CASE REPORT

High-dose thiamine improves the symptoms of Friedreich's ataxia

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SUMMARY

Friedreich's ataxia (FRDA) is an autosomal recessive inherited disorder characterised by progressive gait and limb ataxia, dysarthria, areflexia, loss of position sense and a progressive motor weakness of central origin. Some observations indicate that all symptoms of FRDA ataxia could be the manifestation of a thiamine deficiency because of enzymatic abnormalities. Two patients with FRDA were under rehabilitative treatment from February 2012 to February 2013. The scale for assessment and rating of ataxia was performed. The patient began an intramuscular therapy with 100 mg of thiamine every 3–5 days. Injection of high-dose thiamine was effective in reversing the motor failure. From this clinical observation, it is reasonable to infer that a thiamine deficiency due to enzymatic abnormalities could cause a selective neuronal damage in the centres that are typically affected by this disease.

BACKGROUND

Friedreich's ataxia (FRDA) is an autosomal recessive inherited disorder characterised by progressive gait and limb ataxia, dysarthria, areflexia, loss of position sense and a progressive motor weakness of central origin. Additional features include hypertrophic cardiomyopathy and diabetes. In fact, this disease affects the dorsal root ganglia, sensory peripheral nerves, corticospinal tracts and dentate nuclei, heart, skeleton and endocrine pancreas. The pathogenetic mutation in FRDA is a homozygous guanine–adenine–adenine (GAA) trinucleotide repeat expansion on chromosome 9q13 that causes a transcriptional defect of the frataxin gene. Deficiency of frataxin is responsible for all clinical and morphological manifestation of FRDA. The protein is localised in the mitochondrial internal membrane and in the mitochondrial matrix.[1] Fatigue is a severe and disabling symptom in patients with FRDA, even early in the course of the disease.[2] The diagnosis of FRDA is based on clinical history, physical examination, neuroradiological examination and molecular genetic testing to detect an abnormal GAA trinucleotide repeat expansion of the FXN gene. There is no currently known cure for FRDA.

In July 2011, we treated a 47-year-old man affected by spinocerebellar ataxia type 2 (SCA)2. In this patient, fatigue as well as motor symptoms improved after parenteral high doses of thiamine.[3] Therefore, we formulated the hypothesis that the pathogenesis of some degenerative diseases of the nervous system is linked to a dysfunction of the intracellular transport of thiamine or to structural enzymatic abnormalities responsive to high doses of thiamine. Discrepancies between normal blood thiamine values and low cerebrospinal fluid levels, as well as a significant decrease in thiamine and thiamine monophosphate in the cerebrospinal fluid, have been described in SCA.[4–6] In addition, several authors observed a dysfunction of pyruvate dehydrogenase (PDH) complex in FRDA.[7–9]

In this report, we describe the results obtained with high doses of thiamine in two patients affected by FRDA. We requested a written permission to begin a thiamine-based therapy.

CASE PRESENTATION

Patient 1

A female, 39-year-old, weight 50 kg, affected by FRDA, under rehabilitative treatment from February to July 2012, was selected for this study. The patient reported a progressive ataxic gait for 4 years and dysarthria in the last year. In April 2011, she was admitted to the University Hospital Gemelli in Rome and the final diagnosis was late-onset Friedreich's disease. A younger sister with the same genetic mutation is asymptomatic.

Neurological examination: She had slurred speech, showed unsteadiness of stance and incapacity of tandem walking, gait was autonomous with slightly widened base, and dysmethria was present in four limbs. Segmental strength and sensory examination were normal. Stretch and cutaneous plantar reflexes were normal.

Common biochemical and haematological investigations were normal including thyroid hormones. Blood tests for human circulating tumour markers, autoantibody markers for autoimmune disorders and antineuronal antibodies were negative. Folic acid, B_{12}, E vitamin and plasmatic thiamine were within healthy reference range. Serology for lue, virus hepatitis B and C were negative.

Nuclear magnetic resonance (NMR) imaging showed a reduction in the diameter of the spinal cord at the T2–T4 levels.

