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Fragile X-associated Tremor/Ataxia Syndrome (FXTAS): Clinical Phenotype, Diagnosis and Treatment

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Abstract

Fragile X-associated tremor/ataxia syndrome (FXTAS) is a neurodegenerative disorder caused by a CGG repeat expansion in the premutation range (55-200) in the fragile X mental retardation 1 gene. Onset is typically in the early seventh decade and men are principally affected. The major signs are cerebellar gait ataxia, intention tremor, frontal executive dysfunction, and global brain atrophy. Other frequent findings are parkinsonism (mild), peripheral neuropathy, psychiatric symptoms (depression, anxiety, agitation), and autonomic dysfunction. The clinical presentation is heterogeneous, with individuals presenting with varied dominating signs, such as tremor, dementia or neuropathy. MR imaging shows atrophy and patchy white matter lesions in the cerebral hemispheres and middle cerebellar peduncles. The latter has been designated the 'MCP sign', occurs in about 60% of affected men, and is relatively specific for FXTAS. Affected females generally have less severe disease, less cognitive decline, and some symptoms different from that of men, e.g., muscle pain. Management of FXTAS is complex and includes assessment of the patient's neurological and medical deficits, treatment of symptoms, and provision of relevant referrals, especially genetic counseling. Treatment is empiric, based on anecdotal experience and on knowledge of what works for symptoms of other disorders that also exist in FXTAS. Presently the disorder is under-recognized, since the first published report was in 2001, and since the presentation is variable and mainly consists of a combination of signs common in the elderly. However, accurate diagnosis is critical, for the patient and for the family, as they need education regarding their genetic and health risks.

Keywords

fragile X tremor/ataxia syndrome; FXTAS; fragile X mental retardation 1 gene; treatment

Introduction

Fragile X-associated tremor/ataxia syndrome (FXTAS)([1]) is an inherited degenerative disorder that affects aging persons, primarily men, and is associated with an array of neurological symptoms and medical conditions. The disorder is caused by a CGG repeat expansion in the premutation range (55-200) in the 5′ non-coding region of the fragile X mental retardation 1 (*FMR1*) gene. Expansion of the CGG repeat to >200 results in reduction or absence of fragile X mental retardation protein (FMRP) and, consequentially, fragile X syndrome (FXS), the most common known heritable form of mental retardation and autism. While mutations in *FMR1* cause both FXS and FXTAS, the two disorders are distinct, as illustrated in Figure 1. In FXTAS, FMRP is produced in normal or near normal amounts while *FMR1* mRNA with the expanded repeat is produced in markedly elevated amounts in leukocytes and brain.([2, 3]) The high level of *FMR1* mRNA is likely toxic and the cause of the cellular injury responsible

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for the symptoms. FXTAS is a significant cause of morbidity, especially ataxia in aging men, ([4, 5]) and is the most common known single-gene form of tremor and ataxia, and perhaps also of dementia, in the older adult population.

Clinical Phenotype

The age of onset of tremor and/or ataxia in males is 61.6 ± 7.9 years (mean ± SD).([6]) The classic presentation of FXTAS is a man in his early sixties with progressive cerebellar ataxia, action tremor, parkinsonism and cognitive decline, especially executive dysfunction. Other features, which are present in variable degrees among individually affected persons, are psychiatric disturbances, and autonomic and peripheral neuropathy.([7, 8]) The frequency of these various signs are presented in Table 1. However, as shown in Table 2, a number of different clinical features and presentations with varied dominating signs have been reported in persons with FXTAS. Even within families affected persons have disparate clinical presentations, e.g., a presentation that looks like essential tremor in one brother and a classic FXTAS presentation in another.([9])

About one in 260 females and one in 813 males in the general population are premutation carriers.([10, 11]) Penetrance of FXTAS is age-dependent, with approximately 40% of males over age 50,([12]) and 8% of female carriers over age 40([13]) developing the disorder. Although large scale epidemiologic studies of FXTAS have not conducted, the predicted lifetime cumulated risk among men in the general population has been estimated to be approximately one in 8,000.([14]) Thus, FXTAS is much less common than essential tremor and Parkinson's disease in older adults, but similar in prevalence to that of other neurodegenerative disorders, e.g., other inherited ataxias, amylotrophic lateral sclerosis, and progressive supranuclear palsy. ([15])

