Clinical and functional studies in Myoclonus-Dystonia
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Bilateral pallidal stimulation in Myoclonus-Dystonia: effect of psychiatric comorbidity on functional outcome

E.M.J. Foncke, D. Cath, P.R. Schuurman, J.D. Speelman, M.A.J. Tijssen

Submitted
Abstract

Deep brain stimulation of the GPi is a good treatment option to reduce motor symptoms in medication refractory Myoclonus-Dystonia (M-D) patients. However, the effect of bilateral GPi stimulation on the commonly associated psychiatric symptoms has not been previously reported.

Here, we report the results of bilateral GPi stimulation in four medication refractory M-D patients with psychiatric comorbidity. Motor symptoms improved dramatically in all four patients. Psychiatric symptoms worsened after surgery in three out of four which prevented them from regaining a normal life. The lack of effect, or even deterioration of the psychiatric comorbidity in M-D patients with GPi stimulation should be taken into account when considering deep brain stimulation in M-D.
Introduction

Myoclonus-Dystonia (M-D) is a hyperkinetic movement disorder with an autosomal dominant inheritance pattern, characterized by myoclonus and/or dystonia often associated with psychiatric symptoms. The major gene involved is the epsilon-sarcoglycan gene (SGCE, DYT11), but genetic heterogeneity has been described. M-D shows reduced penetrance due to maternal imprinting. 1

Psychiatric symptoms such as depression, anxiety, panic disorder and obsessive-compulsive disorder (OCD) are considered to be part of the phenotypic spectrum of M-D. Studies have not been able to definitely rule out that the psychiatric symptoms are secondary to the chronically debilitating motor symptoms due to M-D, but current opinion points toward part of the phenotypic spectrum. 2-5 M-D usually has a benign course without interfering with daily life. Some individuals are markedly impaired by the motor symptoms leading to restrictions in the activities of daily living. The effect of pharmacological treatment on the symptoms of myoclonus and dystonia, including clonazepam and trihexyphenidyl is often disappointing. To date, eight M-D patients with medication-refractory motor symptoms successfully treated by deep brain stimulation have been described, seven of whom were treated by chronic stimulation of the GPi and one by thalamic stimulation. 6-11 Data of the pre- and postoperative psychiatric comorbidity in these M-D patients are not available.

In this paper, we describe four DYT11 positive M-D patients with preoperative psychiatric comorbidity who underwent bilateral GPi stimulation for intractable motor symptoms. Motor as well as psychiatric symptoms were assessed extensively preoperatively and 12 months postoperatively.

Methods

Patients

Four DYT11 positive M-D patients were referred to the neurosurgical department of the Academic Medical Center between 2003 and 2007 because of medication refractory motor symptoms. Patient one (mutation in exon 5 (IVS7+2C>T)) and two (de novo mutation in exon 2 (c.179A>C)) have been previously described in a local field potential study. 12 Patient three is the index patient of a previously reported Dutch M-D pedigree with a mutation in exon 7 (c.885insT) 13 Patient four is the index patient of a recently described large Dutch M-D family with a mutation in exon 5 (619delAG). 14 Patient characteristics are shown in table 1. Informed consent was obtained according to the declaration of Helsinki. The study was approved by the ethics committee of our hospital.
Neurological and Psychiatric rating scales

Before and 12 months after surgery, motor symptoms were assessed using the Burke-Fahn-Marsden Dystonia Rating Scale motor part (BFMDRS-motor) and a modified version of the Unified Myoclonus Rating Scale (UMRS). Psychiatric diagnoses according to the DSM-IV axis 1 classification system were assessed using the Structured Clinical Interview on DSM-IV diagnoses (SCID-I) or the Mini International Neuropsychiatric Interview (MINI) version 5.0.0. All psychiatric evaluations were performed by trained neuropsychologists. The evolution of the psychiatric history before and after surgery is described for each patient separately.

Surgery

The procedure for DBS is a one stage bilateral stereotactic approach using microrecording and macrostimulation. The intended coordinates of the posteroverentralateral GPi were 21 mm lateral to the midplane of the third ventricle, 2 mm anterior to the midcommissural point and 5 mm below the AC-PC (anterior-posterior commissure) line. The electrodes used for implantation were model 3389 (Medtronic, Minneapolis, MN, USA) with four platinum–iridium cylindrical surfaces (1.3 mm diameter and 1.5 mm length) and with an intercontact separation of 0.5 mm. Postoperatively the lead position was determined by means of fusion of the postoperative CT-scan and the preoperative MRI-scan of the brain.

