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Original Articles

Long-Term Treatment with High-Dose Thiamine in Parkinson Disease: An Open-Label Pilot Study

Antonio Costantini, MD,[1] Maria Immacolata Pala, BScN,[1] Enzo Grossi, MD,[2] Stella Mondonico, BSc,[3] Luisa Ercoli Cardelli, MD,[4] Carina Jenner, PsychS,[1] Sabrina Proietti, PsychS,[1] Marco Colangeli, BSc,[5] and Roberto Fancellu, MD[6]

Abstract

Objectives: To investigate the potential clinical, restorative, and neuroprotective effects of long-term treatment with thiamine in Parkinson disease (PD).
Design: Observational open-label pilot study.
Setting: Outpatient neurologic rehabilitation clinic.
Patients and Methods: Starting in June 2012, we have recruited 50 patients with PD (33 men and 17 women; mean age, 70.4 ± 12.9 years; mean disease duration, 7.3 ± 6.7 years). All the patients were assessed at baseline with the Unified Parkinson's Disease Rating Scale (UPDRS) and the Fatigue Severity Scale (FSS) and began treatment with 100 mg of thiamine administered intramuscularly twice a week, without any change to personal therapy. All the patients were re-evaluated after 1 month and then every 3 months during treatment.
Results: Thiamine treatment led to significant improvement of motor and nonmotor symptoms: mean UPDRS scores (parts I–IV) improved from 38.55 ± 15.24 to 18.16 ± 15.08 ($p = 2.4 \times 10^{-14}$, *t* test for paired data) within 3 months and remained stable over time; motor UPDRS part III score improved from 22.01 ± 8.57 to 9.92 ± 8.66 ($p = 3.1 \times 10^{-22}$). Some patients with a milder phenotype had complete clinical recovery. FSS scores, in six patients who had fatigue, improved from 53.00 ± 8.17 to 23.60 ± 7.77 ($p < 0.0001$, *t* test for paired data). Follow-up duration ranged from 95 to 831 days (mean, 291.6 ± 207.2 days).
Conclusions: Administration of parenteral high-dose thiamine was effective in reversing PD motor and nonmotor symptoms. The clinical improvement was stable over time in all the patients. From our clinical evidence, we hypothesize that a dysfunction of thiamine-dependent metabolic processes could cause selective neural damage in the centers typically affected by this disease and might be a fundamental molecular event provoking neurodegeneration. Thiamine could have both restorative and neuroprotective action in PD.

Introduction

Parkinson disease (PD) is a progressive neurodegenerative disorder clinically characterized by motor symptoms (bradykinesia, tremor, rigidity, flexed posture, postural instability) and nonmotor symptoms (including impaired olfaction, sleep disorders, gastrointestinal and urinary abnormalities, cardiovascular dysfunction, fatigue, pain, depression, and cognitive disorders).[1] The neuropathologic feature of PD is the degeneration of pigmented dopaminergic neurons in the substantia nigra; in addition, other nuclei are involved in this disease, such as the locus coeruleus, reticular nuclei of brain stem, dorsal motor nucleus of the vagus nerve, basal nucleus of Meynert, amygdala, CA2 area of the hippocampus, and frontal cortex.[2] Nonmotor symptoms may appear before or in parallel with motor deficits.[1] It has been calculated that at the onset of parkinsonian symptoms, the neuron loss is 68% in the lateral ventral part and 48% in the caudal part of the substantia nigra.[3,4]

Levodopa remains the gold standard and most effective therapy for PD. Cathecol-O-methyltransferase inhibitors

[1]Department of Neurological Rehabilitation, Villa Immacolata Clinic, Viterbo, Italy.
[2]Bracco Foundation, Milan, Italy.
[3]Centro Diagnostico Italiano, Milan, Italy.
[4]Lab Analysis, Villa Immacolata Clinic, Viterbo, Italy.
[5]University Studies Abroad Consortium, Viterbo, Italy.
[6]Unit of Neurology, IRCCS San Martino University Hospital IST, Genoa, Italy.

mildly prolong the effect of levodopa therapy. Alternatives to levodopa in PD include dopamine agonists, monoamine-oxidase B inhibitors, and amantadine.[1,5]

