Chapter 9
Treatment and Management of FXTAS

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Abstract Fragile X-associated tremor/ataxia syndrome (FXTAS) affects older adult carriers of the *FMR1* premutation and can be associated with a broad array of clinical symptoms and presentations including tremor, ataxia, parkinsonism, executive function disturbance and dementia, psychiatric symptoms of anxiety, depression and disinhibition, peripheral neuropathy, autonomic dysfunction, hormonal dysfunction, and pain syndromes. Although controlled trials have not demonstrated efficacy for FXTAS symptoms, there is information available regarding symptomatic treatments. Treatment is generally supportive, directed at component symptoms that are most problematic, and makes use of evidence regarding effectiveness of medications and other interventions for treatment of disorders that have phenotypic overlap with FXTAS. This chapter summarizes available treatments and supports that can be helpful for persons with FXTAS.

Keywords Treatment • Tremor • Ataxia • Parkinsonism • Memantine • Therapy • Deep brain stimulation

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General Approaches to Management

FXTAS is an inherited degenerative disorder that affects aging persons and is associated with an array of neurological symptoms and medical conditions. The complexity of the disorder requires the treating clinician to be cognizant of the broad and variable nature of FXTAS. For a detailed description of clinical manifestations, see Chaps. 1 and 3. Management of this multifaceted disorder requires a comprehensive approach, as outlined in Table 9.1.

Unfortunately, there is no specific treatment for FXTAS that is targeted to the underlying pathogenic mechanism of excess *FMR1* mRNA or other proposed mechanisms of disease. Furthermore, due to the recent recognition of the disorder and relatively few identified cases, as yet there have been few therapeutic clinical trials conducted in FXTAS. In a retrospective study of treatment in FXTAS, 56 patients with FXTAS completed a questionnaire to determine if any medications had been effective for neurological symptoms (Hall et al. 2006). This was followed by a review of medical records regarding treatment of their neurological symptoms. The study reported that 60 % were not on medications for their neurological symptoms (Hall et al. 2006). Those individuals with definite or probable FXTAS were more likely to be on medications than those with possible FXTAS, and 30 % of patients with possible or probable FXTAS were taking medications for motor signs (tremor, ataxia, or parkinsonism). The questionnaire study design may have underestimated reported effectiveness due to small sample sizes, cognitive impairment, and lack of insight into some of the symptoms of the disease.

Effective management of FXTAS requires the clinician to be knowledgeable about the whole phenotype and to consider the many symptoms that may be responsive to treatment with medication and other therapies and strategies. While there is no effective treatment that halts or slows the disorder, there has been some success in reducing a number of its disabling and distressing symptoms. Table 9.2 summarizes the categories of disease and symptoms that may be affecting each individual with FXTAS and types of therapy that may be beneficial. The therapeutic strategies we present are based on the questionnaire (Hall et al. 2006) and current experience from our centers and others evaluating and treating FXTAS.

Table 9.1 Management of FXTAS

Treat specific symptoms, e.g., neurological, psychiatric
Refer to appropriate specialists: neurology (e.g., movement disorders), psychiatry, gerontology, urology; physical, occupational, and speech therapy
Monitor for and treat comorbidities
Genetic counseling for the patient and family
Avoid medications and conditions known that may worsen symptoms if possible

Table 9.2 Summary of the symptomatic treatment of FXTAS

Action tremor
Beta-blockers, primidone, topiramate, benzodiazepines, other medications, occupational therapy, thalamic deep brain stimulation
Cerebellar ataxia
Amantadine, riluzole, buspirone, other medications, physical therapy
Parkinsonism
Dopaminergic medications, anticholinergics, beta-blockers for tremor, physical therapy
Painful neuropathy
Gabapentin, pregabalin, duloxetine, lidocaine patches or cream
Autonomic dysfunction
Urinary urgency and frequency[a]
Tricyclic antidepressants, antimuscarinics, botulinum toxin injection
Constipation
↑ fluids and fiber, stool softeners, other standard treatment
Impotence
Testosterone replacement if indicated, urology referral
Orthostatic hypotension
↑ fluids and salt, elevate head of bed, constriction stockings, small frequent meals, fludrocortisone, midodrine, pyridostigmine
Cognitive impairment
Anticholinesterases ± memantine, problem-solving therapy for executive dysfunction
Anxiety, agitation, depression
Selective serotonin reuptake inhibitors, serotonin–norepinephrine reuptake inhibitors (especially venlafaxine)
Dysphagia
Swallowing evaluation and therapy
Fibromyalgia, chronic fatigue, irritable bowel syndrome
Exercise, patient education, cognitive-behavioral therapy, antidepressants, integrative medicine, and other referrals
Thyroid disease
Evaluation and treat as indicated

