CHAPTER

8

FXTAS

New Advances and Treatments

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Fragile X-associated tremor/ataxia syndrome (FXTAS) is one of the four disorders associated with the fragile X mental retardation 1 (*FMR1*) gene, that also include fragile X syndrome (FXS), fragile X-associated primary ovarian insufficiency and fragile X-associated neuropsychiatric disorders (FXAND). FXTAS, first reported in 2001 (Hagerman et al. 2001), is a neurodegenerative disorder of premutation alleles with between 55 and 200 CGG repeats, while FXS present with expansions larger than 200 CGG repeats. Carriers of premutation alleles are as high as 1 in 130 females and 1 in 250 males. However, only around 40% of male carriers and 14% of female carriers will develop FXTAS (Jacquemont et al. 2004; Rodriguez-Revenga et al. 2009). FXTAS is generally less severe in females because they have a second normal X chromosome that is active in about 50% of neurons and it is therefore protective to the brain. The repeat expansion can increase from one generation to the next, being common to find FXTAS in one generation and FXS in following generations within the same family. Nevertheless, less than half of all premutation carriers develop FXTAS and the reason is not known. As in FXS, the *FMR1* premutation is inherited in an X-linked fashion and when the premutation is inherited paternally, it does not expand further outside of the premutation range (Reyniers et al. 1993).

PATHOLOGY AND MOLECULAR MECHANISM OF FXTAS

Central nervous system pathology in FXTAS includes intranuclear inclusions in neurons and astrocytes, white matter disease, iron deposition, and senescent and activated microglial cells (Greco et al. 2002; Ariza et al. 2017; Martinez Cerdeno et al. 2018). In addition, premutation CGG-repeat expansions in the mouse *FMR1* gene have been shown to alter embryonic neocortical development (Cunningham et al. 2011). White matter disease is broad within the cerebrum and cerebellum and mild to moderate cortical atrophy and ventriculomegaly are also present. Intranuclear inclusions in FXTAS are present in neurons and astrocytes but are absent in oligodendrocytes and microglial cells. Inclusions are round and eosinophilic in hematoxylin and eosin stain (H&E), measure 2–5μm in diameter, and are single except for the Purkinje cells, where they can be double and are known as twin inclusions (Fig. 8.1) (Ariza et al. 2016). More than 20 inclusion-associated proteins have been identified on the basis of combined immunohistochemical and mass spectrometric analysis, including a number of neurofilaments and lamin A/C. Proteins in inclusions include at least two RNA binding proteins, heterogeneous nuclear ribonucleoprotein A2, and muscle blind-like protein 1, which are possible mediators of the RNA gain-of-function in

