Deep Brain Stimulation for Treatment of Parkinson's Disease Deep brain stimulation, Parkinson's disease, subthalamic nucleus, stereotactic surgery

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Citation

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Abstract

With the evolution of deep brain stimulation (DBS), stereotactic operative treatment of drug resistant Parkinson's Disease experiences a renaissance. Refined operative techniques using computerized image-fusion programs, intraoperative microrecording and macrostimulation have made the targeting of the region of interest easier. Deep brain stimulation of the subthalamic nucleus is able to reduce major symptoms as tremor, rigor and bradykinesia. Short and middle-term as well as long-term studies have confirmed these results.The rate of intra- and perioperative complications is around 1-2%. However, during the follow-up period hardware-related complications can increase to 4-20%. This is an overview about history, indications, operative technique and results of deep brain stimulation based on the actual literature.

INTRODUCTION

During last years surgical procedures have played an important role in the treatment of drug-refractory central movement disorders. Spiegel und Wycis (24) introduced the stereotactic techniques in neurosurgery: it allows to hit every brain area three-dimensionally in a range of millimeters. In the beginning the application of this procedure was used to treat patients with severe pain syndromes (22). This was followed by interventions in patients with movement disorders and psychiatric diseases. Lacking alternative treatment the so-called "stereotactic lesional procedures" by damage of intracerebral nuclei were the method of choice in the late sixties (13,15). However, with the introduction of Levodopa, there was a loss of interest in stereotactic neurosurgery. Over a long time patients with tremor which was drug resistant remain the only indication for "thalamotomy", whereas in bilateral tremor one side was left untreated.

In 1986 Benabid performed for the first time a combination of unilateral thalamotomy and contralateral thalamic stimulation in a patient with bilateral tremor (2). The results were such successful, that Deep Brain Stimulation (DBS) of the Ventral intermediate nucleus (Vim) of the thalamus has been applied as first choice operative treatment for tremor in the following years (1). The EC-certification for this indication was obtained in 1995.

Using the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) monkey model, Benazzouz et al. (4) found in 1993 that high frequency stimulation of the nucleus suthalamicus (STN) has a remarkable positive effect on rigor and bradykinesia. This resulted in a change of paradigm for operative treatment of PD. The STN was defined as the new target for DBS (3/18), since it influences positively not only Tremor, but also akinesia and rigor. The EC-certification of DBS for the operative treatment of tremor, rigor and akinesia was obtained in 1998.

The great advantage of this procedure versus lesional procedures is the simultaneous stimulation of both hemispheres and/or different target points. Moreover side effects are reversible by regulation of stimulation parameters (7/11) and future treatment options e.g. neurotransplantation are not excluded.

The exact mechanism underlying the beneficial effect of DBS is still unclear and remains a field of active research. It seems to be a combination of inhibition of neurons, modulation of abnormal patterns of activity, and activation of axons (19).

INDICATIONS AND CONTRAINDICATIONS

Besides Parkinson Disease (PD), dystonia and tremor of different origin are the standard indications for DBS. Stereotactic treatment of other neurologic-psychiatric diseases as cluster-headache, epilepsy or obsessive-compulsive disorders (OCD) is actually experimental.

The table 1 gives shows the indications for DBS in PD patients.

Table 1: Indications for DBS in Parkinson's Disease

Contraindications are dementia or psychotic disorders, multiple system atrophia (MSA) and other neurological diseases such as brain tumors or brain atrophy. Furthermore internistic pathologies e.g. coagulation disorders preclude the operative procedure.

OPERATIVE TECHNIQUE

DBS is an extraordinary complex neurosurgical intervention and is performed in different consecutive steps:

STEREOTACTIC PLANNING

To calculate target point, in PD the subthalamic nucleus (STN), T1- and T2-weighted magnetic resonance imaging (MRI) sequences are fused with stereotactic computed tomographic (CT) images using the software of an intra-operative workstation. The target point is three-dimensionally determined with the coordinates X, Y and Z on the base of the stereotactic frame. The entry-point is selected with the same method. The trajectory is starts directly at the cortical surface to avoid loss of CSF from the subarachnoidal space (brain shift). Furthermore brain sulci (damage of small vessels) and contact with the lateral ventricles (electrode dislocation) should be avoided.

Figure 1

Fig.1: Threedimensional approach planning

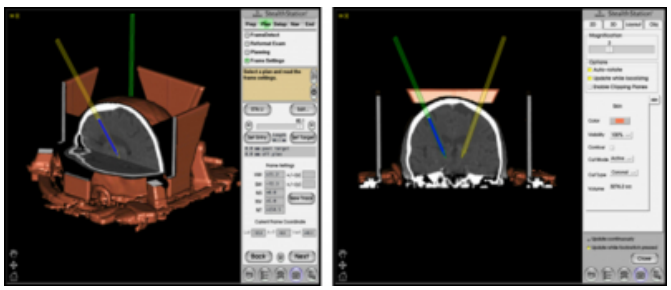
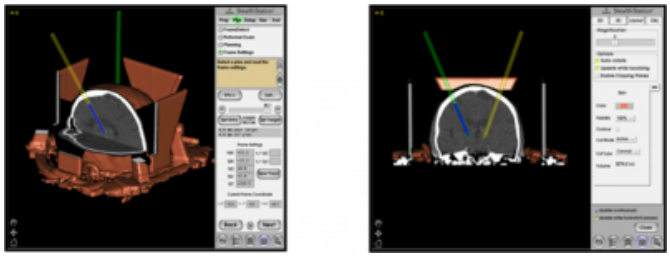