[a]Urological referral is indicated before initiating therapy since patients with FXTAS may have urinary retention

Treatment for the Movement Disorders in FXTAS

Clinical Trial on Memantine in FXTAS

To date, there has been only one clinical trial conducted in FXTAS. A randomized, double-blind, placebo-controlled, 1-year trial of memantine was conducted in men and women with FXTAS (Seritan et al. 2014). Anecdotal reports of memantine, an NMDA receptor antagonist, suggested that the medication might improve neurological and cognitive symptoms of FXTAS. Primary outcome measures in the study

were the Behavioral Dyscontrol Scale (BDS) and intention tremor severity on the CATSYS. The CATSYS is a set of computer-assisted diagnostic instruments that measure intention tremor, postural tremor, postural sway, manual coordination, and reaction time (Despres et al. 2000). Ninety four patients were randomized and 43 and 45 patients, respectively, received memantine or placebo. Intention-to-treat analysis of the 88 subjects in the study showed no improvement of BDS score (16.1 ± 5.4 vs. 15.7 ± 4, $p = 0.727$) nor intention tremor severity (1 ± 0.7 vs. 1.9 ± 2.2, $p = 0.047$) (Seritan et al. 2014). The authors of the trial report that limitations of the study included a moderate sample size, fewer subjects with late FXTAS, using only the CATSYS to record tremor, and psychotropic medication changes during the 12 months of the study. A subgroup of the FXTAS patients ($n = 41$) in the memantine controlled trial were studied with event related potential (ERP) studies at baseline and after 1 year of treatment (Yang et al. 2014). Memantine treatment improved both cued recall memory and the N400 repetition effect amplitude in the ERP studies compared to placebo. Future studies that combine memantine with additional agents may be warranted based on these results (Yang et al. 2014).

Treatment of Tremor

There are few studies published describing medications that are effective tremor in FXTAS. In a case report of single FXTAS patients with kinetic tremor, levetiracetam at 1000 mg/day was effective to reduce the intention tremor and improve handwriting (Saponara et al. 2009). Of the subjects with FXTAS receiving therapy for kinetic tremor in the retrospective questionnaire study, three out of six reported mild to moderate improvement on primidone, three out of eight had moderate improvement in tremor on beta-blockers, and two out of eight had moderate improvement on benzodiazepines (Hall et al. 2006). This suggests that medicines helpful for essential tremor may also be effective in some patients with FXTAS. One subject had improved tremor on memantine, which was prescribed for cognitive decline. There was no improvement in tremor for two subjects on gabapentin.

In the initial case studies utilizing thalamic deep brain stimulation (DBS) for management of tremor in individuals with FXTAS (Leehey et al. 2003; Peters et al. 2006), results were mixed. Of three patients with DBS placed, two patients had substantial improvement in tremor, but speech and ataxia worsened in one and remained stable in the other. Neither of these individuals showed worsening of executive or cognitive function. A subsequent case report of a FXTAS man with nucleus ventralis intermedius (VIM) of the thalamus DBS placement described immediate progression of ataxia, cognitive decline, dysarthria, and apraxia (Mehanna and Itin 2014). More recent studies suggest that some FXTAS patients can have sustained improvement with DBS into the VIM. Three FXTAS men showed improvement for up to 2 years after surgery in both tremor and gait (Weiss et al. 2015). DBS with stimulator placement into the ventro-oralis posterior thalamic nucleus and zona incerta in a FXTAS man with postural and action tremor resulted in significant and stable control of tremor for 20 months (dos Santos Ghilardi et al. 2015). In addition, his ataxia

improved by 50 %. The authors postulated that avoidance of stimulation of the VIM and restricted electrical fields of bipolar stimulation could be responsible for the long-term improvement. Persons with preexisting cognitive dysfunction tend to worsen with DBS (Aybek and Vingerhoets 2007), and the worsening of ataxia and cognition noted in some FXTAS patients is also a significant concern (Hagerman et al. 2012). Thus, careful evaluation is needed before considering DBS, and candidates for this procedure would be limited to individuals with FXTAS and disabling medically resistant tremor and minimal cognitive dysfunction.

