

## CASE REPORT

## High-dose thiamine as initial treatment for Parkinson's disease

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**SUMMARY**

Parkinson's disease (PD) is a systemic disease with motor and non-motor deficits. We recruited three patients with newly diagnosed PD. They were not under anti-Parkinson's therapy. Plasmatic thiamine was within healthy reference range. We performed the Unified Parkinson's Disease Rating Scale (UPDRS) and started a parenteral therapy with high doses of thiamine. The therapy led to a considerable improvement in the motor part of the UPDRS ranging from 31.3% to 77.3%. From this clinical observation, it is reasonable to infer that a focal, severe thiamine deficiency due to a dysfunction of thiamine metabolism could cause a selective neuronal damage in the centres that are typically hit in this disease. Injection of high doses of thiamine was effective in reversing the symptoms, suggesting that the abnormalities in thiamine-dependent processes could be overcome by diffusion-mediated transport at supranormal thiamine concentrations.

**BACKGROUND**

Parkinson's disease (PD) is a progressive neurodegenerative disorder that is manifested clinically by motor symptoms (bradykinesia, tremor, rigidity, flexed posture and postural instability) and non-motor symptoms (including impaired olfaction, sleep disorders, gastrointestinal and urinary abnormalities, cardiovascular dysfunction, fatigue, pain, depression and mood disorders). It is characterised pathologically by the degeneration of pigmented dopaminergic neurons in the substantia nigra. In addition other nuclei are involved such as the locus coeruleus, reticular nuclei of the brain stem, dorsal motor nucleus of the vagus, basal nucleus of the Meynert, the amygdala, cornu ammonis 2 area of the hippocampus and frontal cortex.<sup>1</sup> Non-motor symptoms appear before or in-parallel with motor deficit. Carbidopa-levodopa remains the most effective agent of relief from PD symptoms. Catechol O-methyltransferase inhibitors mildly prolong the effect of levodopa therapy. Alternatives to levodopa in PD include monoamine oxidase-B inhibitors, amantadine and dopamine agonists.<sup>2</sup>

In July 2011, we treated a 47-year-old man affected by spinocerebellar ataxia type 2 (SCA2).<sup>3</sup> In this patient, fatigue as well as motor symptoms improved after parenteral high doses of thiamine. Therefore, we formulated the hypothesis that in some inherited and degenerative diseases of the nervous system, the pathogenesis of the symptoms could be linked to a focal thiamine deficiency due to a dysfunction of the intracellular transport of thiamine or to structural enzymatic abnormalities.

We thought that this dysfunction could be responsive to high-dose thiamine. Furthermore, PD has also been related to mutations associated with SCA2.<sup>4</sup> Some reports have shown trinucleotide repeat expansions in the SCA2 gene in patients with levodopa-responsive parkinsonism. In addition, a number of factors link thiamine to PD.<sup>5</sup> Recently a considerable improvement of motor and non-motor symptoms in patients affected by PD was observed with intramuscular daily doses of 100–200 mg of thiamine.<sup>6</sup>

In this report we describe the results obtained from three patients with newly diagnosed PD. We have decided to treat the patients with high doses of thiamine in order to clarify the potential effect of vitamin B1 alone in the initial therapy of the disease.

**CASE PRESENTATION**

We performed the following examinations: neurological examination, Unified Parkinson's Disease Rating Scale (UPDRS) and total plasmatic thiamine. In one case, we evaluated fatigue with the fatigue severity scale (FSS) and pain with the visual numeric scale (VNS).<sup>7</sup> Total plasmatic thiamine was within the healthy reference range for all patients. The clinical diagnosis of PD was established by experienced neurologists (AC and LC) using the UK Parkinson's Disease Society Brain Bank criteria.<sup>8</sup> The patients did not show neuropathy or cognitive impairment. We prescribed a therapy with 100 mg of thiamine parenterally twice a week, on Mondays and Thursdays. This is because it is easier for the elderly patients to follow the therapy by having fixed days of the week for the intake of the drug rather than having them taking thiamine every 3 or 4 days. As a standard procedure, every time that high doses of thiamine are administered to patients, small doses of all other group B vitamins were administered to the patients of this study. Fifteen days after the beginning of the therapy, we examined the patients and repeated the UPDRS, FSS and VNS (for patient number 3 only) tests (see table 1). The reference period for this study's observations was from 1 October 2012 to 31 January 2013.

