The Fragile X-Associated Tremor Ataxia Syndrome (FXTAS)

Flora Tassone · Elizabeth M. Berry-Kravis
Editors

The Fragile X-Associated Tremor Ataxia Syndrome (FXTAS)

Springer

Editors
Flora Tassone
Department of Biochemistry
and Molecular Medicine
University of California, Davis
Davis, California 95616
USA
ftassone@ucdavis.edu

Elizabeth M. Berry-Kravis
Department of Pediatrics
Neurological Sciences, Biochemistry
Rush University Medical Center
1725 W. Harrison St.
Suite 718
Chicago, Illinois 60612
USA
elizabeth_m_berry-kravis@rush.edu

Additional material to this book can be downloaded from http://extras.springer.com.

ISBN 978-1-4419-5804-4 e-ISBN 978-1-4419-5805-1
DOI 10.1007/978-1-4419-5805-1
Springer New York Dordrecht Heidelberg London

Library of Congress Control Number: 2010926589

Printed on acid-free paper

Springer is part of Springer Science+Business Media (www.springer.com)

We truly meant it when we looked into the future 49 years ago and said 'for better, for worse, in sickness and in health, 'til death do us part'.

–Dorothy and John Kinna (FXTAS family)

Preface

Fragile X-associated tremor/ataxia syndrome, or FXTAS, is one of the few examples of a disorder discovered entirely because of its familial relationship with another disorder, fragile X syndrome. The rather unique and interesting history of FXTAS is a story of families. The discovery of FXTAS illustrates pointedly to the physician, the importance of careful clinical histories and of listening to the patient (and the patient's parents) when they describe things that are concerning to the family but seem unrelated to the primary clinical problem. It stands as an example of what can be learned when the physician becomes so close to the families he or she follows that these families begin to share all of their problems.

FXTAS came into my life at a meeting in Steamboat Springs in early 2001, where Dr. Randi Hagerman and I (Dr. E. Berry-Kravis) were attending a symposium together. She said to me that she thought that premutation carrier grandfathers of her fragile X patients were developing tremor and gait problems. My first reaction was to play the devil's advocate. I said things like "tremor and parkinsonism are fairly common in the elderly" and "how do you know you are not just finding the grandfathers with problems because those are the ones the moms talk to you about" and "you'd have to do some kind of a more comprehensive screening to prove this is not just background neurological problems in the elderly." We agreed I would ask about neurological problems in the grandparents of my patients when I went back to Chicago. As I thought about it I realized that at least five families had asked me if Parkinson's disease is related to fragile X syndrome, and of course I had said "no" but I already knew I had been asked that question a few too many times. By the time I had talked to about 10 families in clinic, I knew that Randi was right, and there was a neurological disease in carrier grandfathers of children with fragile X syndrome. I have collaborated in studies of FXTAS since that time.

FXTAS is a condition that would never have been discovered if it was not genetically linked to fragile X. The condition itself is highly variable. Although tremor and ataxia are the hallmarks, it presents in a variety of disparate ways which are hard to place in a single category of disease, and hence, individuals with FXTAS are seen by a broad range of physicians and in all different neurological subspecialty clinics, including Parkinson's, ataxia, tremor, general movement disorders, dementia, multiple sclerosis, stroke, and neuropathy clinics. Because of the variable presentation in clinics focused on different problems and the varied phenotypes even

between brothers, it would have been extremely hard to ever identify FXTAS as a single genetic diagnosable condition without something to allow the patients with FXTAS to be grouped as a single entity. That something was the mothers of fragile X children, who talked about their children and behavior, the schools, family life and problems, and their fathers who had shaking, fell too much, were moody and socially reclusive, and in some cases were becoming demented. I will never forget my first visit with a little girl with mild developmental problems and ADHD symptoms who came to my clinic about 6 months after I talked to Randi in Steamboat Springs. I was taking the family history and the mother tearfully told me her father had died this year, but was diagnosed with Parkinson's disease and Alzheimer's disease and he had shaking and he had seen neurologists at Northwestern and the University of Chicago, and they were all baffled and thought he had a degenerative disease but was not typical of anything. For the first time I knew this little girl's DNA test would show fragile X just based on the description of her grandfather's disease and had the painful realization that I was about to shatter this mother's world for the second time in a year.

