FOLIA MEDICA CRACOVIENSIA
Vol. LIII, 2, 2013: 15–22
PL ISSN 0015-5616

Wojciech Pietraszko[1], Agata Furgała[2], Agnieszka Gorecka-Mazur[1], Piotr Thor[2], Marek Moskała[1], Jarosław Polak[1], Artur D. Surówka[3], Anna Krygowska-Wajs[4]

EFFICACY OF DEEP BRAIN STIMULATION OF THE SUBTHALAMIC NUCLEUS ON AUTONOMIC DYSFUNCTION IN PATIENTS WITH PARKINSON'S DISEASE

Abstract: Subthalamic nucleus (STN) deep brain stimulation (DBS) is well established for the treatment of the motor symptoms of Parkinson's disease (PD). However, the effect of STN DBS on autonomic symptoms has not been well studied. We examined 19 patients undergoing STN DBS for PD. The patients were administered a questionnaire to evaluate the pre-operative and post-operative autonomic function. All patients reported a significant post DBS improvement of one or more symptoms of the autonomic dysfunction (urinary and gastrointestinal function). In particular, we have shown the most significant improvement in the urinary function after STN DBS. Further larger studies are required with respect to the effect of STN DBS on the autonomic function.

Key words: deep brain stimulation, Parkinson's disease, urinary and gastrointestinal symptoms.

INTRODUCTION

Parkinson's disease is a common neurodegenerative disorder, clinically characterized by the progression of several motor and non-motor neurological functions [1]. Non-motor symptoms including autonomic dysfunction increase with neurological impairment, disease duration and progression of the underlying neurodegenerative process. In recent years it has been increasingly recognized that in some patients the non-motor symptoms of PD can be even more disabling than motor symptoms [2, 3]. In advanced stages of the disease, many patients will experience reduced efficacy of medication with fluctuations in symptoms and dyskinesias. Surgical treatment with deep brain stimulation of the subthalamic nucleus (STN-DBS) is well established for treating the motor symptoms for advanced PD and is the most effective surgical procedure for patients with intractable fluctuations [4, 5]. However, the effect of STN-DBS on autonomic symptoms has not been well studied. Dysautonomia such as constipation, urinary dysfunction including urgency, increased frequency or incontinence is frequently encountered,

particularly at the advanced stages of the disease when DBS is considered as a therapeutic option. It is therefore of clinical relevance to investigate whether DBS has also an effect on the urinary or gastrointestinal function. Previous small studies have indicated that some autonomic symptoms may improve following STN DBS [6–10].

In this study, we investigated whether gastrointestinal and urinary symptoms of PD improve following STN DBS.

MATERIALS AND METHODS

The study enrolled 19 patients (4 females, 15 males) aged 59.37 ± 10.00 years (range 32 to 70 years), and mean duration of a disease of 11.9 ± 4.5 years who were selected to undergo STN-DBS at Jagiellonian University Department of Neurosurgery.

The patients were approved for surgery according to the following selection criteria: diagnosis of PD according to UK Parkinson's Disease Society Brain Bank Clinical diagnostic criteria [11], disease duration >5 years, age under 70 years, disabling motor fluctuations despite optimal adjustment of antiparkinsonian medication, normal magnetic resonance imaging (MRI) studies of the brain, no significant cognitive impairment (score on the Mini-Mental State of Examination, >24), no psychiatric or behavioural disturbances, and no surgical contraindications.

The study was approved by the Ethics Committee of Jagiellonian University Collegium Medicum and the patients submitted their written informed consent.

ASSESSMENTS

Evaluation of signs of PD was performed using the motor components of the Unified Parkinson's disease rating scale (UPDRS). Patients were evaluated preoperatively and post operatively for three months. Assessment of the motor scale was carried out at baseline (before subthalamic nucleus DBS), both in the "on" condition with medication, and without medication after withdrawal overnight in the "off" condition, and for 3 months following the surgery. After the surgery, the motor score was performed in "off" medication and stimulation "on" condition. All patients were evaluated by the same movement disorder specialist at baseline and during the 3 month follow-up visit.

