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Autoreferát disertační práce

Váhové změny u pacientů s Parkinsonovou nemocí, kteří byli léčeni hlubokou mozkovou stimulací

Weight changes in patients with Parkinson's disease treated with Deep Brain Stimulation

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Disertační práce bude nejméně pět pracovních dnů před konáním obhajoby zveřejněna k nahlížení veřejnosti v tištěné podobě na Oddělení pro vědeckou činnost a zahraniční styky Děkanátu 1. lékarské fakulty.

Table of Contents

Souhrn

Váhové změny jsou popisovány v literatuře jak v průběhu Parkinsonovy nemoci (PN), tak u pokročilé Parkinsonovy nemoci léčené oboustrannou hlubokou mozkovou stimulací subthalamického jádra (STN DBS). Váhové změny se u pacientů po STN DBS vyskytují často, jsou popisovány v 50-100% případů. V posledních 15 letech byla vyvinuta velká snaha o porozumění mechanismů těchto změn, ale navzdory tomu se i nadále v literatuře objevují protichůdná sdělení. Mezi důvody váhového přírůstku se mimo jiné spekulovalo o zlepšeném hybném stavu, snížení či vymizení mimovolních pohybů, změn v příjmu potravy, redukci dopaminergní léčby, hormonálních faktorech a regionálním efektu stimulace. Hypotézou práce bylo, že i naši pacienti budou přibývat na hmotnosti (studie 1-2). Jelikož mechanismus váhového přírůstku u STN DBS nebyl dosud uspokojivě objasněn, tak jsme v naší druhé práci pracovali s hypotézou, že k váhovým změnám dochází v důsledku dysregulace hormonů a parametrů příjmu potravy (studie 2). Ve třetí práci jsme hypotezovali, že váhový přírůstek souvisí s pozicí aktivního kontaktu elektrody v STN jádru (studie 3).

Cíle práce: Jsou potvrzení váhového přírůstku a souvisejících antropometrických změn u pokročilých PN pacientů po STN DBS, prozkoumání regulace energetické homeostázy měřením laboratorních parametrů příjmu potravy a ověření, zda pozorovaný váhový přírůstek souvisí s polohou aktivního kontaktu elektrody v STN jádru.

Metodika a výsledky: Studie 1 - Retrospektivní studie ve formě strukturovaného dotazníku byla použita ke zhodnocení váhových změn pacientů v souvislosti s aplikací STN DBS. Studie prokazuje signifikantní váhový přírůstek u všech pacientů v porovnání období před a po STN DBS, přičemž pouze u některých pacientů docházelo ke zvýšení hmotnosti i s odstupem jednoho roku. Váhové změny jsou doprovázeny změnami body mass indexu (BMI) a nebyla nalezena korelace mezi změnami hmotnosti a změnami v Unified Parkinson's Disease Rating Scale (UPDRS), Movement Disorder Society (MDS) skóre dyskinéz ani v levodopa equivalent daily dosage (LEDD). Studie 2 – Antropometrické parametry a hormony zapojené do regulace příjmu potravy (leptin, adiponektin, resistin, ghrelin, cortisol, insulin a thyreotropin) byly měřeny v pravidelných intervalech během období dvanácti měsíců po zavedení elektrod. Nalezli jsme zvýšení hmotnosti, BMI, obvodu pasu i procenta adiposity během celé studie. Signifikantní váhový přírůstek byl pozorován již v prvním měsíci po neurochirurgickém zákroku, naproti tomu se kromě změn hladiny kortizolu, neprokázaly signifikantní změny v testovaných hormonech regulace příjmu potravy. Na základě těchto výsledků se domníváme, že s výjimkou kortizolu nepřispívají změny periferních hormonů k váhovému přírůstku u STN DBS u PN. Studie 3 - T1 vážené MRI obrazy byly vyhotoveny 1 rok po implantaci DBS a byla vypočítána poloha elektrody v STN. Nalezli jsme, že váhový přírůstek souvisí inverzně se vzdáleností kontaktů od stěny III. mozkové komory a že pacienti, kteří měli alespoň jeden kontakt uložen mediálně přibrali na hmotnosti signifikantně více než pacienti s oběma kontakty lokalizovanými laterálně.

Závěry: Potvrdili jsme, že u pacientů s pokročilou PN, kteří jsou léčeni STN DBS, dochází k nárůstu hmotnosti a s ní souvisejícími změnami antropometrických parametrů. Náš výzkum prokázal, že příčinou těchto změn není dysregulace tradičních periferních hormonů příjmu potravy. Dále jsme doložili, že mediální pozice aktivního kontaktu v STN jádře je spojena se signifikantním nárůstem hmotnosti.

