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Aging in fragile X syndrome

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Abstract Many studies have focused on the behavior and cognitive problems in young patients with fragile X syndrome (FXS), but there are no studies about the problems in aging for those with FXS. The discovery of the fragile X-associated tremor ataxia syndrome (FXTAS), a neurodegenerative disorder related to elevated *FMR1*-mRNA, in elderly men and some women with the premutation, intensified the need for aging studies in FXS. Approximately 40% of males with FXS have repeat size mosaicism and as a result, some of these individuals also have elevated levels of *FMR1*-mRNA which theoretically puts them at risk for FXTAS. Here, we have surveyed all of the aging patients with FXS that we have followed over the years to clarify the medical complications of aging seen in those with FXS. Data was collected from 62 individuals with the FXS full mutation (44 males; 18 females) who were at least 40 years old at their most recent clinical examination. We found that the five most frequent medical problems in these patients were neurological problems (38.7%), gastrointestinal problems (30.6%), obesity (28.8%), hypertension (24.2%) and heart problems (24.2%). Movement disorders were significantly different between males and females (38.6% vs.10.2%, p=0.029). We did not find any differences in medical problems between those with a full mutation and those with mosaicism. Identification of medical problems associated with aging in FXS is important to establish appropriate recommendations for medical screening and treatment considerations.

Keywords Aging · Fragile X syndrome · Medical problems · Movement disorder

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Introduction

Fragile X syndrome (FXS) is the most common heritable form of intellectual disability (ID) known. Characteristic physical features include large and prominent ears, long narrow face, macroorchidism, high-arched palate, hyperextensible finger joints, double-jointed thumbs, single palmar crease, flat feet often with pronation and hand calluses. FXS causes a variety of learning, emotional and behavior problems including autism (Hagerman 2002; Chonchaiya et al. 2009). The prevalence of the full mutation was estimated to be 1 in ~3600 males (Crawford et al. 2002), although the allele frequency was found to be 1 in 2633 in newborn screening in Spain (Fernandez-Carvajal et al. 2009).

FXS is caused by a CGG repeat expansion located in 5′ untranslated region of the fragile X mental retardation 1 (*FMR1*) gene. Normally the repeat size is 5–44 CGG repeats, while premutation alleles have 55–200 repeats and full mutation alleles have more than 200 CGG repeats. With expansion beyond 200 repeats, the surrounding promoter region of the *FMR1* gene is hypermethylated, inhibiting *FMR1* transcription and resulting in absence or reduction of the protein product, fragile X mental retardation protein (FMRP) (Oostra and Willemsen 2009). As a result of X-linkage, affected males have a more severe phenotype than affected females, in whom phenotype is modulated by the activation ratio of the normal X chromosome. The variation in the clinical phenotype is also related to variability of the mutation, such as lack of methylation and size mosaicism leading to higher levels of FMRP than are observed in individuals with only a fully methylated full mutation (Jin and Warren 2000; Loesch et al. 2004).

Many studies have focused on the behavior and cognitive problems in young patients with FXS. There are no studies about the problems in aging of those with FXS. There are a few reports of declining IQ as patients progress through childhood and into adulthood (Wright-Talamante et al. 1996; Lachiewicz et al. 1987) and one case of a neurodegenerative course in FXS thought to be due to an additional diagnosis of amyotrophic lateral sclerosis (ALS) (Desai et al. 1990). There have also been reports of rare sudden death in FXS in adulthood and these are presumed to be related to cardiac arrhythmias exacerbated by mitral valve prolapse which is common in adults with FXS (Hagerman 2002). A neuropathological study of 2 older males with FXS demonstrated loss of Purkinje cells and Bergman gliosis in the cerebellum in one of the cases (Sabaratnam 2000). Our neuropathological studies in three cases of older males with FXS have also demonstrated Purkinje cell loss in the cerebellum suggesting a more pronounced affect of aging in those with FXS compared to age matched controls without FXS (Greco et al. 2009). The discovery of the fragile X-associated tremor ataxia syndrome (FXTAS) (Hagerman et al. 2001; Berry-Kravis et al. 2007) in elderly men and some women (Coffey et al. 2008) with the premutation intensified the need for more detailed aging studies in FXS. FXTAS is a neurodegenerative disorder caused by elevated *FMR1*-mRNA. Persons with FXS would not be expected to be at risk for FXTAS, since generally they do not usually produce *FMR1* mRNA. However, approximately 40% of males with FXS have repeat size mosaicism (Nolin et al. 1994) and some of these individuals also have elevated levels of *FMR1*-mRNA (Allen et al. 2004; Tassone et al. 2001). The latter would theoretically be at risk for FXTAS. Although FXTAS has never been reported in a person with FXS (Harris et al. 2008), some families are concerned about cognitive decline in their older members with FXS. These concerns have been intensified because of the recent report that FMRP regulates the translation of amyloid precursor protein (APP), such that the absence of FMRP leads to up-regulation of APP (Westmark and Malter 2007). Thus persons with FXS and absent or diminished FMRP may be at greater risk for Alzheimers Disease (AD).

