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Deep brain stimulation in Bassen-Kornzweig syndrome: Still effective after 22 years

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ABSTRACT

Introduction: Bassen-Kornzweig syndrome or abetalipoproteinemia is a rare autosomal recessive disorder characterized by a malabsorption of dietary fat and fat-soluble vitamins. This deficiency can lead to a variety of symptoms, including hematological (acanthocytosis, bleeding tendency), neurological (tremor, spinocerebellar ataxia), neuromuscular (myopathy), ophthalmological symptoms (retinitis pigmentosa). The thalamic ventral intermediate nucleus (VIM) is a well-established target for deep brain stimulation (DBS) in the treatment of refractory tremor.

Research question: We evaluated the clinical long-term follow-up (22 years) after VIM-DBS for refractory tremor in abetalipoproteinemia. We also evaluated the adjustments of stimulation settings and medication balance after DBS procedure.

Material and methods: We report a 53-year-old male who suffers from abetalipoproteinemia since the age of 17. He underwent bilateral VIM-DBS to treat his disabling refractory intentional tremor at the age of 31. He still has a very good response to his tremor with limited stimulation adaptations over 22 years. For more than two decades follow-up, the treatment significantly improved his ADL functions and therefore also the QoL.

Discussion and conclusion: The VIM target for DBS in the treatment of refractory tremor has been extensively reported in the literature. Thalamic VIM-DBS is a safe and effective treatment for a severe, refractory tremor as a neurological symptom caused by abetalipoproteinemia. It also highlights the importance of a multidisciplinary follow-up, to adjust and optimize the stimulation/medication balance after VIM-DBS surgery.

1. Introduction

Abetalipoproteinemia was first reported by Bassen and Kornzweig in 1950 in a case associated with retinitis pigmentosa, acanthocytes (irregular-shaped erythrocytes) and ataxia (Bassen and Kornzweig, 1950). In 1960 Salt et al. were the first to describe the association of this syndrome with a deficiency of apolipoprotein B-containing lipoproteins, such as very-low-density lipoproteins (VLDL), low-density lipoproteins (LDL) and chylomicrons (Salt et al., 1960). The condition is caused by biallelic mutations in the microsomal triglyceride transfer protein gene (MTTP gene) and is inherited in an autosomal recessive manner (Takahashi et al., 2021).

Intracellularly, MTTP is found in the endoplasmatic reticulum (ER) of hepatocytes and gastrointestinal epithelial cells (Takahashi et al., 2021). This disorder leads to malabsorption, lipid deficiency, and subsequently to a chronic deficiency of dietary fat and fat-soluble vitamins (i.e. A, D, E, K). ApoB-containing lipoproteins are required for efficient absorption and peripheral transport of these fat-soluble vitamins (Takahashi et al., 2021).

Vitamin E deficiency is typically associated with demyelination of spinocerebellar axons, which leads to neurological symptoms (ataxia, tremor, dysmetria) (Takahashi et al., 2021). Neural degeneration, peripheral neuropathy and myositis will lead to neuromuscular symptoms (muscle weakness) due to pigment deposition secondary to loss of antioxidant effect because of the vitamin E deficiency (Takahashi et al., 2021). Abetalipoproteinemia has an incidence less than 1 in a 1.000.000 and a male predominance (Takahashi et al., 2021).

Systemic symptoms arise starting from the first decade and if left

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untreated, this pathology can be lethal by the 3rd decade. The standard treatment consists of high dose vitamin supplementation and prevent deficiency of essential fatty acids or other lipids/nutrients. However, this treatment by supplementation cannot fully prevent or restore existent impairments (Takahashi et al., 2021). More studies are needed to reveal the pathogenesis and potential targets of treatment (gene therapy, …).

2. Case report

As previously published in 1988 by Tack et al. we describe the further follow-up and treatment of a disabling refractory intention tremor and ataxia (Tack, Bourgeois, Devos, Demeester). This 17-year-old patient presented at the time to the neurological outpatient clinic with a disabling intention tremor and ataxia. A clinical work-up confirmed an ApoB deficiency in the blood serum, acanthocytosis and a vitamin E deficiency. Electromyography (EMG) findings showed an axonal neuropathy and somatosensory evoked potentials demonstrated dorsal column dysfunction. His sister also presented with the syndrome (fat deficiency, acanthocytosis) but had no neurological symptoms. Despite Vitamin E suppletion, and treatment with propranolol (up to 160mg/day) and primidone (up to 1500mg/day), the patient had a persistent disabling tremor. In 2000, after a full multidisciplinary work-up (neuropsychological-, neurology-, and neurosurgery counseling) deep brain stimulation was proposed. The patient's file, its proposal for bilateral VIM-DBS, was approved by the national Peer-Review Commission at that time.

