ANALYSIS OF FACTORS IMPACTING THERAPEUTIC DECISION-MAKING IN MOVEMENT DISORDERS

PhD Thesis

Zsuzsanna Aschermann, M.D.

Clinical Neuroscienses

Leader of the Doktoral School and the program:

Prof. Sámuel Komoly M.D., Ph.D., DSc.

Leaders of the project: Prof. Sámuel Komoly M.D., Ph.D., DSc.

and Norbert Kovács M.D., Ph.D.

Department of Neurology

Medical School

University of Pécs, Hungary

Pécs

2016

1. Introduction

Movement disorders

Basal ganglia diseases also called as movement disorders cover conditions with damaged brain motor control resulting in abnormal or involuntary movement patterns. The basal ganglia are large subcortical brain structures comprising several interconnected nuclei in the forebrain, diencephalon and midbrain. Brain structures belonging to the basal ganglia are the striatum (caudate, putamen, nucleus accumbens), the subthalamic nucleus, the globus pallidus, and the substantia nigra. Historically, basal ganglia had been considered as component of the motor system, however through their connections to the frontal cortex and limbic system they play a role in the organisation of cognitive and emotional functions. The movement disorders are divided into two main groups: 1. „hypokinetic" disorders are associated with slowness and poverty of movements, and include Parkinson's disease, and Parkinson's syndromes. 2. „Hyperkinetic" group includes diseases with excessive involuntary movements such as essential tremor, focal and generalized dystonias, and drug-induced movement disorders.

Parkinson's disease

Parkinson's disease is a neurodegenerative disorder with a progressive course. Pathologically it is characterized by the presence of Lewy bodies (inclusion bodies containing synuclein) in the central nervous system. Degeneration of the dopaminergic neurons in the pars compacta of the substantia nigra causes malfunction of the nigrostriatal system leading to the motor symptoms of the disease. Prevalence of the Parkinson's disease is 100-200/100.000 people. Its etiology is unknown, hereditary and environmental factors, and toxic agents are suspected to play a role the development of the disease. The clinical diagnosis is based on the presence of motor symptoms, bradykinesia (powerty of movements), rigor, and/or tremor are required criteria. The tremor is typically a resting tremor. Onset of the symptoms is always asymmetric. Although after few years the disease spreas to both extremities, asymmetricity is a characteristic feature troughout the whole course of the disease. In addition to motor symptoms patients may present non-motor symptoms as well, which frequently significantly impact quality of life, and often associate with therepeutic

challenges. Non-motor symptoms including pain, sleep problems, mood disturbances, and obstipation may start in the premotor phase. In advanced stage of Parkinson's disease late motor symptoms (postural instability, falls, freezing), vegetativ symptoms (ortostatic hypotension, incontinency), and cognitive impairment may also develop. The most effective symptomatic medication in the treatment of the Parkinson's disease is levodopa. Long-term levodopa therapy carries the risk of the development of late motor complications (fluctuations, dyskinesias). Based on the „continuous dopaminerg stimulation" theory individualized drug therapy is desired to prevent and mitigate complications of the levodopa treatment. If motor complications are severe and optimal oral treatment is not able to relieve them „advanced therapies" (deep brain stimulation, levodopa/carbidopa intestinal gel therapy) may be an appropriate option.

Dystonias, cervical dystonia

Dystonia is a movement disorder characterised by the presence of periodic or sustained muscle contractions causing involuntary repetitive movements or abnormal postures. The abnormal motions usually are twisting or tremorous (dystonic tremor). Dystonias may be characterised by clinical featrues (age of onset, affected body parts, associated symptoms), or etiology, genetics, pathology. Based on the etiology primary, and secondary dystonias, and dystonia plus syndomes are differentiated. Patients with primary dystonia have no additional neurological signs, and other etiology (toxic agent, metebolic disorders, etc.) can be excluded. In cases of secundary dystonias the dystonia is a sign of a well-defined disorder. In the dystonia plus syndromes the dystonia is associated with other neurological symptoms (myoclonus, parkinsonism, etc.). Focal dystonia affects a single body part. Involvement of the neck muscles causes cervical dystonia.

Primary cervical dystonia represents one of most common forms of focal dystonias. Cervical dystonia affects about 28-183 people/million people, and women are more prone to it than men. Cervical dystonia is classified into four types based on the principal direction of head posture: torticollis, laterocollis, anterocollis and retrocollis. The diagnosis of the primary cervical dystonia is often challenging, and requires clinical experise. Administartion of Botulinum toxin injections into the affected muscles is the most effective treatment for cervical dystonia, as the majority of the patients show excellent response to this therapy.

2. Aims

The thesis targets three aspects of movement disorders.

1. Pathophysiology of the primary cervical dystonia is currently not entirely understood, and diagnostic biomarkers are not available. We measured the brain iron level in primary cervical dystonia using R2* relaxometry method to study whether pathologic deposition is detectable. Previously, no data were abailable about abnormal brain iron accumulation in patients with primary cervical dystonia.

2. Pain is one of the non-motor symptoms of Parkinson's disease impacting significantly the quality of life, and is often resistant to therapeutic interventions. To investigate the pathophysiology of pain in Parkinson's disease, we performed a functional magnetic resonance imaging (MRI) study with a paradigm developed to investigate the „wind-up" phenomenon. „Wind-up" phenomenon is considered as an electrophysiologic correlate of the central sensitisation. We compared this phenomenon in patients with Parkinson's disease with healthy controls. In addition we examined the pain perception on both side of the body in patients with Parkinson's disease to investigate whether asymmetric symptom presentation of the disease has any modulating effect on the pain processing.

