Successful Treatment of Disabling Paroxysmal Nonkinesigenic Dyskinesia with Deep Brain Stimulation of the Globus Pallidus Internus

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Paroxysmal nonkinesigenic dyskinesia (PNKD) causes episodes of uni- or bilateral involuntary movements, which may include dystonia, chorea, ballism or a combination of these (1). The disorder is classified as part of the paroxysmal dyskinesias and is rare, occurring at an estimated incidence of 1 in 1 million people (2) - significantly less frequent than the paroxysmal kinesigenic dyskinesias. The abnormal movements can be triggered by emotional stress, caffeine or alcohol consumption (3) or can occur spontaneously. Although mostly sporadic and idiopathic, familial and secondary causes have been described (4). Dyskinetic episodes generally last several minutes and can occur several times a week. Genetic studies in familial forms of PNKD have shown at least two mutations in the myofibrillogenesis regulator 1 (MR1) gene where alanine is replaced with valine at either position 7 or 9 (5). These mutations alter the structure of the PNKD protein, probably causing a functional defect, but the precise mechanism in the pathogenesis of familial PKND remains uncertain. Mutations in the MR-1 gene have not yet been found in sporadic cases (6) and some families with no MR-1 mutations have also been seen (7).

Treatment of PNKD is usually difficult and most patients do not respond well to any pharmacological treatment regimen. Familial cases have been shown to respond to clonazepam and other benzodiazepines (2) and some case studies of successful treatment with levetiracetam were reported (8). Deep Brain Stimulation (DBS) of the internal segment of the Globus Pallidus is now an accepted treatment modality in primary dystonia, myoclonic dystonia and some specific forms of secondary dystonia (9, 10). Three case studies of successful treatment of PNKD with DBS were found in the literature: two publications describe stimulation of the internal part of the globus pallidus (11, 12) and in one, DBS of the thalamus was performed (13).

In this report we describe two patients with unilateral PNKD who were treated successfully with DBS of the internal segment of the globus pallidus (GPi) with six months follow up.

Patients and Methods

Patient 1 was a 34 year old male with a 12 year history of intermittent dystonic posturing of the right arm and leg (fig1). Initially he noticed abnormal posturing with writing and writer's cramp was considered as possible cause. In addition, an ulnar nerve entrapment was diagnosed and surgically treated. After this procedure, the patient noticed the development

Fig1: Stills from video indicating onset of paroxysmal hemi-dystonia in the right foot (a), involvement of the hand (b) and the whole right side of the body (c,d,e). Note the normal hand (f and h) and foot (g) position after spotanenous recovery.

a	B	c	d	e	f	g	h

Fig 1
Stills from video indicating onset of paroxysmal hemi-dystonia in the right foot (a), involvement of the hand (b) and the whole right side of the body (c,d,e). Note the normal hand (f and h) and foot (g) position after spotanenous recovery.
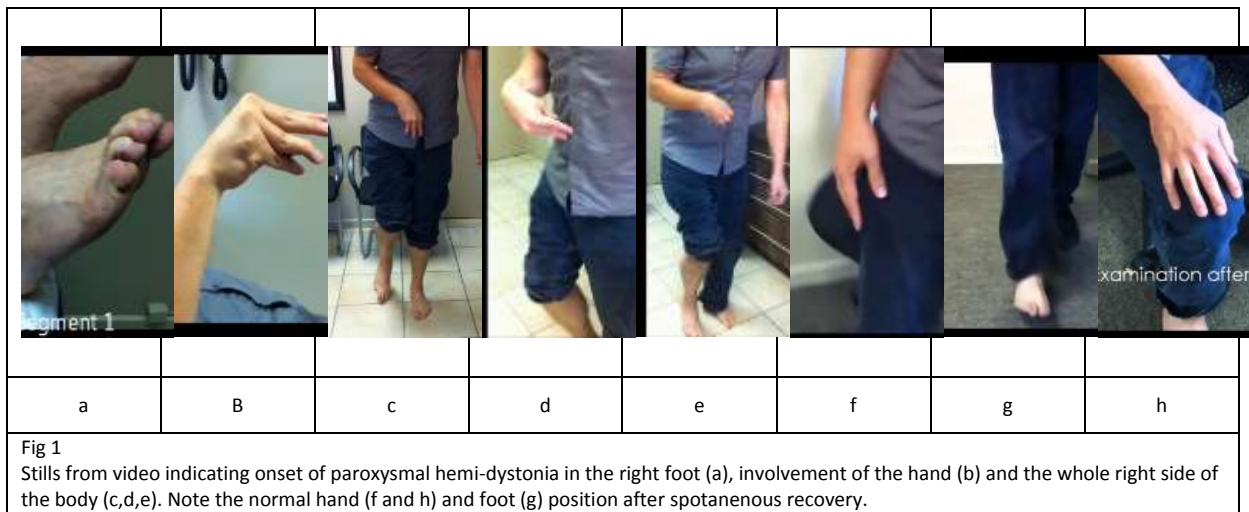
of abnormal and involuntary spasms of the right arm and eventually also of the right leg. The episodes usually lasted less than 10 minutes, but some episodes lasting hours and one episode lasting days were also documented. These episodes occurred several times a week, but sometimes weeks would pass without an episode. Episodes could be triggered by emotional stress but not by exercise, caffeine intake or movement. Most episodes were spontaneous. After the onset of the dystonic movements, treatment for a depressive mood disorder was started with escitalopram. During attacks, dystonic posturing was found affecting the right leg, arm and face (video: segment 1). Gait was severely involved and the arm was not functional during an episode (Video: segment 2). Examination between episodes was normal (video: segment 3). Treatment with several drugs, including clonazepam, valproate, carbamazepine, biperidin and tetrabenazine, was ineffective. Investigations including electro-encephalogram and MRI brain were normal.