Results

Table 1 shows the severity of motor symptoms before and 12 months after surgery (9 months for patient 4). A dramatic improvement could be noticed in all four M-D patients. In Table 2, DSM-IV diagnoses before and 12 months after surgery are displayed.

Patient 1

This 39 year old female patient developed myoclonic jerks at the age of 3 years which progressively worsened over the years. In her teens, dystonia accompanied the myoclonus. Both myoclonus and dystonia responded extremely well to alcohol. She suffered from panic attacks, anxiety and recurrent depression. There was no progression of the clinical picture for several years, except for temporal deterioration during two depressive episodes. Five years before surgery she was referred to our centre because she experienced a considerable worsening of her motor symptoms. This worsening negatively influenced her performance at work (administrative job) and the housekeeping. At the time of evaluation, she was treated with citalopram for depression. Motor symptoms were refractory to several trials of medications, including trihexiphenidyl and clonazepam.

Preoperative psychiatric evaluation (SCID-I) revealed recurrent episodes of major depressive disorder, including a current moderately severe major depression, and a
Table 1. Patient characteristics and pre-and postoperative motor scores

<table>
<thead>
<tr>
<th></th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>F</td>
<td>M</td>
<td>M</td>
<td>M</td>
</tr>
<tr>
<td>Age at onset (yrs)</td>
<td>3</td>
<td>7</td>
<td>17</td>
<td>early childhood</td>
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<tr>
<td>Age at surgery (yrs)</td>
<td>39</td>
<td>18</td>
<td>30</td>
<td>49</td>
</tr>
<tr>
<td>SGCE-mutation</td>
<td>exon 5 (IVS7+2C&gt;T)</td>
<td>exon 2 (c.179A&gt;C)</td>
<td>exon 7 (c.885insT)</td>
<td>exon 5 (619delAG)</td>
</tr>
<tr>
<td>Medication at surgery</td>
<td>Citalopram</td>
<td>Dysport 400IE</td>
<td>-</td>
<td>-</td>
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</tbody>
</table>

Motor scores

<table>
<thead>
<tr>
<th></th>
<th>Pre</th>
<th>Post</th>
<th>Pre</th>
<th>Post</th>
<th>Pre</th>
<th>Post</th>
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<th>Post</th>
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<td>UMRS-rest</td>
<td>42</td>
<td>2</td>
<td>18</td>
<td>4</td>
<td>17</td>
<td>0</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>UMRS-action</td>
<td>38</td>
<td>8</td>
<td>30</td>
<td>3</td>
<td>13</td>
<td>8</td>
<td>43</td>
<td>4</td>
</tr>
<tr>
<td>BFMDRS-motor</td>
<td>22</td>
<td>9</td>
<td>10</td>
<td>4</td>
<td>8</td>
<td>4</td>
<td>25.5</td>
<td>6</td>
</tr>
<tr>
<td>Total motor score</td>
<td>102</td>
<td>19</td>
<td>58</td>
<td>11</td>
<td>38</td>
<td>12</td>
<td>82.5</td>
<td>11</td>
</tr>
</tbody>
</table>

F=female, M=male, Yrs=years, Pre=preoperatively, Post=postoperatively, UMRS=Unified Myoclonus rating scale, BFMDRS-motor= Burke-Fahn-Marsden-Dystonia Rating Scale-motor part.

generalized social phobia. The family history was negative for psychiatric disorders. The degree of psychiatric comorbidity was not considered as a contra-indication for surgery. Postoperatively, the motor improvement was dramatic, as reflected by the changes in the motor scores 12 months postoperatively (Table 1). However, psychiatric assessment 12 months postoperatively (SCID-I) revealed persistence of the generalized social phobia despite the motor improvement obtained. Sixteen months postoperatively, she was admitted to the department of psychiatry at a Belgian hospital because of a severe depression with suicide ideations. Marital problems leading to a divorce were considered as precipitating factor. After 3 months of inpatient psychotherapy and treatment with citalopram and sertraline, she was dismissed in a “stable mental condition”. The motor symptoms were excellently controlled with bilateral monopolar stimulation at contactpoints 0 and 1 with frequency at 130 Hz, pulse with 60 microsec and intensity of

Table 2. DSM-IV diagnoses according to the SCID-1 (or MINI)

