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Axonal Neuropathy in Female Carriers of the Fragile X Premutation with Fragile X-associated Tremor Ataxia Syndrome

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Abstract

Introduction—We examined whether females with the fragile X-associated tremor ataxia syndrome (FXTAS) and non-FXTAS premutation carriers have electrophysiological signs of underlying peripheral neuropathy.

Methods—Nerve conduction studies (NCS) were performed on 19 women with FXTAS, 20 non-FXTAS carriers, and 26 age-matched controls. The results were compared to existing data on corresponding male carriers.

Results—Women with FXTAS and non-FXTAS carriers had reduced sensory nerve action potential amplitudes. Also, there was a strong trend for reduced compound muscle action potential amplitudes observed in women with FXTAS, but not in non-FXTAS carriers. No significant slowing of nerve conduction velocities, prolongation of F-wave latencies, or associations with molecular measures was observed.

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Conflict of interest

Randi Hagerman has received funding from Seaside Therapeutics, Roche, Novartis, Forest, and Curemark to carry out treatment trials. She has also consulted with Novartis and Genentech/Roche regarding treatment in fragile X syndrome. None of the remaining authors/ contributors have reported any conflicts.

Discussion—This study suggests an underlying axonal neuropathy in women with FXTAS. However, in comparison to men with FXTAS, the NCS abnormalities in women were less severe, possibly due to the effect of a normal X-chromosome.

Keywords

nerve conduction studies; fragile X premutation; FXTAS; fragile X-associated tremor ataxia syndrome; *FMR1*

INTRODUCTION

Fragile X-associated tremor/ataxia syndrome (FXTAS) is a progressive neurodegenerative disorder characterized by intention tremor and cerebellar ataxia that affects adult individuals, typically after age 50.[1] The disorder was discovered in 2003 and involves a moderate CGG expansion (55–200 CGG repeats) or premutation in the 5′ UTR of the fragile X mental retardation 1 (*FMR1*) gene located at Xq27.3.[2] Symptoms of FXTAS are usually accompanied by progressive cognitive decline and variable symptoms of multisystem involvement, including Parkinsonism, peripheral neuropathy, lower limb proximal weakness, and autonomic dysfunction.[3–5] The penetrance of FXTAS in elderly male carriers of the premutation is high (about 50% over 70 years), but fewer female carriers develop the syndrome, presumably because of the protective effects of the second, normal X chromosome.[6, 7] The pathogenic mechanism responsible for FXTAS is due to mRNA-dependent gain-of-function toxicity, as premutation carriers display increased *FMR1* mRNA levels. Intranuclear inclusions are observed in neurons and astrocytes of patients with FXTAS,[8] which contain a number of proteins including Lamin A/C (*LMNA*), αB-crystallin, myelin basic protein, and hnRNPA2, Sam 68 among many others.[9] Since changes of the level of expression of LMNA are observed in cells transfected with premutation-sized CGG repeats, and mutations in the gene encoding LMNA are responsible for a hereditary form of neuropathy, it is hypothesized that LMNA dysregulation is associated with the pathogenesis of the neuropathy often observed in patients with FXTAS.[5, 9]

We recently reported that, compared with controls, men with FXTAS had significant reduction of compound muscle action potential (CMAP) amplitudes, slower conduction velocity, prolonged F-wave latencies in the tibial nerve, and reduced sural sensory nerve action potential (SNAP) amplitude.[5] Even carriers with the premutation but without FXTAS had lower SNAP amplitudes compared with controls. We have extended our studies to female carriers of the premutation CGG expansion with and without FXTAS and found that women with FXTAS showed significant reduction in SNAP amplitudes, a statistically non-significant trend in CMAP amplitude reduction, and no significant changes in motor nerve conduction velocities (NCVs). Our findings confirm that axonal neuropathy is a common manifestation in both men and women affected with FXTAS.

METHODS

Clinical Subjects

The clinical study was conducted at the Fragile X Research and Treatment Center of the MIND Institute, University of California, Davis Medical Center. Premutation carriers were ascertained through families with known members affected with fragile X syndrome and women who were self-referred or referred by their physicians because they were concerned about possible FXTAS. Control subjects were recruited from the local community and from non-affected relatives of patients with fragile X mutations. All subjects signed an informed consent approved by the UC Davis Institutional Review Board committee.