While the symptoms of FXTAS vary among individuals, almost all affected persons develop problematic cerebellar gait ataxia as the disorder progresses. Unexplained falls are frequent, and the tandem gait is significantly abnormal in about 50% of male carriers over age 50.(Leehey et al., unpublished data) While cerebellar dysfunction is a nearly constant feature that affects the gait, other impairments such as parkinsonism, sensory neuropathy, and weakness also contribute to poor balance. Hypermetria and dysdiadochokinesis are frequently present in the upper extremities.

Action tremor is a common finding, but the severity is quite variable among individuals. Many affected persons, probably due to poor insight related to executive dysfunction, deny having any tremor despite their spouse noting that a mild, intermittent tremor has been present for months or years. Others have an obvious, severe tremor that impairs daily function. Fifty percent of male carriers have at least mild, and 17% at least moderate intention tremor, compared to 25% and 4%, respectively, of age-matched male controls (Leehey et al., unpublished data). The tremor of FXTAS has not been quantitatively studied, but looks like essential tremor. Further, affected persons usually have definite tremor reduction with use of medications commonly prescribed for essential tremor.

Another frequent motor sign is parkinsonism, which is generally mild and mainly manifested by masked facies, generalized rigidity, overall bradykinesia and slow gait. Occasionally affected persons have a parkinsonian posture. Resting tremor is uncommon, and when present, may be due to reoccurrence of the postural tremor in the rest position. Carriers with parkinsonism generally have minor and only transient improvement with dopaminergic medication, suggesting that the underlying mechanism causing parkinsonism is not the same as in primary Parkinson disease. Gait ataxia, intention tremor, and parkinsonism worsen with increasing age, and the severity of tremor and ataxia correlate strongly with increasing CGG repeat size through the premutation range.([16])

Cognitive dysfunction is a very disabling feature in many aging male carriers.([17]) Male carriers over age 50 selected without regard to motor signs of FXTAS show normal to mild full scale IQ deficits and significant memory and frontal executive dysfunction.([18-21]) Men with motor signs have prominent executive impairment, and as the disease progresses develop global deficits (dementia), affecting intelligence, working memory, declarative learning and memory, remote recall, information processing speed, and temporal sequencing, and perhaps visuospatial functioning. These deficits are suggested to be largely due to the prominent executive dysfunction that occurs in FXTAS.([22]) Of note, verbal comprehension and language are relatively preserved.([21]) The dementia is of a mixed subcortical - cortical pattern, due to involvement of cerebral and cerebellar white matter, frontal cortex, and hippocampus.([23]) Dementia occurs in approximately 40% of men,([23, 24]) less often in females([23]) and the frequency may be higher in late stage FXTAS.

Psychiatric and behavioral disorders, the latter mainly due to impaired executive function, are also common and disabling features of FXTAS. Males over age 50, selected without regard to motor signs, demonstrate increased rates of anxiety, irritability, agitation, hostility, obsessive-compulsiveness, apathy, and depression.([17, 25]) Affected men are unaware of their change in personality and thus will not report these symptoms, but untreated they can lead to significant marital discord. Female carriers have higher rates of depression and obsessive thinking than matched controls.([25])

The peripheral nervous system is also affected in carriers.([1, 8, 26, 27]) Males have greater loss of distal lower extremity tendon reflexes and vibration sense than age-matched male controls. ([28]) Distal leg strength is generally preserved. The neuropathy may be the presenting feature of FXTAS, the only significant neurological finding in a carrier,([26]) or asymptomatic. Electrical studies in males with FXTAS document a predominately axonal sensori-motor polyneuropathy.([27]) The degree of reflex impairment correlates with severity of ataxia, thus, the neuropathy may contribute to gait difficulties in some affected persons.

