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The Preliminary Results of Subthalamic Nucleus Stimulation after Destructive Surgery in Parkinson's Disease

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Objective. The study was aimed at evaluating the efficacy of bilateral electrical stimulation (ES) of the subthalamic nucleus (STN) in patients with Parkinson's disease (PD) after prior pallidotomy or ventrolateral (VL) thalamotomy.

Material and methods. The study included 9 patients with bilateral STN ES, who previously underwent unilateral destructive surgery on the subcortical structures: pallidotomy (5 patients) and VL thalamotomy (4). Control group consisted of 9 patients with STN ES and without prior destructive surgery.

Clinical and neurological examination included quantitative assessment of motor disturbances using the Hoehn—Yahr scale and Unified Parkinson's Disease Rating Scale (UPDRS). UPDRS was used to evaluate the motor activity (part III of the scale) and severity of drug-induced dyskinesia and motor fluctuations (part IV of the scale).

Results. In the group of STN ES with preceding destruction of the subcortical structures, an improvement in motor functions in the early period (6 months) was 45%, and severity of drug-induced complications decreased by 75%. In a group of STN DBS without destruction, motor disturbances were improved by 61%, and drug-induced complications were decreased by 77%. Improvement in motor functions amounted to 51.9% in patients with preceding pallidotomy (GPi destruction) and 37.5% in a group with preceding VL thalamotomy.

The equivalent dose of levodopa was reduced by 51.39%, from 1,008±346 to 490±194, in the study group and by 55.04%, from 963±96 to 433±160, in the control group.

Conclusion. Bilateral STN neurostimulation is effective after unilateral stereotaxic destruction of the subcortical structures in PD patients.

Keywords: Parkinson's disease, bilateral subthalamic nucleus neurostimulation, pallidotomy, VL thalamotomy.

Parkinson's disease (PD) or idiopathic parkinsonism is the second most common (after Alzheimer's disease) neurodegenerative disease [1]. Detectability of PD among individuals older than 65 years is about 1%. Most cases occur at the ages of 60—70 years, but in 15% of cases, PD first occurs at the age of 45 years [1], i.e. in workable and socially active population.

Despite the fact that the replacement dopaminergic therapy is effective, more than 50% of patients develop motor fluctuations within 2—5 years of therapy with levodopa and the risk of dyskinesias increases by 10% every year [2].

In this regard, development of complications or resistance to dopaminergic therapy raises the question of application of more effective non-drug methods to correct parkinsonism symptoms. Neurostimulation of subthalamic nucleus and ventrolateral thalamotomy and pallidotomy are most commonly used for this purpose.

Surgical treatment of PD is effective at all stages of the disease, but the modern trend is toward earlier surgical treatment of patients, which prevents them from losing social activity and enables returning to work [3, 4]. The moment when it is advisable to change from pharmacotherapy to surgery still remains the main disputable issue [4]. It is also being discussed, which method should be offered to the patient: stimulation or destructive interventions in the subcortical brain structures. The unilateral thalamotomy and pallidotomy effectively reduce the severity of tremor and rigidity on the contralateral side, but this treatment has limitations. Complications of VL thalamotomy in the form of hemiparesis, lateropulsion upon walking, dysarthria, and dysphagia (in the case of operation on the dominant hemisphere) occur within the first few days after surgery in almost 1% of operated patients and usually mostly regress within the first weeks after the operation [5, 6]. The incidence and severity of perioperative complications increase considerably after the second operation on the opposite side. According to D. Louw [7], dysarthria and severe mental disorders after bilateral VL thalamotomy developed in 30—60% of cases. In 5—14% of cases, pallidotomy can cause intraoperative and postoperative complications in the form of partial or complete hemianopsia, transient aphasia, and central facial palsy [7—10]. In the case of bilateral symptoms, pallidotomy on the contralateral side is associated with quite high (up to 17%) risk of mental and speech disorders without significant improvement of the results of the first pallidotomy [7, 11].

Bilateral chronic electrical stimulation (ES) of the subthalamic nucleus (STN) reduces the severity of tremor and rigidity on both sides, as well as intensity of hypokinesia, reduces the overall severity of movement disorders and increases daily activity of PD patients, which improves the quality of life of these patients [6, 12, 13].

Thus, pharmacotherapy often cannot solve the problem of multiple PD symptoms and the use of functional neurosurgery methods based on modulation of hyperactivity of the subthalamic nucleus and medial

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segment of the globus pallidus has been acknowledged as the effective treatment of PD patients [12, 13].

