Can long-term thiamine treatment improve the clinical outcomes of myotonic dystrophy type 1?

Antonio Costantini1,2,*, Erika Trevi1, Maria Immacolata Pala3, Roberto Fancellu1

1 Department of Neurological Rehabilitation, “Villa Immacolata” Clinic, Viterbo, Italy
2 School of Physiotherapy, Catholic University of Rome, Rome, Italy
3 Neurology Unit, IRCCS San Martino University Hospital IST, Genoa, Italy

How to cite this article: Costantini A, Trevi E, Pala MI, Fancellu R (2016) Can long-term thiamine treatment improve the clinical outcomes of myotonic dystrophy type 1? Neural Regen Res 11(9):1487-1491.

Abstract

Myotonic dystrophy type 1, also known as Steinert’s disease, is an autosomal dominant disorder with multisystemic clinical features affecting the skeletal and cardiac muscles, the eyes, and the endocrine system. Thiamine (vitamin B1) is a cofactor of fundamental enzymes involved in the energetic cell metabolism; recent studies described its role in oxidative stress, protein processing, peroxisomal function, and gene expression. Thiamine deficiency is critical mainly in the central and peripheral nervous system, as well as in the muscular cells. Our aim was to investigate the potential therapeutic effects of long-term treatment with thiamine in myotonic dystrophy type 1 in an observational open-label pilot study. We described two patients with myotonic dystrophy type 1 treated with intramuscular thiamine 100 mg twice a week for 12 or 11 months. We evaluated the patients using the grading of muscle strength according to Medical Research Council (MRC), the Muscular Impairment Rating Scale (MIRS), and the Modified Barthel index. High-dose thiamine treatment was well tolerated and effective in improving the motor symptomatology, particularly the muscle strength evaluated with the MRC scale, and the patients’ activities of daily living using the Modified Barthel Index. At the end of treatment, the MRC score was 5 in the proximal muscles and 2–4 in the distal muscles (the MRC score before the treatment was 3–4 and 1–3, respectively). The MIRS grade improved by 25% compared to baseline for both patients. In patient #1, the Modified Barthel Index improved by 44%, and in patient #2 by 29%. These findings suggest that clinical outcomes are improved by long-term thiamine treatment.

Key Words: nerve regeneration; myotonic dystrophy type 1; thiamine; Steinert’s disease; muscular strength; activity of daily living; neural regeneration

Introduction

Myotonic dystrophy type 1 (DM1, Steinert’s disease) is an autosomal dominant inherited disorder with multisystemic clinical features affecting the skeletal muscles, the heart, the ocular and the endocrine systems. DM1 is caused by mutations in the dystrophia myotonica protein kinase (DMPK) gene, located on chromosome 19 in position q13.32; the mutation is usually characterized by high cytosine-thymine-guanine (CTG) triplet repeat within the gene. The DMPK gene encodes for a protein called DMPK (Meola and Cardani, 2015). DMPK is part of a mitochondrial multi-molecular complex with antioxidant and pro-survival properties. The specific functions of this protein are partially known: it is involved in the cell shape determination, the regulation of actin-myosin contractility, the activity modulation of the voltage-gated ion channels, the calcium homeostasis control, and the nuclear envelope stability (Kaminsky et al., 1993; Oude Ophuis et al., 2009; Pantic et al., 2013; Meola and Cardani, 2015). Recent evidence suggests that calcium dysregulation is a pivotal event in the pathophysiology of several muscular dystrophies (Vallejo-Illarramendi et al., 2014). The current therapy for DM1 is only symptomatic and aims to correct the hormonal and glycermic balance, removing the cataract, preventing the respiratory failure and, above all, cardiac disturbances (Romeo, 2012). Effective therapies targeted at the pathogenetic mechanism of DM1 are not available yet.

