CASE REPORT

High-dose thiamine and essential tremor

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SUMMARY

Essential tremor is a common neurological disease. The medical treatment of this affection currently involves the use of propranolol, primidone and other drugs. These drugs, however, are often not effective in reducing tremor and cause side effects in a large share of the patients treated. The treatment with intramuscular high-dose thiamine has led to a rapid, remarkable and persistent improvement of the symptoms in two patients with essential tremor. This result suggests the possibility that high doses of intramuscular thiamine may be an affordable alternative, highly effective and long-lasting medical treatment that has shown no relevant side effect.

BACKGROUND

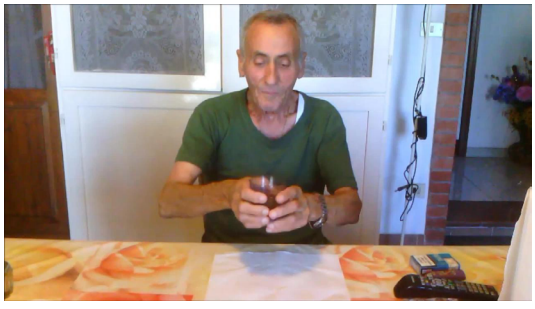
Essential tremor (ET) is a common movement disorder. It is characterised by a postural and kinetic tremor of the arms and other parts of the body; its progression is slow but can lead to an impairment of the activities the patient plays in a typical day at home and at work.[1] The primary cause and the pathogenesis of the symptoms are unknown.

The prevalent involvement seems to be the cerebellar one. It is accompanied by a dysfunction of cerebellar-thalamic-cortical circuits.[2]

The various symptomatic therapies available (eg, propranolol, primidone, and so on) are not always effective and often give side effects which require some adjustments to the treatment or its interruption.[3]

No biochemical studies on the carbohydrate metabolism of neurons affected by the disease are reported in literature. However, studies conducted with F-18-fluorodeoxyglucose-positron emission tomography have found a glucose hypometabolism in the centres whose dysfunction causes the ET.[4 5]

It is well established that thiamine plays a key role in the glucose metabolism, in maintaining brain functions and that thiamine deficiency (TD) causes beriberi and Wernicke-Korsakoff syndrome. Recent studies have found that thiamine is implicated in oxidative stress, peroxisomal function, protein processing, gene expression and calcium-dependent processes.[6 7]



Video 1 Patient 1 before the therapy

Video 2 Patient 2 before the therapy

In the hypothesis that glucose hypometabolism was due to a dysfunction of thiamine-dependent processes, and that energetic hypometabolism would play an important role in the pathogenesis of the symptoms, we treated two patients affected by ET with intramuscular high-dose thiamine.[8]

Patients have signed a consent both to start the treatment and to publish its results. Video recordings documenting the experience are attached to this study.

CASE PRESENTATION

The diagnosis of ET is based on clinical history and physical examination.

Starting in 2014, we evaluated and treated with intramuscular high-dose thiamine some patients affected by ET. ET had been diagnosed by expert neurologists according to diagnostic criteria for ET described by Deuschl *et al* in 1998.[9] The first in time two patients we treated are the subjects of this study. None of the patients had ever been treated with the symptomatic therapies available.

We evaluated the patients with The Essential Tremor Rating Assessment Scale (TETRAS).[10]

TETRAS is composed of two subscales: Activities of Daily Living Subscale (ADLS) and the Performance Subscale (PS) (see table 1).

The patients were evaluated before the beginning of the treatment. Evaluation was only clinical. The follow-ups have been performed 3 months after the beginning of the treatment.

Patient 1. Male, 73 years old, with a weight of 68 kg, affected by diabetes mellitus (in treatment with the oral antidiabetic metformin 500 mg twice a day) for some 10 years. The tremor started at the age of 68 with slight right-hand tremor, with difficulty in the handwriting. Later on, also his head and

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Table 1 Activities of Daily Living Subscale

Scoring 0–4 (absence—strong impairment)	Patient 1 before	Patient 1 after	Patient 2 before	Patient 2 after
1. Speaking	0	0	0	0
2. Feeding with a spoon	2	1	2	0.5
3. Drinking from a glass	3	1	2	0.5
4. Hygiene	1	0.5	1	0.5
5. Dressing	1	0.5	1	0.5
6. Pouring	2	1	2	1
7. Carrying food trays, plate or similar items	2	1	1	0.5
8. Using keys	1	0	1	0
9. Writing	1	0	2	0.5
10. Working	1	0.5	3	1
11. Overall disability with the most affected task	2	1	3	1
12. Social impact	1	0	3	1
Total score (max 48)	17	6.5	21	7

left hand presented postural and kinetic tremor. Tremor slowly increased in intensity in the following 2 years. The patient, at the end of August 2014, at the age of 70, started treatment with an intramuscular injection of 100 mg of thiamine twice a week. No family member was ever affected by the same pathology. Neurological examination was normal except for the postural and kinetic tremor of the head and hands. Common biochemical and haematological investigations were normal. Plasmatic thiamine level was 80 mg/L (normal values 28–85 mg/L). Video 1 shows patient 1 before the therapy.

The ADLS score was 17 points, PS score was 19.5 points (see table 1).

Patient 2. Female, 75 years old, with a weight of 70 kg, no other diseases reported. The postural and kinetic tremor started at the age of 69. She realised that, while decorating objects with tools, her right hand had a very fine tremor. Afterwards she began to have growing difficulties in her decorating work. The patient, at the end of November 2014, at the age of 72, started treatment with an intramuscular injection of 100 mg of thiamine twice a week. There was no case of ET in her family history. Neurological examination was normal except for the postural and kinetic tremor of the head and hands. Common biochemical and haematological investigations were normal. Plasmatic thiamine level was 73 mg/L (normal values 28–85). Video 2 shows patient 2 before the therapy.