The behavior problems in FXS include mood instability and aggression in approximately 75% (Hessl et al. 2008), often resulting in treatment with atypical antipsychotic medication (Hagerman et al. 2009). Prolonged use of antipsychotics in FXS puts individuals at risk for antipsychotic-induced movement disorders including tardive dyskinesia and parkinsonism (Caligiuri et al. 2009; Orti-Pareja et al. 1999; Miller et al. 2005) that can reduce the quality of life in elderly patients. In addition, the dysregulation of dopamine function in the absence of FMRP (Wang et al. 2008) also may put those with FXS at risk for Parkinson's Disease (PD). Although patients with FXS have not previously been reported to have PD or a loss of dopamine in the substancia nigra, there is a dysregulation of dopamine in the neurons in hippocampal slice preparations that can be normalized by adding FMRP or by adding a stimulant medication (Wang et al. 2008).

In this study, we have surveyed all of the aging patients with FXS that we have followed over the years (from 1991 to 2009) to begin to clarify the medical complications of individuals with FXS over 40.

Methods

This is a retrospective uncontrolled study of a convenience sample (patients were either clinically referred for an evaluation of FXS or seen as part of a research protocol). Data was collected from 62 individuals with the FXS full mutation who were at least 40 years old at

their most recent clinical examination. The subjects included 62 patients (44 males and 18 females), ranging from 40–71 years of age, with mean age of 49.7± 8.0 year. Data was identified from clinical and research evaluations of subjects with FXS at one of three sites spanning from 1991 to 2009. Patients and their families consented to use of medical data under specifications of each institution's research review board. Patients were seen at the University of California, Davis, Medical Investigation of Neurodevelopmental Disorders (M.I.N.D) Institute (n=23), University of Colorado, Denver (n=24), and Rush University Medical Center, Chicago (n=15). A common medical history and examination data form was used at all of the centers. This form had been implemented for data collection in previous collaborations and an earliar version of this data sheet was used to collect information for past reports (Riddle et al. 1998).

Full scale IQ, comprehensive medical history, physical characteristics, and current and past medication use were collected from medical records. The number of CGG repeats, percentage of methylation, and percentage of FMRP and mRNA were measured, if samples were available. BMI (weight (kg)/height (m)2 was used to assess obesity; BMI cutoff criteria for overweight and obese were 25 - <30 and ≥30, respectively (Ogden et al. 2006).

Descriptive analyses were done to determine the characteristics of the subjects. The statistical method used was the Fisher Exact Test to compare the medical problems between male and female patients and also between full mutation and mosaic individuals.

Results

Characteristic of the subjects

The mean age in males 50.2±8 y and females 48.5± 7.8 y were not significantly different (p=0.451). There was no significant differences (p=0.752) between mean age of the patients with full mutation alleles (49.6± 7.4 year) compared with patients with mosaic alleles (50.4 ±10.3 year). Of 52 patients for whom measurement of Body Mass Index (BMI) was available, the mean of the BMI was 28.5±5 (28.8% obese and 53.8% overweight). The molecular studies of 60 patients showed that 46 patients (76.7%) had a hypermethylated full mutation whereas 14 (23.3.%) were mosaic patients (either size or methylation mosaicism). Two (3.2%) patients were DNA positive for fragile X (>200 repeats) but their exact CGG repeat number was unavailable. Five of 18 (27.8%) females and 9 of 44 (20.5%) males were mosaics. There was no significant difference between males and females in the percentage with a full mutation or mosaicism (p=0.412).

The full scale IQ was assessed by the Wechsler Adult Intelligence Scale-Third Edition (WAIS-III) , Wechsler Adult Intelligence Scale - Revised (WAIS-R), Wechsler Abbreviated Scale of Intelligence (WASI), or Stanford Binet from 44 patients who completed this testing ranged from 36 to 122 with a mean of 58±19. The mean IQ was significally higher in the group of female patients (77±17.4) than in the male patients (51.5±14.3, p<0.001). Of 43 patients who have IQ data and DNA category available, the IQ of those with mosaicism (69.2± 18.6) was significantly higher than those with the full mutation only (55.4±18 ; p=0.036).

