

Thiamine and Hashimoto's Thyroiditis: A Report of Three Cases

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Abstract

Objectives: In a previous study on fatigue and related disorders in inflammatory bowel disease (IBD), we observed that IBD patients improved after treatment with high-dose thiamine. We hypothesized that the chronic fatigue accompanying inflammatory and autoimmune diseases is the clinical manifestation of a mild thiamine deficiency that is probably due to a dysfunction of the intracellular transport or to enzymatic abnormalities. Hashimoto's thyroiditis is both a common autoimmune disease and cause of hypothyroidism. Although levothyroxine, a thyroid hormone, is the treatment of choice for hypothyroidism, a significant number of patients on thyroid hormone replacement therapy report not feeling well despite having thyroid function tests within the healthy range. Based on our hypothesis, we started treating the fatigue in patients affected by Hashimoto's thyroiditis and taking a thyroid hormone with thiamine. This is a report of the outcomes of three cases in which the fatigue component reported by patients with Hashimoto's thyroiditis was treated with thiamine.

Design: Three patients on thyroid hormone replacement because of Hashimoto's thyroiditis were treated for the fatigue component of the disease from May to July 2011. Fatigue was measured using the Fatigue Severity Scale. Free thiamine in the serum and thiamine pyrophosphate in red cells were tested before and after the therapy. All three patients received oral (600 mg/day) or parenteral (100 mg/ml every four days) doses of thiamine.

Results: Treatment with thiamine led to partial or complete regression of the fatigue within a few hours or days.

Conclusion: As the administration of thiamine led to a partial or complete regression of the fatigue and related disorders, it is reasonable to infer that the administration of large quantities of thiamine restores thiamine-dependent processes. The mild thyroid deficiency suggested by fatigue and related disorders may be due a dysfunction of the intracellular transport of thiamine or to enzymatic abnormalities most likely related to the autoimmune process of the disease.

Introduction

HASHIMOTO'S THYROIDITIS (HT) IS a common disease and the most prevalent cause of hypothyroidism. The common clinical symptoms of hypothyroidism are tiredness, weight gain, dry skin, cold intolerance, constipation and muscle weakness, puffiness around the eyes, hoarseness, and poor memory. As these symptoms are nonspecific and common in the euthyroid population, the diagnosis of hypothyroidism must be made biochemically.

Levothyroxine is the treatment of choice for hypothyroidism, but a significant number of patients on thyroid hormone replacement do not report improvements in fatigue and related disorders even when their thyroid function tests within the healthy reference range.¹ Ott et al. have noted that

hypothyroidism is only a contributing factor to the development of chronic fatigue, irritability, nervousness, and lower quality-of-life levels in women with Hashimoto's thyroiditis who undergo a thyroidectomy for benign goiter.² The authors suggest the possible effect of autoimmunity on the general health and overall quality-of-life of their patients and evaluate both symptom load and quality of life in terms of histological diagnosis and serum anti-thyroid peroxidase (anti-TPO) antibody levels. According to the authors, women with positive anti-TPO results report a significantly higher prevalence of general health symptoms than those without HT.² Other authors have also drawn attention to the importance of thyroid autoimmunity in the HT-associated clinical syndrome. These authors have reported the presence of symptoms similar to those found in patients affected by

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fibromyalgia (FM).³ It would appear that, as of today, the chronic fatigue and related disorders in euthyroid patients with HT remain an enigma.

We started working on chronic fatigue in April 2011, when we studied patients affected by ulcerative colitis (UC), an autoimmune and inflammatory disease. Our clinical observations suggested that UC fatigue and the other extra-intestinal symptoms of the disease were the manifestations of a mild thiamine deficiency. Based on our observations, we developed a pilot study in which patients with fatigue and other extra-intestinal symptoms were treated with high oral doses of thiamine. The findings of the study were extremely encouraging for patients affected by UC.⁴ Therefore, we turned our attention to the chronic fatigue common to different autoimmune and inflammatory diseases, such as rheumatic diseases and multiple sclerosis. We hypothesized that this fatigue was the result of a mild thiamine deficiency and treated patients with high doses of thiamine (data not published).

For this study, we focused on HT, because it too is an inflammatory-autoimmune disease and causes chronic fatigue. We hypothesized that the fatigue and related disorders in euthyroid HT patients who are receiving thyroid hormone replacement therapy are due to a dysfunction of the active transport from the blood to the mitochondria or to structural enzymatic abnormalities probably caused by immune system factors. To find subjects for our study, we turned to endocrinologists as well as general practitioners. All patients who had HT, were under treatment with thyroid hormone replacement, and answered affirmatively to the question "Do you feel tired?" were considered for the study.