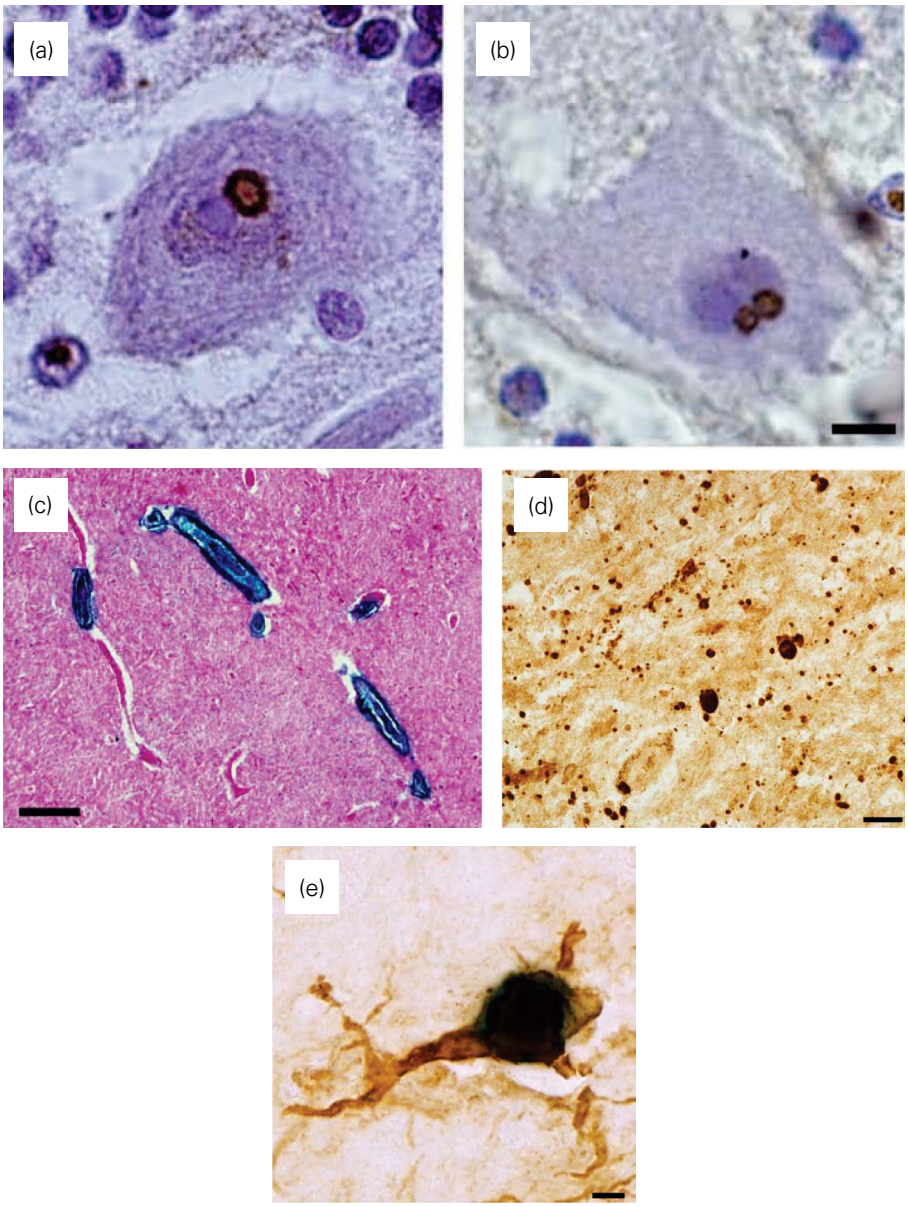

Figure 8.1 Brain tissue from postmortem FXTAS cases. (a) Neuron with a ubiquitin+ intranuclear inclusion (brown). (b) Purkinje cell with intranuclear twin inclusions (brown). (c) Capillaries full of iron (blue) in the putamen (d). Senescent Iba1+ microglial cells (brown) in the putamen. (e) Microglial cell (Iba1+ in brown) with a cytoplasm full of iron (blue). Scale bars: a, b: 10μm, c, d: 50μm, e: 5μm. A colour version of this figure can be seen in the plate section.

FXTAS (Iwahashi et al. 2006). When Parkinson's disease is concomitant, cytoplasmic Lewy bodies are seen in pigmented neurons of the substantia nigra (De Pablo-Fernandez et al. 2015), and when FXTAS coexists with Alzheimer's disease hippocampus pyramidal cells contain neurofibrillary tangles (Tassone et al. 2012).

FXTAS presents with high levels of *FMR1* message RNA (mRNA) and normal or moderately decreased levels of fragile X protein (FMRP). Larger CGG-repeat expansions are associated with higher levels of mRNA and lower levels of protein (Tassone et al. 2000). Two potential mechanisms are proposed to be implicated in FXTAS. The first one implicates a direct toxic gain-of-function of the increased CGG-repeat-containing *FMR1* mRNA (Willemsen et al. 2003; Brouwer et al. 2007). In this proposed mechanism, the CGG repeats in the elevated mRNA levels sequester proteins and block their normal cellular functions (Hagerman and Hagerman 2015). One protein that binds to the CGG is DGCR8–Drosha protein complex, which is a mediator of microRNA (miRNA) production. This sequestration reduces levels of many miRNAs and increases levels of their precursors in brain tissues from individuals with FXTAS (Sellier et al. 2013). The second hypothesis states that the translation of expanded CGG repeats into FMRpolyG alters nuclear lamina architecture and drives pathogenesis in FXTAS (Sellier et al. 2017). The translation of the *FMR1* mRNA from a point upstream of the expanded repeat rather than the AUG start codon, would impede the initiation of translation allowing the generation of RAN translation products that are out of frame with the normal FMRP coding sequence (Todd et al. 2013; Oh et al. 2015). The peptide product (FMRpolyG) contains a polyglycine stretch that is toxic and is found in the inclusions, and therefore may be one of the causes of FXTAS.

The brain in FXTAS is characterized by a state of inflammation. FXTAS presents with an alteration in iron transportation. Postmortem studies showed that iron bound to hemosiderin is present in the putamen in FXTAS (Ariza et al. 2015; Rogers et al. 2016; Ariza et al. 2017), and this iron deposition can be detected as a symmetric hypointensity in the putamen and caudate in T2-weighted spin-echo and diffusion weighted magnetic resonance images (MRI) in FXTAS patients (Scaglione et al. 2008; Wang et al. 2013). Deficits in protein levels that transport and eliminate extra iron from cells (transferrin, ferroportin, and ceruloplasmin) and a concomitant increase in deposition of cellular iron in the choroid plexus, have been also reported (Ariza et al. 2015; Ariza et al. 2017) Iron is essential for cell metabolism; however, uncomplexed iron leads to oxidative stress and inflammation. The FXTAS proinflammatory state is also supported by plasma and fibroblast metabolic studies of mitochondrial function showing that in FXTAS the mitochondrial energetic capacity is compromised (Giulivi et al. 2016; Alvarez-Mora et al. 2017). This alteration in energy production generates reactive oxygen species causing oxidative stress damage and activates apoptotic mechanisms. In addition, inflammation is supported by the lipid profile as well as the increase in oxidative stress–mediated damage to carbohydrates and proteins in serum of patients with FXTAS (Giulivi et al. 2016). Half of FXTAS cases present with activated microglial cells, while the other half present with dystrophic senescent microglial cells, that is the natural progression after a prolonged state of activation in microglia, and microglial cells accumulate a high amount of iron in their cytoplasm (Martinez-Cerdeño et al. 2018). Overall, these data indicate the presence of an inflammatory state in the FXTAS brain.

