

NEUROSURGICAL TREATMENT OF TREMOR IN MITOCHONDRIAL ENCEPHALOPATHY

(Brief report)

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ABSTRACT

A 53-year-old woman underwent several ischemic stroke-like episodes and later developed incomplete, bilateral ophthalmoplegia, left vision deterioration and bilateral tremor. The clinical course, laboratory data and muscle histology led to a diagnosis of mitochondrial encephalomyopathy. No other etiology could be identified in the background of her disabling bilateral postural-kinetic tremor. As this tremor did not respond to pharmacological therapy, left thalamotomy and subsequently right thalamic deep brain stimulator (DBS) implantation were performed, which resulted in an excellent clinical outcome. The Fahn-Tolosa-Marin Tremor Rating Scale improved from 110 to 11 points.

This case suggests that the rare tremor caused by mitochondrial encephalopathy may be treated long-term with either thalamotomy or thalamic DBS implantation.

Keywords: deep brain stimulation; mitochondrial encephalopathy, thalamotomy, tremor

INTRODUCTION

Mitochondrial diseases are due to mutations in either nuclear or mitochondrial DNA encoded genes and often appear in various characteristic syndromes, such as progressive external ophthalmoplegia (PEO), myopathy, encephalopathy, lactic acidosis and stroke-like episodes (MELAS)¹. Besides the effects on the muscles, abnormalities of heart, kidney, the eyes and ears are also frequent. The central nervous system is also involved in approximately 20% of the patients, but tremor is rarely present^{2,3}.

The reported case is that of a patient with a biopsy-proven mitochondrial disorder who developed pharmacologically uncontrollable bilateral, postural-kinetic tremor after several stroke-like episodes. She underwent staged thalamotomy and thalamic deep brain stimulator (DBS) implantation, which resulted in a marked tremor reduction.

CASE REPORT

History

The subject of the present case report was born in 1952 and had an unremarkable family history. Before the complaints reported here, she had had deep vein thrombosis and pulmonary embolism; she was, therefore, on oral anticoagulation.

In 2000, she was admitted twice to our Department of Neurology because of stroke-like episodes. Her major complaints were clumsiness and weakness of the right limbs. Physical examination revealed mild right-sided hemihypalgesia and hemiparesis. Despite the fact that the MRI was unremarkable at that time, ischemic stroke was suspected and antiplatelet therapy was commenced.

Four months later, she returned because of the sudden deterioration of the previous symptoms. Neurological examination demonstrated a decreased visual acuity in the left eye, right trigeminal hypalgesia, a worsened, but still moderate right-sided hemiparesis and hemiataxia. At that time, an

asymmetric, postural tremor of both upper limbs and the head was noted. The tremor affected the right side more seriously and displayed affirmation characteristics on the head. The brain MRI revealed a small subcortical lesion in the left frontal region, while the brain stem and cerebella were intact. The results of laboratory tests on the blood and urine, including the levels of thyroid hormones and copper, were normal.

In 2002, a progressive deterioration in the walking ability and frequent falling episodes occurred. The vision in her left eye decreased markedly, its visual field narrowed in all directions. Symmetric partial external ophthalmoplegia developed on both sides, which did not respect the territory of the oculomotor nerve. Her tremor also worsened and at this point affected both the upper and lower extremities. Not only postural, but also moderate resting and serious intentional tremor components could be detected, with amplitude of several centimeters. Moreover, physical exhaustion resulted in increased tremor amplitude. As the lower extremity tremor interfered greatly with her walking and standing, she became partially dependent.

The brain MRI revealed the absence of the previously observed left frontal lesion and the appearance of a few small lesions subcortically in the area of the centrum semiovale. During the standard bicycle ergometric test, serum lactate proved to be elevated. Immune-serological blood and CSF tests were negative, and did not indicate either autoimmune disease or multiple sclerosis. Muscle biopsy and electron-microscopic examinations revealed myopathic changes with ragged red fibers (RRFs), a decreased cytochrome C oxidase activity and a moderate accumulation of bizarre, large mitochondria in the subsarcolemmal region (**Figure in supplement**). Although a mitochondrial DNA mutation could not be proved, her condition was considered to be a biopsy-demonstrated mitochondrial disorder.