Thiamine (vitamin B1) is a cofactor of enzymes involved in fundamental pathways of energetic cell metabolism (transketolase, α-keto-acid decarboxylase, pyruvate dehydrogenase, α-keto-glutarate dehydrogenase). Thiamine deficiency is a complication of severe malnutrition associated with chronic alcoholism, HIV/AIDS, and gastrointestinal disease, frequently resulting in Wernicke-Korsakoff encephalopathy, a subacute neurologic disorder characterized by ophthalmoplegia, gait ataxia, confusion, and memory loss.[6] The pathophysiology of thiamine deficiency is multifactorial and involves many events, resulting in focal neuronal cell death. Such events (e.g., reduced activity of α-keto-glutarate dehydrogenase, impaired oxidative metabolism, increased oxidative stress, and selective neuronal loss in specific brain regions) are also reported among the pathologic mechanisms involved in different neurodegenerative diseases. Thiamine deficiency could then be a useful model in neurodegeneration.[7,8] Thiamine-dependent processes are critical in glucose metabolism, and recent studies described the role of thiamine in oxidative stress, protein processing, peroxisomal function, and gene expression.[9,10]

Several factors may link thiamine to PD.[11] Decreased activity of thiamine diphosphate-dependent enzymes (mainly α-keto-glutarate dehydrogenase) has been reported in the nigral neurons of patients with PD;[12] this reduction is not related to patient malnutrition.[6,7] Some authors observed lower free thiamine levels in the cerebrospinal fluid of patients with PD compared with controls.[13] Experimental findings showed increased dopamine release in rat striatum after intrastriatal thiamine administration.[14]

In July 2011, we treated a 47-year-old man with spinocerebellar ataxia type 2 (SCA2); in this patient, fatigue as well as motor symptoms improved after parenteral high doses of thiamine.[15] Therefore, we hypothesized 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 dysfunction of intracellular thiamine transport or to structural enzymatic abnormalities. We thought that this dysfunction could be responsive to high-dose thiamine. Furthermore, some reports have shown trinucleotide repeat expansions in the *SCA2* gene in patients with levodopa-responsive parkinsonism.[16] Recently, we observed a considerable improvement of motor and nonmotor symptoms in patients with PD who received intramuscular high-dose thiamine (100 mg) administered twice a week;[17] the clinical improvement was stable over time in all the patients. Therefore, we decided to extend high-dose thiamine treatment to a large series of patients with PD in order to clarify the potential effect of thiamine in this disease.

Materials and Methods

Starting in June 2012, we evaluated 50 consecutive patients with PD who were attending the outpatient movement disorders clinic in the Department of Neurological Rehabilitation of Villa Immacolata Clinic, Viterbo, Italy. PD had been diagnosed according to the UK Parkinson Disease Society Brain Bank Criteria[18] by expert neurologists working in primary Italian neurologic institutes. All the participants provided written informed consent to participate in the study. The ethical committee of our hospital approved the study. Each clinical examination was recorded with a videocamera.

All the patients were evaluated by neurologists expert in movement disorders (A.C. and R.F.) in the morning, during the ''on'' phase, at baseline, 1 month, 3 months, and then every 3 months after the beginning of treatment with thiamine. The examiners used the Unified Parkinson's Disease Rating Scale (UPDRS),[19] parts I–VI, and the Mini-Mental State Examination (MMSE).[20] All the patients were asked whether they experienced fatigue in the weeks before the medical visit; the Fatigue Severity Scale (FSS) was administered to the patients who reported such symptoms.[21] At baseline, all the patients provided a blood sample to dose the plasma level of thiamine, which was measured by using high-performance liquid chromatography.

After baseline evaluation, the patients were continuously treated at their own homes with intramuscular administration of thiamine, 100 mg, twice a week, with no change to personal pharmacologic therapy or rehabilitation program. Thiamine was simply introduced as a possible therapeutic strategy, without emphasis on its potential clinical benefit.

Baseline and follow-up scores at clinical scales for each patient were compared by using a *t* test for paired data; comparisons between data of different subgroups of patients (examined according to age, sex, disease duration, disease stage per Hoehn and Yahr score, and different dopaminergic treatment) were performed with a *t* test for unpaired data. Longitudinal changes in UPDRS score were analyzed by using a panel model (unbalanced population averaged model) to capture both variation over time and variation over patients. Differences with a p-value <0.05 were considered statistically significant. Statistical analyses were performed using STATA13 software (StataCorp. 2013. Stata Statistical Software: Release 13. StataCorp LP, College Station, TX).