Figure 2



In the last step the established data are transferred to the stereotactic targeting system and controlled with the target point simulator. The precision of the anatomical-radiological target point evaluation is dependent essentially from the mechanical features of the stereotactic ring, the slice-thickness of MRI and CT, the brain-shift due to CSF-loss and individual anatomical variations of the patient itself. Therefore it is essential to use intraoperative microrecording of STN-specific cell-potentials and macrostimulation with neurological evaluation of symptoms suppression and stimulation induced side effects to verify the calculated target point.

STEREOTACTIC PLACEMENT OF THE TEST ELECTRODE(S)

The aiming device is connected to the stereotactic frame. According to the calculated approach skin incision and burr-hole trepanation is performed in local anesthesia. The dura mater is coagulated and incised. After this a special application device (micro-manipulator) is used to place the test electrodes (combined micro- and macro-electrodes) in the target area subthalamic nucleus (STN) in submillimetric steps. It is possible, to introduce 5 microelectrodes simultaneously to get a spatial impression of the electrical activity in the region of interest.

INTRAOPERATIVE MICRORECORDING

Intraoperative microrecording is not obligatory, however it is useful to verify electrophysiologically the calculated target area. Different basal nuclei have characteristic discharge patterns. Motoric areas of one region can be differentiated from non-motoric by the detection of neurons, whose discharge frequency is modulated by movements. The spatial resolution is excellent, structural borders can be determined with a precision in a 0.1 mm range. Also the STN has specific discharge patterns, which however cannot be always recorded. Microrecording starts 5mm proximal from the calculated target point reaching distally the substantia nigra. In this way it is possible to define the borders of the STN

electrophysiologically. If the neuroanatomical evaluation of the STN is accurate, in the majority of the patients recording with only one microelectrode is sufficient, but in special cases it is necessary to use up to five microelectrodes. The higher risk of intraoperative hemorrhage using multiple microelectrodes is a matter of controversies (8).

INTRAOPERATIVE MACROSTIMULATION AND NEUROLOGICAL EVALUATION OF SYMPTOM SUPPRESSION AND SIDE EFFECTS

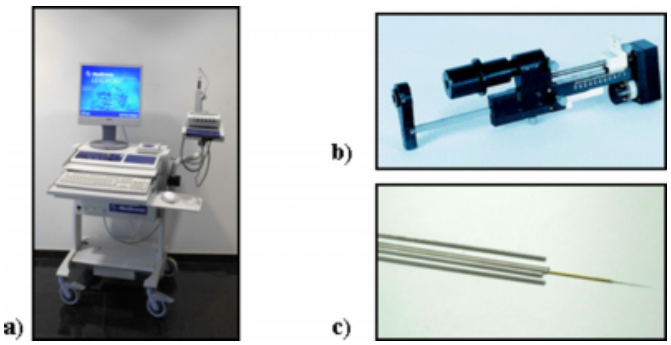
After determination of the STN using preoperative imaging and intraoperative microrecording, macrostimulation is performed. Using a constant frequency (130Hz) the amplitude is raised continuously and the effect on symptoms as well as the side effects are evaluated.

Finger movements are used to prove bradykinesia. Rigor is examined with passive movements of the limbs. The finger-nose test evaluates the residual tremor. If side effects occur under low current intensity (e.g. eye mobility disturbances) should be considered that the target area STN has been reached only in its periphery or has been missed.

Volkmann et al. (26) have exhaustively described the incidence of side effects under intraoperative macrostimulation and associating them to the topographical anatomy around the STN. Their standard work serves as orientation if it is necessary to place further macrostimulation electrodes intraoperatively in correlation to the already placed central electrode. In most cases a marked intraoperative symptom suppression can be noticed in reduction of tremor and rigor. The positive effect of DBS on bradykinesia occurs in the further postoperative course

Figure 3

Equipment for microrecording and macrostimulation: a) recording- and stimulation system, b) microdrive, c) micro- and macroelectrodes



PLACEMENT OF THE PERMANENT DBS-ELECTRODE

After successful macrostimulation the final four-contact DBS-electrode is placed through the incision canal and fixed at the skull bone. The temporary externalization of the electrode is only used for patient in which the intraoperative stimulation result has been uncertain.

SECONDARY IMPLANT OF THE IPG

The IPG-system can be implanted directly after the placement of the permanent DBS-electrodes or during a second surgery after some days. Because of hygienic and technical- surgical reasons it is advisable to perform a two-step operation. The impulse generator is placed regularly in the infraclavicular subcutaneous fat tissue. Alternatively it is possible to use the upper abdominal region for placement of the IPG-system.

