CT-guided Stereotactic Thermolesion and Deep Brain Stimulation in the Treatment of Patients with Parkinson's Disease

Ph.D. Thesis

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Budapest
2011

1. INTRODUCTION

Parkinson's disease (PD) is a progressive, the second most common neurodegenerative disorder, which affects approximately 0.3% of the population. With age, the frequency of PD is expected to increase up to 1-2% of those older than 60 years. Pathologically, PD is characterized by degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNc) coupled with intracytoplasmic inclusions known as Lewy bodies in the remained neurons. The consequence of the dopamine insufficiency is resting tremor, rigidity, bradykinesia posturals instability and gait dysfunction representing the main diagnostic criteria. Additional criteria can be micrography, hypomimia, reduction of blinking rate and freezing of gait. The diagnosis is based on the „United Kingdom Parkinson's Disease Society Brain Bank criteria. An estimated 30% of patients with PD do not have resting tremor, and the MRI, PET and SPECT may give just additional information.

In the treatment of the early stage the use of mono-amine-oxydase-B inhibitors and dopamine agonist is preferable. Anticholinergic therapy can be effective in tremor control, however, with long-term therapy the cognitive decline may have a higher incidence. The effect of NMDA-antagonists is more prominent on bradykinesia and rigor but to a lesser extent on tremor than antocholinergic drugs. As the disease and bradykinesia progress, the substitution therapy can be needed, which is more effective in combination with inhibitors of catechol-O-methyltransferase. As a late complication after 5-10 years of treatment motor fluctuations, dyskinesia are presented in 50-90% of patients. Drug treatment is sufficient for most of patients, but the insufficient control of motor complications, dyskinesia and, frequently, the drug-resistant tremor are indications for surgical intervention.

In the history of treatment of PD surgery had the first, most promising results. In the beginning, tremor meant the main indication and with the use of stereotactic equipment better results could be produced. As a result of the advent of L-dopa, the number of surgeries dramatically dropped, but for the last two decades a renaissance in PD surgery can be experienced after successful treatments of dyskinesias with posteroventral pallidotomy in the 1990s.The interest is raised with high effectiveness of deep brain stimulation (DBS) of GPi presented by Siegfried, Vim and STN presented by Benabid. According to present knowledge, surgery alleviates the main symptoms dramatically, but has no influence on the course of the disease.

Nowadays there are several surgical trends int he treatment of PD: lesion, DBS, transplantation and gene therapy. In clinical practice, lesions and DBS are used for compensating the dysfunction of the basal ganglia.

2. OBJECTIVES

The general objective of the dissertation is to present a 15-year experience in stereotactic functional surgical modalities, technical skills, diagnostic methods and results in the treatment of PD.

Clinical investigations

The assessment of surgery related changes of motor signs, quality of life, activity of daily living of PD patients with clinical scores is to evaluate the influence of different surgical modalities in both short and long terms.

Quantitative measurement of motor symptoms and phonation, evaluation of surgical effectiveness

Changes of resting and postural tremor after surgery measured on passive marker based motion analyser (PAM)

Quantitative measurement of changes in proximal bradykinesia based on pointing test with PAM

Measurement of changes in distal bradykinesia during finger-tapping test with PAM

Elaboration and applying of digital spiral drawing test (DSDT) for quantitative assessment of kinetic tremor

STN-DBS related changes during acoustic voice analysis

Target determination in basal ganglia and stereotactic surgical planning

Individual anatomical target identification based on frameless MRI, ventricular measurements and stereotactic atlases

Development of stereotactic planning software running on personal computer or notebook with ability of importing CT data files

Improvement of CT-guidance accuracy in target coordinates determination

Role of intra-operative test stimulation and microelectrode recording int the final target definition

Investigation of the influence of surgical and drug therapy on the brain activity

Analysis of the effect of GPi-DBS on bradykinesia with activation PET in drug free condition and after L-dopa administration

3. PATIENTS AND METHODS

Between March 1st and June 15th, 2010, a total of 406 surgical procedures were performed on 266 patients. There were 256 radiofrequency lesions (63,1%) on 202 patients, and 150 electrode implantations (36,9%) on 85 patients (29,6%). On 181 patients (68,0%) exclusively ablative procedure, on 64 patients (24,1%) only DBS, and on 21 patients (7,9%) lesion procedure with consecutive DBS was performed. Targets for ablative surgery were in the thalamus and GPi, for DBS in the thalamus, GPi and STN.

3.1. Indications ans contraindications

Thalamotomy was indicated for tremor control in PD patients with good motor performance. Pallidotomy, on one hand, was a choice for second side tremor, as bilateral thalamotomy was abandoned for the reason of a higher complication risk and DBS was feasible only in a limited amount. On the other hand „on-off" fluctuation or dyskinesia was the indication with narrowed therapeutic window of drug therapy. STN-DBS was indicated according to CAPSIT criteria after neuropsychological screening in patients with advanced PD with at least 5-years of history, presenting „on-off" fluctuation and good L-dopa responsiveness. Exclusion criteria were severe cognitive decline, Parkinson plus syndrome, gaze palsy, severe dysphasia or focal neurological signs, severe diffuse cerebral changes, brain atrophy influencing the anatomical measurements or irreversible internal diseases.

