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Case report

Deep brain stimulation or thalamotomy in fragile X-associated tremor/ataxia syndrome? Case report

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ABSTRACT

We present the case of a 66-year-old man who has been treated for essential tremor since the age of 58. He developed mild cerebellar gait ataxia seven years after tremor onset. Moderate, global brain atrophy was identified on MRI scans. At the age of 68, only temporary tremor relief could be achieved by bilateral deep brain stimulation of the ventral intermedius nucleus of the thalamus. Bilateral stimulation of the subthalamic nucleus also resulted only in transient improvement. In the meantime, progressive gait ataxia and tetraataxia developed accompanied by other cerebellar symptoms, such as nystagmus and scanning speech. These correlated with progressive development of bilateral symmetric hyperintensity of the middle cerebellar peduncles on T2 weighted MRI scans. Genetic testing revealed premutation of the FMR1 gene, establishing the diagnosis of fragile X-associated tremor/ataxia syndrome. Although this is a rare disorder, it should be taken into consideration during preoperative evaluation of essential tremor. Postural tremor ceased two years later after thalamotomy on the left side, while kinetic tremor of the right hand also improved.

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1. Introduction

Fragile X-associated tremor/ataxia syndrome (FXTAS) is a rare, hereditary neurodegenerative disorder that predominantly affects men in their sixties; they are carriers of premutation alleles (55–200 cytosine, guanine and guanine [CGG] trinucleotide repeats) of the FMR1 gene on the X chromosome. FXTAS is different from the fragile X syndrome as it is associated with more than 200 CGG repeats of the same gene [1]. The initial symptoms of FXTAS are action, particularly intention tremor or slight cerebellar gait ataxia accompanied by tremor. These are followed by a severe, progressive trunk and limb ataxia after one or several years [2]. Its auxiliary

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features might be executive dysfunction, short-term memory deficiency, autonomic symptoms, polyneuropathy or Parkinsonism [3]. MRI findings involve cerebral and cerebellar cortical volume loss and periventricular, subcortical global white matter disease in the brainstem and cerebellum. Major radiological diagnostic criterion of FXTAS is symmetrical T2 hyperintensity in the middle cerebellar peduncles (MCP sign), that can be observed in 60% of the symptomatic cases [4,5].

In the early phase of FXTAS, its clinical features might be similar to those observed in essential tremor [6,7]. As mild to moderate gait ataxia and balance impairments also often occur in essential tremor, they make differential diagnosis, based only on clinical symptoms, more difficult [8].

2. Case report

A 66-year-old man with essential tremor was referred to preoperative evaluation for deep brain stimulation in 2010. Treatment of hypertension and type 2 diabetes mellitus was reported in his medical history. His hand tremor started at the age of 58, which was characterized by a kinetic, intention tremor with right-sided predominance. He complained of slight instability started at the age of 65. A daily dose of 2× 250 mg primidone was ineffective to reduce his tremor, and changing his medication to 3× 40 mg propranolol per day was only transiently beneficial.

According to his self-report, alcohol consumption did not influence his tremor. Family history did not explore tremor among family members.

A physical examination revealed hypesthesia of both legs distal to the ankles, and also slight cerebellar gait ataxia. Symmetric kinetic tremor with postural tremor of the left hand, and intention tremor of the right hand could also be observed. The scores of the Fahn–Tolosa–Marin Tremor Rating Scale [9] and the Scale for the Assessment and Rating of Ataxia (SARA) [10] during the course of the disease are presented in Table 1. Neuropsychological examination revealed a decline of visual and verbal memory with mild executive dysfunction. The patient achieved 26 out of the maximum of 30 points in the Mini Mental State Examination.

At the age of 68, bilateral implantation of DBS electrodes into the ventral intermedius nucleus of the thalamus (Vim) was carried out; the electrodes were connected to a neurostimulator. Preoperative MRI scans are shown in Fig. 1.