DNA analysis: GAA repeat expansions in the locus FRDA1 for both alleles. Search for SCA1, 2, 3, 6, 7, 17 and for X-fragile permutation were negative.

Cardiological examination, echocardiogram, electromyographic and electroneurographic examinations were normal. Evoked motor potentials were consistent with a damage of the central pathways, more evident in the inferior limbs. Evoked somatosensitive potentials were consistent with a damage of the central pathways, more evident in the inferior limbs. We performed the Scale for

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Assessment and Rating of Ataxia (SARA 0–40) and Fatigue Severity Scale (FSS).

SARA score: 17 points; FSS score, 52 points (see table 1).

The patient began an intramuscular therapy with 100 mg of thiamine and an oral therapy with small doses of other group B vitamins every 5 days right after the evaluation of symptoms and history of the disease. Every time that vitamin B_1 was administered to the patient parenterally, in fact, we also administered one tablet of folic acid (7.5 mg) and one tablet of a mixture of B group vitamins: thiamine chlorhydrate (15 mg), riboflavin (vit B_2) 15 mg, nicotinamide 50 mg, pyridoxine chlorhydrate (vit B_6) 10 mg, pantothenic acid (25 mg), cyanocobalamin (vit B_{12}) 10 µg, biotine 150 µg.

The patient repeated the neurological exam, SARA and FSS 3 months after the beginning of the therapy.

Patient 2

A male, 27-year-old, weight 72 kg, affected by FRDA, under rehabilitative treatment from October 2012, was selected for this study. The patient reported a progressive ataxic gait for 2 years and dysarthria in the last year. In April 2011, he was admitted to the University Hospital Sant'Andrea in Rome and the final diagnosis was late-onset Friedreich's disease.

Neurological examination: She had slurred speech; showed unsteadiness of stance and incapacity of tandem walking; gait was autonomous with slightly widened base; and dysmethria present in four limbs. Stretch reflexes were absent.

Common biochemical and haematological investigations were normal. Blood tests for human circulating tumour markers, autoantibody markers for autoimmune disorders and antineuronal antibodies were negative. Folic acid, B_{12}, E vitamin and plasmatic thiamine were within healthy reference range. Cardiological examination, echocardiogram, electromyographic, electroneurographic examinations were normal. Evoked somatosensitive potentials were consistent with a damage of the central pathways, more evident in the inferior limbs. NMR of the brain and spinal cord was normal.

Tests performed (see table 1): SARA score: 12 points.

The patient began the same therapy as that of patient 1, every 3 days. The patient repeated the neurological exam and SARA for 3 months after the beginning of the therapy.

DNA analysis

The test for FRDA (expansion of the triplets GAA and research of the punctiform mutations of the X25 gene) was performed by the Consiglio Nazionale delle Ricerche, Roma, Genetics Laboratory.

Father: Bands with normal molecular weight: 1 (nv <605 bp, estimated number of triplets <35 GAA).

Bands with increased molecular weight: 1 (1275±50 bp, estimated number of triplets 258±15).

Mother: Bands with normal molecular weight: 1 (<605 bp, estimated number of triplets <35 GAA).

Bands with increased molecular weight: 0

The sequence of the codifying regions of the X25 gene revealed a punctiform mutation in heterozygosis: c.410G>T in the exon 4 of the gene (ref. seq. NM_000144.4) that results into an aminoacid substitution p.Gly137Val. She is an asyntomatic carrier of a punctiform mutation of the X25 gene, involved in the development of the FRDA. The mutation found has uncertain significance since, to date, it has not being described in literature. However, an analysis on Polyphen indicates that there is a high probability that Ms has a pathogenic mutation of one highly conserved nucleotide. It therefore appears possible that Ms an asyntomatic carrier of the FRDA.