We used autonomic function questionnaire explored components of the gastrointestinal and urinary tract. Gastrointestinal symptoms were studied by assessing the patient's bowel function including frequency, bowel dynamics, difficulty with defecation, dysphagia, abdominal discomfort or pain, postprandial bloating and weight loss. Urinary symptoms of PD were studied by assessing the patients' frequency, urgency, nocturia, and satisfaction with their urinary function.

ASSESSMENT OF GASTROINTESTINAL SYMPTOMS

All patients completed a self-administered questionnaire that included nine symptoms (heartburn, abdominal pain, sialorrhea, constipation, intensity of difficulty with defecation, rectal burning during or after defecation, dysphagia, bloating, weight loss) to assess subjective gastrointestinal symptoms. The severity of each of these symptoms was scored (0–5 points) as: absent (0), or severe (5). Factor analyses were also performed.

ASSESSMENT OF URINARY SYMPTOMS

The patients completed a self-reported questionnaire regarding the presence or absence of five urinary symptoms (nocturia, urgency, incontinence, frequency, hesitancy). The severity of each of these symptoms was scored (0–5 points) as: absent (0), or severe (5). Factor analyses were also performed.

SURGICAL PROCEDURE

Pre-operative 1.5T MRI (T2, T1 with contrast enhancement) was performed. The targeting of the subthalamic nucleus (STN) was performed on surgical planning workstation (Stealth, Medtronic Inc., Minneapolis, MN) and software (Framelink, Medtronic Inc.). The target site (STN) was identified on MRI, with reference to a standard stereotactic atlas and coordinates. In the day of the surgery the RM stereotactic frame was placed on the head of the patient under local anesthesia, and CT with contrast enhancement was performed. Fusion of CT and MRI was then performed. Patients received a short-term sedation during drilling of the burr hole and introducing 3–5 microelektrodes. Microelectrode recordings were carried out to identify the neuronal signals of STN. Macrostimulation was then performed to confirm the appropriate location for rigidity, bradykinesia and tremor control and the assess for adverse effects of stimulation. When the best location had been established, permanent electrode (Medtronic 3389, Medtronic Inc.) was inserted in the same position. Under general anesthesia internal pulse generator (IPG) was placed into a subcutaneous pocket in the subclavicular region and connected to the electrode. The next day CT was performed and IPG was turned on. Implantation of the second electrode and IPG, on the other side of the body, was performed usually two weeks later. Standard initial settings of the IPG were as follows: 1–2 V, 130 Hz, 60 μs.

STATISTICAL ANALYSIS

Statistical analysis was performed using a Wilcoxon signed rank test to determine the relative difference between the preoperative and postoperative states in each patient. Furthermore, to verify the normality of distribution of each variable, the

Shapiro–Wilk test was carried out. In case of normally distributed variables the t-test for dependent variables was applied. A Spearman rank test was performed to determine whether there existed any correlations between the quantitative variables. A p value of 0.05 was taken to be the statistical significance threshold. Overall statistical analysis was prepared by means of STATISTICA 10.0 package.

RESULTS

All the procedures were performed without complications. DBS STN significantly improved patients' motor performance ($p < 0.0005$), decreasing UPDRS motor score in average 65%, from 55.2 ± 2.1 to 19.1 ± 1.1 ($p < 0.0002$) in the "off" condition and significant decrease in average 71% from 37.6 ± 1.7 to 10.9 ± 0.8 ($p << 0.0001$) in "on" condition. Table 1 presents the results of the UPDRS before and after DBS-STN. Anti-parkinsonian drugs were reduced by 75% from baseline after the surgery ($p < 0.0002$). The levodopa daily dose from a mean of 1144 (range 600–2000) preoperatively to 283 (range 0–600). Effects of DBS-STN on autonomic symptoms are listed in Table 2. The most common autonomic symptoms reported

Table 1

Effects of bilateral subthalamic nucleus stimulation on UPDRS score.