For this procedure, target coordinates for the Vim were 12 mm lateral to the midline, 5 mm anterior to the posterior commissure, at the level of the intercomissural line both sides. In the operating room, a precoronal burr hole was placed 3 cm lateral to the midline, and a guiding cannula was inserted stereotactically using CRW Radionics stereotactic frame system. Electrophysiological mapping was carried out utilizing five microelectrodes; clinical symptoms were controlled throughout macrostimulation. A quadripolar DBS electrode (Model 3387; Medtronic Inc., Minnesota, USA) was advanced directly through the guiding cannula. Characteristics of the tremor were assessed in advance, throughout, and immediately after the insertion of the electrode. Improvement of tremor at the time of insertion of the lead (''microthalamotomy-like effect'') was considered to indicate good positioning of the electrode. Thresholds for both intrinsic and extrinsic evoked responses were analyzed directly via the implanted electrode with a screening device (Model 3625; Medtronic). Leads were fixed to the cranium with a burr hole ring and cap when satisfactory electrode position was achieved. An Activa PC implantable pulse generator (Medtronic Inc, MN, USA) was implanted in a subcutaneous infraclavicular pouch and it was connected to the DBS leads with subcutaneous extension wires under general anesthesia.

Since Vim stimulation yielded only temporary tremor reduction, stimulation of the STN was indicated after three months. Vim electrodes were subsequently removed, and quadripolar DBS electrodes (model 3389, Medtronic Inc, MN, USA) were implanted in the STN bilaterally.

The direct morphological STN targets were selected on coronal magnetic resonance T2-weighted imaging sequences 13 mm lateral, 4 mm posterior, and 5 mm inferior to the midcommissural point using a Medtronic Framelink 4 Stealth system. Neurophysiological target was verified via microelectrode recording and macrostimulation intraoperatively before lead insertion. Although tremor was suppressed substantially intraoperatively, it was moderately decreased for only three months.

In the meantime, the patient's gait ataxia and postural instability progressed (Table 1) to an extent that he became dependent on a walking aid. Gaze-directed nystagmus, slight dysarthria, symmetric postural tremor, kinetic and especially intention tremor with right-sided preponderance were observed. He complained about urine incontinence, moderate cardiovascular autonomic neuropathy was also detected, while his cognitive status remained unchanged. His immobility

Table 1 – Severity of tremor and ataxia during the course of the disease; results of the neuropsychological testing.

	2010		2011		2013	2014	2015
Fahn–Tolosa–Marin tremor scale (max: 144 points)	51	60			73		66
SARA (max: 40 points)	9	15			22		22.5
MRI scans		Fig. 1		Fig. 2	Fig. 3		
Neurosurgical procedure			Bilateral Vim-DBS	Bilateral STN-DBS		Left-sided thalamotomy	
Neuropsychological testing (points)	MMSE: 26/30; Mattis DRS: 130/144		MMSE: 28/30; ACE: 86/100; Mattis DRS: 136/144			MMSE: 29/30; ACE: 96/100	

SARA: Scale for the Assessment and Rating of Ataxia; MMSE: Mini Mental State Examination; ACE: Addenbrooke Cognitive Examination; Mattis DRS: Mattis Dementia Rating Scale.