Abstract

Body weight changes have been described in the course of Parkinson's disease (PD) as well as following bilateral deep brain stimulation of the subthalamic nucleus (STN DBS) performed in advanced PD. According to the literature weight changes occur in 50-100% of patients who undergo STN DBS. In the last 15 years extensive efforts have been put in understanding the underlying mechanisms behind the weight changes following STN DBS in advanced PD patients however many sources still report conflicting evidence. Improved motor status, reduction in dyskinesias, decrease in energy expenditure, dopaminergic medication reduction, modification of food intake, hormonal factors, regional effects of stimulation were all speculated to cause this weight gain. We hypothesized that patients who underwent STN DBS procedure in our center would gain weight as reported in the literature (study 1, study 2). The etiology of post STN DBS weight gain has not been fully elucidated up to date, in our second study we further hypothesized that the weight changes are due to dysregulation of food related hormones and parameters (study 2). In the third study we hypothesized that weight gain is associated with position of active electrode contact (study 3).

Aims of the study: The primary aims of our studies were to assess body weight changes and related anthropometric parameters following STN DBS in PD (study 1 and 2), to explore regulation of energy homeostasis and food intake by assessment of laboratory parameters involved in body weight and energy metabolism homeostasis, and to assess whether weight gain observed is dependent on the active electrode contact position in STN, particularly with respect to mediolateral direction (study 3).

Methods and results: Study 1. Retrospective survey in the form of structured questionnaire, was used to evaluate body weight changes in our patients with advanced PD treated with STN DBS and the survey was repeated year later from the first one. Significant weight gain was found in all patients comparing to pre-DBS period. In the repeated survey only few patients increased further body weight. Study 2. Anthropometric parameters and food- related hormones such as leptin, adiponectin, resistin, ghrelin, cortisol, insulin, and thyroid stimulating hormone were repeatedly measured during a 12 months period following electrode implantation. On average we found increases in body weight, BMI, waist circumference and body fat percentage during the entire study period. The significant weight change was already apparent in the first month following the surgery. No significant changes were found in food related hormones and biochemical parameters compared to baseline except a significant decrease in cortisol levels. Thus, we concluded, that changes in traditional peripheral food related hormones do not appear to be cause of weight gain in STN DBS treated PD patients. Study 3. T1 weighted magnetic resonance images were acquired one year after DBS implantation and electrode position within the STN was established. We found that weight gain was inversely related to distance of contacts from the wall of third ventricle and the patients who had at least one contact located medially gained significantly more weight than those with both active contacts located laterally.

Conclusions: In our studies we have confirmed post STN DBS weight gain associated with changes in corresponding anthropometric parameters. Our observations conclude that the weight changes are not caused by dysregulation in traditional peripheral food related hormones and parameters, however we further discovered that patients with at least one contact positioned medially within the STN encountered significantly higher weight gain that those patients with both active contacts localized laterally.

Introduction: Weight changes after STN DBS in PD patients

Changes of body weight have been described both in the course of Parkinson's disease (PD) as well as following deep brain stimulation of the subthalamic nucleus (STN DBS) – method currently recognized as a standard and highly effective treatment option for advanced PD. STN DBS effectively influences main motor symptoms of the disease (tremor, rigidity, bradykinesia) and as a main therapeutic advantage over pharmacotherapy, it improves late motor complications of PD. It directly alleviates motor fluctuations and indirectly, allowing for reduction of antiparkinsonian medication, suppresses dopaminergic induced dyskinesias. Besides these largely beneficial outcomes, motor as well as non-motor side effects have been reported. Non motor effects include occasional behavioral changes, affective, motivational and cognitive disorders and weight gain. These findings provide supporting evidence that STN is an important integrative structure for both motor and limbic processing (Baunez, Yelnik et al. 2011).

According to the literature post STN DBS weight changes occur in 50-100% of these patients. Substantial weight gain with high inter-individual variability is observed within the first 3 months after the procedure (Gironell, Pascual-Sedano et al. 2002, Barichella, Marczewska et al. 2003, Krack, Batir et al. 2003, Perlemoine, Macia et al. 2005, Montaurier, Morio et al. 2007). From published literature the weight gain 3 months post-surgery is around 3 kg, at 6 months around 4 kg, and 1 year post STN DBS implantation it is + 7kg. Observations what happens with weight in a long term are inconsistent, and weight loss as well as further weight gain were also described (Locke, Wu et al. 2011, Foubert-Samier, Maurice et al. 2012). The evaluation showed, that the weight increase beyond the first 2 years after surgery is not linear (Foubert-Samier, Maurice et al. 2012), the only ten year follow up study found a trend toward a loss of weight (Castrioto, Lozano et al. 2011). Gender prevalent weight gain remains conflicting, most authors did not find significant difference between the genders (Macia, Perlemoine et al. 2004, Foubert-Samier, Maurice et al. 2012, Strowd, Herco et al. 2016), although there was a trend toward male weight gain preponderance. BMI changes paralleled weight changes most of the time. Percentage of fat mass increases after STN DBS (Macia, Perlemoine et al. 2004), however significant inter individual variations and gender related difference in the quality of body weight gain were reported; in men 2/3 of body weight gain was due to an increase in free fatty mass while women gained only fat (Montaurier, Morio et al. 2007).