Autonomic dysfunction has been described in FXTAS, but controlled studies are needed. In a study of 20 men with FXTAS, 55% reported urinary incontinence and 30% bowel incontinence. ([8]) Urinary and fecal incontinence mainly occurs in late stage FXTAS.([29, 30]) Some individuals have symptomatic orthostasis and syncope.([30-33]) Pugliese and colleagues([31]) reported a 73 year old man that presented with postprandial hypotension, and was then found to have had hand tremor and 73 CGG repeats in *FMR1*. There was no family history suggestive of *FMR1* related disorders and the patient did not have ataxia. This case report suggests that autonomic impairment can be a presenting and dominant feature of FXTAS. Of note, autonomic nervous system involvement has been documented in neuropathologic studies of paraspinal sympathetic ganglia,([34]) myenteric ganglia of the stomach, and subepicardial autonomic ganglia.([30])

Some medical conditions have been reported to be associated with the *FMR1* premutation. Hypertension was more common in male (p=.06)([12]) and female (p=.002)([13]) carriers than controls. Anecdotal evidence suggests that cardiac dysfunction, e.g., arrhythmia, ischemia, and congestive heart failure, may occur more frequently in men with FXTAS. Other disorders also appear to be more common in persons with FXTAS than expected. For example, 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.

FXTAS is a progressive disease, but prospective studies on its natural history are lacking. A retrospective study([29]) on the progression of tremor and ataxia in 55 men with FXTAS found that after the initial motor sign, usually tremor, median delay of onset of ataxia was two years, onset of falls six years, dependence on a walking aid 15 years, inability to do most daily activities 16 years, and death 21 years. Life expectancy ranged from 5 to 25 years, and other reports cite death occurred in five to seven years after presentation for evaluation.([30, 32-34]) Death was due to congestive heart failure, pneumonia, cardiac arrest, or progression of neurologic disease. At end stage affected persons are bedridden, dysphagic, dysarthric, parkinsonian and without bladder or bowel control.([29, 33])

Female Premutation Carriers

Even before the finding that a neurodegenerative disorder, FXTAS, occurs in carriers, females carriers were known to be at increased risk for primary ovarian insufficiency (POI).([35]) About 20% develop POI,([36, 37]) and it does not appear to be related to the risk of FXTAS.([13]) Also, female carriers have been found to have higher rates of depression and anxiety than controls. ([25, 38-40]) While this could be related to the stress of raising a difficult child with fragile X syndrome, recent studies suggest that depression([41]) and anxiety([42]) are secondary, at least in part, to the premutation.

FXTAS affects male carriers more([12]) partially because of a protective effect of the second X chromosome in females.([43, 44]) Most research on FXTAS to date has been in males. The data available on females suggest that the premutation may confer different neurological and medical risks with aging([13, 45]) than those that occur in males, due perhaps to hormonal and other, as yet unknown, factors.

Generally female carriers do not develop as much tremor and ataxia as males.([16, 46]) A quantitative study([16]) showed that females' over age 50 risk for cerebellar ataxia correlated with increasing CGG repeat size only when the activation ratio, the percent of normal *FMR1* alleles that are on the active X chromosome, was factored in. Female carriers without FXTAS report more sensory loss (45%), chronic muscle pain (26%), and tremor (12%) than controls. ([13]) Interestingly, preliminary data suggests that female carriers, regardless of the presence of motor signs, have higher rates of psychogenic signs, including movement disorders and seizures, than expected. (Leehey M & Seritan A, unpublished data).

Some female carriers do develop classic features of FXTAS,([43, 45, 47, 48]) but they also have some distinct differences from affected males. Females with FXTAS probably have less cognitive dysfunction than males,([23, 45]) although individual case reports document that dementia does occur.([49, 50]) Also, chronic muscle pain and a diagnosis of fibromyalgia are frequently reported by affected females. Further, approximately 50% of affected females have been diagnosed with thyroid dysfunction, usually hypothyroidism.([13])