The dual presentation of disease in different generations of families reflects the fact that FXTAS and fragile X syndrome represent a rather unique situation of two entirely different diseases with completely distinct mechanisms resulting from exactly the same mutation, the CGG trinucleotide repeat expansion in *FMR1*. FXTAS results from premutation CGG repeat expansions containing roughly 55–200 repeats, while fragile X syndrome results from expansions of more than 200 repeats. Just a year before my conversation with Dr. Hagerman in Steamboat Springs, in 2000, Dr. Flora Tassone reported the discovery of elevated *FMR1* mRNA levels in premutation carriers, providing the molecular basis to explain the existence of FXTAS. In premutation carriers the mutation is transcribed into the *FMR1* mRNA, and it is this expanded CGG-containing RNA that is incorporated into nuclear inclusions observed in FXTAS and causes cellular toxicity through a gain-of-function mechanism. In fragile X syndrome, the long CGG repeat results in silencing of the gene, so neither the *FMR1* mRNA nor the protein product, FMRP, is made at levels near normal, and the condition thus results from a loss-of-function mechanism. Because the mutation tends to expand further as it is inherited through generations in families, the individuals with FXTAS are in older generations and those with fragile X syndrome in younger generations. Since FXTAS does not present until older age, it does not frequently provide clues about risk of fragile X syndrome in the family before children and grandchildren are born. Rather the mothers of affected children provide the "link" through which the grandparent with FXTAS has typically been ascertained and diagnosed.

Although the mechanisms for fragile X syndrome and FXTAS are distinct, individuals with a large premutation or small full mutation and partial mosaicism may show features of both conditions. Especially in the domain of executive function deficits, it appears that there is clinical overlap between the two conditions, and it is difficult to know whether these deficits represent very early FXTAS, developmental/congenitally determined effects of the premutation, or effects of minimal

reductions in FMRP that relate to diminished translation of large premutation-containing alleles and represent minimal forms of the fragile X phenotype. This of course contributes to the broad range of phenotypes seen in fragile X families.

With the discovery of FXTAS and fragile X-associated primary ovarian insufficiency (FXPOI), which like FXTAS appears to be caused by a mechanism of RNA toxicity and results in infertility problems and premature menopause in female premutation carriers, the concept of fragile X syndrome as a single condition related to a specific *FMR1* mutation has been revised. The three disorders, FXTAS, FXPOI, and fragile X syndrome, are now grouped as fragile X-associated disorders and produce a spectrum of diseases sprinkled throughout fragile X families, resulting in complex disease interactions within families not observed in other genetic conditions. Examples of these kinds of interactions would include the woman with infertility (early FXPOI) who is treated with fertility drugs and has twins or triplets with fragile X syndrome, and the mother who is struggling with her fragile X child's behavior, schooling, and medical issues and at the same time dealing with hot flashes and emotional lability from FXPOI while handling increasing care demands required by her father due to disability from FXTAS. These families need help and support. Increased awareness is needed for physicians to understand the fragile X-associated disorders and their relationships in families, so as to accurately diagnose symptomatic individuals, and avoid management errors due to lack of diagnosis. New treatments based on the underlying mechanisms are needed for all fragile X-associated disorders to provide hope and relief to affected individuals and the families that care for them.

In this book, we strive to present information on all aspects of FXTAS, including clinical features and current supportive management; radiological, psychological, and pathological findings; genotype–phenotype relationships; animal models; and basic molecular mechanisms. The book should serve as a resource for professionals in all fields regarding diagnosis, management, and counseling of patients with FXTAS and their families, while also presenting the molecular basis for the disease, that may lead to new markers to predict disease risk and eventually lead to mechanism-based treatments.

Resources:
http://www.fragilex.org
http://www.FXTAS.ORG
www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=300623

Acknowledgements

All the families living with FXTAS or with the risk of FXTAS, who have participated in research/clinical studies and provided comments and personal experience.

Kirin Basuta for helping with the writing and assembling of the book.

To all authors for their contribution to this book.

Contents

Contributors

Liane Abrams National Fragile X Foundation, Walnut Creek, CA, USA, lianeabrams@hotmail.com

Emily Allen Department of Human Genetics, Emory University School of Medicine, Atlanta, GA, USA, emgrave@emory.edu

Robert F. Berman Department of Neurological Surgery, Neurotherapeutics Research Institute, University of California, Davis, CA, USA, rfberman@ucdavis.edu

Elizabeth Berry-Kravis Departments of Pediatrics, Neurological Sciences, and Biochemistry, Rush University Medical Center, Chicago, IL, USA, elizabeth_m_berry-kravis@rush.edu

James A. Bourgeois Department of Psychiatry and Behavioural Neurosciences, Faculty of Medicine, McMaster University, Hamilton, ON, Canada, james.bourgeois@ucdmc.ucdavis.edu

Angela G. Brega Department of Community and Behavioral Health, Colorado School of Public Health, University of Colorado Denver, Aurora, CO, USA, angela.brega@uchsc.edu

Judith R. Brouwer Department of Clinical Genetics, Erasmus MC, Rotterdam, The Netherlands, j.r.brouwer@erasmusmc.nl

Louise W. Gane UC Davis M.I.N.D. Institute, University of California, Sacramento, CA, USA, louise.gane@ucdmc.ucdavis.edu

Christopher G. Goetz Departments of Neurological Sciences and Pharmacology, Rush University Medical Center, Chicago, IL, USA, christopher_goetz@rsh.net