Extensive efforts have been put in understanding the underlying mechanisms behind the weight changes following STN DBS in advanced PD patients however many sources still report conflicting evidence. Improved motor status, reduction in dyskinesias, decrease in energy expenditure, dopaminergic medication reduction, modification of food intake, hormonal factors, regional effects of stimulation were all speculated to cause this weight gain.

The data on food related parameters in STN DBS PD patients are sparse and rather conflicting. The failure to show consistent correlations between parkinsonian motor symptoms and energy metabolism led to suggestion that neuroendocrine dysregulation is present post STN DBS which induces temporary hypothalamic dysregulation causing the weight gain (Corcuff, Krim et al. 2006, Escamilla-Sevilla, Perez-Navarro et al. 2011, Markaki, Ellul et al. 2012). The main focus laid on orexigenic factors such as ghrelin and NPY; and fat tissue hormone leptin. Markari et al found increased "hunger hormone" ghrelin levels 6 months after the surgery. Observed weight gain significantly correlated with increased ghrelin levels at month 3 and 6. On contrary, Corcuff found no acute changes in ghrelin levels investigating patients with or without ongoing STN stimulation, but when

L dopa was administered to stimulated patient, there was a marked reduction in ghrelin levels (Corcuff, Krim et al. 2006). L dopa reduction post STN DBS is common; therefore, the L dopa reducing effect on ghrelin is mitigated and ghrelin can exert its appetite stimulating effect and thus weight gain. These results are in line with increased ghrelin levels reported (Markaki, Ellul et al. 2012). NPY circulating levels increased significantly 3 months following the procedure (Escamilla-Sevilla, Perez-Navarro et al. 2011, Markaki, Ellul et al. 2012) together with leptin (Escamilla-Sevilla, Perez-Navarro et al. 2011), which raised hypothesis that DBS interferes with the inhibitory action of leptin where physiologically reciprocal inhibition between leptin and NPY exists. The NPY results should be however interpreted with caution since these are measured peripherally but NPY is centrally produced peptide and the peripheral concentration likely does not reflect exact central levels. Based on the limited and contradictory information on food homeostatic parameters we elected to investigate their potential dysregulation.

Structural and functional complexity of subthalamic area, its proximity to the structures involving regulation of energy expenditure and food intake and potential exertion of regional effects of STN DBS on these regions may account for weight gain after the procedure. Our group have further looked at position of active electrode contact which has been postulated as an important predictor of weight gain.

The role of STN in emotional and motivational processing is also well recognized and thus speculating that motivational and associative aspects of food behaviour account or at least be associated with weight gain after STN DBS surgery is certainly of interest. PET study was used to analyse correlation between changes in brain metabolism and weight gain after STN DBS confirming correlations in brain metabolism in limbic and associative areas, including the orbitofrontal cortex, lateral and medial parts of the temporal lobe, anterior cingulate cortex and retrosplenial cortex. (Sauleau, Le Jeune et al. 2014) confirming that changes in associative and limbic processes contribute to weight gain after STN DBS.

1. Aims

Study 1. Frequent weight gain has been found as a non-motor symptom across multiple studies evaluating post-operative changes in patients with PD STN DBS. In agreement with published studies we have as well noticed increasing weight in our patients. The first study aimed to confirm weight changes in group of advanced PD patients treated with STN DBS in our center.

Study 2. As we previously confirmed body weight changes in PD STN DBS by retrospective evaluation we needed to reciprocate these findings by prospectively evaluating weight evolution and related anthropometric parameters after STN DBS. The second aim of Study 2 was to explore whether the weight gain in STN DBS treated patients was associated with changes in hormones involved in the regulation of energy homeostasis and food intake.

Study 3. Based on the anatomical and functional complexity of STN we aimed to explore whether weight changes and motor improvement seen after STN DBS are dependent on active contact position within the STN.

2. Hypothesis

Study 1. We hypothesized that patient treated with STN DBS in our center gain weight in correspondence with published sources.

Study 2. We hypothesized that we will be able to confirm evolution of weight changes following STN DBS PD treated subjects and that these will be accompanied by abnormalities in hormones involved in the regulation of food intake and energy homeostasis.

Study 3. We hypothesized that weight gain may be associated with medial contact position in the STN.

3. Material, methodology and results

3.1. Study 1: Increase in body weight is a non-motor side effect of deep brain stimulation of the subthalamic nucleus in Parkinson's disease

Publication: Novakova, L., E. Ruzicka, R. Jech, T. Serranova, P. Dusek, and D. Urgosik. 2007. 'Increase in body weight is a non-motor side effect of deep brain stimulation of the subthalamic nucleus in Parkinson's disease', Neuro Endocrinol Lett, 28: 21-25. **IF - 1.443. Times cited 35.**

(Hypothesis 1).

Patients and methods

25 patients who received STN DBS were included in the study (16 men and 9 women, mean age in the time of intervention was 55 years (range 42-65), and mean PD duration 14 years (range 9-21). Repeated retrospective survey was used as a method. The mean interval between DBS implantation and the first survey was 19 months (range 1-45). The subjects were provided with a structured questionnaire concerning body weight changes in the period preceding PD, and in the course of PD, before and after the implantation of DBS and medical history focusing on potential presence of metabolic syndrome. Body mass index (BMI) was calculated and patients were divided into BMI categories from underweight to obesity. We repeated the survey with the same group twelve months later. All patients were evaluated using Unified Parkinson Disease Rating Scale (UPDRS) and MDS scale of dyskinesias within one week before and approximately 1 year after DBS implantation. Levodopa Equivalent Daily Dose (LEDD) was calculated.

