figure 1 (A) Linearity test using serial dilutions. The behavior of the analyte in the sample is compared to that of the analyte in another sample. Lack of parallelism between the two samples may be due to the presence of an interferent. (B) Precipitation test with polyethylene glycol (PEG). Percent recovery was 85% in the control and 7% in the patient.

81.66 $\mu\text{IU/mL}$, and FT4 7.79 pg/mL) and clinical improvement.

When high TSH levels are found, the most common diagnosis is primary hypothyroidism, which is initially considered to be subclinical if FT4 levels are still within normal limits.^{1,3} If test results are confirmed, replacement therapy should be started with L-T4, with dose adjustment based on the progressive normalization of TSH after some weeks.⁴

If TSH elevation continues despite replacement therapy, potential interference with hormone absorption such as, for example, the concomitant intake of other drugs or intestinal malabsorption should be considered, and adequate treatment compliance should be verified.⁴ Specifically, acute L-T4 intake by a noncompliant patient before a clinical visit will increase FT4, but will not normalize the serum TSH level. In the reported case, the patient and her rela-

Table 1B Serologic and autoimmunity testing of the patient.

- Antinuclear antibodies (ANA): negative
- Anti-double-stranded DNA antibodies (dsDNA): negative
- Anti-extractable nuclear antigen antibodies (ENA)
 - Anti-SSA-Ro52: negative
 - Anti-SSA-Ro60: negative
 - Anti-SSB: negative
 - Anti-Sm: negative
- Anti-ribonucleoprotein (RNP) antibodies: negative
- Anti-Jo-1 antibodies: negative
- Anti-ribosomal antibodies: negative
- Anti-centromere antibodies: negative
- Anti-histone antibodies: negative
- Anti-nucleosome antibodies: negative
- Tests for autoimmune liver disease:
 - M2: negative
 - LKM: negative
 - SLA: negative
 - LC1: negative
 - F-actin: indeterminate
 - GP 210: negative
 - p 100: negative
- Antimitochondrial antibodies (AMA): negative
- Anti-smooth muscle antibodies: positive 1/40
- Anti-parietal cell antibodies: negative
- Rheumatoid factor: 6690 IU/mL (BNProSpec, Siemens®) and 4800 IU/mL (Olympus® RF Latex®)
- Serologic tests for human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV), and syphilis: negative

tives reported adequate compliance, and interference with absorption was not considered because FT4 increased as replacement therapy was increased.

Another apparently paradoxical cause of dissociation between FT4 and TSH is the syndrome of inappropriate TSH secretion, comprising two conditions: TSH secretion by a pituitary adenoma and non-neoplastic TSH hypersecretion due to a resistance to thyroid hormones. Both conditions were unlikely in our case, because FT4 elevation occurred when replacement therapy was started, not from the beginning. Moreover, these clinical conditions are not usually associated with such marked TSH elevations.^{5,6}

An additional factor to be ruled out was the existence of laboratory artifacts due to the presence of interferents⁷ or macro-TSH.⁸ Tests currently used to measure TSH are highly sensitive and specific, but if heterophile antibodies or rheumatoid factors exist, bridges may be formed between capture and signaling antibodies, generating a false signal that causes an inappropriately high analyte value.⁹ This is more evident in immunometric tests, and the manufacturers of reagents have therefore used various procedures to circumvent the problem, with variable results.¹⁰

In most cases, interference is due to heterophile antibodies, which may show a prevalence of 0.2–15% in the general population.¹¹ However, to our knowledge, only one case of interference by rheumatoid factor has been reported.¹² This

autoantibody may be present in both healthy subjects and patients with rheumatological disease, but since it is not routinely measured, it is difficult to identify it as being responsible for the interference with TSH measurement¹³ and its incidence cannot be clearly established. Because of the high frequency of rheumatoid factor and other heterophile antibodies in the general population, interferences with TSH measurement are likely to be more common than expected.

It is therefore advisable to consider potential interference by rheumatoid factor or other heterophile antibodies in patients with discordances between TSH/FT4 and clinical signs. This possibility must be taken into account because, despite improved immunometric tests, it remains an unsolved problem. In these cases, measurement of TSH by an alternative method may be helpful in diagnosis, thus avoiding unnecessary repeat tests and preventing inadequate treatment approaches which are not free from side effects.

