CASE REPORT

High dose thiamine improves fatigue in multiple sclerosis

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SUMMARY

The majority of the patients with multiple sclerosis (MS) experience fatigue. Some observations indicate that fatigue and related manifestations concomitant with MS could be associated with an intracellular mild thiamine deficiency. We recruited 15 patients with MS who also experience fatigue and assessed the severity of the fatigue using the Fatigue Severity Scale. Although blood thiamine and thiamine pyrophosphate levels were within normal limit in all the patients, high-dose thiamine therapy administered orally or parenterally led to an appreciable improvement of the fatigue. The absence of apparent decrease in blood thiamine despite the presence of symptoms referable to a mild thiamine deficiency suggests that these patients may have a dysfunction of the mechanisms of intracellular transport or structural enzymatic abnormalities. The administration of large quantities of thiamine was effective in reversing the fatigue in MS, suggesting that the abnormalities in thiamine-dependent processes could be overcome by diffusion-mediated transport at supranormal thiamine concentrations.

BACKGROUND

The basis of this report starts from a previous study on fatigue in inflammatory bowel diseases. Some clinical observations suggesting that fatigue in ulcerative colitis (UC) could be the manifestation of a mild thiamine deficiency prompted us to start in June 2010 a clinical open trial. We treated eight patients with UC with high-dose oral thiamine and obtained extremely encouraging findings.[1] Therefore, we decided to apply the same principles to chronic fatigue in different autoimmune and inflammatory diseases.

Fatigue is reported in about 75% of patients with multiple sclerosis (MS) at some point in the course of the disease. For many, fatigue is considered to be the single most debilitating symptom, exceeding pain and even physical disability.[2] Fatigue also imposes significant socio-economic consequences, including loss of work hours and in some instances, loss of employment. Nonetheless, fatigue in MS remains poorly understood in its pathogenic mechanisms and often undervalued. No effective therapy is available.

Fatigue and related disorders (sleep disorders, depression, mood fragility, anxiety, memory loss, attention disorders, lack of tolerance to stress, frequent lack of appetite, episodes of tachycardia and extrasistolia, generalised muscular weakness, muscular cramps, calf and feet sole pain, temperature-variation intolerance and dry skin) resemble the clinic manifestation of a mild thiamine deficiency.[3] Starting from this similarity, we began to research the literature in order to find papers concerning dysfunctions of energetic processes in MS.

A study on cerebrospinal fluid highlighted that in MS disease progression there is an increase of extramitochondrial glucose metabolism which implicates some sort of mitochondrial dysfunction.[4] The results of our previous study could be referable to metabolic alterations produced by a thiamine deficiency.[1] Moreover, several authors have observed that mitochondrial injury, resulting in energy failure, is a key element in MS.[5]

We formulated the hypothesis that the fatigue was the symptom of a mild thiamine deficiency which was intrinsic to the MS disease; therefore, we decided to treat the affected patients with high doses of thiamine.

CASE PRESENTATION

Fifteen patients, nine women and six men (mean (SD) age: 47.2 (10.0) years), affected exclusively by MS in the remitting phase were selected for this study after obtaining informed consent. The average duration of the disease (SD) was 14.1 (7.5) years. Table 1 shows the demographic information of the patients. All patients included in this study fulfilled the following criteria:

- They all had a definite diagnosis of MS according to McDonald criteria (2010).
- None of them presented with cognitive impairment.
- All the patients also showed the other clinical manifestations of mild thiamine deficiency, such as sleep disorders, depression, anxiety, mood fragility, memory loss, attention disorders, lack of tolerance to stress, frequent lack of appetite, episodes of tachycardia and extrasistolia, generalised muscular weakness, muscular cramps, calf and feet sole pain, temperature-variation intolerance and dry skin.
- All participants were outpatients. Eight patients were not previously exposed to any medical treatment. Five patients were receiving only glatiramer acetate (Ga) and two patients, only interferon β during the period of this study. No patient had a notorious cause that could lead to chronic fatigue; in all patients, thyroid function and routine blood tests were within normal limit.

For the evaluation of the fatigue the Fatigue Severity Scale (FSS) was employed.[6] The average value of the FSS was 45.4 before the treatment.