Six months later (2002), the tremor had increased to such a level that she was no longer able to walk and take care of herself. She required permanent help in her daily living activities (e.g. eating, drinking, writing) and was constrained to use a wheel-chair. A moderate resting tremor was observed in all her extremities, which increased under postural and kinetic conditions. Surprisingly,

the frequency of tremor at rest and in the postural position (right: 4.5 Hz, left: 4.9 Hz) differed from that in the kinetic-intentional condition (6.5 and 6.7 Hz) (**Video**). In the repeated MRI scans, the previously described lesions in the centrum semiovale had partially resolved. Since the tremor could not be controlled pharmacologically (levodopa: standard levodopa challenge using 250mg, propranolol: up to 120mg daily, clonazepam: up to 6mg daily, alprazolam: up to 3mg daily, biperidenium up to 5mg daily), neurosurgical treatment was decided on.

Operation

At the time of the first operation, DBS implantation was permitted in Hungary only for the treatment of Parkinson's disease (PD) and essential tremor (ET). Moreover, the literature furnished no evidence of the use of DBS implantation for tremors related to mitochondrial disorders. Since thalamotomy was known to be effective for tremor of any type and the symptoms were more prominent on the right side, left thalamotomy was performed in 2002. During the perioperative interval, antithrombotic treatment was stopped and informed consent was obtained for examinations, surgical procedures and video recordings. Both pre- and postoperatively, detailed neurological and neuropsychological examinations, accelerometric analysis (ADXL-105, Analog Devices Inc., USA) and Fahn-Tolosa-Marin Tremor Rating Scale (FTMTRS)⁴ measurements were performed. The ventral intermedial nucleus (Vim) was calculated from MRI scans 7.3 mm anterior to the posterior commissure, 12.5 mm lateral to the midline and at the level of the intercommissural plane. Semi-microrecordings of the target revealed increased unit activity for active and passive joint movements of the contralateral limbs. After stimulation of the target (100 Hz, 1-3 V), marked tremor suppression was achieved. Subsequently, two permanent lesions were created (at the level of the target, and 3 mm higher along the trajectory). Postoperatively, the tremor in the contralateral extremities disappeared. The brain MRI confirmed the extents and locations of the lesions.

Since the disabling right side tremor had disappeared, thalamic DBS implantation was carried out 7 months later (in 2003) on the right side. The proper placement of the electrode (Medtronic 3387)

was achieved in the same way by using MRI guidance, semi-microelectrode recording and macrostimulation (**Figure 1**). After a successful test period, an impulse generator (Medtronic Soletra, Medtronic, Minneapolis, MN) was implanted.

Postoperative course

After the thalamotomy, the patient was able to drink and eat by using her right hand and to take a short walk with support. Subsequent to the second surgery, she became self-sufficient. The disappearance of bilateral tremor allowed her to use both hands and write. She also got a partial job again. The FTMTRS improved from 69-19-22 points to 6-3-2 points with the following stimulating parameters: 0-,C+, 130Hz, 60 μ s, 1.4V. (**Figure 2**) There was no evidence of postoperative morbidity; her cognition and swallowing ability were unchanged.

During the 3-year postoperative follow-up, the patient's condition has remained stable, although the left-side blurred vision and visual field narrowing are still present. Physical exhaustion can still provoke a slight, clinically irrelevant tremor. Mild proximal tetraparesis and incipient cardiomyopathy could also be demonstrated. With a regimen of combined oral anticoagulation (acenocumarol) and antiplatelet treatment (acetylsalicylic acid), no stroke-like event has occurred since 2002.

DISCUSSION

Mitochondrial encephalomyopathies present variable clinical pictures. Besides the well-known clinical syndromes, mitochondrial degeneration can play an important role in the pathogenesis of many neurodegenerative diseases⁵, such as movement disorders⁶. However, the presentation of tremor as a main symptom is quite rare and has seldom been reported in association with MELAS⁷.