Participants underwent a medical and neurological evaluation. The medical evaluation included a complete clinical history, a detailed review of systems, past medical and surgical history, and a medication history. A physician with expertise in evaluation of premutation carriers and FXTAS (RH) examined all the patients and performed a detailed neurological examination. All participants whose genetic status was not previously known underwent *FMR1* genotyping to establish their carrier status. MRI imaging was also performed to see if the major radiological criteria for the diagnosis of definite FXTAS were documented. The diagnosis of “definite” or “probable” FXTAS was made according to the presence of clinical, radiological, and molecular criteria published elsewhere[4].

A total of 65 women participated in the study. Twenty-six were normal control subjects [mean (SD) age, 61.5 (6.41) years], 20 were non-FXTAS premutation carriers [54.95 (6.98) years], and 19 were premutation carriers with probable or definite FXTAS [64.11 (10.3) years], see Table 1. The mean age of non-FXTAS premutation carriers was significantly lower than premutation carriers with FXTAS ($P < 0.001$) and controls ($P = 0.007$) and were adjusted in the analysis of nerve conduction data. Mean activation ratios were 0.55 (SD 0.23) and 0.55 (SD 0.25) in FXTAS and non-FXTAS groups, respectively, see Table 1.

Nerve conduction studies

Nerve conduction studies were performed with surface electrodes for both stimulation and recording on a Viking IV electromyographic system (CareFusion, San Diego, CA), following guidelines provided by the American Association of Neuromuscular and Electrodiagnostic Medicine (AANEM). Temperature was monitored throughout the test with a skin thermistor probe and was maintained at 33° C. For the tibial nerve studies, the CMAP was recorded with the active surface electrode placed over the belly of the abductor hallucis muscle and the reference electrode placed over the 1st metatarsal bone, while the tibial nerve was stimulated supramaximally behind the medial malleolus at the ankle and in the popliteal fossa. Tibial F-waves were elicited via supramaximal stimulation of the tibial nerve at the ankle. For the sural nerve studies, the SNAP was recorded with an active surface electrode placed behind the lateral malleolus and a 4 cm distal reference electrode using antidromic stimulation delivered slightly distal to the lower border of the belly of the lateral gastrocnemius muscle at a median distance of 130 cm proximal to the active recording electrode. For the superficial fibular nerve, the active electrode was placed near the lateral aspect of the extensor digitorum longus tendon 2 cm proximal to the bimalleolar line and the

reference electrode was placed 4 cm distally; antidromic stimulation was delivered 10 to 15 cm proximal to the recording site adjacent to the border of the lateral aspect of the fibularis longus muscle.

In addition we measured the 3 following parameters:

1. CMAP amplitude, measured in millivolts from peak to peak.
2. F-wave latency, defined as the time elapsed from tibial nerve stimulation to the shortest F-wave latency in 10 consecutive trials.
3. SNAP amplitude measured in microvolts from the first positive peak to the most negative peak.

Molecular Studies

Molecular studies were performed on Genomic DNA and total RNA isolated from 5ml of peripheral blood leukocytes using standard methods. *FMR1* DNA analysis was performed with Southern blot analysis and PCR-based genotyping as described elsewhere.[10] This provides specific allele sizes (the length of CGG repeat expansion) and determination of the activation ratio (AR= fraction of normal *FMR1* expressed as active allele) in females with the premutation. The subjects with a normal *FMR1* gene (< 45 repeats), and premutation (55–200 repeats) were differentiated according to the length of CGG repeat number.[11] Quantification of *FMR1* mRNA levels was determined using the quantitative fluorescence reverse transcription-PCR method.[12]

Statistical analysis

Comparisons of patient characteristics (age and molecular parameters) among groups were performed by analysis of variance (ANOVA). Our main objectives were to examine potential: (1) abnormalities in nerve conduction (specifically tibial nerve CMAP amplitude, F-wave latency, tibial nerve conduction velocity, and SNAP amplitude for sural and superficial fibular nerves) and (2) association with CGG repeat number and *FMR1* mRNA expression levels. Linear regression models adjusted for age were used to compare nerve conduction variables among control, premutation with FXTAS, and permutation without FXTAS groups. For comparisons of nerve conduction, the model includes/adjusts for age if the *P*-value is < 0.1; otherwise, *P*-values for the more parsimonious ANOVA were reported. Similarly, regression models were used to examine association with mRNA and CGG (separately), among premutation carriers. *P*-value adjustment for multiple testing was based on the false discovery rate criterion. In the analysis, we excluded an *FMR1* mRNA level for 1 subject with low quality (extremely high standard error of the mean over replicate RT-PCR measurement; mRNA level 6.1 which exceeded the 6 interquartile range).