At the same time, it is poorly understood how effective is bilateral STN ES after destructive interventions. Additionally, there is no reliable information, whether the result of this procedure in patients after destructive operations is comparable to that in patients, who did not undergo destructive surgery on the subcortical structures, and whether destructive operation provides the patient with any long-term advantages.

The objective of this research was to demonstrate our own experience with bilateral neurostimulation of the subthalamic nucleus in PD patients after previous pallidotomy and VL thalamotomy and evaluate the effectiveness of this method in the early follow-up period.

Material and methods

The study included PD patients with bilateral STN ES after prior destructive surgery. The patients were operated on at the department of functional neurosurgery of the Federal Neurosurgical Center in Novosibirsk from 2013 to 2014.

The study included 9 patients (5 males, 4 females) with STN ES, who previously underwent unilateral destructive operations on the subcortical structures (study group). Of these, pallidotomy was performed in 5 patients, VL thalamotomy was performed in 4 patients. At the time of destructive surgery, average age of patients was 54.9 years (47—64 years), at the time of STN ES — 55.9 years (47—65 years). Disease duration ranged from 5 to 20 years (mean duration, 12 years). The average period between operations was 14 months (5 — 26 months).

Bilateral neurostimulation was carried out in the case of progression of motor disorders.

The control group consisted of 9 patients (5 males, 4 females) with STN ES, which did not undergo destructive surgery. The average age in the group was 54.9 years (48—61 years). The disease duration was 7—16 years (mean duration, 12 years).

Indications for surgery and selection criteria for STN ES were identical in both groups. In patients with bilateral neurostimulation, minimum follow-up time was 12 months, maximum — 30 months (average, 21 months).

Motor disorders were quantified in the clinical neurological study before and after operations on the following scale:

Hoehn-Yahr Scale (M. Hoehn, M. Yahr, 1967) modified by Lindvall, Tetrud, and Langston (O. Lindvall et al, 1987; J. Tetmd, J. Langston, 1987), which includes both the conventional 5-point classification of severity of parkinsonism and 1.5 and 2.5-point severity gradations.

The third edition of the unified PD evaluation scale (Unified Parkinson's Disease Rating Scale, UPDRS), (S. Fahn, R.Elton, 1987) contains 42 criteria. It estimates motor activity (part III) and severity of drug-induced dyskinesias and motor fluctuations (part IV). Each criterion may score 0 to 4 points. The decrease in the total score resulting from treatment was considered as a positive dynamics.

There were no significant differences between study and control group patients in age and duration of history.

In both groups, patients underwent a bilateral STN ES. Neurostimulator programming was carried out 1 month after surgery. Neurostimulation parameters were selected based on better clinical response of motor manifestations and absence of side effects (dysarthria, levodopa-dependent dyskinesia). No surgical complications were observed in patients in the early postoperative period.

Daily dose of dopaminergic preparations was assessed based on determining the equivalent doses of levodopa, which were calculated according to the formula: 100 mg of levodopa = 130 mg of levodopa with controlled drug release = 70 mg of levodopa + catechol-O-methyltransferase inhibitor = 1 mg of pramipexole = 5 mg of ropinirole = 50 mg of piribedil [14]. Calculation was made in the study and control groups before and 12 months after STN neurostimulation.

Results

In the study group, improvement of motor functions after 12 months averaged 45% (22 to 50 UPDRS points) (**Table 1**). Notably, 66.6% of patients in this group had a dextral destruction (**Table 2**).

The number of UPDRS points (part III) 6 months after the destructive intervention in this group decreased by an average of 17% (33—65 points) (see Table 2). This time interval for estimation was determined by the fact that some of patients underwent STN ES in 6 months.

In the control group, improvement of motor disorders in 12 months averaged 61%.

In 12 months, the severity of treatment complications (medicinal dyskinesias and motor fluctuations) decreased by an average of 75% in the main group and by 77% in the control group (**see Table 1**).

Study group patients with bilateral STN ES had various degrees of improvement depending on the location of destruction. In patients with unilateral pallidotomy, improvement of motor disorders was 51.9%, in the group with preceding VL thalamotomy — 37.5% (**Table 3**).

According to UPDRS (part III), clinical presentation before ES was more severe in the control group patients compared to that in the study group. This is due to preserved clinical effect of unilateral stereotaxic destruction in the study group, which occurred in the form of milder rigidity, tremor, and dyskinesias on the contralateral side.