		Baseline	3 months follow-up	Improvement %	p-value
UPDRS Part III	ON	37.6 ± 1.7	10.9 ± 0.8	71	p <<0.0001
	OFF	55.2 ± 2.1	19.1 ± 1.1	65	0.0002

Table 2

Effects of bilateral subthalamic nucleus stimulation on urinary and gastrointestinal dysfunction.

Class	Parameter	Preoperative	Postoperative	Reduction %	p-value
Urinary dysfunction	Urgency	2.7 ± 0.4	0.3 ± 0.2	89	0.001
	Frequency	3.2 ± 0.4	1.0 ± 0.4	69	0.005
	Nocturia	2.1 ± 0.5	0.6 ± 0.3	71	0.01
	Hesistancy	0.8 ± 0.3	0.3 ± 0.2	63	0.04
Gastrointestinal dysfunction	Weight loss	0.7 ± 0.2	0.0 ± 0.0	100	0.005
	The intensity of problem with defecation	2.7 ± 0.4	1.4 ± 0.3	48	0.001
	Constipation	3.8 ± 0.3	1.6 ± 0.3	58	0.0007
	Dysphagia	1.6 ± 0.4	0.6 ± 0.3	63	0.008
	Abdominal pain	1.6 ± 0.4	0.9 ± 0.3	43	0.02
	Rectal burning during or after defecation	1.2 ± 0.3	0.7 ± 0.2	42	0.02
	Sialorrhea	1.0 ± 0.4	0.3 ± 0.1	70	0.02
	Bloating	1.1 ± 0.3	0.8 ± 0.4	27	0.58

prior to surgery were: constipation (95%), urine urgency (84%), frequency (84%) problems with defecation (84%) weight loss (58%) The least prevalent autonomic symptoms were: hesitancy, rectal burning during or after defecation and abdominal pain. None of the patients had heartburn and urinary incontinence.

Following the STN-DBS weight loss was eliminated in all previous patients. The percentage of patients with dysphagia, constipation and difficulties with defecation was significantly reduced. As compared with baseline, after DBS-STN the scores for frequency improved by 69%, those for urgency by 89%, and those for nocturia by 71%. Effects of STN DBS on the most frequent autonomic dysfunction are presented in Figure 1.