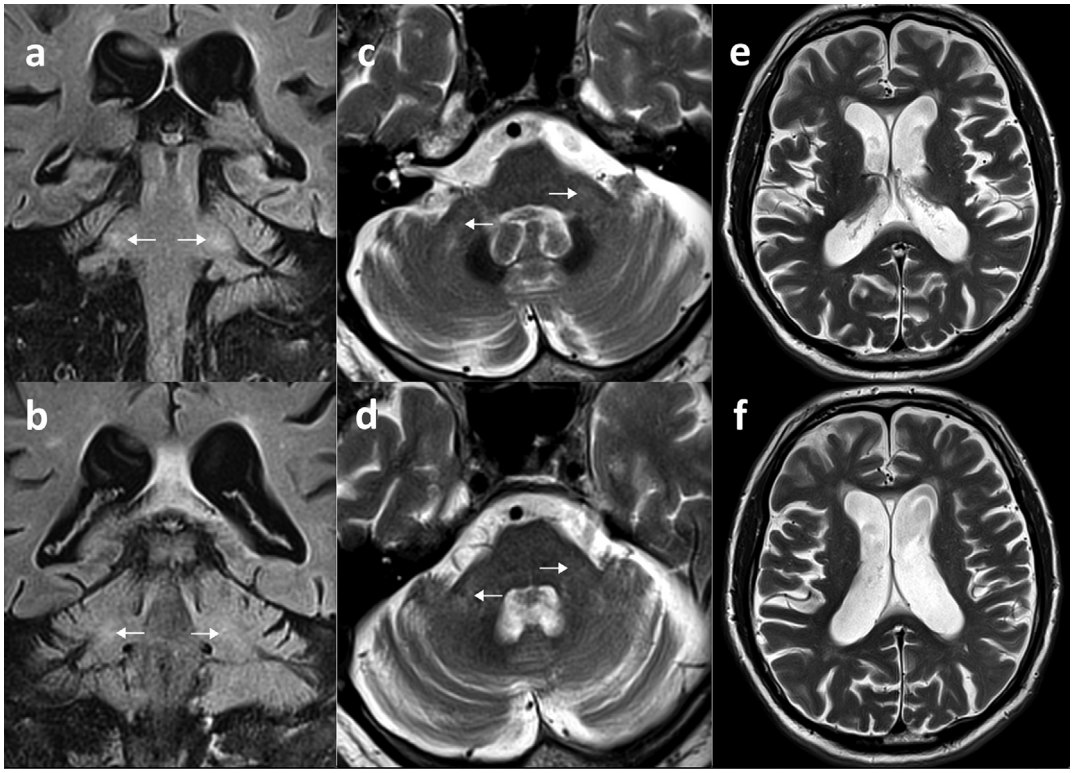

Fig. 1 – Images of the initial MRI performed on a 3.0 T Siemens MR scanner. Coronal FLAIR (a and b) images show mild hyperintensity in the middle cerebellar peduncles (arrows). Minimal hyperintensity on axial turbo spin echo T2 weighted images (c and d, arrows) is hard to distinguish from artifacts. Moderate cortical–subcortical cereberal atrophy and mild hyperintensity of the periventricular white matter are seen on the axial T2 weighted images e and f.

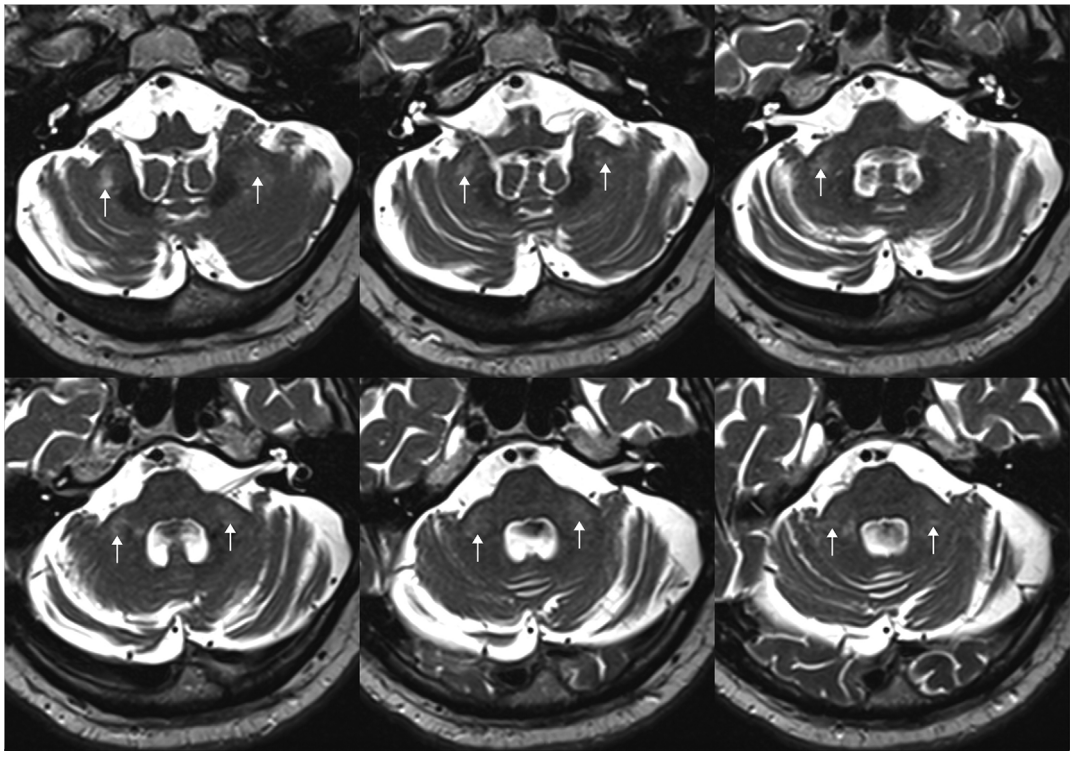

Fig. 2 – A series of images from a turbo spin echo T2 weighted sequence (slice thickness 2 mm, interslice gap 0 mm) performed on a 1.5 T Siemens scanner 7 month later with mild symmetrical hyperintensity in the middle cerebellar peduncles (arrows).