Beta-blockers and primidone are commonly used to treat essential tremor (ET) and would be the likely candidates for therapy for tremor in FXTAS. Information on the effectiveness of treatment may be borrowed from the ET treatment literature, albeit recognizing that medication efficacy in FXTAS may not be the same. Propranolol, a β-adrenergic blocker, is an effective medication for the treatment of ET (Caccia et al. 1989; Calzetti et al. 1990). However, these medications are contraindicated in patients with asthma, second-degree AV block, congestive heart failure, and insulin-dependent diabetes, with fatigability, impotence, lightheadedness, sedation, and even depressive symptoms as common side effects. Sotalol and atenolol (other beta-blockers that may have less side effects than propranolol) may also be effective (Zesiewicz et al. 2011). Primidone has also been shown to be effective in placebo-controlled studies in ET (Koller and Royse 1986), with its anti-tremor effect attributed to its metabolite phenobarbital (Sasso et al. 1991). It is started at low doses to minimize side effects, such as nausea, vomiting, sedation, and confusion. Topiramate is a possible third-line choice for ET (Connor 2002), although this medication may be less ideal given the cognitive side effects in FXTAS patients. Gabapentin has been shown to be effective in small studies in both improving activities of daily living and tremor rating scale scores (Ondo et al. 2000). Benzodiazepines such as alprazolam or clonazepam may also be effective in some patients (Zesiewicz et al. 2011; Gunal et al. 2000). Because tremor is aggravated by anxiety or stress, which are common in *FMR1* premutation carriers, benzodiazepines may help to decrease anxiety and thus reduce tremor secondarily.

Treatment of Ataxia

Most of the gait ataxia in FXTAS is due to cerebellar dysfunction. Gait ataxia improved in one patient who was taking amantadine in the questionnaire study (Hall et al. 2006) and in two additional patients reported by Jacquemont et al. (2004). Amantadine, an NMDA receptor antagonist, has been shown to help ataxia in patients with olivopontocerebellar atrophy (which is similar in phenotype to FXTAS) in a small clinical trial (Botez et al. 1996). Ataxia improved in a 65-year-old man with FXTAS who was treated with varenicline as part of a smoking cessation program (Zesiewicz et al. 2009). He improved from requiring a walker to ambulate to not needing a walking aid, worsened when the varenicline was discontinued, and improved when it was restarted. A randomized, double-blind placebo-controlled trial showed improvement in cerebellar ataxia after treatment with riluzole relative

to placebo (Ristori et al. 2010). One subject in the trial had FXTAS, was in the riluzole group, and showed improvement in ataxia. Gait difficulties may also be caused by parkinsonism, extensive cerebral hemispheric white matter lesions, and peripheral neuropathy. Dopaminergic medications were felt to be beneficial in some parkinsonian persons with gait ataxia (Hall et al. 2006). Buspirone was tested in patients with cerebellar ataxia and found to have improved ataxic kinetic score (Trouillas et al. 1997). Gabapentin has been reported in an open trial to improve cerebellar signs in patients with cerebellar cortical atrophy (Gazulla et al. 2003). Gabapentin may be an especially good option for FXTAS patients with neuropathy and nerve pain. A recent consensus paper on the management of cerebellar ataxia suggests that acetyl-DL-leucine may be safe and improve gait ataxia and dysmetria in patients with cerebellar ataxia of various etiologies (Ilg et al. 2014). However, this compound is not routinely used in the clinic and additional research specifically in FXTAS may be needed.

