

## High-Dose Thiamine Improves Fatigue After Stroke: A Report of Three Cases

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### Abstract

**Background and objectives:** A previous study on fatigue and related disorders in inflammatory bowel disease, patients improved after therapy with high-dose thiamine. Chronic fatigue that accompanies inflammatory and autoimmune diseases could be the clinical manifestation of a mild thiamine deficiency, probably due to a dysfunction of intracellular transport or enzymatic abnormalities. Fatigue is a common symptom after stroke. Some studies show a severe functional effect of this symptom, as well as a high mortality rate. Necrotic cell death after cerebral ischemia triggers the activation of the immune system, followed by an inflammatory response. It is likely that fatigue related to stroke could benefit from high-dose thiamine. Consequently, the authors began treating poststroke patients with oral or parenteral high-dose thiamine.

**Design:** Case study.

**Materials and methods:** Three patients with stroke who also experienced fatigue were recruited. Severity of the fatigue was assessed by using the Fatigue Severity Scale. Blood free thiamine and thiamine pyrophosphate levels were within the healthy reference range in all the patients. Oral or parenteral therapy with high-dose thiamine was started.

**Results:** The therapy led to an appreciable improvement of fatigue.

**Conclusion:** This observation suggests that poststroke fatigue and related disorders could be the manifestation of mild thiamine deficiency due to a dysfunction of intracellular transport of thiamine or to structural enzymatic abnormalities.

### Introduction

FATIGUE IS A COMMON SYMPTOM among patients with neurologic disorders, including stroke. Few studies have documented the high frequency of fatigue in poststroke patients and its negative effect on daily functioning and quality of life. Little is known about therapeutic strategies that may be used to alleviate it. Fatigue occurs in 23%–75% of stroke survivors and is associated with higher mortality.<sup>1</sup> A substantial proportion of patients reported that their fatigue started at the time of their stroke.<sup>2,3</sup> Some studies show sleep disorders and a link between fatigue and depression. Our patients have fatigue, sleep disorders, anxiety, depression, memory loss, attention disorders, muscular cramps, cold intolerance, and dry skin. Fatigue and related disorders seemed to have many similarities with the manifestation of a mild thiamine deficiency.<sup>4</sup>

In June 2010, it was observed that the fatigue and the other “extraintestinal symptoms” in patients with ulcerative

colitis improved after a therapy with high doses of thiamine.<sup>5</sup> The following hypothesis was formulated: Chronic fatigue that accompanies inflammatory and autoimmune diseases could be the clinical manifestation of a mild thiamine deficiency, probably due to a dysfunction of the intracellular transport or to enzymatic abnormalities and responds favorably to high doses of thiamine. From that moment, the authors systematically searched for patients with chronic fatigue in any type of disease and treated them with high doses of thiamine. Consequently, fatigue after stroke was treated with high-dose thiamine among the three patients described in this study.

### Materials and Methods

All patients were under therapy with antihypertensive, antiaggregant, antidepressant drugs, and all patients reported that their fatigue started at the time of their stroke. Thyroid hormones were in healthy reference range in all patients.

After formal consensus, the following were performed: (1) history and objective examination of each patient; (2) evaluation of the fatigue using the Fatigue Severity Scale (FSS); (3) blood dosage of thiamine and thiamine pyrophosphate (TPP); (4) immediate therapy with high doses of thiamine orally or parenterally; (5) repetition of steps 1, 2, and 3 fifteen days after the beginning of the therapy (Table 1).

The scores of FSS were considered as follows: 9 points: no fatigue; up to 36 points: medium-low fatigue; from 36 to 63 points: severe fatigue.

Patient 1 was a 74-year-old woman weighing 68 kg. Seven years earlier she had sustained a right middle cerebral infarction with resultant left hemiparesis. In April 2011, when observations began, the patient had weakness and increase muscle tone in her left limbs; there was mild left pronator drift with clumsiness in the left hand (with movements of the fingers slower and less accurate); she walked with shuffling of her left foot; a left Babinski sign was noted. The sensation of a pinprick was decreased in the arm. Serum thiamine before the therapy was 9.9  $\mu\text{g/L}$  (normal values, 1–4.3  $\mu\text{g/L}$ ), blood TPP before the therapy was 83.4  $\mu\text{g/L}$  (normal values, >49  $\mu\text{g/L}$ ), and the FSS score was 39 points.

Patient 2 was an 86-year-old man weighing 80 kg. He had experienced a right middle cerebral artery infarction with resultant left hemiparesis 3 years earlier. In April 2011, he was ambulating independently with a quad cane and left ankle foot orthosis and required set-up and minimal assistance for upper-extremity bathing and dressing; he also required moderate assistance to put on and take off his shoes and socks. Serum thiamine before the therapy was 7.2  $\mu\text{g/L}$  (normal values, 1–4.3  $\mu\text{g/L}$ ), blood TPP before the therapy was 102.0  $\mu\text{g/L}$  (normal values, >49  $\mu\text{g/L}$ ), and the FSS score was 37 points.