Results

Within one year from DBS implantation, 23 out of 25 patients experienced motor improvement. Two patients were excluded from the study (non-compliance and DBS interruption). All 23 patients reported body weight gain after DBS implantation. In the first survey, we found overall mean increase in weight of 9.4 kg (range 1-25 kg), i.e. +13%, $p<0.0001$. In women, there was an average increase in weight of 12.8 kg (range 6-25 kg), i.e. +21%, $p<0.01$, and in men, weight increased by 7.6 kg (range 1-20 kg), i.e. +10%, $p<0.0001$. Comparing mean weight increases in men and women, there was a trend towards difference in genders ($p=0.07$). In the second survey, 14 subjects lost weight, 3 remained stable, and 6 reported further weight gain compared to the first survey. The mean weight change compared to the first survey was -1.4 kg (range -6 to +11 kg) i.e. –2%, $p=0.11$; -2.4 kg in men (range -6 to+4 kg) i.e.-3%, $p<0.01$ and +0.5 kg in women (range -6 to +11 kg) i.e. +1%, $p=0.79$. Comparing the second survey to the values before DBS, there was a mean change of +13 kg (from -4 to +33 kg) comparing to the lowest weight before PD onset and a mean change of +4kg (from -9 to 25 kg) comparing to the highest weight the patients ever had before PD onset. In this last comparison, body weight increased in thirteen, decreased in nine, and two patients were unable to state their highest weight before PD. No significant correlation was found between changes in UPDRS and MDS scores of dyskinesia and weight changes. Nor did we find any significant correlation between weight changes and the changes in LEDD. After DBS, all patients increased their BMI. The mean BMI before STN DBS was 23.7 kg/m2 (standard deviation 2.9). In the first survey, it increased to 27.0 kg/m2 (±3.6) and in the second survey, it remained nearly unchanged at 26.6 (±3.5) kg/m. Shifts in BMI

categories occurred as well. 12 out of 23 patients (52%) claimed increased appetite which subsequently lead to increased food intake in 42% of patients.

Conclusions

During retrospective evaluation of weight changes after STN DBS we found that all patients gained weight and that body weight changes are indeed common in this patient population. As expected, weight gain was accompanied by BMI changes. Women gained more weight than men in our group. When the survey was repeated one year later we found that majority of patients kept changing weight. No correlation was found between UPDRS, MDS dyskinesia score, LEDD changes and changes in weight.

3.2. Study 2: Hormonal regulators of food intake and weight gain in Parkinson's disease after subthalamic nucleus stimulation

Publication: Novakova, L., M. Haluzik, R. Jech, D. Urgosik, F. Ruzicka, and E. Ruzicka. 2011. 'Hormonal regulators of food intake and weight gain in Parkinson's disease after subthalamic nucleus stimulation', Neuro Endocrinol Lett, 32: 437-41. **IF - 1.296. Times cited 24.**

(Hypothesis 1 and 2)

Patients and methods

Twenty-seven patients that received STN DBS were enrolled in the study (21 men, 6 women; age at time of intervention: mean 56.8±(SD)7 years, range 42-68; disease duration: mean 12.5±4 years, range 7-23. Each subject was evaluated on the day of the interview (baseline, pre-surgery) after at least 12 hours of discontinuing all antiparkinsonian drugs (MED-OFF), then at one month, before the setting-up (MED-OFF/DBS-OFF), after the initiation of stimulation (4 weeks after implantation (MED-OFF/DBS-ON). Further assessments were completed at 2, 4, 6 and 12 months after surgery. Anthropometric examination included body weight and height, BMI, and waist circumference. At each visit, blood was withdrawn following an overnight fast, and serum biochemical parameters and hormones (total protein, albumin, prealbumin, cholesterol, triglycerides, insulin, glycemia, glycated hemoglobin and insulin-like growth factor 1 (IGF-1), thyroid stimulating hormone (TSH), cortisol, leptin, adiponectin, resistin and ghrelin were assessed. Eating related questionnaires were administered at each visit. Motor status was evaluated using UPDRS III. LEDD was calculated at baseline, 1 month, and 12 months following the surgery.