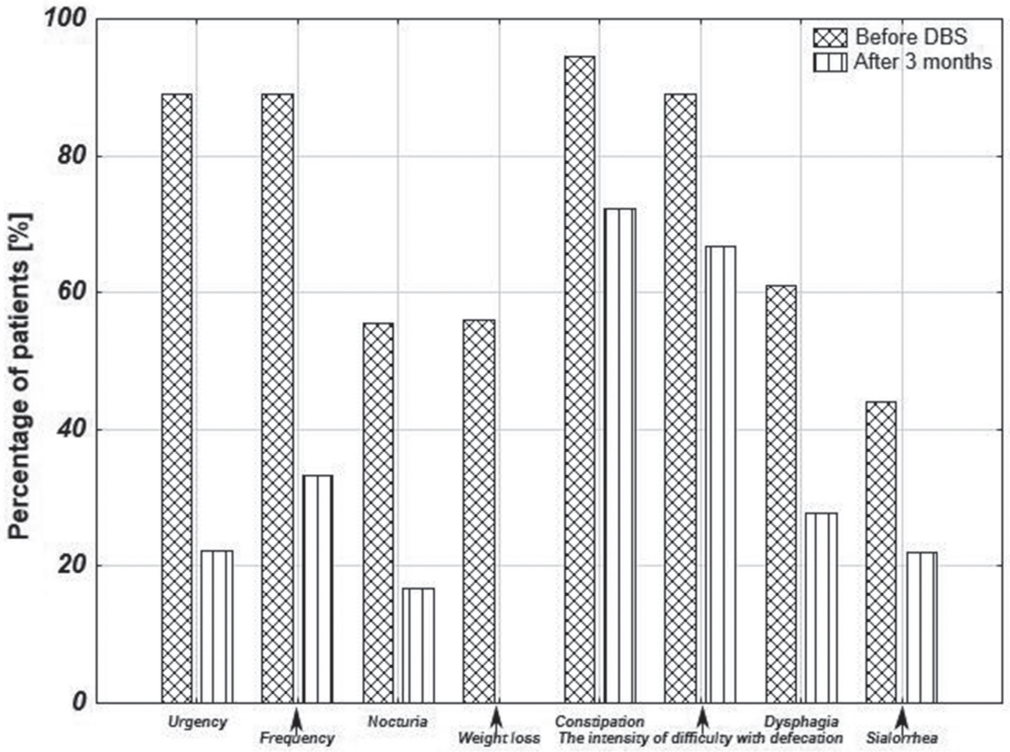

Fig. 1. Effects of bilateral subthalamic stimulation on the most frequent autonomic dysfunction. Ordinate express the percentage of patients who reported these autonomic before and after surgery. Before: preoperative non motor symptom; After: postoperative non motor symptom.

DISCUSSION

Our results show that urinary and gastrointestinal symptoms of autonomic dysfunction associated with PD are widespread and improve significantly in most patients who underwent STN-DBS surgery. After 3 months of STN stimulation all

the patients were improved, but to variable extension. The improvement in the motor scale was in line with most of the data published so far [3, 5]. The autonomic dysfunction decreased considerably under chronic stimulation, in terms of the overall number of symptoms reported. The results of the questionnaire administrated before the electrode implantation were similar to those obtained in the previous study [7–9].

The improvement of dysautonomic fluctuations after chronic stimulation was remarkable especially for some symptoms. Urinary dysfunction showed the greatest reduction in the number of symptoms reported by patients after the surgery. Frequency and urgency, which are one of the most debilitating autonomic symptoms were reported by more than 80% of the patients. After DBS, these symptoms decreased significantly, 31% of patients reported having had a few episodes of urgency and frequency. Gastrointestinal functions were less responsive to STN DBS.

Observed differences between the responses of various autonomic symptoms might be partially explained by the existence of different mechanisms of the autonomic regulation. It is well known that more regions of the brain are involved in PD and underlie the development of non-motor symptoms, including urinary and bowel symptoms. Studies of the basal ganglia in animal models of PD have shown that nigrostriatal degeneration of dopaminergic neurons leads to urgency and frequency [12]. The severity of bladder dysfunction seems to be associated with the relative degeneration of the caudate nucleus, amongst other areas [13]. According to the neuropathological model of disease progression developed by Braak *et al.* the threshold seems to be the involvement of the neocortex in the disease process and the occurrence of bladder symptoms [14]. Functional imaging studies have suggested some STN DBS modulation of brain areas involved in autonomic control. PET studies have supported that STN-DBS leads to changes in neural activation of frontal cortical regions including supplementary motor area [15, 16] as well as anterior cingulate gyrus [16, 17]. These structures play a role in urinary function as has been revealed in PET [18–20] and MRI studies [21]. Gastrointestinal function is associated with autonomic centres such as the frontal cortex, cingulate cortex, insula, thalami, basal ganglia and periaqueductal grey matter [22–24]. The activation of nerve fibres projecting from or to hypothalamus and crossing the subthalamic nucleus might have a possible effect on gastrointestinal function induced by DBS-STN. The discrepancies between urinary and gastrointestinal improvement might result from the fact that the bowel function depends not only on central but also peripheral autonomic structures which might not be the system modulated by STN DBS.

