

Thiamine and Fatigue in Inflammatory Bowel Diseases: An Open-label Pilot Study

Antonio Costantini, MD,^{1,2} and Maria Immacolata Pala¹

Abstract

Objectives: To demonstrate that fatigue and other disorders related to ulcerative colitis and Crohn's disease are the manifestation of an intracellular mild thiamine deficiency and not due to malabsorption, augmented requirements, or nutritional factors, and that this dysfunction is curable with high doses of thiamine administered orally or parenterally.

Design: In this pilot study, we treated fatigue in eight patients with ulcerative colitis and four patients affected by Crohn's disease from January to April 2011. The patients were recruited through general practitioners' surveys and among personnel and affiliated personnel of the clinic Villa Immacolata. Fatigue was measured using the chronic fatigue syndrome scale, and the determination of thiamine and thiamine pyrophosphate levels in the blood was carried out through blood tests. The levels of thiamine and thiamine pyrophosphate in the blood were normal. All patients were assigned to receive high doses of thiamine orally. Depending upon the body weight of each patient, dosage ranged from 600 mg/day (60 kg) to 1,500 mg/day (90 kg). The chronic fatigue syndrome scale as well as thiamine and thiamine pyrophosphate levels in the blood were measured 20 days after the beginning of the therapy.

Results: Ten patients out of twelve showed complete regression of fatigue, while the remaining two patients showed nearly complete regression of fatigue compared to the chronic fatigue syndrome scale scores before therapy.

Conclusions: The absence of blood thiamine deficiency and the efficacy of high-dose thiamine in our patients suggest that fatigue is the manifestation of a thiamine deficiency, likely due to a dysfunction of the active transport of thiamine inside the cells, or due to structural enzymatic abnormalities. The administration of large quantities of thiamine increases the concentration in the blood to levels in which the passive transport restores the normal glucose metabolism in all cells and leads to a complete regression of fatigue.

Introduction

AMONG PATIENTS WITH INFLAMMATORY BOWEL DISEASES (IBD), fatigue is the most commonly reported symptom and one of the most debilitating. Despite its high prevalence and significant impact, fatigue is still poorly understood and often underemphasized because of its complexity and subjective nature. Fatigue is often observed together with sleep disorders, depression, anxiety, and other disturbances that, in this study, were described in detail by our first patient.

The classic syndrome caused primarily by thiamine deficiency in humans is beriberi, for which the benefit of thiamine in prevention and treatment is uncontested.^{1,2} In older texts, beriberi has been divided into categories known as "wet," "dry," and Wernicke-Korsakoff syndrome. Manifested

beriberi and Wernicke-Korsakoff syndrome show evident symptoms, whereas mild forms of thiamine deficiency are less known and the symptoms are often attributed to other pathologies. According to the World Health Organization (1999), "The symptoms of mild thiamine deficiency are vague and can be attributed to other problems, so that diagnosis is often difficult. [...] The symptoms of mild thiamine deficiency clinically improve by the administration of thiamine."²

Characteristic early symptoms include anorexia, weakness, aching, burning sensation in hands and feet, indigestion, irritability, and depression. After 6 to 8 weeks, the only objective signs at rest may be a slight fall in blood pressure and moderate weight loss. After 2 to 3 months, apathy and weakness become extreme, calf muscle tenderness develops,

¹Department of Neurological Rehabilitation, Villa Immacolata, Viterbo, Italy.

²School of Physiotherapy, Università Cattolica di Roma, Rome, Italy.

along with loss of recent memory, confusion, ataxia, and sometimes persistent vomiting.²

Neurologists often see, in the outpatient practice, patients with nonspecific symptoms such as fatigue, irritability, difficulties in concentration, and depression. Our team has seen, from June to November 2010, three subjects with definitive diagnoses of ulcerative colitis (UC) who presented these symptoms in a typical fashion.

The first patient, a 51-year-old woman with a definite diagnosis of ulcerative colitis for about 23 years, presented several "extraintestinal" symptoms of variable intensity during both acute phases and periods of relapse. These symptoms included fatigue immediately upon waking, nightmares, sleep disorders, anxiety, depression, mood fragility, memory loss, attention disorders, lack of tolerance to stress, often lack of appetite, episodes of tachycardia and extrasistolia, generalized muscular weakness, muscular cramps, calf and foot sole pain (of the burning type) mostly during the night, intolerance to cold, and dry skin. The fatigue could vary greatly, even during the same day, from a tolerable degree to one that interrupted all activities and required complete rest.

