CASE REPORT

# Thiamine and spinocerebellar ataxia type 2

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## SUMMARY

Spinocerebellar ataxia type 2 is a genetic disorder characterised by the degeneration of the cerebellum, its connections and degeneration in brainstem areas. Some observations indicate that high doses of thiamine may lead to the partial regression of the symptoms. One patient was under rehabilitative treatment from June 2011 to July 2012. We assessed the level of fatigue using the Fatigue Severity Scale. We performed the Scale for Assessment and Rating of Ataxia and Robertson Profile for Dysarthria (Italian version). Thiamine and thiamine pyrophosphate levels in the blood were within the healthy reference range. We started a parenteral therapy with 100 mg intramuscular every 7 days. The therapy led to a partial regression of fatigue within a few days. After about 3 months, a discreet improvement of motor symptoms especially in speech was observed. The symptoms could derive from a focal thiamine deficiency that could determine a selective neuronal loss.

## BACKGROUND

The basis of this report start from a study on fatigue in inflammatory and autoimmune diseases.

In June 2010, in fact, we studied patients affected by ulcerative colitis fatigue. We started a study from some clinical observations which suggested that ulcerative colitis fatigue and the other 'extraintestinal' symptoms of the disease were the manifestation of a mild thiamine deficiency. We treated the patients with high oral doses of thiamine. The findings of the aforementioned study (accepted for publication) were extremely encouraging for patients affected by ulcerative colitis. Therefore, we decided to apply the same principles used for the therapy of the fatigue in ulcerative colitis to chronic fatigue in different autoimmune and inflammatory diseases such as rheumatic diseases and multiple sclerosis (data not published) with encouraging results.

Consequently, we decided to focus our attention on the fatigue component present in other neurological disorders. We treated a 47-year-old man affected by spinocerebellar ataxia type 2 (SCA2). The patient presented with severe ataxia, marked dysarthria and fatigue. We request written permission to patients to begin a thiamine-based therapy. Administration of high doses of thiamine has improved the fatigue and, surprisingly, the motor symptoms of the disease. As of today, no care is available for this disease.

## CASE PRESENTATION

Patient: male, 47-year-old, weight 110 kg, symptoms appearance at the age of 35. Under therapy for depression, hypertension and cardiomyopathy for several years with antidepressive and antihypertensive drugs. His mother and one brother were affected by spinocerebellar ataxia type 2 and died several years ago.

Neurological examination:

- Walking possible only with strong support.
- Severe dysmetria in nose–finger test and in calf-knee test.
- As for the speech, this was explosive, slurred, nasal sounding, scanning, slow and basically unintelligible, only single words understandable.
- Hypopallesthesia bilateral lower limbs

For several years, the patient suffered from obstructive sleep apnoea syndrome. In October 2010, an echocardiogram was performed in the cardiology department of the Public Hospital of Viterbo, Italy (figure 1). This examination showed the presence of left atriomegalie (the measure of the atrial length was 5 cm).

## INVESTIGATIONS

Test performed:

Scale for Assessment and Rating of Ataxia: total sum 32

Robertson Profile: see table 1

In Italy, the Robertson Profile Test is composed of eight sections and the score pattern assigns low values when the examined function is strongly altered (ie, 1=scarce; 2=discreet; 3=good; 4=optimal).[1] Each section comprises several items (five-to-twenty items) to which a single score is given (from 1 to 4, see above). The sum of the scores of the items in each section gives the overall score of that section. There is no overall test score, but only section-overall section score.

Evaluation of the fatigue using Fatigue Severity Scale (FSS)

We considered the score of the FSS as follows:

Nine points: →no fatigue

Up to 36 points→medium—low fatigue

From 36 to 63 points→severe fatigue

The patient scored 32 points.

Nuclear magnetic resonance (NMR): cerebellum atrophy and brainstem atrophy. The NMR test was performed at Fondazione Santa Lucia, in Rome, Italy.

