Long-term treatment with thiamine in Friedreich ataxia

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Introduction

Thiamine (Vitamin B1)

Thiamine is a cofactor of fundamental enzymes for the energetic cellular metabolism; thiamine deficiency causes disorders affecting both the peripheral and central nervous systems (Wernicke encephalopathy, Beri-beri)

Thiamine-dependent processes are critical in glucose metabolism, oxidative stress, protein processing, peroxisomal function, and gene expression

Thiamine has also non-coenzymatic roles, potentially relevant in neuroprotection

Friedreich ataxia (FRDA)

FRDA is a rare autosomal recessive neurodegenerative disorder caused by a mutation in the *FXN* gene, which encodes a protein named frataxin;
frataxin is extremely reduced but qualitatively normal

FRDA is clinically characterized by:
- spinocerebellar ataxia
- peripheral neuropathy
- hypertrophic cardiomyopathy
- diabetes mellitus
- scoliosis
- optic atrophy

There is no effective or disease-modifying therapy

Several factors may link thiamine to FRDA

- Both FRDA and thiamine deficiency have the same main targets: central nervous system, peripheral nervous system, and heart
- Cerebellum is one of the most involved areas in thiamine deficiency
- Previous studies reported low thiamine levels in the cerebrospinal fluid and pyruvate-dehydrogenase dysfunction in cells of patients with FRDA
- Analogs of frataxin and of protein involved in thiamine biosynthesis are partners of Fe-S cluster proteins
- Thiamine administration causes clinical improvements in diseases due to mutations in thiamine transporter genes

Aims

To investigate in an open label trial whether
a long-term treatment with thiamine in patients with FRDA could
- improve the neurological symptoms and
- upregulate *FXN* expression in an attempt to restore frataxin concentration

Subjects

34 FRDA patients: 13 males, 21 females
Mean age: 36.3 ± 11.1 years
Mean age of onset: 17.1 ± 9.9 years
Baseline total SARA score: 26.6 ± 7.7

Methods

CLINICAL ASSESSMENT
of all the patients, at baseline and every 3 months during treatment
- Scale for Assessment and Rating of Ataxia (SARA)

FUNCTIONAL TESTS
in a subgroup of 20 patients
- Archimedes' spiral
- Fatigue Severity Scale

INSTRUMENTAL EXAMS
- Echocardiogram was performed in a subgroup of 13 patients at baseline and during treatment (472 ± 282 days after baseline)
- Frataxin mRNA level was measured with quantitative real-time RT-PCR in 6 patients at baseline and after 12 months of treatment
- Plasma thiamine at baseline was measured with HPLC in all the patients

Treatment

Intramuscular 100 mg of thiamine twice a week
without any change to pharmacological therapy or rehabilitation program, for a period ranging from 80 to 930 days (m ± sd, 332 ± 257 days)

Statistical analysis

Normal distribution of data: **Shapiro–Wilk test**

Baseline and follow-up scores at clinical scales for normally distributed data: first one-way analysis of variance **(ANOVA) for repeated measures**, followed by Box's conservative test, and then **t-test for paired data**

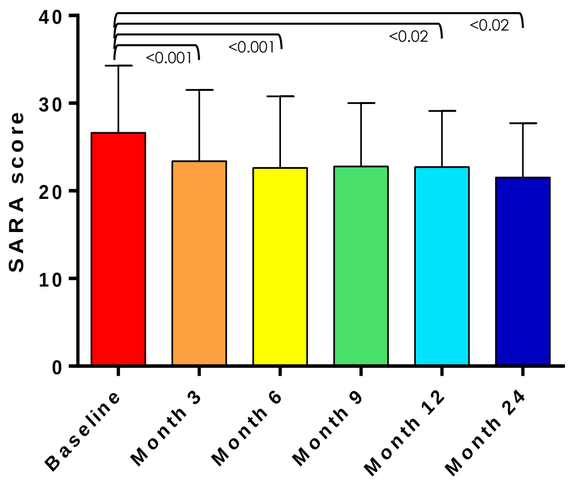
Analysis of non-normally distributed data: **Wilcoxon** matched-pairs signed-ranks test

Comparisons between data of different subgroups of patients, examined by gender, disease stage, or disease onset: **t-test for unpaired data**

FXN gene expression: **t-test for unpaired data** and **Wilcoxon** rank-sum test

Differences with **p<0.05** have been considered statistically significant

Results: Clinical assessment



Treatment with thiamine led to significant improvement of motor symptoms: total SARA score improved from 26.6 ± 7.7 at baseline to 21.5 ± 6.2 at the last control visit (p<0.02)

ANOVA+Box's conservative test
t-test for paired data
a p<0.001; **b** p<0.02; **c** p<0.05; vs. respective baseline