The results of this study show that autonomic symptoms respond to STN DBS. However, the results were not equal to all categories of symptoms. Urinary dysfunction showed a remarkable decrease after the chronic stimulation. Further studies are required with respect to the improvement of non-motor symptoms after STN-DBS.

ACKNOWLEDGMENTS

This study was supported by Polish Ministry of Science and Higher Education and its grants for Scientific Research KBET/240/B/2012.

REFERENCES

1. *Lees A., Hardy J., Revesz T.*: Parkinson's disease. Lancet. 2009; 373: 2055–2066. — **2.** *Chaudhuri K.R., Schapira A.H.*: Non-motor symptoms of Parkinson's disease: dopaminergic pathophysiology and treatment. Lancet Neurol. 2009; 8: 464–474. — **3.** *Witjas T., Kaphan E., Azulay J.P., Blin O., Ceccaldi M., Pouget J., Poncet M., Chérif A.A.*: Nonmotor fluctuations in Parkinson's disease: frequent and disabling. Neurology. 2002; 59: 408–413. — **4.** *Krack P., Batir A., Van Blercom N., Chabardes S., Fraix V., Ardouin C., Koudsie A., Limousin P.D., Benazzouz A., LeBas J.F., Benabid A.L., Pollak P.*: Five year follow-up of biliateral stimulation of the subthalamic nucleus in advanced Parkinon's disease. N Engl J Med. 2003; 349(20): 1925–1934. — **5.** *Fraix V., Houeto J.L., Lagrange C., Le Pen C., Krystkowiak P., Guehl D., Ardouin C., Welter M.L., Maurel F., Defebvre L., Rougier A., Benabid A.L., Mesnage V., Ligier M., Blond S., Burbaud P., Bioulac B., Destée A., Cornu P., Pollak P.; SPARK Study Group.*: Clinical and economic results of bilateral subthalamic nucleus stimulation in Parkinson's disease. J Neurol Neurosurg Psychiatry. 2006; 77: 443–449. — **6.** *Halim A., Baumgartner L., Binder D.K.*: Effect of deep brain stimulation on autonomic dysfunction in patients with Parkinson's disease. J Clin Neurosc. 2011; 18: 804–806. — **7.** *Herzog J., Weiss P.H., Assmus A., Wefer B., Seif C., Braun P.M., Herzog H., Volkmann J., Deuschl G., Fink G.R.*: Subthalamic stimulation modulates cortical control of urinary blader in Parkinson's disease. Brain. 2006; 129: 3366–3375. — **8.** *Trachani E., Constantoyannis C., Sirrou V., Kefalopoulou Z., Markaki E., Chroni E.*: Effects of subthalamic nucleus stimulation on sweating function in Parkinson's disease. Clinical Neurology Neurosurg. 2012; 112: 213–217. — **9.** *Nazzaro J., Pahwa R., Lyons K.*: The impact of bilateral subthalamic stimulation on non-motor symptoms of Parkinson's disease.Parkinsonism Rel Disord. 2011; 17: 606–609. — **10.** *Arai E., Arai M., Uchiyama T., Higuchi Y., Aoyagi K., Yamanaka Y., Yamamoto T., Nagano O., Shiina A., Maruoka D., Matsumura T., Nakagawa T., Katsuno T., Imazeki F., Saeki N., Kuwabara S., Yokosuka O.*: Subthalamic deep brain stimulation can improve gastric emptying in Parkinson's disease. Brain. 2012; 135: 1478–1485.