Materials and Methods

Three patients, all women, affected exclusively by HT, were selected for the study. The patients presented with fatigue, sleep disorders, depression, anxiety, chronic nervousness, memory loss, focus and attention disorders, cold intolerance, and dry skin. The diagnosis of HT had been performed by experienced endocrinologists and according to the current criteria used for this disease. All 3 patients were under medical treatment with levothyroxine. Patients 1 and 3 took 50 mg/day; patient 2, 100 mg/day.

We began with an analysis of clinical history and an objective examination of each patient. Each patient's level of fatigue was evaluated, using the Fatigue Severity Scale (FSS).⁵ The FSS is a short questionnaire that requires the subject to rate his or her own level of fatigue. The obvious problem with

this measure is its subjectivity. The questionnaire contains 9 statements that attempt to explore the severity of fatigue symptoms. The subject is asked to read each statement and circle the number from 1 to 7, that he or she feels best describes how the statement applied to him or her over the preceding week. A low value indicates that the statement is not very appropriate whereas a high value indicates agreement. The scoring can be done by calculating the average response to the questions or as an absolute sum of the values. We chose to calculate the scoring using the absolute sum of the answers.⁵ The FSS score was defined as follows:

- 9 points: no fatigue
- Up to 36 points: medium-low fatigue
- From 36 to 63: severe fatigue

The evaluation of the fatigue using FSS was repeated 20 days after the beginning of the therapy.

Before beginning therapy, enzyme-linked fluorescent assay (E.L.F.A.) tests were used to measure each patient's thyroid stimulating hormone (TSH), free triiodothyronine (FT3), and free levothyroxine (FT4) levels. These tests revealed normal values of TSH, FT3 and FT4 (see Table 1). At the time of the diagnosis, serum anti-thyroid peroxidase (anti-TPO) antibody levels had been measured using microparticle enzyme immunoassay (M.E.I.A.). The results of these tests are also shown in Table 1.

Thiamine and thiamine pyrophosphate (TPP) levels were also determined for each patient. The blood was frozen at -20°C and sent to the Italian Diagnostic Center (Bracco Industries, Milan, Italy), where thiamine and TPP were measured using high-performance liquid chromatography (HPLC). The blood tests for Thiamine and TPP were repeated 20 days after the start of therapy. The results of these tests are shown in Table 2.

Once these tests were completed, we began therapy with high doses of thiamine (oral administration of 600 g/day or 100 mg/ml parenterally every 4 days). The dosage was defined empirically for this study as follows: patients weighing 60 kg (patients 1 and 3) received 600 mg/day; patients (patient 2) weighing 128 kg received 100 mg/ml every 4 days. The following is the rationale of the dosage calibration used in this study:

- female patients weighing <60 kg: 10 mg/kg/day of thiamine
- 60–65 kg: 14 mg/kg/day of thiamine
- 65–70 kg: 17 mg/kg/day of thiamine
- 70–75 kg: 20 mg/kg/day of thiamine
- 75–80 kg: 23 mg/kg/day of thiamine

TABLE 1. BASELINE CHARACTERISTICS OF PATIENTS BEFORE THERAPY

Patient	Weight (kg)	Age (years)	Duration (years)	Anti-TPO ^a n.v.[≤ 120 UI/ml]	TSH ^b n.v. [0.25–5.00 $\mu\text{UI/ml}$]	Ft3 ^c n.v. [2.59–5.38 pgr/ml]	Ft4 ^d n.v. [6.97–15.5 pgr/ml]
1	63	61	3	322	4.1	3.05	10.64
2	128	55	6	526.6	1.54	2.74	13.38
3	55	38	1	1725.40	0.67	3.07	9.47

^aSerum anti-thyroid peroxidase antibody levels at the time of the diagnosis.

^bThyroid stimulating hormone.

^cFree triiodothyronine.

^dFree thyroxine.

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TABLE 2. LABORATORY EXAMS AND FSS BEFORE AND AFTER THERAPY

Patient	Thiamine before therapy n.v. [2,1–4,3 µgr/L]	Thiamine after therapy n.v. [2,1–4,3 µgr/L]	Thiamine Pyrophosphate before therapy n.v. [>49 µgr/L]	Thiamine Pyrophosphate after therapy n.v. [>49 µgr/L]	FSS ^a before therapy	FSS after therapy
1	11.5	210.0	78.1	150.4	26	9
2	11.7	24.2	107.7	101.2	60	9
3	7.1	44.0	79.8	87.5	36	25

^aFSS: Fatigue Severity Scale.