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Table 1 Demographic information of the patients before therapy

Patient	Age	Gender	Disease duration	MS disease therapy	Basic ADL Barthel Index	Fatigue-related disorders	Symptoms
1	46	M	25	Ga	100	Anxiety, muscular cramps, lack of appetite, dry skin	Ataxia tetraparesis
2	51	F	25	Ga	100	Depression, tachycardia, heat intolerance	Ataxia
3	38	M	21	Interferon-β	100	Anxiety, sleep disorders, attention disorders	Ataxia tetraparesis
4	34	F	10	Ga	52	Cold intolerance, lack of tolerance to stress, dry skin	paraparesis
5	38	M	11	No therapy	19	Anxiety, sleep disorders, memory loss	Tetraparesis
6	43	F	4	Ga	100	Anxiety, cold intolerance, lack of tolerance to stress	Sensitive ataxia
7	47	F	13	Ga	100	Anxiety, mood fragility, extrasistolia	Ataxia
8	37	F	18	Interferon β	100	Anxiety, dry skin, extrasistolia	Tetraparesis
9	43	F	10	No therapy	100	Anxiety, cold intolerance, dry skin	Ataxia tetraparesis
10	65	F	13	No therapy	69	Depression, lack of tolerance to stress, dry skin	Paraparesis
11	44	M	19	No therapy	52	Sleep disorders, lack of tolerance to stress, trouble concentrating	Paraparesis
12	55	F	3	No therapy	100	Sleep disorders, lack of tolerance to stress, extrasistolia	Sensory symptoms
13	48	F	11	No therapy	100	Depression, trouble concentrating, cold intolerance	Tetraparesis
14	49	M	24	No therapy	100	Anxiety, lack of tolerance to stress, tachycardia	Ataxia tetraparesis
15	70	M	5	No therapy	52	Anxiety, depression, heat intolerance	Paraparesis

MS, multiple sclerosis; ADL, activities of daily living; Ga, glatiramer acetate.

Blood levels of the thiamine and of the thiamine pyrophosphate (TPP) were determined in a core laboratory (Centro Diagnostico Italiano, Milano, Italy). Vitamin B_1 level in whole blood samples was determined with ClinRep complete kit. In this test, vitamin B_1 level was quantified as TPP using high-performance liquid chromatography (HPLC) with fluorescence detection. Normal values cited in the tables were derived from Lee *et al*.[7] The main data of each patient are shown in table 2.

High-dose thiamine therapy consisted of 600–1 500 mg/day orally or 100 mg/mL once a week parenterally. The oral reference doses were retrieved from our previous study on inflammatory bowel diseases.[1] We used a dosage calibration according to the weight of the patients in this way:

- Patients less than 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;

Table 2 Thiamine, TPP and FSS before and after the therapy

Patient	Thiamine (n.v. 2.1–4.3 μg/L)*		TPP (n.v. >49 kg/L)*		FSS scores	
	Before	After	Before	After	Before	After
1[ab]	7.0	8.4	91.0	48	38	15
2[e]	6.6	73.1	86.2	65.1	37	18
3[ab]	6.3	10.8	50.8	119.4	30	14
4[d]	4.1	7.9	38.8	78.0	51	38
5[d]	11.4	18.4	89.5	101.7	61	34
6[d]	8.2	14.4	72.9	40.1	49	40
7[d]	9.2	14.8	45.2	47.4	55	55
8[e]	8.4	36.4	105.4	73.2	38	21
9[e]	7.3	102.7	73.1	72.8	42	14
10[ac]	10.8	1414.9	86.4	46.7	21	12
11[ab]	5.9	20.6	96.2	69.0	61	48
12[ab]	8.0	29.4	122.2	84.1	40	15
13[d]	9.4	13.0	106.5	42.8	55	24
14[e]	6.1	32.8	73.1	123.5	64	40
15[ab]	21.5	22.0	128.1	132.6	39	15
average±SD	8.7±3.9	121.3±346.6	84.4±25.3	76.3±29.6	45.4±12.0	26.9±13.8
P values by paired *t* test (two-tailed)	0.24		0.42		<0.0000001	

*Normal values derived from Lee *et al*.[7]
TPP, thiamine pyrophosphate; FSS, the Fatigue Severity Scale; a, parenteral administration (the remaining patients were treated orally); b, blood test 2 days after the injection; c, blood test 2 h after the injection; d, fasting blood test in the morning; e, blood test 4 h after the intake of the first daily dose; n.v., normal value.

- 70–75 kg → 20 mg/kg/day of thiamine;
- 75–80 kg → 23 mg/kg/day of thiamine.