Claudia M. Greco Department of Pathology, Davis Medical Center, University of California, Sacramento, CA, USA, claudia.greco@ucdmc.ucdavis.edu

Jim Grigsby Departments of Psychology and Medicine, University of Colorado Denver, Denver, CO, USA, jim.grigsby@ucdenver.edu

Paul J. Hagerman Department of Biochemistry and Molecular Medicine, School of Medicine, University of California, Davis, CA, USA, pjhagerman@ucdavis.edu

Randi J. Hagerman Department of Pediatrics, M.I.N.D. Institute, University of California at Davis Medical Center, Sacramento, CA, USA, randi.hagerman@ucdmc.ucdavis.edu

Deborah A. Hall Department of Neurological Sciences, Rush University Medical Center, Chicago, IL, USA, deborah_a_hall@rush.edu

Katherine Howard University of Colorado Health Sciences Center, Aurora, CO, USA, katherine.howard@uchsc.edu

Michael R. Hunsaker Program in Neuroscience, University of California, Davis, CA, USA, ryanhunsaker@me.com

Sebastien Jacquemont Service de génétique, Centre Hospitalier Universitaire de Lausanne, Lausanne, Switzerland, sebastien.jacquemont@chuv.ch

Peng Jin Department of Human Genetics, Emory University School of Medicine, Atlanta, GA, USA, pjin@genetics.emory.edu

Maureen A. Leehey Department of Neurology, University of Colorado at Denver and Health Sciences Center, Aurora, CO, USA, maureen.leehey@ucdenver.edu; Department of Neurology, University of Colorado Health Sciences Center, Denver, CO, USA, maureen.leehey@uchsc.edu

Yujing Li Department of Human Genetics, Emory University School of Medicine, Atlanta, GA, USA, yli@genetics.emory.edu

Ben A. Oostra Department of Clinical Genetics, Erasmus MC, Rotterdam, The Netherlands, b.oostra@erasmusmc.nl

Susan M. Rivera Department of Psychology, UC Davis Center for Mind and Brain, 202 Cousteau Pl., Davis, CA, USA, srivera@ucdavis.edu

Andreea L. Seritan Department of Psychiatry and Behavioral Sciences, Davis Medical Center, University of California, Sacramento, CA, USA, andreea.seritan@ucdmc.ucdavis.edu

Stephanie Sherman Department of Human Genetics, Emory University School of Medicine, Atlanta, GA, USA, ssherma@emory.edu

Glenn T. Stebbins Department of Neurological Sciences, Rush University Medical Center, Chicago, IL, USA, gstebbin@rush.edu

Flora Tassone Department of Biochemistry and Molecular Medicine, School of Medicine, University of California, Davis, CA, USA, ftassone@ucdavis.edu

Rob Willemsen Department of Clinical Genetics, Erasmus MC, Rotterdam, The Netherlands, r.willemsen@erasmusmc.nl

Chapter 1
Clinical Neurological Phenotype of FXTAS

Maureen A. Leehey, Elizabeth Berry-Kravis, Christopher G. Goetz, and Randi J. Hagerman

Abstract The classic presentation of fragile X-associated tremor/ataxia syndrome (FXTAS) is an aging man with progressive cerebellar gait ataxia, kinetic tremor, mild parkinsonism, and cognitive decline, especially executive dysfunction. Peripheral neuropathy and autonomic dysfunction may be present. MR imaging often reveals global brain atrophy and white matter changes, including hyperintensities of the middle cerebellar peduncles, termed the "MCP sign," and pathology shows intranuclear inclusions in brain. Recent studies, however, have shown that the FXTAS clinical picture is heterogeneous, with variations, for example, that include persons with minor or no tremor and others with predominant dementia or peripheral neuropathy. Onset of motor signs in males is typically in the early 60s, and approximately 40% of male carriers over age 50 and 8% of female carriers over age 40 develop the disorder. Penetrance is age related, such that 75% of men $\geq$80 years of age are affected. While much less data exist regarding FXTAS in female carriers, they appear to have similar but less severe motor signs, perhaps less cognitive impairment, and some different patterns of involvement than seen in males. FXTAS, at present, is underdiagnosed largely because the presentation is often a combination of signs which are common in the elderly. Furthermore, the heterogeneous nature of the disorder facilitates misdiagnosis, especially in the earlier stages. Diagnostic evaluation requires *FMR1* gene testing. Accurate diagnosis is not only important for the affected person but also for their family, as immediate family members may be at risk of having progeny with fragile X syndrome.