Results

On average, we found increases in body weight, BMI, waist circumference and body fat percentage during the entire study period. Notably, a significant change in body weight was observed already at one month following surgery, i.e., before stimulation was started, in comparison to baseline: +1.1±2 kg, range –2.6 to 5.0, ($p<0.05$). Change in mean weight from baseline to 12 months following STN DBS implantation was +5.18±5.8 kg, range –6.30 to +19.80, ($p<0.001$). At month one, taken individually, 17 patients gained weight compared to baseline while weight loss was noted in 10 patients. At month twelve, 24 patients gained weight and 3 patients had lower weight compared to baseline. In examining gender differences, body weight increased at 12 months after STN DBS implantation by 9.0±5 kg in women (range 5.0 to 18.3) and 4.1±6 kg in men (range –6.3 to 19.8). Body weight and BMI differed significantly between the genders, with a greater increase in women ($p<0.05$, $p<0.01$, respectively). A borderline correlation between weight gain following STN DBS and PD duration was observed ($rs = 0.418$, $p<0.05$), but not with age at PD onset. No significant correlation was found between the change in LEDD and change in weight. Most of the subjects did not report any changes in food intake, hunger or appetite. In the MED-OFF/DBS-ON condition at one month after surgery, the mean UPDRS III score significantly decreased to 17.2±6 ($p<0.001$). The MED-OFF/DBS-ON UPDRS III score at 12 months did not significantly change (14.5±7, $p<0.14$) in comparison to one month after surgery. A significant decrease in cortisol levels compared to baseline appeared at month 2 and persisted at 12 months ($p<0.01$, corrected), with no significant changes in other tested hormones or biochemical parameters. A positive correlation between leptin levels and body weight ($rs = 0.299$, $p<0.001$) and body fat percentage ($rs = 0.343$, $p<0.05$) was found. Body weight

negatively correlated with adiponectin ($r_s = -0.604$, $p<0.001$), positively with ghrelin ($r_s = 0.253$, $p<0.01$) and did not significantly correlate with cortisol ($r_s = -0.114$, $p<0.2$).

Conclusions

In this prospective study we confirmed increases of body weight and related anthropometric measures during the entire study period. Except significant decrease in cortisol levels we found only physiological changes in peripheral food related hormones and parameters corresponding to prevalent weight gain.

3.3. Study 3: Weight gain is associated with medial contact site of subthalamic stimulation in Parkinson's disease

Publication: Ruzicka, F., R. Jech, L. Novakova, D. Urgosik, J. Vymazal, and E. Ruzicka. 2012. 'Weight gain is associated with medial contact site of subthalamic stimulation in Parkinson's disease', PLoS One, 7: e38020. **IF- 3.73. Times cited 15.**

(Hypothesis 3)

Patients and methods

Regular body weight measurements were made on the day of surgery and one, two, four, six, twelve and eighteen months after electrode implantation in 20 patients with advanced PD (6 women, 14 men; mean age 56.6±(SD)5.8 years; disease duration 13.2±4.5 years). Eating related questionnaires were administered at each visit. Food intake, hunger, general appetite and preference for sweet food were rated by patients as (0) without any change, (-1) lower or (+1) higher than at the previous visit. Motor status was evaluated using the UPDRS-III. Each subject was examined postoperatively under two conditions at least 12 hours after discontinuing all antiparkinsonian drugs: (1) in the off-neurostimulation state (sOFF) and (2) in the on-neurostimulation state (sON). Magnetic resonance images were acquired at 1.5 T on a Siemens Avanto system in each patient approximately one year after DBS implantation. All four contacts (0,1,2,3) of the DBS electrode produced well defined susceptibility artifacts on the T1-MPRAGE image in each patient. While the coordinates of contacts 0 and 3 were established directly from the center of the distal and proximal artefacts using MRIcro 1.40 software (www.cabiatl.com/mricro, the coordinates of contacts 1 and 2 were calculated. The x coordinate of each contact was measured from the wall of the third ventricle, whereas the y- and z-coordinates were measured from the midcommisural point.

Results

After initiation of STN DBS, the UPDRS-III score dropped on average from 36.76(SD)9.6 (sOFF) to 17.865.5 (sON) ($T = 7.3$, $p < 10^{-7}$) showing good efficacy of neurostimulation treatment. The maximum change in body weight in the eighteen-month period after implantation was on average +6.9 kg64.5 kg (20.3 to +18.3 kg) and was strongly significant ($T = 6.6$, $p < 10^{-5}$). Despite gradually increasing weight during the entire study period, nine patients reached the maximum body weight within the first 6 months after surgery, five patients in months 6– 12 and six patients in months 12–18 after surgery. In individual patients, the maximum weight gain correlated inversely along the x-axis with the distance of the active contact from the wall of the third ventricle in the left hemisphere ($r = -0.48$, $p < 0.05$), right hemisphere ($r = -0.50$, $p < 0.05$), and in pooled data ($r = -0.55$, $p < 0.01$) if only more medial active contact regardless to hemisphere was considered. In addition, the hemi-body UPDRS-III sub scores in sON condition inversely correlated with the distance of the contralateral active contact from the wall of the third ventricle in the mediolateral direction ($r = -0.42$, $p < 0.01$). Patients with at least one active contact within 9.3 mm of the wall of the third ventricle demonstrated significantly greater weight gain (9.4±4.4 kg, N= 11) than those patients with both contacts located more laterally from the wall (3.9±2.7 kg, N=9) (GLM, factor BORDER: $F = 16.1$, $p < 0.001$). The postoperative maximum weight gain significantly differed between genders, with a greater increase in women (N = 6, 10.9±(SD)4.8 kg) than in men (N = 14, 5.2±3.4 kg) (GLM, factor: GENDER, $F = 10.7$, $p < 0.01$).