Treatment of Parkinsonism

In the retrospective questionnaire study, rest tremor was not evaluated exclusively, but parkinsonism (rest tremor, slowness, or stiffness) in patients with FXTAS improved on carbidopa/levodopa in four of ten cases, pramipexole in three of six cases, and eldepryl in one patient (Hall et al. 2006). In FXTAS patients with parkinsonism and gait abnormalities, subjective improvement in gait was seen on carbidopa/levodopa, dopamine agonists, and eldepryl (Hall et al. 2006). Although parkinsonism is considered a minor criteria for FXTAS, some patients are dopamine responsive, similar to patients with primary Parkinson disease. Because motor fluctuations and dyskinesia have not been reported in patients with FXTAS, dopaminergic therapy should be considered if parkinsonism is present and problematic in a patient with FXTAS. Introduction of carbidopa/levodopa must be done with care, however, as worsening of motor control and autonomic and/or cognitive symptoms can occur and hallucinations and significant lethargy can be seen in some individuals with FXTAS. In FXTAS, the rest tremor is not usually disabling and thus by itself may not require treatment. Anticholinergics, such as trihexyphenidyl and benztropine, may be useful in reducing PD rest tremor, but are often not well tolerated in the elderly due to adverse effects, including short-term memory dysfunction, urinary retention, and constipation.

Rehabilitative Therapies for Motor Dysfunction in FXTAS

Physical therapy can be helpful for improving strength and gait in treatment of persons with FXTAS (Hall and O'Keefe 2012). Quantitative gait analysis and even a routine gait evaluation through physical therapy can help the patient understand

what activities they can be independent of and when they need support in the form of a cane or walker and thus prevent falls. Significant improvements in balance, gait ataxia, and activities of daily living have been shown after 4 weeks of intensive physical therapy in patients with degenerative cerebellar ataxia of various causes (Ilg et al. 2014). These improvements persist for a year when the participants maintained a daily home exercise program. Body weight supported treadmill training for gait deficits and computerized dynamic posturography with biofeedback retraining devices are relatively newer options that could be considered for FXTAS patients (Hall and O'Keefe 2012). Occupational therapy may be beneficial in improving performance of functional tasks. OT has been shown to improve disability scores and quality of life in after 15 sessions in patients with spinocerebellar ataxia type 3 (Silva et al. 2010). Assistive technology to aid feeding and computer use in patients with intention tremor may be useful (Feys et al. 2001; Surdilovic and Zhang 2006). Increasing the inertia or viscoelastic resistance of a limb may dampen kinetic tremor. Interventions might include trunk or limb loading with weights or use of trunk vests and trunk stability (Morrice et al. 1990; Gibson-Horn 2008; Marsden and Harris 2011). *FMR1* premutation carriers may be at higher risk of hearing loss and referral to audiology and provision of hearing devices should be considered if warranted.

Treatment for Neuropathy and Pain in FXTAS

Pain is a common problem in patients with FXTAS. Neuropathic pain, particularly in the lower extremities, is seen in both men and women with FXTAS. Neuropathic pain can be difficult to treat and does not often respond well to nonsteroidal anti-inflammatory agents. Many patients, however, can derive meaningful symptomatic relief from other available pharmacologic treatments, including anticonvulsants, antidepressants, and topical analgesics (Gilron et al. 2006). Specific medications that have been shown to be beneficial in other causes of painful neuropathy include gabapentin, pregabalin, or duloxetine. These latter medications thus would be expected to be beneficial in FXTAS. Some women with FXTAS have been diagnosed with concurrent fibromyalgia, which is associated with pain (Coffey et al. 2008; Leehey et al. 2011). Initial treatment for these symptoms should include non-pharmacological approaches such as exercise, patient education, and cognitive-behavioral therapy. The most effective pharmocotherapies include antidepressants, anticonvulsants, or muscle relaxants (Goldenberg et al. 2004). If these treatments are not successful for management of pain, patients should be referred to specialty clinics, such as rheumatology, for further management and if needed can be referred to a pain rehabilitation program. Massage therapy can be helpful at reducing chronic stress, and acupressure/pressure point massage has been shown to be efficacious for pain reduction in fibromyalgia (Tsao 2007). For the elderly, massage therapies can represent an alternative to treatment with pharmacological agents, especially when side effects of medication are a concern or when there are drug interactions, or massage therapy can be complementary or additive to pharmacotherapy.