*Patient 1:* female, 79-year-old, weight 70 kg, had two hip replacement surgery interventions as a consequence of a fall. The patient did not present any other disease. In 2009, she began to experience slowness of the movements and rest tremor in her right hand and her jaw. Neurological examination highlighted: bradykinesia, rigidity, postural instability, mask-like facies with infrequent blinking, loss

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**Table 1** UPDRS before and after the therapy

Patient	Age	Sex	UPDRS before the therapy						UPDRS after the therapy					
			I	II	III	IV	V	VI	I	II	III	IV	V	VI
1	79	F	0	16	31	0	2.5	70%	0	7	18	0	2	90%
2	74	F	0	23	32	0	3	20%	0	16	22	0	2	70%
3	75	M	0	13	22	0	2.5	80%	0	5	5	0	2	100%

UPDRS, Unified Parkinson's Disease Rating Scale.

of the normal associated movements in the arms while walking and continuous rest tremor of the right hand and the jaw. CT of the brain revealed cortical atrophy. UPDRS scores as follows: total sum (parts I–IV) 47, part III 31; modified Hoen and Yahr staging (HYS) 2.5, Schwab and England Activities of Daily Living scale (SE-ADL) 70%.

*Patient 2:* female, 74-year-old, weight 80 kg, presented hypertension and was under medical treatment for it. In 2009 she began to experience slowness of the movements and rest tremor in her right hand. Neurological examination highlighted: akinesia, rigidity, mask-like facies with infrequent blinking, loss of the normal associated movements in the arms while walking and continuous rest tremor of the right hand. The patient could not walk alone. CT of brain revealed cortical atrophy and multiple non-specific foci in the bilateral deep white matter. UPDRS scores as follows: total sum (parts I–IV) 55, part III 31, HYS 3, SE-ADL 20%.

*Patient 3:* male, 75-year-old, had a heart attack in the past, currently on antithrombotic therapy. In 2012, he began to experience slowness of the movements, severe fatigue and pain. Neurological examination highlighted: bradykinesia, rigidity, postural instability, mask-like facies with infrequent blinking and loss of the normal associated movements in the arms while walking. The patient had his mouth open permanently. Moreover, he reported a severe fatigue and diffused pain. CT of brain showed small, multiple areas of hypodensity, bilaterally located in the internal capsule. UPDRS scores as follows: total sum (parts I–IV) 35, part III 22, HYS 2.5, SE-ADL 80%. FSS score: 50, VNS score: 8.

We prescribed a therapy with 100 mg of thiamine parenterally twice a week. As a standard procedure, every time that high doses of thiamine were administrated to patients, small doses of all other group B vitamins were administrated to the patients of this study. Fifteen days after the beginning of the therapy, we examined the patients and repeated the tests.

## OUTCOME AND FOLLOW-UP

After 15 days from the beginning of the therapy, we examined the patient and repeated the same tests. The results were the following (see table 1):

*Patient 1:* the patient presented a normal muscular tone, rest tremor present only intermittently, minimal hypomimia and an increase of arm swings while walking. The patient was able to walk with longer steps and more rapidly than before the beginning of the therapy.

The improvement of the UPDRS parts I–IV was equal to 46.0% and the improvement of the part III was equal to 42.0%.

*Patient 2:* the patient presented a normal muscular tone, rest tremor present only intermittently, minimal hypomimia and an increase of arm swings while walking. The patient was able to walk alone and showed a considerable improvement of the postural stability.

The improvement of the UPDRS parts I–IV was equal to 31.0% and the improvement of the part III was equal to 31.3%.

*Patient 3:* the patient was able to have his mouth closed, presented a minimal hypomimia and hypokinesia and normal muscular tone. The patient smiled and walked nearly normally presenting only minimal impairment. Fatigue regressed almost completely and pain regressed partially.

The improvement of the UPDRS parts I–IV was equal to 69.7% and the improvement of the part III was equal to 77.3%. FSS: 13; VNS: 5.

## DISCUSSION

On the whole, we had a favourable response to thiamine. The patient reported a robust improvement of the symptoms. Compared with other available therapies, thiamine therapy was associated with an equal improvement in motor function, as assessed by reduced scores in the UPDRS.<sup>2</sup> Responsiveness to levodopa (required to exceed 25–30% reduction in the motor part of the UPDRS) is a diagnostic criterion for PD.<sup>2</sup> Moreover, fatigue and pain have improved (likely thanks to the normalisation of the muscular tone). The absence of blood thiamine deficiency and the efficacy of high-dose thiamine in our patients suggest that the symptoms of PD are 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. In other words, we believe that the motor and non-motor symptoms of PD could derive from a chronic thiamine deficiency which is composed by:

