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Sleep apnea in fragile X premutation carriers with and without FXTAS

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Abstract

This report seeks to establish the prevalence of sleep apnea in patients with the *FMRI* premutation with and without FXTAS and to determine any correlation between CGG repeat and *FMRI* mRNA levels with sleep apnea prevalence. Demographic and medical data from 430 (229 males, 201 females) participants were used in this analysis. Participants included premutation carriers with (n=118) and without FXTAS (n=174) as well as controls without the premutation (n=123). Logistic regression models were employed to estimate the odds ratio of sleep apnea relative to controls, adjusted for age and gender, and also to examine potential association with CGG size and *FMRI* mRNA expression level. The observed proportion of sleep apnea in premutation carriers with and without FXTAS and controls are 31.4% (37/118), 8.6% (15/174), and 13.8% (17/123), respectively. The adjusted odds of sleep apnea for premutation carriers with FXTAS is about 3.4 times that compared to controls (odds ratio, OR=3.4, 95% CI 1.8 to 7.4; p=0.001), and similarly relative to premutation carriers without FXTAS (OR=2.9, 95% CI 1.2 to 6.9; p=0.014). The risk of sleep apnea was not different between controls and premutation carriers without FXTAS. The presence of sleep apnea is not associated with CGG repeat numbers nor *FMRI* mRNA expression level among premutation carriers. Our data supports a higher prevalence and risk of sleep apnea in patients with FXTAS. We recommend that all patients diagnosed with FXTAS be screened for

sleep apnea given the negative and perhaps accelerative impact sleep apnea may have on their FXTAS progression.

Keywords

sleep apnea; fragile X-associated tremor/ataxia syndrome; trinucleotide repeat diseases; mitochondrial disorders; gait disorders/ataxia

INTRODUCTION

Fragile X-associated tremor/ataxia syndrome (FXTAS) is seen in a subgroup of older adults who are carriers of premutation alleles (55–200 cytosine, guanine, and guanine [CGG] repeats) of the fragile X mental retardation 1 (*FMRI*) gene [Hagerman *et al.*, 2001; Berry-Kravis *et al.*, 2007; Jacquemont *et al.*, 2007; Leehey *et al.*, 2007]. The pathogenesis of FXTAS results from the direct neural cell toxicity of elevated levels of the expanded-CGG-repeat *FMRI* mRNA (RNA toxic gain-of-function), which leads to protein dysregulation [Arocena *et al.*, 2005; Garcia-Arocena *et al.*, 2010]. The natural history of FXTAS begins with late onset of a movement disorder involving intention tremor and/or gait ataxia, resulting in a progressive decline in mobility [Leehey *et al.*, 2007]. FXTAS also includes neuropathy, usually featuring pain in the lower extremities, and autonomic dysfunction in the majority of patients [Jacquemont *et al.*, 2004; Berry-Kravis *et al.*, 2007, Hagerman *et al.*, 2007].

Psychiatric disorders commonly seen in patients with FXTAS include anxiety, agitation, apathy, and depression [Bacalman *et al.*, 2006; Bourgeois *et al.*, 2010]. Sleep disorders can exacerbate these behavioral issues [Madani *et al.*, 2010], and are often overlooked in those with FXTAS. Approximately 2% of women and 4% of men are estimated to suffer from sleep apnea, according to conventional diagnostic criteria [Young *et al.*, 1993]. Sleep apnea is defined by periods of apneas or hypopneas during sleep and is diagnosed and assessed by the apnea-hypopnea index, or AHI. An apnea is a temporary and often cyclical cessation of breathing during sleep while a hypopnea is the reduction of breathing amplitude. The three types of sleep apnea include obstructive sleep apnea, caused by anatomical barriers to breathing, and central and mixed sleep apnea, which occur due to a lack of respiratory effort independent of or in combination with obstructive sleep apnea, respectively [Dempsey *et al.*, 2010]. Sleep apnea-hypopnea syndrome (SAHS) affects 15–20% of individuals over 65 years [Martinez-Garcia *et al.*, 2010] and obstructive sleep apnea (OSA) is now recognized as a common medical problem [Duran *et al.*, 2001]. All three types of sleep apnea have been variably reported in other neurodegenerative diseases, such as Parkinson's disease, Multiple System Atrophy (MSA), and Alzheimer's disease [Noradina *et al.*, 2010].

We have encountered many patients with FXTAS suffering from sleep apnea, however there are no studies of sleep apnea in patients with FXTAS. Thus, the current study examines the prevalence and relative risk of sleep apnea in patients with the premutation with and without FXTAS and explores any association with *FMRI* premutation CGG expansion and *FMRI* mRNA levels.

