

**Monitoring of changes in motor and cognitive function after stereotactic surgery in  
Parkinson's disease.**

**Ph.D. thesis**

**Dr. Llumiguano Carlos**

**University of Pécs, Faculty of Medicine**

**Department of Neurosurgery**

**Clinical Doctor's School – Clinical Neuroscience Program**

**Program leader: Prof. Dr. Komoly Sámuel**

**Tutor: Prof. Dr. Dóczi Tamás, Dr. Balás István**

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## **1. Introduction**

The Parkinson's disease (PD) was described by James Parkinson in 1817, like a "Shaking Palsy". It is a progressive, degenerative disease of the basal ganglia.

The basic biochemical cause of the Parkinson's disease is the dopamine deficiency in the striatum and other basal ganglia, which is caused by the absence of the dopaminergic neuron cells in the substantia nigra pars compacta.

The cardinal signs of PD are resting tremor, rigidity, bradykinesia / akinesia, and postural instability. Besides this, innumerable motor and non-motor signs can be present, which depend on the duration, progression and treatment of the disease.

## **2. Epidemiology**

PD is a widespread disease, e.g. in USA the prevalence of around 100-250 /100 000, in China 1,7 /100 (95 % CI 1,5-1,9; age  $\geq 65$  y/o). The prevalence can be influenced by social and economic factors, too. The incidence is a very sensitive indicator, e.g. in USA is around 20.5/100 000.

## **3. Diagnosis**

Actually the diagnosis of Parkinson's disease is based on the medical history and on the neurologic physical examination. Frequently the early signs are slight; generally a close following of the patient is necessary before to say a definitive diagnosis.

#### 4. Treatment

- Drugs
- Surgery
  - Stereotactic ablation: pallidotomy, thalamotomy, Subthalamic nucleus ablation
  - Subthalamic nucleus-, Thalamic nucleus ventral intermedius-, Globus pallidum pars interna- deep brain stimulation (DBS).
- Procedures under investigation and evaluation

#### 5. Operative treatment

Pharmacological treatment is the choice of treatment in Parkinson's disease. However, in some special circumstances surgical intervention can also be employed, which we can explain with the following factors. 1/. Following a period of chronic administration, antiparkinsonian drugs become insufficient to control the progressive symptoms and signs of PD. 2/. Development of new neurosurgical and brain-imaging techniques, advances in precise neurophysiological monitoring have made surgical interventions safe and effective. 3/. Extensive studies of the anatomy and the pathophysiology of the basal ganglia and their association system, especially new observations made during experiments in primates with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridin (MPTP) and the development of deep brain stimulation (DBS), have paved the way for novel therapeutic strategies and major advances in the field. In particular, the operative results have demonstrated major improvements in the quality of life of patients with PD.

In ideal conditions surgery will be recommended for the following patients:

- Idiopathic Parkinson's disease,
- relatively young age (<70 years old),
- with main parkinsonian symptoms initially responding to levodopa therapy, but gradually developing unresponsiveness for medical therapy,
- Drug induced dyskinesia or rigidity, tremor, bradykinesia, march and postural instability, motor fluctuation,
- intact cognitive function.

## 6. Aims

1. Evaluation of the effects of ablative pallidotomy, pallidothalamotomy and STN-DBS neurostimulation procedures on the motor functions in Parkinson's disease patients.
2. Evaluation of the effects of STN-DBS neurostimulation on the cognitive functions in Parkinson's disease patients.
3. Evaluation of the effects of ablative pallidotomy, pallidothalamotomy and STN-DBS neurostimulation procedures on the time required for performing certain manual tasks in Parkinson's disease patients.
4. Measurement of certain brain metabolite ratio by using Proton Magnetic Resonance Spectroscopy ( $^1\text{H}$ -MRS) in Parkinson's disease patients treated with STN-DBS.
5. There might be some correlation between the clinical improvements and the changes of brain metabolite ratios occurred after neurostimulations procedure.

## **7. Patient monitoring**

### ***7.1. Motor function evaluation***

#### **7.1.1. Fahn Tolosa Marin test**

The time required for different manual tasks to be performed (i.e. “performance time”) was compared before and after stereotactic surgery using the „B” part of Fahn-Tolosa-Marin Tremor Rating scale. The performance time was measured in seconds by means of a chronometer.