POSTOPERATIVE MANAGEMENT

The further postoperative management PD-patients after implantation is performed by the neurologist. Table 2 shows the essential goals.

Table 2: Postoperative Management

It must be emphasized, that a complete suspension of the medical treatment is possible in only rare cases. The postoperative neurological care is focused on the patient training to manage external control system. The common adjustment parameters of the IPG are frequencies of 130 Hz, impulse width between 60 and 90 µsec according to individual differences.

RESULTS AND DISCUSSION

DBS influences tremor, rigor and bradykinesia. Krack et al. (13) examined in 49 consecutive patients the long-term results (5 years) after bilateral STN-stimulation. They observed a better motoric function in "Off-drug" (54%) and a reduction of dyskinesia in "On-drug". The impairment of other symptoms, as speech disturbances, postural instability and functional cognitive reduction resulted the same compared to patients not treated surgically. Therefore it is crucial to inform the patients before the surgical procedure, that DBS will not stop the natural course of the underlying disease.

In a meta-analysis of 38 studies the short-term, medium-term and long-term results of 471 PD patients who underwent bilateral STN stimulation have been evaluated (8). After

stimulation United Parkinson Disease Rating Scale (UPDRS) score improved in "Off-drug" after 6 months of 50%, after 12 months of 56%, after two years of 51% and after 5 years of 49%, compared to the score before surgery. After 12 months the improvement of the tremor was 81%, on rigor 63% and on bradykinesia 52%. There was a marked improvement on gait (+ 64%) and postural instability (+ 69%). "On"-dykinesia improved of 94% after 12 months. The L-Dopa- equivalent dose was reduced after stimulation to 52%.

In a matched-pair 6-months study Deuschl et al (7) demonstrated that patients treated with stimulation and adjuvant drugs have better results related to mobility, performance in daily life and emotional balance compared with patients who received only pharmacological treatment. These positive results of DBS are confirmed in the last years also in long-term studies (11,12,15,20).

SIDE-EFFECTS AND COMPLICATIONS

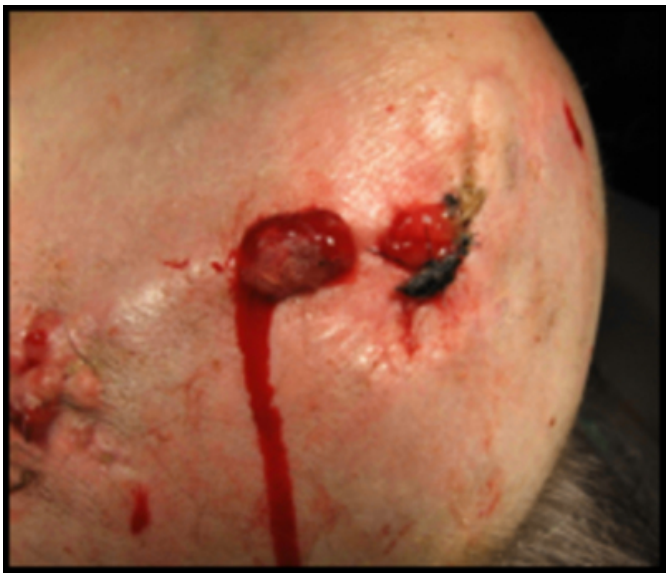
Stimulation side-effects as hypophonia, dysarthria, dykinesia or eyelid apraxia occur in around 19% and are reversible by changing the stimulation parameters. It seems also that frontal cognitive functions can be affected by DBS, however not influence the quality of life remarkably (27).

Intra- or perioperative severe complications are rare. Hamani et al. (8) stated, that in 1-2% of the patients intraopeative hemorrhages cause neurological deficits. Seijo et al. (21) reported in 130 patients with 272 surgical procedures 2.2% of misplaced electrodes, 3.3% of bleedings and 4.1% of convulsions.

The so-called "hardware-related" complications, have a frequency between 4.5 and 20% (4,7,23,24). These complications are: electrode breakages, migrations and skin erosions and infections. Despite the excellent results of DBS, in case of infection, the whole stimulation system has to be removed and the patient has to undergo pharmacological medical treatment. However with the development of miniaturized stimulation systems which can be placed directly under the skull bone without fixation devices and elongation cables these problems can be solved.

Figure 4

Skin erosion along the elongation cable



CONCLUSION

Actually the bilateral high-frequency stimulation of the subthalamic nucleus (STN) is the neurosurgical procedure of choice for patients with drug resistant Parkinson's disease. The indications and contraindications as well as the stereotactic intervention are standardized, side effects are rare and in most cases reversible. DBS improves motoric symptoms, L-Dopa related dyskinesias and the quality of life. Intraoperative complications (e.g. haemorrhages) with severe consecutive neurological symptoms are described 1-2% of the patients. Postoperative complications related to the implanted electrodes and impulse generator system are between 4-20%.

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