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Prevalence of Restless Legs Syndrome and Sleep Quality in Carriers of the Fragile X Premutation

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Abstract

This study examined the relationship between the Fragile X premutation and Restless Legs Syndrome (RLS). Demographic, medical history and survey responses related to sleep were collected from 213 participants (127 carriers and 86 age matched controls). Subjects were asked about the presence of the four formal diagnostic criteria for RLS. Individuals with the premutation were 1.9 times as likely to meet criteria for RLS (95% CI 1.1–3.2, $p=0.025$) as controls. Premutation carriers with RLS also experienced significantly worse symptoms than matched controls with adjusted mean scores of 15.1 ± 8.8 vs. 7.9 ± 4.4 respectively on the International Restless Legs Scale. As markers for domains of sleep disturbance, all subjects completed the Epworth Sleepiness Scale, the Insomnia Severity Index and the Pittsburgh Sleep Quality Index. Premutation carriers demonstrated significantly more pathology on these tests except for the Epworth Sleepiness Scale where there was a trend towards increased daytime sleepiness in carriers. RLS joins a host of other conditions that should be carefully screened for in those carrying the Fragile X premutation and sleep should be a focus for clinicians providing care to them.

Keywords

Restless Legs Syndrome; Fragile X premutation; Sleep; Trinucleotide repeat disorders; Insomnia

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Conflict of Interest Statement

All other authors deny a conflict of interest.

Introduction

The *FMRI* premutation is a relatively common genetic condition occurring in roughly 1 in 200 women and 1 in 400 men (1). It is defined as an expansion in the *FMRI* gene to between 55–200 CGG repeats (2). Repeats above 55 are unstable and can expand when passed on during meiosis to above 200 CGG repeats (termed ‘full mutation’) with consequent silencing of the *FMRI* gene (3). This results in Fragile X syndrome (4), the most common inherited form of X-linked intellectual disability. The premutation phenotype is significantly different, but the past decade of research has demonstrated that it has its own pathology, such as Fragile X-associated Tremor and Ataxia Syndrome (5), which may be mediated through increased levels of *FMRI* mRNA and sequestration of critical proteins for cell function (6).

The present study aimed to examine the relationship between the fragile X premutation and restless legs syndrome (RLS). RLS is a common condition involving a disagreeable feeling in the legs that that can impair one’s ability to fall asleep. Defects in iron regulating proteins have been associated with both RLS (7) and the premutation (8). In addition to this similarity, the impetus for studying the prevalence of RLS in the premutation population is that RLS has been found to be prevalent in other hereditary ataxic syndromes such as spinocerebellar ataxias (9) and Parkinson’s disease (10).

Materials and Methods

Recruitment and Collection

Recruitment and survey participation were approved by the UC Davis Institutional Review Board. Previous adult participants at the UC Davis MIND Institute were contacted by e-mail or phone with an invitation to participate in the online study. Additional control subjects were recruited from flyers and word of mouth referrals. Of all those offered the opportunity to participate by phone or e-mail, 61% responded to the survey including 63% of known premutation carriers and 69% of control subjects. All premutation carriers and 92% of control subjects described themselves as white and non-Hispanic.

Survey Design

The survey collected demographic information including premutation carrier status, history of FXTAS diagnosis, gender and age. Those respondents known to have CGG repeats in the gray zone (45–54), with the full mutation (>200) or mosaicism into either range were excluded. Subjects were asked the four questions considered diagnostic for RLS (11). These included asking if the subject had an urge to move their legs, if that urge worsened during periods of inactivity, if the urge was relieved by movement and if the urge worsened in the evening. Those subjects who answered yes to all four were asked to complete the International Restless Legs Scale (IRLS)(12), a survey about RLS severity in the past week.

Subjects were asked to complete three additional surveys concerning sleep and related issues. The first, the Epworth Sleepiness Scale(ESS)(13), consisted of questions about how likely a subject would be to fall asleep in given situations. The second was the Insomnia

Severity Index (ISI) (14) which covered symptoms specific to types of insomnia and sleep problems. The final sleep survey was the Pittsburgh Sleep Quality Inventory (PSQI) (15) where subjects answered questions about many different domains of sleep.

Statistical Analysis

Prevalence/proportion of RLS was estimated for subjects with and without the premutation. Univariate p-value comparing prevalence between participants with *FMRI* premutation and controls were based on Fisher's exact test. Descriptive comparisons of participant age were based on t-tests. To obtain adjusted relative risk of RLS in participants with the premutation compared to controls, a generalized linear model (GLM) adjusted for age and gender was fitted using a binomial distribution with log link ($n = 213$). Among subjects with RLS ($n = 56$), comparison of RLS severity between participants with the premutation and control subjects was based on linear regression models, again adjusted for age and gender. Comparisons between participants with the premutation and controls with respect to the PSQI, the ISI, and the ESS, were based on linear regression models that included premutation status (yes/no), age, gender, RLS status (yes/no) and premutation status by RLS status interaction. However, these models with effect modification by RLS status did not indicate significant interaction; therefore, we present the results from the more parsimonious models without interaction below.