RESULTS

Nerve conduction studies

The average SNAP amplitudes were significantly reduced in subjects with FXTAS compared to control subjects in the left sural ($P = 0.0164$), right sural ($P = 0.0068$), and left superficial fibular nerves ($P = 0.0069$), see Table 2 and Figure 1. Typically, SNAP

amplitudes in the sural and superficial fibular nerve were lowest for FXTAS, followed by premutation carriers without FXTAS, and then control subjects. There were strong trends for reduced CMAP amplitudes in the right and left tibial nerves between FXTAS and controls ($P = 0.0568$ and $P = 0.0241$, respectively); however, these results were not significant after P-value adjustment for multiple testing. Conduction velocities and F-wave latencies were similar for all groups (all P-values > 0.2). Table 3 provides details of nerve conduction measurements among the 3 study groups.

Molecular Studies

The FXTAS study cohort significantly higher ($P = 0.008$) average levels of *FMR1* mRNA (mean 2.61, SD 0.62) compared to premutation carriers without FXTAS (mean 2.09, SD 0.46). As expected, this corresponded to a larger CGG expansion (mean 88.89 SD 18.45) in the FXTAS group (mean 84.30 SD 16.50 in the non-FXTAS group). Details of the participant characteristics are listed in Table 1. There was no association between *FMR1* mRNA expression levels, activation ratio, and CGG repeat number with nerve conduction measures among premutation carriers (with and without FXTAS).

DISCUSSION

Nerve conduction studies performed in female carriers with FXTAS, when compared with normal controls, demonstrated abnormalities consistent with axonal neuropathy preferentially affecting sensory nerve fibers. We also found differences in CMAP amplitudes in female carriers with FXTAS in comparison with normal controls, but these differences became non-significant after correction for multiple comparisons. In addition, women did not show any abnormalities in either conduction velocity or F-wave latencies compared to controls. The lack of significant abnormalities in conduction velocity and F-waves is in contrast with the results of a previous study involving men[5] and indicate that women with FXTAS are less affected than men in nerve conduction abnormalities even though many complain of neuropathic symptoms, including numbness, tingling, and/or pain.[6]

The pathogenesis of the neuropathy in FXTAS involves RNA toxicity which is reflected by the presence of intracellular inclusion bodies in neurons and glial cells.[8] Furthermore, evidence of neuronal involvement can even be found in peripheral tissue.[13, 14] Neuronal toxicity from excess *FMR1* mRNA would predict axonal dysfunction and a dying –back disruption of axons and myelin, leading to axonal neuropathy. From the electrophysiological standpoint, mild axonal neuropathies are characterized by reduced SNAP and CMAP amplitudes with little or no NCV slowing. In contrast, in severe axonal neuropathies there is NCV slowing and prolongation of F-wave latencies due to the loss of fast-conducting, large-diameter axons.[15, 16] Thus, the reduction of NCVs and increase of F-wave latencies in men, which was not seen in women with FXTAS, likely results from more advanced axonal degeneration rather than from direct myelin involvement. This interpretation is also supported by the fact that in spinal muscular atrophy, another condition characterized by impaired processing of mRNA, NCVs are slow in severely affected infants, but normal in less severely affected children.[17–19]

Peripheral neuropathy is a frequent source of morbidity in persons 55 and older.[20] The list of causes of peripheral neuropathies is very long even though in up to 41% of patients the etiology of the peripheral neuropathy cannot be identified.[21, 22] This report provides yet another cause of neuropathy in adult patients. We recommend that patients with neuropathy be questioned regarding a family history of fragile X mutations and that other FXTAS symptoms be assessed. If there is evidence of premutation problems, then testing for the fragile X gene mutation should be carried out.

