DOI: https://doi.org/10.25121/PNM.2017.30.10.524 Post N Med 2017; XXX(10): 524-529

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Improvement in motor functions and emotional changes in patients with Parkinson's disease after DBS therapy

Poprawa funkcji motorycznych i zmiany emocjonalne u chorych z chorobą Parkinsona leczonych głęboką stymulacją mózgu

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Keywords

Parkinson's disease, DBS, STN stimulation, psychological assessment

Słowa kluczowe

choroba Parkinsona, DBS, stymulacja STN, ocean psychologiczna

Summary

Introduction. Deep brain stimulation (DBS) is a method of treatment in advanced stages of Parkinson's disease (PD).

Aim. The aim of our study was to verified the impact of stimulation of subthalamic nucleus (STN) on the improvement of motor and emotional functions in patients with Parkinson's disease.

Material and methods. We analysed data of 40 patients who underwent bilateral DBS for treatment of Parkinson's disease in our department between September 2009 and December 2014. Patients were assessed with UPDRS motor score before surgery: with and without medicaments and 3 months after surgery. Every patient underwent psychological evaluation during which time level of depression and fear in our patients with BDI were tested. All patients had another psychological evaluation after one year of stimulation.

Results. All stimulators were turned on after 3-4 weeks. The parameters of stimulation were as follows: monopolar stimulation, pulse with (PW) 60 msec., frequency 130 Hz, amplitude average 2.6 mA. The only one contact was active in 88% of cases, 2 contacts active in 12% of cases. Diminishing of depression tendencies and the level of anxiety were observed.

The reduction in motor UPDRS score by 62% and a reduction in daily levodopa-equivalent dose by 71% were achieved.

Conclusions. Stimulation of subthalamic nucleus allows to achieve significant improvement in motor functions in patients with advanced stages of Parkinson's disease and to diminish the amount of taken medicaments. Improvement in motors function in patients with advanced stages of Parkinson's disease have a positive effect on the of the emotional sphere.

Streszczenie

Wstęp. Głęboka stymulacja mózgowa (DBS) jest znaną metodą leczenia pacjentów z chorobą Parkinsona (PD).

Cel pracy. Celem naszych badań było określenie, jaki wpływ ma stymulacja jądra niskowzgórzowego (STN) na poprawę funkcji motorycznych i emocjonalnych u tych chorych.

Materiał i metody. Analizowano dane 40 osób z chorobą Parkinsona leczonych metodą głębokiej stymulacji w naszej klinice w okresie od września 2009 do grudnia 2014 roku. Przed zabiegiem wszyscy chorzy byli oceniani w skali UPDRS bez leków i po przyjęciu leków przeciwparkinsonowskich oraz ponownie 3 miesiące po operacji. Każdy chory przeszedł badanie neuropsychologiczne na obecność depresji przy pomocy testu BDI. Wszyscy chorzy byli ponownie badani przez neuropsychologa po upływie roku.

Wyniki. Stymulacja została włączona 3-4 tygodnie po zabiegu. Parametry stymulacji: stymulacja monopolarna, szerokość impulsu 60 msec, częstotliwość 130 Hz, średnia amplituda 2,6 mA. Tylko jeden kontakt był włączony u 88% chorych, dwa kontakty aktywne u 12% chorych. Obserwowano zmniejszenie tendencji depresyjnych i niepokoju. Uzyskano poprawę w skali UPDRS u około 62% chorych i zmniejszono dzienną dawkę lewodopy o 71%.

Wnioski. Stymulacja jądra niskowzgórzowego pozwala uzyskać istotną poprawę funkcji ruchowych u pacjentów z zaawansowaną postacią choroby Parkinsona i zmniejszyć ilość przyjmowanych leków. Poprawa funkcji ruchowych wpływa pozytywnie na sferę emocjonalną chorych.

Conflict of interest
Konflikt interesów

None
Brak konfliktu interesów

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INTRODUCTION

Parkinson's disease (PD) is a disabling neurological illness characterized by motor and non motor symptoms. The main motor symptoms are:

- resting tremor often of hand, arm or leg,
- bradykinesia – slowed and limited movements,
- rigidity – muscle stiffness.

The other motor symptoms of PD may include: impaired posture and impaired balance, talking and swallowing disturbance, speech difficulties, loss of movement in the fascial muscles can cause facial expression known as "Parkinson's mask", difficulty with walking, small steps and shuffle with feet together.