For about 15 years, the patient had laboratory signs of a slight renal insufficiency due to interstitial glomerulopathy. Over the last three years, episodes of migraine appeared almost every weekend, along with nausea and vomiting, which required an anti-migraine therapy.

The patient was under gastroenterologist care and followed therapy with mesalazine and azathioprine. Blood tests, except the renal function, were normal. Brain nuclear magnetic resonance (RM) and cardiology checkup were normal.

Besides the numerous subjective symptoms, an objective examination showed slight muscular hypotone, a stabbing pain when pressing calves and soles of feet, and slight edema in the ankles. Stretching reflexes were present and symmetrical. At the time of the checkup, the disease was quiescent and the intestinal disturbances were minimal.

The patient's diet varied, but rice and potatoes (poor in vitamin B1) were strongly represented. Some aspects of the diet (strong consumption of rice), and clinical features such as (1) cardiac symptoms; (2) symptoms related to a predominantly sensitive polyneuropathy; (3) central nervous system symptoms; and (4) symptoms due to multiorganic suffering led the authors to conclude that the patient could be affected by a thiamine deficiency that was secondary to absorption deficiency.^{1,2}

We proposed a therapy comprising 50 mg of thiamine intramuscular (IM) for three days, to be continued if positive in effect, with an oral maintenance dose of 600 mg/day.^{1,3} The thiamine does not have any known collateral effects even if administered at high doses for prolonged periods of time.³

A few hours after the first IM administration, the fatigue completely disappeared and, day after day, the related symptoms remitted. Renal laboratory tests showed normalization in a week's time. Within 20 days, the patient regained complete wellness.

In August, one of the co-authors visited a relative, a 50-year-old woman affected by UC for 20 years. The patient showed a symptomatic background similar to the case above, along with constipation. The therapy, comprising 600 mg of oral thiamine per day, led to the disappearance of fatigue and other extraintestinal symptoms within a few days.

The third patient was a 40-year-old woman affected by UC for five years in a relapsing disease phase. The patient had about 10 episodes of diarrhea during the day and 5 at night and was affected by extreme fatigue. The oral therapy of 600 mg of thiamine per day led to disappearance of the fatigue within 48 hours. An unexpected event occurred leading to a dramatic improvement of the intestinal functions. At this point, the authors formulated the hypothesis that fatigue and all extraintestinal symptoms were the expression of thiamine deficiency.

Materials and Methods

The authors studied eight patients affected exclusively by UC in remission and four patients affected exclusively by Crohn's disease (CD) in quiescent phase. All patients presented fatigue and other extraintestinal symptoms (as previously described). The patients were recruited by a survey among the general practitioners of the study area, personnel of the Clinic, and those affiliated with the personnel between January and April 2011. All had a definite diagnosis performed according to the current criteria used for this disease.

Among the patients with UC there were six women and two men (average age 40.2 years). The average duration of the disease was 15.1 years. Two patients were not under any medical treatment. The other patients used either mesalazine, salazopirine, or mesalazine and azathioprine together. Three patients had surgery previously: two of them underwent an ileal-anal pouch anastomosis and one a colectomy. In addition, only one patient had constant tachycardia (100–110 beats per minute).

The subjects with CD were women (average age 62), and the average duration of the disease was 13.5 years. The patients used mesalazine or a combined therapy with mesalazine and azathioprine. Two of the patients previously underwent emicolectomies. Blood tests were normal, including thyroid hormone levels.

We proceeded with the following:

- 1) History and objective examination of each patient.
- 2) Evaluation of fatigue using the chronic fatigue syndrome (CFS) scale.⁴
- 3) Blood dosage of thiamine and thiamine pyrophosphate (TPP); blood withdrawal was frozen at -20°C and sent to the Italian Diagnostic Center of Bracco Industries, Milan, Italy.
- 4) Immediate oral therapy of 600 mg/day of thiamine (available in Italy 300 mg tablets and 100 mg/ml phials).

The dosage was defined empirically for this study as follows: first administration was 600 mg/day for each patient. Every two days, there was a consultation with the patient to assess the therapy. In those cases in which the regression of the fatigue was not satisfactory, an increment of 300 mg/day of thiamine was prescribed in addition to the 600 mg/day.

This last step—consultation with the medical doctor regarding the condition of the patient—has been the most important calibration tool for this research. Patients weighing 60 kg responded to the therapy at doses of 600 mg/day. Proportionally, patients weighing 60+ kg responded to the therapy accordingly to higher doses (up to 1,500 mg/day for patients weighting 90 kg). In general, this is the rationale for the following dosage calibration used in this study.