Treatment for Autonomic Symptoms in FXTAS

Autonomic dysfunction in FXTAS may include impotence, orthostatic hypotension, urinary frequency or incontinence, and bowel incontinence (in the later stages) (Jacquemont et al. 2003). Most men with average fluid intake urinate about every 3 h, but this may become as frequent as every 20 min in severely affected individuals with FXTAS. Micturition can be associated with difficulty starting the stream, emptying the bladder, and dribbling. Although detailed urological studies have not been conducted in FXTAS, hyperactive detrusor activity is possible since some individuals with FXTAS respond well to small doses of tricyclic antidepressants or to muscarinic receptor antagonists. In patients refractory to this therapy, there may be poor bladder contractility or sphincter dyssynergia. In one patient with FXTAS, a more effective treatment was botulinum toxin injection into the submucosal lining of the bladder, carried out by cystoscopy with a small diameter cystoscope under local anesthesia (Hagerman et al. 2008). This procedure was well tolerated and mild hematuria resolved within 3–5 days. Antibiotics were used postinjection and infections are considered rare with this procedure. The effects of the botulinum can last from 3 to 4 months or longer. Rare patients with FXTAS will develop an inability to urinate, and self-catheterization will need to be taught.

Constipation is common in the elderly and can be a problem in FXTAS. Treatment of chronic constipation in these patients would begin with dietary changes, high fiber supplements, and over-the-counter medications such as stool softeners and milk of magnesia to encourage normal peristalsis. Laxatives can be used in more severe cases. Side effects, particularly diarrhea, may require modifying laxative regimens. The rationale behind a bowel regimen is to slowly train the bowel to constrict down to a more normal size. Further studies of this problem in FXTAS may help to clarify treatment protocols.

Orthostatic hypotension is seen in a subset of patients with FXTAS and can be treated nonpharmacologically with increased fluid and salt intake, elevating the head of the bed at night, use of Jobst stockings, and eating frequent small meals. Medications effective for orthostatic hypotension include mineralocorticoids such as fludrocortisone to expand blood volume and improve perfusion and orthostatic symptoms. Midodrine, an alpha-1 adrenergic agonist which increases blood pressure, may also be used. This medication may cause vasoconstriction, pupil dilation, a “hair standing on end” sensation, and itching or paresthesia of the scalp. Patients need to be warned not to lie flat for 4 h after a dose, as dangerously high blood pressure can occur. Doses can be increased quickly until a response occurs or a dose of 30 mg/day is attained (Wright et al. 1998). Midodrine has the advantage that it does not cross the blood–brain barrier and therefore does not have CNS side effects. Midodrine has been shown to be helpful in controlled trials (Wright et al. 1998); however, some patients require a combination of both midodrine and fludrocortisone. Orthostasis can also be treated with pyridostigmine (Gales and Gales 2008), a reversible acetylcholinesterase inhibitor that enhances sympathetic cholinergic signal transduction and thus increases peripheral vascular resistance and baroreceptor

sensitivity. This mechanism allows for improved orthostatic symptoms without exacerbation of supine hypertension. Droxidopa, recently approved, is an option in refractory cases (Kaufmann et al. 2014).

Treatment for Swallowing Difficulties

Swallowing difficulties are a common, typically late symptom in FXTAS. In patients with dysphagia, routine monitoring and therapy by a speech therapist may be useful to prevent aspiration and maintain communication with others (Revuelta and Wilmot 2010). Depending on the nature of the dysphagia, the patient can be educated regarding techniques to enhance proper delivery of the food to the stomach, including positional changes when they are swallowing. For patients with more severe problems, a modified diet may be necessary to avoid aspiration pneumonia. One individual with FXTAS and swallowing difficulties had an excellent response to pyridostigmine (Hagerman et al. 2008). Adverse effects of pyridostigmine treatment may occur due to stimulation of the parasympathetic nervous system via muscarinic cholinergic receptors and can include sweating, salivation, nausea, vomiting, diarrhea, and abdominal cramping.