3. The levodopa/carbidopa intestinal gel (LCIG) is a therapeutic method to treat patients with Parkinson's disease when their symptoms are not manageable anymore by oral medication. In our study we examinated the changes of quality of life, motor and non-motor symptoms in patients with advanced-stage Parkinson's disease treated with LCIG at the Departement of Neurology, University of Pécs. Evaluation of patients was perfomed by scoring scales.

3. Experiments

3.1 Examination of brain iron deposition in primary cervical dystonia: a magnetic resonance imaging study

Introduction

Similary to majority of other primary dystonias types, the cause of cervical dystonia is unknown. Conventional imaging methods (CT, MRI) do not detect central nervous system lesions or morphological abnormalities. Modern MRI techniques – such as voxel-based morphometry (VBM) and diffusion tensor imaging (DTI) – have revealed subtle brain differences, but these results are inconsistent.

Brain iron has an essential role in normal physiology. However, abnormal accumulation of iron can potentiate the generation of highly reactive and toxic free radicals that may induce oxidative stress. Increased iron deposition has been described in many movement disorders including essential tremor, Parkinson's disease, Parkinson's syndroms, Huntington's disease, and Fridreich's ataxia. On the other hand dystonia is frequently occurs in brain iron accumulation disorders (e.g PKAN).

R2* relaxometry is a quantitative MRI technique, that is widely used and accepted for in-vivo brain iron quantification. The linear dependence of R2* relaxation rate on brain iron level has been validated in a postmortem study. R2* relaxometry method has been succesfully utilized in healty and patient groups.

Currently, no data are available on abnormal brain iron deposition in patients with primary cervical dystonia. Our study aimed to investigate the role of brain iron levels in the pathophysiology of primary cervical dystonia using the R2* relaxometry method.

Patients and methods

Twenty-three female patients were included in the study (mean age: 45.4±8.0 years). Patients were recruited from the Department of Neurology, University of Pécs. All of them had primary cervical dystonia (torticollis or laterocollis) without a family history, and any psychiatric or other major disease. Each patient was regulary treated with botulinum toxin type A. The severity of cervical dystonia was assessed immediately before the last botulinum toxin treatment using the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS). The

MRI was performed on the same day of the clinical visit. Twelve age and sex matched healthy subjects (mean age: 45.0±8.0 years) with no known disease served as a control group. All subjects received detailed information about the study protocol, and gave informed consent prior to the examination. The study was approved by the local ethical committee.

The MRI measurements were performed on a 3T MRI scanner (MAGNETOM Trio a Tim System, Siemens AG, Erlangen, Germany) with a 12-channel head coil. The conventional imaging protocol included a T2-weighted 2D turbo spin-echo, a 2D turbo spin-echo FLAIR, a T1-weighted 3D MPRAGE sequence. For R2* mapping a multi-echo 3D FLASH sequence with 12 equally speced echo was used.

The image analyses were performed using Matlab (MathWorks, Natick, MA), FLIRT (FMRIB's Linear Image Registration Tool), and FIRST (FMRIB's Image Registration Segmentation Tool).

The statistical analyses were executed with SPSS 20.0 software (SPSS Inc, Chicago, IL). Mann-Whitney U-test, multiple linear regression analysis, and Spermann correlation were applied.

Results

Compared with control subjects, patients with cervical dystonia showed elevated R2* values in the globus pallidus. The difference remained significant after statistically controlling for age with multiple linear regression analysis.

We found no evidence for between-group differences in the other three brain structures (thalamus, nucleus caudatus, putamen).

Multiple linear regression analysis indicated significant positiv correlation between age and R2* values in the putamen. There was no intercation between group membership and age in any of the analyses performed.

No significant correlation were found between R2* relaxations rates and clinical data (i.e. TWSTRS, disease duration).

Discussion

Using R2* relaxometry method our study showed as first that brain iron levels are increased in primary cervical dystonia. We found significantly elevated R2* relaxation rate in the globus pallidus in patients with cervical dystonia compared with healthy controls. Previous studies, using fMRI, positron emission tomography, VBM, and DTI also suggested altered pallidal function in primary focal dystonias. Our finding of iron deposition in the globus pallidus is also consistent with the positive effects of pallidal deep brain stimulation in primary cervical dystonia.

Our study cannot clarify the mechanism and the role of brain iron accumulation in cervical dystonia. However, it is well recognised that increased brain iron levels exert toxic effects by the formation of free radicals, which may lead to neurodegeneration. Therefore iron accumulation in primary cervical dystonia may also refer to a neurodegeneration process.

Our data did not reveal any relationship between R2* data and disease chracteristics. The lack of correlations can be explained by several factors. Firstly, disease duration does not correlate with disease severity. Moreover, TWISTR scores obtained at the last treatment visit may be affected by residual botulinum toxin effect from previous injection.

We found significant positive correlation between age and R2* values in the putamen, suggesting that iron deposition in the putamen increases over time. The age-related increase in brain iron levels is well known from both postmortem and in-vivo MRI studies. In agreement with our data, some previous works demonstrated that the constant age-related iron accumulation (up to about 60 years) is especially pronounced in the putamen. We found no significant association between age and R2* values in the thalamus and globus pallidus. This is not surprising, when we consider the hypothesis that the elevation of iron level in the thalamus and globus pallidus begins after about 30 years of age, and our study subjects were mostly middle-aged individuals. We found that R2* rate in the caudate nucleus did not change with age. Previous studies also failed to reveal age-related iron increase in the caudate nucleus, but the literature is conflicting.

