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Review article

The spectrum of tremor among carriers of the *FMR1* premutation with or without the fragile X-associated tremor/ataxia syndrome (FXTAS)

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ABSTRACT

Fragile X-associated tremor/ataxia syndrome (FXTAS) is a genetically determined neurodegenerative disease which is caused by a 55–200 expansion of CGG repeat element in the promoter region of the fragile X mental retardation 1 (FMR1) gene. The major clinical manifestations are tremor and cerebellar ataxia. Different types of tremor are described in patients with FXTAS: essential tremor-like, rest tremor and cerebellar tremor, and the different tremor types may coexist. There is no effective disease modifying therapy for FXTAS, but troublesome tremor may be treated by pharmacological and surgical approaches used for other more common disorders such as essential tremor and Parkinson's disease.

1. Introduction

Tremor is the most common movement disorder seen in clinical practice, defined as an involuntary rhythmic movement of any body part.

The onset of tremor could be the first sign of Parkinson's disease (PD), but there are other tremor disorders which are more common, such as essential tremor (ET) and there are rare but important multi-symptomatic disorders that may present with tremor. One of the latter is the Fragile X-associated tremor/ataxia syndrome (FXTAS), a neurodegenerative disease recognized which is caused by a 55–200 expansion of CGG repeat element in the promoter region of the *fragile X mental retardation 1* (*FMR1)* gene, known as a premutation. Full-mutation carriers with over 200 repeats have the Fragile X Syndrome (FXS), which is characterized by childhood-onset intellectual disability, seizures and autism.

FXTAS, which is usually observed in normally developed people over the age of fifty, presents with a set of clinical manifestations which include kinetic tremor, cerebellar ataxia, cognitive decline and parkinsonism [1–3]. Additional features are peripheral neuropathy [4], autonomic dysfunction [5,6] and psychiatric symptoms [7]. The course is progressive and increasing impairment, disability and handicap is apt to emerge over 15–20 years [8].

FXTAS is associated with distinct features on magnetic resonance imaging (MRI), including cerebral and cerebellar atrophy, and subcortical and/or ponto-cerebellar white matter (WM) lesions [9] which are present in males and to a lesser extent in females with FXTAS. About 58% of males and 13% of females with FXTAS display T2 hyperintense lesions in the middle cerebellar peduncles (MCP), known as the MCP sign [10]. Hyperintensities in the splenium of the corpus callosum on MRI may be seen in up to 68% [11].

Neuropathologically, FXTAS is distinguished by characteristic ubiquitin-positive intranuclear inclusions in brain and spinal cord neurons as well as in peripheral tissues [9,12].

Population studies investigating the prevalence of FXTAS in the general population have not been conducted. The estimated prevalence of the *FMR1* premutation is between 1/151 and 1/209 in women and 1/430–1/468 in men [13,14]. The estimated prevalence of the FXTAS phenotype in premutation carriers (PMC) older than 50 years is approximately 40% in men and 8–16% in women [2,15,16]. Given this data and the fact that clinical signs are assumed to appear in patients with CGG repeats > 60 it is estimated that the prevalence of FXTAS in

Abbreviations: PD, Parkinson's disease; ET, Essential tremor; FXS, fragile X syndrome; FXTAS, Fragile X-associated tremor/ataxia syndrome; *FMR1*, fragile X mental retardation 1; MRI, magnetic resonance imaging; WM, white matter; MCP, middle cerebellar peduncle; PMC, premutation carriers; POF, premature ovarian failure; LL, lower limbs; UL, upper limbs; RUL, right upper limb; MoCA, Montreal Cognitive Assessment; NIDDM, non-insulin dependent diabetes mellitus; CRST, Clinical Rating Scale for Tremor; SARA, Scale for the assessment and rating of ataxia; MRgFUS, MR-guided Focused ultrasound; DBS, deep brain stimulation; GK, Gamma Knife

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the general population is 1:4000 in males and 1:7800 in females [17]. The age of onset of both tremor and ataxia have been found to correlate with CGG repeat length [18].

As tremor is an early and typical sign of FXTAS, we present this Case series and literature review focusing on the tremor associated with FXTAS. Various types of tremor can be distinguished clinically, based on the activation condition (as rest and action tremors, task-specific tremors etc.), frequency and topographical distribution. The type of tremor can be further defined according to association with additional neurological abnormalities suggestive of parkinsonism, cerebellar ataxia, polyneuropathy and others.