Introduction

The core clinical features of fragile X-associated tremor/ataxia syndrome (FXTAS) are cerebellar gait ataxia and action tremor (Hagerman et al. 2001; Leehey

M.A. Leehey (✉)
Department of Neurology, University of Colorado at Denver and Health Sciences Center, Aurora, CO, USA
e-mail: maureen.leehey@uchsc.edu

F. Tassone, E.M. Berry-Kravis (eds.), *The Fragile X-Associated Tremor Ataxia Syndrome (FXTAS)*, DOI 10.1007/978-1-4419-5805-1_1,

et al. 2002). Cognitive dysfunction, particularly frontal executive dysfunction, is a very common and disabling manifestation (Grigsby et al. 2008, see Chapter 3). Parkinsonism and dystonia can also occur in varying degrees, and other signs are neuropathy and autonomic dysfunction (Jacquemont et al. 2003). Predictable radiographic abnormalities are global brain atrophy and cerebral and cerebellar white matter changes, including involvement of the middle cerebellar peduncles (Brunberg et al. 2002, see Chapter 4). Intranuclear inclusions are seen in many areas of the brain from individuals with FXTAS at autopsy (Greco et al. 2002, see Chapter 5) and represent a pathological hallmark of the condition, likely mediated by the RNA toxicity mechanism proposed for this disease (Hagerman and Hagerman 2004, see Chapter 6). While these features encompass a "classic" FXTAS presentation (see Fig. 1.1), accumulating data suggest that the clinical phenotype may vary considerably among affected persons. Below is a case report of a subject with a typical presentation of FXTAS.

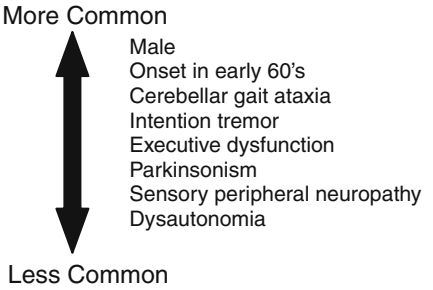

Fig. 1.1 Clinical characteristics of FXTAS

Case 1. A retired geologist was brought to a clinic at age 77 by his wife, although he insisted he was not having any problems and did not need to be seen. During the visit he admitted to balance difficulty starting at age 65 when he played tennis. At age 69, his wife noticed bilateral hand tremor, especially when holding up a newspaper. The tremor progressed slowly. The patient still did not appreciate any impairment from shaking nor even acknowledge the tremor. At age 71 he gave up tennis and began having occasional falls. His primary care physician started donepezil, which was not helpful. Antidepressant medication was recommended and refused. At age 74 he took levodopa, but after a year it was stopped as there was no obvious benefit. In recent years people have commented that he stumbles like a "drunken sailor." One year ago he began leaning to the right, and an MRI done for possible stroke showed moderate generalized atrophy with very large ventricles and white matter T2 hyperintensities in the cerebral hemispheres. He was being treated for hypertension and hyperlipidemia and drank two beers per night. There was no history of alcohol abuse. One of his daughters had a son with fragile X syndrome. On examination at age 77, he had a high-average verbal IQ and significantly below-average performance IQ. Short-term memory, capacity to learn and retain new information, and speed of information processing were impaired.

MMSE was 26/30. He had slightly masked facies, a mild intention tremor bilaterally in the arms, mild slowing and incoordination of rapid alternating movements, moderately increased tone of a gegenhalten quality in both arms, reduced reflexes in the legs, and no perception of vibration in his great toes. He was unable to perform or even initiate tandem gait. Casual gait was slightly wide based and mildly slow, with irregular foot placement. He leaned to the right and was somewhat stooped forward in a parkinsonian fashion. Repeat MRI showed atrophy and white matter changes (Fig. 1.2), and the radiologist felt it was consistent with normal pressure hydrocephalus. The patient is now 80 years old and has moderate dementia (MMSE is 21/30), frequent falls, mild intention tremor, and occasional urinary incontinence. He takes venlafaxine for agitation. *FMR1* gene analysis showed 125 CGG repeats.

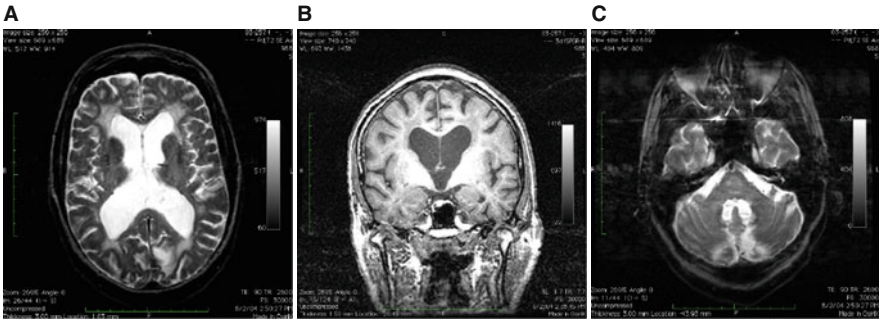

Fig. 1.2 Brain MR images of case 1. A T2-weighted axial image showing large ventricles and cerebral white matter hyperintensities (**a**), a gradient-echo T1-weighted coronal image showing large ventricles and frontal cerebral atrophy (**b**), and a T2-weighted axial image showing there is no hyperintensity in the middle cerebellar peduncles, i.e., the MCP sign (**c**). The latter, when present, is a distinctive finding in FXTAS that occurs in approximately 60% of affected males and 13% of affected females (Adams et al. 2007). See Chapter 4 for more details on radiological findings

As an X-linked disorder, FXTAS mainly affects male premutation carriers (Jacquemont et al. 2004), due in part to the protective influence of a second X chromosome in females (Hagerman et al. 2004; Berry-Kravis et al. 2005; Jacquemont et al. 2005). Most research done to date, therefore, has studied males. The data available on females suggest that the premutation may confer different medical risks with aging than those that occur in males, due to hormonal and other, as yet unknown, factors. A section in this chapter is specifically devoted to the current knowledge regarding female carriers.