Results

The main clinical and demographic characteristics of the patients are reported in Table 1. Detailed data on each patient are displayed in Table 2. Thirty-three patients were male and 17 were female. The mean age (± standard deviation) was 70.4 ± 12.9 years, and the mean disease duration was 7.3 ± 6.7 years. Seven patients were newly diagnosed and drug-naive; the other 43 patients were receiving treatment with dopaminergic drugs (2 with dopamine agonists only, 17 with levodopa only, and 24 with levodopa associated with other antiparkinsonian drugs; see Table 2). According to the date of treatment start and the date of last evaluation, follow-up duration ranged from 95 to 831 days; Table 2 lists UPDRS scores at baseline evaluation and at last follow-up visit of each patient. Basal levels of plasma thiamine were normal in all the patients.

Treatment with thiamine led to significant improvement of motor symptoms: mean UPDRS scores (parts I–IV) improved from 38.55 ± 15.24 to 18.16 ± 15.08 ($p = 2.4 \times 10^{-14}$) within 3 months and remained stable during time. In addition, the scores of each UPDRS subscale improved significantly, as shown in Table 1, particularly the motor subscale, UPDRS part III (from 22.01 ± 8.57 to 9.92 ± 8.66; $p = 3.1 \times 10^{-22}$). (Table 1, Supplementary Fig. S1, Supplementary Fig. S2; Supplementary materials are available online at www.liebertpub.com/acm).

Table 1. Patients' Demographic and Clinical Data at Baseline and During Follow-Up

Variable	*Baseline visit*	*Follow-up visit (month 3)*	p-*Value* (t *test for paired data)*
Total patients (male/female), *n* (*n/n*)	50 (33/17)		
Age (y)	70.4 ± 12.9		
Disease duration (y)	7.3 ± 6.7		
Daily levodopa dose (mg)[a]	539.0 ± 257.0	539.0 ± 257.0	–
UPDRS score			
Part I	1.08 ± 1.81	0.36 ± 0.92	0.0003
Part II	14.46 ± 6.03	7.24 ± 6.17	7.9×10^{-18}
Part III	22.01 ± 8.57	9.92 ± 8.66	3.1×10^{-22}
Part IV	1.00 ± 3.00	0.64 ± 1.90	0.0349
Hoehn and Yahr score (part V)	3.02 ± 0.97	2.18 ± 1.32	5.7×10^{-8}
Schwab and England score (part VI)	66.80 ± 25.75	84.00 ± 21.76	2.9×10^{-13}
Fatigue Severity Scale score[b]	53.00 ± 8.17	23.17 ± 7.03	2.0×10^{-5}

Unless otherwise noted, data are expressed as mean ± standard deviation. All *p*-values denote significant differences.
[a]Mean values were calculated on 43 patients treated with levodopa.
[b]Fatigue Severity Scale was administered to six patients only. See text for details.
UPDRS, Unified Parkinson's Disease Rating Scale.

The Hoehn and Yahr score (UPDRS part V), a disease stage measure, significantly improved from 3.02 ± 0.97 to 2.18 ± 1.32 ($p = 5.7 \times 10^{-8}$); the Schwab and England functional score (UPDRS part VI) significantly improved from 66.80 ± 25.75 to 84.00 ± 21.76 ($p = 2.9 \times 10^{-13}$) (Table 1).

Analysis of scores on different parts of the UPDRS in patients grouped according to age (patients younger versus older than 70 years), to sex (male versus female), and to therapy (patients treated with levodopa versus patients not treated with levodopa) did not show differences: in each analysis, both groups of patients significantly improved during treatment with thiamine (Table 3). The patients were also compared according to disease duration (<7 years versus ≥7 years of disease). Both groups significantly improved (Table 3); the group with longer disease duration improved more than the other group on UPDRS part IV score ($p < 0.001$). Grouping the patients on the basis of Hoehn and Yahr stage (scores of 0–2.5, without postural instability, versus scores of 3–5, with postural instability and progressive impairment) revealed a significant improvement in both subgroups (Table 3). The group of more impaired patients improved more than the other group on UPDRS part II ($p < 0.01$) and part VI ($p < 0.001$). The improvement was also evident in the drug-naive patients ($n = 7$; mean disease duration, 2.7 years [range, 1–5 years]; mean age, 71.7 years [range, 51–77 years]).

Because the patients were evaluated at baseline and 1 month, 3 months, and then every 3 months after the beginning of thiamine treatment, repeated measurements at different time points on the same patient are available. Repeated *t* test for paired data showed significant variations at each visit compared with baseline ($p < 0.001$; data not shown). To analyze longitudinal changes in UPDRS score, we used a panel model that allowed us to capture both variation over time and variation over patients. We applied an unbalanced population-averaged model because the patients were characterized by various treatment periods (from months to years). The results indicated a significant visit effect, which was confirmed after adjustment for disease duration, age, and sex (Table 4).