Although the genetic background has not been proved in the case reported here, the clinical presentation, laboratory data and muscle histology are sufficient for the diagnosis of mitochondrial

disorder to be made^{1,3}. The clinical picture (ophthalmoplegia plus syndrome with RRFs and an elevated lactate level) suggested the presence of a mitochondrial disorder, presumably a PEO-MELAS overlap syndrome.

Other than this mitochondrial disorder, no etiology could be revealed for the tremor. PD could not be diagnosed because of the ineffective response to a levodopa-challenge and the absence of other Parkinsonian signs during the follow-up of almost 5 years. ET was not likely either, since the tremor was quite asymmetric affecting all four extremities with marked intentional and moderate resting components. Physical exhaustion resulted in a worsened postural-kinetic tremor, and neither alcohol nor propranolol (up to 120 mg/day) improved the tremor. Since no lesion could be detected in either the brain stem or the cerebella, the symptoms could not be identified as Holmes' tremor. A vascular origin of the tremor was likewise unlikely, since neither native nor gadolinium-enhanced MRI images revealed any abnormalities besides transient subcortical lesions in the left frontal lobe. Moreover, the stroke-like events clinically affected only the left hemisphere, while the tremor was bilateral. Clinical and neuropsychological tests were used to exclude psychogenic tremor. The frequency of tremor in the DBS turned-off state and the preoperative state were equal, even when the patient's attention was distracted through the use of various mental and physical exercises. A paraneoplastic, polyneuropathic or infectious origin could similarly not be presumed.

The pharmacologically uncontrollable, handicapping tremor necessitated surgery. The lack of experience in the treatment of mitochondrial tremor led us to perform thalamotomy first; its success then encouraged us to implant a DBS contralaterally. The staged thalamotomy and thalamic DBS implantation achieved the long-term elimination of the disabling tremor; the FTMTRS improved from 110 to 11 points. As the handicapping tremor vanished and no postoperative side-effect appeared, the patient's quality of life improved: she can now take full care of herself and walk again. Her writing too has normalized.

This case suggests that the rare tremor caused by a mitochondrial encephalopathy may be treated long-term with either thalamotomy or thalamic DBS implantation.

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LEGENDS

Video

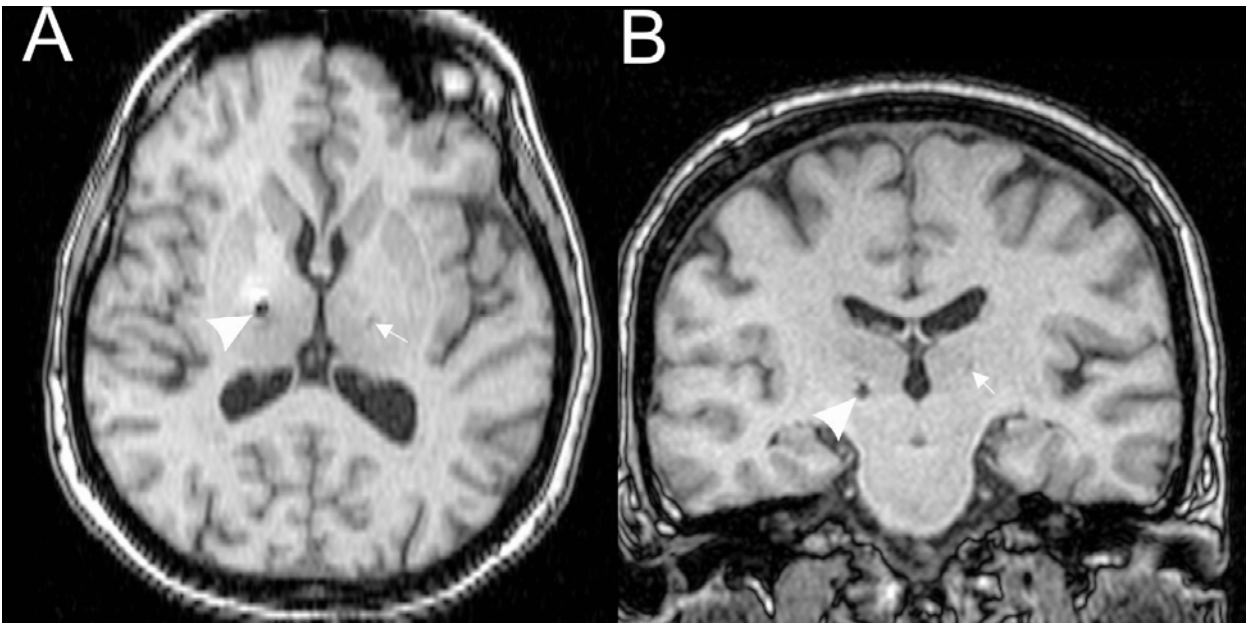
Part 1. Before the left thalamotomy.