Treatment for Dementia in FXTAS

Cognitive changes in patients with FXTAS include executive function deficits and memory problems (Grigsby et al. 2006), see Chap. 3. The cognitive changes progress at a variable rate and dementia develops in at least 50 % of men with FXTAS (Bourgeois et al. 2006). Although the profile of cognitive deficits in FXTAS appears to be different from that classically seen in AD, the use of medications that slow cognitive decline in other dementias may be warranted. Clinical intervention with psychopharmacological agents, as is typically done for other subtypes of dementia, appears advisable in FXTAS dementia and may serve to stabilize cognitive function, at least in the short term.

Donepezil and other cholinesterase inhibitors can be considered in patients with FXTAS and memory impairment. In the early months of treatment, memory function may be improved resulting in enhanced quality of life, even if the eventual trajectory of memory decline is not substantially changed. In the questionnaire study, slowing of cognitive decline was reported by family members in three out of nine patients with FXTAS treated with acetylcholinesterase inhibitors (Hall et al. 2006). Combination therapy of donepezil and venlafaxine over a 2-year duration has been reported to improve and stabilize the dementia and mood alterations (depression, anxiety, agitation, hostility, and irritability) in a case report of a FXTAS patient who had multiple neurological symptoms (Bourgeois et al. 2006). Other acetylcholinesterase inhibitors could be considered depending on the side effect profile and preferences of the patient

(for example, use of a patch rather than pills). The use of memantine is summarized earlier in this chapter.

Evaluation for other causes of dementia, particularly reversible contributing causes, such as hypothyroidism, B_{12} deficiency, B_6 deficiency, and folate deficiency, is essential, with vitamin supplementation in cases in which levels are low. Exercise has been found to be helpful for executive cognitive and depressive symptoms in Alzheimer's disease, and an exercise program that includes walking, strength, balance, and flexibility training may be therapeutic in FXTAS. This should be guided by the physical therapist for individuals with substantial motor dysfunction. Some patients with FXTAS have significant brain atrophy with dilation of the ventricles that is mistaken for normal pressure hydrocephalus (NPH) (Hall et al. 2005). However, surgery for presumed NPH has resulted in deterioration when performed in patients with FXTAS (Jacquemont et al. 2004). Support for family caretakers during the dementia process is crucial, and the decision to place a patient with FXTAS in a specialized center for the care of individuals with dementia may be necessary. Supportive help in the household is frequently needed prior to placement of the patient in a chronic care facility. Involvement of social workers with expertise in aged populations can greatly facilitate transitions to other living environments or finding resources for respite for caregivers.

Some patients with neurological disease, including FXTAS, do not tolerate major surgery with general anesthesia well and further deterioration in both motor and cognitive abilities may occur. It is unclear if there is a specific relationship to FXTAS, anesthesia, or the surgery itself. Elective surgery, therefore, should be considered cautiously in any patient with significant neurological disability, including patients with FXTAS.

Treatment for Psychiatric Symptoms in FXTAS

Psychiatric problems commonly seen in patients with FXTAS include anxiety, agitation, apathy, and depression (Bacalman et al. 2006). Both the anxiety and the depressive disorders associated with FXTAS may benefit from management with antidepressant medications, such as selective serotonin reuptake inhibitors (SSRIs) or serotonin–norepinephrine reuptake inhibitors (SNRIs) (Hall et al. 2006; Jacquemont et al. 2004). The selective serotonin–norepinephrine reuptake inhibitors (SNRIs; venlafaxine and duloxetine) may be effective for both depressive and anxiety symptoms and should be considered as their noradrenergic activity may be desirable. Both SNRIs need to be used with caution in renal failure. In the questionnaire study, anxiety improved in two out of six patients with FXTAS on venlafaxine and five out of eight patients on benzodiazepines (Hall et al. 2006). Due to the progressive nature of FXTAS and presence of dementia in some affected individuals, benzodiazepines (which may impair cognitive function) and tricyclic antidepressants (which are anticholinergic and thus can theoretically be problematic in patients with cognitive impairment) should be used cautiously (Gray et al. 1999; Oxman 1996). Intervention

with antidepressants for coexisting mood and anxiety disorders may, however, improve cognitive function due to improvement in the emotional state (Bourgeois et al. 2006) and two of six patients treated with venlafaxine reported slowing of cognitive decline (Hall et al. 2006). Individuals with dementia and secondary psychotic symptoms (e.g., delusions and hallucinations) may benefit from cautious use of atypical antipsychotic agents (Bourgeois et al. 2006).