NEUROIMAGING

By comparing with age- and sex-matched healthy controls, MRI studies have revealed widespread brain atrophy and loss of microstructural integrity in the white matter in premutation carriers with FXTAS whilst only subtle structural changes (e.g. in the cerebellum and brainstem) have been detected in carriers without a clinical diagnosis of FXTAS (Brunberg et al. 2002; Hashimoto et al. 2011a; Hashimoto et al. 2011b; Wang et al. 2012b; Battistella et al. 2013). Amongst these changes, microstructural integrity loss in the middle cerebellar peduncle (MCP) and superior cerebellar peduncles (SCP) showed significant associations with CGG-repeat expansion and mRNA elevation and advances in FXTAS severity (Hashimoto et al. 2011b; Battistella et al. 2013; Wang et al. 2013b), highlighting the importance of the cerebellum in FXTAS pathophysiology.

Recent studies extended early MRI studies and further demonstrated that the cerebellum and brainstem were likely affected during both neurodevelopment and FXTAS-associated neurodegeneration (Wang et al. 2017). Premutation carriers without FXTAS aged 8–75 years exhibited accelerated age-related reduction in cerebellar volume and flatter U-shaped trajectory of brainstem volume compared with controls. Significant volume changes were estimated to occur at around age 28 for the brainstem and age 30 for the cerebellum, which are decades before the average age of onset for FXTAS (60 years) (Leehey et al. 2007; Shelton et al. 2018). Consistent with these change patterns, the FXTAS group exhibited cerebellar atrophy and accelerated brainstem atrophy compared with both older controls and the premutation non-FXTAS groups (age>50) (Fig. 8.2). Three MRI studies explored functional consequence of cerebellar atrophy and revealed associations with postural-control impairment in carriers with and without FXTAS using three different methods (Birch et al. 2015; Birch et al. 2017; Hocking et al. 2017). In addition, thalamic atrophy showed a correlation with increased gait variability (Birch et al. 2017) while atrophy of the caudate nucleus showed association with executive dysfunction in a separate study of premutation without FXTAS (Cvejic et al. 2019). Progress has also been made to understand neuronal substrates of motor control and emotional processing using functional MRI. When contrasting sequential versus random finger tapping conditions, male carriers without FXTAS showed reduced activation in the cerebellar and hippocampal regions compared with age-matched controls and age-related reduction in hippocampal and cortical activation (Brown et al. 2018).

White matter lesions shown as white matter hyperintensities (WMHs) on T2-weighted MRI are commonly observed in FXTAS in both cerebral and cerebellar white matter. WMHs are important features of FXTAS showing significantly higher volume in FXTAS compared with age-related controls and carriers without FXTAS (Adams et al. 2007). WMHs occur in brain regions unique to FXTAS and each gender. About 52–83% male carriers with neurological symptoms of FXTAS had WMHs in the MCP in contrast to only 0–13% female carriers showing the MCP sign (Brunberg et al. 2002; Adams et al. 2007; Apartis et al. 2012; Renaud et al. 2015). In comparison, WMHs in the splenium of the corpus callosum (CCS) occur in similar frequencies in males (65–72%) and females with FXTAS (50–60%), (Apartis et al. 2012; Renaud et al. 2015). In addition, the presence of both the MCP and CCS signs is much more frequent in FXTAS (41%) than other neurodegenerative diseases including multiple system atrophy-cerebellar type (0%), essential tremor (0%), Parkinson's disease (0%), Alzheimer's disease (0%), and stroke (3%) (Renaud et al. 2015). These findings support the use of WMHs in the MCP as major radiological criteria for definite FXTAS diagnosis and WMHs in the CCS and cerebral white matter as a minor radiological criterion (Hall et al. 2014).

The pathogenesis of WMHs is currently unknown. Two recent studies have explored the link between WMHs and mitochondrial dysfunction and cellular stress. Scores of WMHs in the supertentorial region showed positive correlation with mitochondrial respiratory activity in cultured lymphoblasts, which was elevated in premutation carriers compared with controls (Loesch et al. 2017). Scores of WMHs also showed correlation with tremor/ataxia scores and cellular stress assessed using enzyme AMP-activated protein kinase (AMPK) in lymphoblasts (Loesch et al. 2018). However, no age-related changes were reported in these two studies.