3.2. Methods for clinical assessment

After receiving written consents before surgery and at the follow-up, the condition of the patients was video-recorded according to the prescribed scenario. Clinical assessment has been done according to the modified Hoehn and Yahr stage (H-Y) and modified, Unified Parkinson's Disease Rating Scale (UPDRS). The activity of daily living was assessed with the UPDRS-II score and with the Schwab and England (S&E) scale. The tremor score was calculated as the sum of items 20 and 21, rigidity as the score of item 22, bradykinesia as the sum of 23 to 26 items. The Postural Instability Gait Disorder (PIGD) score was derived from the sum of items 13, 15, 29 and 30. Evaluation of speech according to item 18, at voice analysis as the sum of items 5 and 18, evaluation of dyskinesia as the sum of items 32-35, the fluctuation sum of items 36-39 of UPDRS-IV.

Patients with "on-off" were evaluated after a 12 hour, or in case of retard drugs after a 24 hour withdrawal of dopaminergic treatment (OFF), and in medicated state (ON). DBS-treated patients were additionally assessed with turned off (StimOFF) and turned on (StimON) stimulator. Quality of life assessment was based on PDQ-39 (Parkinson's disease Questionnaire). Changes of drug therapy were expressed in daily L-dopa equivalent doses (LED) and benztropine units.

3.3. Radiological diagnostic methods

The individual anatomy of the basal ganglia was studied on multiplanar MRI. The acquisition was in parallel and orthogonal directions to the anterior comissure-posterior comissure (AC-PC) plane. T1-weighted 3-D MPRAGE (TR 10 msec, TE 4 msec) 1 mm sclices, and T2-weighted IR-FSE (TE 3500 msec, TR 30 msec) 2 mm slices were used with 256x256 matrix, before 2003 with 1.0-T, later with 1,5-T and 3,0-T magnetic field. The data after 2001 were digitally stored. Stereotactis coordinate calculation and lesion or electrode position control was performed with high-resolution CT-scanning with 512x512 matrix and 1.0 mm slice thickness, which in a 240 mm FOV provided a 0.47x0.47x1 mm voxel size. The data has been digitally stored since 2001.

The mechanisms of improvement of bradykinesia after Gpi-DBS and L-dopa were studied with an activation ^{15}*O-butanol-PET* study in 5 conditions: A) 12 hours after withdrawal of drug therapy in rest condition with auditory paces; B) with randomly paced joystick movements in OFF condition; C) at auditory paced movements with StimON; D) at aditory paced jostick movements after administration of 100 mg L-dopa with StimOFF; and E) with L-dopa and GPi-DBS StimON. Data acquisition was performed in all patients on the same day and with a 10-20 sec delay after intravenous administration in 13 min intervals of a 1.8 GBq (50 mCi) dose of ^{15}O-butanol (half life 2.05 min) with a GE 4096 Plus PET scanner. From each patient in each condition 10 emission scans were acquired with 90 sec acquisition time. The voxel size of reconstructed images was 2.0x2.0x6.5 mm. The Ethical Committee of the University of Debrecen has approved the study protocol. The perfusion images and the condition effect were assessed with the SPM99 software.

3.4. Motion analysis

The kinetic tremor was recorded and measured with a Genius MousePen 8x6 (KYE Systems Corp., Taipei Hsien, Taiwan), commercially available tablet at subject's hand movements with a pen by a custom-developed *DSDT (Digital Spiral Drawing Test)* software. The movements of the tip of the digital in X and Y directions and pressure with 10 bit resolution were registered with a sampling rate of 110/s and stored. The spatial resolution was 0.012 mm.

Professor Ákos Jobbágy and co-workers in the Department of Measurement and Information Systems Budapest University of Technology and Economics developed a system with digital video-camera for passive markers based analyser of motions (PAM) of the subject's body with registration of the markers' X and Y coordinates from the left upper corner of the frame. The sampling rate is 50/s, and depending on the recording type, the system initiates the evaluating algorithm on OCTAVE platform. The detailed motion analysis with sptectrograms has been performed on program, developed by the author and implemented in MATLAB (Mathworks, Sherborn, MA, USA). The measurement of rest and postural tremor was performed with markers on the second phalanx of both index fingers. Tremor intensity was calculated as the root-mean-square of accceleration, derivated from displacement. At the frequency domain analysis the mean frequency (KF) measures the frequency below which lies 50% of the power in the spectrum and above which lies the other 50%; frequency dispersion (FD) measures the width of an interval centred at the median frequency that contains 68% of the power in the spectrum; dominant frequency (CSF) gives the highest peak in the spectrum; frequency concentration (FK50) measueres the interval near the dominant frequency, which has the 50% of the total power; Harmonics index (HI) shows how close the spectrum is to a single narrow peak normalized to the height of the highest peak (trend to1) or it has more components (trend to 0); proportional power in the 4 to 6 Hz range (4-6Hz PW) quantifies how far this frequency range contributes to tremor. Approximate entropy (ApEn) characterises the tremor regularity (from 0 to 2). The values were calculated from filtered time series with published algorithms. The cross-coherence analysis of the sides was also performed for exclusion of contralateral effect. The calculated values and graphical results were observed and collected with a custom- developed TremDat softwaare. With PAM we applied tests for objective measurement of proximal and distal bradykinesia. During *pointing test* the subjects had to touch two points alternatively as fast and accurately as possible. The equipmnet automatically calculates the pointing test score (PTS) from the smoothness, velocity and accuracy of the movements. The finger-tapping test includes the examination of the consecutive movements of piano-playing from the 5th to index fingers with both hands. The finger-tapping test score (FTTS) is higher with faster and higher finger movements.