2. Case series, Movement Disorders Institute at Sheba Medical Center

We followed a patient cohort of nine *FMR1* PMCs that presented with various neurological symptoms and referred to the Movement Disorders Institute at Sheba Medical Center between 2015 and 2017. As part of a *FMR1* carrier neurological observational study all patients underwent a detailed neurological examination and the Montreal Cognitive Assessment (MoCA) [19]. Their FXTAS status was determined according to the FXTAS diagnostic criteria [1]. Eight patients who had tremor are listed in Table 1. Our patient cohort includes an additional patient with ataxia but no evidence of tremor who is not included.

The study was approved by our institutional IRB and all patients signed a consent form prior to recruitment.

We will present four of these cases in detail, each representing a different type of tremor syndrome. Our purpose in this review is to focus on specific tremor prototypes seen in FXTAS and these are represented by four cases described in detail. The other patients in our series mentioned in the table do not contribute additional insights on clinical features and thus are not presented in detail in this manuscript.

2.1. Case 1- A patient with orthostatic tremor

A 59-year-old banker, mother of three (Case 1 of Table 1), with a medical history of hypothyroidism, hypertension and premature ovarian failure (POF) at the age of 37 years, presented with a 3-year history of tremor of her lower limbs (LL) which appeared only when standing. After 2 years she began experiencing additional symptoms including postural and action tremor in both upper limbs (UL) and problems walking with instability. The UL tremor bothered her mostly while working on the computer, however she had no trouble dressing or feeding.

Upon examination her MoCA score was 22 (impaired mainly on memory and language). She showed a prominent tremor disorder that consisted mainly of moderate action and postural tremor of the hands with prominent intentional worsening, marked postural tremor of both legs when held up while she lay down, but no rest tremor. Upon standing a fine tremor of the legs was both palpable and visible.

The patient displayed cerebellar signs on oculomotor testing with saccadic intrusion into smooth pursuit and dysmetria on saccades. She had UL dysmetria and mild parkinsonian signs with slight rigidity of her right UL with contralateral movement, mild UL bradykinesia and moderate LL bradykinesia. Her stance was wide-based, as was her gait which was a slightly hesitant and slow and she was unable to tandem walk.

Brain MRI demonstrated cerebellar atrophy but no WM abnormalities, MCP sign or cerebral atrophy. Her daughter was diagnosed with FXS and carried a full-mutation allele (> 200 CGG repeats). Upon testing the patient was found to carry an *FMR1* premutation allele of 82 CGG repeats.

As her tremor caused most of her UL and gait disability as well as embarrassment, she was prescribed several drugs that she tried sequentially, including primidone, propranolol, amantadine and clonazepam, escalating to full doses and for reasonable periods but gained no benefit. She experienced some improvement in tremor and balance with medical marijuana which she smoked daily at a monthly dose of 30 g.

2.2. Case 2- Rest tremor-parkinsonism phenotype

An 81-year old, retired factory worker (Case 2 of Table 1) father of three, with a past medical history of ischemic heart disease and benign prostate hypertrophy, presented with a 9-year history of slowly progressive unilateral right UL (RUL) rest tremor followed by gait imbalance for which he used a cane. Since his early 70's he had noticed decreased olfaction, constipation and his wife noticed episodes of active dreaming movements during sleep suggestive of rapid eye movement (REM) sleep behavior disorder (RBD). Urinary hesitancy along with frequency and urgency worsened to a state of urinary incontinence during the past few years. There was no history or present symptoms of depression, but he had become more forgetful and somewhat apathetic.

He seemed demented and on examination his MoCA score was 12 out of 30. He had moderate rest tremor that persisted during walking

Table 1
Clinical characteristics of patients with Fragile X-associated tremor/ataxia syndrome in Sheba Medical Center.