Combined psychopharmacological approaches with antidepressants and antipsychotics along with medications to slow cognitive decline may be indicated. SSRIs with minimal drug–drug interaction profiles (e.g., sertraline, citalopram, escitalopram) are preferred for use in the elderly, but all medications in this class may be effective. Mirtazapine can be helpful for sedation and appetite stimulation, but it requires a reduced dose in renal failure. For psychotic symptoms, cautious doses of atypical antipsychotics are recommended with close follow-up. Quetiapine and clozapine are the best choices as they are unlikely to exacerbate underlying parkinsonism. Treatment with clozapine requires frequent blood draws to monitor for pancytopenia and has the potential to aggravate orthostatic hypotension. Thus, while it can be quite beneficial for psychosis and parkinsonism, quetiapine may be a better first choice.

Psychosocial Approaches to Cognitive and Psychiatric Problems in FXTAS

It is important to provide the patient and family with education and supportive intervention and it is helpful to deliver psychiatric care in the context of a multidisciplinary team. Since several members in the same family are often affected, intervention plans need to target the patient and the family, and consistent longitudinal follow-up is crucial.

Problem-solving therapy (PST) has been shown to improve depressive symptoms and functioning in elderly patients with executive dysfunction and depression, cognitively unimpaired depressed elderly, and younger adults with minor and major depression (Arean et al. 1993). Active intervention with a depression "care manager" may also improve outcomes, even in individuals with cognitive dysfunction (Steffens et al. 2006). By extension, caregiver well-being may also improve as symptoms of depression and anxiety in the patient become less problematic (Hagerman et al. 2008).

Psychological support for caregivers is an important issue to be addressed in the management of FXTAS. Women constitute the majority of caregivers for patients with FXTAS and 70 % of the caregiving population (Hagerman et al. 2008). Women were found to have significantly higher caregiver burden than male caregivers. Poor perceived physical health and more behavior disturbance in the patient were associated with higher levels of caregiver burden and depression (Gallicchio et al. 2002). Based on clinical experience depression seems to be very common in the wives of men with FXTAS and they may do well with supportive counseling and referral for treatment of

their depression. In a study of dementia caregivers' reaction to the death of their care recipient relative, 20% of caregivers experienced complicated grief along with high levels of depressive symptomatology (Schulz et al. 2006). Caregivers with high levels of pre-loss depressive symptoms and burden, who reported positive features of the caregiving experience, and cared for a more cognitively impaired patient were more likely to report complicated bereavement post-loss. The importance of caregiver support, however, was illustrated by the finding that caregivers who were enrolled in a psychosocial caregiver intervention designed to reduce depression and burden reported lower levels of complicated grief (Schulz et al. 2006).

Treatment of Hormonal Dysfunction

Recent studies have broadened our concept of FXTAS to include hormonal dysfunction. Inclusions have been documented in the anterior and posterior pituitary (Louis et al. 2006; Greco et al. 2007) and in the Leydig cells in the testicles that produce testosterone. Testosterone deficiency has been reported in five of eight premutation carriers that have been tested and may be related to the pituitary and Leydig cell involvement (Greco et al. 2007). Affected individuals may become aware of erectile dysfunction before the onset of other neurological signs. Because low testosterone can cause impotence, testosterone replacement may improve libido and sexual function in patients with FXTAS. Other problems associated with FXTAS which might improve from testosterone replacement include cognition, memory, energy level, and mood (Cherrier et al. 2003). Hormone replacement in patients with FXTAS would follow the same paradigm as with other hypogonadal states. Preferred regimens, used in other diseases, would include transcutaneous testosterone administration or intramuscular injection. Further studies of testosterone deficiency in FXTAS are warranted and the benefits and risks of testosterone replacement require study. Treatment with testosterone may increase the risk of prostate cancer, and careful follow-up with PSA levels and frequent examination are recommended if testosterone treatment is utilized. In addition to hormonal dysfunction and primary ovarian insufficiency seen in female carriers, hypothyroidism appears to be a frequent problem in females with the premutation. Thyroid dysfunction occurred in 50% of women with FXTAS in one study suggesting that routine thyroid function testing is indicated yearly for women with FXTAS (Coffey et al. 2008). Replacement is indicated for hypothyroidism, which can aggravate baseline emotional and psychiatric problems observed in premutation carriers (Devdhar et al. 2007).