Neuroimaging

Imaging in FXTAS is useful because it typically shows atrophy, white matter changes, and a distinctive abnormality of the middle cerebellar peduncles. These finding are typically more severe in affected males than females.([51]) MR imaging reveals atrophy of the cerebrum, cerebellar cortex, corpus callosum and pons. The cerebral and cerebellar white matter has increased T2 and decreased T1 signal intensity. These white matter image changes resemble that typically seen in microvascular ischemia, except that it is often subcortical and patchy. ([52]) The middle cerebellar peduncles have increased T2 signal in about 60% of affected men and 13% of affected women.([51, 52]) This is called the ‘MCP sign’ and is relatively specific for FXTAS. It has also been reported in multiple system atrophy,([53, 54]) acquired hepatocerebral degeneration,([55]) and recessive ataxia.([54]) To date, however, there have been only two patients,

one with recessive ataxia and one with multiple system atrophy,([54]) reported with the MCP sign that were tested and not found to have the *FMR1* premutation.

Some asymptomatic carriers have atrophy also. Brain stem volume was significantly smaller in unaffected male carriers compared to controls.([56]) Aging male carriers selected without regard to motor signs had reduced total brain, cerebrum, cerebellum, cerebral cortex, amygdalo-hippocampal complex, and thalamus size.([57, 58])

Diagnosis of FXTAS

The diagnosis of FXTAS is often missed, for two reasons. First, since it has only recently been described,([1]) many physicians are not yet familiar with it. Second, the presentation can be quite variable, resulting in misdiagnosis. Correct diagnosis is not only vital for the patient but also for their family; ensuing generations are at high risk for fragile X syndrome. Guidelines to aid the physician in deciding who to test for FXTAS, are shown in Table 3; and generally accepted diagnostic criteria are presented in Table 4.([8]) Diagnosis of a premutation carrier requires provision of genetic counseling for the patient and their family.

Management and Therapy

While the patient diagnosed with FXTAS may have presented with a specific complaint, often a motor symptom, the management of FXTAS is complex and involves other considerations. Appropriate management consists of assessment of the patient's neurological and medical deficits, prescription of appropriate medications and rehabilitative services, genetic counseling for the patient and family and provision of relevant referrals. Evaluation for other causes of dementia, particularly reversible contributing causes, such as hypothyroidism, B12 deficiency, folate deficiency and depression is essential. Further, patients need counseling regarding conditions and medications which may worsen FXTAS, e.g. some chemotherapeutic agents, e.g., carboplantin,([59]) and major surgery. Referrals are often indicated to urology, rehabilitative medicine, genetic counseling, and social work. The most disabling symptoms are falls, intention tremor, psychiatric problems such as depression, anxiety, agitation, and disinhibition, and cognitive dysfunction, ranging from memory loss to dementia. In addition, many women complain bitterly of fibromyalgia symptoms and some affected persons have severe neuropathic leg pain.([60])

To date there have not been any controlled trials reported that evaluate disease modifying or symptomatic therapies. Thus, intervention is limited to symptomatic therapy. Current recommendations are based on anecdotal reports and on knowledge of what works for symptoms of other disorders that also exist in FXTAS. For example, the action tremor and the parkinsonism in FXTAS may respond to medications used effectively for essential tremor and Parkinson's disease, respectively.

Falls are mainly due to cerebellar dysfunction, which generally does not respond to medical therapy.([61]) A few persons with FXTAS and other disorders with cerebellar ataxia have shown at least transient improvement with amantadine at standard doses([62, 63]) and with varenicline at 0.5 to 1 mg per day.([64, 65]) However anecdotal reports suggest that varenicline may worsen tremor and exacerbate psychiatric symptoms in FXTAS. Gait difficulties may also be caused by parkinsonism, peripheral neuropathy, extensive CNS white matter lesions, and weakness, especially of the proximal lower extremities. Dopaminergic medications improved ataxia in some persons with parkinsonism.([66]) Physical therapy aimed at improving strength and flexibility may reduce falls and improve function.

