Chapter 6

Deep brain stimulation for dystonia: patient selection and outcomes

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Adapted from:
ABSTRACT

In a literature survey, 341 patients with primary and 109 with secondary dystonias treated with deep brain stimulation (DBS) of the internal segment of the globus pallidus (GPi) were identified. In general, the outcomes for primary dystonias were more favourable compared to the secondary forms. For some secondary dystonias – like tardive dystonia, myoclonus-dystonia (M-D), NBIA (PANK2), the outcome was very good. Only for the primary generalized dystonias, the efficacy of GPI-DBS has been confirmed in randomised controlled trials. Predictors of outcome are the experience and dedication of the stereotactic team, the selection of patients – the diagnosis and pre-operative screening – and the quality of the post-operative care. Predictors of negative outcome are long duration of the disease – with contractures or scoliosis – and concomitant symptoms like spasticity and cerebellar dysfunction. More studies are required to establish the role of GPI-DBS in the treatment of secondary dystonias.
INTRODUCTION

In this manuscript, we discuss the factors that may influence the outcome of GPI-DBS for dystonias. The pioneering work by Coubes and collaborators1 was the incentive for other groups to explore the role of GPI-DBS for the treatment of dystonias. Initial observations suggested that GPI-DBS was very effective for the primary generalized dystonias, with a few exceptions, and it appeared that for the secondary dystonias results were less favourable.2 After 9 years and more than 450 patient operations (see below), it seemed appropriate to investigate possible predictors of outcome and to discuss the selection of patients with dystonia for GPI-DBS.

General predictors of outcome

The surgical team

The major determinant of a favourable outcome of functional surgery is the quality of the surgical team. Most consider that the team responsible for the selection of patients and the DBS surgery should be multidisciplinary, with a neurosurgeon well trained in the stereotactic technique, a neurologist experienced in movement disorders, a neuropsychologist, a physicist, and a nurse or social worker knowledgeable in movement disorders. Rehabilitation specialists and psychiatrists must be easily accessible. Furthermore, the care and guidance of patients, including their relatives, have to be guaranteed and the outcomes, positive and negative, have to be discussed within the team and with the patients.

Patient selection

For the selection of patients, a ‘rule of five’ can be applied: (i) a correct diagnosis; ii) a disabling condition; iii) insufficient improvement by medical treatments; (iv) no physical nor psychiatric contraindications; and (v) patient’s consent. Moreover, six other factors have to be considered in the process of selecting patients with dystonia for stereotactic surgery: (i) is the target symptom the predominant source of disability; (ii) are there other possible sources of disability; (iii) is it possible that DBS will improve the target symptoms; (iv) what is the risk of surgical adverse events; (v) formulation of realistic goals for the rehabilitation of the patient; and (vi) the relation of the patient’s own expectation from the surgery for these goals.3

Outcome of GPI-DBS for the different forms of dystonia

We performed a literature search of PubMed up to August 2008, using keyword of ‘dystonia’ and ‘GPI-DBS’. From the literature analysed, we identified 450 reported patients. The cohort can be divided into 341 patients with primary dystonias and 109 with secondary dystonias. Primary dystonias
Primary generalized dystonias
Recently, Ostrem and Starr reviewed the effects of DBS on dystonias. They analysed the outcome of 246 patients with primary generalized dystonias. Almost all references for primary dystonias can be found in their review. Two randomised controlled trials confirmed the beneficial effect of GPI-DBS for patients with primary generalized dystonia. The Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) motor score improved between 21-95% – mostly between 60–70% – following GPI-DBS and the BFMDRS functional part 40%. However, the effect on speech was disappointing. There was no difference in the outcome for DYT1-positive versus DYT1-negative patients. A possible recommendation could be to operate on patients at an early stage, before the developments of contractures and skeletal deformities. There was a subgroup of patients with only modest improvements. This may be attributed to inappropriate patient selection, suboptimal surgery, or an incorrect diagnosis.