In addition, the postoperative maximum weight gain in all patients inversely correlated with preoperative body weight ($r = -0.62$, $p < 0.05$ corrected). Maximum weight gain did not

significantly depend on UPDRS-III improvement after switching the stimulation on (r =-38, p =0.1), and no correlation between weight gain at the 18th month and stimulation intensity was found. Analysis of eating behavior failed to demonstrate any change in hunger, appetite, preference for sweet food or food intake in our patients. However, there was a positive correlation between food intake and body weight gain at the 18th month (rho = 0.66, $P<0.05$ corrected).

Conclusions

In conclusion in this third study we confirmed that patients with at least one contact medially in the STN gain significantly more weight than those with both active contacts laterally and this result support hypothesis that STN DBS produces a regional effect on adjacent structures involved in energy homeostasis.

4. Discussion

4.1. Discussion of results study 1

The aim of our study was to confirm previous findings of weight increases after STN DBS (Barichella, Marczewska et al. 2003, Krack, Batir et al. 2003, Macia, Perlemoine et al. 2004, Tuite, Maxwell et al. 2005). Indeed, our retrospective study reciprocated these outcomes including the degree of weight gain observed. Weight gain did not correlate with any of the clinical variables reflecting motor improvement nor with reduction of dopaminergic treatment following STN DBS. We repeated the same survey on the study group one year later and found that at longer intervals following DBS both weight gain and weight loss can be observed. The mechanism behind weight gain was still unclear and various hypothetical explanations were suggested.

Firstly, weight gain following STN DBS might reflect a reversal of previous weight loss in PD. Indeed, weight loss has been observed since the early stages of PD and it usually progresses during its course (Marcus HS 1992, Marcus HS 1993, Davies, King et al. 1994, Beyer, Palarino et al. 1995). Multiple explanations for weight loss have been proposed – worsened exploitation of energy from food due to gastrointestinal visceromotor impairment (Braak, Ghebremedhin et al. 2004), olfactory dysfunction leading to decreased energetic input (Abbott, Cox et al. 1992, Beyer, Palarino et al. 1995), increased energetic output due to increased muscle rigidity and dyskinesias (Levi, Cox et al. 1990, Marcus HS 1992, Ondo, Ben-Aire et al. 2000). Consequently, weight gain after STN DBS can be due to motor improvement following DBS (Macia, Perlemoine et al. 2004). Nevertheless, in agreement with our results, the study did not find and correlation between weight gain and the reduction of dyskinesias according to detailed dyskinesia scales (Macia, Perlemoine et al. 2004).

Secondly, weight gain can be related to the reduction or withdrawal of dopaminergic drugs, however in accordance to previous work (Barichella, Marczewska et al. 2003), weight gain did not correlate with LEDD reduction in our patients.

Finally, weight changes could reflect a direct influence of DBS on autonomous functions and metabolic regulation.

In this context, the closed anatomic relationship between the subthalamic nucleus and lateral hypothalamus should be taken into account. Hypothalamic pathways and connections of "chemical systems" traverse the medial forebrain bundle in close vicinity to STN, together with STN connections to the brainstem. Consequently, STN DBS has a chance to influence these pathways as well as adjacent neurons in the lateral hypothalamic area that are involved in feed habits and energy expenditure regulation (Cerri and Morrison 2005).

4.2. Discussion of results study 2

In this prospective study, we tested the hypothesis that weight changes in PD patients treated with STN DBS are connected with abnormalities in the hormonal regulation of food intake. In concordance with previous studies (Barichella, Marczewska et al. 2003, Macia, Perlemoine et al. 2004, Perlemoine, Macia et al. 2005, Tuite, Maxwell et al. 2005, Montaurier, Morio et al. 2007), body weight increased in most of our patients, together with increasing BMI, waist circumference and body fat percentage within one year on STN DBS. Body weight correlated positively with serum levels of leptin and inversely with adiponectin, which correspond to the physiological regulatory mechanisms of food related processes (Meier and Gressner 2004). In addition, ghrelin positively correlated with weight in our

patients. This corroborates previous findings that were considered paradoxical in PD patients where weight loss usually occurs with the disease progression – the lower BMI was, the lower ghrelin levels were found (Fiszer, Michalowska et al. 2010). However, in accordance with Corcuff *et al.*, we did not observe any increase in ghrelin following STN DBS (Corcuff, Krim et al. 2006). As the most prominent hormonal change, serum levels of cortisol were found to significantly decrease on STN DBS, although cortisol should typically increase in the course of truncal fat accumulation and increasing body weight (Reynolds 2010). This finding was also observed in Markaki's study (Markaki, Ellul et al. 2012), where at 3 months after STN DBS, Markaki and colleagues noticed significant decrease in blood cortisol (-23.9%, $p < 0.0002$), in our study cortisol lowered significantly at 2 months and remained significantly reduced compared to baseline at 12 months after DBS implantation. Hence, direct effects of STN stimulation on adjacent nerve fibers and nuclei must be considered. STN DBS may hypothetically act on the hypothalamus by suppressing the secretion of CRF with a subsequent decrease in the production of cortisol. Since the level of corticotropin-releasing factor is low, its catabolic effect is mitigated: therefore, the homeostatic balance shifts towards predominance in anabolic reactions. Indeed, in rats exposed to high-frequency electrical stimulation of the lateral hypothalamus, body weight changes occurred even if no difference was observed in food intake between stimulated and unstimulated animals (Sani, Jobe et al. 2007).