FSS was administered to six patients who had fatigue as a relevant symptom at baseline (Table 2). In these patients, FSS scores improved from 53.00 ± 8.17 to 23.17 ± 7.03 ($p = 2.0 \times 10^{-5}$) (Table 1).

Three patients with clear symptoms of dementia at baseline showed a basal MMSE score below the normal cutoff of 24 of 30 (Table 2, patients 5, 33, and 35). All three patients had improved cognitive scores at follow-up: from 21 to 29, 18.7 to 21.7, and 16 to 21 of 30, respectively. Psychiatric symptoms, such as hallucinations, did not show significant variations.

No patient receiving levodopa treatment had an increase in daily levodopa dosage; the seven drug-naive patients did not need to begin treatment with levodopa or dopamine agonists. No patients experienced adverse events or discontinued treatment; the only clinical issue to monitor in patients with diabetes treated with insulin was the slightly increase of glycemia levels and subsequent increased insulin dosage.

Discussion

The results of our study showed a markedly positive response to thiamine administration in patients with PD: parenteral high doses of thiamine were effective in reversing motor and nonmotor symptoms, as shown by UPDRS scores, suggesting that the abnormalities in thiamine-dependent processes could be overcome by diffusion-mediated transport at supranormal thiamine concentrations.

Compared with other currently available therapies, treatment with thiamine was associated with a similar improvement in motor functions, as assessed by reduction in UPDRS scores.[1,5] Responsiveness to levodopa is a diagnostic criterion for PD: the reduction in the UPDRS motor score must exceed 30%.[5] In our patients treated with thiamine, we observed a mean improvement in UPDRS part III of 59.61% ± 23.63%. This clinical improvement was stable over time in all the patients, who did not show impairment of motor performances even after 2 years of follow-up. Furthermore, six patients with milder motor phenotype who received dopaminergic therapy had complete clinical recovery. The improvement was significant in all patient subgroups, without differences for age, sex, disease duration, type of current

Table 2. Clinical Data for Each Patient at Baseline and During Follow-Up

Pt no.	*Sex*	*Age (y)*	*Disease duration (y)*	*Follow-up duration (d)*	*Baseline scores*[a]							*Follow-up scores*[a,b]							*Daily levodopa (mg)*	*Other antiparkinsonian drugs*[c]	*Diagnostic brain neuroimaging*
					I	*II*	*III*	*IV*	*V*	*VI*	*FSS*	*I*	*II*	*III*	*IV*	*V*	*VI*	*FSS*			
1	M	76	5	831	0	8	20	0	2.5	80	–	0	0	0	0	0	100	–	400	Ras1	MRI
2	M	58	10	818	0	12	17	0	3	80	–	0	0	0	0	0	100	–	450	Pr2.62, E600, Ras1	MRI, DaTscan™
3	M	87	12	725	0	17	23	0	2.5	80	–	0	4	7	0	2	90	–	600	Rot8	CT
4	M	78	21	713	3	14	23	9	2.5	80	–	2	10	12	6	2	80	–	1000	Rop8, E800	MRI
5	M	73	5	712	5	18	25	0	4	50	–	1	3	9	0	2	80	–	600	None	MRI
6	F	81	4	668	0	14	20	0	3	70	37	0	0	0	0	0	100	11	300	Pr1.57	MRI
7	M	80	13	642	0	22	30	0	2.5	70	–	0	10	12	0	2	90	–	800	Rot8, Am100	MRI
8	M	72	9	543	0	9	17	0	2.5	90	–	0	4	6	0	2	100	–	300	Rop8	MRI
9	M	86	21	542	0	20	18	11	4	50	57	0	9	11	8	2	80	30	1100	E1000, Rop4, Ras1	MRI
10	M	73	5	521	0	9	17	0	2.5	80	–	0	0	0	0	0	100	–	400	Pr2.1	MRI
11	M	82	5	521	0	12	19	0	2.5	80	–	0	2	6	0	2	100	–	400	None	MRI
12	F	67	6	503	0	24	33	3	4	40	56	0	9	9	3	2	80	23	500	Rop8	MRI
13	M	51	1	493	0	3	10	0	1.5	100	–	0	0	1	0	1	100	–	0	None	MRI, DaTscan™
14	M	79	4	479	3	15	23	0	2.5	80	–	2	9	15	0	2.5	80	–	600	E600, Rot16	CT
15	F	79	4	458	7	15	23	0	3	70	59	2	7	9	0	2.5	80	21	800	None	CT
16	F	75	2	451	2	19	35	0	3	60	57	0	5	16	0	2	80	30	350	Pr0.26	MRI
17	M	79	6	418	0	18	33	0	3	70	–	0	4	9	0	2	100	–	400	None	MRI
18	M	48	8	355	0	29	36	0	5	10	–	0	21	30	0	5	20	–	700	None	MRI
19	M	74	34	333	0	17	21	11	3	80	–	0	8	7	7	2.5	90	–	1300	Rop16, Am300	MRI
20	M	63	3	332	0	11	18	0	1.5	90	–	0	2	4	0	1	100	–	0	None	CT
21	F	74	15	311	3	11	13	0	2	90	–	2	5	5	0	2	90	–	500	Pr2.1	CT
22	F	64	5	299	2	13	17	0	2.5	70	52	0	5	3	0	2	100	24	500	E600, Rot8	MRI, DaTscan™
23	M	77	2	294	4	10	20	0	2.5	70	–	2	6	12	0	2.5	80	–	600	None	MRI
24	M	71	6	265	0	12	17	0	2.5	60	–	0	5	6	0	2.5	90	–	300	None	MRI
25	M	79	5	265	0	12	17	0	2.5	60	–	0	5	7	0	2.5	90	–	150	None	CT
26	F	83	6	262	5	30	39	0	5	10	–	5	30	38	0	5	10	–	600	E600, Pr0.52	MRI
27	F	69	2	259	0	7	15	0	2.5	90	–	0	4	10	0	2	90	–	400	None	MRI
28	F	79	5	249	0	21	27	0	4	30	–	0	15	16	0	4	70	–	0	None	MRI