Case	Age, years	Gender	FXTAS Classification	CGG Repeats	Gait Ataxia	Action Tremor	Orthostatic Tremor	Postural Tremor	Rest Tremor	Bradykinesia	Rigidity	Signs of Neuropathy	MoCA Score
1	59	F	probable	82	Y	Y	Y	Y	N	Y	Y	N	22
2	81	M	probable	85	Y	Y	N	Y	Y	Y	Y	Y	12
3	72	M	definite	90	Y	Y	N	Y	Y	Y	N	N	21
4	73	M	definite	87	Y	Y	N	Y	Y	Y	Y	N	18
5	68	M	probable	110	Y	Y	N	N	N	Y	N	Y	25
6	84	M	probable	71	Y	y	N	Y	Y	Y	Y	Y	23
7	72	F	probable	NA	Y	Y	N	Y	Y	Y	Y	Y	25
8	68	M	definite	100	Y	Y	Y	Y	Y	Y	Y	Y	19

The table includes part of a patient cohort of FMR1 premutation carriers referred to the Movement Disorders Institute at Sheba Medical Center between 2015 and 2017 due to neurological symptoms. Only patients who had tremor are listed in this table. All patients underwent a detailed neurological examination as well as the Montreal Cognitive Assessment (MoCA). Their FXTAS status was determined according to the FXTAS diagnostic criteria [1]:
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.
Radiological: Major-MRI white matter lesions in MCP's and or brain stem. Minor- MRI white matter lesions in cerebral white matter/Moderate to severe generalized atrophy.
Clinical: Major- Intention tremor/Gait ataxia. Minor- Parkinsonism/Moderate to severe short-term memory deficiency/Executive function deficit.
M = Male F = Female Y = present N = absent.

along with slight postural tremor of his RUL and slight action tremor of both UL. Upon oculomotor testing his ocular pursuit was slightly saccadic. He had additional parkinsonian signs of decreased facial expression, nuchal and bilateral UL cogwheel rigidity and moderate UL bradykinesia (more so on the right). His gait was slow, with a slightly widened base of support but also short-stepped and shuffling.

Brain MRI demonstrated generalized and cerebellar atrophy and discrete hyperintense lesions were seen in the cerebral WM and in the splenium of the corpus callosum.

All of his three daughters were carriers of the *FMR1* premutation and two of his grandchildren had been diagnosed with FXS. He was found to carry a premutation allele with 85 repeats.

He was treated with 300 mg of L-dopa a day with some improvement. He developed no motor fluctuations or dyskinesia within a period of 2 years.

2.3. Case 3- Intention tremor –cerebellar ataxia phenotype

A 72-year-old teacher, father of five (Case 3 of Table 1), with a past medical history of hypertension, hypothyroidism and non-insulin dependent diabetes mellitus (NIDDM), presented with a 22-year history of bilateral UL action tremor and progressive UL dysfunction followed by 10 years of imbalance and falls along with cognitive decline. He complained that tremor impaired his writing, playing cards, holding a glass and drinking. He could still eat independently using maneuvers for stabilization. He also complained of choking when drinking and that people often couldn't understand his speech.

On examination his MoCA score was 21 (mostly due to memory and language skills). On oculomotor testing he had some difficulty performing smooth pursuit and his saccades were hypermetric. He had prominent symmetrical UL and LL postural and intentional tremor, and slight rest tremor in his RUL. He also had moderate dysmetria and ataxia of all limbs. He had mild bradykinesia in all limbs. He had no rigidity. Gait was slow, wide-based and ataxic, needing assistance.

Brain MRI demonstrated generalized and cerebellar atrophy, hyperintense lesions in the cerebral WM as well as in the MCP and cerebellum. He received no pharmacologic treatment. He had been aided by a cane but for 2 years it was no more helpful as falls became frequent and a walker was recommended.

His daughter was found to be a carrier of the *FMR1* premutation during pregestational genetic screening and he was found to carry a *FMR1* premutation allele with 90 repeats.

2.4. Case 4- Essential tremor phenotype

A 72-year-old university psychology professor, father of four (Case 4 of Table 1), with a medical history of hypertension, hypothyroidism, dyslipidemia and NIDDM presented with a 9-year history of cognitive decline, 4 years of gait imbalance and 2 years of UL tremor. On examination his MoCA was impaired, scoring 18. He had slight head tremor along with some tongue tremor, voice tremor and facial tremor (cheeks, eyebrows). There was a prominent bilateral symmetrical UL postural tremor with some inconsistent rest and action tremor as well. When he lay down and held up his legs there was LL postural tremor. Oculomotor testing revealed slightly saccadic ocular pursuit and dysmetria of saccades. There was some UL and LL bradykinesia and rigidity. He needed no assistance getting up and walking but had a slightly wide based gait with some festination and propulsion. Minimal dystonic posturing of his right UL was seen during walking.