Patient 2 was a 24 year old male with a 5 year history of episodic painful spasms of the left side of the face, neck and arm. The episodes occurred three to four times a week and generally lasted for several minutes. Two episodes lasted longer than 12 hours and were only terminated with intravenous midazolam. Episodes were mostly spontaneous but could be triggered by emotional stress and caffeine intake. Exercise did not induce episodes. The movements were mostly sudden, dystonic with laterocollis posturing of the neck and anterior displacement of his left shoulder and a combination of chorea and dystonic movements of the left arm.

In adolescence, the patient had been diagnosed with Ehlers-Danlos Syndrome (type VII-D) and had had bilateral arthrodesis of his shoulder joints to prevent repeated dislocations. He was treated for a depressive mood disorder with venlafaxine for the last four years, but there was no history of neuroleptic drug use. As a teenager, he experimented with recreational drugs (cannabis and cocaine). The episodic movements were mostly dystonic with laterocollis and anterior displacement of the left shoulder and dystonic tremor of the left arm. Gait was not affected during episodes. Electro-encephalogram and MRI of the brain were normal. Standard investigations to exclude other secondary causes for dystonia were negative. Treatment with botulinum toxin type A, biperidin, baclofen, valproate, carbamazepine, clonazepam and tetrabenazine was not effective in managing the frequency of the episodes. The intensity of the episodes was mildly reduced with clonazepam.

Deep Brain Stimulation surgery of the Globus Pallidus internus was performed in a one stage procedure in both patients. Micro-electrode recordings and standard macro-electrode stimulation were used to assist with optimal lead placement (3389, Medtronic) (14, 15). Post-operative CT/MRI merge confirmed placement of the leads in the postero-ventral GPi. Implantation of the Implantable Pulse Generator (IPG) (Activa PC, Medtronic) was then performed as part of the same procedure.

Non-stereotactic imaging was performed for both patients under general anaesthesia. Stereotactic planning software was used (Framelink version 5.2.4, Medtronic Inc, Minneapolis, MN, USA)(16). Neuronavigation compatible sequences were acquired which were contiguous. T1 weighted 3D isotropic voxel (1 mm) sequences were acquired with and without double dose contrast. T2 sequences (2 mm) were acquired; coronal sequences were centred on the mid-commissural point (MCP). T2 axial sequences were inverted to enhance the visualization of the lentiform nucleus and the posterior limb of the internal capsule.

Direct targeting was used to identify the posterior limb of the internal capsule, internal medullary lamina (separating internal and external pallidum) and optic (17). At the intercommissural plane level the long axis of the GPi was drawn and this was the most medial margin of the GPi. This long axis of the GPi was parallel to the optic track, 4-6 mm inferior to the intercommissural plane. The long axis was divided into four quadrants. The centre of the third quadrant from anterior was chosen as the target. This was along a line drawn perpendicular to the long axis of the GPi and at least 2 mm away from the posterior limb of the internal capsule. Additionally, it was verified that the target was medial to the internal medullary lamina. This gave us the lateral and anterior-posterior functional coordinates (with respect to MCP). The vertical functional coordinate was calculated by scrolling inferiorly in 1

mm steps from the intercommissural plane to the slice on which the optic track was first visualized. Once the optic track was identified, we selected a vertical coordinate superior to this slice and just above the ambient cistern. A safe trajectory was planned. The functional plan was fused with the stereotactic post-contrast CT to transform functional coordinates to stereotactic coordinates. The Luminant universal localiser (Integralife Sciences Corporation, Burlington, Massachusetts, USA) was used in both patients.

