Nucleus Ventralis Oralis Deep Brain Stimulation in Postanoxic Dystonia

Deep brain stimulation (DBS) of the thalamus, zona incerta, subthalamic nucleus, and pallidum has been used for the treatment of dystonia. Reports on thalamic DBS for dystonia were published as early as 1977. Thalamic stimulation may increase the dystonic symptoms, especially when the Vim nucleus is the target of the stimulation. However, targeting the thalamus was abandoned because several publications suggested that the globus pallidus internus (GPi) is a better choice for stereotaxy in patients with dystonia. An interesting issue is what happens in case of a structural lesion in the GPi? Structural lesions of the GPi are not considered an absolute contraindication for the DBS electrode placement; however, thalamic nuclei could be an alternative target. We describe the case of a female hemidystonic patient with bilateral structural abnormalities of the GPi, due to postanoxic damage, who was treated successfully with DBS of ventralis oralis anterior (Voa) nucleus.

A 37-year-old woman presented with a right side hemidystonia. There was no family history of dystonic conditions. The pregnancy was normal and the delivery was spontaneous at term, but complicated by prolonged labor and insufficient blood supply from the umbilical artery. The perinatal adaptation and motor development were normal. At the age of 3, she started to develop a right lower limb dystonia that led to walking impairment. Hemidystonia developed progressively, and within years walking became impossible. The patient was wheelchair bound and required assistance in dressing and hygiene, for the last 9 years (Video 1).

The neurological examination revealed a dystonic posture of the right side of her body, with the lower limb more severely affected. The right hand was kept periodically in a hyper flexed claw-like fashion, and the foot exhibited permanent dorsiflexion and extortion. She had normal power of all muscle groups on the affected right side. The tendon reflexes were symmetrical, and no pathological reflexes were present. The neurological examination of the left side of the body was normal. Her vital signs and general physical examination were unremarkable.

The laboratory tests, including cooper level and ceruloplasmin, were within normal limits. Preoperative magnetic resonance imaging (MRI) showed bilateral postanoxic lesions in the globus pallidus (Fig. 1). The GPi was totally damaged bilaterally. Several medications (L-dopa, tizarnidine, baclofen, tetrabenazine) had been unsuccessful in improving the patient’s symptoms.

Dystonia was videotaped and assessed using the Burke, Fahn, Marsden Dystonia rating scale (BFMDRS) preoperatively and postoperatively at monthly intervals for the first year and at 3-month intervals thereafter.

The patient underwent a stereotactic implantation of an electrode (model 3387, Medtronic, Minneapolis, MN) in the left nucleus Voa. The correct position of the electrode was evaluated postoperatively by MRI scan and the Frame-Link software. The final electrode position was at the base of the Voa nucleus close to the Voa/Vop border. The active contacts of the electrode were the contacts 0 and 1 inside the Voa nucleus (Fig. 2). The initial postoperative stimulation parameters were 2.5 volts, 185 Hz, 250 µsec, with monopolar stimulation on contacts 0 and 1, respectively. Further adjustments of the stimulation parameters were performed during the follow-up period. The amplitude ranged between 2.5 and 3.6 volts, pulse width ranged between 250 and 450 µsec while the frequency was kept stable at 185 Hz. The functional status and the daily life activities were gradually improved after 6 months postoperatively, having the best results on the 12 month follow-up assessment. The good outcome lasts up today (28 months postoperatively). The BFMD dystonia scale improved by 76% in total (disability scale improved from 13/30 to 6/30 and movement scale improved from 20/120 to 2/120). The patient is now able to walk again after 9 years use of a wheelchair with the stimulator always on function (Video 2). She still suffers intermittently, under stress conditions, from minor jerky movements of the right hand, but the movements of the right upper limb are less prominent compared with the preoperative condition.

Additional Supporting Information may be found in the online version of this article.

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Structural brain lesions are common in secondary dystonia. It is possible that lesions of the GPi may result in loss of inhibitory pallidal projections to the thalamus and thus, provoke the hyperkinetic condition. The main stimuli of the pallidum are via the Voa and the centromedian-parafascicular nucleus. Targeting the Voa nucleus for DBS could act directly on the last distal link in the retroactive feedback system to the motor cortex of the GPi. To our knowledge, this is the only case with follow-up up to 28 months. A similar report, with only a 4-month follow-up, has been published by Ghika et al.