3.2. Pain in Parkinson's disease. Analysis of „wind-up" phenomena: a functional magnetic resonance imaging (fMRI) study

Introduction

Pain occurs in 40-85% of patients with Parkinson's disease. Ford classified pain occurring in Parkinson's disease into five categories: musculosceletal, radicular or neuropathic, dystonia-related, akatitic-related, and central pain. Defazio et al. had found that in Parkinson's disease beside the typical off-dystonic parkinsonian pain, muscular cramping and central neuropathic pain are more frequent than in healty subjects. The DoPaMiP (Douleur et maladie de Parkinson en Midi-Pyrénées) study had shown that two-third of Parkinson's patients suffers from chronic pain. Recent clinical, neurophysiological, and neuroimaging studies suggest that pain sensation in Parkinson's disease is impaired.

The pathomechanism of parkinsonian painful syndroms is still not fully understood. Pain could be related to peripheral factors, and abnormal processing of nociceptive imputs in the central nervous system. Abnormality of the nociceptive processing might be caused by damaged sensitisation.

Pain processing can be tested by repeated painful stimulation. The „wind-up" phenomenon described by Lorne Mendell in 1965 is a frequency dependent facilitation of the measured responses in the spinal cord mediated by afferent C-fibres. Mendel suggested that „wind-up" is due to a reverberatory activity of the interneurons in the spinal cord lasting for 2-3 seconds. If another stimulus arrives to the spinal cord within this period, it sums with the ongoing activity and produce a more intense discharge in the interneurons. Similar to the selective stimulation of the afferent C-fibres, the repetitive painful heat stimulation with interstimulus intervals of 3 secundum or less will also procreate a phenomenon of temporal summation in the evoked painful sensation. This temporal summation of second pain is also called as „wind-up". „Wind-up" is usually associated with chronic pain and central sensitisation. It is an ideal tool to examine some aspects of central sensitisation and central pain syndromes.

We presumed that in the case of Parkinson's disease, pain or pain severeness might be caused by the aggravation of the „wind-up" phenomenon due to any central or peripheral nervous system lesions or functional alterations. We aimed to measure the difference in this

phenomenon between Parkinson's patients and healthy controls. We also hypothesized that pain sensation might be asymmetric considering that the asymmetric symptoms of Parkinson's disease have any modulating effect on the pain processing itslef.

Patients and methods

Twelve Parkinson's patients and six age- and sex-matched healthy subjects were included in the study. Patients were recruited from the Department of Neurology, University of Pécs.

Table 3.2.1. The demographical and disease-related data of the participiants

group	number of subjects	age (years±SD)	disease duration (years±SD)	Hoehn-Yahr (±SD)	UPDRS III (±SD)
left-dominant PD	6	62.2 ± 12.2	6.2 ± 5.6	2.0 ± 0.6	11.2 ± 4.9
right-dominant PD	6	58.8 ± 13.0	5.5 ± 2.0	2.1 ± 0.6	15.8 ± 4.2
control subjects	6	59.0 ± 7.29	-	-	-

PD: Parkinson's disease

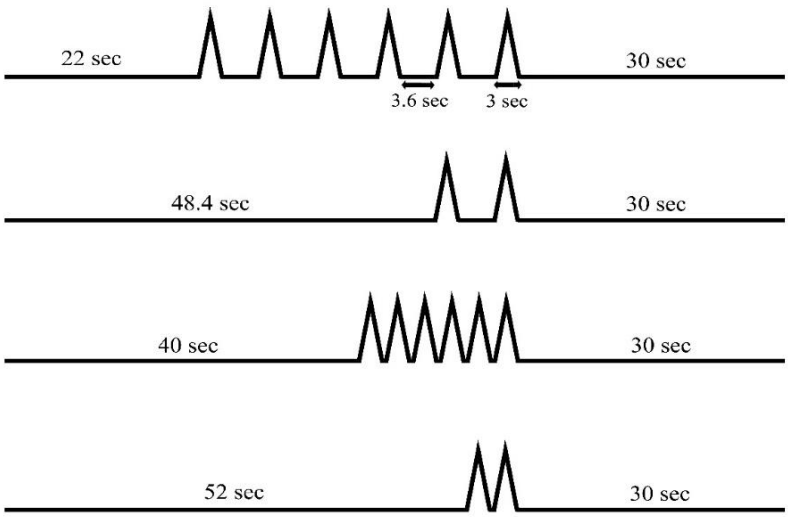
All participiants were right-handed male, and had no history of drug or alcohol abuse, analgetics or anidepressant taking. Inclusion criteria included idiopathic Parkinson's disease according to the UKPDSBB (United Kingdom Parkinson's Disease Society Brain Bank) criteria. All of the patients were „optimally treated". All patients were examined in the „on" phase. None of the patients suffered from acute or chronic pain. Subjects with cognitiv defects (MMSE <28) were excluded. All participiants gave written informed consent. The experimental protocoll was approved by the regional ethical committee.

