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Hypertension in *FMR1* Premutation Males With and Without Fragile X-Associated Tremor/Ataxia Syndrome (FXTAS)

Alyssa A. Hamlin[1,2], **Dina Sukharev**[1,2], **Luis Campos**[3], **Yi Mu**[3], **Flora Tassone**[2,4], **David Hessl**[2,5], **Danh V. Nguyen**[3], **Danuta Loesch**[6], and **Randi J. Hagerman**[1,2,*]

[1]Department of Pediatrics, University of California at Davis Medical Center, Sacramento, California

[2]MIND Institute, University of California at Davis Medical Center, Sacramento, California

[3]Department of Public Health Sciences, University of California at Davis School of Medicine, Davis, California

[4]Department of Biochemistry and Molecular Medicine, University of California at Davis School of Medicine, Davis, California

[5]Department of Psychiatry, University of California at Davis School of Medicine, Davis, California

[6]Department of Psychological Science, LaTrobe University, Melbourne, Australia

Abstract

Fragile X-associated tremor ataxia syndrome (FXTAS) is a late onset neurodegenerative disease that affects carriers of the fragile X premutation. This study seeks to assess hypertension risk and susceptibility in male premutation carriers with FXTAS. Although many symptoms and diagnostic criteria have been identified, hypertension risk has not been examined in this population. Data from 92 premutation carriers without FXTAS, 100 premutation carriers with FXTAS, and 186 controls was collected via patient medical interview. Age-adjusted logistic regression analysis was used to examine the relative odds of hypertension. We observed a significantly elevated odds ratio (OR) of hypertension relative to controls for premutation carriers with FXTAS (OR = 3.22, 95% CI: 1.72–6.04; $P = 0.0003$) among participants over 40-year old. The age-adjusted estimated odds of hypertension in premutation carriers without FXTAS in the over 40-year-old age group was higher compared to controls (OR = 1.61, 95% CI: 0.82–3.16), but was not statistically significant ($P = 0.164$). Chronic hypertension contributes to cardiovascular complications, dementia, and increased risk of stroke. Our results indicate that the risk of hypertension is significantly elevated in male premutation carriers with FXTAS compared with carriers without FXTAS and controls. Thus, evaluation of hypertension in patients diagnosed with FXTAS should be a routine part of the treatment monitoring and intervention for this disease.

Keywords

hypertension; *FMR1* premutation; fragile X-associated tremor/ataxia syndrome; autonomic disease

*Correspondence to: Randi J. Hagerman, MIND Institute, Department of Pediatrics, University of California at Davis Medical Center, 2825 50th Street, Sacramento, CA 95817. randi.hagerman@ucdmc.ucdavis.edu.

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INTRODUCTION

Fragile X-associated tremor/ataxia syndrome (FXTAS) is a neurodegenerative disease found in carriers of the premutation (55–200 CGG repeats) at the 5′-end of the fragile X mental retardation 1 (*FMR1*) gene. It has been estimated that one-third of male pre-mutation carriers over 50 years [Jacquemont et al., 2004a] and approximately 8–16% of female carriers develop FXTAS [Coffey et al., 2008; Rodriguez-Revenga et al., 2009].

Diagnostic criteria describing FXTAS have been reported [Jacquemont et al., 2003; Hagerman and Hagerman, 2004]. The major clinical phenotype of FXTAS is intention tremor and gait ataxia, but parkinsonism, moderate-to-severe short-term memory deficiency, and executive function deficits are also commonly seen [Loesch et al., 2005a; Grigsby et al., 2006; Berry-Kravis et al., 2007]. There are also psychiatric aspects of FXTAS, including depression, anxiety, irritability, and apathy [Bacalman et al., 2006; Bourgeois et al., 2009, 2011]. MRI features of FXTAS include white matter lesions involving the subcortical and periventricular regions and the middle cerebellar peduncles (MCP) [Brunberg et al., 2002]. The presence of this MCP sign is observed in approximately 60% of affected males and 13% of affected females [Adams et al., 2007]. However, this sign is not specific for FXTAS, and not all patients with FXTAS develop the MCP sign. Cerebral, brainstem, and cerebellar volume loss compared to age-matched controls is observed [Loesch et al., 2005b; Cohen et al., 2006; Adams et al., 2007].