The non-motor symptoms of Parkinson's disease are as follows: change in taste and smell, choking, nausea and vomiting, constipations, drooling, urinary dysfunction, orthostatic hypotension, insomnia, excessive sweating, double vision, rest leg syndrome, leg swelling, dementia and cognitive impairment, depression, anxiety, hallucinations, sexual dysfunction (1, 2).

Over the first years of treatment Parkinsonian signs can be effectively controlled by oral administration of antiparkinsonian drugs. Progression of disease brings problems with unpredictable motor fluctuations. In many patients there is a satisfactory response to levodopa over the first years duration of the disease, but after this period motor fluctuations develop which limit the pharmacological treatment effectiveness. When the pharmacological treatment is insufficient the surgical intervention is recommended. Significant improvement in quality of life and motor function have been obtained with subthalamic nucleus (STN) stimulation (3). Deep brain stimulation (DBS) is a well known method of treatment in the advanced stages of Parkinson's disease (PD). The aim of therapy is to improve of the most disabling parkinsonian symptoms such as rigidity, bradykinesia and tremor to positively influence patient's quality of life.

The aim of the study was to assess the effects of stimulation of subthalamic nucleus (STN) on behavioural changes in patients with Parkinson's disease. Contentment with life (4) is being described as the general evaluation of the quality of life in the aspects chosen by patients. A subjective well-being is comprised of the level of satisfaction with life, positive feelings and the lack of negative feelings (5, 6). The evaluation of contentment with life is a result of comparing personal situation with standards the person has set before himself. The feeling of satisfaction is the result of a positive outcome of this comparison.

Behavioural differences in response to the illness depend on many socio-cultural and psychological factors influencing the level of suffering from the symptoms and perceived psychological state (7). Illness and its consequences constitute a complex stress syndrome (8). This has a negative influence on the functioning and emotional experiences of patient. Stress effects depend mostly on the choice of strategy of coping with difficult situation. To keep stress under control a person undertakes actions to reduce or eliminate the threat. These actions consist of many strategies of coping with the direct stress including attempts to control emotional tension or changing the situation towards solving of the problem (7). The individual methods of handling stressful situations play a major role in the process of emotion control and adaptation.

Parkinson's disease affects as many as 60 thousands people in Poland (9).

Bilateral STN DBS is a method of treatment in patients with idiopathic Parkinson's disease. Relief of the motor symptoms as: rigidity, bradykinesia and tremor can be achieved (10-12). The influence of DBS on non-motor symptoms in Parkinson's disease is rather limited.

There are three commonly recognised targets for stimulation:

- subthalamic nucleus (STN) – aiming at improvement of all motor-symptoms: rigidity, termor and bradykinesia, postural and gait on the off period (13). Reduction of dyskinesias connected with reduction of levodopa's doses (14). Elongation of "on" period. Improvement of daily activity,
- the ventral intermediate nucleus of the thalamus (Vim) is the best choice for patients with severe pharmacoresistant tremor,
- globus pallidus pars internal (GPi) – the best choice for patients with severe rigidity.

AIM

The aim of the study was to evaluate the benefits of deep brain stimulation in improvement of motor symptoms and reduction of daily levodopa equivalent dose after neurosurgical DBS treatment of patients with idiopathic Parkinson's disease. Another purpose of this study was to estimate the risk of the surgery and to assess the effects of stimulation of subthalamic nucleus (STN) on behavioural changes in patients with Parkinson's disease.

MATERIAL AND METHODS

The data of 40 consecutive patients with Parkinson's disease treated in the Department of Neurosurgery of the Medical University in Lublin were evaluated. All patients were referred to Neurosurgical Department by a neurologist, who confirmed diagnosis of Parkinson's disease and expressed an opinion that there is no further effective pharmacological treatment for those patients available. All candidates for DBS underwent a levodopa/dopaminergic challenge test. During levodopa/dopaminergic challenge test patients stop taking antiparkinsonian medicaments for 12 hours and after that patients are evaluated in UPDRS scale. Afterwards the patients are given suprathreshold dose of levodopa and then again evaluated with UPDRS in his best "on" state. Optimal surgical candidates demonstrate at least 30% improvement in the motor part (Part III) of the UPDRS. The test excludes patients with parkinsonian syndromes, which are levodopa unresponsive (15, 16).

Before surgery the patients were examined in neurosurgical outpatient clinic to prove that they are good candidates for surgery (no history of anticoagulants, terminal neoplasm, infections and immunological deficiency etc.). Eligible patients were subjected to neuropsychological assessment. The level of depression and fear has been assessed with Beck Depression Inventory (BDI) test and an ISCL test. Patients with psychiatric problems, major depression and severely impaired cognitive functions were excluded from the surgical treatment. The exclusion criteria from the examined group was a high level of fear assessed by the ISCL test and high level of depression in the BDI test before surgery.