Thermal pulses were generated by the combined fMRI model of the Pathway Pain Evaluation System (Medoc Advanced Medical Systems, Ramat Yishai, Israel) with CHEPS (Contact Heat Evokated Potential Stimulator) thermode. This thermode provides extremely fast heating rates (up to 70 °C/s) and fast cooling rates (40 °C/s) on a 27-mm diameter circular skin area. The thermode was placed on the right forearm in case of control subjects and right-side dominant Parkinson's patients and on the left forearm for the left-side dominant Parkinson's patients. The pain threshold measurement used a 0.15 Hz stimulation paradigm (Figure 3.2.1.). The stimulation started with six 46°C pulses, then during the 30-s interstimulus

inteval the subject were asked to rate the pain sensation of the last pulse on a Verbal Analogue Scale (VAS) rating from 0 to 10 (0=no sensation, 10=worst pain imaginable). The values were recorded and the stimulation continued with 1°C warmer pulses. This loop was continued until the subject reported a VAS score 4 or 5 (4=discrete pain, 5=mild pain). This resulting temperature was used for the following examinations.

The MRI measurements were performed on a 3T MRI scanner (MAGNETOM Trio a Tim System, Siemens AG, Erlangen, Germany) with a 12-channel head coil. FMRI utilized a standard 2D EPI sequence. Anatomical images were obtained from a T1-weighted axial 3D-MPRAGE sequence. For the communication with the subjects Nordic NeuroLab's fMRI Hardware was used. No brain abnormalities were detected based on the visual analysis of the MRI images.

Figure 3.2.1. Paradigm used for the fMRI measurements: modified version of „wind-up" protocol described by Straud et al.



The figure shows the stucture of one block in the experimental paradigm. There are four 88-s long runs. The first two has a stimulation frequency 0.15 Hz with six and two stimulations. The last ones are similar, but with a stimulation frequency of 0.33 Hz, where the temporal summation of second pain appears.

The used paradigm was hierarchically built, and consisted of blocks. The blocks were identical, and the paradigm included three blocks on each side. Every block has four 88-secundum long runs, giving 24 separate fMRI measurements/subject (24 = 3 blocks x 4 runs x 2 sides).

FMRI data were processed and statistical analized with the use of FEAT (FMRI Expert Analysis Tool, Version 5.98, part of FSL), and other software tools within FMRIB's Software Library. A three-stage, multi-level analysis was implemented. As result eight original and six derived contrasts were created: original: LS6, RS6, LS2, RS2, LF6, RF6, LF2, RF2, derived: LF6-LS6, LS6-LS2, LF6-LF2, RF6-RS6, RS6-RS2, RF6-RF2 (R=right, L=left, S=slow, 0.15 Hz, F=fast, 0.33 Hz, 6=6 stimulations, 2=2 stimulations). Analysis of three group (LD-PD=left dominant Parkinson's disease, RD-PD=right dominant Parkinson's disease and control) differencies gave four new contrasts e.g. in case of LD-PD versus control comparison these were: LD-PD (group average), control (control average), LD-PD>control (group difference), LD-PD<control (group difference).

To collect clinical data, after each 88-secundum run the scanner was stopped, the subject was asked to rate the last pulse on VAS scale, and these values were recorded (0-10). The average values were calculated for every group for the following stimulations : LF6, LS6, RF6 and RS6. The left and right „wind-up" was calculated as the relative difference between the fast and slow six-repeat stimulation.

GraphPad Prism 4.0 was used for all statistical analysis in this study.

Results

Statistical analysis showed no significant differences in the VAS score at the pain threshold investigations between patients with Parkinsons's disease and healthy controls. Correlation analysis of the left- and right-sided „wind-up" showed in the group of the healthy subject correlation (LF6-LS6 and RF6-RS6). In the group of the Parkinson's patients the „wind-up" on the more affected side was lower by 5% compared to the less affected side. This trend is visible in both the left dominant and right dominant groups, however due to the small number of patients this difference was not statistically significant. The average „wind-up" scores (both sides) were elevated in the patients versus control group, patients reported 10% higher average „wind-up" score than control subjects.

In the fMRI analysis we had considered two main aspects of pain processing in Parkinson's disease:

1. Is there any difference between pain processing of Parkinson's patients and healthy controls?

The fMRI data show two main areas where Parkinson's patients have higher activation during „wind-up" compared to control subjects. These are the posterior division of the cingulate gyrus and the precuneus cortex. These areas were more activated in Parkinson's patients regardless of dominance or the side of stimulation. Two more areas appeared to differe, the intracalcarine cortex and the angular gyrus, however these findings were not uniform to all Parkinson's groups (dominance, side of activation), and had lower statistical significance. The lateral occipital cortex showed high statistical significance, but the difference occurred in only one of the four comparisons.

2. Do the asymmetric symptoms of the Parkinson's disease exert any modulating effect on the pain processing?

It is no rational to compare directly the identical sides between the Parkinson's groups (e.g. left arm stimulation in the left-dominant Parkinson's patient vs. left arm stimulation in the right-dominant Parkinson's patient), because we cannot rule out the possibility that the less affected arm of a patient from one group is somewhat more affected than the affected arm of a given patient from the other group. For that very reason, we compared the side differences between groups (LD-PD RS6-LS6 vs. RD-PD RS6-LS6). The comparison suggested bilaterally activated anterior and posterior divisions of the supramarginal gyrus and postcentral gyrus.