In Italy, thiamine is commonly sold in pharmacies in two forms: 300 mg pills (off the shelf) or 100 mg/ml phials (sold under prescription). Because of the large number of pills required daily for patients whose weight is greater than 80 kg, we suggest intramuscular therapy with one 100 mg/ml phial every 4 to 7 days.

Every 3 days, the patients were contacted in order to track the course of the treatment.

Results

While the laboratory values of thiamine and thiamine pyrophosphate were normal in all 3 patients before therapy, after therapy, these values had increased significantly in patients 1 and 3 who were tested 4 hours after the oral administration of thiamine. Patient 2 received an intramuscular administration of thiamine and was tested 2 days after its administration. (See Table 2 for thiamine and thiamine pyrophosphate levels before and after therapy.) In all 3 patients, the administration of the large quantities of thiamine led to a partial (in patient 3) or complete (in patients 1 and 2) regression of the fatigue. In patient 2, who received intramuscular therapy, fatigue regressed within 6 hours. In patients 1 and 3, who received oral therapy, fatigue regressed within 3 to 5 days.

It is not known at present how long treatment must continue, but further study may shed some light on this question. Our patients are still under the same treatment prescribed at the beginning of the therapy and symptomatic improvements are consistent. A low-dose integration of all the other vitamins of the B group is strongly advised.⁴ The patients have reported a significant improvement of all fatigue-related symptoms and have regained complete wellness.

Discussion

On the whole, we had a favorable response to thiamine administration, and in presence of thiamine deficiency, the response to therapy is considered diagnostic.^{6,7} The presence of a mild thiamine deficiency syndrome in patients with normal concentrations of thiamine and TPP may be explained by a consideration of a form of thiamine deficiency due to a dysfunction of the vitamin B1 active transport mechanism from the blood to the mitochondria or, perhaps, to structural enzymatic abnormalities. The administration, either orally or parenterally, of large quantities of thiamine increases the concentration of thiamine in the blood to levels at which passive transport restores the normal glucose metabolism in all cells, and fatigue disappears. Some authors believe the dysfunction of the active transport mechanism

may be overcome by diffusion mediated at supranormal thiamine concentrations.^{6,7} Other authors believe that high doses of thiamine may be able to induce greater expression of the thiamine transporter encoded genes.⁸

In 2006, before our observations on autoimmune conditions, a dysfunction of intracellular thiamine transport was described for genetic diseases that were characterized by mutations in thiamine-transporter genes.⁷ In 2011, there was a case published describing Wernicke's encephalopathy in a nonalcoholic patient with a normal blood thiamine level. Specifically, it was a case of a 64-year old woman who had never consumed alcohol presented to hospital a several-day history of vomiting and severe diarrhea, secondary to *Clostridium difficile* colitis.¹⁰ A number of inborn errors of metabolism have also been described in which clinical improvements after the administration of pharmacological doses of thiamine can be documented. Among these are thiamine-responsive megaloblastic anemia and Wernicke's-like encephalopathy.⁷

Substantial efforts are being made to understand the genetic and biochemical determinants of thiamine deficiency-related disorders and of the differential vulnerabilities of tissues and cell types to thiamine deficiency. While further studies are necessary to confirm our findings, we strongly believe that our observations represent an important contribution to the relief of many patients. Although at present, the necessary length of treatment is unknown, there is, to date, no mention in literature of thiamine-related collateral effects even at high doses and for long periods of time.⁹

Conclusions

Our case experience with these 3 patients supports the hypothesis that the chronic fatigue and related disorders accompanying Hashimoto's thyroiditis are manifestations of a mild thiamine deficiency that may be due to either a dysfunction of the active transport from the blood to the mitochondria or to structural enzymatic abnormalities likely caused by immune system factors. We deem that it would be interesting to find out if other forms of hypothyroidism and the fatigue associated with them would respond to thiamine therapy in a similar manner to these cases.

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Disclosure Statement

No competing financial interests exist.

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AU1: I'm afraid we are not familiar with this degree (Nursing Diploma). Is there an abbreviation for it? Is it the equivalent of the American RN (Registered Nurse)?

AU2: Please note the phrase "women with positive anti-TPO title" has been changed to "women with positive anti-TPO results" Is this acceptable?

AU3: Please note the sections on thiamine and TPP have been grouped together and, because they are displayed in Table 2 now follow the discussion of the tests shown in table 1.

AU4: Is this an acceptable way to explain that you determined thiamine, enzyme, and hormone levels before beginning therapy?

AU5: Information concerning anti-TPO levels added to footnote bottom of table along with definitions of anti-TPO, TSH, Ft3, and Ft4 to aid in the reader's understanding of the table.