The patients with severe and mild depressive syndromes were referred to psychiatric clinic for pharmacological therapy, and after the antidepressant treatment were repeatedly evaluated and eventually accepted as the candidates for surgery.

Neurological condition was evaluated using Unified Parkinson's Disease Rating Scale (UPDRS). UPDRS is commonly used for the clinical study of Parkinson's disease. The scale itself is composed of six parts: part I – evaluation of mental activity and state of mind or cognition, behaviour and mood; part II – evaluation of the daily activities and daily living; part III – evaluation of motor functions; part IV – evaluation of complications of treatment; part V – Hoehn and Yahr scale staging of the severity of Parkinson's disease; part VI – Schwab and England Activities of Daily Living scale (17). Parts I, II and III contain 44 questions and each items is measured on a five-point scale, part IV contains 11 questions evaluated from 0 to 23. Each part of the scale determines the areas and level of disability, together with four sections that evaluates complication of treatment. Each answer in the scale was analysed during the patient interview. The scale required multiple grades evaluation with a possible maximum of 199 points. A score of 199 points on the UPDRS scale represents the worst disability, and zero means no disability (2).

All patients underwent psychological assessment before and after surgery, in the end only 12 patients have been selected to the research group for analysing changes in the emotional sphere: eight male and four female in age from 47 to 73. Three people were actively working and nine living on pension. The level of depression and fear in the examined patients has been assessed with ISCL test and Beck Depression Inventory (BDI) test. BDI consists of series of questions to measure the intensity, severity and depth of depression. Test contains 21 questions each with four possible responses to establish a specific symptom of depression. Each response is assigned a score from zero to three, depending of the severity of symptoms. Questions of the BDI evaluate mood, pessimism, guilt, sense of failure, self-dissatisfaction, self-dislike, self-accusation, suicidal ideas, crying, irritability, social withdrawal, work difficulties, fatigue, insomnia, weight loss, loss of libido. The sum of the scores correlates with the severity of depression. The BDI score was used to detect, assess and monitor depressive symptoms. The criteria of excluding from the examined group were a high level of fear reached in the ISCL test and a high intensity of depression in the BDI test before surgery.

To verify the functioning after surgery two research methods have been applied: a self-made questionnaire and The Satisfaction with Life Scale – SWLS (authors: Ed Diener, R. A. Emmons, R. J. Larson, S. Griffin; adaptation: Zygfryd Juczynski). To analyse the results of SWLS test sten score is used. SWLS scale is a short score which comprises five statements evaluated in a five-point scale. The self-made questionnaire assessed functioning in social, professional and social life, feeling of contentment about the state of life and the possibilities of carrying out daily activities.

All the patients underwent bilateral STN DBS procedure between September 2009 and December 2014. The analysed group consisted of women and man, mean age 60 years (49-73y).

Patients were admitted to the neurosurgical ward two days before surgery. On the first day MRI imaging (1.5 tesla) were performed – T1 pulse sequence 1 mm thick slices and T2 pulse sequence 1.5 mm thick slices. After MRI antiparkinsonian medications were withheld 24 hours before surgery. Direct planning was done using Brain-Lab® planning software. Informed consent was obtained from each patient before surgery. On the day of surgery stereotactic Lexel-frame was fixed under local anaesthesia and CT scans were done. The planning was performed with Brain-Lab® planning software, the target was defined on real T1 and T2 MRI pictures fused with CT scans. All patients underwent guided microelectrode recording with five, four or three microelectrodes introduced simultaneously and the patterns of neuronal activity of STN was recorded to establish boundaries of STN. Then macrostimulation of the STN was performed with the current of 60 msec. pulse width (PW) and 130 Hz frequency: first with a low amplitude (1-3 mA) to evaluate clinical effects and then with a higher amplitude (4 mA and above) to obtain transient neurological deficit (mainly from internal capsule) to establish safe "gap" between the treatment dose and the overdose producing side effects. Postoperative CT images confirmed appropriate lead placement. Programming began 3 or 4 weeks after the surgery. Settings were selected based on the maximum clinical effects with minimal side effects. The parameters of stimulation were as follows: monopolar stimulation, pulse width 90 msec., frequency 130 Hz, amplitude average 2.6 mA.

All patient underwent clinical and psychological evaluation before surgery and three months after. Outcomes of subthalamic nucleus stimulation were tested with UPDRS. Before surgery all patients were evaluated in all parts of UPDRS, after surgery patients were evaluated with part III UPDRS to establish changes in motor functions.