Discussion

„Wind-up" is a stable and reproducible phenomenon that is ideal to investigate the processing of nociceptive information in the central nervous system. Under normal circumstances it appears in the first 3-4 stimuli, thus 4-8 stimuli/trains are generelly accepted as an optimal designe for such experiments. „Wind-up" is considered as an electrophysiological correlate of central sensitisation (Herrero et al). Moreover, as being a purely central phenomenon, it offers the possibility for the differentiation between central and peripheral components of nociceptiv stimuli processing in different experimental settings.

In our study „wind-up" was different between the groups in several ways. First, it was generally more pronunced in Parkinson's patients compared the healthy subjets indicating a central processing alteration in patients with Parkinson's disease. Second, in the control group

the „wind-up" scores of the right side highly correlated with the „wind-up" scores of the left side, however in case of Parkinson's patients the disease dominant side seemed to express lower „wind-up" scores. The cause of this may come from peripheral factors.

Peripheral damage in the pain processing had been demonstrated in Parkinson's disease. Nolano et al showed cutan denervation, significant loss of epidermal unmyelinated nerve fibres in Parkinson's patients compared to healthy controls. The loss of epidermal nerve fibres was more severe on the dominant side. These findings are in line with our results: the peripheral conduction deficiency might explain lower „wind-up" values on the dominant side.

The fMRI results in the Parkinson's groups suggest that less affected side shows higher activation in the supramarginal and postcentral gyri (SI, SII). Both regions are activated by painful stimulation in healthy subjects as well as patients with allodynia or chronic pain (e.g. fibromyalgia). These results suggest that the processing of the painful stimulus at a higher central nervous system level differ between the more affected and less affected side in patients with Parkinson's disease. This difference may arise from the deficiency of the efferent information, and neurodegeneration may have a modulating effect on this as well.

Herrero at al hypothesized that „wind-up" may be a compensatory mechanism, which has evolved to overcome the limitations of the unmyelinated C-fibres. The higher „wind-up" values of Parkinson's patients compared to healthy controls may represent a global compensatory mechanism that tries to counterweight the loss of fine unmyelinated axons.

The fMRI comparison, aiming to assess the differences between the Parkinson's patients and control subjects, revealed two areas where Parkinson's patients had consistently higher activation during „wind-up" compared to control subjects regardless of dominance or the side of stimulation. These areas were the posterior cingulate gyrus division and the precuneus.

The posterior division of the cingulate gyrus encompasses the posterior mid-cingulate- and the posterior cingulate gyri. Previously these areas had been mainly thought to be responsible for the intensity coding of noxious stimuli. A newer approach suggests that mid-cingulate cortex is mainly involved in response selection, and is usually engagned in cognitive tasks that may not require movement and decision. This approach also suggests that posterior cingulate cortex is involved in visuospatial orientation, and one of its main functions is to orient the body towards noxious somatosensory stimuli. The posterior cingular cortex may share some functions with the perigenual anterior cingulate cortex, the key structure within the cingulate cortex for pain processing associated with the suffering component of pain.

The other structure where differences were found between Parkinson's patients and healthy controls is the precuneus. Marguiles at al. distinguishe three subregion of precuneus: the sensorimotor anterior, cognitive/associative central, and visual posterior regions. Based on this parcellation the significant difference between Parkinson's patients and controls is localized around the boundary of the first and second region, but mainly located in the cognitiv/associative central precuneal subfield. The first part has connections to motor areas, dorsal mid-cingulate gyrus, and insula. The central area of the precuneus has connections with the multisensory associative regions, and the dorsolateral prefrontal cortex. Dorsolateral prefrontal cortex has a prominent role in pain processing, as it is proposed to exert active control on pain percepcion by modulating the cortico-subcortical and cortico-cortical pathways.

To sum up, the results of this study show that Parkinson's patients process painful stimuli differently from healthy controls regarding. These differences may arise from different factors: cutaneous denervation, and compensatory neuronal mechanisms, neurodegeneration within the central nervous system, and central sensitisation might explain the differences.

3.3 The impact of levodopa/carbidopa intestinal gel treatment on quality of life

Introduction

In the advanced stage of Parkinson's disease the effectiveness of the oral medications becomes unstable. Motor complications caused by variable drug absorption, low therapeutic range, and pulsatile drug level fluctuations induce unpredictable motor performance deteriorating the quality of life of Parkinson's patients. In the advanced-stage, when motor complications do not improve by optimal oral treatment change to deep brain stimulation or levodopa/carbidopa intestinal gel (LCIG) therapy might be the appropriate therapeutic choice. Over thr LCIG treatment patients receive continuously levodopa/carbidopa intestinal gel via a PEG/PEJ tube connected to a perfusor. This method when applied for the right patient may improve movement efficiency, decrease the OFF time, and increase the ON time, modify the dyskinesias, improve non-motor symptoms, and improve the quality of life.

In our study aim was to assess the improvement of the condition of Parkinson's patients treated with LCIG at Departement of Neurology, University of Pécs.

Patients and methods

Twenty-two Parkinson's patients treated with LCIG were recruited from the Department of Neurology at the University of Pécs. The mean age of patients was 68.9±4.9 years, the mean disease duration was 15.2±7.0 years, and duration of fluctuations to the begining of LCIG treatement was 7.9±3.3 years. Fourteen patients had akinetic-rigid type, eight patients had mixed type Parkinsons'disease. The LCIG therapies were indicated due to motor complications not controlled by oral treatment (peak-dose dyskinesia, unpredictable OFF, OFF dystonia). All subjects gave consent prior to examination.