Cervical dystonias
In the literature, 98 patients could be traced with GPI-DBS and cervical dystonia: 62 patients with only focal cervical dystonia and 36 with a segmental dystonia, involving the neck musculature and/or upper limbs and/or trunk muscles. One class II and one class III study were published with limited numbers of patients. A number of case reports have also been published, the majority with less than 10 patients. Currently, GPI-DBS for cervical dystonia meets the criteria of a probably established treatment. More RCTs and large cohort studies are necessary. Motor improvements are reported between 43-76%, but several reports mention minor improvements in motor scores accompanied by significant improvements of pain. Yianni et al. report a high incidence of hardware problems. A couple of patients have been reported with unilateral GPI-DBS and a favourable outcome. The electrodes were placed in the GPI contralateral to the hyperactive sternocleidomastoid muscle.

Meige’s syndrome (cranial-cervical dystonia)
So far, only 18 patients with GPI-DBS for Meige’s syndrome have been published; one report with six patients, 14 one with three patient, and some single case reports. Short-term improvements of 45-80% on the BFMDRS motor part are described. In a few patients, bradykinesia caused by the bilateral GPI-DBS was reported. More information regarding the efficacy of GPI-DBS for primary cranial-cervical dystonia (Meige’s syndrome) is needed.

Secondary dystonias
The literature search only yielded case reports. A total of 109 patients with secondary dystonia and GPI-DBS were traced (Table 1).
Table 1. Literature overview of GPI-DBS for secondary dystonias (n=109 patients)

<table>
<thead>
<tr>
<th>Category</th>
<th>Number of patients reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dystonia-plus syndromes</td>
<td>13</td>
</tr>
<tr>
<td>Myoclonus-dystonias (M-D)</td>
<td>12</td>
</tr>
<tr>
<td>Rapid-onset dystonia-parkinsonism</td>
<td>1</td>
</tr>
<tr>
<td>Hereditary conditions associated with neurodegeneration</td>
<td>22</td>
</tr>
<tr>
<td>NBIA (Pank2)</td>
<td>13</td>
</tr>
<tr>
<td>Lesh-Nyhan</td>
<td>4</td>
</tr>
<tr>
<td>Mitochondrial diseases</td>
<td>3</td>
</tr>
<tr>
<td>Lubag</td>
<td>1</td>
</tr>
<tr>
<td>GM1 gangliosidosis type 3</td>
<td>1</td>
</tr>
<tr>
<td>Acquired/exogenous causes</td>
<td>70</td>
</tr>
<tr>
<td>Tardive dystonias</td>
<td>38</td>
</tr>
<tr>
<td>Cerebral palsy</td>
<td>18</td>
</tr>
<tr>
<td>Post-anoxic (generalized)</td>
<td>2</td>
</tr>
<tr>
<td>Post-traumatic (2 generalized, 3 hemidystonias)</td>
<td>5</td>
</tr>
<tr>
<td>Post-ischemic (2 generalized, 2 hemidystonia, 1 segmental)</td>
<td>5</td>
</tr>
<tr>
<td>Post-radiation encephalopathy (generalized)</td>
<td>1</td>
</tr>
<tr>
<td>Icterus (hemidystonia)</td>
<td>1</td>
</tr>
<tr>
<td>Other</td>
<td>2</td>
</tr>
<tr>
<td>Calcifications in striatum</td>
<td>1</td>
</tr>
<tr>
<td>Paroxysmal non-kinesiogenic dystonia</td>
<td>1</td>
</tr>
<tr>
<td>Unknown origin (1 generalized, 1 hemidystonia)</td>
<td>2</td>
</tr>
</tbody>
</table>

Pank2, pantothenate kinase 2; NBIA, neurodegeneration with brain iron accumulation.

In general, the secondary dystonias as a group had a less favourable outcome following GPI-DBS. But in nearly all groups, some cases with favourable outcomes were reported. In three disease categories, each containing more than five operated patients, a more favourable surgical outcome was observed (Table 2).