Two channel simultaneous recording was performed in the central and anterior trajectory of the Ben's gun in the "+" orientation (Stardrive, FHC Inc, Bowdoin, Maine, USA). CRW-Precision stereotactic frame (Integralife Sciences Corporation, Burlington, Massachusetts, USA) with a phantom was used to perform the procedures. MER and MES (Leadpoint 5+3, Medtronic Inc, Minneapolis, USA) were used to physiologically confirm the anatomically determined target. It was ascertained by verifying on the stereotactic planning workstation that the medial and posterior trajectory would be very close to the posterior limb of the internal capsule and the lateral trajectory would be in the globus pallidus externa or the internal medullary lamina. In the + configuration of the Ben's gun (Microdrive) each of the trajectories are offset by 2 mm centre to centre. MER was performed from 10 mm above the calculated target in steps of 0.5 mm. The pattern of MER was classified as silent (depicting laminae, fluid filled spaces/peri-vascular spaces) or active (depicting GPe or GPi). In both patients the differences between GPe and GPi were not apparent, though this could be inferred with respect to reviewing the complete trace retrospectively. In all instances, the target was taken as the inferior-most limit and no MER/MES was performed beyond this limit. MES was performed at 120 µ seconds and 450 µ seconds within safe charge density limits up to supramaximal thresholds. Amplitudes of up to 5 mA were used at 120 µ seconds and up to 1.5 mA were used at   µ seconds. Patients were asked to report phosphenes at target stimulation.

Patient 1:

MER was performed with anterior and central micro-electrodes and recordings were obtained 4mm up to target on the right and 2mm up to target on the left.

MES was done with the test electrode (model 22670 FHC Inc, Bowdoin, Maine, USA) in position using the central electrode on both sides and stimulating with 1-5mA, 120 µ seconds and 130Hz on both sides. Stimulation was done at three levels above target with 2mm intervals. Capsular side effects were recorded at supra-maximal stimulation, mostly consisting of pulling of the hand and foot at stimulation above 4.5mA. No side effects were observed at 1.5 mA on 450 µ seconds. No visual side effects were noted at target.

The micro/macro-stimulation electrodes were removed and permanent leads (3389 lead, Medtronic Inc, Minneapolis, USA) implanted in the central trajectory as directed by imaging, MER and MAS under fluoroscopy guidance in the lateral orientation using crosshairs.

Patient 2:

The central and anterior electrodes were again used and positive activity recorded 2.5mm above target on both sides. Macro-electrode stimulation was done in the same way as in patient 1. Capsular side effects (pulling of the thumb) were found with stimulation above 2.5mA on the right and above 4.0mA on the left (pulling of the hand) at 120 μ seconds. No side effects were observed at 1.5 mA on 450 μ seconds. No visual side effects indicating stimulation of the optic tract were found.

The permanent lead (3389 lead, Medtronic Inc, Minneapolis, USA) was implanted using the central MER guide under fluoroscopy guidance in the lateral orientation using crosshairs.

Post-operative imaging:

An immediate post-operative audit was conducted on both patients using the Framelink planning software. A CT scan was acquired with the base ring of the stereotactic frame without the localiser. This was fused with the pre-operative plan and a detailed audit of the trajectory followed by the permanent lead in probes eye view was done. The depth at which the leads were implanted was evaluated in the trajectory view. Thereafter the blended exams were studied (80% of T2 weighted axial inverted MRI and 20% of CT). Windowing in the post-operative CT scan ensured that the artefact of the lead was reduced to a realistic geometry (actual lead diameter 1.27 mm; artefact about 1.5 mm). No pneumocephalus was observed in either patient. The lead location was studied with respect to the planned target depth and chosen trajectory and found to be satisfactory in both patients.

Programming of the IPG was undertaken the day after surgery in both patients. As both patients predominantly had symptoms unilaterally, only the contralateral GPi was programmed. Standard programming procedures were used to identify optimal electrode selection and settings. Settings are summarized in Table 1.