The age of onset of one or both of the core motor signs of FXTAS, tremor and ataxia, in males is 61.6 $\pm$ 7.9 years (mean $\pm$ SD) (Tassone et al. 2007). Using established diagnostic criteria (Jacquemont et al. 2003), approximately 40% of male carriers over age 50 (Jacquemont et al. 2004) and 8% of female carriers over age 40 (Coffey et al. 2008) develop the disorder. Penetrance, however, is age related, such that 75% of men $\geq$80 years of age are affected, as shown in Fig. 1.3 (Jacquemont et al. 2004).

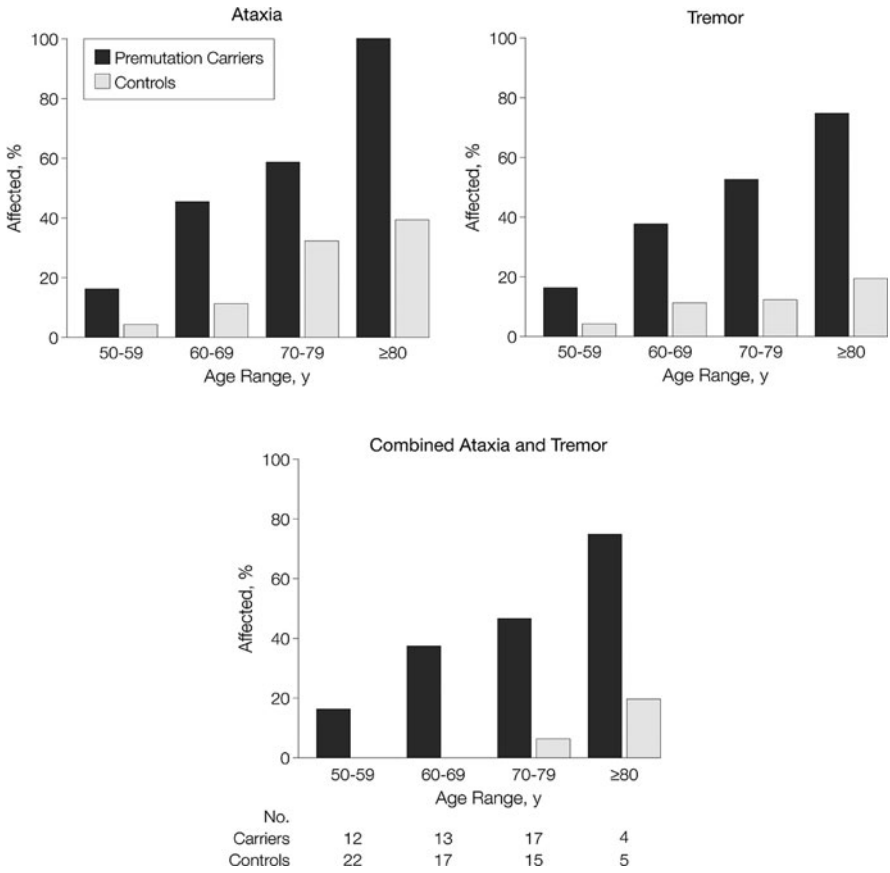

Fig. 1.3 Percentage of men with self-reported symptoms of gait disturbance, intention tremor, or combined ataxia and tremor. Reprinted with permission from Jacquemont et al. (2004); Copyright © 2004, American Medical Association. All Rights reserved

Clinical Signs of FXTAS

The average age of onset of tremor in male carriers is 62.6 ± 8.1 years (range 39–78 years) (Tassone et al. 2007). Most have action tremor as the initial motor manifestation (Leehey et al. 2007), but in many cases the tremor is minor and not noticed by the patient, as in the case report. It may not be evident until late in disease. In a study of 54 premutation males with a mean age of 67 that were selected without regard to neurological signs (Leehey et al. 2008), 50% had tremor and the mean severity was rated as slight by movement disorders neurologists. Seventeen percent (9/54) had a tremor in at least one arm that was rated as moderate or severe (unpublished data). The classic FXTAS tremor is a relatively symmetric kinetic tremor that increases in amplitude at endpoint, and a milder postural tremor is often present.