Preoperatively, the neurological examination showed a severe head tremor, voice tremor and bilateral tremor of the upper extremities with left-sided predominance and aggravation during action (shown in Fig. 1, Video 1). Furthermore, there was an ataxic and wide-based gait with posterior column deficits (disturbed deep sensation with reduced distal vibration and joint positioning sense). Motor function was normal, but deep tendon reflexes were absent. Finger-to-nose testing as well as heel-to-shin testing showed a clear dysmetria and intentional tremor, most pronounced at the left-hand side (shown in Video 1). Romberg's sign was positive with loss of balance. A brain MRI (1.5T) showed no abnormalities. Best medical treatment did not suppress the tremor in a sufficient way. At this time the patient had a score of 95 on the Fahn-Tolosa-Marin (FTM) scale (Fahn et al., 1988). There was severe impairment of his activities of daily living (ADL), which resulted in a significant decrease in quality of life (QoL).

Supplementary video related to this article can be found at https://doi.org/10.1016/j.bas.2023.101762

2.1. Surgical procedure

The ventral intermediate nucleus (VIM) thalamic target for DBS in the treatment of refractory tremor has been extensively reported in the literature (Mammis et al., 2012; Flora et al., 2010; Benabid et al., 1991). In 2000, aged 31, a bilateral VIM-DBS procedure was performed on the patient in awake conditions with microelectrode recordings (MER), including bilateral implantation of an Itrell-III pulse generator (Medtronic ©, MN, USA). In 2000, the surgery was performed after determination of the stereotactic coordinates of the thalamic VIM by indirect targeting using contrast radiographs (iodoventriculography) and stereotactic atlases. The stereotactic coordinates were X = −14.15, Y = −5.69, Z = 0.45 for the left VIM nucleus, and X = 13.84, Y = −6.41, Z = 0.44 for the right VIM nucleus (with X = Lat, Y = A-P, Z = Vert). Decision on final lead positioning was assessed perioperatively by MER guidance and through macrostimulation with bilateral tremor arrest (Fig. 2).

2.2. Postoperative period and follow-up

On the first postoperative day the stimulation was initiated according to the same stimulation parameters in the DBS treatment for essential tremor, i.e. multiple contacts with intermediate high voltage (shown in Table 1). During follow-up at the outpatient clinic stimulation settings were slightly changed, but still provide excellent control of his disabling symptoms (shown in Table 1). At 1,5 year postoperative a score of 20 on the FTM scale was assessed by the treating neurologist, which corresponds with a reduction in tremor score of 78,9%. The patient confirmed an important impact on QoL and reports that he would repeat the surgery at any time. The patient is able to function in a complete independent way. He drives a car, looks after his own affairs and takes care of his son. He was able to do sports and drove a motorcycle for years. The patient does have an ataxic gait as part of the pathology process. Furthermore, the treatment with propranolol was gradually reduced and completely stopped after 1 year. The patient reported no stimulation-related side effects. During off-stimulation settings there is an immediate return to the severity of symptoms (shown in Video 1). There were 3 pulse generator replacement procedures for end-of-life during these 22 years (first an Itrel-III ipg, whereas the last 2 were changed to a Medtronic Activa SC pulse generator).

Until now the patient, aged 53, has an excellent durable response for his tremor with limited stimulation adaptations for 22 years (shown in Video 1).

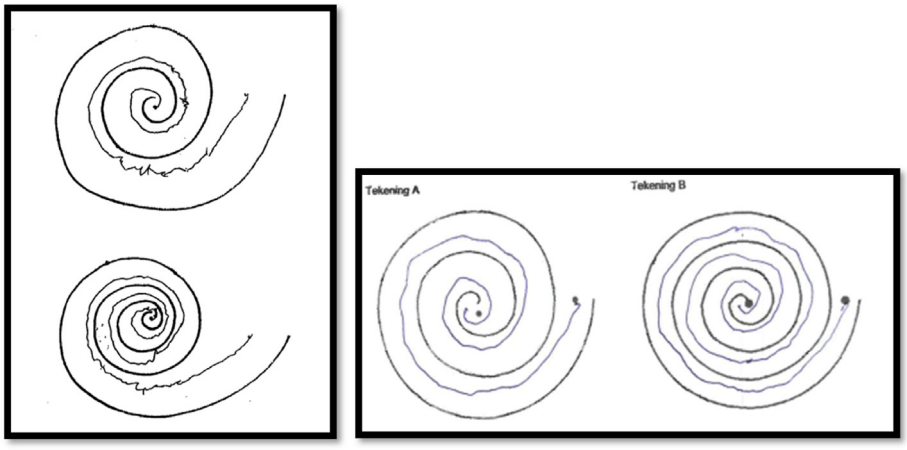

Fig. 1. Spiral drawings pre- (left) and post VIM-DBS (right).