11. *Fahn S., Elton R.*: Members of the UPDRS Development Comitee The Unified Parkinson's Disease Rating Scale. [In:] S. Fahn, C.D. Marsden, D.B. Calne, M. Goldstein (Eds.). Recent developments in Parkinson's disease, vol. 2 Mcmellam Health Care Information, Florham Park NJ 1987; 153–163. — **12.** *Seki S., Igawa Y., Kaidoh K., Ishizuka O., Nishizawa O., Andersson K.E.*: Role of dopamine D1 and D2 receptors in the micturition reflex in conscious rats. Neurourol Urodyn. 2001; 20: 105–113. — **13.** *Fowler C.J., Dalton C., Panicker Jn.*: Review of neurologic diseases for the urologist. Urol Clin North Am. 2010; 37: 517–526. — **14.** *Braak H., Ghebremedhin E., Rüb U., Bratzke H., Del Tredici K.*: Stages in the development of Parkinson's disease related pathology. Cell Tissue Res. 2004; 318: 121–134. — **15.** *Thobis S., Dominey P., Fraix V., Mertens P., Guenot M., Zimmer L., Pollak P., Benabid A.L., Broussolle E.*: Effects of subthalamic nucleus stimulation on actual and imagined movement in Parkinson's disease; a PET study. J Neurol. 2002; 249: 1689–1698. — **16.** *Strafella A.P., Dagher A., Sadikot A.F.*: Cerebral blood flow changes induced by subthalamic stimulation in Parkinson's disease. Neurology. 2003; 60: 1039–1042. — **17.** *Lomousion P., Greene J., Pollak P., Rothwell J., Benabid A.L., Frackowiak R.*: Changes in cerebral activity pattern due to subthalamic nucleus or internal palladium stimulation in Parkinson's disease. Ann Neurol. 1997; 42: 283–291. — **18.** *Nour S., Svarer C., Kristensen J.K., Paulson O.B., Law I.*: Cerebral activation during micturition in normal men. Brain. 2000; 123: 781–789. — **19.** *Athwal B.S., Berkley K.J., Hussain I., Brennan A., Craggs M., Sakakibara R., Frackowiak R.S.J., Fowler C.J.*: Brain responses to changes in bladder volume and urge to void in healthy men. Brain. 2001; 124: 369–377. — **20.** *Matsuura S., Kakizaki H., Mitsui T.,*

Shiga T., Tamaki N., Koyanagi T.: Human brain region response to distention or cold stimulation of the bladder: a positron emission tomography study. J Urol. 2002; 168: 2035–2039.

21. *Kuhtz-Buschbeck J.P., van der Horst C., Pott C., Wolff S., Nabavi A., Jansen O., Jünemann K.P.*: Cortical representation of the urge to void: a functional magnetic resonance study. J Urol. 2005; 174: 1477–1481. **— 22.** *Ladabaum U., Minoshima S., Hasler W.L., Cross D., Chey W.D., Owyang C.*: Gastric distention correlates with activation of multiple cortiocal and subcortical regions. Gastroenterology. 2001; 120(2): 369–376. **— 23.** *Stephan E., Pardo J.V., Faris P.L., Hartman B.K., Kim S.W., Ivanov E.H., Daughters R.S., Costello P.A., Goodale R.L.*: Functional neuroimaging of gastric distention. J Gastrointest Surg. 2003; 7(6): 740–749. **— 24.** *Vandenbergh J., Dupont P., Fischler B., Bormans G., Persoons P., Janssens J., Tack J.*: Regional brain activation during proximal stomach distention in humans: A positron emission tomography study. Gastroenterology. 2005; 128(3): 564–573.

[1] Department of Neurosurgery
Jagiellonian University Medical College
ul. Botaniczna 3, 31-503 Kraków, Poland

[2] Department of Pathophysiology
Jagiellonian University Medical College
ul. Czysta 18, 31-121 Kraków, Poland

[3] AGH University of Science and Technology
Faculty of Physics and Applied Computer Science
al. Mickiewicza 30, 30-059 Kraków, Poland

[4] Department of Neurology
Jagiellonian University Medical College
ul. Botaniczna 3, 31-503 Kraków, Poland

Corresponding author:
Anna Krygowska-Wajs MD, Prof.
Department of Neurology
Jagiellonian University Medical College
ul. Botaniczna 3, 31-503 Kraków, Poland
E-mail: krygowska@neuro.cm-uj.krakow.pl