Total SARA score	BASELINE vs MONTH 3		BASELINE vs MONTH 6		BASELINE vs MONTH 12		BASELINE vs MONTH 24	
	26.1±8.0	**23.4±8.1a**	**24.9±8.1**	**22.6±8.2a**	**24.5±6.0**	**22.7±6.4b**	**24.9±6.6**	**21.5±6.2b**
1) Gait	6.8±1.9	6.8±1.9	6.6 ±1.8	6.5±1.9	6.7±1.9	6.6±1.9	6.8±1.7	6.6±1.7
2) Stance	5.0±1.7	4.9±1.9	4.9±1.7	4.8±2.0	4.9±1.6	4.9±1.7	5.0±1.4	4.9±1.6
3) Sitting	**2.7±1.4**	**2.0±1.5a**	**2.4±1.4**	**1.7±1.6c**	**2.4±1.2**	**1.7±1.3c**	2.5±1.3	1.4±1.3
4) Speech disturbance	**2.5±1.1**	**1.8±1.1a**	**2.4±0.9**	**1.9±0.9a**	2.3±0.6	1.9±0.5	**2.1±0.6**	**1.4±0.7b**
5) Finger chase	**1.9±1.0**	**1.6±1.1c**	**1.8±1.1**	**1.6±0.8c**	1.7±0.6	1.6±0.7	1.8±1.0	1.4±0.7
6) Nose-finger test	**1.5±1.5**	**1.1±1.2c**	1.2±1.4	1.1±1.2	0.8±0.9	0.4±0.6	0.8±1.1	0.6±0.7
7) Fast altern. hand mov.	**2.6±0.9**	**2.4±1.0c**	2.7±0.8	2.4±0.9	2.6±0.6	2.4±0.8	2.8±0.5	2.3±1.0
8) Heel-shin slide	**3.2±1.0**	**2.9±1.3c**	3.1±0.9	2.8±1.3	3.1±0.7	3.1±1.2	3.2±0.8	3.1±1.2
	(N=29)		(N=20)		(N=14)		(N=8)	

COMPARISON TO NATURAL HISTORY OF DISEASE

- Mean progression annual rate in FRDA: increase of 1.36 ± 2.3 points (Marelli et al.) or 0.56 ± 1.17 points (Reetz et al.) in SARA total score
- Our study: **significant decrease of -1.82 ± 0.68** in SARA total score after 12 months of treatment (p=0.018)
- In our series, the progression rate is lower than in natural history (p<0.001)

➔ Therefore, **the clinical progression of our patients was significantly better than the natural disease progressive impairment**

➔ 16 out of 28 patients with absence of deep tendon reflexes at baseline, revealed **presence of deep tendon reflexes** during treatment
➔ **Dysphagia improved** in 14 out of 22 patients with swallowing symptoms at baseline

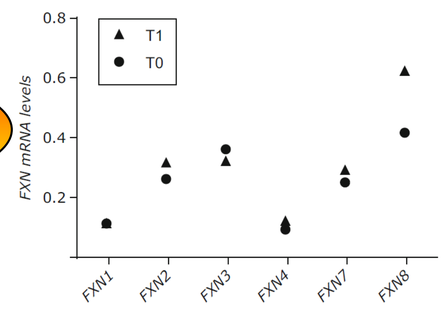
Results: Functional tests

➔ ARCHIMEDES' SPIRAL: improvement with a tendency to statistical significance, from 73.9 ± 48.2 s at baseline to 44.3 ± 26.3 s at 6-month follow-up (p=0.081) and to 41.5 ± 22.1 s at 24-month follow-up (p=0.098)
➔ FATIGUE SEVERITY SCALE: no significant changes

Results: Instrumental exams

ECHOCARDIOGRAM
➔ **Significant decrease of the interventricular septum thickness**
from 9.54 ± 1.76 to 8.85 ± 2.00 mm (p=0.016)
Thickness of left ventricle posterior wall and ejection fraction: no changes

FRATAXIN mRNA LEVEL



Non-uniform response, with an upregulation from 20 to 40 % in four patients and no effect in the remaining two.
A combined analysis of all the patients did not show a statistically significant increase (p=0.078, Wilcoxon test).

Basal levels of plasma thiamine, routine biochemical and hematological investigations, thyroid hormones, TSH, folic acid, B12 vitamin: within the **normal** range

Conclusions

After treatment with thiamine in patients with FRDA we observed:

- **Significant clinical improvement**, especially considering the rate of clinical impairment in natural disease progression
- Stable clinical improvement over time in all the patients, even after 2 years of treatment
- **Significant reduction of thickness of cardiac interventricular septum**
- Re-occurrence of deep tendon reflexes (47% of patients) and improvement of dysphagia (41% of patients)
- No problems of safety, even in long-lasting treatment

Open questions

Is FRDA symptomatology the effect of focal neuronal thiamine deficiency?
Has thiamine a direct influence on *FXN* expression?
Is it possible to **confirm these results in a placebo-controlled trial**?