While the frequency (Hz) of the kinetic tremor in FXTAS has not been quantitatively defined, its characteristics, including frequency, are very similar to essential tremor. Rest tremor is less common than action tremor, and in at least some of the more severe cases is likely a re-emergence of the postural tremor. As the disease progresses the kinetic tremor increases in amplitude and is associated with hypermetria on finger-nose testing. Large-amplitude tremor and dysmetria may interfere greatly with eating, writing, and other daily activities that require fine motor control. Handwriting becomes large, untidy, and tremulous.

The mean age of onset of cerebellar gait ataxia, another defining feature of FXTAS, is 63.6 ± 7.2 years (range 47–78 years) (Tassone et al. 2007). The stance broadens, the gait slows, and foot placement is irregular. Progressive difficulty with tandem gait (considering normal as 10 perfectly placed consecutive steps) (Huntington Study Group 1996) likely occurs a few years before the carrier begins falling or develops a feeling of instability. Progressive gait instability is a major source of disability in FXTAS, with falls frequently resulting in injury, such as fractures, lacerations, and even subdural hematomas. Slowed, poorly coordinated hand movement, i.e., dysdiadochokinesias, and abnormalities of heel-shin testing occur in later stages or in those with a predominately cerebellar presentation.

Parkinsonism is another motor feature of FXTAS. The major signs are hypomimia and rigidity, but the latter is frequently gegenhalten in character rather than typical parkinsonian cogwheel rigidity. Rest tremor is also uncommon and is more often seen in persons with advanced disease and prominent action tremor. Some affected persons have a mildly stooped parkinsonian posture. While generally the parkinsonian signs are mild in FXTAS, 24% of premutation carriers were initially diagnosed with Parkinson disease in one study (Hall et al. 2005). These persons generally have an inadequate response to levodopa. However, some carriers have a predominant parkinsonian presentation indistinguishable from primary Parkinson disease. Hall et al. (2009) described four such premutation carriers, all with good levodopa response. Whether the premutation plays a role in their parkinsonism is unclear, but some of these individuals may manifest a complex, mixed disease process. This is supported by the finding of both Lewy bodies and FXTAS intranuclear inclusions on pathological examination of brain from a premutation carrier with a predominantly parkinsonian presentation (Greco et al. 2002).

Cognitive dysfunction and behavioral changes are a very problematic and disabling aspect of FXTAS (see Chapter 3 for more details). In part, they are likely a source of the common dichotomy between the family's recognition of tremor and the patient's lack of recognition or concern. Studies suggest that dementia occurs in about 40% of men with the disorder (Bourgeois et al. 2007; Seritan et al. 2008), less often in females (Hagerman et al. 2004), and that the frequency may be higher in late-stage FXTAS. The dementia is of a mixed cortical–subcortical pattern, due to involvement of cortical (frontal, hippocampal) and subcortical (white matter of the cerebral and cerebellar hemispheres) structures (Seritan et al. 2008).

The largest, most comprehensive examination of cognitive impairment in premutation carriers (Grigsby et al. 2008) showed that men with FXTAS have substantial executive impairment and diffuse deficits in other cognitive functions. Affected

men performed worse than controls on intelligence, executive cognitive functioning, working memory, remote recall, declarative learning and memory, information processing speed, and temporal sequencing, as well as one measure of visuospatial functioning. Language and verbal comprehension was relatively preserved. Even the male carriers without motor signs performed worse than controls on executive function and declarative learning and memory. These findings have been confirmed in other studies (Moore et al. 2004; Loesch et al. 2005a; Seritan et al. 2008) and suggest that the executive dysfunction, especially control of inhibition (Cornish et al. 2008), is an early sign of cognitive impairment and remains a prominent deficit as the disorder progresses. Moreover, further data analysis suggests that the impairment of non-executive cognitive skills in FXTAS is largely secondary to executive dysfunction (Brega et al. 2008).

Psychiatric symptoms are also common (Bourgeois et al. 2006). Studies show there are increased rates of anxiety, irritability, agitation, hostility, obsessive-compulsiveness, apathy, and depression occurring in male premutation carriers over age 50 with and without FXTAS. Female carriers, with and without FXTAS, have a higher rate of depressive symptoms compared to published norms (Hessl et al. 2005; Roberts et al. 2009).

The peripheral nervous system is involved in FXTAS. Peripheral neuropathy was present in the five men that were originally described with FXTAS, in 60% of men in a descriptive study of 20 affected men (Jacquemont et al. 2003), and in 53% of 17 affected females (Coffey et al. 2008). A large controlled study (Berry-Kravis et al. 2007) reported that male carriers had more neuropathic signs than controls (p=0.0014) and that the severity of the signs correlated with CGG repeat size and with the presence of ataxia. Female carriers tended to have more neuropathic signs than controls (p=0.17) and severity correlated with ataxia. Hagerman et al. (2007) described three men and one woman with FXTAS that presented with neuropathy and a male carrier that had neuropathy and no other signs of FXTAS. Electrophysiological findings in males with FXTAS compared to controls were found to be consistently abnormal and in male carriers without FXTAS were slightly but not significantly abnormal. CGG repeat length and mRNA level correlated with severity of some of the electrophysiological findings. These electrodiagnostic studies document a predominantly axonal sensorimotor polyneuropathy (Soontarapornchai et al. 2008). Some affected persons have marked neuropathic pain, suggesting involvement of small fibers. The neuropathy may be severe enough in some carriers to exacerbate gait ataxia.