The reduction in daily levodopa – equivalent dose was evaluated on the base of the history of pharmacological treatment before and after surgery.

RESULTS

Forty patients with disabling motor fluctuations and dyskinesias underwent DBS surgery at the Department of Neurosurgery Medical University in Lublin between September 2009 and December 2014. The analysed group consisted in 43% women and in 57% of man, mean age 60 (49-73y).

Duration of the disease was approximately 10 years, the shortest time 5 years and the longest 20 years.

The worst parkinsonian symptoms which patients complained of were: rigidity in 66% of cases, tremor in 19% and bradykinesia in 15%.

Forty patients had intraoperative recording evaluation with 5, 4 or 3 electrodes followed by macrostimulation. Decision of elimination of one or two microelectrodes was always due to the conflict of the trajectory with the brain vessels in MRI-planning.

In 62% of patients all 5 microelectrodes were used for DBS, in 25% there were 4 and in 13% there were 3 microelectrodes.

The place of anterior microelectrode was chosen in 40% as the position of permanent lead, in 35% of patients as the position of permanent lead was the place of central, in 25% there was the position of posterior, medial or lateral microelectrode.

The time of procedure in the operating theatre was about 2 hours and 25 min/per lead in our series.

All pacemakers were turned on 3 or 4 weeks after electrode implantation, current parameters were as follows:

- there was a monopolar stimulation,
- pulse width (PW) 60 msec.,
- frequency (Fr) 130 Hz,
- amplitude average 2.5 mA (2-3.6),
- in 88% of cases one contact was stimulated, in 75% it was the first contact,
- in 12% two contacts were turned on.

All patients were examined again three months after surgery and an improvement in motor-UPDRS of about 65%. The reduction in daily levodopa-equivalent dose was 55%.

Three patients developed infections in the place where a battery was implanted. Then the device was disconnected and removed, antibiotic treatment was introduced. Six months after removal of the stimulator, a new pulse generator was inserted and DBS therapy was turned on.

In one patient position of the permanent electrode was improper in postoperative CT scans. This patient underwent another surgery to correct position of the electrode. Surgical procedure was performed – CT scans with stereotactic frame were obtained, the individual planning was done and the improperly positioned electrode was removed and the new electrode was inserted. Postoperative CT confirmed appropriate lead placement.

There was no bleeding complication observed in our series.

All patients had another psychological evaluation after one year from the beginning of the stimulation. We observed a diminishing depression level and the reduction of anxiety. Results of self-made questionnaire are presented in table 1.

Results of SWLS after surgery are presented in table 2.

Tab. 1. Results of the self-made questionnaire after surgery

	Functioning in professional life	**Functioning in family life**	**Functioning in social life**
Improvement after surgery	3	9	7
Same as before the surgery	8	3	3
Worsening after surgery	1	0	2
	feeling of contentment with life	capacity to carry out daily activities	
Same as before the surgery	–	2	
Has risen after surgery	10	10	
Has declined after surgery	2	–	

Tab. 2. SWLS results after surgery

Value	**Number of patients**
High level of contentment with life (7-10)	4
Average level of contentment with life (5-6)	2
Low level of contentment with life (1-4)	6

DISCUSSION

Bilateral STN DBS is a well known method of treatment of patients with idiopathic Parkinson's disease. The aim of therapy is to achieve relief of symptoms such as: rigidity, stiffness and tremor which results in improvement of motor functions, motor proficiency and therefore to improvement of quality of live and satisfaction of live (10, 11, 18).

The levodopa response is mandatory criteria at those parkinsonian patients who are candidates for surgical treatment. The clinical results of stimulation with optimal placement of the electrodes into the STN are comparable with the best optimal adjustment of levodopa (19).

Severe dyskinesias are another clinical indications for DBS therapy at patients with Parkinson's disease. The mechanism of dyskinesias is related to pulsatile administration of levodopa. Severe levodopa related dyskinesias are usually significantly improved after surgery, which plays a major role in the improvement of quality of life. Decrease of levodopa doses after surgery allowed by stimulation restores a more normal pharmacokinetic regimen of the striatal dopaminergic receptors (20).

Cognitive deficits and dementia are considered as contraindications to DBS therapy.

Surgical contraindication for DBS therapy are anticoagulants, terminal cancer, infectious disease and immunological.

The factors badly affecting prognosis are:
- age – worse results in older patients,
- speech difficulties – hypophonia before surgery might be worsened after,
- gait disturbance – if the freezing of gait is not improved in on-medication period, this is usually not improved after surgery. The patient and family should be clearly informed.