MATERIALS AND METHODS

SUBJECTS

Data relevant to sleep apnea and other associated medical issues was collected over several years on 430 participants age 35 and older, including controls and those with the premutation. Out of the 430 study participants, 229 were males and 201 were females. The premutation carriers with and without FXTAS were actively recruited to the MIND Institute related to specific research protocols that included a medical history. Controls are either family members of individuals with a fragile X mutation or unrelated control participants.

Premutation status was determined molecularly based on CGG repeat number. The presence of FXTAS was based on a physician's assessment of the diagnostic criteria [Jacquemont *et al.*, 2003] and clinical stage of the participants [Bacalman *et al.*, 2006]. For analysis purposes, any subject with possible, probable, or definite FXTAS as defined by Jacquemont *et al.* (2003) diagnostic criteria was considered to have FXTAS [Jacquemont *et al.*, 2003]. The severity/stage of FXTAS (Stage 1: Subtle or questionable signs i.e. subtle tremor or mild balance problems, but no interference with activities; Stage 2: Minor, but clear, tremor and/or balance problems: minor interference with activities; Stage 3: Moderate balance and/or tremor problems interfering with activities of daily living and at least occasional falls; Stage 4: Severe tremor and/or balance problem. Requires assistance with activities of daily living and uses a cane or walker; Stage 5: Uses wheelchair on a daily basis) was determined as defined in Bacalman *et al* (2006).

DATA COLLECTION METHODS

Data for this analysis was collected via a medical history sheet filled out during a patient appointment and medical assessment. For those patients who reported a history of sleep apnea, the diagnosis was usually suspected by a primary care physician who then referred the patient to undergo a sleep study during which the diagnosis was confirmed. During these sleep studies, treatment options were recommended to patients, and many started continuous positive airway pressure, or CPAP. A small minority of patients have not undergone sleep studies, but for our analysis any diagnosis of sleep apnea made by a physician was sufficient to qualify them as having sleep apnea.

MOLECULAR ANALYSIS

CGG trinucleotide expansion was used as the determinant for premutation status. Repeat sizes below 50 were considered controls while repeats of 55 to 200 were defined as premutation carriers. Grey zone individuals of 50–54 repeats, mosaics, and full mutation subjects (>200 CGG repeats) were not used in this study. DNA analyses were completed using blood samples in accordance with the protocol outlined in Tassone *et al.* (2000, 2004) and Saluto *et al.* (2005) [Tassone *et al.*, 2000; Tassone *et al.*, 2004; Saluto *et al.*, 2005]. CGG repeat expansions were established using an Alpha Innotech FloorChem 8800 Image Detection System.

In addition to the above molecular data, *FMRI* mRNA levels were analyzed as a possible correlate to sleep apnea. Blood samples were also used to attain this data according to methods described in Tassone *et al* (2000) [Tassone *et al.*, 2000].

STATISTICAL ANALYSIS

Characteristics of study participants were compared among groups (control and premutation carriers with and without FXTAS) using analysis of variance F-test and Fisher's exact method for continuous (e.g., age) and categorical variables, respectively. To assess the risk of sleep apnea among groups, we used logistic regression analysis to estimate the odds ratio of sleep apnea in patients with FXTAS, adjusted for age and sex. Association of sleep apnea risk with CGG size and mRNA level among premutation carriers was also determined using logistic regression models. Similarly, we examined among premutation carriers with FXTAS whether the likelihood of sleep apnea is associated with the severity (stages 1 to 5) of FXTAS.

RESULTS

Table I summarizes the study participant characteristics, including 123 controls, 174 premutation carriers without FXTAS, and 118 premutation carriers with FXTAS aged 35 to 89. As expected, the FXTAS group is older (mean age 65.5, SD 9.1) compared to premutation carriers without FXTAS (mean age 47.4, SD 10.6) and control groups (mean age 55.1, SD 13.4). Differences in age are statistically significant ($p < 0.001$) as is gender ($p < 0.001$) and we adjust for these factors in the logistic regression models of the risk of sleep apnea.

The observed proportion of sleep apnea in premutation carriers with FXTAS is higher, 31.4% (37/118), compared to premutation carriers without FXTAS (8.6%, 15/174) and the control group (13.8%, 17/123) (Table II). The adjusted odds of sleep apnea for premutation carriers with FXTAS is about 3.4 times that compared to controls (odds ratio, OR=3.4, 95% confidence interval, CI 1.8 to 7.4; $p=0.001$). Similarly, odds of sleep apnea is about three-fold higher for premutation carriers with FXTAS relative to premutation carriers without FXTAS (OR=2.9, 95% CI 1.2 to 6.9; $p=0.014$). The risk of sleep apnea was not different between control and premutation carriers without FXTAS groups. Sleep apnea is also not associated with CGG size ($p=0.618$) and mRNA expression level ($p=0.504$) among premutation carriers (Table II). Results and conclusions remain unchanged when analysis was performed based on definite FXTAS exclusively, or based on probable and definite FXTAS combined.