Complaints of autonomic dysfunction have been reported frequently, but controlled studies are lacking. In a study of 20 men with FXTAS, 55% complained of urinary incontinence and 30% bowel incontinence (Jacquemont et al. 2003). Urinary frequency and urgency is a common complaint of premutation carriers over age 50. A controlled study found that male carriers reported urinary incontinence more than controls, but the difference was not significant (p=0.07) and there was no difference in females (Jacquemont et al. 2004). Urinary and fecal incontinence is present in late-stage FXTAS (Leehey et al. 2007; Gokden et al. 2008). Some carriers have symptomatic orthostasis or syncope (Kamm et al. 2005; Louis et al. 2006; Gokden

et al. 2008). Pugliese and colleagues (Pugliese et al. 2004) reported a 73-year-old gentleman that presented with postprandial hypotension and was found to have had bilateral hand tremor for the prior 2 years and 73 CGG repeats in *FMR1*. The patient had no ataxia or family history suggestive of *FMR1*-related disorders. This case report implies that autonomic dysfunction can be a dominant feature of FXTAS.

Studies suggest that hypertension tends to be more common in carriers than controls, with significance levels of $p=0.06$ for males (Jacquemont et al. 2004) and $p=0.002$ for females (Coffey et al. 2008). Anecdotal evidence suggests that cardiac dysfunction, including ischemia, congestive heart failure, and arrhythmia, may also occur more frequently in men with FXTAS, but controlled studies are needed. Involvement of the autonomic nervous system has been documented in neuropathologic studies which showed intranuclear inclusion bodies typical of FXTAS in paraspinal sympathetic ganglia (Greco et al. 2006), myenteric ganglia of the stomach, and subepicardial autonomic ganglia (Gokden et al. 2008).

Other disorders appear to be more common in FXTAS, but again, controlled data are lacking. Many men with advancing FXTAS have diet-controlled hyperglycemia that leads to diabetes requiring oral therapy. Also, many affected men have episodes of dizziness. In some cases these episodes appear to be due to lightheadedness related to orthostatic hypotension and in other instances appear to be due to vestibular dysfunction. Studies of hyperglycemia and vestibular dysfunction in FXTAS are needed to determine if and how these are related to the *FMR1* premutation.

Female Premutation Carriers

Females with the premutation have a higher rate of primary ovarian insufficiency (POI) compared to other women (Cronister et al. 1991). Approximately 16–20% of females have POI with an increasing prevalence as the CGG repeat number increases to about 100 repeats, above which there is a gradual fall in prevalence (Sullivan et al. 2005; Wittenberger et al. 2007). Consistently elevated FSH levels are seen in carriers compared to controls, even when they still have menstrual cycles (Welt et al. 2004). As ovarian insufficiency ensues, the FSH levels increase. POI was previously called premature ovarian failure (POF); however, several women were able to conceive after their menses stopped, so this problem was renamed POI (Welt 2008). The premutation is thought to result in POI because of a direct effect of RNA toxicity (see Chapter 6) in the ovary, although endocrine dysfunction related to toxic RNA effects in the pituitary and the hypothalamus may also be related to POI. The finding of POI, however, does not apparently increase the risk of FXTAS in women (Coffey et al. 2008), although prospective studies are needed.

Thyroid dysfunction is also increased in women with the premutation. Approximately 50% of women with FXTAS have thyroid dysfunction, usually hypothyroidism (Coffey et al. 2008). This problem may be diagnosed in early or mid-adulthood, usually long before neurological difficulties. For many this is related to an autoimmune mechanism. A suggestion of an increased rate of multiple

sclerosis and the finding of fibromyalgia in over 40% of females with FXTAS (Coffey et al. 2008) provides further evidence for a predisposition to autoimmune disease in women with the premutation.

In a study of 146 female premutation carriers, the frequency of FXTAS was approximately 8% in those over age 40 (Coffey et al. 2008). However, in carrier females without FXTAS there was a significant history of chronic muscle pain (26%), tremor (12%), and sensory loss (45%) compared to age-matched controls (Coffey et al. 2008). These problems are likely related to the toxicity of the premutation, although they may not progress to full FXTAS. The normal X chromosome may be protective and limit development of the full FXTAS phenotype. Cognitive decline is suggested to be less frequent in women with the premutation (Hagerman et al. 2004). However, Karmon and Gadoth (2008) recently reported that a 62-year-old female with 75 repeats had classic FXTAS including severe dementia. Of note, we have seen two cases of dementia in females with FXTAS who also had neuropathologic findings of Alzheimer's disease in addition to FXTAS inclusions (Greco CM, et al. unpublished data).