Patients were assessed before the initiation of LCIG treatment, during the treatment at six month (6±2 montha), and one year (12±2 month) .

The severity of Parkinson's disease was determined by the Hoehn-Yahr Scale, Clinical Global Impairment-Severity (CGI), and MDS-UPDRS (Movement Disorders Society-Unified Parkinson's Disease Rating Scale). The quality of life (QoL) was assessed using EuroQol EQ-5D(-5L), and PDQ-39 scales. The EQ-5D is a general quality of life scale. The first part measures five segments of health-related quality of life: mobility, self-care, usual activities, pain-discomfort,

and anxiety. The second part is a visual analog scale where the patients characterize own health status. The PDQ-39 is a Parkinson's disease-specific quality of life assessment scale. This scale investigates eight areas: mobility, activities of daily living, emotional well-being, stigma, social support, communication, and body discomfort. The non-motor symptoms were evalueted using Parkinson's Disease Sleep Scale 2nd version (PDSS-2), Epworth Sleepiness Scale, and Beck Depression self-administered questionnaire. The duration of the fluctuations were calculated based on patients' diary, in which patients evaluated their own activity every half hour (ON without dyskinesia, ON without troubelsome dyskinesia, ON with troubelsome dyskinesia, OFF state, sleep). The severity of the flucuations was determined using Unique Dyskinesia Rating Scale (UDysRS).

Statistical analyses were performed by IBM SPSS 21.0 software (IBM Inc., USA).

Results

Administration of LCIG therapy resulted in statistically significant improvement among the Parkinson's symptoms severity rating scales in the MDS-UPDRS part of every day life motor symptoms (M-EDL), and part of the motor complications (MC), the MDS-UPDRS global score, the UDysRS global score, and the Clinical Global Imrovement-Severity. The Hoehn-Yahr Scale and the MDS-UPDRS motor symptoms subscale (ME) showed a trend like improvement . The EQ-5D scale summary index, the visual analog scale, and the Mobility and Pain-Discomfort subsores improved as well. LCIG treatment also was associated with statistically improvement in the PDQ-39 scale summary index, the Mobility, the Activities of Daily Living, the Stigma, the Communication subsores. With the LCIG therapy the nightime sleeping quality (PDSS-2) significantly, the depression (based on Beck Depresszion self-administered questionnaire), and daytime sleepiness (Epworth Scale) tend to improve. After one year of LCIG treatment the average ON time increased from 4.5 hours to 10.5 hours, in paralell the OFF time decreased from 5.0 hours to 0.5 hours, and duration of severe dyskinesias from 2.0 hours to 0.0 hours. Daytime sleep was unaffected, and the amount of nightime sleep increased with near 2 hours indirectly indicating the impovement of the sleep quality.

Discussion

The quality of life of Parkinson's patients treated with LCIG showed improvement measured by general QoL scale (EQ-5D) or Parkinson's specific QoL scale (PDQ-39). Our results are in line with the international data. The time of the ON stage withouth dyskinesias increased, the time of the OFF stage about 4.5 hours decreased, the life of patients became more predictable. The disability caused by motor symptoms (MDS-UPDRS nM-EDL: everyday life motor symptoms) showed remarkable decrease. We observed major improvement not only in the motor symptoms, but in non-motor symptoms as well.

4. Summary of the thesis

In the thesis we investigated three different topics related to the movement disorders.

1. In the first part of the thesis we examined the brain iron accumulation in patients with primary cervical dystonia using the R2* relaxometry method. Our work provides the first support for increased brain iron deposition in cervical dystonia. We found significantly elevated R2* relaxation rate in the globus pallidus of dystonic patients compared with healthy controls. The elevated iron level of globus pallidus may develop into a valuable biomarker of this type of dystonias. Our study could not clarify whether the excess iron is a primary cause or merely an epiphenomenon of cervical dystonias. Further longitudinal investigations are needed in larger cohort of patients to better understand the link between brain iron accumulation and clinical data.

2. In the second part of the thesis our investigations related to the study of the origin of Parkinson's pain. We performed clinical and functional MRI measurements using a paradigm developed to produce the „wind-up" phenomenon. „Wind-up" is considered as an electrophysiological correlate of central sensitisation. We aimed to examine the difference between Parkinson's patients and healthy controls. We also investigated the asymmetry of pain perception to determine the asymmetric symptoms of Parkinson's disease have any modulating effect on the pain processing. We have found clinical and functional MRI differencies in the pain processing between Parkinson's patients and healthy controls. In addition, the asymmetry of Parkinson's disease manifests in the pain processing as well. These discrepancies probably arise from peripheral factors, cutaneous denervation and the compensatory neuronal mechanisms. Central factors, central sensitisation, neurodegeneration within the central nervous system could explain the other differences. Our results suggest, that managament of Parkinson's pain requires the broadening our horizons, and the consideration of central pain therapeutic options.

3. The third part of the thesis analysis the results of a clinical trial, in patients with Parkinson's disease were treated with levodopa/carbidopa intestinalis gel at Depertment of

Neurology at the University of Pécs. The LCIG therapy is applicable for patients who have symptoms not possible to impact with the optimal oral treatment. Our study in accodrdance with international data demonstrated, that LCIG therapy is associated with the increase of ON time, decrease of the disability caused by the motor symptoms, the improvement of non-motor symptoms (sleep, mood, pain), and a more predeictabe life of the patients.