MRI studies of female carriers reported non-overlapping findings with those of male carriers. Females with FXTAS exhibited cerebellar atrophy and increased WMHs compared with controls but the amount of atrophy and WMHs in the MCP were reduced compared with males with FXTAS (Adams et al. 2007). Reduced hippocampal volume has been shown to correlate with anxiety in female carriers but the association was with paranoid ideation in male carriers (Adams et al. 2010). A recent functional MRI study of females without FXTAS (Shelton et al. 2017a) showed reduced activation in the prefrontal cortex and differential cortical activation pattern compared with controls during the test of executive function using a prosaccade/antisaccade interleaved ocular motor task. The other two studies of the

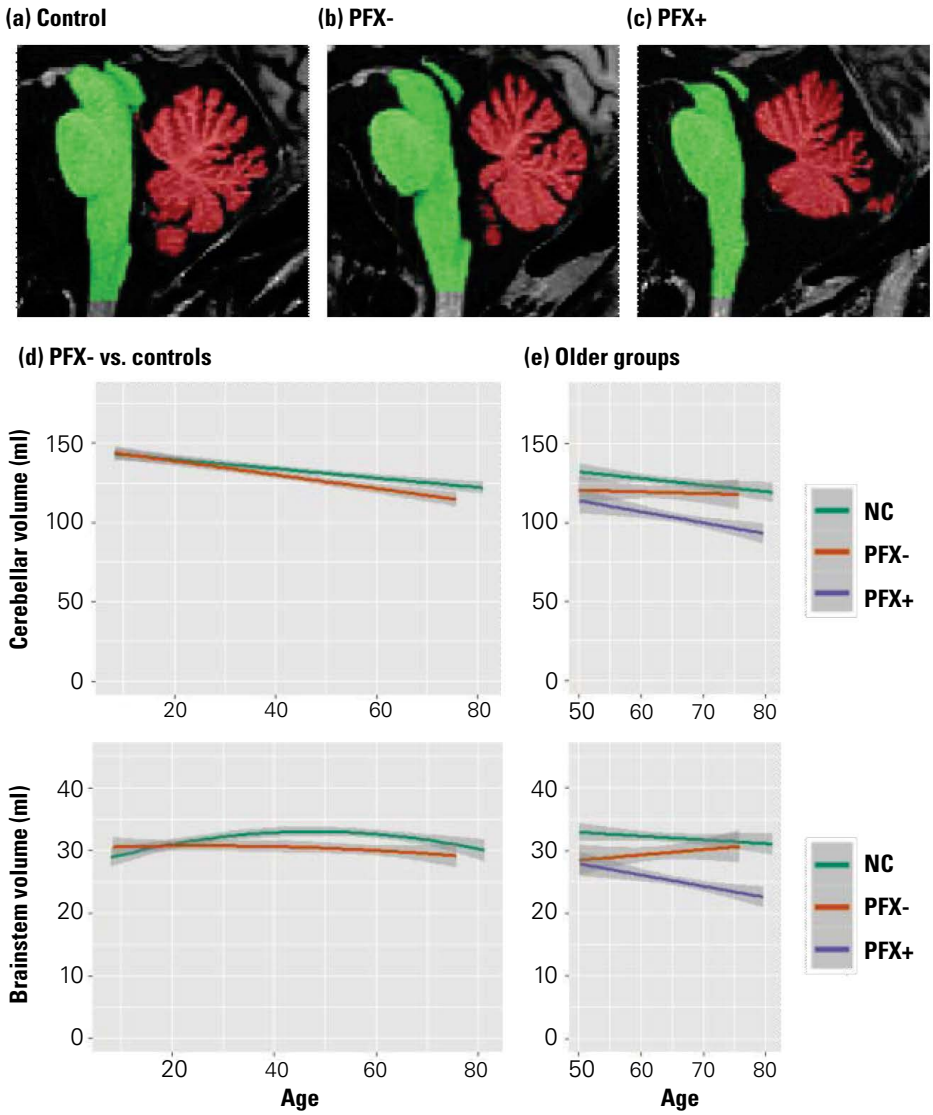

Figure 8.2 Sample segmentation of the cerebellum and brainstem using T1-weighted MRI and plots of age-related volume changes. Segmentation of the cerebellum and brainstem from (a) a 68-year-old healthy control; (b) a 69-year-old premutation carrier at FXTAS stage 1; and (c) a 68-year-old premutation carrier at FXTAS stage 4. Scatter plots showing age-related changed in cerebellar and brainstem volumes in (d) premutation carriers without FXTAS (PFX-, at FXTAS stage 0 or 1), premutation carriers with FXTAS (PF+) and healthy controls (NC) and (e) older groups (age >50 years). A colour version of this figure can be seen in the plate section.

same group of participants reported positive associations between methylation in *FMR1* intron 1 region and executive dysfunction, frontal and parietal cortical thickness, and white matter *hypointensities* on T1-weighted MRI (Shelton et al. 2016), as well as a negative association with mean diffusivity in the cerebellar peduncles (Shelton et al. 2017b). Positive associations between executive function and fractional

anisotropy in the corpus callosum and cerebellar peduncles were also observed in this study, which was consistent with findings from male carriers (Wang et al. 2013a).