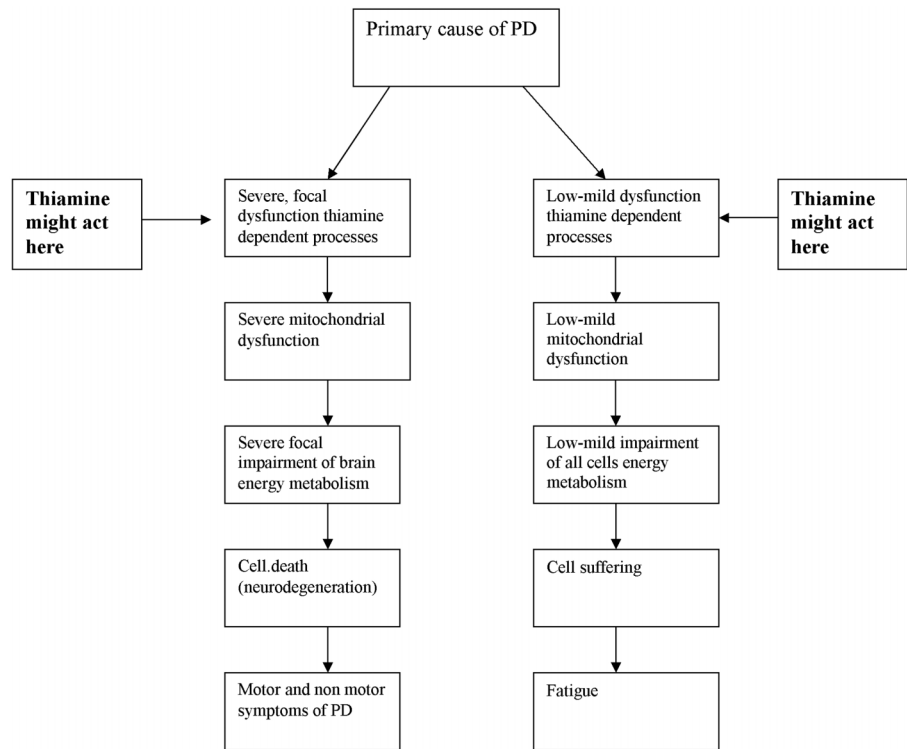
1. Severe focal thiamine deficiency that could determine a progressive dysfunction and selective neuronal loss in the substantia nigra pars compacta and in other centres that are typically hit in this disease.
2. Mild thiamine deficiency in all other cells that could lead the cells to a suffering state and the presence of fatigue. Fatigue could be the true systemic symptom of the disease. In our opinion, the primary cause of PD is less expressed in all other cells where the disease determines a mild thiamine deficiency that causes fatigue and related disorders.<sup>3</sup>

Moreover, a dysfunction of intracellular thiamine transport was described for genetic diseases characterised by mutations in thiamine-transporter genes.<sup>9–11</sup> A number of in-born 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 anaemia and Wernicke's like encephalopathy.<sup>9–11</sup> Genetic disorders of thiamine metabolism that lead to neurological disease can be treated with large doses of thiamine.<sup>12</sup>

The exact mechanism of thiamine responsiveness in these patients is unknown.

In any case, the injection of high doses of thiamine was effective in reversing all symptoms, suggesting that the abnormalities in

**Figure 1** Pathogenesis of the symptoms of the Parkinson's disease and proposed role of high-dose thiamine.



Modified from Jhala and Hazell, 2011.<sup>14</sup>

thiamine-dependent processes could be overcome by diffusion-mediated transport at supranormal thiamine concentrations.

Furthermore, we believe that parenteral thiamine administration may play an important role in restoring survivor neurons and in limiting the progression of the disease because the dysfunction of thiamine-dependent processes could be a primary pathogenic pathway leading to the demise of dopaminergic and non-dopaminergic neurons in PD (figure 1).<sup>13 14</sup>

In literature, there is no mention of thiamine-related adverse effects even at high doses and for very long periods of time.<sup>15</sup>

In conclusion, we believe that this report represents an important contribution to the subject; nonetheless, further experience is necessary to confirm the present observations.

### Learning points

- ▶ The treatment described in this paper is immediately available for the care of Parkinson's disease (PD).
- ▶ In literature, there is no study that has observed side-effects linked to the daily use of high doses of thiamine.
- ▶ We believe that this report opens a ray of hope for therapy of PD.

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**Competing interests** None.

**Patient consent** Obtained.

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