Prevalence of neuropathy in Friedreich's ataxia patients and in subjects heterozygous for GAA trinucleotide repeat in FXN gene.

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Introduction

Friedreich's ataxia (FA) is the most common autosomic recessive ataxia, caused by homozygous expansion of GAA trinucleotide repeat in the frataxin gene leading to decreased expression of mitochondrial frataxin. Frataxin deficiency and its molecular consequences (iron sulfur protein defects and oxidative stress) affects primarily the dorsal root ganglia, the posterior column, the spinocerebellar and the pyramidal tracts of the spinal cord leading to ataxia, dysarthria and areflexia.
Sensory neuropathy has also been described where motor nerves were reported unaffected.
We sought to investigate peripheral nervous system alterations in FA patients and in healthy subjects heterozygous for GAA trinucleotide repeat in FXN gene (HS-FXN).

Methods

Between January 2016 and March 2017, 14 FA (mean age 32 years, SD 11.76) and 16 HS-FXN (mean age 52 years, SD 11.0) patients were screened for the presence of neuropathy, after other common causes of neuropathy have been excluded with the exception of diabetes mellitus (DM), wich can be a manifestation of the disease. All patients underwent nerve conduction studies (NCS) of four motor (median, ulnar, peroneal and tibial) and three sensory (median, ulnar and sural) nerves, and F waves studies from ulnar and peroneal nerve. Abnormalities were defined comparing NCS findings with our laboratory control values (severe: more than 2.5 SD; mild < 2.5 SD) and patients categorized in 3 groups according to the type of nerves involved:1) pure motor neuropathy, 2) motor-sensory neuropathy and 3) pure sensitive neuropathy.

Results

Demographic and clinical data of FA patients and HS-FXN are summarized in Table 1.

In FA subjects:
Two patients showed no abnormalities in motor NCS, five showed mild motor alterations, and 5 severe motor alterations (Table 2).
Motor conduction velocity was slowed in the median nerve in 2 patients (14%), in the ulnar in 2 (14%), in the peroneal in 8 (57%) and in the tibial nerve in 9 (64%) patients.
CMAP amplitude was reduced in the peroneal nerve in two patients (14%).

Sensitive NCS were more affected than motor NCS in all FA patients who presented with both ulnar and sural SNAP and CV reduction in virtually all cases.
Sensitive conduction velocity was slowed in the median nerve in 3 patients (21%), in the ulnar in 12 (86%), in the sural in 100% of patients.
SNAP amplitude was reduced in the median nerve in 7 patients (50%), in ulnar and sural in 100% of patients. (Table 3)

In HS-FNX subjects:
Motor NCS were unaffected with the exception of 1 subject who presented slow CV in both ulnar and peroneal nerves.
Sensitive conduction velocity was slowed in the median in 2 patients (13%), in the ulnar in 1 patient, in the sural in 3 (19%) patients.
SNAP amplitude was reduced in the median nerve in 3 patients (19%), in sural nerve in 10 (63%) patients.

Fifty percent of FA patients were categorized as pure sensory neuropathy, the remaining patients had a motor-sensory neuropathy. In HS-FNX group, the majority of subjects presented with a pure sensitive neuropathy (81%).

Conclusion.

In addition to the expected sensory neuropathy, we observed that most FA patients have also alterations in motor nerves, potentially suggesting a peripheral motor-sensory neuropathy as FA feature. In particular, we observed a demielinating neuropathy of lower limbs.
Moreover, we observed a high rate of sensory neuropathy also in HS-FNZ patients.
Our findings suggest that Frataxin mutation, both in omozygosis and heterozygosis, could be a rare cause of neuropathy.

Table 1 Baseline characteristics of population of FA and HS-FNX subjects. Mean (SD). DM: Diabetes Mellitus.

	FA subjects (N=14)	HS-FXN subjects (N=16)
Age	32 (16-52)y	52 (23-69)y
Sex	F 7 (50%)	F 10 (63%)
Age of onset (SD)	15 (7-30)y	-
Comorbidities DM	1 (7%)	1 (6%)
GAA trinucleotide repeats	1557 (525-3000)	-
SARA score at EMG	18 (3-33)	-
FARS score at EMG	55 (20-95)	-

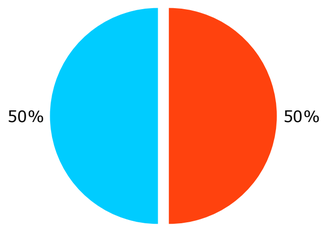
Table 2 Motor NCS parameters of FA patients. CMAP: compound motor action potential. CV: conduction velocity.

	Distal latency (ms)	CMAP amplitude (mV)	CV (m/s)
Median			
normal	12 (86%)	14 (100%)	12 (86%)
abnormal	2 (14%)	0	2 (14%)
mean (SD)	3.6 (0.7)	9.9 (2.4)	54.4 (6.7)
Ulnar			
normal	14 (100%)	14 (100%)	12 (86%)
abnormal	0	0	2 (14%)
mean (SD)	2.5 (0.4)	12.6 (1.9)	52.5 (7.4)
Peroneal			
normal	10 (71%)	12(86%)	6 (43%)
abnormal	4 (29%)	2 (14%)	**8 (57%)**
mean (SD)	4.7 (1.8)	5.1 (3.0)	**36.8 (17.2)**
Tibial			
normal	13 (93%)	14 (100%)	5 (36%)
abnormal	1 (7%)	0	**9 (64%)**
mean (SD)	4.1 (0.8)	18.1 (7.9)	**40.5 (6.5)**

Table 3 Sensory NCS parameters of FA patients. SNAP: sensory nerve action potential. CV: conduction velocity.

	Distal latency (ms)	SNAP amplitude (uV)	CV (m/s)
Median			
normal	12 (86%)	7 (50%)	11 (79%)
abnormal	2 (14%)	7 (50%)	3 (21%)
mean (SD)	3.1 (0.6)	2.3 (2.0)	45.1 (23.2)
Ulnar			
normal	6 (43%)	0	2 (14%)
abnormal	**8 (57%)**	**14 (100%)**	**12 (86%)**
mean (SD)	3.0 (0.8)	4.2 (4.6)	**35.9 (19.3)**
Sural			
normal	0	0	0
abnormal	**14 (100%)**	**14 (100%)**	**14 (100%)**
mean (SD)	--	---	**---**

Neuropathy in FA subjects



Neuropathy in HS-FXN subjects

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