Action tremor may respond to beta-blockers, primidone, and topiramate, at the doses used to treat essential tremor.([66, 67]) Benzodiazepines such as alprazolam may also be effective in

some patients,([68]) since tremor is aggravated by anxiety and stress. Other options with less published support are gabapentin, levetiracetam, clonazepam, clozapine, nadolol, nimodipine and botulinum toxin.([69]) Regarding the latter, injection of just the flexor muscles and not the extensors reduces the occurrence of excessive weakness (personal communication, J Jankovic). Occupational therapy may offer techniques to improve function, such as wrist weights or use of the Assistive Mouse Adapter (IBM Watson Research Center), which is designed to assist persons with tremor use a keyboard.([70]) Thalamic deep brain stimulation is an option for severe, medically intractable tremor,([9, 71]) and perhaps should be limited to unilateral treatment since bilateral surgery is more likely to worsen cognition([72]) and gait.([71])

While minimal use of psychoactive medication is indicated in elderly persons with relatively advanced stage FXTAS, judicious treatment of psychiatric symptoms and cognitive decline is generally rewarding. Regarding depression, selective serotonin reuptake inhibitors (SSRIs) with minimal drug-drug interaction (e.g. citalopram, sertraline, escitalopram) are preferred for use in the elderly, rather than paroxetine, fluvoxamine, are fluoxetine. Anecdotal experience suggests that the selective serotonin norepinephrine reuptake inhibitors (SNRIs; venlafaxine and duloxetine) are especially effective,([60]) not only for depression but also for anxiety, agitation, hostility and irritability.([60])

Cognitive decline has been reported to slow in a few persons with FXTAS with use of acetylcholinesterase inhibitors.([66]) This may be because pathological studies in FXTAS show marked pathology in the hippocampus, ([73]), although the clinical profile of cognitive deficits in Alzheimer's disease and FXTAS are distinct.([23]) Addition of memantine is indicated in Alzheimer's disease to treat the memory deficit, and is suspected to reduce glutamate-associated excitotoxicity in neurodegenerative disorders. Anecdotal reports suggest memantine may be helpful in FXTAS at the same dose used in Alzheimer's disease.([60])

Pain from peripheral neuropathy may be reduced with anticonvulsants (especially gabapentin and pregabilin), antidepressants (especially cymbalta), and topical analgesics (such as lidocaine cream). Pain from fibromyalgia in women with FXTAS may respond to pregabalin ([74]) and standard therapy.([75]) Standard therapy includes exercise, psychotherapy, and antidepressants.

Although parkinsonism is usually mild in FXTAS, some patients improve with dopaminergic medications and anticholinergics, at standard doses used in Parkinson disease. In the later stages of FXTAS, when patients are more fragile, levodopa is expected to be better tolerated than dopamine agonists, and anticholinergics need monitoring for exacerbation of memory and urinary problems. Physical therapy, especially step and gait training, has been shown to improve function in Parkinson disease,([76, 77]) so may be beneficial in carriers with parkinsonism.

Autonomic dysfunction in FXTAS may include impotence, orthostatic hypotension, urinary frequency or incontinence, and bowel incontinence (in the later stages). Urological referral will dictate which types of medication may be helpful for the urinary symptoms. Hyperactive detrusor activity responds to small doses of tricyclic antidepressants, to muscarinic receptor antagonists, and to botulinum toxin injections. Initial treatment of orthostatic hypotension consists of increased salt and fluid intake, eating frequent small meals, use of Jobst stockings, and elevation of the head of the bed at night. Useful medications include mineralocorticoids (fludrocortisones) and midodrine, an alpha-1 adrenergic agonist which increases blood pressure. Regarding midodrin, patients need to be warned not to lie flat for four hours after a dose, as dangerously high blood pressure can occur.([78]) Some patients benefit from use of both midodrine and fludrocortisones. Orthostasis also responds to pyridostigmine.([60, 79])

A few other points regarding the management of FXTAS are worth noting. Caretakers are often in need of support, emotional and practical, as the patient's disease progresses. Depression and/or anxiety are common in spouses, and treatment with an SSRI can be quite helpful. Appropriate referrals are needed to assist the caretaker in obtaining help in the household, legal guardianship, and, eventually, placement of the patient in a specialized chronic care facility. Another important point is that persons with FXTAS will sometimes be misdiagnosed as having normal pressure hydrocephalus. However, surgery for this condition in persons with FXTAS has resulted in deterioration.([12, 60])