Results

The mean ages for premutation carriers and control subjects were 64 (SD 10.2) and 67 (SD 7.7), respectively ($p=0.014$). There was no difference in gender between premutation carriers and controls ($p=0.1623$) (Table 1). The prevalence of RLS in premutation subjects was 33.1% (42/127), which was significantly higher than the prevalence of RLS among controls, 16.3% (14/86), $p = 0.007$ (Table 2). The relative risk (RR) of RLS in premutation carriers relative to controls was 1.86 (95% confidence interval [CI] 1.08–3.2; $p = 0.0246$). The RR of RLS was not associated with age, although the risk of RLS in males was lower, with a RR of 0.54 (95% CI 0.31–0.92, $p = 0.0232$). Average RLS severity for premutation subjects (mean 15.1, SD 8.8) was significantly higher than control subjects (mean 7.9, SD 4.4), $p = 0.0061$. Also, premutation subjects showed significantly more severe insomnia ($p = 0.009$), lower quality of sleep ($p = 0.0398$) and a trend towards higher levels of sleepiness ($p = 0.0708$) (Table 3).

In one separate analysis, no significant difference was found in the prevalence of RLS, mean ESS score, mean ISI score or total PSQI score in the 76 premutation carriers with a diagnosis of FXTAS as compared to the 51 carriers without such a diagnosis. In a second separate analysis limiting comparison to white non-Hispanic premutation carriers to white non-Hispanic controls, the RR of RLS was 1.65 (95% CI 0.95–2.87, $p=0.0755$).

Discussion

The present study demonstrated a significant relationship between the fragile X premutation and RLS with nearly twice the likelihood of RLS in the carrier population as compared to controls. The raw prevalence of RLS in premutation carriers is similar to that seen in the

spinocerebellar ataxias (20–30%)(9) and Parkinson's disease (20–24%) (10). Dopamine dysfunction has been hypothesized in the mechanism of RLS (16) and this may explain a relationship to Parkinson's disease while also partially explaining the relationship to the premutation. FMRP, the protein expressed through the *FMR1* gene and normal or lowered in premutation carriers, has been shown to be involved in dopamine activity (17).

This work also looked at the sleep of premutation carriers. Two surveys, the ISI and PSQI, showed a significant difference between carriers and controls. These also showed a very tight correlation with RLS status, whereas the ESS showed no correlation to RLS and only trended towards a difference between controls and premutation carriers. The ESS has previously shown a mixed picture in the RLS population (18) which does not make this result surprising. The ISI would seem to be more directly related to RLS both because of the nature of its prevention of sleep induction. The ISI has not been commonly used to study the severity or progression of RLS, but our results may argue for its greater use. The PSQI has previously been shown to have a good correlation with RLS severity (19).

The study limitations included a lack of correlation with other common sleep problems such as sleep apnea, no information on the age of onset of RLS and a lack of ethnic diversity in subjects, so the results may not be generalized to the whole premutation population.

Our results demonstrate that RLS and sleep disturbances are more common in carriers compared to controls. These problems should be clinically assessed in carriers, so that treatment, if needed, can be initiated. The cause of these disturbances may be related to iron dysregulation that has been reported in carriers related to *FMR1*-RNA toxicity (8).

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References

1. Tassone F, Iong KP, Tong TH, et al. FMR1 CGG allele size and prevalence ascertained through newborn screening in the United States. *Genome medicine*. 2012; 4:100. [PubMed: 23259642]
2. Fu Y-H, Kuhl DPA, Pizzuti A, et al. Variation of the CGG repeat at the fragile X site results in genetic instability: Resolution of the Sherman paradox. *Cell*. 1991; 67:1047–1058. [PubMed: 1760838]
3. Pieretti M, Zhang FP, Fu YH, et al. Absence of expression of the FMR-1 gene in fragile X syndrome. *Cell*. 1991; 66:817–822. [PubMed: 1878973]
4. Harvey J, Judge C, Wiener S. Familial X-linked mental retardation with an X chromosome abnormality. *Journal of medical genetics*. 1977; 14:46–50. [PubMed: 839500]