3.5. Voice analysis

The effect of bilateral STN-DBS on phoonation was studied in 22 patients at least 6 months after surgery in StimOFF, StimON and over-stimulated conditions (StimOVER) while the amplitude was increased by 20-30%**,** but remained under the threshold of motor and sensory side effects by at least 0.3V. The speech was recorded on a computer hard disk with Dr. Speech Real Analysis for Windows, Version 4.50 software (Tiger DRS, Inc. Seattle, WA, USA) in a silent room (<50 db). In each condition, the patients were asked to repeat a set of Hungarian words twice by heart in a normal conversational style, with a total number of 58 words (names of months and days), then the subjects were asked to emit sustained /a/, /i/, /o/, /u/, and a forced high /i/, the capture was at 16 bit resolution and sampling frequency of 11.025 Hz. The perceptual analysis was carried out from audio recordings according to the GRBAS (grade, roughness, b+ pathologists. The most stable 6-second window with the highest amplitude and without pitch drops was selected for acoustic measurements.

Praat 5.1 software measured the average perturbation voice characteristics, like percent jitter, percent shimmer and NHR. Then the 6-second window was divided into non-overlapping segments with 1000 samples (0.0972 sec intervals) of the signal, and the parameters were calculated from subsequent segments and stored in a data file for discriminant analysis.

The nonlinear dynamic analysis (NDA) was performed with software, implemented in MATLAB 7.1. Digitally normalized samples were analysed by published algorithms for fast detrended fluctuation analysis (DFA) with calculation of normalized scaling exponent α_{norm}, which is the ratio of the logarithm of the fluctuation (F) to the logarithm of the width of a chosen time window (L) over which that fluctuation was taking place. The value of α_{norm} lies between 0 and 1, and shows an increase for the disordered voice.

The time-delayed state-space recurrence analysis gives the recurrence period probability density and measured with entropy (RPDE), representing the uncertainty in the periodicity of the voice signal. H_{norm} is the normalized entropy of a probability density which lies between 0 (perfect periodicity) and 1 (complete randomness).

3.6. Calculations and statistical mehods

The approximate lesion volume was calculated from the equation $V=m\pi*(R^2+Rr+r^2)/3+2\pi*(R+r)^3/3$, when R and r are respectively the radiuses of outer and inner lesions, and the m is the distance between the two half spheres. The stimulation energy was calculated from the equation: Energy (μW) = (V x μsec x Hz/impedane (Ω)) ^{2}.

The data with normal distribution was analyzed with Student's T-test, other variables with Wilcoxon paired signed rank test with P=0.05 significance. The statistical calculations were performed with the SPSS 17.0 (SPSS, Chicago, IL, USA) software. The consistency of acoustic measurements and assessments were analyzed with Cronbach's alpha. The segmental jitter-shimmer, jitter–NHR, shimmer-NHR and α_{norm}-H_{norm} pairs of data for separation of the StimON-OFF and StimOFF-OVER conditions were used for Fisher's quadratic discriminant analysis (QDA), implemented on MATLAB 7.1. The correct classification percentage was compared with the signed test. For post hoc analysis the Mann-Whitney U-test, for correlation analysis the Spearman's correlation test on ranks, and for the influence of other variables on gender differences the ANCOVA was used.

3.7. Target determination and preoperative MRI

The targets for treatment of PD were defined in the 3rd ventricular coordinate system. The border of the bottom of Vop and Vim nuclei according to the Schaltenbrand-Wahren atlas on the AC-PC plane was defined on the border of the posterior and middle third of the inter-comissural distance and from 11.8 to 13.5 mm lateral from the midline. The Vim was localised 2 mm posterior. The laterality is the most variable distance as it is influenced by the width of the 3rd ventricle and by the predominantly affected upper or lower extremity as well.

The Gpi coordinates were calculated individually from the frameless multiplanar MRI measurements and from the coordinates of the CT-determined 3rd ventricular reference point coordinates. The individual target variations were from 19 to 23 mm laterally, from 1.5 to 3.5 mm anterior from the AC-PC midpoint and 1 mm above the optic tract. The STN was localised from 0 to 3 mm behind, from 10.5 to 12.5 mm laterally and from 4 to 5 mm below the mid-commissural point on the T-2 weighted MR images.