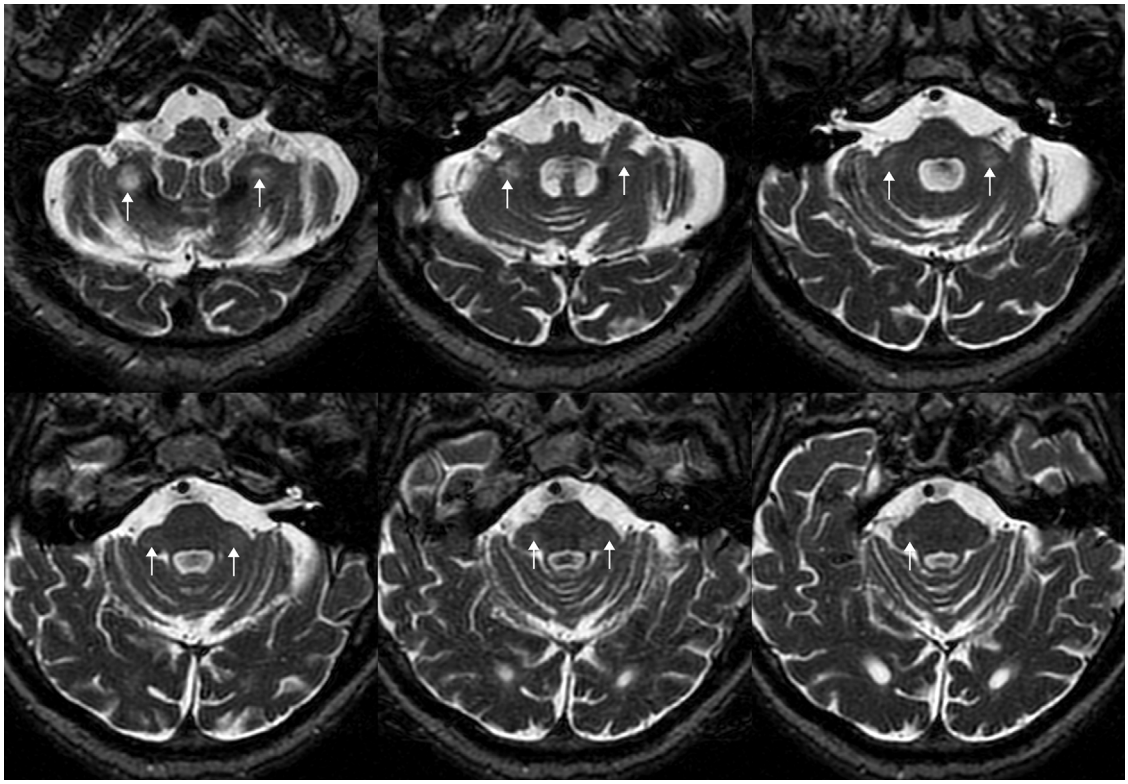

Fig. 3 – A series of images from a turbo spin echo T2 weighted sequence (slice thickness 2 mm, interslice gap 0 mm) performed on a 1.5 T General Electric scanner 2 years later with more pronounced symmetrical hyperintensity in the middle cerebellar peduncles (arrows).

progressed further after 10 months, first with the need of a walker until he became wheelchair bound. His speech turned into scanning. Impedance measurement suggested a breakage of the left DBS lead, thus control MRI examination was performed (Fig. 3). Global brain atrophy and a more pronounced symmetrical, bilateral T2 hyperintensity in the middle cerebellar peduncles were observed. Genetic testing revealed 95 CGG trinucleotide repeat in the FMR1 gene, supporting the diagnosis of Fragile X-associated tremor/ataxia syndrome.