More precisely, the odds of sleep apnea was increased in possible FXTAS compared to controls (OR=2.64, $p=0.0245$), probable and definite FXTAS compared to controls (OR=4.55, $p<0.001$) and relative to premutation carriers without FXTAS (OR=2.89, $p=0.005$). Similarly, the likelihood of sleep apnea is also increased in patients with definite FXTAS compared to premutation without FXTAS (OR=4.85, $p=0.002$) and compared to controls (OR=5.63, $p<0.001$). Next, we examined whether the likelihood of sleep apnea is associated with the severity/stage of premutation carriers with FXTAS. We found that the OR = 1.9 (95% CI: 1.12 to 3.31; $p=0.019$) per increase in severity/stage.

DISCUSSION

Until this report, sleep apnea had not been studied in relation to FXTAS or the fragile X premutation. However, there is much ongoing research regarding correlations between molecular genetics and sleep disorders, particularly with regards to candidate and susceptibility genes that are imperative to early diagnosis and appropriate treatment [Caylak E. 2009; Caylak E. 2011]. For instance, genetic research regarding narcolepsy and restless legs syndrome have identified chromosomal regions as well as candidate genes linked to these disorders. Although our study is not an association study, the results provide knowledge to guide ongoing and future research in the field of sleep disorders and neurodegenerative diseases.

The results we obtained indicate that there is a statistically significant increased risk of sleep apnea in premutation carriers with possible, probable, and definite FXTAS (increased odds of ~2.6 to ~5.6 relative to controls and premutation carriers without FXTAS). The rate of sleep apnea in FXTAS (32%) is similar to the rates in other neurodegenerative diseases, perhaps due to their common involvement with central neurobiological mechanisms [Naismith *et al.*, 2011]. Prevalence of sleep apnea in patients with MSA is 30% [Kuzniar *et al.*, 2009], with Alzheimer's Disease is 40% [Ancoli-Israel *et al.*, 1991], and with Parkinson's Disease ranges from 20% to 66% [Schulte and Winkelmann, 2011]. We hypothesize that the reduced brainstem volume in FXTAS and the dysfunction of the autonomic system is likely to predispose patients with FXTAS to respiratory problems [Cohen, *et al.*, 2006].

There is also increased fragility and sensitivity of premutation neurons to cell death in culture and presumably in vivo. Chen *et al.* (2010) found that premutation neurons demonstrated reduced dendritic complexity, elevated stress markers, and enhanced cell death by 21 days in culture, which was significantly different from controls [Chen *et al.*, 2010]. Mitochondrial dysfunction is also seen in fibroblasts and neurons of premutation carriers with and without FXTAS [Ross-Inta *et al.*, 2010]. These cells have lower oxygen uptake, problems in electron transport and ATP synthesis, lower mitochondrial protein production, and increased oxidative stress [Ross-Inta *et al.*, 2010]. All of these problems contribute to premutation neuron fragility and lower ATP production levels, which is likely to add to the neurodegeneration seen in patients with FXTAS. [Ross-Inta *et al.*, 2010].

The common hypoxic periods of sleep apnea are detrimental to cellular function, and neurons in particular. [Chiang, 2006]. Due to the increased fragility of premutation neurons [Chen *et al.*, 2010], oxidative stress such as oxygen deprivation at the hand of sleep apnea would have enhanced effects, exacerbating the compromise of these neurons from RNA toxicity related to the premutation. Since premutation neurons already have decreased oxygen uptake [Ross-Inta *et al.*, 2010], frequent hypoxic events would result in even less oxygen available to mitochondria, causing a greater ATP deficit in the brain. Further premutation neuron damage and death would negatively affect neurocognitive function, and thus perhaps accelerate the progression of FXTAS in patients suffering from sleep apnea. A similar accelerative effect can be observed with exposure of patients with FXTAS to

neurotoxins, particularly during chemotherapy, and early cell death and brain disease were observed with such exposure [Paul *et al.*, 2010; O'Dwyer *et al.*, 2005].

Further follow-up analysis examining the association of sleep apnea to severity/stage among premutation carriers with FXTAS found increased risk of sleep apnea as the disease severity increases.