3.8. Frame placement, CT-guidance and surgical planning

The surgical procedures were performed with Riechert-Mundinger or MHT (Freiburg, Germany) stereotactic devices. In the beginning the coordinates were calculated from CT-films with gantry independent „CT-LOC" (Leibinger ®, Freiburg, Germany) localising system. In 2000 I started the development of VISTER *planing software* running on Windows operating system, with importing CT-scans in DICOM format, which is dedicated to facilitate all steps of surgical planning. With this software we have performed more than 500 stereotactic procedures so far. In all cases with PD the target coordinates were determined and calculated from the AC-PC plane. Vop and Vim targets are defined on the reference plan. IN case of GPi and STN targets, we used simultaneously 2 targeting methods. As both of the targets are below the reference plane, one method is to calculate the coordinate of the plane crossing point of the electrode trajectory (TRA) from known sagittal and coronar passing and the distance from this point to access the target. The second method is the *3-D coordinate transformation*. In an ideal case the axial plane of the CT scanning is perpendicular to the midsagittal plane of the brain, but this happens accidentally. If the target is close to the midline, it has no significant effect, but in case of Gpi target the laterality is approximately 20 mm, and the level is 4-7 mm below the reference plane, due to rotation around Y axis and this may cause a significant rotational error in X and Z coordinates.

The 3-D coordinate transformation is indirect, software-based calculation of target coordinate, based on AC, PC and midsagittal (Falx) coordinates and on distances from the ventricular reference (MC or PC) points. In 10 cases we used automatic CT-MR image fusion with BrainLab-Target 1.13 software but the elaborated 3-D coordinate transformation method was more simple and accurate. The electrode trajectory can be followed on 1 to 16 multiimage series. From the target end entry coordinates the software calculates the setting values of Riechert-Mundinger or MHT equipment. Along with the storage of planning images the software calculates stores the surgical planning in *. pdf format and prints the protocol for the operation. Great advantage of the Riechert-Mindinger and MHT stereotactic devices that the setting of instrument holder and aiming bow is performed on a target point simulator phantom, which practically excludes the possibility of misplacement or side mismatch.

3.9. Electrode insertion and intraoperative testing

Before thermolesion the hair is shaved in 5 cm around the entry point. After local anaesthesia and a 5 mm skin incision, through a 3.2 mm twist drill burr hole after monopolar coagulation the dura is penetrated by electrode suitable for test stimulation and lesion. Connecting the electrode to the Neuron N-50 generator we are able to *monitor the impedance*, to perform stimulation testing, to measure the temperature and current and to produce radiofrequency lesion. During penetration with monitoring of impedance changes between gray and white matter can be detected.

During ablative surgery and DBS, equally the stimulation testing is obligatory. The effect and side effect depends on stimulation parameters and on distance from the stimulated structure, which has a strong predictive value.

Micro-electrode recording (MER) is useful for assessment of spontaneous, or movement and sensory-related activity of neural cells. In early cases we performed 1-channel, in 2006 we began 5-channnel recording with manual and FHC micro-drive and LeadPoint amplifier and recording system.

3.10. Thermo-controlled radiofrequency lesion

During *thalamotomy* for tremor control we performed 2 or 3 lesions via electrode with 1,8 mm diameter and 3.0 mm active tip in a distance of 2-3 mm at 72-80 ^{o}C and 60 sec exposition time. The Neuro-N50 generator provides heating of brain tissue with 500 kHz radiofrequency waves. Due to the vicinity of internal capsule and optic tract and to follow the anatomy of surrounding structures we preferred to produce a conic *pallidotomy* lesion shape. The deeper lesion was smaller, and after electrode withdrawal it was followed by a bigger lesion.

3.11. Deep Brain stimulation (DBS)

ITREL3, Soletra with 1 channel, Kinetra és Activa PC dual channel (Medtronic Inc.) neurostimulation systems were used with implantation in two step surgery. The first surgery was perormed under local anaesthesia with Ct-guided stereotactic implantation of lead (∅1.27 mm, 4 platinum-iridium contacts of 1.5 mm with a distance of 0.5 or 1.5 mm, modell 3389, 3387) into the calculated target with fixation to the skull with a patent or StimLOC burrhole cover. Until 2006 the electrode was connected to external extension for 5-10 day screening period. The second step of surgery was the connection of the lead via internal extension to the pulse generator and its subcutaneous implantation into the subclavicular region. The system since 2006 has usually been internalised without external screening in one procedure. The optimal setting of stimulation and contacts is arranged with a programming device. A patient programmer also can be used for changing of stimulation settings within the allowed limits.

3.12. Postoperative follow-up

After ablative surgery the hospital stay was usually 3-5 days. The postoperative oedema can be seen up to 4-6 weeks after surgery. After 4 weeks the tremor abolition is practically stabile, recurrence of tremor in later period is not typical. During the 1st year control, the examination was performed 1, 3, 6 and 12. months later annually. After DBS surgery the lead position was controlled with CT scanning and the optimal setting was adjusted after 3-4 months of follow-up. The stimulation setting can be monopolar or bipolar, stimulation with multiple contacts is also available. All the patients were informed concerning the necessary changes in lifestyle for avoiding mechanical and electrostatic influences both personally and in a written form.