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Skin changes associated to hypothyroidism[☆]

Alteraciones dermatológicas asociadas a hipotiroidismo

Skin changes associated with thyroid disease include specific lesions such as thyroglossal duct cyst and skin metastases, nonspecific signs such as those secondary to hormonal changes due to hyperfunction and hypofunction, and dermatological changes associated with thyroid diseases, of which we provide two clinical examples.

The prevalence rate of primary autoimmune hypothyroidism (PAIH) is 5%, and up to 8.3% if subclinical hypothyroidism is included.¹ Skin manifestations associated with PAIH include a number of skin diseases common to patients with this condition (defined as the presence of autoantibodies even in a euthyroid state) and others directly dependent on thyroid function.

In the former group, the frequency of thyroid dysfunction is variable, occurring in 40–70% of patients with melanin spots of centrofacial location, in 42% of males and 62% of females with vitiligo, in 50% of patients with chronic mucocutaneous candidiasis, in 34% of patients with herpetiform dermatitis, in 8% of delayed hypersensitivity reactions, and in 8% of patients with alopecia areata. Autoimmune thyroid disease is also commonly associated with pemphigus and other bullous diseases, systemic lupus erythematosus, scleroderma, Kaposi's sarcoma, erythema annulare centrifugum, generalized granuloma annulare, multicentric reticulohistiocytosis, elastic pseudoxanthoma, reticular erythematous mucinosis, anemia (pernicious anemia, red blood cell aplasia), herpes gestationis, dermatomyositis, Sjögren's syndrome, polymyositis, other endocrine diseases (acanthosis nigricans, multiple endocrine neoplasia, McCune-Albright syndrome, Sweet's syndrome), CREST syndrome (calcinosis, Raynaud's syndrome, esophageal dysfunction, scleroderma, and telangiectasis), psoriasis, Cowden syndrome with multiple hamartomas, ANOTHER syndrome (alopecia, nail dystrophy, hypohydrosis, and ephelides), acropachies,² and atopic manifestations such as urticaria, dermatographism and angioedema.^{3–5}

Skin changes directly dependent on thyroid hypofunction include:

- Typically dry, pale, and cold skin due to decreased capillary flow, sweating, and thermogenesis; palmoplantar keratoderma, which may become generalized and convert into xeroderma, but dramatically responds to replacement therapy.
- Keratosis pilaris of follicles leading to permanent alopecia, thinned hair, and lateral loss of eyebrows. It may be associated with livedo reticularis in the limbs.⁶
- Generalized myxedema or cutaneous mucinosis, due to the accumulation of hyaluronic acid and glycosaminoglycans in the skin. This causes the characteristic hypothyroid facies: thick skin, periorbital edema, and mucosal thickening with dysphonia. There may be periocular hyperpigmentation (Jellinek's sign)⁷ and hypercarotene-mia due to the lack of hepatic metabolism of carotene, which accumulates in the corneal layer, is excreted in sweat, and becomes deposited in areas rich in sebaceous glands.
- An uncommon lesion related to primary hypothyroidism and autoimmune polyglandular syndrome type I, erythema annulare centrifugum, consists of a ring-shaped eruption with central clearing occurring in the buttocks, thighs, and proximal part of the arms. Histological examination shows a perivascular lymphocyte infiltrate in the middle and deep dermis.⁸
- Granuloma annulare and oral lichen planus, not well known by most endocrinologists, may also be associated with hypothyroidism. Two cases are reported here, and their relationship to autoimmune thyroid disease is analyzed.

Case 1

A female patient was referred at 41 years of age for hypothyroidism. Her history included a daughter with vitiligo and PAIH, and the patient herself had undergone surgery for melanoma *in situ* two years before and was in remission. Laboratory tests requested by the dermatology department revealed subclinical PAIH (TSH [thyroid-stimulating hormone]: 8.7 mcU/mL, FT4 [free thyroxine]: 0.92 ng/dL, ATA-TPO [antiperoxidase antibodies]: >1300 U/mL) which was monitored at the clinic without treatment. Nine years later, the patient reported aphonia, dry skin, and asthenia with postmenopausal menstrual changes (TSH: 8.34 mcU/mL, FT4: 0.98 ng/dL). She had grade I goiter with an irregular surface and a hypoechoic, pseudonodular ultrasound image 8.7 mm in size in the upper pole of the left lobe.

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