Thiamine (vitamin B1) is a cofactor of enzymes involved in fundamental pathways of the energetic cell metabolism, especially in the metabolism of glucose (transketolase, alpha-keto-acid deoxcarboxylase, piruvate dehydrogenase, alpha-keto-glutarate dehydrogenase). Thiamine plays a relevant role in oxidative stress, protein processing, peroxisomal function, calcium store control, and in gene expression. In fact, recent studies suggest that thiamine has also non-enzymatic roles, potentially relevant in neuroprotection processes (Lonsdale, 2006, 2015; Huang et al., 2014; Mkrtchyan et al., 2015). Thiamine deficiency is usually a complication of severe malnutrition, and frequently causes Wernicke-Korsakoff encephalopathy, a subacute neurologic disorder characterized by ophthalmoplegia, gait ataxia, confusion, and memory loss (Butterworth, 2003). The pathophysiology of thiamine deficiency is multifactorial and involves several events, including reduced activity of alpha-keto-glutarate dehydrogenase, impaired oxidative metabolism, increased oxidative stress, and selective neuronal loss in specific brain regions. These processes lead to focal neuronal cell death and are also reported among the pathological mechanisms involved in different
neurodegenerative diseases. The dynamics of thiamine deficiency may constitute a useful model for the study of neurodegeneration (Butterworth, 2003; Jhala and Hazell, 2011).

Some findings suggest that in some inherited and degenerative diseases of the nervous system, including some triplet repeat expansion diseases, the pathophysiology could be partly related to a selective thiamine deficiency due to dysfunction of the intracellular thiamine transport or to structural enzymatic abnormalities (Butterworth, 2003; Jhala and Hazell, 2011; Costantini et al., 2013, 2016; Mkrtchyan et al., 2015). We supposed that this dysfunction could be responsive to the administration of thiamine.

Thiamine deficiency may contribute to myocardial weakness by limiting the energy available for cardiac muscle contraction (Ahmed et al., 2015), while the degree of phosphorylation of thiamine derivatives tends to be lower in patients suffering from cardiac insufficiency (Gangolf et al., 2010). In cellular and animal studies, thiamine deficiency causes cardiac structural changes (Zangen and Shainberg, 2007; Roman-Campos et al., 2009; Santos-Miranda et al., 2015). Furthermore, experimental data show that thiamine levels in humans are diffusely low in several tissues and are particularly reduced in heart cells and skeletal muscle cells (Gangolf et al., 2010). These data may explain the high sensitivity of humans to thiamine deficiency. Finally, in an animal study, thiamine deficiency caused atrophy and necrosis of skeletal muscle fibers (Juntunen et al., 1979).

Therefore, we decided to treat two DM1 patients with long-term high-dose thiamine, in order to clarify the potential thiamine effect in the treatment of this disease.

Patients and Methods

We evaluated two outpatient women (mother and daughter) affected by DM1, who received treatment in the Department of Neurological Rehabilitation of "Villa Immacolata" Clinic in Viterbo, Italy. The diagnosis of DM1 was based on the clinical history, the physical examination, the neurophysiological study, and the molecular genetic test detecting high CTG triplet expansion in DMPK gene (19q13.32). The common biochemical and hematological investigations showed that blood thiamine levels were normal.

We assessed muscular strength according to the grading system recommended by the Medical Research Council (MRC) (Medical Research Council, 1981). MRC score is an extensively used six-point rating scale; briefly, the strength of each muscle is evaluated and scored (0: no contraction; 1: minimal contraction; 2: active movement with gravity eliminated; 3: active movement against gravity; 4: active movement against gravity and moderate resistance; 5: normal strength).

We also evaluated the patients with a specific scale for DM1, the Muscular Impairment Rating Scale (MIRS) (Mathieu et al., 2001). The MIRS was established in accordance with the clinically recognized distal to proximal progression of the muscular involvement in DM1, based partly on a manual muscle testing of 11 muscle groups. It is an ordinal five-point rating scale (1: no muscular impairment; 2: minimal signs of myotonia; 3: distal weakness; 4: mild to moderate proximal weakness; 5: severe (MRC scale < 3/5) proximal weakness). The MIRS is a quick, simple, and reliable measurement of muscular impairment in DM1.

Moreover, in order to assess the functional activity in daily life, we determined the Modified Barthel Index (MBI) (Shah and Cooper, 1991). MBI is a widely used scale measuring the functional independence in the activities of the daily life. Ten domains (feeding, bathing, personal toilet, dressing, bowel control, bladder control, toilet transfers, chair-bed transfers, ambulation, stair climbing) are explored and scored according to the level of independence in each specific activity (in Table 1, the minimum and maximum scores for each item are indicated). The sum of item scores is the MBI, ranging from 0 (total dependence) to 100 (full independence).