(*continued*)

TABLE 2. (CONTINUED)

Pt no.	Sex	Age (y)	Disease duration (y)	Follow-up duration (d)	Baseline scores[a]							Follow-up scores[a,b]							Daily levodopa (mg)	Other antiparkinsonian drugs[c]	Diagnostic brain neuroimaging
					I	II	III	IV	V	VI	FSS	I	II	III	IV	V	VI	FSS			
29	M	73	9	242	2	23	46	0	5	10	–	0	22	35	0	5	20	–	500	E1000	MRI
30	M	59	2	217	1	7	16	0	2.5	90	–	0	1	3	0	1	100	–	300	Pr2.1	DaTscan™
31	F	56	7	215	0	10	12	0	3	90	–	0	6	8	0	3	100	–	0	Pr3.15, Bip4, Ras1	CT
32	M	68	10	213	1	17	28	0	4	40	–	0	10	14	0	4	70	–	800	Ras1	MRI
33	M	77	2	189	3	13	22	0	2.5	50	–	1	11	6.5	0	2.5	70	–	500	None	CT
34	M	58	25	187	0	17	18	0	2.5	70	–	0	14	11	0	2.5	80	–	600	Rot8	MRI
35	M	88	5	175	6	24	37	0	5	20	–	1	14	26	0	4	50	–	400	None	CT
36	F	83	6	173	2	21	35	0	5	10	–	0	11	25	0	4	50	–	500	None	MRI
37	F	75	15	166	0	17	31	12	5	20	–	0	11	11	6	2.5	70	–	1100	None	MRI
38	M	38	6	165	0	4	7	0	2.5	100	–	0	0	0	0	0	100	–	600	Rop12	MRI
39	M	70	15	160	0	11	14	4	2.5	90	–	0	9	8	2	2.5	100	–	750	Pr2.1	MRI
40	M	72	10	153	0	21	37	0	5	40	–	0	14	24	0	5	60	–	400	None	MRI
41	M	20	2	153	2	15	18	0	2.5	90	–	0	9	11	0	2	100	–	150	Pr1.05	MRI, DaTscan™
42	F	82	3	150	0	12	19.5	0	3	70	–	0	3	6	0	2	100	–	0	None	MRI
43	M	50	3	147	0	20	21	0	2	60	–	0	12	8.5	0	1	80	–	300	None	MRI, DaTscan™
44	F	60	8	144	0	9	15	0	2.5	80	–	0	9	8	0	2.5	90	–	600	Rop12	MRI
45	F	68	3	144	3	7	10	0	2.5	90	–	0	0	0	0	0	100	–	300	None	MRI
46	F	64	2	139	0	10	18	0	2.5	80	–	0	3	7	0	2	100	–	250	None	MRI
47	M	77	2	129	0	12	14	0	3	90	–	0	5	7	0	3	100	–	0	None	MRI
48	F	75	1	111	0	7	16	0	2.5	90	–	0	4	6	0	1	100	–	0	Pr2.1, Bip4	MRI
49	M	74	3	103	0	10	16	0	2.5	90	–	0	2	2	0	1	100	–	0	None	MRI, DaTscan™
50	M	77	2	95	0	14	24	0	2	80	–	0	10	9	0	1.5	90	–	0	None	MRI