The most common problems of women with the premutation in mid-adulthood are anxiety and depression (Franke et al. 1996; Sobesky et al. 1996; Franke et al. 1998; Hessl et al. 2005; Roberts et al. 2009). This has long been considered to relate to the stress of raising a difficult child with fragile X syndrome, although there is emerging evidence of an enhanced response to stress in premutation carriers (Brouwer et al. 2008). Enhanced cortisol release after stress is likely related to dysregulation of the hypothalamic–pituitary axis which again may be secondary to an RNA toxicity effect. Typical FXTAS inclusions have been documented in the adrenals, pituitary, amygdala, hypothalamus, and hippocampus of the premutation mouse (Brouwer et al. 2008) and in these same areas in humans (Louis et al. 2006; Greco et al. 2007; Gokden et al. 2008). Recently Adams et al. (2009) documented an inverse correlation between the size of the hippocampus and the level of anxiety as measured by the SCL-90, a psychological scale, in females with the premutation (smaller hippocampus with greater anxiety). These data imply that psychological problems, especially anxiety, may have a detrimental effect on the hippocampus and therefore long-term cognitive function. Such data suggest that early treatment of psychological problems is warranted, and this treatment is outlined in Chapter 9. Regarding depression, a controlled study of 34 mothers of children with fragile X syndrome found that the premutation by itself could be responsible for a tendency to depression in these mothers (Rodriguez-Revenga et al. 2008).

The following case history demonstrates a typical case of FXTAS in a female carrier.

Case 2. A 79-year-old woman presented with weakness and inability to walk. Her neurological symptoms began at age 67 with pain in her legs and a feeling of tightness in her feet as if she was wearing tight boots. She also developed pain in the muscles of her low back. She was treated with hydrocodone and required higher doses as the pain became chronic. She developed hypertension and swelling in her legs. Electrodiagnostic studies documented a length-dependent polyneuropathy. At age 75 she was diagnosed with fibromyalgia by her rheumatologist and chronic

inflammatory demyelinating polyneuropathy by her neurologist. She was treated with intravenous gamma globulin and prednisone but her symptoms worsened. By age 76 she needed a four-pronged cane due to weakness in her legs and gait ataxia; 2 years later she was dependent on a wheelchair. Her family noticed an intention tremor at age 78, but the patient denied any tremor. When examined at age 79 she had marked weakness and severe edema in the lower extremities with absent ankle reflexes. She had no vibration sense and decreased cold and pinprick sensation in her distal lower extremities. She was unable to walk or stand, even with full support. An action tremor was present in the right hand. Cognition was normal for age but she appeared depressed. Brain MRI demonstrated moderate brain atrophy and widespread subcortical and periventricular white matter disease without a clear MCP sign. *FMR1* gene analysis showed her CGG repeat sizes to be 30 and 73. She has 10 children, many of whom are carriers, and multiple grandchildren with fragile X syndrome.

Natural History of FXTAS

Little is known about the natural history of FXTAS, and only one retrospective chart review study has been reported (Leehey et al. 2007). This report studied the progression of tremor and ataxia in 55 men with FXTAS. After the initial motor sign, usually tremor, median delay of onset of ataxia was 2 years, onset of falls 6 years, dependence on a walking aid 15 years, inability to do most daily activities 16 years, and death 21 years. However, life expectancy ranged from 5 to 25 years, and several cases of death within 5–7 years after seeking medical care have been reported (Kamm et al. 2005; Greco et al. 2006; Louis et al. 2006; Gokden et al. 2008). Cause of death is usually due to cardiopulmonary problems, including pneumonia, cardiac arrest, congestive heart failure, and progression of neurological disease. In the months before death patients are bedridden, dysarthric, dysphagic, without bladder or bowel control, rigid, and bradykinetic (Louis et al. 2006; Leehey et al. 2007).

Diagnosis of FXTAS

While tremor and ataxia are the core motor signs in FXTAS, accumulating literature documents the wide variation in clinical presentation. Some persons present with predominant dementia (Bourgeois et al. 2006; Goncalves et al. 2007), neuropathy (Hagerman et al. 2007), parkinsonism (Louis et al. 2006; Hall et al. 2009), dysautonomia (Pugliese et al. 2004), or action tremor without much ataxia (Leehey et al. 2003). Some have spasticity in the legs and other pyramidal tract signs (Jacquemont et al. 2005; Kamm et al. 2005; Cellini et al. 2006). A recent retrospective study of diagnoses that were given to persons with FXTAS (n=56) before FXTAS was a known clinical entity demonstrates the heterogeneity of presentations: 24% were diagnosed with parkinsonism, 20% with tremor, 17% with ataxia,