Two examiners (AC and ET) evaluated together both patients at each examination. The participants signed an informed consent to begin thiamine therapy and to have each clinical examination recorded with a video camera. The Ethical Committee of our Hospital approved the study.

Patient #1

The patient #1 was a 66-year-old female, with a weight of 67 kg. Her father died at the age of 68 years because of a malignant tumor, her mother at the age of 90 years. The patient did not remember anybody in her family with manifest signs of muscular disease. In 1980, she started to have some gait difficulties due to weakness at her left lower limb. In 1999, she noticed a thinning at her left upper limb. In the same year, the electromyographies (EMG) performed at the Hospital of Viterbo and at the University of Siena detected some signs, in the right extensor digitorum communis muscle, suggestive for Steinert's disease. The Siena University Genetic Lab performed DNA analysis by using PCR and Southern blot molecular analysis in order to define the number of CTG triplet repeats in DMPK gene. PCR analysis detected an estimated number of 18 repeats (normal range: 5 to 37), while Southern analysis found a normal 3,500 bp-band and an expanded 3,900 bp-band obtained from the genomic DNA digestion by Sac1 enzyme. In conclusion, one allele has CTG triplets in the normal range, while the other allele had a triplet number of 150 CTG (range E1, < 170 repeats). This test confirmed the diagnosis of DM1.

During the following years, the patient underwent two periods of 2 months of physical rehabilitation per year. In 2003, she was diagnosed with diabetes mellitus and started the treatment first with oral anti-diabetic drugs and then with insulin. We evaluated the patient in November 2014. The neurological examination detected a less emotionally expressive myopathic face, and a light bilateral palpebral ptosis; the postural passages and the gait were possible only with help, the muscular weakness and hypotrophy were predominant distally at the four limbs. The muscular weakness assessed with MRC Scale was scored 3–4 at the proximal muscles, and 1–3 at the distal muscles; it was predominant in the right wrist, extensor digitorum manus muscles, and in the intrinsic foot muscles. The strength of interosseous and
The myotonic phenomenon was barely detectable with the percussion. The deep tendon reflexes were present and symmetrical. The MIRS grade was 4. The total score of the Modified Barthel Index was 52 (Table 1).

**Patient #2**

The patient #2 is a 46-year-old female, weighing 72 kg; she is the daughter of the patient #1. Because of light gait troubles when she was 31 years old, in February 2000 she underwent an EMG that showed typical findings for a myotonic dystrophy. The genetic analysis was performed: the PCR analysis detected an estimated number of 13 repeats (normal range: 5 to 37), while the Southern analysis found a normal 3,500-bp band. DNA digestion by Sac1 enzyme. Also in this case, one allele has a repeat number in the normal range, while the other allele has a repeat number of 600 CTG (range E2, 500-1,000 repeats). This test confirmed the diagnosis of DM1.

We visited the patient in December 2014: the postural changes and the gait were possible only with help. The muscular weakness was higher in the distal regions; it was assessed with the MRC Scale and the score was 3–4 in the proximal muscles, 1–3 in the distal muscles, and was predominant at the flexor digitorum and the intrinsic muscles of hands and feet. The interosseous and lumbrical muscles was only slightly lower than normal. The myotonic phenomenon was barely detectable with the percussion. The deep tendon reflexes were present and symmetrical. The MIRS grade was 4. The total Modified Barthel Index was 59 (Table 1).

Both patients began an intramuscular therapy with 100 mg of thiamine twice a week; thiamine was administered with single-point injections in the gluteus muscle. The patient #1 started the treatment just after the baseline evaluation of symptoms and signs of the disease, while the patient #2 started the treatment one month after the patient #1, i.e., when the mother was noticed the first clinical improvements.

Both patients were assessed with neurological examination, evaluation of muscular strength, and Modified Barthel Index nearly every 30 days. They did not sign the informed consent for an EMG examination before starting the treatment.