Brain MRI demonstrated cerebral and cerebellar atrophy, hyperintense lesions in the splenium of the corpus callosum as well as a bilateral MCP sign.

His grandson was diagnosed with FXS and his daughter was found to be a carrier of the *FMR1* premutation. He was found to carry a premutation allele with 87 repeats.

He was treated with rivastigmine with some subjective cognitive improvement; He was intolerant to primidone and propranolol. L-dopa had no effect.

3. Tremor in FXTAS-review

In 2001 Hagerman and colleagues [20] reported of five men with the *FMR1* premutation who had action tremors associated with executive function deficits in the context of a slowly progressive neurodegenerative condition. In all cases the symptoms started with an action tremor involving one hand and then also affected the other hand, and later tremor occurred also at rest; during the coming years, the action tremor remained the most prominent symptom for all patients and it became progressively more debilitating. All patients exhibited additional but slight parkinsonian symptoms and signs, which were responsive to L-dopa in a couple. In 2003 FXTAS was defined and intention tremor (a synonym for kinetic action tremor) was determined as one of the major clinical FXTAS criteria, as it was a very common finding in persons with the disorder [1].

The prevalence of tremor in men with FXTAS is about 80% [1,21–23]. Kinetic tremor of the hands has been found the most common at presentation and the most prevalent through-out the disease course.

Juncos et al. [23] examined 50 male *FMR1* PMC with tremor and/or ataxia and detected tremor in 35 (70%) of them. Intention tremor and postural tremor were common, mostly in the arms. Titubation and/or voice tremor were present in 5 patients. Rest tremor was present in 7 patients but always involved an additional type of tremor. Using the clinical rating scale for tremor (CRST) [24] the mean tremor severity score for the group was 12.9 ± 15 with most of the severity stemming from the intention tremor. Intention and/or postural tremor were the presenting motor signs in 28 of the 46 subjects. In 8 out of 20 subjects who presented with tremor and later developed other motor symptoms, tremor preceded the onset of the additional motor symptoms by more than 10 years. One definite, 2 probable and one indeterminate FXTAS subjects had postural tremor for 20 years or more and thus presented with an ET-like condition before the onset of FXTAS-associated symptoms. Leehey had reported a similar Case in 2007 [8].

A study which evaluated 20 *FMR1* PMC over 50 years of age, who presented with at least one clinical major criterion (ataxic gait or intention tremor) and one radiological major criterion (presence of symmetric MCP signs), showed that 70% of them had intention tremor, 10% had resting tremor alone and 30% had a combination of tremor types. Five out of 6 additional patients, who met the clinical criteria but not the radiological criteria, had intention tremor, one had resting tremor alone and another had a combination of tremor types [1].

Another study of 64 male FXTAS patients of 50 years and older found intention tremor in 88% and rest tremor in 42%. Out of 23 male PMC of 50 years and older who did not meet diagnostic criteria of FXTAS, 9% had intention tremor and none had rest tremor [25].

In a study of 55 male PMC diagnosed with either possible, probable or definite FXTAS, tremor was found typically to precede ataxia, to become disabling within 13 years from the onset of motor symptoms, and to substantially interfere with the activities of daily living by 16 years from onset in half of the patients [8].

FMR1 CGG repeat length, with control for age, was positively and highly correlated with impairment on motor scores in a cohort of 50 PMC over the age of 50. This correlation was primarily driven by the strong correlation between increasing CGG and motor impairment in men, and the correlation was more robust for tremor and ataxia than for Parkinsonism. Women PMC showed only a trend toward worsening of motor scores with increasing CGG repeat length [26].

3.1. Rest tremor and parkinsonism in FXTAS

The prevalence of rest tremor is lower than that of action tremor. In one study rest tremor was found in 26% of 38 patients (30 males) with

probable or possible FXTAS [27]. Another paper describes 4 patients with the *FMR1* premutation (60–86 repeats) who met the criteria for PD. These patients demonstrated bradykinesia, rigidity and rest tremor, and 3 of them were treated with L-dopa with a good response. They did not have either a kinetic tremor nor gait ataxia and their brain imaging was normal [28]. Other cases were reported of PMC not meeting the FXTAS clinical criteria with clinical features consistent with PD, including rest tremor. On autopsy ubiquitinated nuclear inclusions were found in the cortex and hippocampus characteristic of FXTAS but no Lewy bodies [5].