Neuropathological findings of FXTAS include intranuclear inclusions in neurons and astrocytes throughout the brain [Greco et al., 2006] and in the peripheral nervous system [Gokden et al., 2009]. The inclusions are likely caused by an RNA gain-of-function effect from elevated *FMR1*-mRNA in the premutation [Hagerman and Hagerman, 2004]. The excess mRNA appears to sequester additional proteins, including an RNA-binding protein involved in splicing regulation, Sam 68. Dysfunction of Sam 68 leads to mis-splicing of mRNAs, including that of the SMN gene that is mutated in spinal muscular atrophy [Sellier et al., 2010].

Autonomic dysfunction has been widely noted in patients with FXTAS. Erectile dysfunction typically begins before the onset of tremor and ataxia while other autonomic dysfunction, such as bladder and bowel incontinence, occur late in the course of FXTAS [Greco et al., 2007]. Hypertension has been reported in over 60% of females with FXTAS, a significant increase compared to age-matched controls [Coffey et al., 2008]. Preliminary data suggest that this problem is not uncommon in males with FXTAS [Hagerman and Hagerman, 2004; Jacquemont et al., 2004b]. Here, we explore hypertension in males with the premutation, with and without FXTAS, compared with age-matched controls.

MATERIALS AND METHODS

Subjects

Over the last 3 years data from 192 adult premutation carrier males and 186 adult male controls contributed to this study. Most of the patients were recruited through three studies taking place at the MIND Institute at the University of California, Davis. The study protocols involved a medical history and physical examination that routinely included blood pressure measurement. In addition, data on 32 males (9 controls and 23 premutation carriers) was collected from Melbourne, Australia at the La Trobe University. Controls are mostly family members of patients with the fragile X mutation or individuals recruited to the MIND by staff and faculty. All data used in this study is from consented patients participating in research protocols both at the MIND as well as in Australia.

The 192 premutation carriers were divided into two groups based on their FXTAS diagnosis. Individuals were considered to have FXTAS if they met criteria for definite or probable FXTAS according to the most recent classifications as defined by Jacquemont et al. [2003]. This assessment includes both radiological and clinical symptoms. The two groups analyzed were 92 premutation carriers without FXTAS and 100 premutation carriers with FXTAS.

METHODS

Clinical data including hypertension, blood pressure, and age of onset of hypertension was gathered during a medical appointment or interview. For most patients, a self-reported diagnosis of hypertension by another physician was sufficient to consider them having hypertension. Alternatively, at the MIND Institute, any patient with a blood pressure measurement over 140/90 taken during the appointment was also considered hypertensive. Lastly, any patient on blood pressure medication was categorized to have hypertension diagnosed by the prescribing physician, even if a normal blood pressure measurement was reported during the examination.

All blood pressure values for this study are those directly measured during examinations rather than being self-reported by the patient. For patients with multiple visits to the MIND and thus with multiple blood pressure measurements, the latest observation was used in order to have a single data entry for each patient.

Age of onset of hypertension was also recorded or self-reported during the medical examination and was typically the age when the patient began to take antihypertensive medication.

Molecular Analysis

CGG repeat status was used as the basis to determine premutation carriers and controls. Patients with repeat numbers between 55 and 200 were considered to be premutation carriers while those with 50 repeats or less were considered controls. Gray zone patients (51–54 repeats) and mosaics were not used in this study. Blood samples were analyzed utilizing the methods outlined by Tassone et al. [2000, 2004] and Saluto et al. [2005]. Determination of trinucleotide expansion was completed using an Alpha Innotech FlourChem 8800 Image Detection System.

Statistical Analysis

Comparison of patient characteristics among groups was based on analysis of variance (ANOVA) for continuous variables and Fisher’s exact test for categorical variables, completed separately for individuals below and above age 40 years. To examine the association between hypertension and the patients group (control, premutation with FXTAS, and premutation without FXTAS), logistic regression model adjusted for age was used. The results are presented in terms of odds ratios (OR) and 95% confidence intervals (CI). Because hypertension is correlated with age, our model adjusts for age of individuals.