The results of tests were similar in both groups 12 months after connection of neurostimulator (**see**

Table 1). Prior to STN ES, study group scored 51 UPDRS points (35—65), control group — 74 points (63—82). During STN ES, study and control groups scored 28 (22—50) and 29 points (20—42), respectively (**see Table 1**). After bilateral neurostimulation, equivalent dose of levodopa decreased by 51.39%, from 1008±346 to 490±194, in the study group, and by 55.04%, from 963±96 to 433±160, in the control group.

Discussion

Stereotactic thermal destruction of the deep structures of the brain is a technique that enabled safe and effective suppression of PD symptoms at certain stage of the disease [6].

Unilateral pallidotomy (destruction of the internal segment of the globus pallidus, GPI) effectively treats medicamentous dyskinesia in the contralateral limbs, and, to a lesser extent, in the ipsilateral limbs, and also reduces fluctuations of daily motor activity [9].

For many years, ventrolateral thalamotomy was used to treat pharmacoresistant tremor in PD patients [9, 15, 16]. In this case, the incidence and severity of perioperative complications significantly increase after the second operation on the contralateral side [7].

Despite the excellent initial clinical effect in the case of optimal positioning of destruction point, 10—15% of patients resume preoperative symptoms within 1—2 years after the operation, often in the ipsilateral extremities and axial muscles, which is associated with progression of the disease [15]. Therefore, further surgery is required in the future. Bilateral destructive interventions are associated with high risk of complications. According to J. Siegfried and B. Lippitz [17], chronic ES of subcortical structures is the method of choice in PD patients, who previously underwent stereotactic destruction. This method uses autonomous implantable systems, which enable chronic neurostimulation [18].

The main advantages of ES include minimal injury to the brain tissue, which occurs during implantation of the electrode, and reversibility of neurostimulation effects. Modern neurostimulators enable noninvasive correction of many parameters of stimulation program (the use of monopolar or bipolar stimulation, various intensity of electrical stimulation) [19]. Minimal invasiveness of this techniques prevent from persistent neurological complications characteristic of destructive methods [12, 20].

Minimal invasiveness of this technique enables single-stage bilateral surgery even in elderly patients [4, 20, 21]. The results of postmortem studies of operated patients, who died of intercurrent diseases, have shown that prolonged exposure to electrical stimulation does not cause damage to the structures around the active electrode [22]. The possibility of noninvasive correction of neurostimulation parameters enables selecting an individual effective and comfortable treatment program, and eliminates side effects of neurostimulation [4].

The literature provides scarce information on the effectiveness of STN ES in patients with previous destructive interventions. The study of G. Kleiner-Fisman et al. [23] showed that prior unilateral pallidotomy does not impair the effectiveness of the subsequent bilateral STN ES. In this study, electrophysiological parameters also did not change significantly in the study and control groups.

Our study showed that decrease in the severity of motor disorders as assesses on the UPDRS scale was lower in the group of patients with bilateral STN EN preceded by unilateral pallidotomy and VL thalamotomy as compared to the control group. This is due to preserved clinical effect of previous unilateral stereotaxic destruction, which occurs in the form of milder rigidity, tremor and/or drug-induced dyskinesias on the side contralateral to destruction area. Similar results were obtained in the work of W. Ondo et al. [14]. In our study, improvement in motor disturbances resulting from STN ES were less pronounced in the group with prior VL thalamotomy compared to the group with prior destruction of GPi.

Assessment of the dynamics of drug-induced complications showed that improvement was similar in the study and control groups, which is consistent with the aforementioned studies [14, 23]. Decrease in the equivalent dose of levodopa in the study and control

Table 1. **Characteristics of STN ES group patients, who previously underwent destruction, and STN EN group without prior destruction**

Parameter	Study group with previous destruction (*n*=9)	Control group without destruction (*n*=9)
Age at the time of stimulation, years	55,58 (47—65)	54,88 (48—61)
Sex:		
M	5 (56%)	5 (56%)
UPDRS part III prior to STN neurostimulation (off)	51 (35—65)	74 (63—82)
UPDRS part III after STN neurostimulation in 12 months (off)	28 (22—50), 45%	29 (20—42), 61%
UPDRS part IV prior to STN neurostimulation	8 (5—11)	9 (5—12)
UPDRS part III after STN neurostimulation in 12 months	2 (1—3), 75%	2 (1—4), 77%

Table 2. **Characteristics of patients with ES, who previously underwent stereotactic destruction (study group)**