In summary, our data suggest that abnormalities of NCVs are less common and less severe in women with FXTAS compared to men with FXTAS.[5] Sometimes even when patients are symptomatic with numbness, tingling, or pain in their extremities, there may not be nerve conduction abnormalities that are significantly different from controls, as we have reported here. MRI findings in women with FXTAS are also less likely to demonstrate the same degree of brain atrophy or white matter disease when compared with men with FXTAS.[3] In addition, the classical finding of the middle cerebellar peduncle sign (MCP sign) is seen in only 13% of women with FXTAS compared to 60% of affected men.[3] Women with FXTAS have less severe involvement likely because of the presence of the normal X chromosome, which can apparently modify the central and peripheral nervous system toxicity. However, many female carriers have neuropathy symptoms, including numbness, paresthesias, and pain, and individuals who present with such symptoms along with a history of the fragile X mutation in the family, or with other symptoms of premutation carriers such as cerebellar ataxia, tremor, premature ovarian failure, or infertility, should have fragile X DNA testing to document if they are premutation carriers.[23]

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Abbreviations

FXTAS	Fragile X-associated Tremor/Ataxia Syndrome
NCS	Nerve Conduction Studies
FMR1	fragile X mental retardation 1
LMNA	lamin A/C
CMAP	Compound Muscle Action Potential
SNAP	Sensory Nerve Action Potential
SD	standard deviation
AANEM	American Association of Neuromuscular and Electrodiagnostic Medicine
DNA	deoxyribonucleic acid
RNA	ribonucleic acid

mRNA	messenger ribonucleic acid
PCR	polymerase chain reaction
AR	activation ratio
ANOVA	analysis of variance
RT-PCR	reverse transcription polymerase chain reaction
NCV	nerve conduction velocity
MCP sign	middle cerebellar peduncle sign

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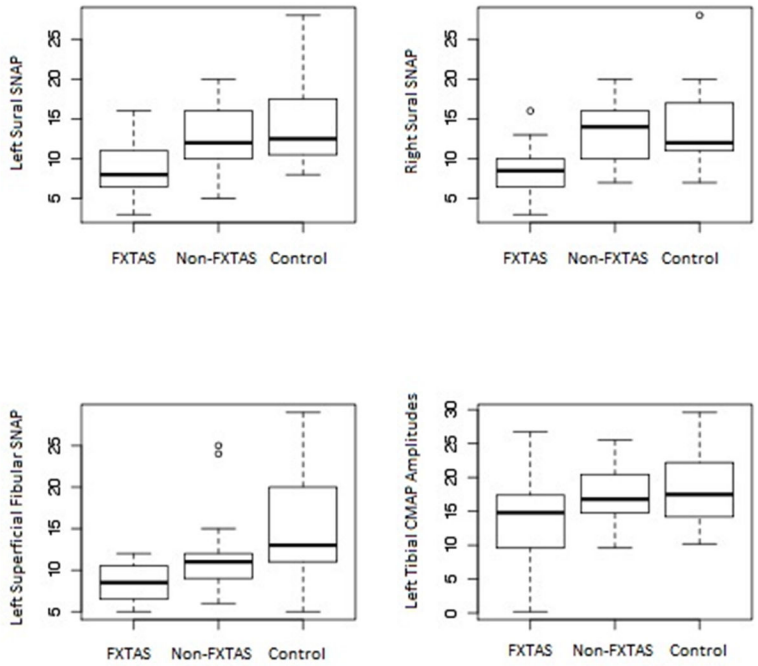

Figure 1.

Nerve conduction differences among groups. FXTAS versus control comparisons: left and right sural SNAP amplitudes, FXTAS vs. control, $P = 0.0164$, $P = 0.0068$, respectively; left superficial fibular, $P = 0.0069$; and left tibial CMAP amplitudes, $P = 0.0241$. Each boxplot shows the 1st (Q1) and 3rd (Q3) quartiles (box edges) and the median (50th percentile - solid line) along “whiskers” [which are 1.5 times the interquartile range (IQR = Q3-Q1)]. Observations outside the whiskers are indicated as open circles.

Table 1

Age and molecular characteristics of study participants.