In summary, considerable progresses have been made to understand neuronal substrates of psychiatric and neurological features of premutation carriers using structural and function MRI. Longitudinal studies are needed to further delineate the range of brain changes associated with FXTAS development and their functional consequences. Investigation of the link between atypical neurodevelopment and neurodegeneration during aging is also needed to understand the disease mechanisms underlying the spectrum of premutation-associated symptomology throughout lifespan.

CLINICAL FEATURES OF FXTAS

The diagnostic criteria for FXTAS is tremor (an action or intention tremor) and ataxia (perceived as balance problems) associated with brain atrophy, and white matter disease (Hagerman et al. 2001; Jacquemont et al. 2003). Over the years we have learned about other clinical features of FXTAS including neuropathy symptoms such as pain and/or numbness or tingling in the lower extremities; development of a head tremor; autonomic dysfunction including orthostatic hypotension and erectile dysfunction; Parkinsonian symptoms including resting tremor, slow movement, shuffling gait, stiffness in extremities or in facial expressions (masked facies), difficulty in initiating a movement such as standing up; and psychiatric symptoms including disinhibited behavior, such as off color jokes or inappropriate advances to others, deficits in the immune system leading to frequent infections; depression or apathy, and cognitive decline (Table 8.1). Other clinical symptoms such as hypertension, chronic fatigue, sleep apnea, and chronic pain symptoms are seen more commonly in those with FXTAS compared to those without FXTAS of the same age. The mitochondrial dysfunction present in FXTAS may lead to the weakness and fatigue that is experienced by most with FXTAS.

Usually the tremor begins in the early 60s followed by the balance problems (ataxia) that can be manifested by falling (Leehey 2009). When the motor symptoms begin, we usually can detect memory problems or executive function deficits including problems with attention, planning, and working memory. For some individuals, the symptoms can advance rapidly particularly if one's lifestyle is unhealthy such as drinking heavily, taking deleterious illicit drugs, addiction to opioids, lack of treatment for hypertension, diabetes type 2 or hypothyroidism, or a sedentary lifestyle with obesity and lack of exercise. Having a secondary condition such as Alzheimer's disease or Parkinson's disease

Table 8.1 Diagnostic Criteria for FXTAS

	Major (signs/symptoms)	**Minor (signs/symptoms)**
Radiological	White matter disease in the middle cerebellar peduncles (MCP)	White matter lesions in cerebrum
		Moderate-to-severe generalized brain atrophy
		White matter disease in splenium of the corpus callosum (CCS)
Clinical signs	Intention tremor	Parkinsonism (bradykinesia, slow gait, masked facies)
	Cerebellar ataxia	Neuropathy
		Executive function and memory deficits
Neuropathological signs	FXTAS inclusions in central and peripheral nervous system	

or other neurodegenerative condition can be additive to FXTAS and lead to more rapid motor and cognitive decline.

Many carriers worry that they will develop FXTAS and when minor symptoms develop, they feel that FXTAS is coming. Usually this is not the case, although if a family member with the premutation has a tremor or balance problem we recommend that an MRI be carried out with parameters that assess possible white matter disease called T2/FLAIR MRI. This demonstrates if the typical white matter disease seen with FXTAS is present. The stages of FXTAS are based on the severity of motor symptoms. Stage 1: refers to questionable symptoms; Stage 2: minor but clear tremor or balance problems and minor interference in activities of daily living (ADLs); Stage 3: moderate tremor or balance problems that interferes significantly with ADLs and at least occasional falls; Stage 4: severe tremor or balance problems requiring use of a cane or walker; Stage 5: severe tremor or balance problems requiring a wheelchair on a daily basis; Stage 6: bedridden. Table 8.1 outlines the current diagnostic criteria of FXTAS (Hagerman and Hagerman 2016; Hall et al. 2017). We recommend that carriers who have symptoms of FXTAS should be seen by a neurologist who specializes in movement disorders. Sometimes the physician may be unfamiliar with FXTAS so current papers that describe FXTAS and treatment should be brought to the physician. For carriers who are worried that they may develop FXTAS, the best prophylaxis against FXTAS is daily exercise, healthful eating with foods high in antioxidants such as blueberries, green tea, fresh vegetables, and fruits (Polussa et al. 2014). In addition, treatment of hypertension, hypothyroidism, sleep apnea, obesity, and type 2 diabetes, is recommended in addition to avoidance of toxins in the environment such as isofluranes in general anesthesia, volatile toxins such as verathane, pesticides, cigarette smoke, excessive alcohol, and illicit drugs.