5. Bibliography

5.1 Publications related to the thesises

1. Zsuzsanna Aschermann, Ferenc Nagy, Gabor Perlaki, Jozsef Janszky, Attila Schwarcz, Norbert Kovacs, Peter Bogner, Samuel Komoly, Gergely Orsi: "Wind-up" in Parkinson's Disease: a Functional Magnetic Resonance Imaging Study European Journal of Pain 2015 Mar 12. doi: 10.1002/ejp.659. IF: 2.928

2. Norbert Kovács, Zsuzsanna Aschermann, Péter Ács, Edit Bosnyák, Gabriella Deli, József Janszky, Sámuel Komoly: The impact of levodopa-carbidopa intestinal gel on health-related quality of life in Parkinson's disease Ideggyógyászati szemle 2014; 67(7-8):245-50 IF:0.386

3. Zsuzsanna Aschermann*****, Gábor Perlaki*, Gergely Orsi, Szilvia Anett Nagy, Andrea Horvath, Beata Bone, Katalin Bihari, Peter Acs, Jozsef Janszky, Samuel Komoly, Peter Bogner: Quantitative assessment of brain iron by R2* relaxometry in patients with cervical dystonia Mov Disord. 2015 Sep;30(10):1422-6. doi: 10.1002/mds.26306. Epub 2015 Jul 30. (*equal contribution in first authorship) IF:5.68

5.2 Other publications

Aschermann Z, Gomori E, Kovacs GG, Pal E, Simon G, Komoly S, Marodi L Illes Z: X-linked hyper-IgM syndrome associated with rapid course of progressive multifocal leukoencephalopathy Arch.Neurol. 2007 Feb, 64(2): 273-6 IF:5.783

Pál Endre, Aschermann Zsuzsanna, Gömöri Éva, Kovács Gábor Géza, Simon Gábor, Maróti László, Komoly Sámuel, Illés Zsolt: Progresszív multifokális leukoencephalopathia Ideggyogy Sz 2007 May 30, 60 (5-6):263-268

Aschermann Z, Szalay F, Schmidt E, Komoly S, Illés Z.: Persistent akinetic-rigid side effects of neuroleptics may indicate Wilson’s disease Ideggyogy Sz 2007 Sep30, 60 (9-10):404-405

Kovács Norbert dr., Balás István dr., Llumiguano Carlos dr., Aschermann Zsuzsanna dr., Bóné Beáta dr., Tasnádi Emese dr., Nagy Ferenc dr., Janszky József dr., Dóczi Tamás dr., Varga Dezső dr., Hollódy Katalin dr., Karádi Kázmér dr., Illés Zsolt dr., Komoly Sámuel dr.: Mély agyi stimuláció – a disztónia kezelésének egy új perspektívája Gyermekorvos Továbbképzés 2008, 7:(Suppl A) 1-20

Kovács N, Balás I, Janszky J, Aschermann Z, Nagy F, Dóczi T, Komoly S.: Special aspects of patient care after implantation of deep-brain-stimulator Ideggyogy Sz. 2008 Jan 30; 61(1-2):4-15.

Kovács N, Balás I, Llumiguano C, Aschermann Z, Nagy F, Janszky J, Dóczi T, Komoly S: Mély agyi stimuláció: egy új perspektíva a mozgászavarok kezelésében Lege artis medicinea 2009, 19:(2) 119-126

Aschermann Zsuzsanna dr, Kovács Norbert dr, Komoly Sámuel dr: A Parkinson-kór és Parkinson-szindrómák klinikai elkülönítése és korszerű kezelése Gyógyszerész Továbbképzés 2010, 4 (3):53-56

Pal E, Nagy F, Aschermann Z, Balazs E, Kovacs N. The impact of left prefrontal repetitive transcranial magnetic stimulation on depression in Parkinson's disease: a randomized, double-blind, placebo-controlled study Mov Disord. 2010 Oct 30; 25(14):2311-7. IF: 4.48

Fehér G, Balás I, Komoly S, Dóczi T, Janszky J, Aschermann Z, Balázs E, Nagy F, Kovács N. Analysis of antiparkinsonian drug reduction after bilateral subthalamic deep brain stimulation Ideggyogy Sz. 2010 Sep 30; 63(9-10):314-9. IF:0.236

Kalmar Z, Kovacs N, Perlaki G, Nagy F, Aschermann Z, Kerekes Z, Kaszas B, Balas I, Orsi G, Komoly S, Schwarcz A, Janszky J. Reorganization of motor system in Parkinson's disease. Eur Neurol. 2011;66(4):220-6. IF:1.811

Kaszás B, Kovács N, Balás I, Kállai J, Aschermann Z, Kerekes Z, Komoly S, Nagy F, Janszky J, Lucza T, Karádi K. Sensitivity and specificity of Addenbrooke's Cognitive Examination, Mattis

Dementia Rating Scale, Frontal Assessment Battery and Mini Mental State Examination for diagnosing dementia in Parkinson's disease. Parkinsonism Relat Disord. 2012 Jun; 18(5):553-6. IF: 3,274

Deli G, Balás I, Komoly S, Dóczi T, Janszky J, Illés Z, Aschermann Z, Tasnádi E, Nagy F, Pfund Z, Bóné B, Bosnyák E, Kuliffay Z, Szijjartó G, Kovács N. Treatment of dystonia by deep brain stimulation: a summary of 40 cases Ideggyogy Sz. 2012 Jul 30; 65(7-8):249-60. IF:0.348

Aschermann Z, Kovács N, Komoly S. Continuous dopaminergic stimulation in Parkinson disease: possibilities in 2013 Ideggyogy Sz. 2013 May 30; 66(5-6):209-10. IF:0.343

Horváth K, Aschermann Z, Komoly S, Kovács A, Kovács N. Treatment of tardive syndromes Psychiatr Hung. 2014;29(2):214-224.