[a]I, II, III, IV, V, and VI indicate parts of Unified Parkinson's Disease Rating Scale (UPDRS).
[b]"Follow-up score" refers to the score at the last follow-up visit for each patient (see "Follow-up duration" column).
[c]Daily doses are expressed in milligrams.
FSS, Fatigue Severity Scale; M, male; Ras, rasagiline; MRI, magnetic resonance imaging; Pr, pramipexole; E, entacapone; Rot, rotigotine; CT, computed tomography; Rop, ropinirole; F, female; Am, amantadine; Bip, biperidene.

Table 3. Improvement in UPDRS Scores in Patient Subgroups

Variable	Patients (n)	UPDRS variations: baseline score – follow-up score[a]					
		I	*II*	*III*	*IV*	*V*	*VI*
Age							
<70 y	17	0.53 ± 0.94	6.47 ± 3.61	10.68 ± 5.10	0.00 ± 0.00	0.91 ± 1.00	−14.12 ± 11.21
≥70 y	33	0.82 ± 1.45	7.61 ± 3.97	12.82 ± 4.89	0.55 ± 1.42	0.80 ± 0.90	−18.79 ± 12.69
Sex							
Male	33	0.64 ± 1.22	7.30 ± 3.57	12.21 ± 4.37	0.36 ± 1.03	0.77 ± 0.90	−15.45 ± 9.71
Female	17	0.88 ± 1.45	7.06 ± 4.46	11.85 ± 6.22	0.35 ± 1.46	0.97 ± 0.99	−20.59 ± 16.00
Treatment							
With levodopa	41	0.88 ± 1.38	7.51 ± 4.06	12.37 ± 5.26	0.44 ± 1.29	0.89 ± 0.98	−17.80 ± 12.35
Without levodopa	9	0.00 ± 0.00	5.89 ± 2.47	10.83 ± 3.71	0.00 ± 0.00	0.61 ± 0.60	−14.44 ± 12.36
Treatment status							
Drug-naive	7	0.00 ± 0.00	6.57 ± 2.37	11.93 ± 3.01	0.00 ± 0.00	0.57 ± 0.53	−15.71 ± 13.97
Treated	43	0.84 ± 1.36	7.33 ± 4.05	12.12 ± 5.30	0.42 ± 1.26	0.88 ± 0.97	−17.44 ± 12.17
Disease duration							
<7 y	33	0.94 ± 1.50	7.61 ± 3.79	12.56 ± 5.13	0.00 ± 0.00[b]	0.97 ± 0.90	−18.18 ± 12.36
≥7 y	17	0.29 ± 0.59	6.47 ± 3.97	11.18 ± 4.80	1.06 ± 1.85[b]	0.59 ± 0.96	−15.29 ± 12.31
Hoehn and Yahr score							
0–2.5	29	0.52 ± 0.87	6.00 ± 3.05[c]	11.31 ± 3.88	0.17 ± 0.66	0.74 ± 0.84	−12.41 ± 9.12[d]
3–5	21	1.00 ± 1.70	8.90 ± 4.27[c]	13.17 ± 6.21	0.62 ± 1.63	0.98 ± 1.04	−23.81 ± 13.22[d]

[a]Each cell represents positive clinical variation (expressed as mean ± standard deviation) between baseline score and follow-up score in each subpart of UPDRS scale, in different subgroups of patients according to age, sex, treatment with or without levodopa, disease duration, and Hoehn and Yahr disease stage. ''Follow-up score'' refers to the score at the last follow-up visit for each patient (see ''Follow-up duration'' column in Table 2). Each subgroup of patients improved significantly during treatment in each UPDRS part (see text); further significant differences between subgroups are indicated according to footnotes b, c, and d.

[b]The subgroup with longer disease duration improved more than the subgroup with shorter disease duration on UPDRS part IV ($p = 0.002$, t test for unpaired data).