4.3. Discussion of results study 3

We observed weight gain inversely related to the distance of the contacts from the wall of the third ventricle, and patients with at least one contact located medially in the STN experienced significantly greater weight gain than those with both active contacts located laterally. Thus, our results are consistent with the hypothesis that STN DBS exerts a regional effect on adjacent structures involved in energy balance. The maximum weight gain in our study was significantly larger in women than in men. Although women may be more susceptible to weight gain (Mueller, Anwander et al. 2011), previous studies have proven no significant sex-related differences in weight gain after unilateral or bilateral STN DBS (Barichella, Marczewska et al. 2003, Macia, Perlemoine et al. 2004, Montaurier, Morio et al. 2007, Bannier, Montaurier et al. 2009, Walker, Lyerly et al. 2009, Lee, Kurundkar et al. 2011). These findings are in agreement with our observation that weight gain in all six women of our study was associated with the medial contact site and that no interaction between active contact position and gender was found. Similar to other studies (Hamani, Saint-Cyr et al. 2004, Herzog, Fietzek et al. 2004, Godinho, Thobois et al. 2006), we found an inverse correlation between unilateral motor outcome (measured for rigidity, akinesia and tremor using hemi-body UPDRS-III sub score) and contralateral position of the active contact. Thus, patients with the lowest motor score (best motor condition) had contacts located more laterally from the wall of the third ventricle. Such results most likely reflect the internal organization of the STN with the sensorimotor part located dorsolaterally in the nucleus (Hamani, Saint-Cyr et al. 2004).

4.4. Summary of discussions

Deep brain stimulation of the subthalamic nucleus (STN DBS) is recognized as a standard and effective treatment method for motor symptoms of advanced Parkinson's disease.

About 15 years ago first reports of weight gain after STN DBS in PD patients have emerged. Since than these findings were reciprocated by numerous works and weight gain is now recognized as a common side effect seen in PD patients undergoing STN DBS (Gironell, Pascual-Sedano et al. 2002, Barichella, Marczewska et al. 2003, Macia, Perlemoine et al. 2004, Tuite, Maxwell et al. 2005, Montaurier, Morio et al. 2007, Novakova, Ruzicka et al. 2007, Bannier, Montaurier et al. 2009, Sauleau, Leray et al. 2009, Strowd, Cartwright et al. 2010, Novakova, Haluzik et al. 2011, Ruzicka, Jech et al. 2012, Strowd, Herco et al. 2016). We now acknowledge that it is not only a "simple" weight gain, but that number of patients are becoming overweight or even obese which subsequently predisposes them to multiple pathological conditions associated mainly with metabolic syndrome. Also, it has been considered that significant weight gain increases functional disability which is already reduced in this patient population. Therefore, all PD patients planned for STN DBS are now uniformly informed of this frequent side effect; careful monitoring of weight is recommended and potential referral to dietician counselling might be also needed in case of excessive weight gain.

In agreement, patients evaluated in our studies also gained weight following STN DBS and it was accompanied by increase in BMI and other anthropometric parameters (Novakova, Ruzicka et al. 2007, Novakova, Haluzik et al. 2011, Ruzicka, Jech et al. 2012). The mean increase of weight was in line with increases reported by others.

The mechanisms behind the weight gain have been of interest of many movement disorders teams and extensive efforts have been put in place to elucidate these outcomes. Some of the most logical justifications which comes to everyone's mind such as that the weight gain is related to normalization of energy expenditure due to decreased rigidity and improvement in dyskinesias or to the reduction in dopaminergic therapies were however not confirmed across all studies (Barichella, Marczewska et al. 2003, Macia, Perlemoine et al. 2004, Montaurier, Morio et al. 2007, Novakova, Ruzicka et al. 2007, Balestrino, Baroncini et al. 2017). Number of studies also failed to report any modification of food intake or appetite in these patients (Barichella, Marczewska et al. 2003, Macia, Perlemoine et al. 2004, Novakova, Ruzicka et al. 2007, Novakova, Haluzik et al. 2011)

Our research group hypothesized that weight gain is associated with hormonal dysregulation of energy homeostasis and food intake, however we failed to demonstrate non-physiological variation of food related hormones. Interestingly, consistently with Greek colleagues (Markaki, Ellul et al. 2012), we found markedly reduced morning cortisol levels following STN DBS (Novakova, Haluzik et al. 2011, Ruzicka, Novakova et al. 2012) which we thought can influence food regulation by shifting homeostatic balance to anabolic state. Other teams interested at the STN DBS effect on the hypothalamic –pituitary- adrenal axis (HPA) however failed to reciprocate the cortisol changes findings (Seifried, Boehncke et al. 2013), however the methodology may be responsible for this contradictory findings (Ruzicka, Jech et al. 2015).