<table>
<thead>
<tr>
<th>DSM-IV diagnoses preoperatively</th>
<th>DSM-IV diagnoses postoperatively</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>depressive period in the past, current moderate depressive episode, current moderate generalized social phobia</td>
</tr>
<tr>
<td>Patient 2</td>
<td>depressive period in the past, current depressive episode, severe social phobia, mild obsessive compulsive behavior, alcohol-and cannabis abuse, borderline personality traits</td>
</tr>
<tr>
<td>Patient 3</td>
<td>recurrent depression in the past</td>
</tr>
<tr>
<td>Patient 4</td>
<td>Chronic depression, moderate generalized anxiety and social phobia, mild obsessive compulsive disorder</td>
</tr>
</tbody>
</table>
3.5 Volts bilaterally. Twenty-one months postoperatively, she was admitted to the AMC hospital because of worsening of the motor symptoms. Adjustment of the stimulation parameters by increasing the voltage with 0.5 V gave satisfactory results. During this admission, repeated attacks of loss of consciousness did occur. Several of them were witnessed by a neurologist and definitely considered as psychogenic attacks. Confronting her with the presumed psychogenic nature of the attacks exacerbated a new depressive episode and the next day she did a suicide attempt taking a large amount of pain killers (ibuprofen). She was transferred to a psychiatric hospital where she was hospitalised for 3 months to treat the depression. During the next year, depressive symptoms decreased enabling a normalisation of the patient’s professional and private life. Currently, she is re-admitted to a psychiatric hospital because of a new depressive period.

Patient 2
This 18 year old man experienced writing difficulties at the age of seven years due to myoclonus of the upper limbs. With disease progression, myoclonus spread to the head and neck and dystonia of the neck was noticed. Alcohol improved both myoclonus and dystonia. Psychiatric history was positive for social isolation and two suicide attempts. Family history revealed that a maternal uncle had a “psychotic disorder” and his paternal grandfather was diagnosed with schizophrenia. His mother was suffering from alcohol dependence. Neither of these family members had a mutation in the SGCE gene. Treatment of the motor symptoms with clonazepam was not successful. Botulinum toxin for the neck dystonia gave some relief. Preoperative psychiatric evaluation (SCID-I) revealed a major depressive episode, a severe generalized social phobia, mild obsessive compulsive disorder, alcohol- and cannabis abuse. Further, clinically borderline personality traits were established. Postoperatively, the motor improvement was dramatic as reflected by the changes in the motor scores 12 months postoperatively (see table 1). However, six months postoperatively, the patient had to be admitted to the psychiatric emergency department because of psychotic decompensation with paranoid delusions, a manic episode with inflated self-esteem, delusions of grandiosity, and auditory and visual hallucinations. Two weeks before admission, stimulation parameters had been minimally adjusted: bilateral monopolar stimulation at contactpoint 1 with frequency at 130 Hz, pulse with 90 microsec and intensity of 2.8 Volts was changed to an intensity of 3.0 V bilaterally. According to his mother, he had recently restarted taking cannabis and excessive amounts of alcohol a few weeks before admission. Switching off the neurostimulation for two weeks did not change the psychiatric symptoms but the motor symptoms re-emerged immediately. The psychotic symptoms did improve with olanzapine 20 mg daily and valproic acid 800 mg twice daily and the symptoms did not worsen after switching on the neurostimulation with similar stimulation parameters. It was concluded that the psychotic period was probably the first episode of a schizoaffective disorder. The following 15 months, his psychiatric condition remained stable with the chronic use of neuroleptics and a mood stabilizer.
Motor symptoms were excellently controlled. However, social and professional life was not easy. Excessive use of cannabis and failure of therapy compliance (he recently decided to stop taking any medication) prompted him into a new manic psychotic episode. He was again admitted to a closed unit of a psychiatric hospital where temporally separation was necessary.

No changes to the stimulation parameters had been made over the past period. Reintroducing valproic acid and clozapine was successful in controlling the mania and auditory hallucinations. This episode was considered as a second manic psychosis due to schizoaffective disorder. To date (twelve months after the second psychosis), motor symptoms as well as psychiatric symptoms are controlled, he is building up some social life and working in a sheltered work environment.