## Results

### Clinical assessment

The patient #1 had five follow-ups, and the patient #2 had four follow-ups (Table 1). Both patients had a marked improvement in the muscular symptomatology and in the independence of daily living, already 30 days after the beginning of the therapy. This improvement stabilized after 3 months. After 3 months of treatment, the MRC score for muscular strength was 5 in the proximal muscles and 2–4 in the distal muscles (the scores before the treatment were 3–4 and 1–3, respectively). The MIRS grade was 3 for both patients and remained constant in the following 9 months (25% improvement compared to baseline). The Modified Barthel Index showed a progressive improvement (Table 1). In the patient #1, the Modified Barthel Index improved by 44% over 4 months, and in the patient #2 by 29% over 3 months. The patients were treated with intramuscular thiamine 100 mg, twice a week for 12 (for mother) and 11 months (for daughter) respectively. Their clinical improvement remained stable during the period of treatment. The patients did not experience any side effect and continue uninterruptedly the same treatment; glycemic balance and diabetic therapy did not have any change during thiamine treatment. The videos of our patients, recorded at baseline and during therapy, are available as Supplementary Videos 1 and 2 online.

### Table 1 Modified Barthel index of patients before and during treatment with thiamine

| Item (range)          | Date of examination | Patient #1 | Patient #2 |
|-----------------------|---------------------|------------|------------|
|                       | 12 Nov 2014*        | 19 Dec 2014| 23 Jan 2015| 20 Mar 2015| 21 Nov 2015| 19 Dec 2014*| 23 Jan 2015| 20 Mar 2015| 21 Nov 2015|
| Feeding (0–10)        | 2                   | 8          | 8          | 10         | 10         | 5           | 8           | 8           | 8           |
| Bathing (0–5)         | 1                   | 3          | 3          | 3          | 3          | 1           | 3           | 3           | 3           |
| Personal toilet       | 3                   | 5          | 5          | 5          | 4          | 5           | 5           | 5           | 5           |
| Dressing (0–10)       | 8                   | 8          | 10         | 10         | 8          | 10          | 10          | 10          | 10          |
| Bowel control (0–10)  | 10                  | 10         | 10         | 10         | 10         | 10          | 10          | 10          | 10          |
| Bladder control (0–10)| 10                  | 10         | 10         | 10         | 10         | 10          | 10          | 10          | 10          |
| Toilet transfers (0–10)| 5                | 10         | 10         | 10         | 10         | 5           | 10          | 10          | 10          |
| Chair-bed transfers   | 8                   | 15         | 15         | 15         | 15         | 8           | 12          | 15          | 15          |
| Ambulation (0–15)     | 3                   | 15         | 15         | 15         | 15         | 8           | 12          | 12          | 12          |
| Stair climbing (0–10) | 2                   | 8          | 8          | 8          | 8          | 0           | 0           | 5           | 5           |
| Wheelchair /ambulation| –                   | –          | –          | –          | –          | –           | –           | –           | –           |
| Total**               | 52                  | 92         | 94         | 96         | 96         | 59          | 80          | 88          | 88          |

*Baseline visit, before starting treatment with thiamine. **Score: 0–20 total dependence, 21–60 severe dependence, 61-90 moderate dependence, 91–99 slight dependence, 100 independence. Nov: November; Dec: December; Jan: January; Mar: March.
Neurophysiological results
After 3 months of treatment, the patient #1 gave her consent to perform an EMG examination at the right extensor digitorum muscle. The graph presented recruitment too early to permit the analysis of the single motor units (this analysis could be possible in the previous examination in 1999, because the examiner described motor units with low amplitude and reduced duration of the action potentials). The present EMG graph showed frequent myotonic discharges and a low amplitude similar to the previous exam. Considering the clinical progression of the disease and the consequent progressive amplitude reduction of the action potentials, it should not be excluded that the therapy was effective, also even after several years of disease, since the amplitude would be expected to be much lower than what was assessed.

Discussion
We describe two patients affected by DM1 and treated with high doses of intramuscular thiamine for a year in an observational open-label pilot study. The patients had a positive response to the thiamine treatment, especially concerning the improvement of the muscular strength and of the daily life independence. This clinical improvement is stable in both patients, who did not show impairment of motor performances since the beginning of the therapy.

The absence of plasma thiamine deficiency at baseline and the efficacy of the continuous treatment with high doses of thiamine in our patients cannot rule out that some DM1 symptoms could be the expression of a muscular thiamine deficiency. Some abnormality in thiamine-dependent processes could be improved by a diffusion-mediated transport at elevated thiamine concentrations (Serrano et al., 2012; Brown, 2014).