4. RESULTS

4.1. Accuracy of the targeting technique

The accuracy of targeting technique in *thalamotomy* has been studied in 45 cases. The X-ray control of electrode position in the planned target point was performed in 25 cases. The difference between the Ct-guided and „Angioloc”-controlled coordinates according to the X, Y and Z-axes was 0.3±0.2 mm, 0.5±0.4 mm and 0.7±0.5 mm. The difference in impedance between white and gray matter was significant (28.7%, P=0.0005). From the 45 cases, the macrostimulation-defined final target in 1 case was more, and in 28 cases was less than ±2.0 mm, from the tentative target, including 22 cases, where the distance was less than ±1.0 mm, and 16 cases it coincided with the tentative target. The mean difference in medio-lateral direction was 0.2±0.6 mm, in antero-posterior direction was -0.9±1.4 mm, in dorso-ventral direction was 1.2±1.4 mm, and in the 3-D space was 1.8±1.8 mm. The mean lesion volume in 45 procedures was 64.3±25.8 (45-88) mm^3. Correction with side-electrode according to the learning curve at the early 50 cases was needed in 6 patients (12%), including 5 cases with the width of 3rd ventricle more than 10 mm. In the latter series it was needed in 7% of procedures. Test lesion was applied in 12 cases (7%) from the 158 consecutive thalamotomies, when the patients’ cooperation during stimulation testing was not sufficient.

After *pallidotomy* the MRI and 3-D coordinate transformation based tantative target (TENT) was 2.2±0.4 mm-re (1.5-3.0 mm) anterior, 21.2±1.2 mm-re (18.5-23.0 mm) lateral, and 5.3±0.9 mm (2.0-7.0 mm) ventral from the MCP. The TRA was placed significantly more lateral and ventral than the TENT, and more ventrally than the final target. The difference was highly significant in the 3-D space, the TRA was in a 2.49±1.63 mm distance from the final target, and the difference was significant only in the antero-posterior direction. The TENT coincided with the final target in 11 cases, while the TRA did only in 1 case.

The number of lesions varied between 2 and 4, the mean volume was 105±18 mm^3 (85-155 mm^3). The lesion site was measured after 24 procedures, and in call cases involved the GPi, in 6 cases it was also extended to the neighbouring part of the Gpe. Neither the optic tract, nor the corticospinal tract was involved.

In all cases with *GPi-DBS,* the tip of implanted electrodes was positioned just above the optic tract, laterally from the cortico-spinal tract in the GPi. The deviation of the active tip coordinates during intra-operative X-ray control along the X, Y and Z-axis was 0.5/0.8/1.3 mm from the initial target. No bleedings were observed in the postoperative CT and MR images. Optimal settings were stabilised 3-6 weeks after surgery. In 4 patients monopolar, in 1 patient unipolar setting was adjusted, in 1 patient 2 contacts with lower voltage were activated.

The AC-PC related position of active contacts, and the electrode trajectory angle and the stimulation parameters were delineated in the 22 cases with *STN-DBS* undergoing acoustic voice analysis. In one patient on the right side 2 contacts were activated, in all of the cases monopolar setting was applied. The active contacts were located within the Guiot’s scheme in 18 patents, in other cases it was above the dorsolateral border.

4.2. Intraoperative electrophysiology

In 32 patients MER was performed during thalamotomy and Vim-DBS. In all cases a 1-channel recording was applied and the depth of the final target had to be modified with 0.9±0.6 (1.0-2.0) mm in the trajectory channel.

In bilateral STN-DBS MER was applied in 24 cases, with 1-channel in 7 cases, and with 5-channel recording in 17 cases. After the 1-channel recording the target depth was modified by 1.5±0.8 (1.0-3.0) mm in the particular trajectory. Following the 5-channel recording, except for 1 case, the lateral channel was the optimal on both sides, in other cases the central channel was chosen for the lead. The depth of the position was modified 1.2±0.8 (0.0-3.0) mm.

4.3. Clinical results

Ablative procedures

Between March 1st, 1996 and June 15th, 2010, a total of 256 (145 left and 111 right side) lesion surgeries were performed on 202 patients (121 males, 81 females).

In all 158 *thalamotomies* were performed, including two reoperations. 112 tremordominant patients (81 males, 41 females) underwent only unilateral thalamotomy, 46 patients (29.5%) later underwent additional surgery. The mean follow-up was 79.7±33.7 months (13-152 months)**.** At the 6-months follow-up after 131 thalamotomies we observed total abolition of tremor (82.9%), in 20 patients subtotal abolition of tremor (12.7%), in 7 patients (4.4%) a significant recurrence, including 4 patients (2.5%) with successful reoperation: in 2 patients thalamotomy, in 1 patient pallidotomy and in 1 patient Vim-DBS was performed. The MS improved by 49%, the tremor score in the contra-lateral side improved by 93.1%, the rigidity by 58.1%, the bradykinesia by 15.9% (P=0.02), the PIGD score improvement was 6.2% but non-significant. Contra-lateral synkinesia of the upper limb significantly improved in 24 patients. At the 2-year follow-up 87 patients were assessed, 72 patients were tremor free (82.8%). The MS improvement was 30.2%, the tremor and rigidity score was 93.2% and 51.8% better, the bradykinesia score 8.4% better than at the baseline. In comparison to the results of the 6-months follow-up the tremor, rigidity and bradykinesia scores did not change significantly.

Within the 46 patients who underwent assessment after 5 years, 37 patients were still tremor free (80.4%). None of the patients who were tremor free at 2 years, developed contra-lateral to surgery side tremor, but in 3 cases with residual tremor we observed progression. Compared to the baseline, the tremor and rigidity score improved by 92.1% and 29.6%. In comparison with previous follow-up scores the progression of tremor and rigidity was not, but of bradykinesia and axial symptoms was significant.