#### **7.1.2. Unified Parkinson Disease Rating Scale – Motor Examination subscore – (UPDRS- part III)**

The UPDRS part III is apt for motor function examination (maximum 108 point): among other things we can evaluate the hand movements, tremor, walking, posture, speech, rigidity, etc. In normal case 4, and in severe cases 0 can be given.

### ***7.2. Cognitive function evaluation***

#### **Neuropsychologic tests:**

- Mini Mental State Examination (MSE)
- Auditory Verbal Learning (AVLT)
- Raven test (PRM)
- Bergen test (BRFT)
- Montgomery-Asberg Depression Rating Scale (MADRS)
- Hungarian Wechsler Intelligency Test (MAWI)
- Verbal fluency

### ***7.3. Proton magnetic resonance spectroscopy (<sup>1</sup>H -MRS)***

Proton magnetic resonance spectroscopy (<sup>1</sup>H -MRS) is a useful noninvasive method used to study central nervous system pathologies, and allows in vivo investigation of a number of cerebral metabolites such as *N*- acetylaspartate (NAA), choline (Cho), creatine (Cr), myoinositol (My), phosphocreatine (PCr) and lactate. Cho (altered neuronal membrane synthesis and degradation can result in changes in Choline) and Cr (a key energetic metabolite and, therefore, a possible indicator of defective energy metabolism) are present in all brain cells, whereas NAA has been localized in and is a putative marker of viable neurons and, therefore, a possible indicator of neuron loss.

## **8. Patients and methods**

### ***8.1. Effect of Pallidotomy and pallidothalamotomy on the motor function and the performance time***

Twenty-eight consecutive, right-handed patients with Parkinson's disease participated in the prospective study (mean age was  $58,8 \pm 3,53$  years old; male 12, female 16; mean disease duration was  $6,5 \pm 4,5$  years). Pallidotomy (mean age was 60,14 years; mean disease duration was 6,5 years) and combined pallidothalamotomy (mean age was 57,6 years; mean disease duration was 6,5 years) was performed in 10 and 18 patients, respectively. On the basis of the presenting symptoms and signs, the patients were divided into two groups.

Group "A" patients were characterized by presenting mainly hypo- or akinesia, rigidity, on/off fluctuation and L-dopa induced dyskinesia.

Group "B" patients were showing not only the symptoms and signs of Group „A" patients but also severe tremor.

In patients of Group "A" stereotactic pallidotomy was performed, and in patients of group "B" pallidotomy was supplemented with stereotactic thalamotomy.

For motor function examination the UPDRS part III and Fahn-Tolosa-Marin test were used. The evaluations were compared before the operation, and 2 days, 3 and 6 months postoperatively.

## ***8.2. Effect of the STN-DBS on the motor, cognitive functions and the performance time***

Thirteen (mean age was  $59.37 \pm 6.53$  years old; male:9, female:4; mean disease duration was  $15.415 \pm 5.6$  years) consecutive, right-handed patient with Parkinson's disease participated in the prospective study.

The time required for different manual tasks to be performed was measured and the motor function evaluations were made while the patients were "on" (currently taking levodopa and others PD medications, clinically "on") medication since most of them were unable to perform tasks under "off" (>12 hours off levodopa, and without others PD medications, clinically defined "off" ) medication. For motor function examination the UPDRS part III and Fahn-Tolosa-Marin test were used, and the cognitive function

was evaluated by a previously assembled neuropsychologic tests. These evaluations were performed before the operation, and 3 months postoperatively.

### **8.3. *<sup>1</sup>H- MR Spectroscopy assay***

Thirteen consecutive, right-handed patients (mean age was  $59.3 \pm 6.5$  years old; male:9, female:4; mean disease duration was  $15.4 \pm 5.6$  years) with Parkinson's disease participated in the prospective study.

All patients underwent single-voxel <sup>1</sup>H -MRS of the Gp and the FBC, using a single voxel system implemented on a 1 tesla scanner (Siemens). A short TE stimulated echo acquisition mode (STEAM) technique (TR = 2000 ms, TE = 30 ms, TM = 10 ms, 128 scans accumulated for signal averaging, volume of interest (VOI) dimension = 20x20x20 mm, water suppression 35 Hz, acquisition duration = 853 ms) was employed. The VOI was centered on the left and right Gp, and on the FBC. NAA/Cho, NAA/Cr, and Cho/Cr ratios were obtained.

The <sup>1</sup>H-MRS results (NAA/Cho, NAA/Cr, and Cho/Cr ratios) were compared before the operation (patients were in the "off state"), and 3 months postoperatively (stimulator was off).