Patient 3 was a 70-year-old woman weighing 50 kg. She had a history of left middle cerebral artery infarction within the past 15 months, without residual deficits. Serum thiamine before the therapy was 8.2  $\mu\text{g/L}$  (normal values, 1–4.3  $\mu\text{g/L}$ ), blood TPP before the therapy was 78.0  $\mu\text{g/L}$  (normal values >49  $\mu\text{g/L}$ ), and the FSS score was 52 points.

Patients were contacted every 15 days during the first 90 days of the therapy, then every 3 months. Patients 1 and 3 were treated with 600 mg/d orally; patient 2 was treated with 100 mg per week, parenterally. The improvements have been tangible since the beginning of the study (therapeutic dose shows its efficiency after about 48 hours) and as of this writing the patients continue to show benefit. Because of the

limited number of patients in this case study, no control group could be provided. The lack of a control group makes the results preliminary and more difficult to interpret.<sup>6</sup>

## Results

All patients had definite improvement, with relief of the fatigue and related symptoms, within a week from the starting of the treatment.

Patient's status after the therapy was as follows (see also Table 1): For patient 1, the FSS score was 10 points (decrease of 74.4%); for patient 2, the FSS score was 14 points (decrease of 62.4%); for patient 3, the FSS score was 9 points (complete regression of the fatigue).

Blood samples before therapy were taken after an overnight fast. After the beginning of the therapy, for patients 1 and 3 blood samples were taken 4 hours after the administration of 300 mg of thiamine (orally) while for patient 2, samples were obtained 2 days after the thiamine injection. All patients are currently continuing the same therapy. A recent check-up of the patients showed no decrease in the efficacy of the therapy.

## Discussion

The response to thiamine was favorable and, in presence of the symptoms of thiamine deficiency, the response to therapy is considered diagnostic.<sup>7</sup> The normal concentrations of thiamine and TPP in the blood indicate that thiamine uptake by the small intestines is normal. The presence of symptoms of mild thiamine deficiency 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 intracellular active transport mechanisms or to enzymatic abnormalities. The oral administration of large quantities of thiamine was effective in reversing fatigue, suggesting that the abnormalities in thiamine-dependent processes could be overcome by diffusion-mediated transport at supranormal thiamine concentrations.<sup>7</sup> The glucose metabolism of all organs goes back to normal values and fatigue improves. The authors consider lifelong use of high doses of thiamine in affected patients to be necessary. The patients described here are still receiving the same treatment.

The presence of thiamine deficiency symptoms in patients with normal blood concentrations of thiamine was reported and described for one case of Wernicke encephalopathy in a nonalcoholic patient with normal thiamine level, in a case of

TABLE 1. PATIENTS' CHARACTERISTICS AND STATISTICAL ANALYSIS

Patient	Sex	Weight (kg)	Thiamine before therapy ( $\mu\text{g/L}$ )	Thiamine after therapy ( $\mu\text{g/L}$ )	TPP before therapy ( $\mu\text{g/L}$ )	TPP after therapy ( $\mu\text{g/L}$ )	FSS score before therapy	FSS score after therapy
1	F	68	9.9	205.4	83.4	152.8	39	10
2	M	80	7.2	12.6	102.0	154.5	37	14
3	F	50	8.2	44.0	78.0	125.5	52	9
Mean $\pm$ SD			8.43 $\pm$ 1.37	87.33 $\pm$ 103.45	87.80 $\pm$ 12.59	144.27 $\pm$ 16.27	42.67 $\pm$ 8.14	11.00 $\pm$ 2.65
<i>p</i> -Value (paired <i>t</i> -test)				0.3127		0.0135		0.0333

TPP, thiamine pyrophosphate; FSS, Fatigue Severity Scale; F, female; M, male; SD, standard deviation.

vomiting and severe diarrhea secondary to *Clostridium difficile* colitis, in inflammatory bowel disease, in fibromyalgia, and in multiple sclerosis.<sup>5,7-9</sup>

Many inborn errors of metabolism have been described in which clinical improvements can be documented after administration of pharmacologic doses of thiamine, such as thiamine-responsive megaloblastic anemia and Wernicke-like encephalopathy.<sup>7</sup>

This study was not able to identify the pathogenesis of intracellular mild thiamine deficiency, which is probably due to an autoimmune-inflammatory process. The necrotic cell death after cerebral ischemia triggers the activation of the immune system followed an inflammatory response. Convincing evidence suggests that inflammatory cascades and cytokine signalling precipitated by the infarct promote fatigue.<sup>10</sup> During this study, no adverse effects were observed. Further studies are necessary to confirm these observations.

### Conclusions

It is likely that fatigue related to other neurologic diseases could benefit from the same therapy. 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. Although additional studies are needed, the observations reported here represent an important contribution to the relief of many patients.

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### Author Disclosure Statement

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