Treatment of Other Comorbidities

Hypertension (HTN) was more common in men with FXTAS in a study that evaluated two cohorts of FXTAS men and controls (Hamlin et al. 2012). Both chart review and blood pressure measurements (HTN defined >140/90) in clinic were

utilized to define subjects with HTN. FXTAS men had an odds ratio of 3.22 (CI: 1.72–6.04) compared to controls. Because hypertension can lead to small vessel ischemia, exacerbating existing white matter disease from FXTAS itself, it is important to treat it early and aggressively.

Migraine headaches have been reported to be increased in premutation carriers compared to controls (Au et al. 2013). Migraines in premutation carriers often begin in the third or fourth decade and can persist and even worsen in individuals with FXTAS. Persistent migraines can also be associated with white matter disease and it is possible that persistent migraine may exacerbate white matter disease in FXTAS.

A careful history may reveal other comorbidities that may exacerbate FXTAS including substance abuse particularly alcohol or opioids (Muzar et al. 2014). In addition, sleep apnea is common in FXTAS and the hypoxia associated with sleep apnea can be treated with CPAP and oxygen (Hamlin et al. 2011). A sleep apnea study should be ordered if the history is suggestive of this problem.

Genetic Counseling

FXTAS is an inherited condition and because diagnosis of FXTAS nearly always implies that other individuals in the family will be at risk for *FMR1*-related disorders, genetic counseling is an important part of the treatment plan once a diagnosis is made. Many individuals are diagnosed with FXTAS as a result of diagnosis of fragile X syndrome in another family member, such as a child or a grandchild, and a genetic counselor may already be working with the family. Particularly if FXTAS is diagnosed without prior knowledge of *FMR1* mutations in the family, it is crucial that the male patient understand that all of his daughters will be *FMR1* carriers and are at risk for children with fragile X syndrome and themselves at risk for primary ovarian insufficiency. Women diagnosed with FXTAS must understand that all their children have a 50 % risk of being *FMR1* carriers or being affected with fragile X syndrome. There will also likely be numerous brothers, sisters, nephews, nieces, cousins, and other relatives who will be at risk for an *FMR1*-related disorder, making genetic counseling imperative so that the patient is provided with knowledge about this situation and recommendations on how to approach relatives with this information. The reader is referred to Chap. 10 for a thorough discussion of approaches to genetic counseling.

Future Treatments to Target the Underlying Mechanism of Disease in FXTAS

Development of therapeutic interventions that target the core molecular processes that result in FXTAS is essential. Such therapeutics would target the pathogenic trigger, the toxic expanded CGG repeat *FMR1* mRNA itself, or downstream

pathways that are altered as a consequence of the toxic mRNA expression. A conceptually simple approach would be to use antisense or RNA interference agents to reduce the pathogenic RNA itself; however, a difficulty inherent in this approach would be the general inability of these agents to cross the blood–brain barrier. Increased knowledge about proteins involved in the toxic response to the repeat-containing RNA and downstream pathways is expected to provide additional targets for interruption of the underlying molecular process through which FXTAS occurs.

Summary

There is currently no cure that can reverse the pathophysiology of FXTAS. However, there are a number of symptomatic treatments that may improve the quality of life of these patients. Identification of the disorder may be the first hurdle for individuals with FXTAS and referral to appropriate specialists may be very helpful, depending on the most problematic symptoms. As the underlying etiology of FXTAS is better delineated, neuroprotective agents or agents targeted at the underlying toxic RNA mechanism may be added to symptomatic therapy to slow down or stall the disease progression.

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