Apartis and colleagues [11] delineated the clinical, neurophysiologic, and morphologic characteristics of 22 patients with FXTAS (4 women). 86% of patients had tremor and 3 electro-clinical tremor patterns were identified: essential-like (35%), cerebellar (29%), and parkinsonian (12%). Four patients had no detectable tremor.

Features of parkinsonism are common among individuals with FXTAS with bradykinesia (57%) and rest tremor in (26%) [27]. In a study by Scaglione et al. [29] [123I]FP-CIT (DaTscan) SPECT brain imaging was performed in 4 patients diagnosed with FXTAS and in 3 of them it showed asymmetrically decreased striatal uptake, which was mild in two patients and marked in one. Pathological studies have shown dual pathology in some cases of FXTAS, with both the ubiquitin-positive and 1C2-negative neuronal and glial intranuclear inclusions with mild Purkinje cell depletion (consistent with FXTAS) as well as loss of pigmented neurons in the substantia nigra with α-synuclein-positive Lewy bodies [9,13,30]. This suggests that the presence of PD symptoms and pathology may be coincidental in some FXTAS cases. In other cases, Parkinsonism is probably caused by the FXTAS pathology alone.

It is speculated that the development of neuropathological conditions such as PD in *FMR1* PMC might be facilitated by the molecular dysregulation that occurs and leads to mitochondrial dysfunction and extracellular deposition of iron [31–33].

Investigations have been conducted to assess the frequency of *FMR1* premutation in persons with parkinsonism and PD. The presence of the premutation was found not to be significantly higher in patients with PD hence screening PD patients for *FMR1* CGG expansions is not routinely recommended [34]. Another study assessed whether the size of triplet repeats of the fragile X mental retardation genes *FMR1* and *FMR2* (found at the FRAXA and FRAXE loci) is associated with PD. They found that frequencies of FRAXA and FRAXE intermediate alleles were similar between PD and control groups [35]. However, it is prudent to screen PD patients with a family history of possible or known *FMR1*-related disease for the premutation.

3.2. Essential tremor and FXTAS

Apartis and colleagues [11] described the patients with essential-like tremor. The typical picture was patients with bilateral, symmetric or asymmetric small-amplitude tremor involving wrist and fingers only, which occurred during postural maintenance and action, without intentional worsening. Mean distal frequency was 5.3 ± 0.68 Hz (range 4.7–6.5).

A wide variety of prior diagnoses, mainly within categories of parkinsonism (24%) and tremor (20%) have been given to patients with FXTAS [36]. However, when DNA of cohorts of ET or parkinsonism was screened for the *FMR1* premutation, there was no excess of carriers. Garcia Arocena and colleagues [37] screened 81 ET patients (40 of them males) for expanded *FMR1* alleles but none of the ET cases had the premutation genotype. Clark and colleagues [38] performed an association analysis of *FMR1* CGG repeats in 321 ET cases and 296 controls ranging from 10 to 49 repeats, through gray zone alleles (41–54 CGG repeats) and to the premutation range and found no evidence for association of premutation or gray zone alleles with ET. These data suggest that *FMR1* CGG repeat expansion is not a genetic risk factor for ET.

3.3. Cerebellar tremor in FXTAS

Apartis and colleagues [11] described patients with cerebellar-type tremor – they had bilateral symmetric or asymmetric proximo-distal UL tremor, always associated with cervical (n = 4) or diffuse cervico-dorso-lumbar axial tremor (n = 1). Tremor was always absent at rest, even during mental or motor activation tests and it occurred during postural maintenance and non-goal-directed movements and worsened during target-directed movements. The cerebellar-type UL tremor had a higher amplitude than essential-like tremor. The mean distal UL frequencies were 3.4 ± 0.28 Hz (range 3.2–3.8). Cerebellar tremor was associated with a higher score on the Scale for the assessment and rating of ataxia (SARA).

Orthostatic tremor in addition to postural and action tremor was also described in one patient diagnosed with multiple system atrophy (MSA) within a screening study for *FMR1* mutations in patients diagnosed with MSA [39].