Our observations are further supported by structural and functional complexity of subthalamic area, its proximity to the structures involving regulation of energy expenditure and food intake and potential exertion of regional effects of STN DBS on these regions accounting for weight gain after the procedure.

Our group have further looked at position of active electrode contact which has been postulated as an important predictor of weight gain, finding that patients with at least one contact located medially in the STN experience greater weight gain than those with both active contacts located laterally (Ruzicka, Jech et al. 2012), this finding was recently confirmed by additional report (Balestrino, Baroncini et al. 2017). Team led by Dr. Ruzicka has also confirmed our previous postulation that STN DBS exerts influence on the HPA axis by confirming that morning cortisol changes are in close relation to the mediolateral position of the active electrode within the STN. The team has further found that the cortisol changes are accompanied by increased postoperative anxiety and that patients with higher anxiety and lower cortisol levels have higher weight gain than those with lower anxiety (Ruzicka, Jech et al. 2015).

The role of STN in emotional and motivational processing is also well recognized and thus speculating that motivational and associative aspects of food behavior account or at least be associated with weight gain after STN DBS surgery is certainly of interest. PET study was used to analyze correlation between changes in brain metabolism and weight gain after STN DBS confirming correlations in brain metabolism in limbic and associative areas, including the orbitofrontal cortex, lateral and medial parts of the temporal lobe, anterior cingulate cortex and retrosplenial cortex (Sauleau, Le Jeune et al. 2014) confirming that changes in associative and limbic processes contribute to weight gain after STN DBS.

Indeed, it has been confirmed increased motivational relevance of aversive stimuli together with increased sensitivity to food reward cues in PD patients with post-operative weight gain. It has been reported that wanting low calorie food, not liking is associated with weight gain (Aiello, Eleopra et al. 2017).

In conclusion, weight gain is a frequent non-motor side effect of STN DBS. Putative mechanisms behind this weight gain have been extensively discussed in literature.

Based on the current knowledge it is believed that the weight gain is of multifactorial origin.

5. Conclusions

We observed weight gain following STN DBS in all studied patients in retrospective study, the weight gain was accompanied by motor improvement. Women tended to gain more weight than men which was in contrary to other reports. Weight gain was accompanied by an increase in body mass index with number of patients shifting BMI category. We found that if observing patients for longer interval after STN DBS the weight fluctuations are still existing. Thus, our findings are consistent with hypothesis that advanced PD patients treated with STN DBS gain weight.

Weight gain in our group of patients did not correlate with any clinical variables of motor improvement nor with the reduction of dopaminergic treatment following STN DBS which is in agreement with literature.

We observed increase in body weight, BMI, weight circumference and body fat percentage during the entire prospective study. Significant body weight gain was already noticed at one moth following STN DBS. We found that body weight and BMI differed significantly in genders, with greater increase in women.

Besides cortisol, we found no significant changes in tested hormones and food related parameters. There was a positive correlation between leptin levels and body weight and body fat percentage. Body weight also negatively correlated with adiponectin, positively with ghrelin. These finding reflect physiological regulatory mechanisms of food homeostasis. Thus, the outcomes indicate that changes in peripheral food related hormones do not appear to be causing weight gain in this patient population. We may speculate that there is direct or indirect effect of subthalamic stimulation on the hypothalamic homeostatic centers regulating energy balance, resulting weight gain.

Significant decrease of cortisol levels compared to baseline was observed in our study. Thus, direct effect of STN stimulation on adjacent fibers and nuclei was considered. We may speculate that STN DBS acts on the hypothalamus by suppressing the secretion of CRF with subsequent decrease in the production of cortisol, leading to a predominance in anabolic reactions.

We found that weight gain inversely correlates to the distance of the contacts from the wall of the third ventricle. Patients with at least one contact positioned medially within the STN encountered significantly higher weight gain that those patients with both active contacts localized laterally. We may therefore speculate that STN DBS exerts regional effects on neighboring structures involved energy homeostasis.

6. Literature

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7. Publication list

Original articles related to the Thesis:

Novakova, L., M. Haluzik, R. Jech, D. Urgosik, F. Ruzicka, and E. Ruzicka. 2011. 'Hormonal regulators of food intake and weight gain in Parkinson's disease after subthalamic nucleus stimulation', Neuro Endocrinol Lett, 32: 437-41. **IF - 1.296. Times cited 24.**

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Ruzicka, F., R. Jech, L. Novakova, D. Urgosik, O. Bezdicek, J. Vymazal, and E. Ruzicka. 2015. 'Chronic stress-like syndrome as a consequence of medial site subthalamic stimulation in Parkinson's disease', Psychoneuroendocrinology, 52: 302-10. **IF- 4.704.**

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