RESULTS

Patient Characteristics

Premutation carriers without FXTAS ranged in age from 18 to 84 years, with a mean of 51.28 (SD = 16.94 years), and were divided into two groups, age 18–39 and 40–84. All premutation carriers with FXTAS were above age 40, with a range of 52–89 and an average age of 67 years (SD = 7.58 year). Controls ranged in age from 19 to 88 years, had an average age of 47 (SD = 15.58 years) and were also divided into two age groups (Table I).

The average age of controls and premutation carriers without FXTAS in the 18–40 age range was not statistically significantly different ($P = 0.276$), with controls averaging 32 years and premutation carriers averaging 30 years. However, age is significantly different between controls (mean 56, SD 11.08) and premutation carriers without FXTAS in the over 40 age range (mean 60, SD 12.18; $P = 0.021$). The premutation individuals with FXTAS (mean 67, SD 7.58) were significantly older than controls and premutation carriers without FXTAS in the over 40 range ($P < 0.0001$, respectively). Characteristics of participants are provided in Table I.

Hypertension in Premutation Carriers With and Without FXTAS

Among 18- to 40-year-old subjects, 1 of the 27 premutation carriers without FXTAS (3.70%) and 11 out of 69 controls (15.94%) had hypertension. However, the difference was not statistically significant ($P = 0.134$). Among 65 over 40-year-old premutation carriers without FXTAS, 27 (41.54%) had hypertension while 38 (58.46%) did not. In contrast, among the 117 controls, 32 (27.35%) had hypertension; 85 (72.65%) did not (Table II). Although the age-adjusted estimated risk of hypertension in premutation carriers without FXTAS in the over 40 age group was higher compared to controls (OR = 1.61, 95% CI: 0.82–3.16), this was not statistically significant ($P = 0.164$).

In 100 over 40-year-old premutation males with FXTAS, 67 (67%) had hypertension while only 33 (33%) did not. The age-adjusted OR of hypertension relative to controls was OR = 3.22 (CI: 1.72–6.04) and was statistically significant ($P = 0.0003$). Age was positively associated with hypertension with approximately 6% increased odds for a 1 year increase in age (OR = 1.062, 95% CI: 1.03–1.09; $P < 0.0001$).

Blood Pressure

Because many patients suffering from hypertension took medication to lower their blood pressure, blood pressure values were not significantly different between any group and their age-matched controls. The average measurements taken for controls, premutation carriers without FXTAS and premutation carriers with FXTAS were 130.4/80.2, 132.2/78.9, and 135.8/77.0, respectively (Table I).

Age of Onset of Hypertension

Based on limited availability of data regarding age of onset, there appears to be little difference between both premutation groups compared to age-matched controls, although we emphasize that this should be considered descriptive only. There is limited data available for controls and premutation carriers without FXTAS, with only 11 and 6 records for the age of onset, respectively. This is compared to the 38 age of onset records for premutation carriers with FXTAS. Also due to the onset of hypertension later in life, we had age of onset data only for patients older than 40 years. Controls had an average age of onset of 56, premutation carriers without FXTAS of 54, and premutation carriers with FXTAS of 53 years. Since our study lacks sufficient data on hypertension onset and contributing factors, further studies are needed to delineate the age of onset of hypertension in premutation carriers, including modifying factors.

DISCUSSION

Hypertension and related autonomic dysfunction have been discussed as symptoms of FXTAS in previous publications [Jacquemont et al., 2003, 2004b; Coffey et al., 2008]; however, extensive controlled studies in males have not been performed. Coffey et al. [2008] reported hypertension as significantly more common in female carriers with FXTAS compared to controls, but not so in premutation carriers without FXTAS. Based on the data

collected in this study, a similar result was found in males. There is a significantly higher age-adjusted risk (odds) of hypertension associated with FXTAS compared to controls among male subjects over age 40 years. However, the odds of hypertension in premutation carriers without FXTAS were not different from controls. It should be noted that in this study and in Coffey et al. [2008], medical data were collected via self-report, along with documentation of medication to treat hypertension. Potential bias resulting from this data collection method is limited by the similarity of the collection methods used for patients and age-matched controls.

The cause of hypertension is likely related to the autonomic dysfunction seen in FXTAS [Jacquemont et al., 2003; Leehey, 2009]. These problems may be related to the inclusion involvement of the peripheral nervous system, including both sympathetic and parasympathetic ganglia and pericardial ganglia [Gokden et al., 2009]. However, centers in the brain coordinating autonomic responses, including the insula, thalamus, and hypothalamus, are also affected by white matter disease [Greco et al., 2006, 2008; Hashimoto et al., 2011].