TABLE 1. THIAMINE, TPP AND CFS SCORES BEFORE THE THERAPY

Ulcerative C.	Thiamine, n.v. 2,1-4,3 µgr/L	TPP, n.v. > 49 µgr/L	CFS scores
Patient			
1	12.6	77.1	26
2	8.6	76	9
3	6.6	92	14
4	10.5	140	10
5	3.9	74	17
6	7.8	95.4	13
7	12.8	78.5	9
8	12.05	91.7	13

TPP, thiamine pyrophosphate; CFS, chronic fatigue syndrome.

Female patients:

- 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

For male patients, the doses need to be increased by one-third compared to females:

- Patients weighing <60 kg → 14 mg/kg/day of thiamine
- 60-65 kg → 18 mg/kg/day of thiamine
- 65-70 kg → 23 mg/kg/day of thiamine
- 70-75 kg → 30 mg/kg/day of thiamine
- 75-80 kg → 35 mg/kg/day of thiamine

For patients whose weight is higher than 80 kg, our team suggests switching to an intramuscular therapy with one 100 mg/ml vial every 7 to 10 days. This is due to patients' reluctance to ingest the large number of pills necessary for those weighing more than 80 kg.

The neurological examination was normal in 11 out of 12 subjects. Only one patient showed a muscular weakness that did not allow him to stand up from the squatting position. Moreover, the patient had a deficit of extension of the toes. In addition, one patient showed tachycardia at 100 beats per minute, and the echocardiogram was normal.

We considered the score of the CFS scale as follows:

- Zero points → no fatigue
- Up to 13 points → medium-low fatigue (five cases UC and three CD)
- From 13 to 26 points → severe fatigue (three cases UC and one CD)

TABLE 2. THIAMINE, TPP AND CFS SCORES BEFORE THE THERAPY

Crohn's D.	Thiamine, n.v. 2,1-4,3 µgr/L	TPP, n.v. > 49 µgr/L	CFS scores
Patient			
1	20.64	119.0	8
2	13.6	100.22	7
3	12.6	77.1	13
4	12.05	91.7	9

TABLE 3. THIAMINE, TPP AND CFS SCORES AFTER THE THERAPY

Ulcerative C.	Thiamine, n.v. 2,1-4,3 µgr/L	TPP, n.v. > 49 µgr/L	CFS scores
Patient			
1	20.64	137.6	0
2	69.0	118.0	0
3	34.4	115.5	0
4	177.1	180.1	5
5	23.2	122.9	0
6	56.7	141.0	0
7	71.8	156.4	3
8	181.7	161.58	0

The total sum of the points was 148.0. The average was 12.3. Evaluation of fatigue using the CFS scale was repeated after 20 days. The blood test for thiamine was also repeated after 20 days. See Table 1 (patients with UC) and Table 2 (patients with CD) for the values of thiamine, TPP, and CFS scores before therapy.

Results

In 10 patients, the values of the CFS scale after therapy was equal to zero. They showed a complete regression of fatigue. The remaining two patients did not show total regression of the fatigue, but nearly complete regression was evaluated. Indeed, one of the subjects was equal to 3 (from previous 9 points before therapy, thus 66.6% regression), and the other patient was equal to 5 (from previous 10 points before therapy, thus 50% regression). All patients also reported a complete regression of the symptoms correlated with fatigue. Tables 3 and 4 also includes the values of thiamine, TPP, and CFS scores after therapy.

Blood samples were taken a few hours after the last administration of thiamine. Collateral effects: one patient treated with 1,200 mg/day of thiamine showed a mild tachycardia that completely regressed by reducing the dose to 900 mg/day. If the thiamine doses administered are excessive for the patient's needs, this patient experiences tachycardia. High doses of thiamine (1,200-1,500 mg/day), if administered at night, may cause sleep difficulties. In order to reduce the incidents of this effect, the authors administered the last dose of thiamine before 5:00 pm.

Discussion

On the whole, we had a favorable response to thiamine. In the presence of thiamine deficiency, the response to therapy is considered diagnostic.¹

TABLE 4. THIAMINE, TPP AND CFS SCORES AFTER THE THERAPY

Crohn's D.	Thiamine n.v. 2,1-4,3 µgr/L	TPP, n.v. > 49 µgr/L	CFS scores
Patient			
1	87.5	137.0	0
2	118.2	180.0	0
3	56.7	141.0	0
4	22.0	132.6	0

The normal concentrations of thiamine and TPP in the blood indicates that thiamine uptake by the small intestines is normal. The presence of the symptoms of mild thiamine deficiency in patients with normal concentrations of thiamine and TPP in the blood could be explained by a form of thiamine deficiency that's due to dysfunction of the vitamin B1 active transport mechanism from the blood to the mitochondria, or to structural enzymatic abnormalities.