Deuschl et al. reported results of DBS therapy in randomised unblinded trial on 156 patients under 75 years of age with advanced Parkinson's disease and severe motor fluctuations. The mean UPDRS-III score improved by 41% in the off medication state and by 23% in the on medication state. The dopaminergic equivalents were reduced by 50% (14).

The data of Krack et al. (21) showed improvement in the total score of UPDRS as compared to the baseline value over the period of five years. The improvement in UPDRS part III was 75% for tremor, 71% for rigidity and 49% for bradykinesia. The total score of UPDRS part II, as compared to the baseline improved by 66% at 1 year, 51% at three years and 49% at five years. They reported a significant improvement postoperatively in the off medication state. Patients were independent in the most activities of daily living.

In our series we observed comparable effects- the improvement in UPDRS part III about 65% and reduction levodopa equivalent dose in about 55%.

Numerous authors reported improvement of motor function in patients with Parkinson's disease after surgery. Results of STN stimulation in Parkinson's disease in the literature are presented in table 3.

Tab. 3. Results of STN stimulation in Parkinson's disease in the literature

Author	Reduction in UPDRS part III	Reduction in levodopa equivalent dose
Tabbal (2007) (22)	47%	45%
Starr (2002) (23)	45%	–
Volkman (2001) (24)	67%	72%
Bejjani (2000) (25)	62%	70%
Moro (1999) (26)	42%	60%
Limousin (1998) (11)	60%	50%

An improvement in UPDRS part III score and a reduction of daily levodopa-equivalent dose in our series were comparable with those in the literature.

The neuronal activity of the subthalamic nucleus is altered in patients with Parkinson's disease. High frequency stimulation mimics the effects of ablative lesions in the STN, however it does not create a lesion and all mechanisms of its action are only temporary and are reversible. High frequency stimulation decreases firing rate of the STN neurons and that should slow down the neurodegenerative process (27).

The adverse effects reported in the literature were as follows: the complications in our series were infections – 4%, improper lead placement – 2%.

Surgically inducted bleeding during DBS procedure has been reported as follows: Herzog et al. (28) encountered bleeding in 4% of cases in their series, Starr et al. (23) observed bleeding in 2.6% of operated patients and Tabbal et al. (29) in 0.9% of cases.

Starr et al. (23) reported incorrect lead placement in 1.3% of cases and Klainer-Fishman et al. (18) in 4% of cases.

In a subjective assessment of 40 patients an improvement in family life has been observed in seven cases, two persons stated that they are functioning in the same way in family life after the procedure as they did before. One patient claimed that in family life his functioning has considerably worsened after the surgery, however it is not connected with the effects of the procedure or with the symptoms of the disease but with experiencing a difficult family situation (four months after the surgery patients wife has died of cancer).

In most cases subjective assessment functioning in professional life after the surgery remained constant. Nine people claiming that the effects of the procedure did not influence their professional lives were unemployed before the surgery. They lived on pensions, which most likely caused the lack of consequences in that area. Three patients that have been actively working before the surgery, reported that their functioning in professional lives has significantly improved.

A feeling of better functioning in social life after the DBS appeared in seven cases, three people felt a complete lack of change in the area. On the other side a decline in social life has been experienced by two patients: one was mourning after a loss of his wife, another complained about drowsiness and sleepiness during the day.

A general feeling of contentment about the state of one's life after the procedure has been observed in ten cases, only two persons claimed the contrary because they expected a greater improvement after the procedure than the one really achieved.

The capacity of executing daily activities of ten people has improved after the surgery, in two patients remained the same in comparison to the state before the procedure.

CONCLUSIONS

In patients with advanced stages of Parkinson's disease STN BDS offers significant improvement in motors function and allows to reduce the amount of medicaments taken. This has a positive effect on the emotional status of the patients. In The Satisfaction of Life Scale concerning various aspects of wellbeing a high level of contentment with life has been achieved. It is known that DBS is a method of treatment, which generates improvement in three major areas, that is rigidity, bradykinesia and tremor. Despite providing the patients with an accurate information about the possible positive results of surgery their own expectations of the treatment outcome were greater than its true capacity. Patients with a low level of happiness concerning

life (in SWLS) in their imagination expected a return to all roles which they fulfilled before illness after the procedure. On the other hand people achieving a high or an average score in SWLS had realistic expectations of the effects of the procedure. They were content with the improvement of symptoms after the surgery even when some of them still remained.

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received/otrzymano: 08.09.2017
accepted/zaakceptowano: 29.09.2017