NEUROPSYCHIATRY

Impairment of cognitive functioning is sufficiently prevalent in FXTAS that its presence is one of the minor diagnostic criteria of the disorder (Berry-Kravis et al. 2007). Although considered a minor criterion, the deficits associated with FXTAS appear to affect nearly everyone who develops this condition – both males and females – to some extent. As FXTAS progresses, this impairment typically becomes progressively worse, eventually resulting in considerable disability (Polussa et al. 2014).

Cognition has been investigated by means of neuropsychological assessment, electrophysiology (especially event-related potentials, ERPs), and functional neuroimaging, especially functional magnetic resonance imaging (fMRI) (e.g. Brega et al. 2008; Olichney et al. 2010; Wang et al. 2012a; Yang et al. 2012; Wang et al. 2013b). The most prominent cognitive difficulties among people with FXTAS include slowed processing of information, a disturbance of working (short-term) memory, deficits of executive functioning, and deficient declarative learning, especially the acquisition of new facts and information. Although deficits of this sort cause a range of behavioral, functional, and neuropsychiatric functioning, general measures of verbal and nonverbal reasoning such as IQ scores may remain in the average range until late in the trajectory of the disorder (Grigsby et al. 2008). This may be the reason why cognitive deficits in such areas as executive function are initially subtle and of insidious onset, becoming more obvious with the passage of time. Their onset in relation to neurologic signs and symptoms such as action tremor and gait ataxia has not been definitively established, although in many cases they may precede development of the movement disorder (Yang et al. 2013). Particularly striking is the impairment of executive functioning (EF), which is an individual's capacity to regulate his or her behavior and attention (Brega et al. 2008; Grigsby et al. 2014). EF is a complex functional system comprising several subcomponents. Those most severely affected have deficits in the initiation of purposeful, goal-directed activity, inhibition of irrelevant and/or inappropriate behavior, distractibility, and the ability to plan,

Table 8.2 Medications for FXTAS

Movement disorders	Other neurological symptoms	Psychiatry symptoms
Tremor:	**Cognitive decline/memory loss:**	**Hallucination:**
Propanolol	Donezepil	Quetiapine
Primidone	Rivestigmine	Clozapine
Topiramate	Galantamine	
Gabapentin	Memantine	**Anxiety and depression:**
		Fluoxetine
Ataxia:	**Nerve pain:**	Sertraline
Riluzole	Gabapentin	Venlafaxine
Amantamide	Pregabalin	
Buspirone	Topical CBD or Lidocaine	
Varenicline		
Sinemet		

organize, and monitor one's behavior in accordance with situational constraints and demands. There is inter-individual variability with respect to the relative impairment of these subcomponents, and in some cases one or more may be relatively preserved in relation to others (Table 8.2).

Although the cognitive-neuropsychological phenotype of males and females is grossly similar, men have been somewhat more thoroughly studied than women, and there may be sex differences that have not yet been identified. However, the cognitive phenotype tends to be less severe among women (Tassone et al. 2012), probably due to the presence among heterozygotes of a second, typical *FMR1* allele.

There is no clear anatomic focus for the cognitive impairment seen in FXTAS. Rather, it seems probable that extensive degeneration of the cerebellum, including the middle and superior cerebellar peduncles that link cerebellum and other areas of the brain, in conjunction with white matter lesions along tracts that connect prefrontal cortex and other regions of the EF networks, play a major role (Greco et al. 2006). For the most part, the cognitive phenotype is in many respects similar to what is observed in other white matter and cerebellar syndromes (Filley et al. 2015). As FXTAS progresses, the hippocampi and subcortical white matter tracts tend to develop lesions, and volume loss becomes apparent in the splenium and genu of the corpus callosum (Hall et al. 2017). White matter disease most likely disrupts distributed networks involved in executive functioning, working memory, and related functions (Tullberg et al. 2004).

Language is typically unaffected until relatively late-stage FXTAS; however, speech problems (dysarthria and slowing) may be present earlier. Late in the trajectory of FXTAS, frank dementia, significant impairment of primary memory, and focal cortical signs including such phenomena as ideomotor apraxia are often observed (Tassone et al. 2012; Seritan et al. 2013). Although the relationships have not been extensively studied, the cognitive and motor impairment associated with FXTAS affects functional status adversely. Brega et al. (2009) reported that the performance of men with FXTAS on basic physical functioning (e.g. grasping, reaching, stooping, climbing stairs), activities of daily living (ADLs, e.g. eating, bathing, dressing, grooming), and instrumental activities of daily living (IADLs, e.g. managing medications, meal preparation, managing money, shopping) was significantly impaired compared with unaffected carriers and controls on all dependent measures. Even if not dependent in ADLs/IADLs, many people with FXTAS are only able to perform ADLs and IADLs on their own by modifying the method or frequency with which they perform specific tasks.