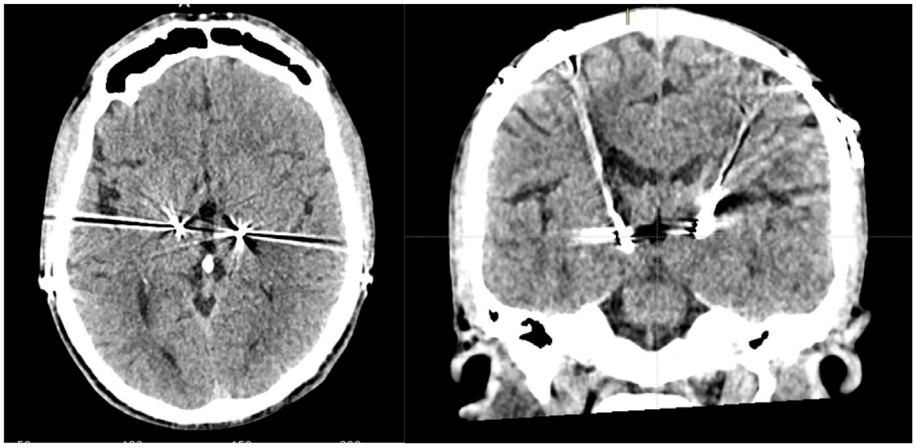

Fig. 2. Postoperative brain CT (axial and coronal section) with final lead positioning.

Table 1
Postoperative day 1 and current DBS stimulation settings.

	Postoperative settings		Current settings	
	Left	Right	Left	Right
Setting	Monopolar	Bipolar	Monopolar	Bipolar
Contacts	1-	2- 1–0 + 3+	1-	0- 1+
Current (V)	3.2	3.6	3.8	4.0
Pulse Width (μs)	60	240	60	60
Frequency (Hz)	130	130	130	130

3. Discussion

The VIM target for DBS in the treatment of refractory tremor has been extensively reported in the literature (Mammis et al., 2012; Flora et al., 2010; Benabid et al., 1991). To our knowledge, there is only one case report about abetalipoproteinemia treated with VIM-DBS with an 8-month follow-up, published in 2012 by Mammis et al. (2012). Nevertheless, this is the first long-term case with more than two decades follow-up after DBS treatment for tremor in abetalipoproteinemia. Our patient presented with similar neurological findings and relieve of intention tremor after thalamic DBS treatment. Stimulation settings were initiated according to the same stimulation parameters in the DBS treatment for essential tremor. This confirms a durable response, which can be achieved by DBS with limited stimulation alterations. The treatment significantly improved the ADL functions and therefore his QoL. Due to limited number of cases, clinical studies are probably difficult to set up, which proves the merit of this report. In conclusion, based on these 2 case reports, thalamic VIM-DBS can be a safe and effective treatment for a severe, refractory tremor as a neurological symptom caused by abetalipoproteinemia. It also highlights the importance of a multidisciplinary follow-up, to adjust and optimize the stimulation/medication balance after VIM-DBS surgery.

Statement of ethics

Ethical approval is not required for this study in accordance with local guidelines (local Ethics committee). The authors confirm that the approval of an institutional review board was not required for this work. Informed consent from the patient was obtained for the inclusion of clinical and video data in scientific publications. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

Consent to publish statement

Written informed consent was obtained from the patient for publication of this case report and any accompanying images/videos.

Conflict of interest

The authors have no conflicts of interest to declare.

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Author contributions

1. Research project: A. Conception, B. Organization, C. Execution.
2. Manuscript preparation: A. Writing of the first draft, B. Review and critique.

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D.V.: 1A, 2B.
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J.V.L.: 1A, 2B.
P.T.: 1A, 2B.
S.D.F.: 1A, 2B.
O.V.D.: 1A, 1B, 1C, 2B.

Data availability statement

The data is shared directly in this case report (shown in Table 1). No further data availability is applicable.

Structured review

The merit of this report is the unique and rare presentation of the pathology, as well as its long-term follow-up. To our knowledge, there is only one case report about abetalipoproteinemia treated with VIM-DBS with an 8-month follow-up, published in 2012 by Mammis et al. (2012). Nevertheless, this is the first long-term case with more than two decades follow-up after DBS treatment for tremor in abetalipoproteinemia. The VIM target for DBS in the treatment of refractory tremor has been extensively reported in the literature (Mammis et al., 2012; Flora et al., 2010; Benabid et al., 1991). Our patient presented with similar neurological findings and relieve of intention tremor after thalamic DBS

treatment. Stimulation settings were initiated according to the same stimulation parameters in the DBS treatment for essential tremor. This confirms a durable response, which can be achieved by DBS with limited stimulation alterations. The treatment significantly improved the ADL functions and therefore his QoL.Due to limited number of cases, clinical studies are probably difficult to set up, which proves the merit of this report.In conclusion, b ased on these 2 case reports, thalamic VIM-DBS can be a safe and effective treatment for a severe, refractory tremor as a neurological symptom caused by abetalipoproteinemia. It also highlights the importance of a multidisciplinary follow-up, to adjust and optimize the stimulation/medication balance after VIM-DBS surgery.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bas.2023.101762.

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