## **9. Results**

### ***9.1. Effect of Pallidotomy and Pallidothalamotomy on the motor function and the performance time***

#### **Pallidotomy**

The following results were obtained after pallidotomy by using the UPDRS part III. : “On state” preoperative mean was 51,2 pts, at 2<sup>nd</sup> day postoperative 29,5, at 3<sup>rd</sup> and 6<sup>th</sup> month 26,0. “Off state” preoperative mean was 64,3 pts, at 2<sup>nd</sup> day postoperative 31,6, at 3<sup>rd</sup> and 6<sup>th</sup> month 26,0 pts.

- 1) During the **drawing** of large and small Archimedes spiral (task A & B), mean performance times preoperatively, and 2 days, 3 months and 6 months postoperatively were as follows: 42,7 s, 17,0 s, 15,3 s, and 13,0 s respectively.
- 2) The analogous data in task C were 18,7 s, 5,8 s, 5,8 s. and 4,3 s.
- 3) The **handwriting** performance times at the same timepoints were 22,7 s, 15,0 s, 14,7 s, and 10,6 s.

In all four evaluated qualities (i.e. task A, B, C and handwriting) the performance times improved significantly ( $p < 0,0001$ ).

#### **Combined pallidothalamotomy**

The following results were obtained by using the UPDRS III.: “**On state**” preoperative mean was 43,5 pts, at 2<sup>nd</sup> day postoperatively 27,9, at 3<sup>rd</sup> month 22,9, at 6<sup>th</sup> month 22,8 pts. “**Off state**” preoperative mean was 62,6, at 2<sup>nd</sup> day postoperatively 38, at 3<sup>rd</sup> month 30, at 6<sup>th</sup> month 31,8 pts.

1) In **tasks A & B**, the respective times were as follows: 16,7 s, 12,6 s, 13,6 s and 13,8 s. 2) In **task C**, the times were: 22,5 s, 14,0 s, 14,0 s and 15,0 s. 3) The following results were obtained for the **handwriting** performance times: 25,9 s, 20,4 s, 21,3 s and 22,5 s.

In all four evaluated qualities (i.e. tasks A, B, C and handwriting) the performance times improved significantly (**Student "t"-tests,  $p < 0,001$** ).

### ***9.2. Effect of the STN-DBS on the motor, cognitive function and the performance time***

The following results were obtained by measuring the performance times and motor (UPDRS – III) function:

1. **“On” state**: during the drawing of the *large Archimedes spiral* (task A), mean performance times preoperatively (on medication), and 3 months (on medication/on DBS) postoperatively were 15,3 s and 8,9 s, respectively. For the *small Archimedes spiral* (task B), the corresponding data were 18,5 s and 10,6 s. The analogous data in *task C* were 9,0 s and 3,9 s.
2. **“Off” state**: during the drawing of the *large Archimedes spiral* (task A), mean performance times preoperatively (off medication), and 3 months (off medication/on DBS) postoperatively were 28,0 s and 8,3 s, respectively. For the *small Archimedes spiral* (task B), the corresponding data were 30,1 s and 10,8 s. The analogous data in *task C* were 24,6 s and 3,7 s.
3. The **handwriting** performance times at the same timepoints were: “on” state - (on medication) 32,7 s, and (on medication/on DBS) 17,8 s; “off” state - (off medication) 66,0 s, and (off medication/on DBS) 16,9 s.

In all four evaluated qualities (i.e. task A, B, C and handwriting) the performance times improved significantly (**Student "t"- test,  $p < 0.1$** ).

The following results were obtained after DBS of the STN implantation by using the UPDRS part III.: “*On state*” preoperative mean (on medication) 57,2/108 pts, at 3<sup>rd</sup> month (on medication/on DBS) 12,6 pts. “*Off state*” preoperative mean (off medication) 73,5/108 pts, at 3<sup>rd</sup> month (off medication/on DBS) 22,5 pts. All results obtained during “off medication/off DBS” state evaluation were close to the preoperative “off” state.

The difference obtained in motor function by using UPDRS – III was significant (**Student "t"-test, "on phase"  $p = 3.0E-07$ , "off phase"  $p < 0.01$**  )

The results obtained by using the neuropsychologic tests for the cognitive function evaluation are showing on the table # 2. During the evaluation of the cognitive function only the AVLT showed significant improvement.