Variable	N*	Mean(SD†)	Min	Max
Age				
Controls	26	61.50(6.41)	50	78
Premutation	20	54.95(6.98)	40	64
FXTAS	19	64.11(10.3)	46	80
Activation ratio				
Controls‡	--	--	--	--
Premutation	19	0.55(0.25)	0.10	0.91
FXTAS	19	0.55(0.23)	0.15	0.91
FMR1 mRNA				
Controls	24	1.40(0.24)	0.92	1.89
Premutation	20	2.09(0.46)	1.26	3.03
FXTAS	18	2.61(0.62)	1.57	3.89
CGG repeats				
Controls	25	28.68(5.83)	17	41
Premutation	20	84.30(16.5)	65	127
FXTAS	19	88.89(18.45)	57	134

*N = number of patients with respective values.

†SD = standard deviation.

‡Controls do not have an activation ratio, because it is related to the percentage of cells that have the normal X as the active X vs the premutation X. The controls do not have a premutation X.

Table 2

Nerve conduction measure *P* values among groups

Variable	*P* value*		
	FXTAS vs. Control	FXTAS vs. Pre	Pre vs. Control
Right Tibial CMAP, mV‡	0.0568	0.1566	0.7763
Right Tibial CV, m/s§	0.4805	0.4068	0.8564
Right Tibial F-wave, mV‡	0.8619	0.0731	0.0723
Left Tibial CMAP, mV‡	0.0241	0.0706	0.6242
Left Tibial CV, m/s§	0.2734	0.6481	0.5506
Left Tibial F-wave, mV‡	0.5587	0.8695	0.6739
Left Sural SNAP, μV‖	0.0164†	0.0874	0.3274
Right Sural SNAP, μV‖	0.0068†	0.0066†	0.6186
Left Superficial Fibular SNAP, μV‖	0.0069†	0.2693	0.0585
Right Superficial Fibular SNAP, μV‖	0.1010	0.4105	0.3926

*Model adjusted for age – see methods section.

†Significant after FDR adjustment.

‡mV = millivolts

§m/s = meters per second

‖μV = microvolts

Table 3

Nerve conduction measures among groups.

Variable	N*	Mean (SD†)	Min	Max
Right Tibial CMAP, mV‡				
Controls	25	18.22(6.77)	6	29.6
Premutation	19	19.48(5.57)	10.2	30.5
FXTAS	18	13.72(8.43)	0.2	28.1
Right Tibial CV, m/s§				
Controls	25	45.88(4.66)	40	60
Premutation	19	46.16(3.64)	41	52
FXTAS	18	44.78(6.55)	24	53
Right Tibial F-wave, mV‡				
Controls	24	48.96(3.96)	41.7	58.3
Premutation	18	46.7(3.17)	40.3	55
FXTAS	16	49.18(4.68)	41.1	61.1
Left Tibial CMAP, mV‡				
Controls	21	18.41(5.72)	10.2	29.6
Premutation	19	17.49(4.26)	9.6	25.5
FXTAS	13	13.57(7.94)	0.2	26.7
Left Tibial CV, m/s§				
Controls	21	46.24(3.18)	39	53
Premutation	19	46.47(4.75)	41	57
FXTAS	13	43.85(7.5)	24	53
Left Tibial F-wave, mV‡				
Controls	19	49.31(2.93)	45.2	55.1
Premutation	17	47.84(3.51)	40.3	55
FXTAS	11	49.02(4.51)	41.1	56.9
Left Sural SNAP, μV‖				
Controls	12	14.67(5.61)	8	28
Premutation	14	12.79(4.21)	5	20
FXTAS	7	8.86(4.38)	3	16
Right Sural SNAP, μV‖				
Controls	9	14.22(6.44)	7	28
Premutation	19	13.32(3.87)	7	20
FXTAS	12	8.58(3.5)	3	16
Left Superficial Fibular SNAP, μV‖				
Controls	13	15.15(7.59)	5	29
Premutation	17	12.24(5.19)	6	25
FXTAS	8	8.5(2.45)	5	12
Right Superficial Fibular SNAP, μV‖				

Variable	N*	Mean (SD†)	Min	Max
Controls	14	11.79(5.45)	4	22
Premutation	15	9.73(2.22)	6	14
FXTAS	9	9.11(3.82)	4	17

*N = number of patients with respective values

†SD = standard deviation

‡mV = millivolts

§m/s = meters per second

||μV = microvolts