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Short communication

Long-term outcome of deep brain stimulation in fragile X-associated tremor/ataxia syndrome

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ABSTRACT

Introduction: Fragile X-associated tremor/ataxia syndrome (FXTAS) presents as complex movement disorder including tremor and cerebellar ataxia. The efficacy and safety of deep brain stimulation of the nucleus ventralis intermedius of the thalamus in atypical tremor syndromes like FXTAS remains to be determined.
Methods: Here, we report the long-term outcome of three male genetically confirmed FXTAS patients treated with bilateral neurostimulation of the nucleus ventralis intermedius for up to four years.
Results: All patients demonstrated sustained improvement of both tremor and ataxia – the latter included improvement of intention tremor and axial tremor. Kinematic gait analyses further demonstrated a regularization of the gait cycle. Initial improvements of hand functional disability were not sustained and reached the preoperative level of impairment within one to two years from surgery.
Conclusion: Our data on patients with a genetic cause of tremor show favorable outcome and may contribute to improved patient stratification for neurostimulation therapy in the future.

1. Introduction

Fragile X-associated tremor/ataxia syndrome (FXTAS) is an inherited, X-linked, adult-onset neurodegenerative disorder caused by expanded trinucleotide repeats in the 5′ untranslated region of the fragile X mental retardation 1 (*FMR1*) gene. Typically, pathological increases in repeat length represent the most common cause for inherited early mental retardation in males. However, premutation alleles with 55–200 repeats may cause a late-onset progressive movement disorder based on elevated *FMR1* mRNA levels and the related gain-of-function toxicity. The clinical manifestation of FXTAS includes predominantly action and postural tremor, and cerebellar ataxia. Furthermore, rest and intention tremor, parkinsonism, and non-motor features including cognitive impairment, peripheral neuropathy and autonomic symptoms may emerge to variable degree. The penetrance of FXTAS was determined as 40% in male carriers over age 50 years and increases up to 75% at age 80 years [1]. Pharmacological tremor treatment showed limited efficacy using both first line medications, i.e. primidone or propranolol, and other second-line medications [2]. Deep brain stimulation was therefore considered in FXTAS with resistant tremor. To date, only few single cases with variable outcome of

Abbreviations: FXTAS, fragile X-associated tremor/ataxia syndrome; DBS, deep brain stimulation; Vim, nucleus ventralis intermedius thalami; gait, balance.

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tremor and ataxia based on different surgical targeting approaches were reported [3–10]. As the tremor signal is generally propagated through the cerebello-thalamic pathway, the Vim and subthalamic fiber tracts can be considered plausible neurostimulation targets. Here, we report the long-term therapeutic outcomes of neurostimulation in a series of three subsequent FXTAS patients followed for up to 4 years.

2. Methods

Three genetically confirmed male FXTAS patients (Table 1) received DBS after medical treatment failure (Activa® PC pulse generator; Medtronic, Meerbusch, Germany) under routine clinical practice. Patients gave written consent to the genetic diagnostics and surgical procedure within diagnostic and therapeutic settings. There was no sufficient treatment effect on tremor with conventional medication therapy including propranolol, primidone and several further second-line medications in all three patients. A detailed clinical assessment was performed preoperatively during the regular DBS screening. Bilateral electrode implantation considered the ventral intermediate thalamus (Vim) or adjacent subthalamic fiber tracts in a single operative session in all patients. The final electrode localization was clinically defined intra-operatively following test stimulation in the awake patients. The perioperative procedure was free from complications. Correct localization of the electrodes was defined by postoperative T1-weighted MR imaging and confirmed localization of the most caudal active electrode contacts in the bilateral Vim region (FXTAS-2, FXTAS-3), or the bilateral caudal border zone of Vim and subthalamic fiber tracts (FXTAS-1) (Table 1) as generally applied in tremor [11,12]. All three patients underwent regular clinical reevaluation at two months, at one year, and at two years from DBS surgery (FXTAS-3 not available at one year) in both 'stimulation off' (StimOff) and 'stimulation on' (StimOn) conditions. Two patients underwent the four-year assessment (FXTAS-2, FXTAS-3). DBS parameters were determined along best clinical care. Our center follows several standards that align with the current state-of-the-art: we generally chose the most caudal electrode contacts in line with previous recommendations [11,12]. To obtain optimal therapeutic efficacy and therapeutic width, we first used monopolar parameters but changed to bipolar parameters if side effects occurred. We introduced a second caudal contact if tremor response remained incomplete with one contact. Eventually, stimulation frequencies were increased. When latest evidence came up that lower impulse widths may improve the therapeutic width in DBS treatment for tremor (avoiding ataxia), we implemented this concept to our programming routine [13]. Clinical motor outcome was monitored with the Tremor Rating Scale (TRS) and International Cooperative Ataxia Rating Scale (ICARS). The tremor-related hand functional disability was assessed with the "Columbia University Assessment of Disability in Essential Tremor" (CADET-A, anamnestic part). We further evaluated the PDQ-39 quality of life, Mini-Mental Status Examination (MMSE) for cognitive functions, and Beck's Depression Inventory (BDI). Patients FXTAS-1 and FXTAS-2 were available for kinematic gait analysis (APDM, Portland, USA) in both StimOff and StimOn at final assessment.