Patient: Bands with normal molecular weight: 1 (<605 bp, estimated number of triplets <35 GAA). Bands with increased molecular weight: 1 (1343±50 bp, estimated number of triplets 281±15). The sequence of the codifying regions of the X25 gene revealed a punctiform mutation in heterozygosis: c.410G>T in the exon 4 of the gene (ref. seq. NM_000144.4) that results into an aminoacid substitution p.Gly137Val. The patient is heterozygote for an expansion of triplets GAA and heterozygote for a punctiform mutation of X25 gene. The analysis of the parents has shown that the mutations are on different chromosome. Therefore we deem possible the diagnosis of FRDA that have to be evaluated also in light of clinical examination.

Table 1 SARA (Scale for Assessment and Rating of Ataxia) scores for patients 1 and 2

	Patient 1 SARA scores		Patient 2 SARA scores	
SARA	Before therapy	After therapy	Before therapy	After therapy
Gait	4	4	4	4
Stance	3	0	2	0
Sitting	0	0	0	0
Speech disturbance	2	1	2	0
Finger chase	2	1	1	0
Nouse-finger test	2	0	1	0
Fast alternative hand movements	2	0	1	0
Heel-shin slide	2	1	1	0

OUTCOME AND FOLLOW-UP

Patient 1

The patient had a definite improvement with regard to fatigue 6 h after the first injection. The motor symptoms seemed to have a slightly improvement even after a month; however, at that time, we attributed this fact to the reduction of fatigue. About 3 months after the beginning of the therapy, the patient returned to the clinic for a further evaluation. Walking was now possible with a more restricted base surface; dysmetria appeared to have improved as well: the patient could walk with less fatigue and more stability than before.

The fatigue and motor symptoms had a remarkable improvement:

SARA score (see table 1): 7 points (improvement: 58.9%); FSS score 23 points (improvement 57.8%).

Patient 2

Fifteen days after the beginning of the therapy, all deep tendon reflexes were normal. A further evaluation was performed 3 months after the start of the therapy. Walking was now possible with a more restricted base surface; dysmetria and speech disturbance appeared to have improved as well. The patient could walk with more stability than before.

SARA score (see table 1): 4 points (improvement: 66.7%).

DISCUSSION

The patients have a favourable response to thiamine both in the fatigue and motor symptoms. Injection of high-dose thiamine was effective in reversing the fatigue and motor failure,

suggesting that the abnormalities in thiamine-dependent processes could be overcome by a diffusion-mediated transport at supranormal thiamine concentrations. The presence of symptoms owing to a thiamine deficiency in patients with normal concentrations of plasmatic thiamine could be explained if referred to a form of thiamine deficiency due to structural enzymatic abnormalities. Frataxin could be a component of the PDH complex and its deficiency could be the cause of the enzymatic dysfunction.[7–9] Obviously, Frataxin protein may have other functions, according to many other authors' opinion.[1]

Thiamine-responsive PDH deficiency has been reported in other inborn errors of metabolism that led to neurological diseases.[10 11] Genetic disorders of thiamine metabolism that led to neurological diseases can be treated with large doses of thiamine.[12 13] The exact mechanism of thiamine responsiveness in this patient is unknown.

From this clinical observation, it is reasonable to infer that symptoms featuring FRDA could derive from a severe, focal thiamine deficiency that determines a selective neuronal loss in the centres where the expression of the FXN gene is higher and that are typically affected by this disease. Frataxin gene is less expressed in other organs and systems which determines a mild thiamine deficiency that causes fatigue and related disorders.[14] The administration of large quantities of vitamin B_1 intramuscularly, increases the intracellular passive transport of thiamine, and symptoms decrease when the glucose metabolism and other thiamine-dependent processes are led back to physiological levels.[10]

The patients reported a general improvement of the voluntary motility and speech. As we write this report, they maintain the same motor conditions without any side effects. We believe that the therapy may play an important role in limiting the progression of the disease and we deem necessary a lifelong use of high doses of thiamine in affected subjects.

In the literature, there is no mention of thiamine-related adverse effects even at high doses and for very long periods of time.[15]

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

Learning points

- The treatment described in this paper is immediately available for the care of Friedreich's ataxia.
- In the literature, there is no study that has observed the 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 some genetic and degenerative diseases of the nervous system.

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Competing interests None.

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