The direct involvement of skeletal muscle has been rarely described in thiamine deficiency, although myalgia and fatigue are frequently reported. In fact, in the literature, there is a case report of myopathy in thiamine deficiency, confirmed by laboratory exams (high levels of CK, myoglobin, lactate, pyruvate, and low levels of thiamine), by muscular magnetic resonance imaging, and by muscular biopsy. All these alterations improved with thiamine supplementation (Koike et al., 2006).

In skeletal muscles, the reduction of thiamine availability decreases the production of ATP and increases pyruvate and lactate; these metabolic changes can even lead to threatening metabolic acidosis (Klein et al., 2004). Moreover, mitochondrial diseases show similar features to thiamine deficiency. A family has been described with mitochondrial DNA mutation (A3243G, related to mitochondrial encephalopathy, lactic acidosis and stroke-like episodes, MELAS) associated with familial thiamine deficiency. The supplementation of thiamine improved myopathy and decreased serum levels of muscular enzymes (Sato et al., 2000). Thiamine is one of the drugs used in the treatment of mitochondrial diseases.

The exact mechanism of responsiveness to thiamine in our patients affected by DM1 is unknown. Our clinical observation led to suppose that symptoms of DM1 patients could derive from a muscular thiamine deficiency that determines a selective skeletal muscular impairment. In other words, a selective thiamine deficiency could have an important role in DM1 pathophysiology. The administration of large amounts of parenteral thiamine increases the intracellular passive transport of the thiamine; the symptoms decrease when the energetic metabolism and other thiamine-dependent processes return to physiologic levels (Serrano et al., 2012; Brown, 2014). We also cannot exclude the role of the relevant non-coenzymatic actions of thiamine (Mkrtchyan et al., 2015).

It is known that some genetic disorders of the thiamine metabolism lead to neurological diseases (Serrano et al., 2012; Alfadhel et al., 2013; Brown, 2014). In addition, thiamine deficiency has been reported in some genetically determined neurological diseases (van Dongen et al., 2015). Both groups of diseases can be successfully treated with high doses of thiamine. Recently, some authors achieved positive results with the same treatment in sporadic degenerative diseases, such as Parkinson’s disease (Costantini et al., 2015).

We suppose that in DM1 this therapy may contribute to sustain the muscular action and we suggest a lifelong use of high-dose thiamine in affected subjects. Our two patients reported a general improvement of the voluntary motility, maintaining stable the motor conditions, without any side effect. In literature, there is no mention of thiamine-related adverse effects even at higher doses and for very long periods of time (Smithline et al., 2012). We noticed, during the treatment of other neurological diseases (e.g. Parkinson’s disease, dystonias), further improvement six months after the beginning of the therapy, even maintaining the same dose schedule (personal data, not yet published).

We are aware that our observation, however, has many limitations, the most relevant being the small sample and the absence of a placebo-controlled group of patients. Although the clinical improvement of our patients is continuous and stable during the follow-up period (up to one year), the lack of a placebo-controlled group leads to consider these results as preliminary and it requires careful interpretation. Another important issue is that our patients are related to each other and this might affect their response to the therapy, since the disease is genetic.

In conclusion, we believe that this report represents an important contribution to the issue of DM1 treatment; nonetheless, further experience at molecular, cellular, clinical, and neurophysiological level is needed to confirm the present observations.

Acknowledgments: We would like to thank the patients, Mirella Ciambella and Maurizio Ciambella (external collaborators of Villa Immacolata Clinic, Viterbo) for their precious collaboration.

Author contributions: All authors participated in conception and design of the study, data acquisition, data analysis and interpretation, drafting, critical revision, supervision of this paper, and approved the final version of this paper.

Conflicts of interest: None declared.
Supplementary information: Supplemental data associated with this paper can be found, in the online version, by visiting www.nrronline.org.

Plagiarism check: This paper was screened twice using Cross-Check to verify originality before publication.

Peer review: This paper was double-blinded and stringently reviewed by international expert reviewers.

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Costantini A, et al. / Neural Regeneration Research. 2016;11(9):1487-1491.