Krisztina Horváth; Zsuzsanna Aschermann; Péter Ács; Edit Bosnyák; Gabriella Deli; Endre Pál; Ildikó Késmárki; Réka Horváth; Katalin Takács; Sámuel Komoly; et al. Validation of the Hungarian MDS-UPDRS: Why do we need a new Parkinson scale? Ideggyogyaszati Szemle. 2014;67(3-4):129-134. IF:0.386

Edit Bosnyák, Mihály Herceg, Endre Pál, Zsuzsanna Aschermann, József Janszky, Ildikó Késmárki, Sámuel Komoly, Kázmér Karádi, Tamás Dóczi, Ferenc Nagy, Norbert Kovács: Are Branded and Generic Extended-Release Ropinirole Formulations Equally Efficacious? A Rater-Blinded, Switch-Over, Multicenter Study Parkinson's Disease. 2014, 2014: 158353 IF:2.098

Krisztina Horváth, Zsuzsanna Aschermann, Péter Acs, Edit Bosnyák, Gabriella Deli, Endre Pál, József Janszky, Béla Faludi, Ildikó Késmárki, Sámuel Komoly, György Dibó, László Vécsei, Annamária Takáts, Adrián Tóth, Piroska Imre, Ferenc Nagy, Mihály Herceg, Anita Kamondi, Eszter Hidasi, Norbert Kovács: Is the MDS-UPDRS a Good Screening Tool for Detecting Sleep Problems and Daytime Sleepiness in Parkinson's Disease? Parkinson's disease 2014, 2014:806169 IF: 2.098

Krisztina Horváth**,** Zsuzsanna Aschermann, Péter Acs, Gabriella Deli, József Janszky, Kázmér Karádi, Sámuel Komoly, Béla Faludi, Norbert Kovács: Test-Retest Validity of Parkinson's

Disease Sleep Scale 2nd Version (PDSS-2) Journal of Parkinson's Disease 2014 Jan 1;4(4):687-91 IF:1.083

Kázmér Karádi, Tivadar Lucza, Zsuzsanna Aschermann, Sámuel Komoly, Gabriella Deli, Edit Bosnyák, Péter Ács, Réka Horváth, József Janszky, Norbert Kovács, Taylor and Francis Visuospatial impairment in Parkinson's disease: The role of laterality Laterality Laterality: 2015; 20(1):112-27 IF:1.335

Deli G, Aschermann Z, Ács P, Bosnyák E, Janszky J, Faludi B, Makkos A, Kovács M, Komoly S, Balás I, Dóczi T, Kovács N. Bilateral Subthalamic Stimulation can Improve Sleep Quality in Parkinson's Disease J Parkinsons Dis. 2015;5(2):361 IF: 1.91

Lucza T, Karádi K, Komoly S, Janszky J, Kállai J, Makkos A, Kovács M, Weintraut R, Deli G, Aschermann Z, Kovács N.: Neurocognitive disorder in Parkinson's disease Orv Hetil. 2015 Jun 7; 156(23):915-26.

Horváth K, Aschermann Z, Ács P, Bosnyák E, Deli G, Pál E, Késmárki I, Horvath R, Takacs K, Balázs E, Komoly S, Bokor M, Rigó E, Lajtos J, Takáts A, Tóth A, Klivényi P, Dibó G, Vecsei L, Hidasi E, Nagy F, Herceg M, Imre P, Kovács N. Validation of the Hungarian Unified Dyskinesia Rating Scale Ideggyogy Sz. 2015 May 30; 68(5-6):183-8. IF: 0.386

Gabriella Deli, István Balás, Tamás Dóczi, József Janszky, Kázmér Karádi, Zsuzsanna Aschermann, Ferenc Nagy, Attila Makkos, Márton Kovács, Edit Bosnyák, Norbert Kovács and Sámuel Komoly: Deep Brain Stimulation Can Preserve Working Status in Parkinson's Disease Parkinson's Disease Volume 2015, Article ID 936865 IF: 2.01

Cumulative impact factor: 35.575

Cumulative impact factor of published papers related to the thesises: 8.994

6. Acknowledgements

I woluld like to thank the head of the Doctoral School, Professor Sámuel Komoly for the opportunity and support which served as the basis of this work. I am also grateful to Dr. Ferenc Nagy for the help in „Pain in Parkinson's disease. Analysis of „wind-up" phenomena: a functional magnetic resonance imaging (fMRI) study". I am thankful to Dr. Norber Kovács for many years working together in the field of movement disorders. I greatly appreciate the contribution of Professor Péter Bogner, Gergely Orsi, and Gábor Perlaki, this work could not have been done without their knowledge and professionality. I wish to thank to Beáta Bóné, Péter Ács, and Nóra Fülöp-Szeifert for the help in „Examination of brain iron deposition in primary cervical dystonia: a magnetic resonance imaging (MRI) study". „The impact of levodopa/carbidopa intestinal gel treatment on quality of life" study could not have been done without the work of Éva Balázs and Katalin Takács, special thank for their diligence. Finally, I wish to thank my friends and my family for their emotional support during this project.