In his family, his sister suffered from primary ovarian insufficiency. She had a healthy daughter, and a son with mental retardation. His sister's grandchildren from her healthy daughter, two girls and a boy, were all asymptomatic. His mother's sister also had a son with mental retardation.

Despite the previous bilateral Vim and STN stimulation the tremor considerably worsened with time to an extent that the patient was not able perform ordinary daily activities. At his request, an additional operation was planned; an MRI guided stereotactic thalamotomy on the left side as a last resort surgical option. Stereotactic coordinates for the left Vim remained the same as it was during the previous Vim stimulation (5 mm anterior to the posterior commissure, 12 mm lateral to the midline, and at the level of intercommissural plane). A CRW Radionics lesioning electrode was introduced into the Vim after the removal of both STN leads. Intraoperative stimulation (3 V, 100 Hz, 1 ms) of the left Vim attenuated both static and kinetic components of his tremor. Radiofrequency lesion (70 °C for 60 s and 80 °C for 60 s) was made after an uneventful test stimulation resulting in a markedly improved postural tremor of the proximal and distal arm, while a mild kinetic tremor remained. The effect was unchanged after a six-month observation period (Table 1). Dysarthria and cognitive function (Table 1) did not worsen after the procedure.

3. Conclusions

Intention tremor combined with ataxia leads to severe disability in patients with FXTAS. Symptomatic treatment of this progressive disorder is restricted. Although some case reports documented the improvement of tremor after deep brain stimulation in the ventral intermedius nucleus of the thalamus in FXTAS [7,11–15], in some cases, the effect was only transient [6,16]. Similar result achieved by unilateral stimulation of the posterior subthalamic area (PSA) has been already published [17]. In our case, bilateral stimulation of the Vim and the STN could only provide transient cessation of tremor. Ataxia worsened following these procedures; it could be correlated with the delayed expanse of bilateral MCP signs. Increase of ataxia was considered as a complication of bilateral Vim electrode implantation in earlier studies. In these cases, ataxia was only mild [11,14] or even absent [6] before operation similarly to our case. Contrarily, in some cases, unilateral [12,13,16] and bilateral [7,15] Vim stimulation, and unilateral PSA stimulation [17] did not worsen ataxia further if an already

marked ataxia was documented before implantation. Accordingly, progression of ataxia could coincide with the time of the operation in former cases. Further studies are necessary in this regard. We also hypothesize that increased ataxia may not be a complication of the bilateral Vim electrode implantation; as it is more likely the result of the natural progression of the disease [11].

In our case, thalamotomy on the left side ceased the postural tremor and improved the kinetic tremor and thereby the function of the right hand. Therefore, we suggest unilateral thalamotomy if DBS had no satisfactory effect on tremor.

Thalamotomy can be an option for tremor in case of tolerance to Vim DBS [18]. We only have assumptions why thalamotomy was more effective than bilateral Vim stimulation; it may be that the lesioned tissue after thalamotomy was larger and it might have a different shape compared to that of the stimulated tissue. It may be that the stimulation could not affect tremorogenic locations close to the ventral posterolateral (VPL) nucleus and the internal capsule due to side effects; these locations might contributed later to the reoccurrence of tremor after a transient relief. Nevertheless, the tremorogenic tissue could finally be lesioned with thalamotomy without any side effects. Furthermore, different modes of action of the two procedures should also be considered [18].

Even if FXTAS is much less common (1 in 8000 males over the age of 50 years in the general population [19]) than essential tremor (13.0–50.5 per 1000 people over the age of 60 years [20]), their differential diagnosis can be an important issue during preoperative evaluation [6], and should precipitate the genetic counseling of the family.

During the preoperative evaluation, differential diagnosis of FXTAS is recommended in essential tremor cases associated with mild or moderate cerebellar gait ataxia and global brain atrophy with white matter changes on MRI scans. While obtaining a family history in these cases, questions should be targeted not only regarding tremor, but also mental retardation, autism and behavioral/learning disorders in children or grandchildren; infertility and premature menopause in female relatives; a combination of a movement disorder and psychiatric problems, including dementia, in family members [21].

Conflict of interest

None declared.

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None declared.

Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; Uniform Requirements for manuscripts submitted to Biomedical journals.

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