It appeared that bilateral GPI-DBS had a very favourable outcome for disabling tardive dyskinesia/dystonia with an impressive improvement for 27 patients and a mild improvement for an additional six. The effects on disability were only reported for eight patients and were very favourable.4,18-22

Surprisingly, eight of the 13 patients with neurodegeneration with brain iron accumulation (NBIA) because of the pantothenate kinase 2 mutations had a striking improvement on the motor scales, whilst another five improved between 30-50%. However, the functional improvement for six patients was less impressive.4,23-26 In myoclonus-dystonia (M-D), all patients showed a clear improvement on the motor scales.4 However, three of our own patients, with intermittent episodes of psychosis considered to be part of the M-D, needed psychiatric care and were intermittently admitted because of these symptoms. Nevertheless, all three claim that the motor changes improved their quality of life considerably. For the 18 patients with cerebral palsy, because of different aetiologies, GPI-DBS had a favourable
outcome in seven patients, two patients had a motor improvement of 50-75%, five of 30-50% and 11 experienced no or only minimal improvement. For eight patients, disability scores were reported and these showed no or minimal improvements; however, these patients also had minimal changes on the motor scores.\textsuperscript{6,27-29} In the group of nine patients with secondary generalized dystonia of different aetiologies, the patients with generalized dystonia because of post-radiation encephalopathy and one with unknown cause of his secondary generalized dystonia improved 50-75% on the BFMDRS motor part, and three between 30-50%, whilst the other three showed only minimal or slight improvement. Of four patients the effect on disability had been assessed, with a good improvement in only two, which was in accordance with the physical improvements.\textsuperscript{15,27-31} The four patients with \textit{Lesch-Nyhan syndrome} improved between 30-50% on the BFMDRS motor score, but only one showed a satisfactory improvement on the BFMDRS disability part.\textsuperscript{32,33} We identified five patients with \textit{acquired hemidystonia}; in three patients of post-traumatic origin and in two patients because of a stroke. Four patients had a motor improvement >50% and one between 30-50%. The post-traumatic patients also improved between 30-75% on the functional scale, whilst the two post-stroke hemidystonia patients did not show functional improvement.\textsuperscript{29,31,34}

**Table 2.** Secondary dystonias and GPI-DBS with overall a favourable outcome and at least five patients per diagnosis.

<table>
<thead>
<tr>
<th>Diagnosis (n. of patients)</th>
<th>Improvement on the BFMDRS-motor part</th>
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<tbody>
<tr>
<td></td>
<td>Very good (&gt;75%)</td>
</tr>
<tr>
<td>Tardive dystonias (39)</td>
<td>16 (41%)</td>
</tr>
<tr>
<td>PKAN (13)</td>
<td>1 (8%)</td>
</tr>
<tr>
<td>Myoclonus-Dystonia (12)</td>
<td>12 (100%)</td>
</tr>
</tbody>
</table>

**Predictors of outcome of GPI-DBS for the different forms of dystonias**

**Primary dystonias**

Most patients with different types of primary dystonias had a satisfying outcome. Clear clinical or epidemiological indices predicting outcome are not known. Probably, the presence of symptoms for more than 15 years has a negative effect on the outcome of GPI-DBS, because of the development of muscle contractures and skeletal deformities.\textsuperscript{7} Also, the location and type of symptoms are of importance, because oro-mandibular and speech problems improve rarely. Phasic dystonic contractions and hyperkinesias of extremities and trunk improve faster and to a greater extent than the static types of dystonia. In general, the outcome for DYT1-positive primary dystonias is the same as for the DYT-negative patients.
Secondary dystonias
The structural brain damage causing the dystonia is probably not the major determinant of the surgical outcome in itself as evidenced by the improvement seen in patients with hemidystonia and NBIA, although the location and extension of a focal lesion may hinder the optimal positioning of the DBS electrode. Another important factor is the presence of concomitant neurological features, such as spasticity or cerebellar symptoms, which will not improve with GPI-DBS, and in general have a negative effect on the functional outcome. In cases with a disappointing outcome, suboptimal position of the electrodes, sometimes because of postoperative displacement, should be considered, in addition to a wrong diagnosis and suboptimal stimulation settings.

CONCLUSIONS

In general, GPI-DBS is an efficacious treatment for the primary dystonias, although the effects are less well established for cervical dystonia. Considering the nature of the data for the secondary dystonias, firm advice cannot be given, although it seems that the effects of GPI-DBS are very heterogeneous. Currently, it is not possible to predict with accuracy which individual with secondary dystonia will improve.7

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REFERENCE LIST


DBS for dystonia: patients selection