Patient	Follow up	Side programmed	Electrode configuration (Activa PC, Medtronic)	Volt	Pulse width	Frequency
Patient 1	3 months	Left GPi	Monopolar 0 -, case+	2.0V	120us	130Hz
	6 months	Left GPi	Monopolar 0 -, case+	2.0V	120us	130Hz
Patient 2	3 months	Right GPi	Monopolar 8 -, case+	1.5V	120us	130Hz
	6 months	Right GPi	Inter-leaving monopolar 8-, case +	2.5V	120us	125Hz
		Left GPi	Monopolar 0-/C+	1.5V	120us	125Hz

Table 2: Stereotactic coordinates:

	Patient 1: left GPi	Patient 1: right GPi	Patient 2: left GPi	Patient 2: right GPi
Lateral	-21.3	+18.3	-25.7	+17.5
AP	-6.2	-0.4	-3.4	-0.7
Vertical	-23.2	-22.0	-13.7	-12.2

At six month follow-up, patient 1 reported complete resolution of symptoms with no further episodes of dystonia. All his oral medications had been discontinued. No stimulation related side effects were reported or found on examination and he was fully functional and able to return to work. Patient 2 had a week long episode of repeated short duration dystonic episodes of the left arm that settled with addition of a second electrode and then in month six also developed dystonic episodes involving the right arm that settled with additional stimulation of the left GPi: deepest electrode at minimal stimulation settings.

Discussion

PNKD is a movement disorder characterized by episodic, sudden, unprovoked episodes of abnormal dystonic or choreiform movements causing varying degrees of disability. Treatment is generally difficult and most patients have to adjust their lives according to the disability. Genetic mutations in MR-1 have been described and patients with the mutation seem to have a different clinical and treatment course (3). Due to logistic limitations we did not do genetic analysis in our patients.

The use of DBS in dystonia has made a significant difference in the treatment and disability of patients with other forms of dystonia. Although most large studies showed efficacy in patients with primary dystonia, some evidence for dystonia-plus syndromes are emerging. In myoclonus-dystonia, DBS has been shown to be effective and safe in treating the movement disorder (18) but not in improving the psychiatric co-morbidity (19).

The use of deep brain stimulation in PNKD has been reported in three patients since 2001. Loher (13) described chronic thalamic stimulation in a patient who was severely affected with PNKD. Unilateral stimulation of the contralateral thalamic ventral intermediate (Vim) nucleus improved the movement disorder, with continued success over a period of at least four years. Dystonic episodes recurred when the device was accidentally switched off. Long term follow up was reported after 9 years and showed mild loss of stimulation effect. The effect was regained when the target was changed to the GPi (20). Two other case reports described DBS of the globus pallidus internus (11, 12). Yamada (11) presented a case of unilateral post traumatic PNKD with complete suppression of abnormal movements after implantation of GPi DBS, and Kaufmann (12) reported a difficult case with a generalized movement disorder with superimposed bilateral PNKD which, although with atypical elements, showed a significant reduction in the frequency and intensity of the episodic dystonic episodes.

We present two patients with PNKD in whom the dystonic episodes resulted in significant disability and loss of employment. All treatment options had failed. DBS was then performed with targeting of the GPi using standard procedures as for dystonia. Both patients responded extremely well with low stimulation parameters and no stimulation side effects. One patient had complete resolution of symptoms and although the second patient had some further dystonia this also settled with adjustment of stimulation. Both patients were functional and able to return to work.

Patients with dystonia who are treated with DBS may take several weeks to show improvement, but in patients with levodopa induced dyskinesia and phasic dystonia GPi DBS causes rapid reduction in abnormal movements (21). Our patients showed immediate benefit post DBS and although the follow up time might still be short in these two cases, the effect of micro-lesioning and placebo should have worn off, thus reflecting actual

improvement brought about by stimulation. The remarkable feature of reversibility in DBS allows for blinded assessments: patients can participate in a blinded study in both roles as active and placebo participant. Unfortunately, neither patient was willing to participate in a blinded evaluation since the response to DBS had been so impressive.

In rare medical conditions it may be difficult to find enough patients to perform controlled trials for the assessment of the efficacy of a treatment modality. In these conditions, case reports and small case series assume greater importance. We propose that GPi DBS is a possible treatment option in patients with disabling PNKD not responding to standard medical treatment. Further evaluation with larger numbers of patients and blinded evaluation will be necessary to support this statement. In addition, standardized criteria for the diagnosis of PNKD need to be agreed upon (22) to avoid overlap with other movement disorders.

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Legends to Video:

Segment 1: Onset of hemi-dystonia during examination. Dystonic posturing started in toes and over seconds involved the leg and arm. The episode lasted six minutes.

Segment 2: Demonstration of gait during episode of hemi-dystonia.

Segment 3: Normal neurological examination 5 minutes after spontaneous resolution of dystonia.