Patient 3

This 30 year old man developed myoclonus of the neck, face and shoulders at the age of 17. With disease progression dystonia of the neck and trunk was noticed. Since several years, he experienced difficulties with walking, although only sporadic myoclonus of the proximal leg could be detected at neurological examination. However, electromyography of the quadriceps muscles revealed pronounced myoclonic jerks during standing position and during walking a short distance. Chronic low back and neck pain superimposed on the motor symptoms prevented him to work. Treatment with trihexiphenidyl, clobazam, tramadol and Botulinum toxin injections were not effective. During childhood and adolescence he suffered from periods of amnesia that were considered to be partial complex seizures. After taking a single dose of clonazepam 4 mg, he suddenly became uncontrollably aggressive and fell through a window. He had amnesia for this accident. He injured his right hand and several years later he developed dystonia of the right hand.

Psychiatric history was positive for recurrent major depressive episodes. Preoperative psychiatric evaluation (SCID-I) did not reveal other psychiatric diagnoses, especially no obsessive compulsive behaviour nor anxiety. There was no current depressive episode. Family history was positive for antisocial personality disorder of his younger brother (SGCE mutation carrier) and schizoaffective disorder of a paternal uncle (not genotyped).

Postoperatively, myoclonus as well as dystonia improved significantly, including the myoclonus of the legs as reflected by the postoperative electromyographic findings. He experienced less pronounced walking difficulties.

Psychiatric evaluation (SCID-I) 12 months postoperatively was unchanged. However, chronic pain and fatigue complaints did influence his tenacity during the activities of daily living. Adjustment of the stimulation parameters with an increase of 0.5 Volt bilateral (the current parameters are bilateral monopolar stimulation at contactpoint 2- left and 3- right with 130 Hz, 90 microsec and 3.6 Volt left, 2.8 Volt right) did not influence these complaints.
Patient 4

This 49 year old patient developed myoclonus of the leg in early childhood. Dystonia of the trunk had been noted in his teens. He was treated for recurrent depressive episodes and had suffered from alcohol abuse in the past. On neurological examination, rhythmic movements of the trunk were noted along with dystonia of the trunk and the feet and myoclonus of the hands, legs, and trunk. Despite treatment with a combination of trihexyphenidyl, clonazepam and botulinum toxin injections, motor symptoms remained very disabling in daily life.

Preoperative psychiatric evaluation (SCID-I) revealed a chronic major depressive disorder, moderately severe generalized anxiety disorder, generalized social phobia and a mild obsessive compulsive disorder. He was considered to be eligible for stereotactic surgery because of a stable psychiatric condition due to treatment with paroxetine. The family history reveals that a brother of his father has committed suicide when the patient was a child, and a granduncle from father's side has been chronically admitted in a psychiatric hospital. Neither of these family members had a mutation in the SGCE gene.

Postoperatively, a dramatic improvement of the motor symptoms was noticed after 3 weeks of active stimulation with stimulation parameters at contactpoint 0- left and 2- right (130 Hz, 60 microsec and 1.5 Volt bilaterally). Despite this motor improvement, he developed a new major depressive period 6 months postoperatively. This period was followed by a period with hypomanic thoughts and actions, such as imprudent car driving, spending excessive amounts of money, decreased sleep and irritability. Turning the stimulation off for 2 weeks did not influence the psychiatric picture.

Psychiatric evaluation (MINI) 9 months post-operatively revealed a bipolar disorder II with rapid cycling and an obsessive compulsive disorder. Switching off the stimulation for 2 weeks and rechallenge with active stimulation did not change the psychiatric picture. He is currently being installed on lithiumcarbonate and receives cognitive behavioral therapy to help him control his impulsive behavior. According to the patient, the increase of psychiatric complaints is due to the death of his mother, with whom he lived together and controlled his spending behavior.

Discussion

The present study of four medication refractory DYT11 positive M-D patients confirms the previously reported positive effects of bilateral GPi stimulation on the symptoms of myoclonus and dystonia. Due to persisting or worsening of psychiatric illness, three out of four M-D patients were not able to take part in normal social life, limiting the favourable functional outcome after bilateral GPi stimulation in M-D.
Psychiatric symptoms such as depression, anxiety disorder and OCD, are often accompanying the motor symptoms in M-D. Thus, either the presence of preoperatively psychiatric comorbidity or the worsening of pre-existent psychiatric symptoms postoperatively, may be a rate-limiting factor with respect to the favorable outcome of DBS in M-D. It has been suggested that psychopathology is co-segregating with the DYT11 mutation. However, conflicting results in the studies systematically addressing the presence of psychiatric symptoms in M-D, fail to determine whether the psychiatric symptoms are part of or secondary to the DYT11 phenotype. Nevertheless, it is important to integrate the psychiatric comorbidity into the decision making process of DBS in M-D patients. This may include rigorous treatment with psychopharmaca or behavioural therapy for a longer period preoperatively and intensive psychiatric follow-up postoperatively.