Medical problems

We found that the five most frequent medical problems in patients with FXS ≥ 40 years of age were neurological problems (38.7%), gastrointestinal problems (30.6%), obesity (28.8%), hypertension (24.2%) and heart problems including mitral valve prolapse (MVP), cardiac conduction abnormalities, heart attack, and heart rhythm disorder (24.2%) (see Table 1). Males had a significantly higher percentage of neurological problems compared with females (47.7% vs 16.7%, p=0.021). However, only movement disorders were significantly different between males (38.6%) and females (10.2%, p=0.029). The symptoms/diagnoses that were included in movement disorders are tremor (9 patients, 14.5%), Parkinson's Disease (PD) (4 patients, 6.5%), bradykinesia without PD (5 patients, 8.1%), tardive dyskinesia (4 patients, 6.5%), and tics (3 patients, 4.8%). There were 12 patients with a history of seizures and the onset of seizures was in adulthood for 5 (8.1%) patients (3 patients had seizures at over 40 years of age).

Overall, of 52 patients who had BMI measurements, 43 (82.6%) were in the obese (28.8%) or overweight (53.8%) category. The mean BMI in females (32±5.4) was significantly higher (p<0.001) than that of males (26.9± 3.9). Accordingly, significantly less males (13.9%) than females (62.5%; p=0.001) were obese. However, more males (63.9%) met criteria for being overweight than females (31.2%). There were no significant differences in medical problems between those with a full mutation as compared to those with mosaicism.

Medication

Table 2 shows the current medications of the subjects. Almost half of the patients were taking psychopharmacologic medication including selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors

Table 1 The number and percentage of medical problems in patients with FXS ≥ 40 years

Problems	Sex[a]				DNA Status[b]				Total subjects (n=62)
	n	Male (n=44)	Female (n=18)	p	n	Full mutation (n=46)	Mosaic (n=14)	p	
All neurological problems	62	21 (47.7%)	3(16.7%)	0.021*	60	19(41.3%)	3(21.4%)	0.150	24(38.7%)
Movement disorder	62	17(38.6%)	2(10.2%)	0.029*	60	14(30.4%)	3(21.4%)	0.386	19(30.6%)
• Tremor	62	8(18.2%)	1(5.6%)	0.192	60	7(15.2%)	2(14.3%)	0.651	9(14.5%)
• Ataxia	62	6(13.6%)	1(5.6%)	0.336	60	4(8.7%)	3(21.4%)	0.199	7(11.3%)
• Parkinsonism	62	4(9.1%)	0	0.243	60	2(4.3%)	2(14.3%)	0.230	4(6.5%)
• Tardive dyskinesia	62	4(9.1%)	0	0.243	60	1(2.2%)	1(7.1%)	0.415	4(6.5%)
• Bradykinesia without PD	62	5(11.4%)	0	0.168	60	5(10.9%)	0	0.251	5(8.1%)
• Tics	62	2(4.5%)	1(5.6%)	0.650	60	3(6.5%)	0	0.444	3(4.8%)
Seizure	62	10(22.7%)	2 (11.1%)	0.249	60	10(21.7%)	1(7.1%)	0.205	12(19.4%)
Multiple Sclerosis	62	1(2.3%)	0	0.710	60	0	0		1(1.6%)
Gastrointestinal Problem	62	14(31.8%)	5(27.8%)	0.503	60	13(28.3%)	4(28.6%)	0.614	19(30.6%)
Obesity	52[#]	5(13.9%)	10(62.5%)	0.001*	51[$]	12(30.0%)	3(27.3%)	0.589	15(28.8%)
Hypertension	62	9(20.5%)	6(33.3%)	0.224	60	12 (26.1%)	2(14.3%)	0.300	15(24.2%)
Heart problem	62	13(29.5%)	2(11.1%)	0.110	60	12 (26.1%)	2(14.3%)	0.300	15(24.2%)
History of Decline	62	10(22.7%)	4(22.2%)	0.437	60	9(19.6%)	3(21.4%)	0.574	14(22.6%)
Autonomic problem	62	9(20.5%)	2(11.1%)	0.316	60	7(15.2%)	3(21.4%)	0.426	11(17.7%)
Memory problem	62	9(20.5%)	2(11.1%)	0.316	60	8(17.4%)	3(21.4%)	0.502	11(17.7)
Dementia/cognitive decline	62	4(9.1%)	2(11.1%)	0.567	60	4(8.7%)	1(7.1%)	0.669	6 (9.7%)
Kidney Problem	62	5(11.4%)	2(11.1%)	0.674	60	6(13.0%)	1(7.1%)	0.478	7(11.3%)
Respiratory Problem	62	4(9.1%)	2(11.1%)	0.567	60	4(8.7%)	1(7.1%)	0.669	6(9.7%)
Swallowing Problem	62	4(9.1%)	0	0.243	60	2 (4.3%)	1(7.1%)	0.556	4(6.5%)
Diabetes	62	3(6.8%)	1(5.6%)	0.671	60	3(6.5%)	1(7.1%)	0.665	4(6.5%)
Thyroid problems	62	3(6.8%)	1(5.6%)	0.671	60	3(6.5%)	1(7.1)0	0.665	4(6.5%)
Cancer	62	2 (4.5%)	0	0.500	60	0	1(7.15)	0.233	2(3.2%)