In patients more than 80 kg, parenteral administration was performed due to the patient's reluctance to take large amount of pills. We considered the score of the FSS as follows:

- Up to 9 points → no fatigue;
- More than 9, up to 36 points → medium-low fatigue (two cases);
- More than 36 points → severe fatigue (13 cases).[6]

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

OUTCOME AND FOLLOW-UP

The evaluation of the fatigue using the FSS scale was repeated 20 days after the beginning of the therapy. A partial regression of the fatigue was shown in 14 patients out of 15 (except for patient 7) (93.3% of the cases) (table 2). A detailed observation revealed that improvement of fatigue was obtained within hours from the first parenteral administration or within 2–3 days after the beginning of the oral therapy. The average value of the FSS before the therapy was 45.4 while the average value of the FSS after the therapy was 26.8, showing a statistically significant improvement by 41% (paired *t* test, $p<0.0001$, table 2). The patients moreover reported an almost complete disappearance of fatigue-related symptoms such as an improvement of the intolerance to heat variations, sleep disorders, depression, anxiety, irritability, dry skin, lower leg swelling and tachycardia. Motor and other neurological symptoms did not show an appreciable clinical improvement.

During this study, we have never recorded any side effect.[8] A recent check-up (after 18 months of treatment) did not show any decrease of the efficacy of the therapy.

DISCUSSION

This pilot study showed that treatment with high doses of thiamine was associated to a remarkable improvement of fatigue-related symptoms in MS, which closely resemble a mild thiamine deficiency.[9 10] During this study we have never recorded any side effect.

The presence of manifestations of a mild thiamine deficiency even in patients with normal concentrations of thiamine and TPP in the blood could be explained if referred to a form of thiamine deficiency due to a dysfunction of the vitamin B_1 active intracellular transport, or to structural enzymatic abnormalities.[9 11] We deem that the concentration of thiamine in the blood before and after the therapy has higher relevance in understanding the action of vitamin B_1 in these cases because, it is known that thiamine is converted into TPP within the cells and thus, TPP concentration in the blood may not be related to improvement of the diffusion mechanism throughout the organism.[12] On the other hand, the much higher content of thiamine in the blood after the high-dose therapy leads to an increment of the intracellular TPP and to an improvement of the manifestations as shown in our observations. In the 1950s and 1960 s, several authors treated MS using TPP without any result.[13] We deem that if the aforementioned early studies focused on administration of thiamine rather than TPP, they might have witnessed an improvement of the fatigue due to the action of thiamine at cellular level in favouring the production of TPP.

Unfortunately, for the current study we were not in the position to measure the TPP levels in the cells. However, whatever be the kind of dysfunction taking place in our patients, the symptoms were responsive to administration of large quantities of thiamine. The administration of large quantities of thiamine orally or parenterally increases its concentration in the blood to the levels which the passive transport restores the normal glucose metabolism. According to literature, the dysfunction of active intracellular transport or enzymatic abnormalities could be overcome by diffusion mediated at supranormal thiamine concentrations.[9 11] Other mechanisms have been thought to be responsible of the efficacy of high doses of thiamine, but we reckon these are less likely.[11]

The doses employed in this study were calculated empirically based on previous studies on inflammatory bowel diseases and they may be defined with higher accuracy as a result of further studies, in order to improve the efficiency of the therapy.

As of today, there is only one non-alcoholic case report of Wernicke's encephalopathy manifesting with symptoms of thiamine deficiency with normal blood concentrations of thiamine level, caused by vomiting and severe diarrhoea secondary to *Clostridium difficile* colitis.[14] Clinical improvements are documented following administration of pharmacological doses of thiamine in patients with inborn errors of metabolism such as thiamine-responsive megaloblastic anaemia and Wernicke's like encephalopathy.[9 11]

In addition, recently, improvement of fatigue with high doses of thiamine was observed in a case of Spinocerebellar Ataxia type 2.[15]

In conclusion, the current pilot study demonstrated the possible effectiveness of high-dose thiamine therapy in fatigue of patients with MS. In order to confirm our observations, placebo-controlled randomised trials and further studies enable to explain the exact pathogenesis of intracellular thiamine deficiency are warranted.

Learning points

- The treatment described in this paper, that is, high-dose thiamine supplementation in patients with multiple sclerosis and fatigue, is immediately available.
- In literature there is no study that has observed side effects linked to daily use of high doses of thiamine.
- We believe that this report opens a ray of hope for the therapy of chronic fatigue.

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