3.4. Treatment of tremor in FXTAS

As of today, there is no effective disease modifying therapy for FXTAS; however, there are medications and surgical approaches that are being used for symptomatic treatment of tremor in patients with FXTAS.

Hall et al. [40] reported on the experience with 56 patients with FXTAS treated medically for their neurological symptoms. Seventy percent of the patients with definite FXTAS and 30% of those with possible or probable FXTAS were taking medications for motor signs. Of the subjects receiving therapy for action tremor; 3/6 reported mild to moderate improvement on primidone, 3/8 had moderate improvement of tremor on beta-blockers, 2/8 had moderate improvement on benzodiazepines. One subject reported improved tremor on memantine, which was prescribed for cognitive decline. Signs of parkinsonism including rest tremor improved in 2/8 patients treated with carbidopa/levodopa and in 1/2 patients treated with pramipexole. No improvement of tremor was found in 2 patients treated with Gabapentin.

In a Case report of a 66-year-old FXTAS patient administration of levetiracetam was associated with subjective and objective improvement of tremor [41].

Memantine (an NMDA receptor antagonist) was tried on 43 individuals aged 34–80 years with probable or possible FXTAS within the frame of a randomized, double-blind, placebo-controlled 1-year long trial; the study failed to show improvement with respect to intention tremor severity [42].

Botulinum toxin type A (BoNT-A), is most commonly used in treating conditions that involve involuntary muscle contraction, such as dystonia and spasticity but it is used less frequently for treating tremor [43]. There has been one report of a FXTAS patient with disabling arm tremor, who had significant functional improvement following BoNT-A injections in the flexor digitorum superficialis, flexor digitorum profundus, and extensor digitorum muscles [44].

There are no reports on the effect of cannabinoids on tremor in FXTAS patients however there is some evidence for positive effects on tremor in PD [45,46]. It is worth noting that two of our patients used medical marijuana with reported improvement of their tremor. One is the patient described in Case 1, who experienced some improvement of the tremor as well as the imbalance with medical marijuana, smoked daily at a monthly dose of 30 g. The other is case 7 presented in Table 1, who used daily oral medical marijuana oil at a monthly dose of 30 g for osteoarthritic pain, and reported a beneficial effect on her tremor as well.

An open-label interventional study assessed whether allopregnanolone (neurosteroid promoting regeneration and repair) can improve clinical symptoms, brain activity, and MRI measurements in patients with FXTAS. Six patients underwent weekly intravenous infusions of

Table 2
Stereotactic neurosurgical interventions for tremor in patients with Fragile X-associated tremor/ataxia syndrome.

Reference	N	Procedure	Brain targets	tremor	Ataxia
Leehey et al. Arch Neurol. 2003 [44]	1	DBS	Bilateral VIM	Improved	Worsened
Peters et al. Mov Disord. 2006 [45]	1	DBS	Bilateral VIM	Improved	Stable
Ferrara et al. Mov Disord. 2009 [46]	1	DBS	Bilateral VIM	Improved	Worsened
Senova et al. Mov Disord. 2012 [47]	1	DBS	Unilateral VIM	Improved	Stable
Hagerman et al. Brain Disorders & Therapy 2012 [48]	3	DBS	Bilateral VIM	Improved	2 Improved 1 worsened
Xie et al. Mov Disord. 2012 [49]	1	DBS	Unilateral VIM	Improved	Stable
Mehanna and Itin Cerebellum 2014 [50]	1	DBS	Staged bilateral VIM	Improved	Worsened
Oyama et al. Neuromodulation 2014 [51]	1	DBS	Unilateral PSA	Improved	Stable
Weiss et al. Parkinsonism Relat Disord 2015 [52]	3	DBS	Bilateral VIM(2), bilateral Vim + PSA (1)	Improved	Improved
Dos Santos Ghilardi et al. Neurology 2015 [53]	1	DBS	Bilateral VOP/ZI	Improved	Improved
Tamás et al. Neurol Neurochir Pol 2015 [54]	1	DBS followed by unilateral thalamotomy	bilateral VIM, followed by bilateral STN	Transient tremor cessation after VIM and STN	Worsened
Fasano et al. Neurology. 2016 [60]	1	MRgFUS	Unilateral VIM	Improved	Stable
Cerquera et al. Parkinsonism Relat Disord. 2016 [61]	1	MRgFUS	Unilateral VIM	Improved	Stable
Alster et al. Front Neurol. 2018 [62]	1	GK	Unilateral VIM	Improved	Stable