Part 2. Two days before right thalamic deep brain stimulator implantation.

Part 3. Three years after the implantation, DBS turned off

Part 4. Three years after the implantation, DBS turned on

Figure 1



Axial (A) and coronal (B) postoperative T1-weighted MRI of the patient. The ablative tissue damage of the left Vim (white arrow) and the stimulating electrode of the right Vim (white triangle) can be identified.

Figure 2

Signature samples, and line and Archimedes spiral drawings by the patient (right hand). (A) Before the operation in 2002. Since the patient was unable to write, her signature could not be presented. (B) Two months after the left thalamotomy. (C) Samples taken when the right thalamic DBS was turned off or (D) turned on.

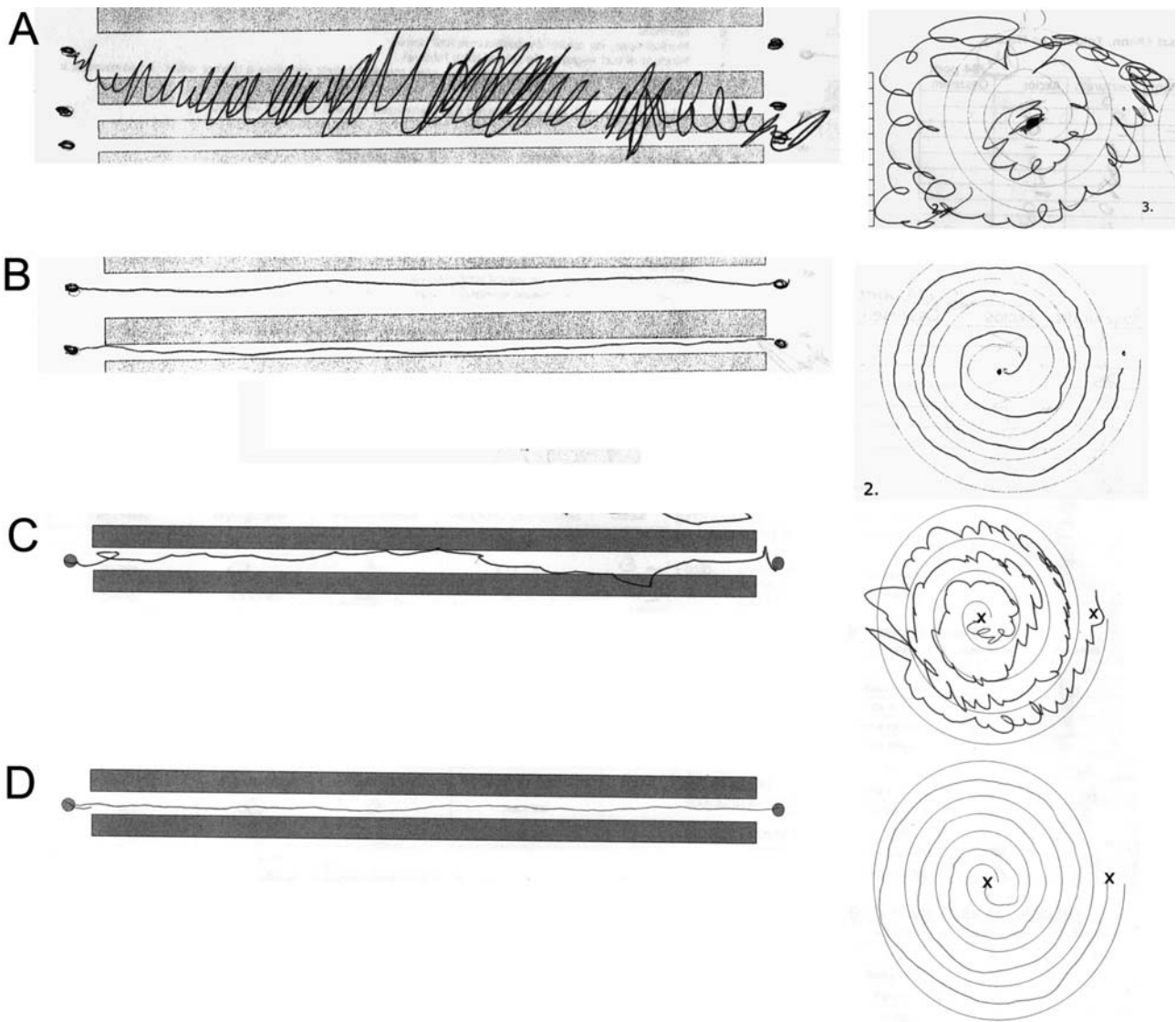
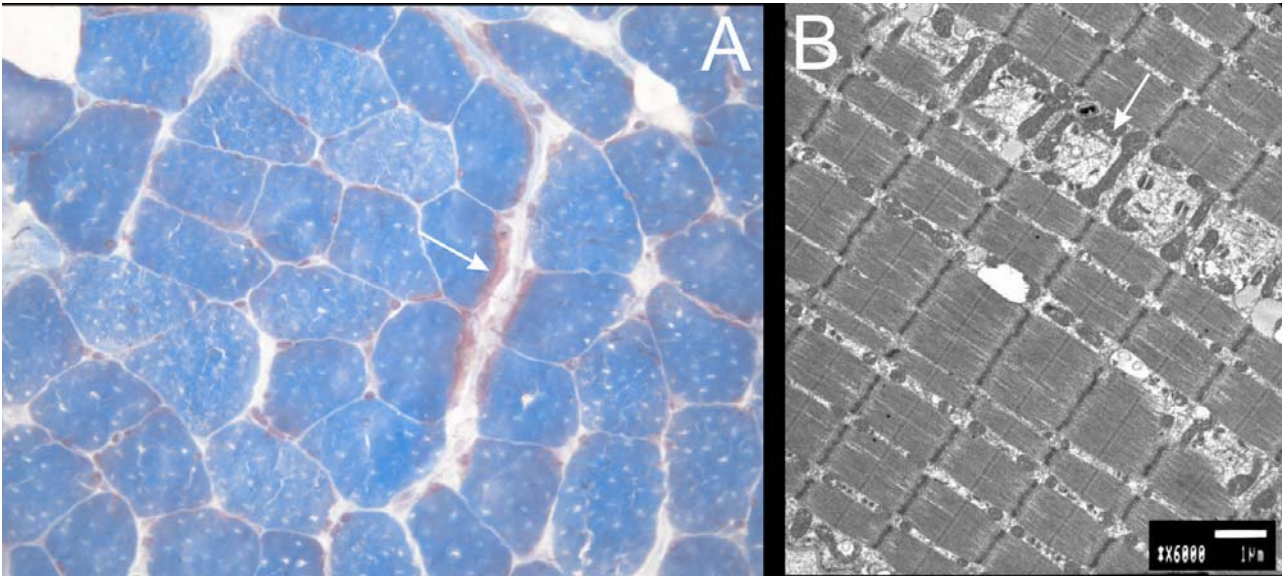


Figure in Supplement



(A) Microscopic picture of the deltoid muscle using modified Gomori trichrome staining. Ragged red fibers (RRFs) are demonstrated by a red color in the periphery of the fibers. (Magnification: 40x, white arrow.) (B) Electron microscopic findings of the biopsy of the same muscle. Focal lesion of myofibrils with accumulation of mitochondria and glycogen can be observed. (Magnification: 6000x, white arrow.)