Video 3 Patient 1 after therapy

ADLS score was 21 points (table 1), PS score was 17 points (table 2).

OUTCOME AND FOLLOW-UP

Both patients began to show an appreciable improvement of the tremor with the first injections. The decrease in tremor continued for about 2 months and then stabilised. After 3 months from the beginning of the therapy, we examined the patients again and repeated the same tests.

The patients had a remarkable improvement of tremor.

A set of video recordings was performed to track such improvement:

Patient 1 after the therapy (video 3)

Patient 1 two years after the therapy (video 4)

Patient 1 three years after the therapy (video 5)

Patient 2 after the therapy (video 6)

The improvement is also confirmed by the scale scores:

Patient 1. The ADLS score was 6.5 points (61.8% improvement) (table 1); PS score was 6.5 points (66.8% improvement) (table 2).

Patient 2 showed a similar improvement of TETRAS:

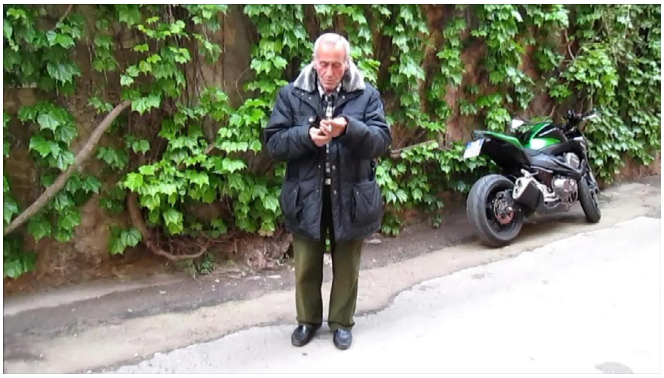
ADLS score was 7 points (66.7% improvement) (table 1); PS score was 6.5 points (61.8% improvement) (table 2).

DISCUSSION

With intramuscular administration of thiamine, patients showed significant improvement of the symptoms of ET. It is common

Table 2 Performance Subscale

Scoring is 0–4 (absence—strong tremor)	Patient 1 before		Patient 1 after		Patient 2 before		Patient 2 after	
1. Head tremor	2	0.5	2	0				
2. Face (including jaw) tremor	0	0	0	0				
3. Voice tremor	0	0	0	0				
4. Upper limb tremor	Right	Left	Right	Left	Right	Left	Right	Left
4.1. Forward outstretched postural tremor	2.5	1.5	1.5	0	2.5	0.5	1.5	0
4.2. Lateral 'wing beating' postural tremor	2.5	1.5	1.5	0	2.5	0.5	1.5	0
4.3. Kinetic tremor	2.5	1.5	1.5	0	2.5	0.5	1.5	0
5. Lower limb tremor	0	0	0	0				
6. Archimedes spirals	2		1		2		1	
7. Handwriting	1	0	2	0.5				
8. Dot approximation task	1.5	1	0.5	0	1.5	0.5	0.5	0
9. Standing tremor	0	0	0	0				
Total score (max 64)	19.5	6.5	17	6.5				



Video 4 Patient 1 two years after therapy

Video 6 Patient 2 after therapy

evidence that in the presence of TD the patient's response to therapy is diagnostic.[11] The intramuscular high-dose thiamine, through passive diffusion transport, by increasing the concentration of the molecule within the cells, seems to restore the function of thiamine-dependent mechanisms in the centres responsible for motor dysfunction resulting in improvements of the tremor. Enzymatic abnormalities or dysfunction of the circulation of thiamine in the intracellular space may cause intracellular TD with normal plasma values.[12] It is worth mentioning that being metformin an inhibitor of the human thiamine transporter, THTR-2 (SLC19A3), this drug may be the cause of TD with normal blood thiamine.[13–15] The perturbed intracellular transport of thiamine due to metformin treatment may play a role in the genesis of the thiamine-responsive ET in patient 1. We could not measure the intracellular levels of erythrocytic transketolase activity without and with thiamine diphosphate because such test is not available in Italy. Such an exam would indeed be a useful aid to study the intracellular TD.

Our clinical observation led to suppose that symptoms featuring ET could derive from a focal, intracellular TD that determines a selective neuronal dysfunction. In other words, TD could have an important role in the pathogenesis of the symptoms of ET. The administration of large quantities of intramuscular vitamin B1 increases the intracellular passive transport of the thiamine and symptoms decrease when the glucose metabolism and other thiamine-dependent processes are led back to physiologic levels.

Disorders of thiamine transporter genes that lead to neurological damage can be treated with high-dose thiamine.[12 16] Recently, some authors achieved good results in sporadic degenerative diseases with the same treatment.[17] The exact mechanism of thiamine responsiveness in these patients is unknown. The patients reported an improvement of the symptoms. As we are writing this report (about 3 years have passed since the beginning of the treatment), they are continuing the same therapy and still have the same improved motor conditions, without any side effect. Thus, it seems that the therapy may play an important role in limiting the progression of the disease and we deem necessary a lifelong use of high-dose thiamine in affected subjects. No side effects have been reported in patients treated with high doses of thiamine, without interruption, even for years.[17 18]

In conclusion, we hope that this report raises interest in the scientific community and leads to other studies that can confirm the present observation.

Video 5 Patient 1 three years after therapy

Learning points

- Intramuscular administration of thiamine appears to be highly effective for the treatment of essential tremor.
- Metformin can cause thiamine deficiency.
- The use of thiamine is also safe for prolonged treatments over time.
- The improvement of the symptoms, while continuing the treatment, persists over time. Thiamine could have a restorative and neuroprotective effect on the neurons of affected nerve centres.

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