Conclusion

Mutation of the *FMR1* gene is associated with FXS, POI, and FXTAS. The premutation, which causes POI and FXTAS, is relatively common in the general population, and thus an important source of morbidity. To date most persons with FXTAS have been identified only after a grandchild is diagnosed with FXS. FXTAS is under-recognized and misdiagnosed, since it has only recently been described, and because its' presentation is variable and mainly consists a combination of signs that are common in the elderly. However, accurate diagnosis is important, not only for the patient, but so that family members can be educated about serious genetic and health risks.

Many important questions about *FMR1* premutation related disease remain. For example, prospective studies of disease progression and modifying factors would provide valuable information needed for life planning. Most importantly, the basic mechanisms by which the *FMR1* premutation cause symptoms need further study, so that effective treatment can be developed to slow and prevent disease.

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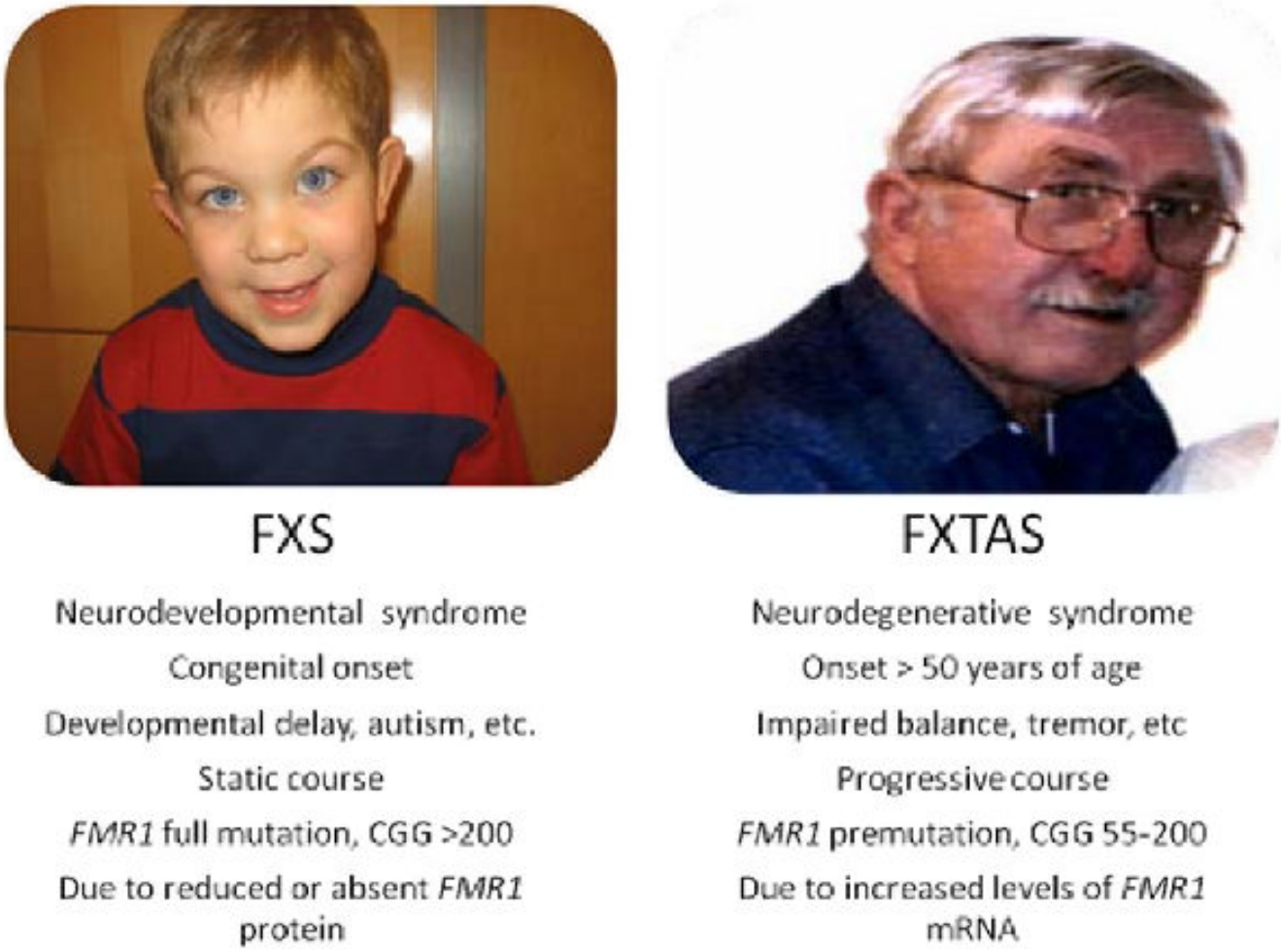