DNA analysis (executed at Consiglio Nazionale delle Ricerche, Istituto di Neurobiologia e Medicina Molecolare): SCA2; detected abnormal cytosine-adenine-guanine (CAG) trinucleotide repeat expansion of the ATXN2 gene

CAG trinucleotide repeats: 22 (allele A); 43 (allele B)

Blood dosage of the thiamine and of the thiamine pyrophosphate (TPP): The patient had a concentration in the blood of thiamine equal to

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**Table 1** SARA and Robertson profile scores before and after Thiamine therapy

| SARA | Scores before therapy | Scores after therapy | Robertson profile | Scores before therapy | | Scores after therapy | |
|---|---|---|---|---|---|---|---|
| Gait | 6 | 6 | | Items | Scores | Items | Scores |
| Stance | 5 | 5 | Respiration | 5 | 5/20 | 5 | 12/20 |
| Sitting | 4 | 2 | Phonation | 12 | 12/48 | 12 | 27/48 |
| Speech disturbance | 5 | 2 | Facial musculature | 20 | 24/80 | 20 | 52/80 |
| Finger chase | 3 | 2 | Diadochokinesis | 11 | 11/44 | 11 | 22/44 |
| Nose–finger test | 3 | 2 | Reflexes | 7 | 10/28 | 7 | 19/28 |
| Fast alternating hand movements | 3 | 2 | Articulation | 5 | 5/20 | 5 | 13/20 |
| Heel-shin slide | 3 | 2 | Intelligibility | 6 | 6/24 | 6 | 19/24 |
| Total | 32 | 23 | Prosody | 5 | 5/20 | 5 | 10/20 |

SARA, Scale for Assessment and Rating of Ataxia.

10.5 μg/l (normal values 2.1–4.3 μg/l), and levels of thiamine pyrophosphate equal to 79.4 μg/l (normal values >49 μg/l). Every 3 days, the patient was contacted in order to monitor the course of the treatment.

The evaluation of the fatigue using FSS was repeated after 30 days.

An echocardiogram was performed 25 days after the thiamine therapy.

The patient repeated the Scale for Assessment and Rating of Ataxia test roughly 100 days after the beginning of the therapy.

## TREATMENT

Once the examination phase was accomplished, we began a parenteral therapy with 100 mg/ml of thiamine every 7 days. As a standard procedure, every time that high doses of vitamin B1 is administered to patients, small doses of all other group B vitamins were administered to the patient of this study. Our patient is still on the same treatment and the high-dose thiamine therapy was never interrupted.

## OUTCOME AND FOLLOW-UP

The parenteral therapy with 100 mg/ml of thiamine every 7 days led to a partial regression of fatigue within a few days or hours. Fatigue Severity Scale score after therapy=19 (before it was 32).

The patient had a remarkable improvement already after 6 h from the injection.

The patient performed an echocardiogram 25 days after the thiamine therapy in the same facility as the previous time (see figure 2). The length of the atrium was normal, 3.38 cm. Sleep apnoea completely regressed.

After 1 month from the beginning of the therapy also, the motor symptoms seemed to have slightly improved. At that time, we attributed this fact to the reduction of the fatigue.

Some 100 days after the beginning of the therapy, the patient returned to the clinic for a further examination. The motor symptoms had improved.

Walking and stance were now possible with a more restricted base surface if compared to the beginning of the therapy and without the disturbance of strong lateropulsions. Dysmetria appeared to have improved as well. The patient could walk with less fatigue and more stability than before, although he still needed a stroller and an accompanying person.

The speech completely lost its characteristic of explosiveness and was well understandable.

The Scale for Assessment and Rating of Ataxia score was total sum 23.

The scores of the Robertson Profile for the patient after the therapy improved (table 1).

As we write this case report, the patient maintains the same motor and cardiac conditions obtained right after the beginning of the therapy.