The 7-years follow-up data was available for 27 patients. 24 (88.9%) patients were still tremor free, 3 patients (11.1%) were with residual tremor. The UPDRS tremor score was 90.9%, the rigidity score was 32.3% better than at the baseline. The bradykinesia and PIGD score compared to the data at 6 months showed significant progresssion.

The H-Y stage at 6 months did not change, later as the result of disease progression showed a mild but significant elevation.

Generally the effect of thalamotomy on tremor and rigidity was significant and sustained. The bradykinesia and axial symptoms after short-term benefit showed a significant progression, which corresponds to the natural course of the disease.

At 6 months and 2 years we observed a 21% and 11% LED reduction, but at 5 years and 7 years a significant 14% and 37% increase of LED. The anticholinerg therapy decreased by 32/53/64/76% and was replaced in combined therapy The dose of selegiline and amantadine has not been changed significantly.

Due to second side tremor we performed bilateral thalamotomy only in 4 early cases.

76 patients with advanced PD (mean H-Y 3.9±0.7) underwent 98 *pallidotomies,* including 22 cases with staged bilateral procedures with interval of 3 months, and 28 cases for tremor control after previous thalamotomy on the other side. The mean follow-up was 61.3±18.1 (30-81) months. Before the DBS era in 27 cases for second side, and in 1 case for the same

side after thalamotomy. However, the tremor control was less effective than after thalamotomy, it was at 6 months/2 years/5years as high as 70/68/60%. The rigidity and bradykinesia also improved significantly by 45/48/44% and 30/22/13%. The LED at the first and second follow-up was reduced by 9-9%, but at 5 year it was 10% higher than at the baseline. The anticholinergic treatment remained under the initial level.

In 26 patients with „on-off" fluctuation and dyskinesia *unilateral pallidotomy* was performed. The mean follow-up was 46.8±10.5 (30-72) months. At 3 months data after first surgery of patients with bilateral procedures was also included. At the 1-year follow-up data of 24 patients, at 3.5 years data of 13 patients was available. There was an extremely high 92.2/93.0/90.4% improvement in contralateral ON dyskinesias. In OFF state the improvement of tremor was 64.7/65.8/60.0%, of rigor 51.2/22.2/16.3%-os, of bradikinesia 52.2/46.0/39.5%s, and of fluctuation 69.2/63.5/48.6%, respectively. The procedure on PIGD scores was less effective (40.5/39.1/34.9 %), the speech did not change significantly, either. The LED at 1 year changed from 596±438 mg to 445±331 mg (26%), but after 3,5 years with 610±454 mg it was non-significantly higher than at the baseline. In 6 patients with bilateral tremor the L-dopa therapy was suspended for at least 1 year.

Bilateral pallidotomy was performed as a staged procedure in 22 patients with a 3 months interval. The mean follow-up was 45.2±11.8 (24-122) months. The S&E ADL showed a 66.7/45.1/39.0% the ON dyskinesia a 90.3/90.8/87.7, the OFF tremor a 67.3/81.2/86.2%, the rigidity a 57.4/61.6/70.2%, the bradikinesia a 51.3/36.4//84.7% and the fluctuation a 57.1/52.5/54.8% improvement. The LED at 1 year decreased from 915±457 mg to 521±389 (43%), and after 3.5 years it was 832±467 mg and 9% lower than at the baseline. In 4 patients we could suspend the replacement therapy for 9 months.

Deep Brain stimulation (DBS)

From November 1st, 1998 to June 15th, 2010, 87 neurostimulation systems were implanted for 85 PD patients (63 male, 22 female) altogether. 150 leads were implanted bilaterally in 63 patients and unilaterally in 24 patients.

Unilateral Vim-DBS was applied in 19 patients, particularly in 12 cases after previous contra-lateral in 1 case ipsilateral but ineffective thalamotomy. In 15 patients with a mean follow-up of 40.5±11.8 (22-78) months the stimulation setting was not changed significantly. The tremor control based on tremor score was 84.3%, and had a long lasting effect. With time the reduction of effect on rigidity and bradykinesia was observed. The changes of axial symptoms were minimal or could not be observed.

Bilateral Vim-DBS was used in 11 patients, in 1 patient the pulse generator was removed due to an infection. During the follow-up 1 patient died for cardiovascular reasons, 6 patients were followed for 31.6±5.1 (26-41) months. On the left side the pulse width of the stimulation parameters had to be significantly decreased. The 6 months/2,5 data showed a 78.3/82.9% of tremor, a 40.7/41.7% of rigidity and a 34.6/29.3% of bradykinesia improvement In long-term the postural stability, gait and speech without significant changes in StimOFF and StimON conditions.

The LED 2.5 years non-significantly increased by 7% to 318±282 mg after unilateral Vim-DBS, and by 10% to 461±109 mg after bilateral Vim-DBS.

Between 1998 and 2000 while the STN-DBS was not an accepted procedure, we implanted *unilateral GPi-DBS* in 5 patients with dyskinesia. The MS significantly improved by 51.5% in OFF, and by 12.6% in OFF state. The OFF tremor score improved by 60.0%, the rigidity score by 75.0%, the bradykinesia by 53.5%. The dyskinesia was completely abolished in all cases (100%), the tremor reduction was 50%, the rigidity reduced by 60%, and the bradykinesia improved by 42.9% in the ON state. The ADL improvement was 45%

in OFF and 15% in ON. The LED 3 years after surgery was still 22% lower than the initial dose.