In addition, individuals with the premutation with and without FXTAS often have depression, anxiety, and other psychiatric problems [Hessl et al., 2005; Bourgeois et al., 2009, 2011; Leehey, 2009], which may also be related to elevated blood pressure. Although the precise correlation between hypertension and depression has yet to be established, they often occur together [Scalco et al., 2005]. Depressive symptoms, anxiety, and stress are associated with elevated corticosteroid levels. Premutation mice have an elevated corticosteroid response to stress when they age, and it is likely that this also occurs in humans with the premutation [Brouwer et al., 2008].

Untreated hypertension can result in cardiovascular complications, dementia, and an increased risk of stroke [Perry et al., 2000; Chobanian et al., 2003; Nagai et al., 2010]. More controversially, chronic hypertension may result in an increased incidence of white matter disease [Sierra and Coca, 2006; Gottesman et al., 2010]. Treatment of hypertension and subsequent reduction of blood pressure can slow the progression of white matter disease, and thus in turn reduce the risk of stroke and increasing dementia [Godin et al., 2011]. These benefits may also be seen in those with FXTAS who are treated for their hypertension and thus deserves further study.

There are a number of interventions that can treat hypertension in FXTAS carriers. Attention to the psychiatric problems and daily stresses should be discussed. Antidepressants, including selective serotonin reuptake inhibitors (SSRIs), which can also stimulate neurogenesis, can be utilized to treat depression or anxiety in addition to psychotherapy [Hagerman et al., 2008; Bourgeois et al., 2009]. Behavioral treatment of hypertension includes weight loss, salt restriction, exercise, and a healthy diet with reduced cholesterol and fat intake. When lifestyle adjustments are not enough to lower blood pressure, medical and pharmacological treatments are used [Chobanian et al., 2003].

There is currently no cure for FXTAS. However, treatment options for cognitive decline, tremor, gait ataxia, and other FXTAS symptoms have been reported [Hagerman et al., 2008; Berry-Kravis et al., 2010]. Elevated hypertension risk has been established in female premutation carriers with FXTAS [Coffey et al., 2008]. This study supports the same outcome for males. Therefore, all pre-mutation carriers with FXTAS should be screened for hypertension and treated as needed.

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TABLE I

Participant Characteristics

	Age <40		Age ≥40		All data	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Group						
Pre with FXTAS	—	—	100	67.19 (7.58)	100	67.19 (7.58)
Pre without FXTAS	27	30.21 (7.15)	65	60.02 (11.06)	92	51.28 (16.94)
Control	69	31.98 (5.25)	117	56.26 (12.18)	186	47.22 (15.58)

	Age <40		Age ≥40		All data	
	N*/N	Mean (SD)	N*/N	Mean (SD)	N*/N	Mean (SD)
SBP						
Pre with FXTAS	—	—	88/100	135.78 (18.33)	88/100	135.78 (18.33)
Pre without FXTAS	23/27	123.39 (11.26)	44/65	136.73 (14.5)	67/92	132.15 (14.83)
Control	56/69	126.27 (13.33)	90/117	133.01 (14.36)	146/186	130.42 (14.31)
DBP						
Pre with FXTAS	—	—	88/100	76.95 (8.8)	88/100	76.95 (8.8)
Pre without FXTAS	23/27	73.91 (12.93)	44/65	81.45 (7.99)	67/92	78.87 (10.51)
Control	56/69	79.13 (8.67)	90/117	80.89 (8.38)	146/186	80.21 (8.51)

N, number of subjects in group; N*, number of blood pressure measurements collected in group; SBP, systolic blood pressure; DBP, diastolic blood pressure.

TABLE II

Hypertension in Subjects Age ≥40 Years

	Hypertension		
	Absent	**Present**	**Total**
Pre with FXTAS	33 (33.0%)	67 (67.0%)	100
Pre without FXTAS	38 (58.5%)	27 (41.5%)	65
Control	85 (72.6%)	32 (27.4%)	117
Total	156 (55.3%)	126 (44.7%)	282