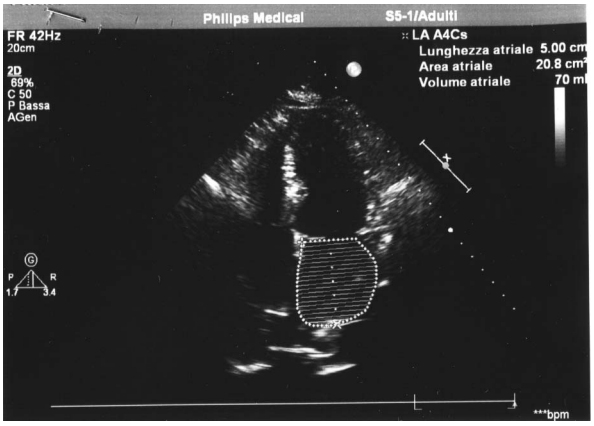


**Figure 1** Echocardiogram before therapy. Notice the measure of the atrial length, 5 cm.

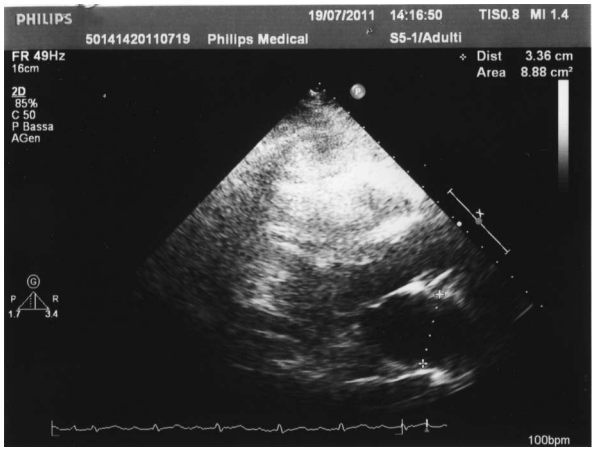


**Figure 2** Echocardiogram after therapy: length of the atrium is normal, 3.38 cm.

## DISCUSSION

SCA2 is a genetic disorder characterised by the degeneration of the cerebellum, its connections and degeneration in brainstem areas. It is characterised by a progressive cerebellar syndrome associated with peripheral neuropathy, saccadic slowing, cognitive disorders, and other multisystem features. SCA2 is caused by an abnormal expansion of CAG triplet repeats in the encoding region of the ATXN2 gene. Fatigue is severe and disabling in patients with SCA2, even early in the course of the disease and it is present in roughly 70% of the patients.[2]

The diagnosis of SCA2 is based on clinical history, physical examination, neuroradiological examination and molecular genetic testing to detect an abnormal CAG trinucleotide repeat expansion of the ATXN2 gene. Affected individuals have alleles with 32 or more CAG trinucleotide repeats. Such testing detects nearly 100% of the cases. There is no currently known cure for spinocerebellar ataxia, which is considered to be a progressive disease.

In the literature, few studies consider the possible connections between SCA2 and the concentrations of thiamine in the nervous tissue and in the cerebrospinal fluid and one recent study discusses fatigue in spinocerebellar ataxia. A discrepancy between normal blood thiamine values and low cerebrospinal fluid thiamine levels and a significant decrease in thiamine and thiamine monophosphate in the brain have been described in SCA.[3–5] Distinct cerebellar lactate (Lac) peaks were detected in several patients with SCA2 using proton magnetic resonance spectroscopic imaging.[6] As it is well known, in the presence of thiamine deficiency, the oxidative metabolism of the pyruvate decreases, and consequently, the concentration of lactate in the blood and in the cells increases.

On the whole, we had a favourable response to thiamine. The patient reported an improvement of the motor symptoms, of fatigue and a complete regression of cardiac alteration and sleep apnoea. The presence of symptoms due to a severe thiamine deficiency in patients with normal concentrations of thiamine and TPP in the blood could be explained if referred to a form of thiamine deficiency due to a dysfunction of the vitamin B1 active transport mechanism from the blood to the mitochondria, or to structural enzymatic abnormalities. The administration of large quantities of vitamin B1 parenterally, increases the concentration in the blood to a level apt to restore a normal glucose metabolism in all cells and leads to the partial regression of motor and non-motor symptoms of the disease. The glucose metabolism of all cells goes back to normal values since the concentration of thiamine inside the cells increases as a consequence of the passive transport at high concentrations of thiamine.[7 8]

One author, reported that high doses of thiamine may be able to induce the greater expression of the thiamine transporter-encoded genes.[9]

### A more detailed explanation of the possible mechanism that led to the improvement of the symptoms

#### Motor symptoms

Motor symptoms could derive from a severe, focal thiamine deficiency that could determine a selective neuronal loss in the centres that are typically hit in this type of disease. Therefore, high doses of thiamine may reduce the cerebellar incoordination. The presence of symptoms due to a severe thiamine deficiency in patients with normal concentrations of thiamine and TPP in the blood could be explained if referred to a form of thiamine deficiency due to a dysfunction of the vitamin B1-active transport mechanism from the blood to the mitochondria, or to structural enzymatic abnormalities. The patient reported a general improvement of the voluntary motility of the trunk, of the limbs and of the speech.