The persistence or worsening of psychiatric symptoms in three out of the four M-D patients despite a dramatic effect of GPI stimulation on the motor symptoms suggests that the psychiatric symptoms are not a consequence of the severity of motor symptoms. Moreover, one would expect that a dramatic improvement of the motor symptoms after bilateral GPI stimulation subsequently would lead to an improvement of the psychiatric symptoms. However, difficulties in coping with the new life and the disappearance of the “sick person” image may also contribute to persistence of psychiatric symptoms. Of interest is the worsening of the psychiatric symptomatology after surgery, i.e. psychotic episodes in patient 2 and manic behavior in patient 4. One should consider the possibility of a stimulation-induced luxation of a preoperative stable psychiatric condition. However, it is unclear whether the natural course of the disease would have resulted in a similar psychiatric evolution. The positive family history for schizo-affective disorder and suicide in two out of the four M-D patients may point to a genetic susceptibility for psychiatric decompensation after DBS surgery. However, because not all family members with psychiatric disorders have been screened for a SGCE mutation, it is unclear whether the SGCE mutation itself is responsible for this genetic vulnerability or whether other genes or environmental factors are involved.

The delay in worsening of psychiatric symptoms after surgery while active stimulation was present and the persistence of symptoms after switching off the stimulation in patient 2 and 4 argues against a stimulation-induced side-effect. Behavioural disturbances, including suicide have been reported after subthalamic nucleus (STN) or GPI stimulation in Parkinson’s disease and to a lesser extent in dystonia. Chronic stimulation of the STN seems to induce more behavioural complications compared to GPI stimulation in Parkinson’s disease. So far, it is unclear whether pre-existent psychiatric comorbidity or unintended stimulation of nearby limbic structures are responsible for the psychiatric complications after DBS-surgery. The experience with chronic stimulation of the GPI in other movement disorders with psychiatric comorbidity is limited. Deep brain stimulation for patients with Gilles de la Tourette syndrome (GTS) refractory to conventional therapy has focussed on the thalamus. Only three GTS patients were treated with bilateral GPI stimulation.
patient, both GPi and thalamus were targeted. Motor symptoms as well as behavioural symptoms significantly improved with both procedures. Remarkably, selectively stimulating the GPi in the patient with both GPi and thalamic stimulation worsened the symptoms of anxiety in contrast to the positive effect on anxiety when selectively stimulating the thalamus. However, it should be mentioned that the anteromedial limbic part in this patient was targeted and not the “classic” posteroventrolateral motor part of the GPi used in Parkinson’s disease and dystonia. These results are in contrast with the positive effect of GPi stimulation on the automutilating behavior in Lesch-Nyhan patients. In three out of the four Lesch-Nyhan patients, four electrodes were implanted with two electrodes in the posterior motor part and two electrodes in the anterior limbic part of the GPi. In the other patient, the GPi target was supposed to lie more anterior than the classic posteroventrolateral GPi target. These results indicate that stimulation of the GPi, known to take part in the limbic circuitry of the basal ganglia, may influence emotional processing due to functional changes induced by chronic stimulation of deranged neuronal circuits. Whether electrode localisation in the GPi plays a role in influencing behaviour remains to be elucidated.

Motor symptoms but not psychiatric symptoms were effectively controlled with stimulation of the motor part of the GPi in the four M-D patients. Based on the positive results of thalamic stimulation on both motor and behavioral symptoms in Tourette patients and the positive results of anterior GPi stimulation in Tourette and Lesch Nyhan patients, one may consider the thalamus or the anterior part of the GPi as preferable target in medication-refractory M-D patients, especially when psychiatric symptoms are associated.

The present study stresses the importance of an extensive structured psychiatric evaluation preoperatively by trained psychiatrists or psychologists when considering patients with movement disorders and associated psychiatric disturbances for DBS. Future studies should address to which extent the psychiatric symptoms can be sufficiently treated preoperatively or whether psychiatric comorbidity should be considered as a relative contra-indication for DBS in M-D patients.

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