PSA posterior subthalamic area, STN subthalamic nucleus, VIM ventralis intermedius, VOP ventralis oralis posterior, ZI zona incerta MRgFUS -MR-guided Focus ultrasound thalamotomy, DBS- deep brain stimulation, GK- Gamma Knife thalamotomy.

allopregnanolone, however none of them experienced improvement of their tremor [47].

Stereotactically placed lesions or high frequency stimulation electrodes in the thalamus connected to an implanted pulse generator have provided dramatic clinical benefit for people with tremor due to ET and PD.

The first Case of deep brain stimulation (DBS) for FXTAS was reported in 2003, the tremor improved but the patient experienced worsening of ataxia. Thereafter there have been additional reports of unilateral (n = 4, one of them the first step in a staged bilateral procedure) or bilateral (n = 11) thalamic DBS. In 5 of the patients ataxia had worsened with bilateral DBS. These cases are summarized in Table 2 [44–54].

It has been published that some ET patients treated with bilateral thalamic DBS develop a progressive cerebellar syndrome consisting of gait ataxia, dysmetria, worsening of intention tremor and dysarthria, manifesting several months after an initially effective surgical response, representing a reversible cerebellar syndrome caused by current spread and a maladaptive response to neurostimulation of the subthalamic area [49]. Thus, it is not surprising that some FXTAS patients with pre-existing ataxia would worsen.

There has been renewed interest in unilateral lesioning of the VIM of patients with tremor disorders, especially ET, thanks to the emergence of a nonsurgical ablative procedure- MR-guided focused ultrasound (MRgFUS) thalamotomy. Efficacy and safety for patients with tremor due to ET as well as for PD has been demonstrated in several studies [50–53]. Adverse events were reported, including paresthesia and balance disturbances and a decay of the benefit is seen over time [50].

Reports on two patients with FXTAS treated with unilateral VIM thalamotomy using MRgFUS have been recently published [54,55] and showed improvement of tremor with no worsening of ataxia. These cases are also summarized in Table 2.

A Case of a 73-year-old male with a 20-years history of tremor and ataxia due to FXTAS, and resistant to primidone and propranolol, who underwent left VIM radiosurgical thalamotomy using Gamma Knife (GK), was also reported. The contralateral UL postural tremor and head tremor improved along with his daily activities while adverse effects attributed to the procedure were not observed. During the year after the procedure the patient demonstrated dynamic and static imbalance that was not present before the procedure, that was attributed to the progressive nature of FXTAS [56]. This case is also summarized in Table 2.

4. Conclusions

FXTAS is an age-dependent neurodegenerative disorder caused by a premutation expanded CGG repeat in the FMR1 gene. The pathogenetic mechanisms are complex and involve sequestration of one or more neuronal proteins by the expanded CGG repeat in the mRNA 5′ thus reducing their capacity to carry out their normal cerebral functions. Two general downstream pathways probably mediate cellular dysregulation and dysfunction, specifically, altered mitochondrial function and altered calcium ($Ca^{2}+$) metabolism [57]. The extensive involvement of the cerebellar, brainstem and basal ganglionic areas seen in MRI and neuropathology contribute to the evolution of tremor.

Different types of tremor are seen in FXTAS patients, intention tremor either cerebellar or ET like, in 64–88% of patients [1,11,22,25], but also rest tremor in up to 12–30% [1,11,22,25,27].

FXTAS should be on the list of differential diagnosis of all late-onset tremor disorders, exhibiting kinetic tremor or other types, such as rest tremor, cerebellar tremor and orthostatic tremor. These may also be observed in *FMR1* PMC that do not fulfill FXTAS criteria [25].

Tremor in FXTAS patients is a troublesome and disabling symptom treated by pharmacological and surgical approaches used for other more common disorders such as ET and PD. Evidence-based data on efficacy and safety is still lacking. Finally, the goal of disease modifying treatment for FXTAS will be achieved as the mechanisms of disease are fully deciphered.

Declarations of interest

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