Bilateral STN-DBS was implanted in 52 patients with advanced PD with severe „on-off" fluctuation. 1 patient was followed for less than 6 months because of a suicide attempt, in 1 patient with a recurrent infection we had to remove the system. The short-term effect was assessed at 6 months, the long-term effect at the last visit. From the 51 patients, until June 15, 2010 two patients died of cardio-vascular diseases. The mean follow-up period was more than 3.5 years, 44.9±20.1 (15-109) months. The S&E ADL showed a 117,9/86,0 % improvement, in OFF state the tremor had a 82.6/80.0% the rigidity a 66.7/52.5%, the bradykinesia a 54.2/46.5%- and the fluctuation a 64.7/48.3 % improvement. The ON dyskinesia was reduced by 87.2/76.5%. The LED at 6 months decreased from 819±421 mg to 447±408 mg (45%), and after 3.5 years it was 553±453 mg and 32% lower than at the baseline. In 4 patients we could suspend the replacement therapy for 9 months.

4.4. Results of the quantitative motion analysis

The *DSDT* results of thalamotomy and Vim-DBS, equally, in 15 patients were compared to the results of 15 control subjects. All of the calculated parameters improved significantly. The tremor intensity reduced by 88.9% after thalamotomy, while Vim-DBS resulted in a 76.2% temor supression. Other calculated parameters had a significant trend to change towards physiologic tremor values.

PAM tremorometry was performed in 15 control subjects and in 15 patients with thalamotomy and with Vim-DBS after both with turned off and turned on stimulator.

After thalamotomy the intensity of the rest tremor was reduced by 90.8%, of the postural tremor was reduced by 90.8%. Vim-DBS resulted in this reduction by 94% and 90%. All other parameters had a significant trend to change towards physiologic values.

PAM pointing test in 24 patients was measured after bilateral STN-DBS (20 right-handed) with StimOFF and StimOn in OFF state. The PTS on the left side from 0.52±0.28 to 0.84±0.39, on the right side from 0.50±0.27 to 0.85±0.35 improved significantly and uniformly. (P=0.001). The OFF score and the changes were not significantly different between the sides.

PAM tapping test of age matched control subjects had a mean FTTS right/left 26.4±8.8/26.8/9.1 m/sec, the patients with H-Y stage 1 had a decreased mean 8.7±4.9/9.1±4.7 m/sec score. At least 6 months after surgery 28 patients were measured. The FTTS significantly (P=0.001) decreased from 3.8±3.0 to 11.0±8.9 on the left side and from 4.1±3.5 to 12.6±9.0 on the right side. The mean scores of the sides were not significantly different either in StimOFF (P=0.278), or in StimON (P=0.071).

4.5. Results of the voice analysis

In the cases of the 22 patients who were studied with voice analysis the mean LED was reduceed from 713.5±307.8 mg to 347.9±191.0 mg by 51.2±7.4%. The MS either in OFF (55.3±7.2%), or in ON (12.6±3.2%) was reduced after STN-DBS. L-dopa improved the MS by 57.1±6.8% but in StimOVER it was decreased by 8.7±4.5%-os (p=0.001) compared to StimON. The VHI-was 36.1±28.2 (VHI-e=11.3±10.5; VHI-p=12.2±9.4; VHI-f=11.9±9.1). The speech UPDRS score in StimON worsened non-significantly (p=0.107), in StimOVER it significantly (p=0.0001) did.

The internal consistency of the *perceptual analysis* was acceptable with Cronbach-alpha between 0.88 and 0.98. The speech improved in both StimON and OVER conditions compared to StimOFF without significant difference between them. The G-score of sustained vowels in StimON was significantly impaired, but in StimOVER except of high /i/ it was improved.

The internal consistency of *acoustic measurements* with sustained vowels according to Cronbach-alpha was between 0.82 and 0.97. *Perturbation measures* were only significantly higher in StimON compared to StimOFF of /u/. In StimON-OVER comparison, there were no changes, and only jitter showed a difference between StimOFF and StimOVER. The *NDA* was more sensitive: α_{norm} at StimON during /o/ and /u/ was significantly higher than in StimOFF, during /a/, /i/, /o/ and /u/ was higher than in StimOVER. The H_{norm} in StimON during /i/ and /u/ was significantly higher than in StimOFF-ban, and during /i/, /o/ and /u/ significantly higher than in StimOVER. Generally, the acoustic parameters worsened during StimON , while during StimOVER had a trend to return to StimOFF values.

At the *QDA* the correct classification percentage with NDA values were significantly higher than with the perturbation values. At the StimOFF-StimON classification the correct classification with segmental α_{norm}-H_{norm} pairs of data was between 83.2% and 90.6% with higher values during /o/ and /u/ sustained vowels. At the StimON-StimOVER QDA a 78.4-93.8% of correct classification was achieved with best results during /i/ vowel.