### **9.3. *<sup>1</sup>H- MR Spectroscopy experiment***

The following results were obtained from <sup>1</sup>H-MRS measures: significant increases of the NAA/Cho (**stud. “t”: 0.046**) and NAA/Cr (**stud. “t”: 0.032**), and significant decreases of the Cho/Cr (**stud. “t”: 0.036**) ratios were observed from the selected voxel in the **left FBC**. In all patients, decreases in NAA/Cho ratios were observed from the selected voxels in left and right Gp, however these changes were not significant.

The following results were obtained after DBS of the STN implantation by using the **UPDRS part III**: “*On state*” preoperative mean (on medication) was 57,2/108 pts, at 3<sup>rd</sup>

month (on medication/on DBS) 12,6 pts; **Stud. “t” p=3.08346E-07**. “Off state” preoperative mean (off medication) was 73,5/108 pts, at 3<sup>rd</sup> month (off medication/on DBS) 22,5 pts; **Stud. “t” p<0.01**. All results obtained during “off medication/off DBS state” evaluation were close to the preoperative “off” state.

## 10. Complications

### 1. Effect of Pallidotomy and pallidothalamotomy on the motor function and the performance time

No complications developed following pallidotomy.

Pallido-thalamotomy caused transient adverse effects in 2 patients, and 1 patient developed permanent adverse effects such as dysarthria and loss of balance.

### 2. Effect of the STN-DBS on the motor, cognitive function and the performance time

One patient died postoperatively (4 months) after an intracerebral hemorrhage, and one patient who was treated surgically, developed wound seroma around IPG (impulse generator); his IPG was removed and implanted four weeks after on the other side without complications

### 3. <sup>1</sup>H-MR Spectroscopy

During <sup>1</sup>H-MR Spectroscopy experiments complications were not detected.

## 11. Summary

Pallidotomy does not suppress tremor to such a significant degree as thalamotomy does. Therefore, the introduction of a combined procedure (Gpi and Vim ablation) was logical. Based on many bibliographical data, combined surgical interventions (pallido-thalamotomy) alleviate not only the hyperkinetic (tremor) but also the hypokinetic symptoms such as rigidity, bradykinesia, march and postural instability. Pallidotomy (Gpi) can improve the executory movements (movement tasks), such as pronation, supination and agility of the hands and fingers (dexterity), as well as movements of the arm. The hand becomes more punctual and subtle. These are appreciated in lesser degree in the ipsilateral side than in the contralateral side.

Thalamotomy primarily is apt for tremor attenuation. Ablative intervention in the thalamus (Vim) can be effective not only in suppressing the tremor, but also in increasing and improving the agility of the hand-movements.

The effects of the stereotactic procedures were evaluated by certain parts of the Fahn–Tolosa–Marín Tremor Rating Scale. The performance time was measured before the operation, and 2 days, 3 and 6 months postoperatively.

We came to the conclusion that pallidotomy diminished the manual task performance time significantly. The additional therapeutic effects such as acceleration and improvement of subtlety of the hand movements can be ascribed to the suppression or relief of the rigidity and hypokinesia also brought about by the operation. The decrease of the performance time observed in the course of observation, may be due to movement therapy applied after the surgical procedure.

The decrease of the performance time observed after combined pallidotomy procedures was not significant such as after pallidotomy. This phenomenon can be explained with the following fact, that the combined procedures were used mostly in Parkinson's disease patients with severe clinical symptoms, in whose besides for the pallidotomy indications tremor was also a characteristic sign. Furthermore, Parkinson's tremor is mainly resting in quality and doesn't intensify to action, hereby this kind of tremor may have less influence on the performance time.

There has been little data published concerning the speed of performance in handwriting and drawing following STN-DBS implantation. In this prospective study, the performance times - measured preoperatively and at 3 months postoperatively - clearly revealed that STN-DBS diminished the performance time for manual tasks, and improved motor scores (UPDRS III, specially finger tapping, hand pronation – supination, hand opening – closing) significantly, showing that might be a partial restoration of an “open-loop” automatic performance. Effects of the STN-DBS on the acceleration of performance time are not exactly known, but seems to be ascribed to the suppression or relief of symptoms brought about by the operation. These improvements may strongly be correlated with improvements in motor function (UPDRS III), primarily with regard to bradykinesia, and in particular with improvements of the sequential hand movements (finger tapping, hand pronation – supination, hand opening – closing).

The evidence of motor score improvement after STN-DBS is in concordance with the findings of other authors. These authors described motor score improvements in UPDRS III. Our observations indicate that STN-DBS improves not only motor scores (UPDRS III), but significantly diminishes the time required for certain manual performances, as well. We have

reported similar improvements after ablative procedures (pallidotomy and pallido-/thalamotomy).