Figure 1.
Fragile X Syndrome (FXS) vs. Fragile X-associated Tremor/Ataxia Syndrome (FXTAS). This figure demonstrates that FXS and FXTAS are very different disorders, and that each results from a different length of the repeat expansion that occurs in the same gene, fragile X mental retardation 1 (*FMR1*). Two males are shown, because males are more affected than females since the gene mutation is on the X chromosome.

Table 1

Clinical signs in FXTAS*

Clinical Feature	Affected Subjects (%) (n=20)
Cerebellar ataxia	
Dysarthria	78
Dysmetria	93
Postural & gait abnormalities	86
Tremor	
Intention	70
Resting alone	10
Parkinsonism	
Mild bradykinesia	57
Mild rigidity	
Upper extremity	71
Lower extremity	35
Cogwheeling	5
Peripheral neuropathy	60
Other medical conditions	
Urinary incontinence	55
Fecal incontinence	30
Impotence	80
History of congestive heart failure	55
Hypertension	50

* Adapted from a review of 20 men with FXTAS identified because of a family history of fragile X syndrome, mean age (± SD) 71 ± 6, mean CGG repeat 84 (range 69-99), from Jacquemont et al. ([8])

Table 2

FXTAS has a variable clinical phenotype

Variably associated features
Autonomic dysfunction([30-33])
Large-fiber sensory neuropathy([26-28])
Psychiatric features: depression, anxiety, irritability([17,25])
Cognitive decline and dementia([21])
Oculomotor dysfunction([80])
Focal dystonia (limb, cervical, laryngeal)([81,82])
Spastic paraparesis([44])
Uncommon presentations
Essential tremor-like syndrome([9,71])
MSA-like syndrome([32])
Rapidly progressive dementia([83])
CMT-like neuropathy([26])
Spastic paraparesis([44])
Clinical heterogeneity within the same family([9,84])

Table 3

Guidelines for who test for FXTAS

Cerebellar ataxia	≥ age 50 & Unknown cause
Action tremor	Presence of cerebellar ataxia, parkinsonism or dementia & ≥ age 50 & Unknown cause
Dementia	Presence of cerebellar ataxia, parkinsonism or action tremor & ≥ age 50 & Unknown cause
Some FXTAS signs	Middle cerebellar peduncle sign or Patient or family history of premature ovarian insufficiency or Family history of *FMR1* related disease
Multiple system atrophy, cerebellar subtype*	

*Especially if has action tremor or longer than expected disease duration

Table 4

FXTAS diagnostic criteria in *FMR1* premutation carriers([8])

Diagnostic Categories	
Definite:	Presence of one major radiological sign plus one major clinical symptom
Probable:	Presence of either one major radiological sign plus one minor clinical symptom or has the two major clinical symptoms
Possible:	Presence of one minor radiological sign plus one major clinical symptom
Symptom Types	
Radiological	
Major	MRI white matter lesions in MCPs and or brain stem
Minor	MRI white matter lesions in cerebral white matter
Minor	Moderate to severe generalized atrophy
Clinical	
Major	Intention tremor
Major	Gait ataxia
Minor	Parkinsonism
Minor	Moderate to severe short-term memory deficiency
Minor	Executive function deficit

MCP = middle cerebellar peduncle