4.6. Results of the functional PET

During sequential movements, an increase of activity could be seen in the contra-lateral primary sensorimotor (S1/M1) and premotor (PMC) cortex (BA6), and in the supplementary motor area (SMA), bilaterally. There were also bilateral clusters with increased activity in the region of inferior parietal S2 (BA40) and ipsilateral PMC. A trend to non-significant hypoperfusion was detected in the ipsilateral PMC, mesial frontal, dorsolateral prefrontal (DLPFC) cortices, and with contra-lateral dominancy in the head of caudate nuclei, bilaterally.

Gpi-DBS caused a significant (*P*<0,001) increase of motor activity in the right PMC and caudal SMA and anterior insular cortex (IC), and the decrease of activity in the left M1/S1. During ON state along with similar changes in the right PMC and caudal SMA and anterior IC, activation was detected in the left superior parietal cortex (PC). Along with the decrease of activity of the left VL thalamus and PMC, the hypoactivation of the DLPFC was increased.

The *L-dopa* alone increased the motor activity of the left ventrolateral (VL) thalamus significantly and decreased in the left superior parietal cortex (PC), during GPi-DBS along with the caudal SMA, PC and right anterior IC activation, the hypactivation of the DLPFC was increased.

GPI-DBS and L-dopa common effect resulted in the increase of activity of the right PMC/caudal SMA, left VL thalamus and right anterior IC. The overactivity of M1/S1 and lateral PMC on the stimulated side was significantly reduced.

overactivity of M1/S1 and lateral PMC on the stimulated side significantly was reduced.

4.7. Changes in the quality of life

The quality of life was studied after 1 year in 53 patients with thalamotomy. The dimensions of mobility (MOB), activity of daily living (DLA), emotional well-being (EWB), stigma (ST) and body dyscomfort (BD) were significantly improved. The index improved substantially from 47.9±77 to 29.2±6.5 (39%). At 5 years the index was impaired by MOB, DLA, COG and BD but was still more improved by 22% than at the baseline.

The quality of life was assessed in 31 patients with bilateral STN-DBS, after 5 years in 15 patients. At the long-term follow-up, in the cases of whom the dimensions of MOB, DLA, EWB and BD significantly improved at 1 year, had no impairment, the ST and COM impaired, but the index was still better by 24% than at the baseline.

4.8. Complications

After unilateral *thalamotomy* perioral hypaesthesia (6.6%), slight contra-lateral facial weakness, dysequilibrium (4.7-4.7%), dysarthria (4%) and somnolence (4%) were the most common complications. In two patients with somnolence, thalamic bleeding occurred without residual symptoms. After *pallidotomy* the somnolence (9.3%) was the most frequent complication, in 1.9% equally, hypersalivation and visual field reduction, and intracerebral heamorrhage occurred. The most frequent permanent complication of bilateral surgery was hypersalivation (22,7%). Following the 256 ablatíve procedures 1 patient (0.4 %) died of intracerebral haemorrhage in the early postoperative period after pallidotomy.

After unilateral *Vim-DBS* in 21% of patients, following bilateral Vim-DBS 27% of patients had minor complications. After *GPi-DBS* in 20%, following *STN-DBS* in 29% of patients had minor complications. Paraesthesia in 15.8% equally after Vim-DBS and STN-DBS, dysarthria in 27,3% vs. 7,7% were the most frequent complications, but improved with stimulation adjustment, hypersalivation occurred in 18.2 vs. 5.8% of patients. Both surgery and implant-related complications most frequently occurred in STN-DBS patients with more advanced disease stage. In elderly patients and after 5-channel MER we observed subdural air, somnolence and postoperative desorientation more frequently.

5. CONCLUSIONS

With the applied clinical scales and objective instrunental methods the improvement in patients condition can be well measured after surgery

The developed planning software and the technique with improved accuracy contributed to have good postoperative results in comparison to the literature data. The patients' quality of life improved substantially, however, impacts on the natural disease progression could not be sensed. Unilateral thalamotomy with a low complication rate is highly effective in tremor cessation, with a sustained effect up to 7 years.

Pallidotomy, in short-term, alleviates tremor, bradykinesia and dyskinesa, whereas its long-term effects mainly have influence on dyskinesias.

DBS provides reversible and adjustable effects with a lower neurological complication rate, but has a higher rate of surgical complications than ablative procedures.

Vim-DBS, according to the clinical scales and quantitative measurements, is highly effective in tremordominant PD patients equally for both unilateral and bilateral tremor.

With GPi-DBS we had a small number of patients, but based on the data of publications remains as option for dyskinetic patients, who do not pass the selection criteria for STN-DBS.

The ^{15}O-butanol functional PET contrary to fMRI can be performed in patients with DBS and highly sensitive during motor activation paradigms. In the mechanism of the effects of L-dopa and GPi-DBS we found similar and different components.

Based on the clinical scales and quantitative measurements, STN-DBS, in both short and long-term, alleviates all main motor symptoms of PD substantially. Along with the effects on motor symptoms some attention has to be paid on the effect on speech, as it may have an impact on the quality of life.

Acoustic analysis of sustained vowels with an appropriate test battery and software package can be a helpful tool for optimising the stimulation parameters and recognising the over-stimulated condition in STN-DBS.

6. LIST OF PUBLICATIONS

6.1. First author publications related to the topic of dissertation

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Cumulative impact factor of the publications: **12.3**