[c]The subgroup of more impaired patients according to Hoehn and Yahr stage (3–5) improved more than the other group on UPDRS part II ($p = 0.007$, t test for unpaired data).

[d]The subgroup of more impaired patients according to Hoehn and Yahr stage (3–5) improved more than the other group on UPDRS part VI ($p = 0.001$, t test for unpaired data).

dopaminergic treatment, or degree of functional disability according to Hoehn and Yahr stage. We also observed improvement in fatigue and cognitive status (as nonmotor symptoms). The improvement was also evident in the drug-naive patients. We cannot exclude the possibility that these patients may evolve differently (e.g., versus atypical parkinsonism). However, some of these patients were not newly diagnosed, and all of them improved with thiamine treatment, with no differences between this subgroup and the remaining treated patients.

We suppose that the improvement of the energetic metabolism of the survivor neurons in the substantia nigra, due to high doses of thiamine, could lead to increased synthesis and release of the endogenous dopamine, increased activity of thiamine-dependent enzymes, or better utilization of exogenous levodopa.[11–14,17,22,23]

The absence of blood thiamine deficiency at baseline and the efficacy of continuous treatment with high doses of thiamine in our patients may indicate that PD symptoms are the manifestation of neuronal thiamine deficiency, probably due to dysfunction of the active intracellular transport of thiamine or to structural enzymatic abnormalities. We hypothesize that motor and nonmotor symptoms of PD could derive from a chronic intracellular thiamine deficiency, characterized by the following: (1) a severe and focal thiamine deficiency in the substantia nigra pars compacta and in other centers that are typically involved in PD, which could determine a progressive dysfunction and selective neuronal

Table 4. Difference in UPDRS Scores at Follow-Up Visits Compared with Baseline Visit, Controlled for Disease Duration, Age, and Sex

Visit (mo)	UPDRS part II (95% confidence interval)	p-Value	UPDRS part III (95% confidence interval)	p-Value
3	−7.22 (−8.10 to −6.34)	0.000	−12.09 (−13.55 to −10.63)	0.000
6	−6.95 (−7.89 to −6.01)	0.000	−11.85 (−13.42 to −10.27)	0.000
9	−7.32 (−8.38 to −6.26)	0.000	−12.15 (−13.93 to −10.36)	0.000
12	−7.92 (−9.14 to −6.70)	0.000	−12.86 (−14.92 to −10.81)	0.000
15	−8.15 (−9.48 to −6.82)	0.000	−12.90 (−15.14 to −10.66)	0.000
18	−8.08 (−9.63 to −6.53)	0.000	−13.25 (−15.86 to −10.65)	0.000
21	−8.06 (−9.93 to −6.18)	0.000	−13.55 (−16.70 to −10.40)	0.000
24	−8.18 (−10.36 to −6.00)	0.000	−13.44 (−17.09 to −9.78)	0.000
27	−8.02 (−11.36 to −4.69)	0.000	−13.64 (−19.22 to −8.05)	0.000

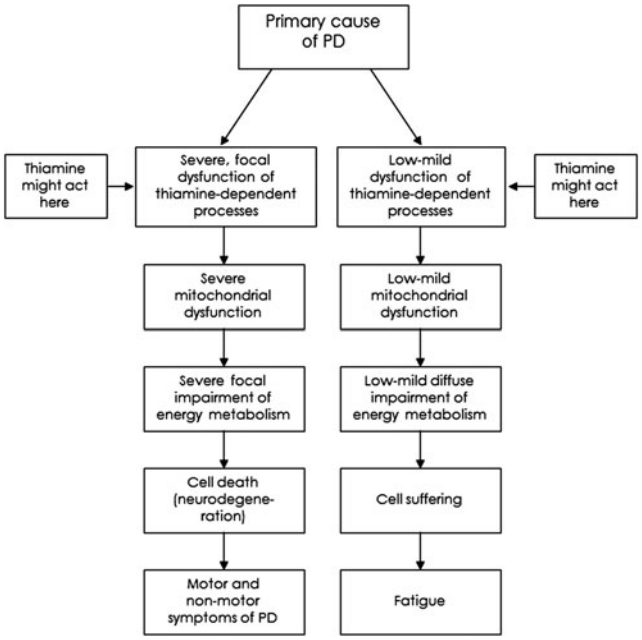

FIG. 1. Suggested pathogenetic mechanisms of thiamine deficiency in Parkinson disease (PD).

loss, and (2) a mild thiamine deficiency in all other cells, which could determine cell suffering (Fig. 1).