5. Hagerman RJ, Leehey M, Heinrichs W, et al. Intention tremor, parkinsonism, and generalized brain atrophy in male carriers of fragile X. *Neurology*. 2001; 57:127–130. [PubMed: 11445641]
6. Sellier C, Freyermuth F, Tabet R, et al. Sequestration of DROSHA and DGCR8 by expanded CGG RNA repeats alters microRNA processing in fragile X-associated tremor/ataxia syndrome. *Cell reports*. 2013; 3:869–880. [PubMed: 23478018]
7. Allen RP, Earley CJ. The role of iron in restless legs syndrome. *Movement Disorders*. 2007; 22:S440–S448. [PubMed: 17566122]
8. Napoli E, Ross-Inta C, Wong S, et al. Altered zinc transport disrupts mitochondrial protein processing/import in fragile X-associated tremor/ataxia syndrome. *Human molecular genetics*. 2011; 20:3079–3092. [PubMed: 21558427]
9. Abele M, Burk K, Laccone F, et al. Restless legs syndrome in spinocerebellar ataxia types 1, 2, and 3. *Journal of neurology*. 2001; 248:311–314. [PubMed: 11374096]
10. Ondo WG, Vuong KD, Jankovic J. Exploring the relationship between Parkinson disease and restless legs syndrome. *Archives of neurology*. 2002; 59:421–424. [PubMed: 11890847]
11. Allen RP, Picchiatti D, Hening WA, et al. Restless legs syndrome: diagnostic criteria, special considerations, and epidemiology. A report from the restless legs syndrome diagnosis and epidemiology workshop at the National Institutes of Health. *Sleep medicine*. 2003; 4:101–119. [PubMed: 14592341]
12. Walters AS, LeBrocq C, Dhar A, et al. Validation of the International Restless Legs Syndrome Study Group rating scale for restless legs syndrome. *Sleep medicine*. 2003; 4:121–132. [PubMed: 14592342]
13. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep*. 1991; 14:540–545. [PubMed: 1798888]
14. Bastien CH, Vallieres A, Morin CM. Validation of the Insomnia Severity Index as an outcome measure for insomnia research. *Sleep medicine*. 2001; 2:297–307. [PubMed: 11438246]
15. Buysse DJ, Reynolds Iii CF, Monk TH, et al. The Pittsburgh sleep quality index: A new instrument for psychiatric practice and research. *Psychiatry research*. 1989; 28:193–213. [PubMed: 2748771]
16. Eisensehr I, Wetter TC, Linke R, et al. Normal IPT and IBZM SPECT in drug-naive and levodopa-treated idiopathic restless legs syndrome. *Neurology*. 2001; 57:1307–1309. [PubMed: 11591854]
17. Wang H, Wu LJ, Kim SS, et al. FMRP acts as a key messenger for dopamine modulation in the forebrain. *Neuron*. 2008; 59:634–647. [PubMed: 18760699]
18. Fulda S, Wetter TC. Is daytime sleepiness a neglected problem in patients with restless legs syndrome? *Movement Disorders*. 2007; 22:S409–S413. [PubMed: 17588232]
19. Cuellar NG, Strumpf NE, Ratcliffe SJ. Symptoms of restless legs syndrome in older adults: outcomes on sleep quality, sleepiness, fatigue, depression, and quality of life. *Journal of the American Geriatrics Society*. 2007; 55:1387–1392. [PubMed: 17915343]

Table 1

Demographics

Variable	Control	Premutation	P-value
Count	86	127	
# of Women (%)	39 (45.3)	71 (55.9)	0.162
Mean Age in Years (SD)	67 (7.7)	64 (10.2)	0.014

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Summary of outcome variables: RLS (yes/no), severity, sleepiness, sleep quality and insomnia severity rating in premutation carriers and controls

Table 2

Variable	Control		Premutation	
	Count	Percent	Count	Percent
Restless Legs Syndrome (RLS)	No	72 83.72	85 66.93	
	Yes	14 16.28	42 33.07	
	N	Mean	SD	N
International Restless Legs Scale (IRLS)*	14	7.93	4.38	42
Epworth Sleepiness Scale (ESS)	86	6.69	3.92	127
Insomnia Severity Index (ISI)	86	6.24	5.02	126
Pittsburgh Sleep Quality Inventory (PSQI)	85	6.32	3.12	126
				Mean
				SD
				8.81
				4.90
				7.22
				4.52

* Among participants with RLS

Age- and gender-adjusted models of the (A) relative risk of RLS, (B) RLS severity, sleepiness, sleep quality and insomnia severity rating in premenutation carriers and controls

Table 3

Variable	Relative Risk (95% CI) [*] P-value		
	Premutation relative to control	Age	Male relative to female
(A) Restless Legs Syndrome (RLS)	1.86 (1.08–3.20) 0.0246	1.0 (0.98–1.01) 0.6289	0.54 (0.31–0.92) 0.0232
Coefficient Estimates (P-value)			
	Premutation	Age	Male relative to female
(B) Restless Legs Syndrome Rating Scale Severity ^{**}	7.24 (0.0061)	-0.02 (0.885)	1.89 (0.4215)
Epworth Sleepiness Survey (ESS)	1.18 (0.0708)	-0.06 (0.0995)	1.10 (0.0923)
Insomnia Severity Index (ISI)	2.19 (0.009)	-0.12 (0.0089)	-2.04 (0.0152)
Pittsburgh Sleep Quality Inventory (PSQI)	1.08 (0.0398)	-0.03 (0.2778)	-1.64 (0.0019)
			3.22 (<0.0001)
			RLS status
			--
			0.09 (0.9026)
			4.80 (<0.0001)

* Confidence Interval

** Among participants with RLS