The administration of large quantities of vitamin B1 oral increases the concentration in the blood to levels in which the passive transport restores the normal glucose metabolism.³ The glucose metabolism of all organs goes back to normal values and fatigue disappears.

One author hypothesized a different mechanism that could explain the increase of vitamin B1 from the blood to the tissues. The solute carrier (SLC) gene family is composed of three transporter proteins with significant structural similarity, transporting substrates with different structure and ionic charge. The gene *SLC19A3*, a gene encoding human thiamine transporter 2 (hTHTR2), is also capable of transporting biotin, whereas the gene *SLC19A2* encodes the thiamine transporter 1 (hTHTR1), a B1-only transporter. This author states that in the presence of a genetic dysfunction of the *SLC19A3*, high doses of thiamine may induce the expression of the *SLC19A2* that encodes for the transporter 1 (hTHTR1), thereby increasing intracellular thiamine transport in enterocytes and neuronal cells, which were the object of the cited study.⁵

All patients reported a complete regression of the symptoms correlated with fatigue. The majority of the patients also showed an improvement of the intestinal functionality, with a substantial reduction in the number of diarrhetic events. We deem necessary a lifelong use of high doses of thiamine in affected subjects.

This study highlighted that if thiamine doses administered are excessive for the patient's needs, the only collateral effects are mild tachycardia and insomnia. In this case, it is necessary to reduce the dosage in order to obtain the best results in terms of fatigue reduction without side effects.

In literature, there is no mention of thiamine-related collateral effects even at high doses and for long periods of time.³ Additionally, there is no study that has observed collateral effects linked to daily use of high doses (both orally or intramuscular) of thiamine comparable to those in our therapy. The diseases treated with high doses of vitamin B1, and for long periods of time, are Alzheimer's disease and thiamine responsive megaloblastic anemia (TRMA). The doses employed in TRMA are similar to ours and have been administered for several years. In Alzheimer's disease, doses equal to 3 to 8 grams per day were administered for one year without observing any collateral effect.^{6,7}

A study presented by Magee et al.⁸ demonstrated that thiamine-rich foods decrease disease activity in patients affected by UC. Various cases of Wernicke encephalopathy and reports of fulminant beriberi during total parenteral nutrition have been described with IBD (without testing thiamine levels in the blood).⁹⁻¹⁴ These observations confirm our results.

Literature has never clearly stated that the chronic fatigue in IBD is a mild thiamine deficiency, which affects up to 40% of the patients. The presence of the symptoms of mild thiamine deficiency in our patients with normal blood concen-

tration of vitamin B1 may indicate a dysfunction of intracellular thiamine transport or structural enzymatic abnormalities.¹⁵

As of today, a possible dysfunction of the intracellular thiamine transporter was reported and described for one case of Wernicke's encephalopathy in a nonalcoholic patient with a normal blood thiamine level. Specifically, a 64-year-old woman who had never consumed alcohol presented a several-day history of vomiting and severe diarrhea, secondary to *Clostridium difficile* colitis.¹⁶ Moreover, a dysfunction of intracellular thiamine transport was described for genetic diseases characterized by mutations in thiamine transporter genes.^{5,17}

A number of inborn errors of metabolism have been described in which clinical improvements can be documented following administration of pharmacological doses of thiamine, such as thiamine-responsive megaloblastic anemia and Wernicke's-like encephalopathy.^{5,6,17} This study is not able to state whether the dysfunction of intracellular thiamine transport or enzymatic abnormalities are due to a genetic component or to an autoimmune inflammatory process.

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. Further studies are necessary to confirm our observations. However, we strongly believe that our observations represent an important contribution to the relief of many patients.

Conclusion

This small case series presents a simple remedy for what is a significant, complex problem of fatigue in IBD patients, and this latter fact, to the best of our knowledge, represents a complete novelty in the treatment of this symptom. Moreover, our team is convinced that the fatigue correlated with all autoimmune inflammatory diseases is a manifestation of an intracellular mild thiamine deficiency likely due to thiamine transporter deficiency or to enzymatic dysfunctions.

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Disclosure Statement

No competing financial interests exist.

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Address correspondence to:
Antonio Costantini, MD
Villa Immacolata
Strada Sarmartinese 65A
01100, Viterbo
Italy
E-mail: carapetata@libero.it