ADL/IADL and physical functioning disabilities are mediated in large part by fine motor and EF deficits. Hence, tremor causes difficulty with such basic ADLs as eating, drinking, and fastening buttons, while gait ataxia and EF impairment both increase the risk of injuries from falls while standing, walking,

sitting, or other postural changes (O'Keefe et al. 2018). Over time, people with FXTAS grow increasingly dependent on others for assistance as the performance of ADLs and IADLs becomes moderately to severely compromised (Brega et al. 2009).

The lifetime prevalence of mood and anxiety disorders among people with FXTAS has been reported to be 65% and 52% respectively (Seritan et al. 2013). Other emotional and behavioral symptoms include agitation, apathy, depression, panic disorder, social phobias, obsessive-compulsive behavior, sleep problems, and substance use disorders (Bourgeois et al. 2009; Hessl et al. 2007; Birch et al. 2014; Grigsby et al. 2016; Hagerman et al. 2018). These may manifest prior to or after the onset of tremor and ataxia and are typically compounded by the gradual development of a severe dysexecutive syndrome, marked by disinhibition, difficulty initiating goal-directed activity, and a lack of insight (Brega et al. 2008). Neuropsychiatric conditions may develop in the absence of movement disorder, resulting in what Hagerman et al. (2018) have called fragile X-associated neuropsychiatric disorders (FXAND) (Hagerman et al. 2018).

The neuropsychological changes that contribute to neuropsychiatric disorders in early FXTAS are frequently subtle and are often perceived by spouses and family as 'personality change'. At least a subset of asymptomatic carriers show a mildly impaired capacity for inhibition, and perhaps subtle deficits in some other cognitive abilities as well (Cornish et al. 2011). An important but unresolved issue at this stage is whether these mild deficits reflect a neurodevelopmental characteristic of the premutation, are early signs of FXTAS, or both (Moore et al. 2004; Cornish et al. 2011; Hunter et al. 2012). The extent to which mild EF deficits are cognitive features of a premutation phenotype (i.e. neurodevelopmental phenomena) or early manifestations of a neurodegenerative process remains unclear. Using the Neuropsychiatric Inventory (NPI) (Cummings et al. 1994), and Revised Symptom Checklist-90 (SCL-90-R) (LR 1994), Grigsby et al. (2016) found that not only is the prevalence of these symptoms high among males with FXTAS, but that a large percentage of these men are likely to have diagnosable, clinically important psychiatric disorders. Moreover, much of this psychiatric morbidity – especially disinhibition, apathy, irritability/hostility, and depression – is mediated by the deficient ability for behavioral and attentional self-regulation that is a fundamental feature of the dysexecutive syndrome.

FXTAS is characterized by a pattern of cognitive-neuropsychological impairment that may vary in severity across individuals, but that is relatively consistent in its nature. The functional systems most affected include executive functioning, working memory, speed of information processing, and declarative memory. This impairment is progressive, and may lead to a severe dysexecutive syndrome, and frank dementia in the late stages of FXTAS. Commonly observed neuropsychiatric disorders of FXTAS include depression, anxiety disorders, agitation, apathy, panic disorder, social phobias, obsessive-compulsive behavior, sleep problems, and substance use disorders. In conjunction with the action tremor and ataxia that accompany FXTAS, the progressive neuropsychological-neuropsychiatric phenotype of FXTAS typically results in significant functional disability affecting the entire range of basic and instrumental activities of daily living.

TREATMENT

Patients with FXTAS have a variety of neurological and associated symptoms. Each patient may find that their quality of life is affected by symptoms that are not an issue for another patient with FXTAS. For example, a patient with FXTAS may have tremor that is bothersome enough to warrant medications while another patient may have balance problems and need physical therapy. This means that each patient should discuss their signs and symptoms with a physician who is trained to treat the variety of neurological and psychiatric issues that occur in the disease. Some patients may not have insight into

their symptoms. Because of this feature of FXTAS, typically in affected men, patients are best seen in the clinic with a caregiver or family member who is familiar with the types of problems they are encountering in their daily activities. In general, medications and therapies that are prescribed in FXTAS are treatments that are used in other similar disorders. The strategy of remaining physically active, cognitively active, and maintaining social interactions is of key importance in FXTAS. Various treatments will be discussed below.