• Percentage within sex[a] and DNA status[b]

• # n=52, male=36, female=16 ; $ n=51, full=40, mosaic=11

(SNRIs), atypical neuroleptics, first generation neuroleptics (thioridazine) and other medication (benzodiazepines, bupropion, buspirone).

Discussion

This is the only study to date to describe the medical problems in patients with FXS 40 years and older. The neurodegeneration seen in aging premutation carriers with FXTAS is thought to be secondary to the elevated level of *FMR1* mRNA which usually does not occur in those with FXS. However, rarely elevated *FMR1* mRNA can be seen in those with the full mutation and a high level of mosaicism, although this has not been associated with neurodegeneration or autism (Harris et al. 2008; Tassone et al. 2001, 2000). In this review of 62 patients, we did not identify any patients with FXS who have FXTAS. However, we did find significant neurological problems with aging, more so in males than females, including PD and movement disorders. While overall the presence of neurological problems was not related to the molecular status (mosaicism) of the patient, we found PD in four of 44 males (9.1%), and the one with earliest onset at age 42, had mosaicism with the highest mRNA level (10.29±0.78). There were 3 of 12 males (20%) over age 55 with PD compared to the expected rate of 1.2% of males with PD seen in the general population 55 years old and older (de Rijk et al. 1995). A larger study of aging patients with FXS is needed to understand whether the rate of PD is higher in FXS compared to the general population as found in this study. All of the patients with PD and FXS had been treated for many years with antipsychotics, although usually atypical antipsychotics have been used since they became available in the 1990s. The atypical antipsychotics have a lower incidence of movement disorder sequelae, particularly tartive dyskinesias, than first generation antipsychotics, although even these newer drugs can be associated with symptoms of PD (Cortese et al. 2008). It is

Table 2 Current medication documented in study patients (n=62)

Medical Class	Number and percentage
All medication	47 (75.8%)
Psychopharmacologic medication	29 (46.8%)
• SSRI/ SNRI	20 (68.9%)[$]
• Atypical neuroleptic	13 (44.8%)[$]
• Stimulant	0
• Other including benzodiazepines, bupropion, buspirone, thioridazine	12(41.4%)[$]
Anticonvulsants/mood stabilizer	8 (12.9%)
HBP and other CV medications	18 (29%)
Gastrointestinal medications	9 (14.5%)

[$] Percentage represents the % of those who took psychopharmacological medications;*HBP* high blood pressure; *CV* cardiovascular

possible that the high occurence of PD in the FXS cases reported here relates to this treatment. These patients were taken off neuroleptics when PD symptoms started but their PD progressed. In one patient lowering the dose of the atypical antipsychotic seemed to decrease the symptoms of PD and in others the symptoms of motor dysfunction improved with lowering the dose of atypicals also. However, it is also possible that the PD-like symptoms such as tremor or balance problems seen in FXS are exacerbated by the loss of Purkinje cells and resultant cerebellar compromise. There is also cellular evidence for significant dysfunction of the dopamine system in FXS related to the lack of FMRP (Wang et al. 2008), although the substantia nigra has not been directly studied in FXS. In those patients with PD and FXS there was cognitive decline and this can occur in PD in general (Muslimovic et al. 2009).