#### Heart condition

The authors deem that atriomegalie could be a cardiac manifestation of a mild-severe thiamine deficiency. The patient, over the last 5 years, was prescribed a consistent therapy with antihypertension drugs. Our team excludes that the normalisation of the cardiac condition could be the consequence of the antihypertension therapy. Such a consistent therapy, in fact, did not lead to any improvement from 2006 to November 2010 as documented by the patient's past record, when the patient performed the echocardiogram (in November 2010; figure 1), whereas it would have led to the reduction of the atriomegalie (in July 2011, as shown in figure 2) only within the last 8 months (November 2010 through July 2011).

The connection between different forms of heart failure and obstructive sleep apnoea is well established in literature. In patients with heart failure, nocturnal rostral fluid shift is associated with an overnight increase in the neck circumference and with obstructive sleep apnoea. The disappearance of obstructive sleep apnoea in our patient followed the regression of its atriomegalie and this suggests a consistent link between atriomegalie, sleep apnoea and the treatment with thiamine.

#### Fatigue

Fatigue and related disorders could be the classic manifestation of a mild thiamine deficiency.

As we write this case report, the patient maintains the same motor and cardiac conditions obtained right after the beginning of the therapy, and therefore, we deem necessary a lifelong use of high doses of thiamine in affected subjects.

No collateral effect due to the dose of thiamine administrated to the patient was observed during this study.

In literature, there is no study that has observed collateral effects linked to daily use of high doses (both orally or intramuscular) of thiamine comparable to those of our therapy.[10 11] Moreover, the diseases treated with high doses of vitamin B1, and for long periods of time, are Alzheimer's disease and thiamine-responsive megaloblastic anaemia (TRMA). The doses, employed in TRMA, are similar to ours and have been administrated for several years. In Alzheimer's disease, doses equal to 3–8 g/day were administrated for 1 year without observing any collateral effect.[11]

To date, a dysfunction of intracellular thiamine transport was described for genetic diseases characterised by mutations in thiamine-transporter genes.[7 9]

A number of inborn 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.[7 9]

In spinocerebellar ataxias, different authors have observed a reduction of the concentration of thiamine in the cerebrospinal fluid. In spinocerebellar ataxia type 1, one author reported a reduction of the activity of α-ketoglutarate dehydrogenase.[12]

Summarising, we believe that, the polyglutamine protein mutated (naturally present in all structures of the cell and in all cells), encoded by the ATXN2 gene and known as *ataxin 2*, causes progressive neuronal death of Purkinje cells and several pontine, mesencephalic, thalamic neurons and fatigue owing to a dysfunction of the active transport from the blood to the mitochondria of vitamin B1 or structural enzymatic

abnormalities. In any case, this phenomenon has been found responsive to the administration of high doses of thiamine.

It is likely that other forms of spinocerebellar ataxia may benefit from the same therapy. Moreover, recent studies have suggested that expanded ATXN2 repeats are a genetic risk factor for amyotrophic later sclerosis (ALS).[13] Furthermore, Parkinson's disease has also been related to mutations associated with SCA2.[14] Last, there are several evidence suggesting that thiamine deficiency produces alterations in brain function and structural damage that closely model a number of diseases in which neurodegeneration is a characteristic feature, including Alzheimer's disease, ALS, Parkinson's disease and others.[15]

Starting from the aforementioned considerations, we have treated some patients affected by Parkinson's disease and one case of Friedreich ataxia with good results. We are currently treating one case of cortico-basal degeneration and three cases of ALS with encouraging preliminary results.

Substantial efforts are being made to understand the genetic and biochemical determinants of thiamine-deficiency-related disorders and of the differential vulnerabilities of tissues and cell types to thiamine deficiency.

Further studies are necessary to confirm our observations. However, we strongly believe that our observations represent an important contribution to the relief of these patients.

## Learning points

- The treatment, described in this paper, is immediately available for the care of spinocerebellar ataxia type 2.
- In literature, there is no study that has observed collateral effects linked to daily use of high doses thiamine.
- We believe that this report opens a ray of hope for therapy of some genetic and degenerative diseases of nervous system.

**Competing interests** None.

**Patient consent** Obtained.

**Provenance and peer review** Not commissioned; externally peer reviewed.

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