Previous experiments suggest that thiamine deficiency reduces the activity of thiamine-dependent enzymes (e.g., α-keto-glutarate dehydrogenase) with regional selectivity because different cerebral areas are affected by different degrees of severity.[24] Thus, the primary cause of PD could be clearly expressed in dopaminergic cells, causing severe thiamine deficiency and motor symptoms, and less expressed in all other cells, causing mild thiamine deficiency, central fatigue, and related disorders.[15,24,25] Fatigue could then be considered a systemic symptom of the disease.

The precise role played by thiamine in PD pathogenesis has not previously been extensively investigated. Some authors found selective loss of mitochondrial complex I and α-ketoglutarate dehydrogenase complex in the nigral neurons of patients with PD.[12,23,26] Reduction in brain glucose metabolism and oxidative stress occurs in PD. Thiamine-dependent processes are critical in glucose metabolism, and recent studies implicate thiamine in oxidative stress, protein processing, peroxisomal function, and gene expression.[8,27,28]

An interesting study about an α-synuclein fission yeast model found that thiamine lowers α-synuclein expression in a dose-dependent manner and that *A53T*-mutated α-synuclein aggregates at lower concentrations than wild-type α-synuclein. These data suggest that an increase of intracellular thiamine could reduce α-synuclein concentration and then α-synuclein aggregation.[28]

Moreover, a dysfunction of intracellular thiamine transport has been described in genetic diseases characterized by mutations in thiamine-transporters genes. Several inborn errors of metabolism have been described, in which clinical improvements were documented after administration of pharmacologic doses of thiamine, such as Wernicke-like encephalopathy.[9,29] Genetic disorders of thiamine metabolism that lead to neurologic diseases can be treated with large doses of thiamine.[15,29,30] The exact mechanism of thiamine responsiveness in these patients is still unknown.

Our study has several limitations, the most relevant being the absence of a placebo-controlled group. Although placebo interventions in PD may have immediate subjective improvement but no significant objective motor changes compared with levodopa,[31] and although clinical improvement of our patients has been continuous and stable for a long period of follow-up (>2 years), the lack of a placebo group makes these results preliminary and to be interpreted carefully.[32] Another issue is the possibility of selection, information, and observational biases. We tried to eliminate selection bias, including all the consecutive patients with PD we visited in our department, and we diminished information bias by introducing thiamine treatment without a discussion about its potential to have a positive influence. Observational bias was more difficult to reduce because of the open-label trial design; we obtained video recordings for each examination to re-evaluate the patients, and we extended as long as possible the follow-up visits to reduce this bias in multiple observations. We are planning to organize a placebo-controlled trial in order to verify our preliminary observations, but we are also confident that these results represent a significant contribution to the issue of PD treatment.

Administration of high doses of thiamine to patients with PD was effective in reversing all parkinsonian symptoms; we propose that parenteral thiamine supplementation may play an important role in restoring survivor neurons and in limiting the disease progression and that the dysfunction of thiamine-dependent processes could be a primary pathogenic pathway leading to the death of dopaminergic and non-dopaminergic neurons in PD (Fig. 1).[33] We propose a neuroprotective effect of thiamine because of long-lasting results and stability of clinical conditions in patients affected by this slow and progressive neurodegenerative disease.

Long-term treatment with thiamine, as demonstrated in our study, is also safe; we did not observe any adverse events (except for the need to monitor glycemia and adjust insulin dosage). The literature does not mention thiamine-related adverse effects even at high doses and over very long periods of administration.[34,35]

Moreover, the thiamine-dependent processes are impaired in cerebral tissues of patients with several neurodegenerative diseases, and activity reduction of thiamine-dependent enzymes can be readily linked to symptoms and pathology of the disorders. Most neurodegenerative diseases share similarities and could be responsive to high doses of thiamine.[8,9,35,36]

In conclusion, long-term intramuscular treatment with thiamine led to improvement of motor and nonmotor symptoms in patients with PD; this improvement was stable over time and was not associated with adverse effects. Our report represents an important contribution to PD therapy, but further experience is necessary to exclude a placebo effect and to confirm the present observation with clinical, cellular, and molecular data.

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Author Disclosure Statement

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Address correspondence to:
Antonio Costantini, MD
Department of Neurological Rehabilitation
Villa Immacolata Clinic
Strada Sammartinese 65A
01100 Viterbo
Italy

E-mail: carapetata@libero.it