3. Results

At final assessment, all three patients reported overall subjective improvement when comparing StimOff and StimOn conditions under physician survey. All three patients revealed considerable and sustained tremor improvement (TRS) when comparing StimOff and StimOn conditions (Table 2), and the TRS in StimOn at final assessment was superior to the preoperative score in all three patients. Postoperatively, all three patients showed a gradual increase of tremor in consecutive StimOff assessments, presumably reflecting the underlying disease progression. Ataxia scores (ICARS) gradually worsened in StimOff over time and improved with StimOn throughout the whole observation period. This finding may in part reflect the sustained improvement of intention tremor. Additionally, at final assessment, we found a positive effect of Vim-DBS on gait based on kinematic gait measures in two patients (FXTAS-1, FXTAS-2). Gait analysis revealed improved step length, more regular gait cycles, and improved axial tremor around 3 Hz (Appendix 1). Preoperatively, hand functional disability was severe

Table 2
Clinical outcome on tremor, functional disability, ataxia, quality of life, cognition and depressive symptoms.

	FXTAS-1		FXTAS-2		FXTAS-3	
TRS preoperative	11		21		21	
2 month (StimOff/StimOn)	11	11	18	8	n.a.	3
1 year	12	8	26	8	n.a.	n.a.
2 years	19	6	16	7	45	8
4 years			30	12	34	7
ICARS preoperative	45		n.a.		31	
2 month (StimOff/StimOn)	39	39	43	18	36	12
1 year	71	48	45	26	n.a.	n.a.
2 years	62	37	64	38	75	36
4 years			79	50	63	26
CADET-A preoperative	60		58		60	
2 month	45		37		16	
1 year	62		59		n.a.	
2 years	51		62		62	
4 years			57		31	
PDQ-39 preoperative	58		33		23	
2 month	63		16		4	
1 year	41		43		n.a.	
2 years	41		41		22	
4 years			60		23	
MMSE preoperative	26/28		28/30		27/28	
2 month (StimOff/StimOn)	28/28		29/30		27/30	
1 year	26/28		29/30		n.a.	
2 years	28/30		24/28		26/30	
4 years			25/30		24/30	
BDI preoperative	11		11		1	
2 month	8		3		0	
1 year	14		3		n.a.	
2 years	8		5		10	
4 years			28		15	

Pre- and postoperative scores of tremor and ataxia. All postoperative scores are given as StimOff (left column) and StimOn (right column). Abbreviations: CADET-A – Columbia University Assessment of Disability in Essential Tremor, anamnestic part; ICARS – International Co-Operative Ataxia Rating Scale; StimOff – stimulation off; StimOn – stimulation on; TRS – tremor rating scale; PDQ-39 – quality of life, summary index; MMSE – Mini Mental State Examination (note that items 29 and 30 required handwriting and could not always be assessed owing to tremor interference); BDI – Beck's Depression Inventory.

Table 1
Clinical characteristics.

	FXTAS-1	FXTAS-2	FXTAS-3
Gender	Male	Male	Male
FMR1 gene CGG triplet repeats	100	101	100
Disease duration at surgery (years)	8	7	20
Age at surgery (years)	70	63	70
Postoperative observation (years)	2	4	4
Electrode coordinates[a]	L: −15, −21, −3	L: −15, −19, 3	L: −16, −19, 2
(caudal active contacts relative to AC; x, y, z)	R: 17, −19, −1	R: 16, −19, 2	R: 17, −21, 3
Final stimulation parameters	L: 0-1-C+, 1.7 V, 150 μs, 125 Hz	L: 0-1-2+, 5.4 V, 60 μs, 170 Hz	L: 0-C+, 4.9 V, 120 μs, 150 Hz
	R: 8-9-10-C+, 1.5 V, 150 μs, 125 Hz	R: 8-9-10+, 4.4 V, 90 μs, 170 Hz	R: 8-9+, 4.6 V, 120 μs, 150 Hz

Abbreviations: AC – anterior commissure, L = left electrode, R = right electrode; x = medio-lateral, y = anterio-posterior, z = rostro-caudal (all in mm and reference to individual AC). Electrode contacts: 0–3 indicate left-sided electrode labels, 8–11 right-sided electrode labels according to convention for Activa® impulse generators (Medtronic, Minneapolis, USA).

[a] Note that all three patients presented with global brain atrophy and increased width of the third ventricle ranging from 10 to 13 mm.