The prevalence of obesity has increased in the US population over the last decade so it is not unexpected to see significant rates of obesity in those with FXS in the current study. The obesity epidemic in the US is related to the lack of physical activity (Brock DW, 2009) and our diet composition (Murtaugh MA, 2007). Additionally, in those with FXS the tendency for more reclusive behavior with age (Hatton et al. 2006), the use of atypicals that increase the appetite and the presence of the Prader-Willi phenotype (seen in less than 10% of patients with FXS) leading to hyperphagia (Nowicki et al. 2007) may exacerbate the obesity problem. In this study, 82.6% of patients with FXS have either obesity (28.8%) or they are overweight (53.8%). The percentage of obesity in these patients is slightly lower than in the general population (34%) but the overweight percentage is much higher than estimated in the general population (33%) (Khan et al. 2009).

Hypertension is common in men with FXS, but the prevalence has never been studied in detail (Hagerman 2002). Recently, the prevalence rate of hypertension in the US general population was reported as 28.9% overall (Cutler et al. 2008). Hypertension may be underrecognized by the physician because anxiety and tactile defensiveness in the clinical setting often leads to increased BP in patients with FXS. Thus, a high value is often interpreted with consideration of the stress and anxiety associated with the medical visit. In this study 24% were diagnosed with hypertension, and although this is not significantly different from the general population it may be an underestimate of the true incidence of this problem in FXS. Hypertension may be more likely in individuals with FXS because of the sympathetic hyperarousal documented in this syndrome (Miller et al. 1999) and possibly because of elastin abnormalities in the vessel walls as was documented in one patient with FXS (Waldstein and Hagerman 1988). A recent neuropathology study of three older men with FXS who died (they are included in this study) showed significant evidence of hyaloid changes in the blood vessels presumed to be secondary to hypertensive disease. (Greco et al. 2009). These results emphasize the need to diagnose hypertension in those with FXS and treat it appropriately.

Kidney problems have been previously considered rare in patients with FXS. We found 7 (11.3%) patients have kidney problems including acute renal failure (2 patients), urinary tract infection (2 patients), kidney stones (1 patient), small cysts (1 patient), and 1 patient with a kidney problem but unclear diagnosis. Connective tissue dysplasia, documented to be related to elastin abnormalities (Waldstein et al. 1986) in FXS may lead to reflux and ureteral dilation leading to renal failure and nephrectomy in one previous case (Hagerman 2002). In this study, one patient had severe prostate enlargement which lead to obstruction and renal failure and this was relieved by surgery.

Two male patients were diagnosed with cancer including one with an adenocarcinoma of the testicle and the other with a malignant liver cancer that did not have a pathological diagnosis. Some studies suggest a decreased risk of cancer in individuals with FXS (Schultz-Pedersen et al. 2001; Sund et al. 2009) perhaps related to *PTEN* down regulation. However, there is also upregulation of the mTOR pathway in FXS (Hoeffer et al. 2009) which can lead to an increased risk of cancer (Matsumoto et al. 2009).

Typically seizures in FXS occur in childhood in about 15–20% and they are usually well controlled with anti-convulsants (Berry-Kravis 2002). However, our study found that 8.1% of the patients had seizures that began in adulthood with 3 patients developing seizures after age 40. Further studies of seizures in aging are needed to assess whether seizures in FXS tend to be a complication of aging and whether a second peak of seizure onset (in addition to that described in childhood) occurs late in life in FXS (Hagerman and Stafstorm 2009). Clinicians should be alert to the possibility of seizures in adult and aging patients with FXS.

An additional notable finding in our study is the lack of significant atherosclerotic heart disease or late onset complications of mitral valve prolapse which is thought to be present in over 50% of adult males with FXS (Hagerman 2002).

The limitations of this study include lack of typical or intellectually impaired controls, intellectually impaired subjects, cohort effects due to the small sample size, retrospective chart review and referral bias to well-known FXS clinics. However, this study is a first step toward understanding the medical problems associated with aging in those with FXS.

In summary, we have found a number of medical problems associated with aging in individuals with FXS that may be related to the neurobiological changes in this disorder. Of most concern is the higher incidence of PD and other movement disorders. Since these may be related to long term use of atypical antipsychotics, the risks and benefits for continued use should be weighed in aging individuals with FXS. All of the atypical antipsychotics can be associated with parkinsonism except quetiapine (seroquel), which is frequently used for managing hallucinations in the PD population because of it's minimal motor side effects (Cortese et al. 2008). In addition, vigorous identification and treatment of hypertension is warranted because of the CNS effects of untreated hypertension.

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