A weakness of our study is the lack of analysis of documented sleep study results in order to confirm sleep apnea diagnoses. Such results are difficult to obtain in a retrospective study and the format in which they are carried out varies among centers, making comparisons difficult. According to our medical history most individuals had polysomnography and the rest were diagnosed as having sleep apnea by their physicians. Currently, polysomnography is a medical practice in high demand and also not a feasible option for all participants due to accessibility or financial issues [Mulgrew *et al.*, 2007; McNicholas, 2008].

The clinical implications of this study are important. Sleep apnea in premutation carriers with FXTAS is usually treatable, but if it is not treated it may accelerate neuronal cell damage and cell death, and perhaps the progression of FXTAS. Likewise, diagnosis and treatment of sleep apnea can prevent the hypoxic episodes that can intensify oxidative stress in patients with FXTAS and thus perhaps slow the progression of their disease. Further research is needed to determine the exact relationship between FXTAS and sleep apnea. We recognize the issues associated with sleep studies—in particular the problems with expenses and accessibility—however we recommend sleep studies for those diagnosed with FXTAS.

There is currently no specific sleep apnea treatment recommendation for patients with FXTAS. The most common form of treatment for sleep apnea is a positive pressure airway device, or CPAP [McNicholas, 2008]. However, not all patients with sleep apnea respond well to this treatment or tolerate its use [Javaheri, 2006]. In patients with obstructive sleep apnea, CPAP can be very effective [Gay *et al.*, 2006]. However, for patients with central sleep apnea, its effectiveness is more contentious [Javaheri, 2006]. Other treatments for central sleep apnea include nocturnal administration of oxygen or medications such as theophylline and acetazolamide [Javaheri, 2006].

The use of CPAP in patients with central sleep apnea who also suffer from cardiovascular conditions is more complicated [Javaheri, 2006]. Due to the diversity in treatment options for patients with sleep apnea, especially for those with co-morbid diseases, we recommend that patients with FXTAS who suffer from sleep apnea see a neurologist, pulmonologist, or sleep specialist for appropriate treatment options.

In addition to preventing further neuronal damage, proper treatment of sleep apnea can also have significant benefits in the daily lives of sleep apnea sufferers. Common complications of sleep apnea include depression, daytime somnolence, neurocognitive dysfunction, and general performance impairment [Flemons *et al.*, 1997]. Therefore, if available and accessible, treatment of sleep apnea in patients with FXTAS may also improve their quality of life.

It has been reported that untreated obstructive sleep apnea in Alzheimer's disease patients results in worsening cognitive functioning over time [Cooke JR et al., 2009]. In a study of sustained CPAP treatment in this patient population it was discovered that patients treated with CPAP suffered from less cognitive, sleep, and mood problems than did those not treated with CPAP [Cooke *et al.*, 2009]. Due the similar neurodegenerative nature of FXTAS and Alzheimer's disease, it is likely that a similar effect could be observed in patients with FXTAS and sleep apnea. Additional research into treatment possibilities for patients with FXTAS would not only determine the most advantageous treatment option for this patient population but also help to better elucidate the relationships between sleep apnea and FXTAS.

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Table 1

Study Participant Characteristics

Variable	Control (N=123)			Premutation carriers without FXTAS (N=174)			Premutation carriers with FXTAS (N=118)			P-Value
	N	Mean	SD	N	Mean	SD	N	Mean	SD	
Age	123	55.1	13.4	174	47.4	10.6	118	65.5	9.1	<0.001
CGG Size	123	29.0	4.8	174	91.0	20.8	118	91.0	19.5	<0.001
mRNA Level	87	1.5	1.0	135	2.5	0.8	107	2.9	0.8	<0.001
Gender		Count	Percent		Count	Percent		Count	Percent	
Female		35	28.5		148	85.0		35.0	29.9	<0.001
Male		88	71.5		26	14.9		82.0	70.1	<0.001

Table II

Adjusted risk of sleep apnea and association with FMR1 mRNA and CGG

	Odds Ratio	95% CI ¹	P-value
Model: Risk of Sleep Apnea ²			
Premutation carriers with FXTAS vs. controls	3.42	1.82–7.45	0.0011
Premutation carriers without FXTAS vs. controls	1.17	0.50–2.4	0.7186
Premutation carriers with vs. without FXTAS	2.93	1.24–6.92	0.0142
Model: Association with mRNA and CGG ³			
FMR1 mRNA	1.18	0.73–1.91	0.5043
CGG Size	1.01	0.99–1.02	0.6178

¹ Confidence interval
² Adjusted for age and sex
³ Among premutation carriers, adjusted for age and sex