Our observations indicate that stereotactic surgery for patients with Parkinson's disease improves not only motor function, but significantly diminishes the time required for certain manual performances, as well.

To our knowledge, this is the first study applying a parallel evaluation of <sup>1</sup>H-MRS results and clinical improvement in Parkinson's disease patients following STN-DBS. Using this technique, we have demonstrated that cortical (LFBC) NAA/Cho and NAA/Cr ratios were significantly increased; paired with a significant decrease of Cho/Cr ratio in all patients treated with STN-DBS. An insignificant decrease of the NAA/Cho ratio was observed in the selected voxels in Gp.

The underlying mechanism that might influence the observed concentration changes of the metabolites after STN-DBS is not elucidated yet. We consider that DBS may possibly increase the metabolism of neurons, or a sort of way can restore the function of a damaged neuron cells. Clinically these are showing in motor and cognitive function improvement.

Besides the metabolic changes, significant motor score improvements were observed (UPDRS III) 3 months following STN-DBS procedure, and these improvements were also highly correlated with amelioration in motor function, primarily regarding bradykinesia. After 3 months of the STN-DBS procedures during the cognitive function evaluation, just the AVLT improvements were significant; and the results of the other applied neuropsychologic tests were not significantly different. The deterioration of the cognitive function firstly can be

due to the disorder of the motor function, and to the decrease of the capacity of visuospatial orientation, in other way may be a consequence of the advanced age of life, and the frontal, parietal, and occipital cortical dysfunction. Taking bibliographic data into account, we suppose that the significant improvement of the AVLT may be explained with the motor function improvements occurred after STN-DBS, and possibly herewith linear concentration- and visuospatial orientation capacity improvements.

This study is still in progress and the number of patients is too small for any definite considerations. However our results suggest that NAA/Cho and NAA/Crea ratios may be a valuable criterion for evaluation of Parkinson's disease patients with the clinical improvement following STN-DBS. <sup>1</sup>H-MRS may be a useful utility as an aid in better understanding the pathophysiological process in Parkinson's disease patients on the basis of the variation of NAA/Cho and NAA/Crea ratios, and may be regarded as an useful technique to monitor disease progression. This data also suggests that NAA/Cho and NAA/Cr ratios could be a measure of functional impairment of cortical neurons in PD, but to certify these more studies are needed.

## **12. New results**

1. We demonstrate that pallidotomy diminished the manual task performance time significantly.
2. After combined pallidothalamotomy the decrease of the manual performance time was not significant such as after pallidotomy.

3. We demonstrate that STN-DBS diminished significantly the performance time for manual tasks, and improved motor scores (UPDRS III, specially finger tapping, hand pronation – supination, hand opening – closing) significantly.
4. Our observations have indicated that stereotactic surgery for patients with Parkinson's disease improves not only motor function, but significantly diminishes the time required for certain manual performances, as well.
5. To our knowledge, this is the first study applying a parallel evaluation of <sup>1</sup>H-MRS results and clinical improvement in Parkinson's disease patients following STN-DBS.
6. Using <sup>1</sup>H-MRS, we have demonstrated that cortical (LFBC) NAA/Cho and NAA/Cr ratios were significantly increased; paired with the significant decrease of Cho/Cr ratio in all patients treated with STN-DBS.
7. Using <sup>1</sup>H-MRS, we observed that the decrease of the NAA/Cho ratio in the selected voxels in Gp was insignificant.
8. We demonstrate, that besides the metabolic changes, significant motor score improvements were observed (UPDRS III) 3 months following STN-DBS procedure, and these improvements were also highly correlated with amelioration in motor function, primarily regarding bradykinesia.

9. After 3 months of the STN-DBS procedures during the cognitive function evaluation, just the AVLT improvements were significant. and the results of the other applied neuropsychologic tests were not significantly different.

## Publications

### Publications related to the thesis:

1. Balás I, **Llumiguano C**, Horváth Z, Kövér F, Dóczi T.: MRI guided stereotactic thalamotomy for the treatment of the neurogenic pain. Rev Neurol 2000;31(6):531–533. **If:0,692.** idézés:6
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Total: 6

English: 6

**Impact factor: 5,986**

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**Foreign citations:22**

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Total: 6

English: 4

Spanish: 2

**Impact factor: 9,561**

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**Foreign:2**

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