Preceding destruction						Following STN ES			
Sex	Age at the time of destruction, years	Destruction nucleus	Location (R, right; L, left)	Motor disturbances before destruction (off)	Motor disturbances after destruction in 6 months (off)	Age at the time of stimulation, years	Location (B, bilateral)	Motor disturbances before neurostimulation (off)	Motor disturbances after neurostimulation in 6 months (off)
M	54	Gpi	R	55	45	55	B	55	25
F	62	Vim	L	59	54	63	B	54	25
M	53	Gpi	L	67	62	53	B	62	31
M	47	Vim	R	65	65	47	B	65	50
M	59	Vim	R	57	33	60	B	35	22
F	64	Gpi	L	52	40	65	B	50	28
F	47	Gpi	R	57	46	50	B	54	22
M	51	Vim	R	56	39	53	B	37	22
F	57	Gpi	R	53	49	57	B	50	23
	54,88 (47—64)			58 (52—67)	48 (33—65)	55,88 (47—65)		51 (35—65)	28 (22—50)

Table 3. **Study group with preceding stereotactic destruction**

GPI					VIM				
Sex	Age at the time of stimulation, years	Duration of disease history, years	Motor disturbances before neurostimulation (off)	Motor disturbances after neurostimulation in 6 months (off)	Sex	Age at the time of stimulation, years	Duration of disease history, years	Motor disturbances before neurostimulation (off)	Motor disturbances after neurostimulation in 6 months (off)
M	55	15	55	25	F	63	11	54	25
M	53	13	62	31	M	47	5	65	50
F	65	12	50	28	M	60	11	35	22
F	50	15	54	22	M	53	20	37	22
F	57	10	50	23	3m/1f	55,75 (47—63)	12 (5—20)	48 (35—65)	30 (22—50)
2 m/3 f	56 (50—65)	13 (10—15)	54 (50—62)	26 (22—31)					
51,85%									

groups before STN EN and after 12 months of ES also did not differ significantly.

W. Ondo et al. [14] believe that unilateral VL thalamotomy may cause insufficiently accurate positioning of STN EN electrode on the side of prior destruction. A. Zaidel et al. [24] reported change and decrease in neuronal activity of the subthalamic nucleus after previous pallidotomy. In this regard, in patients with preserved good clinical effect of destructive operations or extensive destruction area, an option of unilateral STN ES on the side contralateral to the destruction area may be considered in the case of further progression of the disease and emergence of indications to STN ES.

Conflicting results of analyzed studies may be due to a small number of patients with prior destruction of subcortical structures in all these studies.

Methods of functional neurosurgery are currently an integral part of the treatment of PD patients [25, 26]. Modern trends are towards earlier surgical treatment of patients [3, 4]. In some patients, motor disorders can be significantly reduced by unilateral stereotactic interventions [14, 23]. However, disease progression is accompanied by depletion of reserves of pharmacotherapy, and some patients, who previously underwent destructive operations, may require repeated surgery [27, 28].

Conclusion

The literature data and the results of our study show that bilateral STN electrostimulation is effective and can be used in patients with Parkinson's disease, who previously underwent unilateral stereotactic destructive operations on subcortical structures.

There is no conflict of interest.

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Commentary

The article focuses on electrical stimulation (ES) of the subthalamic nucleus (STN) in patients with Parkinson's disease, who previously underwent destructive operation on the deep structures of the brain. Modern literature provides numerous publications dealing with ES of STN and the internal segment of the globus pallidus. The effectiveness of this method of treatment during short follow-up period was proved by a number of randomized trials; there are also publications reporting long-term results. A large number of studies cover the issues of the effect of neurostimulation on various manifestations of Parkinson's disease: motor symptoms, cognitive impairment, balance and gait disorders, impulsive-compulsive disorders.

In recent years, destructive operations were abandoned in favor of neurostimulation all over the world, which is very promising due to the adjustability of its effect. However, destructive operations still can be used in some cases with predominance of unilateral manifestations of Parkinson's disease. At the same time, patients who underwent destructive operations can be sent for neurostimulation in the case of disease progression.

In recent studies dealing with neurostimulation, previous destructive operation was considered as an exclusion criterion. However, there are several studies containing information on the use of STN ES in small groups of patients, who previously underwent destruction, and its effectiveness.

In general, this study is highly relevant and the results are interesting and important for functional neurosurgery of Parkinson's disease. Further studies will provide valuable data to develop the optimal strategy of neurosurgical treatment of Parkinson's disease.

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