Clinicians with specialty training are best informed regarding treatments that may be most helpful in FXTAS. Movement disorder neurologists, who are typically located in academic settings, see large volumes of patients with tremor, ataxia, and Parkinson's disease and are well equipped to treat these types of symptoms in patients. However, many patients may not have access to a movement disorder neurologist. A general neurologist would be a good option but may need some education regarding FXTAS and its various symptoms. Psychiatric issues, if mild, can be addressed by a neurologist or primary care physician. Moderate to severe psychiatric issues are best handled by a psychiatrist. Most psychiatrists will not be familiar with FXTAS and education may be recommended for them as well. Resources for physicians can be found on the National Fragile X Foundation website.

Medications for FXTAS can be grouped into a few different categories (Table 8.2): medications for movement disorders, other neurological signs, and psychiatric symptoms. Tremor in FXTAS can either occur at rest (when the arms are resting in one's lap) or with action (when doing a movement). Action tremor is most common and can be treated with medicines that are typically used for essential tremor. This includes propranolol, a beta blocker, or primidone, an anti-epilepsy medicine. These medications can be effective in up to 50% of patients with essential tremor but may be less effective in patients with FXTAS. Beta-blockers are not ideal in patients with diabetes or asthma and may be associated with a low heart rate. Primidone, in higher doses, can cause sleepiness or balance issues and patients should be monitored as the dose is escalated. Other medicines for tremor can include topiramate, which is associated with kidney stones and weight loss, and gabapentin, which may also be effective for ataxia at high doses. Surgical options for tremor, such as deep brain stimulation (DBS) or focused ultrasound, could be considered if medications fail. Gait ataxia is harder to treat than tremor. Riluzole, first developed for another neurological disease, has the best data to support its use in ataxia, but the liver needs to be monitored and can be difficult to get approved by insurance. Amantadine, an anti-flu medicine, can also be helpful for other signs and is cheaper and more readily available. Buspirone, an anxiety medicine, has mixed results in studies and varenicline, tested in other ataxias may be considered as well. Rest tremor, slowness, stiffness, or balance issues can be treated with medicines used in Parkinson's disease. Carbidopa/levodopa, or Sinemet, is converted to dopamine in the brain and may be the most effective. Many patients with FXTAS have found it to be helpful. It can be associated with nausea and should be started slowly.

Cognitive decline or memory loss can occur in FXTAS and frequently medicines used in Alzheimer's disease are used in this case. Donepezil, rivastigmine, and galantamine are in a class of medicines that slow cognitive decline in Alzheimer's disease and are generally well tolerated. A small proportion of patients will have diarrhea from these medicines and they should be warned ahead of time. Memantine, which has been studied in FXTAS and it improved ERP parameters, may also be added. Nerve pain may occur in some patients with FXTAS. Gabapentin or pregabalin can be used for this and are preferred to narcotics for pain. They can be associated with weight gain or leg swelling. Last, dizziness may need to be treated depending on whether it is related to vertigo, low blood pressure, or another cause.

Some patients with FXTAS will hallucinate. In this situation, medicines that will not worsen movement are ideal. These include quetiapine and clozapine. Both have warnings regarding their use and are best prescribed by a neurologist or psychiatrist. For patients who have depression or anxiety, medications in the Prozac family (selective serotonin reuptake inhibitors – SSRIs) are a good choice, but may worsen

balance disorders. Clinicians should continue to monitor or discontinue their use as balance worsens in the disease. Medications such as venlafaxine (a selective serotonin norepinephrine reuptake inhibitor – SNRI) may be a better choice as it has less impact on the balance.

Physical therapy has been shown to be effective in many movement disorders and should be prescribed frequently once the patient is symptomatic. Occupational therapy can also be beneficial. Patients with speech abnormalities may benefit from speech therapy or an evaluation for swallowing if choking has occurred. Other alternative therapies, such as acupuncture for tremor, may be helpful for various symptoms or to reduce overall stress, which can exacerbate symptoms. Exercise is very important to maintain the ability to move and is recommended 5 days weekly for at least 30 minutes. Although the type of exercise is less important, it should be vigorous. Cognitive exercise: doing puzzles, taking up new hobbies, or engaging in other activities that require new brain connections, such as video games, should be considered to maintain cognitive health. Last, socialization is protective and although FXTAS patients can be reclusive, they should be encouraged to interact with others.

Good overall health is very important to maintain a slow progression of FXTAS. Large insults to the system, such as big surgeries, infections, or major life stressors, can worsen symptoms in the short and long term. Patients should see their care provider regularly and have aggressive rehabilitation if one of these events occurs. Patients with FXTAS can live for decades with a slowly progressive disease and have good quality of life. When the disease advances in later stages, palliative care experts can be consulted to provide additional assistance. Good caregiving from family, maximizing time at home, and avoiding inpatient hospital stays will also contribute to better quality of life. Patients with FXTAS can also help the scientific community as advances occur, by participating in medication studies as this may speed the move of new treatments to the clinic for all patients. There is much to be done to help patients with FXTAS. Look for a provider that can team up with you and your family to make this happen.

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