A patient with generalized postanoxic dystonia was treated initially with DBS of GPi and then with DBS of Voa. The patient showed a dramatic improvement after the Voa DBS procedure. The placement of the electrode in the Voa nucleus was confirmed by autopsy. In our case, the correct position of the electrodes in the Voa nucleus was confirmed by a postoperative MRI, the Frame-Link software and was further validated by image registration and fusion software.

Our report concurs with that of Ghika, that the Voa nucleus may well be an effective alternative when there is a damaged GPi or in cases of GPi DBS failure. In addition to the report of Ghika, the follow-up of our patient, over a period of 28 months, revealed that the Voa nucleus offers, not only temporary, but satisfactory long-term results.

Nevertheless, since our case reflects just the experience on one patient, further studies are deemed necessary to achieve a more informed perceptive as to who would benefit from thalamic or GPi DBS.

Legends to the Video

Video 1. Preoperative video showing the right leg in dorsiflexion and the patient unable to walk.

Video 2. Postoperative video with the patient walking independently.

References

A prominent role for mitochondrial dysfunction in the pathogenesis of Parkinson’s disease (PD) has been suspected ever since the description of parkinsonism caused by the complex 1 inhibitor 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). The connection with mitochondrial dysfunction was further strengthened by linkage of recessive PD to mutations in PINK1, a gene encoding a mitochondrial kinase. In addition, mutations in POLG, the gene encoding polymerase γ, the only mitochondrial DNA (mtDNA) polymerase, can cause parkinsonism, usually in combination with progressive external ophthalmoplegia (PEO). We report a patient with neurodegenerative parkinsonism, PEO, and a mutation in PEO1, the gene for the mtDNA helicase Twinkle, a protein that closely collaborates with polymerase γ in the replication and maintenance of mtDNA.

The proband (subject III-1), a 51-year-old Flemish right-handed professional cook, presented in 2007 with a 1-year history of slowly progressive rest tremor of the right hand and, to a lesser extent, the right leg. Emotional stress tended to aggravate the tremor. His handwriting had become smaller and he reported slight difficulty buttoning clothes with the right hand. He had experienced reduced sense of smell since the age of 30 years. Interestingly, he had noticed slowly progressive eyelid drooping without diplopia since the age of 30 years. He had undergone corrective eyelid surgery twice (around 1997 and 2002), with only temporary improvement. His medical history was otherwise unremarkable and he took no medication.

The patient had no children or siblings. According to the patient, his mother (subject II-1), maternal aunt (subject II-2), and grandmother (subject I-1) had droopy eyelids, but no tremor or Parkinsonism (Fig. 1A).

Clinical examination of III-1 in 2007 (see video) revealed mild hypokinesia, intermittent rest tremor, and cogwheel rigidity of the right arm. Gait was normal except for reduced right arm swing. Cognition, speech, muscle strength, tendon reflexes, plantar reflexes, coordination, and sensation were normal. There was no muscle atrophy.

The patient’s parkinsonism was also caused by the PEO1 mutation in Twinkle. A deltoid muscle biopsy was performed in 1997; light microscopy including hematoxylin/eosin, Gomori trichrome, succinate dehydrogenase, and cytochrome c oxidase staining was normal. Sequencing of the exons of the POLG gene was normal. Sequencing of the PEO1 gene showed a heterozygous mutation predicting a R334Q substitution. Sequencing of the exons of the PINK1 gene was normal. Sequencing of the POLG gene was normal. Sequencing of the PEO1 gene showed a heterozygous mutation predicting a R334Q substitution in Twinkle.

Dopaminergic medication was proposed, but the patient preferred to wait because functional impairment was only mild. We provide the first description of a patient with PEO, parkinsonism, a Twinkle R334Q substitution and a normal POLG sequence. PEO1 mutations are an established cause of autosomal dominant PEO. It appears highly likely that this patient’s parkinsonism was also caused by the PEO1 mutation, for two reasons. First, a similar clinical syndrome of PEO with subsequent development of parkinsonism has been clearly associated with POLG mutations. Given the intricate functional interplay between polymerase γ and Twinkle in the maintenance of mtDNA, extensive phenotypic overlap between PEO1 and POLG mutations would be biologically plausible. Second, Baloh et al. recently reported a family...